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Description

The present invention relates to new 19-nor steroid or 19-nor D-homosteroid compounds substituted at position 11β , the process for preparing them, their use
5 as medicaments, the compositions containing them and the new intermediates obtained.

In French Patent BF 2,377,417 are described steroids containing, at position 3, a blocked ketone radical, at position 5α a hydroxy radical, at position 9(10) a
10 double bond and at position 11β a radical R_1 , R_1 being a straight or branched, saturated alkyl radical containing from 1 to 12 carbon atoms or an unsaturated alkyl radical containing from 2 to 8 carbon atoms, possibly substituted, an aralkyl radical containing from 7 to 13
15 carbon atoms, possibly substituted, or a heterocyclic radical containing one or more sulphur or oxygen atoms.

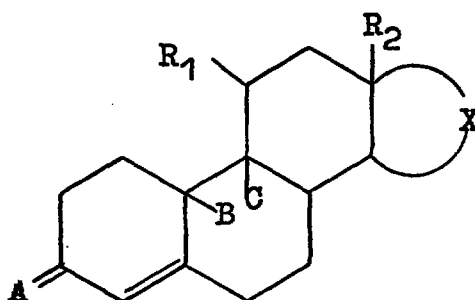
In French Patent BF 2,377,418 are described 3-keto $\Delta^{4,9}$ steroids containing at position 11β a radical R_1 identical to the radical R_1 of the products described
20 in * Patent BF 2,377,417.

However, the aforementioned French Patents do not describe any product in which the substituent R_1 contains a nitrogen atom.

The subject of the invention is the compounds of
25 formula (I')

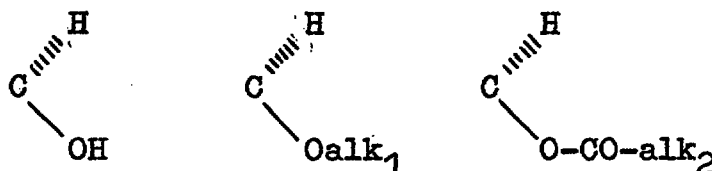
*Translator's note: The French "bevet" is clearly a misprint for "brevet" = "patent".

(18)



(I)

in which R_1 represents an organic radical containing from 1 to 18 carbon atoms, containing at least one nitrogen, phosphorus or silicon atom, the atom immediately adjacent the carbon at [position] 11 being a carbon atom, R_2 represents a hydrocarbon radical containing from 1 to 8 carbon atoms, X represents the residue of a pentagonal or hexagonal ring, possibly substituted and possibly bearing an unsaturation, the group C = A at position 3 represents an oxo group, free or blocked in ketal form, a group



a group C=NOH, a group C=NO-alk₃ or a group CH₂, alk₁, alk₂ and alk₃ representing an alkyl radical containing from 1 to 8 carbon atoms or an aralkyl group containing from 7 to 15 carbon atoms and B and C together form a double bond or an epoxide bridge.

Preferably R_2 represents a straight or branched, saturated alkyl radical, containing from 1 to 4 carbon atoms, for example a methyl, ethyl, n-propyl or butyl

radical.

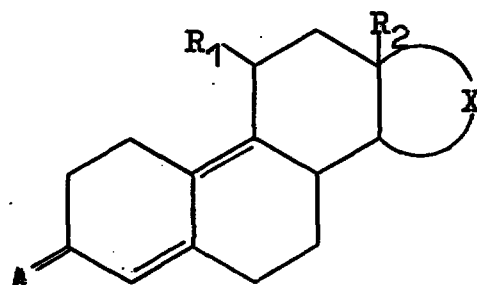
When alk_1 , alk_2 or alk_3 represents an alkyl radical, this is preferably the methyl, ethyl, n-propyl or isopropyl radical.

5 When alk_1 , alk_2 or alk_3 represents an aralkyl radical, this is preferably the benzyl radical.

Preferably X represents the residue of a possibly-substituted pentagonal ring.

10 The invention extends, of course, to the salts of addition with acids of the compounds of formula (I') such as, for example, the salts formed with hydrochloric, hydrobromic, nitric, sulphuric, phosphoric, acetic, formic, propionic, benzoic, maleic, fumaric, succinic, tartaric, citric, oxalic, glyoxylic [and] aspartic acids,
15 alkane sulphonic [acids] such as methane or ethane sulphonic acids, arylsulphonic [acids] such as benzene or paratoluene sulphonic acids and arylcarboxylic [acids].

20 The subject of the invention is especially the compounds of formula (I'), as defined before, corresponding to the formula (I):



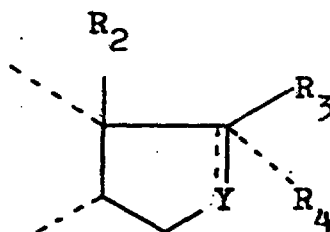
(I)

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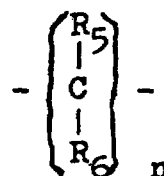
in which R_1 , R_2 , X and A are defined as before.

The subject of the invention is, more particularly, the compounds of formula (I'), for which R_2 represents a methyl radical.

- 5 The subject of the invention is especially the compounds of formula (I') for which X represents the residue of a ring of formula:



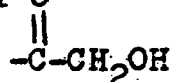
- in which R_2 keeps the same meaning as before, the dotted line at 16 - 17 symbolizes the possible presence of a
10 double bond, Y represents a radical



n represents the number 1 or 2, R_5 represents a hydrogen atom, an alkyl radical containing from 1 to 8 carbon atoms, an alkenyl or alkynyl radical containing from 2 to 8 carbon atoms, an aryl radical containing from 6 to 14

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carbon atoms or an aralkyl radical containing from 7 to 15 carbon atoms, R_6 , [being] the same as or different from R_5 , can take one of the values indicated for R_5 and can also represent a hydroxyl radical, R_3 and R_4 , [being] the same or different, represent either a hydrogen atom, or a radical OH, Oalk₄ [or] O-CO-alk₅, alk₄ and alk₅ representing an alkyl radical containing from 1 to 8 carbon atoms or [an] aralkyl [radical] containing from 7 to 15 carbon atoms, or an alkenyl or alkynyl radical containing from 2 to 8 carbon atoms, or a radical O



or a radical

-COCH₂OCOalk₆, in which alk₆ represents an alkyl radical containing from 1 to 8 carbon atoms, possibly substituted, or an aralkyl radical containing from 7 to 15 carbon atoms or a radical CO-CO₂H or CO-CO₂alk₇ in which alk₇ represents an alkyl radical containing from 1 to 8 carbon atoms, or

a radical $\begin{array}{c} \text{H} \\ | \\ -\text{C}=\text{O} \end{array}$, or a radical $\begin{array}{c} \text{NHalk}_8 \\ | \\ -\text{C}=\text{O} \end{array}$, in which alk₈ represents a alkyl radical containing from 1 to 8 carbon atoms or an aralkyl radical containing from 7 to 15 carbon atoms, or a radical -C≡N, or R_3 and R_4 together form a

radical $\begin{array}{c} \text{CH}_3 \\ | \\ \text{HC}-\text{O} \text{ } Z_1 \\ | \\ -\text{C}- \text{ } Z_2 \\ | \end{array}$ in which Z_1 represents a hydrogen atom,

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an alkyl radical or an acyl radical containing from 1 to 8 carbon atoms and Z_2 [represents] an alkyl radical containing from 1 to 8 carbon atoms.

R_5 is preferably different from R_6 .

5 When R_5 or R_6 represents an alkyl radical, this is preferably the methyl or ethyl radical.

When R_5 or R_6 represents an alkenyl radical, this is preferably the vinyl, isopropenyl or allyl radical.

10 When R_5 or R_6 represents an alkynyl radical, this is preferably the ethynyl or propynyl radical.

When R_5 or R_6 represents an aryl or aralkyl radical, this is preferably the phenyl or benzyl radical.

15 When R_3 or R_4 represents a radical $Oalk_4$ or $OCOalk_5$, alk_4 and alk_5 represent preferably a methyl, ethyl, n-propyl, butyl, pentyl, hexyl or benzyl radical.

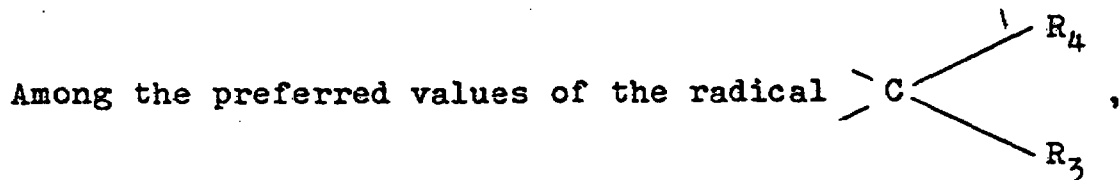
When R_3 or R_4 represent an alkenyl radical, this is preferably the vinyl, isopropenyl, allyl or 2-methylallyl radical.

20 When R_3 or R_4 represents an alkynyl radical, this is preferably the radical $-C\equiv CH$ or $-C\equiv C-alk_9$, alk_9 representing preferably a methyl, ethyl, propyl, isopropyl, isopropenyl, butyl, benzyl or trifluoromethyl radical.

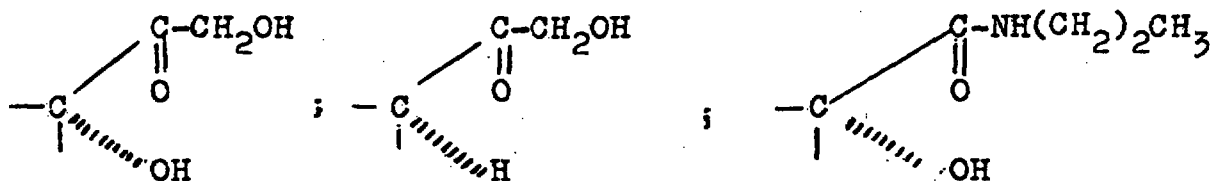
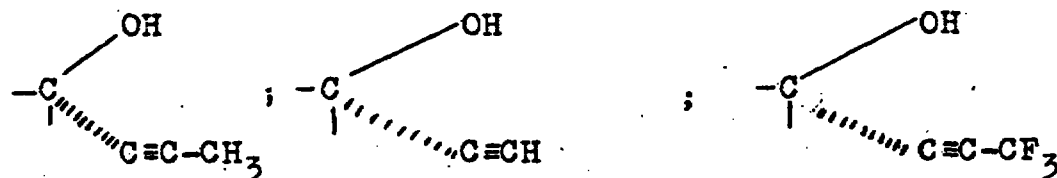
Alk_6 , alk_7 and alk_8 represent preferably one of the preferred values of alk_4 or alk_5 .

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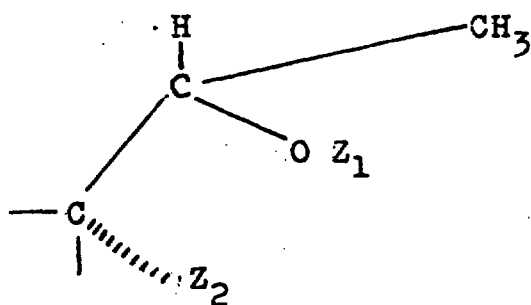
The preferred compounds are those for which the radicals R_3 and R_4 are different except in the case in which R_3 and R_4 each represent a hydrogen atom.



5 there may be mentioned the radicals:



or



2A

in which Z_1 represents a hydrogen atom, an alkyl radical containing from 1 to 8 carbon atoms or an acyl radical containing from 2 to 8 carbon atoms, for example an acetyloxy or benzoyl radical and Z_2 represents an alkyl radical containing from 1 to 8 carbon atoms, for example a methyl radical.

The subject of the invention is especially the compounds of formula (I') for which the ring D does not bear any ethylenic unsaturation, R_5 and R_6 represent a hydrogen atom and n is equal to 1, as well as the compounds for which $C=A$ represent an oxo group.

The subject of the invention is, more particularly, the compounds of formula (I') for which R_1 represents a hydrocarbon radical containing from 1 to 18 carbon atoms and containing at least one nitrogen atom.

Among these compounds, there may be mentioned especially the compounds for which R_1 represents a primary, secondary or tertiary alkyl radical containing from 1 to 8 carbon atoms, containing one or more heteroatoms selected from the group constituted by oxygen, nitrogen and sulphur, of which at least one [is a] nitrogen atom, or substituted by a heterocycle containing at least one nitrogen atom.

By alkyl radical there is understood preferably the methyl, ethyl, n-propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl radical.

*Translator's note: The French "on" = "one" would appear to be a misprint for "ou" = "or".

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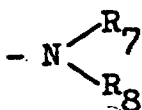
By heterocycle containing at least one nitrogen atom, there may be mentioned the 3,4- or 2-pyridyl radical, [or] the thiazolyl or piperidiny radical.

5 There may also be mentioned as preferred compounds of the invention the compounds for which R_1 represents a heterocyclic radical containing at least one nitrogen atom, possibly substituted by an alkyl radical containing from 1 to 8 carbon atoms.

10 By heterocyclic radical there is understood preferably one of the radicals mentioned above.

When R_1 represents a heterocyclic radical containing at least one nitrogen atom, substituted by an alkyl radical, this is most often a heterocycle substituted by a methyl, ethyl or n-propyl radical.

15 Among the preferred compounds of the invention there may be mentioned also the compounds for which R_1 represents an aryl or aralkyl radical bearing an amine function



20 , in which R_7 and R_8 represent an alkyl radical containing from 1 to 8 carbon atoms or a primary secondary or tertiary alkyl radical containing from 1 to 8 carbon atoms, containing one or more heteroatoms selected from the group constituted by oxygen, nitrogen and sulphur, of which at least one [is a] nitrogen atom, or substituted by a heterocycle containing at least one
25 nitrogen atom.

(2)

By alkyl radical there is understood preferably one of the radicals mentioned above.

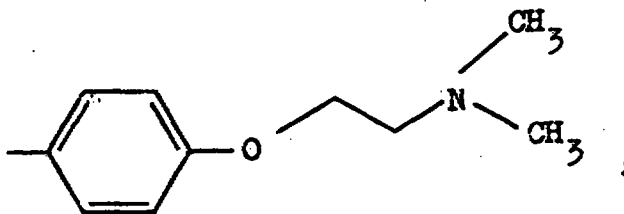
By aryl or aralkyl radical there is understood preferably the phenyl or benzyl radical.

5 By heterocyclic radical there is understood preferably one of the heterocyclic radicals mentioned above.

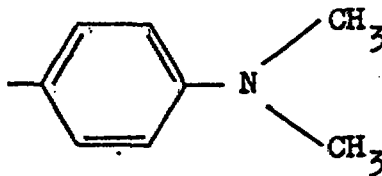
The subject of the invention is especially the compounds for which R_1 represents a 2-, 3- or 4-pyridyl

10 radical, a radical $-(CH_2)_n - N \begin{matrix} \diagup CH_3 \\ \diagdown CH_3 \end{matrix} (n \geq 3),$

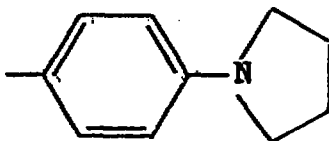
a radical



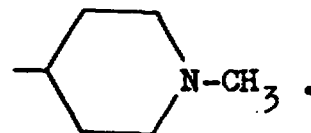
a radical



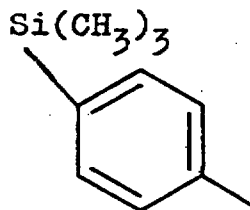
a radical



or a radical



The subject of the invention is also, in particular,
the compounds for which R_1 represents a radical:



Among the compounds of the invention there may also
be mentioned the compounds in which R_1 contains an oxidized
5 nitrogen atom, as well as those in which B and C together
form an epoxy bridge.

Among the preferred compounds of the invention there
may of course be mentioned the compounds of which the
preparation is given further on in the experimental part
10 and especially the compounds of Examples 1, 3, 4, 8, 10,
11, 12, 14, 16, 17, 20, 22, 28 and 29.

The compounds of formula (I') as well as their salts
of addition with pharmaceutically-acceptable acids are
products [which are] particularly interesting from the
15 pharmacological point of view; they possess in particular
remarkable antigluocorticoid activity as is shown by the
accompanying test results.

The study of the products on hormone receptors has
enabled progestomimetic or anti-progestomimetic, androgenic
20 or anti-androgenic activity to be made evident.

*
The compounds of formula (I') as well as their salts of addition with the pharmaceutically-acceptable acids can therefore be used as medicaments to control mainly side effects of glucocorticoids; they also permit
5 control of disorders due to hypersecretion of glucocorticoids and especially of ageing in general and more particularly of hypertension, atherosclerosis, osteoporosis, diabetes, obesity as well as immunity depression and insomnia.

10 The compounds of formula (I'), as well as their salts of addition with the pharmaceutically-acceptable acids, which possess anti-progestomimetic properties can be used to prepare original contraceptives; they can also be used against hormonal irregularities and, in addition, they can
15 be of advantage in the treatment of hormone-dependent cancers.

Certain compounds of formula (I') as well as their salts of addition with the pharmaceutically-acceptable acids can also display progestomimetic properties and can
20 thus be used in the treatment of amenorrhoea, dysmenorrhoea and luteal insufficiencies.

The compounds of formula (I'), as well as their salts of addition with the pharmaceutically-acceptable acids, which display anti-androgenic properties, can be used in the
25 treatment of hypertrophia and of cancer of the prostate gland, of hyperandrogenia, of anaemia, of hirsutism and of acne.

* Translator's note: The French "composés" is clearly a misprint for "composés" = "compounds"

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5 The subject of the invention is, therefore, as medicaments, the compounds of formula (I') [which are] pharmaceutically-acceptable, that is to say non-toxic at the doses used, as well as their salts of addition with the pharmaceutically-acceptable acids.

The usual dosage varies depending upon the complaint to be treated and the route of administration; it can vary, for example, from 10 mg to 1 g and preferably from 100 mg to 1 g per day in the adult by oral route.

10 The new compounds of formula (I') and their salts, as defined above, can be used to prepare pharmaceutical compositions containing, as active principle, one at least of the said compounds.

15 The compounds of formula (I') and their salts are used by digestive, parenteral or local route. They can be prescribed in the form of plain or sugar-coated compressed tablets, gelatin capsules, granules, suppositories, injectable preparations, ointments, creams [and] gels which are prepared according to the usual methods.

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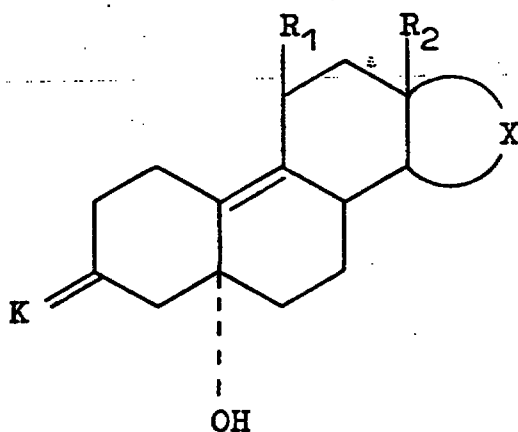
The active principle or principles can be incorporated in excipients usually employed in pharmaceutical compositions such as talc, gum arabic, lactose, starch,

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magnesium stearate, cocoa butter, aqueous or non[aqueous] vehicles, fatty substances of animal or vegetable origin, paraffin derivatives, glycols, various wetting, dispersing or emulsifying agents[and]preservatives.

5 The subject of the invention is, therefore, the pharmaceutical compositions containing as active principle at least one compound of formula (I').

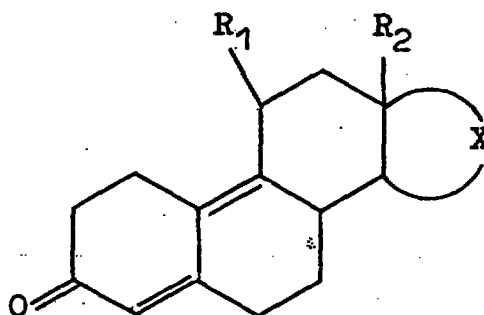
10 The subject of the invention is also a process for preparing the compounds of formula (I'), characterized in that a compound of general formula (II):



(II)

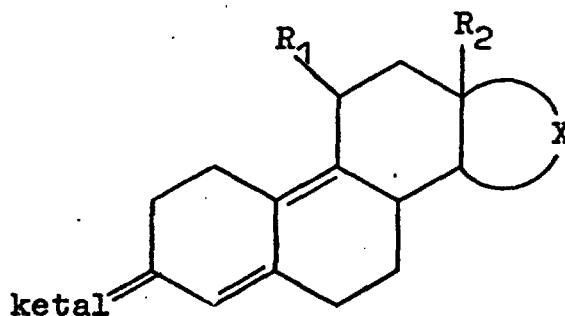
* Translator's note: The French "(U')" is clearly a misprint for "(I')".

in which K represents a ketone group blocked in [the]
 form of [a]ketal, thioketal, oxime or methyloxime, [and]
 R₁, R₂ and X keep the same meaning as before, is
 subjected to the action of a dehydrating agent capable of
 5 releasing the ketone function, to obtain a compound of
 formula (I'_A):



(I'_A)

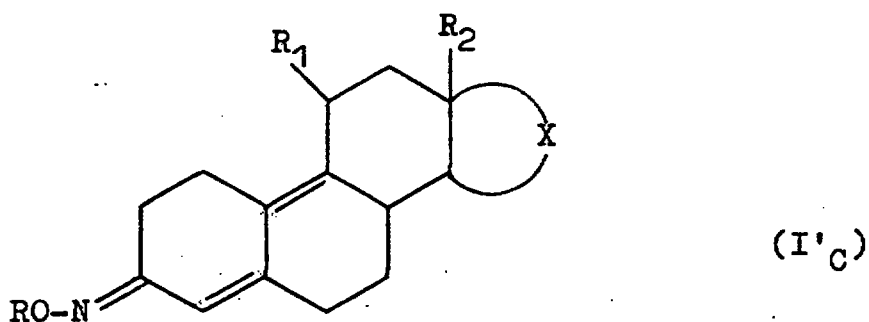
which is subjected, if necessary,
 either to the action of a ketalisation agent to obtain
 the compound of formula (I'_B) in which the ketone function
 10 at [position] 3 is blocked in [the] form of [a]ketal:



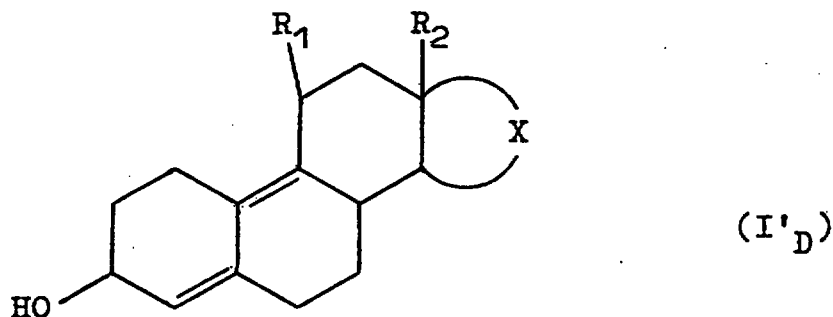
(I'_B)

(22)

or to the action of the free hydroxylamine NH_2OH or [the hydroxylamine] blocked in the form [of] $\text{NH}_2\text{-O-alk}_3$ in which alk_3 keeps its previous meaning, to obtain the compound of formula (I'_C):



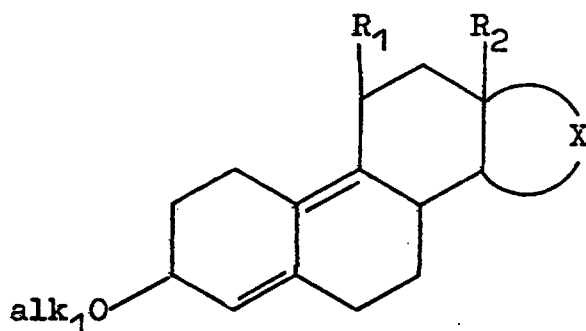
- 5 in which R represents a hydrogen atom or a group alk_3 ,
or to the action of a reducing agent capable of reducing selectively the ketone function at [position] 3, to obtain the compound of formula (I'_D):



*Translator's note: The French "da" is clearly a misprint for "sa" = "its".

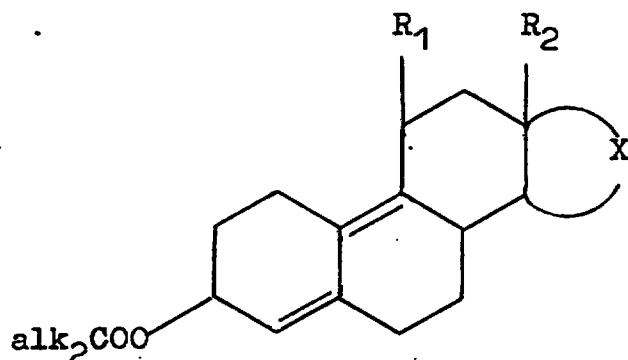
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which is subjected, if necessary, either to the action of an etherification agent capable of introducing the radical alk_1 to obtain a compound of formula (I'_E):



(I'_E)

or to the action of an esterification agent capable of introducing the group CO alk_2 in which alk_2 keeps its previous meaning, to obtain a compound of formula (I'_F):



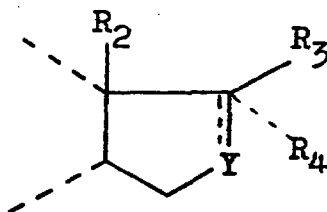
(I'_F)

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- 18 -

or, which compound of formula (I'_A) is converted, if necessary, according to the known methods, into a derivative for which C=A represents a group CH₂ and which compound of formula (I'_A), (I'_B), (I'_C), (I'_D) (I'_E), or (I'_F), if necessary, is subjected to the action of an acid to obtain a salt or to the action of an oxidizing agent to obtain either, if the radical R₁ contains a nitrogen atom, a derivative containing at [position] 11β a radical of which the nitrogen atom is oxidized and in which the radicals B and C form possibly an epoxide bridge, or, if the radical R₁ does not contain a nitrogen atom, a derivative in which the radicals B and C form an epoxide bridge and in which compound at the same time the radical R₁ contains an oxidized nitrogen atom and B and C together form an epoxide bridge which, if necessary, is reduced selectively at the level of the oxidized nitrogen atom contained in the radical R₁ and which, if necessary, is subjected to the action of an acid to obtain a salt.

The subject of the invention is, more particularly, a process as defined before for preparing the products of formula (I') for which X represents the residue of a ring of formula:



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in which R_2 , R_3 , R_4 , Y and the dotted line at [position] 16-17 are defined as before.

5 In a preferred method of carrying out the process, the dehydration agent capable of releasing the ketone function is a sulphonic resin (acid form), for example a commercial sulphonic resin with a polystyrene support or with a styrene / divinylbenzene polymer support; but a mineral acid such as hydrochloric acid or sulphuric acid in a lower alkanol or perchloric acid 10 in acetic acid, or a sulphonic acid such as paratoluene sulphonic acid can also be used.

The ketalisation agent is preferably an alcohol or a dialcohol in the presence of an organic acid such as, for example, oxalic acid or paratoluene sulphonic acid.

15 The agent for reducing the ketone function is preferably an alkali metal hydride. (See on this subject the article by E. R. Walkis in Chemical Society Reviews 1976, Vol. 5, no 1, page 23.)

20 The etherification agent is preferably an alkyl halide in the presence of a base.

The esterification agent is preferably a carboxylic acid derivative, for example a chloride or an anhydride, in the presence of a base such as pyridine.

25 It is self evident that when one of the radicals R_3 or R_4 of the products of formula (I') obtained previously represents a radical OH, the said radical OH of these products of formula (I') can be subjected to the



action of an etherification or esterification agent.

This etherification or esterification agent is preferably one of those which have been mentioned above.

When R_3 or R_4 represents an acyloxy radical at
5 [position] 17, this acyloxy group can possibly be saponified.
The saponification agent used is preferably a base such as
sodium hydroxide, potassium hydroxide, potassium amide or
potassium tert-butyrate, the saponification reaction being
carried out preferably in a lower alcohol such as methanol
10 or ethanol; it can also be lithium acetylide in ethylene
diamine.

The oxydising agent is preferably a peracid such as
metachloroperbenzoic acid, peracetic acid or perphthalic
acid or else hydrogen peroxide alone or in the presence
15 of hexachloro- or hexafluoroacetone. When it is desired
to obtain a compound in which only the nitrogen atom of
the radical R_1 is oxidized, one equivalent of oxidizing
agent is used. When it is desired to obtain a compound
in which, in addition, B and C form an epoxide bridge,
20 two equivalents of oxidizing agent are used.

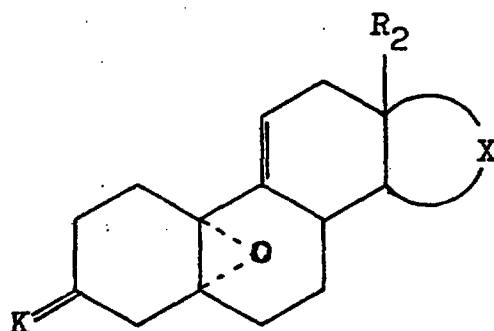
The agent for selectively reducing the N-oxide function
is preferably triphenylphosphine and work can be carried
out, for example, in acetic acid.

The subject of the invention is also a preparation
25 process as defined before, characterized in that the
starting product of formula (II) is prepared by subjecting

*Translator's note: The French "paracétique" would appear
to be a misprint for "peracétique" = "peracetic".

3A

a compound of formula (III)::



(III)

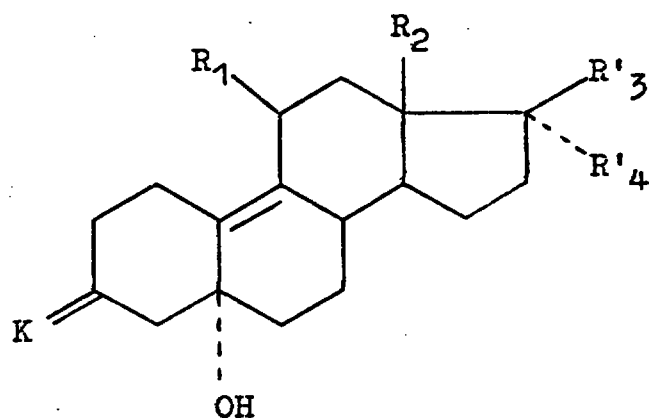
to the action of a compound selected from the group constituted by the compounds of formula $(R_1)_2 Cu Li$, of formula $R_1 Mg Hal$ and of formula $R_1 Li$, in which R_1 keeps the same meaning as before and Hal represents a halogen atom, if necessary, in the presence of copper halide, to obtain the corresponding compound of formula (II).

In a preferred method of carrying out the process of the invention:

- the reaction takes place at ambient temperature,
- the compound of formula (III) is subjected to the action of a compound of formula $R_1 Mg Hal$ in the presence of copper salts.

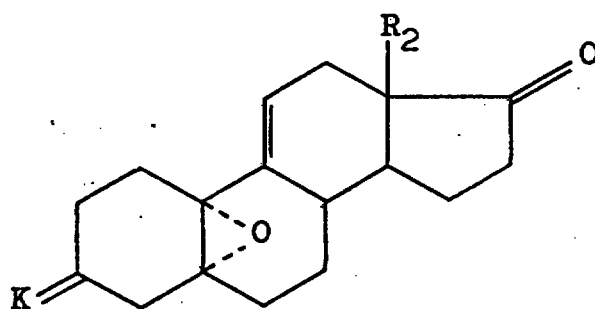
The subject of the invention is also a preparation process as defined before, characterized in that the starting product, responding to the formula (II'):

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(II')

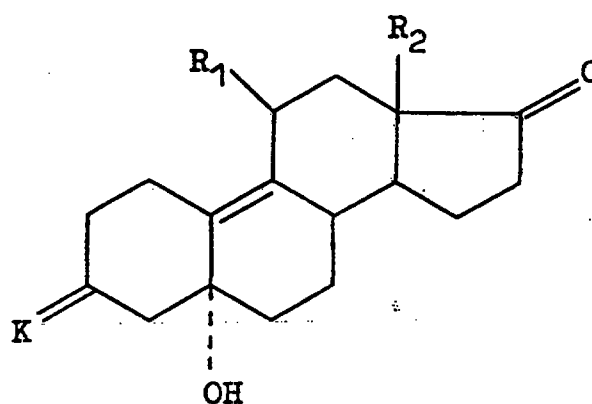
in which R₁, R₂ and K are defined as before, R'₃ represents a hydroxy radical or a radical OR_c in which R_c represents the residue alk₄ of an ether group or COalk₅ of an ester group, alk₄ and alk₅ being defined as before and R'₄ represents a hydrogen atom or an alkenyl or alkynyl radical containing from 2 to 8 carbon atoms, is prepared by subjecting a compound of formula (IV):



(IV)

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to the action of a compound selected from the group constituted by the compounds of formula $(R_1)_2 Cu Li$, of formula $R_1 MgHal$ and of formula $R_1 Li$, in which R_1 and Hal are defined as before, if necessary in the presence of copper halide, to obtain the compound of formula (V):



(V)

which is subjected either to the action of a reducing agent, to obtain the corresponding 17-hydroxy compound or to the action of an appropriate magnesium derivative, to obtain the corresponding 17 β -hydroxy 17 α -substituted compound or to the action of an organometallic derivative such as a lithium derivative or a potassium derivative, to obtain the corresponding 17 β -hydroxy 17 α -substituted compound, or a) to the action of a cyanidation agent, to obtain the corresponding 17 β -cyano 17 α -hydroxy compound, of which the hydroxy function is protected, then b) to the action of an organometallic derivative as described before, to obtain the corresponding 17 β -hydroxy

17~~x~~-substituted compound and in that, if necessary, one or other of the 17-hydroxy compounds obtained above is subjected to the action of an esterification or etherification agent and in that, if necessary, one
5 or other of the 17-substituted compounds obtained above, in which the substituent at [position] 17 contains a triple bond, is subjected to the action of a reducing agent, to obtain the corresponding ethylenic[derivative]

10 In a preferred method^{*} of carrying out the process of the invention, the reaction of the compound (IV) with the compound R_1 Mg Hal, $(R_1)_2$ Cu Li or R_1 Li is carried out under the conditions already described before.

15 The different reagents which are reacted with the compound of formula (V) are well known in the chemistry of the steroids. The experimental part hereinafter describes some of the reactions with the compound of formula (V).

20 The compounds of formula (II) as well as the compounds of formula (V) are new chemical products.

The compounds of formula (III) and especially, among these, the compounds of formula (IV), used to
25 prepare the compounds of formula (II) or (V) are generally-known products, which can be prepared by subjecting the corresponding $\Delta^5(10)$, 9(11) compounds

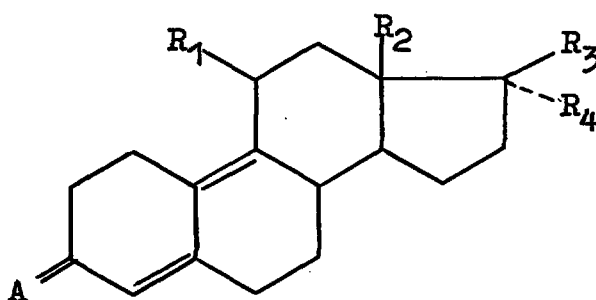
*Translator's note: The French "mod" is clearly a misprint for "mode" = "method".

(41)

to the action of an agent for selectively epoxidizing the double bond 5(10). Thus the $\Delta 5(10)$, 9(11) compounds can be subjected, for example, to the action of hydrogen peroxide used in the presence of hexachloroacetone or hexafluoroacetone, according to the process described and claimed in French Patent 2,423,486. 3,3[1,2-ethane diyl bis (oxy)] 17 α -[1-propynyl] estr-9-(11)-en 5 α ,10 α -epoxy 17 β -ol is a product [which is] not described, of which the preparation is given further on in the experimental part.

In addition to the products described in the examples which illustrate the invention without, however, limiting it, the following products constitute products **capable of being obtained within the scope of the present invention.

A) The products of formula:

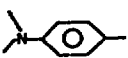
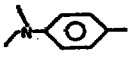
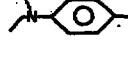
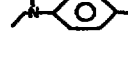
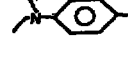
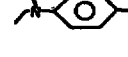
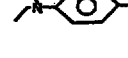
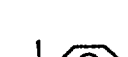


*in which the substituents A, R₁, R₂, R₃ and R₄ have the following meanings. (The sigla " signifies that the substituent is the same as the one before).

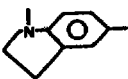
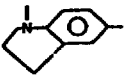
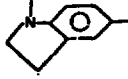
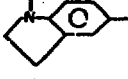
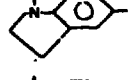
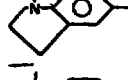
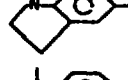
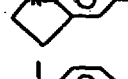
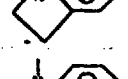
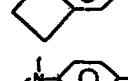
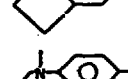
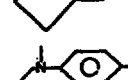
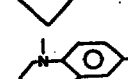
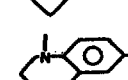
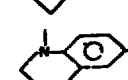
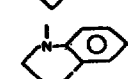
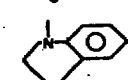
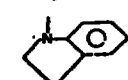
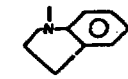
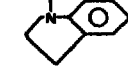
*Translator's note: I believe that the three lines 28 to 30 in the French text preceding the formula should, in fact, follow it as in my translation.

** Clearly the French "pouvent être" is a misprint for "pouvant être" = "capable of being".

(42)

A	R ₁	R ₂	R ₃	R ₄
0		CH ₃	OH	-C≡C-H
0		CH ₃	OH	-C≡C-CF ₃
0		CH ₃	OH	-C≡C-CH ₂ CH ₃
0		CH ₃	OH	-CH ₂ -C≡C-H
0		CH ₃	OH	-C≡C-SiMe ₃
0		CH ₃	-C≡C-H	OH
0		CH ₃	-C≡C-SiMe ₃	OH
0		CH ₂ CH ₃	OH	-C≡C-H
0		CH ₂ CH ₃	OH	-C≡C-CH ₃
0		CH ₂ CH ₃	OH	-CH ₂ -C≡C-H
0		CH ₃	$\begin{array}{c} \text{-C-CH}_2\text{OH} \\ \parallel \\ \text{O} \end{array}$	H
0		CH ₃	$\begin{array}{c} \text{-C-CH}_2\text{OH} \\ \parallel \\ \text{O} \end{array}$	OH
HO-N=(E)		CH ₃	OH	-C≡C-H
HO-N=(E)		CH ₃	OH	-C≡C-CH ₃
HO-N=(E)		CH ₃	-C≡C-H	OH
HO-N=(E)		CH ₃	OH	-CH ₂ -C≡C-H
HO-N=(Z)		CH ₃	OH	-C≡C-H
HO-N=(Z)		CH ₃	OH	-C≡C-CH ₃
HO-N=(Z)		CH ₃	OH	-CH ₂ -C≡C-H
HO-N=(Z)		CH ₃	-C≡C-H	OH
0		CH ₃	OH	-C≡C-H

(13)

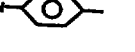
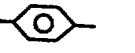
A	R ₁	R ₂	R ₃	R ₄
0		CH ₃	OH	-C≡C-CF ₃
0		CH ₃	OH	-CH ₂ -C≡C-H
0		CH ₃	OH	-C≡C-CH ₂ CH ₃
0		CH ₃	OH	-C≡C-Cl
0		CH ₃	OH	-C≡C-SiMe ₃
0		CH ₃	-C≡C-H	OH
0		CH ₃	-C≡C-SiMe ₃	OH
0		CH ₂ CH ₃	OH	-C≡C-H
0		CH ₂ CH ₃	OH	-C≡C-CH ₃
0		CH ₂ CH ₃	OH	-CH ₂ -C≡C-H
0		CH ₃	$\begin{array}{c} \text{-C-CH}_2\text{OH} \\ \\ \text{O} \\ \\ \text{-C-CH}_2\text{OH} \\ \\ \text{O} \end{array}$	-H
0		CH ₃	$\begin{array}{c} \text{-C-CH}_2\text{OH} \\ \\ \text{O} \\ \\ \text{-C-CH}_3 \\ \\ \text{O} \end{array}$	-OH
0		CH ₃	$\begin{array}{c} \text{-C-CH}_3 \\ \\ \text{O} \end{array}$	-H
HO-N=(E)		CH ₃	-OH	-C≡C-H
HO-N=(E)		CH ₃	-OH	-C≡C-CH ₃
HO-N=(E)		CH ₃	-OH	-C≡C-CH ₂ CH ₃
HO-N=(E)		CH ₃	-OH	-CH ₂ -C≡C-H
HO-N=(E)		CH ₃	-C≡C-H	-OH
HO-N=(E)		CH ₃	$\begin{array}{c} \text{O} \\ \\ \text{-C-CH}_2\text{OH} \\ \\ \text{O} \\ \\ \text{-C-CH}_2\text{OH} \end{array}$	H
HO-N=(Z)		CH ₃	$\begin{array}{c} \text{O} \\ \\ \text{-C-CH}_2\text{OH} \\ \\ \text{O} \\ \\ \text{-C-CH}_2\text{OH} \end{array}$	H
HO-N=(Z)		CH ₃	OH	-C≡C-H

0 057 115

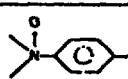
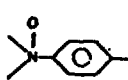
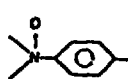
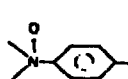
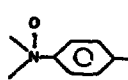
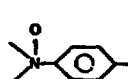
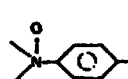
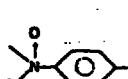
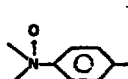
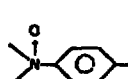
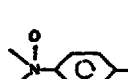
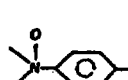
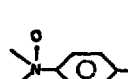
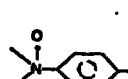
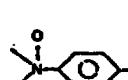
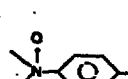


A	R ₁	R ₂	R ₃	R ₄
HO-N=(Z)		CH ₃	OH	-C≡C-CH ₃
HO-N=(Z)		CH ₃	OH	-C≡C-CH ₂ CH ₃
HO-N=(Z)		CH ₃	OH	-CH ₂ -C≡C-H
HO-N=(Z)		CH ₃	-C≡C-H	-OH
O		CH ₃	-C≡C-H	-OH
O		CH ₃	OH	-C≡C-H
O		CH ₃	OH	-C≡C-CF ₃
O		CH ₃	OH	-C≡C-Cl
O		CH ₃	OH	-C≡C-CH ₂ CH ₃
O		CH ₃	OH	-CH ₂ -C≡C-H
O		CH ₃	OH	-C≡C-SiMe ₃
O		CH ₃		-H
HO-N=(E)		CH ₃	OH	-C≡C-H
HO-N=(E)		CH ₃	OH	-C≡C-CH ₃
HO-N=(E)		CH ₃	OH	-CH ₂ -C≡C-H
HO-N=(E)		CH ₃	-C≡C-H	OH
HO-N=(Z)		CH ₃	-C≡C-H	OH
HO-N=(Z)		CH ₃	OH	-C≡C-H
HO-N=(Z)		CH ₃	OH	-C≡C-CH ₃
HO-N=(Z)		CH ₃	OH	-CH ₂ -C≡C-H
O		CH ₃	OH	-C≡C-CH ₂ CH ₃

(45)

A	R ₁	R ₂	R ₃	R ₄
O		CH ₃	OH	-C≡C-CF ₃
O		CH ₃	-C≡C-SiMe ₃	-OH
O		CH ₃	-C-CH ₂ OH O	-H
O		CH ₃	-C-CH ₂ OH O	-OH
O		CH ₃	-C-CH ₃ O	-H
O		-CH ₂ CH ₃	OH	-C≡C-H
O		-CH ₂ CH ₃	OH	-C≡C-CH ₃
O		-CH ₂ CH ₃	OH	-C≡C-Cl
O		-CH ₂ CH ₃	OH	-C≡C-CH ₂ -CH ₃
O		-CH ₂ CH ₃	OH	-C≡C-SiMe ₃
O		-CH ₂ CH ₃	OH	-CH ₂ -C≡C-H
O		-CH ₂ CH ₃	-C-CH ₂ OH O	-H
HO-N-(E)		CH ₃	-C≡C-H	-OH
HO-N-(E)		CH ₃	-C-CH ₂ OH O	-H
HO-N-(E)		CH ₃	OH	-CH ₂ -C≡C-H
HO-N-(Z)		CH ₃	OH	-CH ₂ -C≡C-H
HO-N-(Z)		CH ₃	-C≡C-H	-OH
HO-N-(Z)		CH ₃	-C-CH ₂ OH O	-H
O		CH ₃	-C-CH ₂ OH O	-H
O		CH ₃	-C≡C-H	-OH

(16)

A	R ₁	R ₂	R ₃	R ₄
O		CH ₃	OH	-CH ₂ -C≡C-H
O		CH ₃	OH	-C≡C-CH ₂ CH ₃
O		CH ₃	OH	-C≡C-CF ₃
O		CH ₃	OH	-C≡C-H
O		CH ₃	OH	-C≡C-SiMe ₃
HO-N=(E)		CH ₃	OH	-C≡C-H
HO-N=(E)		CH ₃	OH	-C≡C-CH ₃
HO-N=(E)		CH ₃	OH	-C≡C-CH ₂ CH ₃
HO-N=(E)		CH ₃	OH	-C≡C-Cl
HO-N=(E)		CH ₃	OH	-C≡C-SiMe ₃
HO-N=(E)		CH ₃	OH	-CH ₂ -C≡C-H
HO-N=(E)		CH ₃	-C≡C-H	-OH
HO-N=(Z)		CH ₃	-C≡C-H	-OH
HO-N=(Z)		CH ₃	OH	-C≡C-H
HO-N=(Z)		CH ₃	OH	-C≡C-CH ₃
HO-N=(Z)		CH ₃	OH	-C≡C-CH ₂ -CH ₃

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A	R ₁	R ₂	R ₃	R ₄
HO-N=(Z)		CH ₃	OH	-C≡C-Cl
HO-N=(Z)		CH ₃	OH	-C≡C-SiMe ₃
HO-N=(Z)		CH ₃	OH	-CH ₂ -C≡C-H
O		CH ₃	OH	-C≡C-H
O		CH ₃	OH	-C≡C-CF ₃
O		CH ₃	OH	-C≡C-CH ₃
O		CH ₃	OH	-C≡C-Cl
O		CH ₃	OH	-CH ₂ -C≡C-H
O		CH ₃	OH	-H
O		CH ₃	-C≡C-H	-OH
O		CH ₃		-H
O		CH ₃		-H
O		CH ₃	OH	-C≡C-H
O		CH ₃	OH	-C≡C-CH ₃
O		CH ₃	OH	-C≡C-Cl
O		CH ₃	OH	-CH ₂ -C≡C-H
O		CH ₃	-C≡C-H	-OH
O		CH ₃	-C≡C-H	-OH
O		CH ₃	OH	-C≡C-H
O		CH ₃	OH	-C≡C-CF ₃

A	R ₁	R ₂	R ₃	R ₄
0		CH ₃	OH	-C≡C-CH ₃
0		CH ₃	OH	-CH ₂ -C≡C-H
0		CH ₃	OH	-H
0		CH ₃	OH	-C≡C-H
0		CH ₃	OH	-CH ₂ -C≡C-H
0		CH ₃	-C≡C-H	-OH
0		CH ₃		-H
0		CH ₃		-H
0		CH ₃	-C≡C-H	-OH
0		CH ₃	-OH	-C≡C-H
0		CH ₃	-OH	-C≡C-CH ₃
0		CH ₃	-OH	-CH ₂ -C≡C-H
0		CH ₃	-OH	-C≡C-H
0		CH ₃	-OH	-C≡C-CH ₃
0		CH ₃	-OH	-CH ₂ -C≡C-H
0		CH ₃	-OH	-C≡C-H
0		CH ₃	-OH	-C≡C-CH ₃
0		CH ₃	-OH	-CH ₂ -C≡C-H
0		CH ₃	-OH	-C≡C-H
0		CH ₃	-OH	-C≡C-CH ₃
0		CH ₃	-OH	-CH ₂ -C≡C-H
0		CH ₃	-OH	-C≡C-H
0		CH ₃	-OH	-C≡C-CH ₃
0		CH ₃	-OH	-CH ₂ -C≡C-H
0		CH ₃	-OH	-C≡C-H
0		CH ₃	-OH	-C≡C-CH ₃
0		CH ₃	-OH	-CH ₂ -C≡C-H
0		CH ₃	-OH	-C≡C-H
0		CH ₃	-OH	-C≡C-CH ₃
0		CH ₃	-OH	-CH ₂ -C≡C-H
0		CH ₃	-OH	-C≡C-H
0		CH ₃	-OH	-C≡C-CH ₃
0		CH ₃	-OH	-CH ₂ -C≡C-H
0		CH ₃	-OH	-C≡C-H
0		CH ₃	-OH	-C≡C-CH ₃
0		CH ₃	-OH	-CH ₂ -C≡C-H
0		CH ₃	-OH	-C≡C-H
0		CH ₃	-OH	-C≡C-CH ₃
0		CH ₃	-OH	-CH ₂ -C≡C-H
0		CH ₃	-OH	-C≡C-H
0		CH ₃	-OH	-C≡C-CH ₃
0		CH ₃	-OH	-CH ₂ -C≡C-H
0		CH ₃	-OH	-C≡C-H
0		CH ₃	-OH	-C≡C-CH ₃
0		CH ₃	-OH	-CH ₂ -C≡C-H
0		CH ₃	-OH	-C≡C-H
0		CH ₃	-OH	-C≡C-CH ₃
0		CH ₃	-OH	-CH ₂ -C≡C-H
0		CH ₃	-OH	-C≡C-H
0		CH ₃	-OH	-C≡C-CH ₃
0		CH ₃	-OH	-CH ₂ -C≡C-H
0		CH ₃	-OH	-C≡C-H
0		CH ₃	-OH	-C≡C-CH ₃
0		CH ₃	-OH	-CH ₂ -C≡C-H
0		CH ₃	-OH	-C≡C-H
0		CH ₃	-OH	-C≡C-CH ₃
0		CH ₃	-OH	-CH ₂ -C≡C-H
0		CH ₃	-OH	-C≡C-H
0		CH ₃	-OH	-C≡C-CH ₃
0		CH ₃	-OH	-CH ₂ -C≡C-H
0		CH ₃	-OH	-C≡C-H
0		CH ₃	-OH	-C≡C-CH ₃
0		CH ₃	-OH	-CH ₂ -C≡C-H
0		CH ₃	-OH	-C≡C-H
0		CH ₃	-OH	-C≡C-CH ₃
0		CH ₃	-OH	-CH ₂ -C≡C-H
0		CH ₃	-OH	-C≡C-H
0		CH ₃	-OH	-C≡C-CH ₃
0		CH ₃	-OH	-CH ₂ -C≡C-H
0		CH ₃	-OH	-C≡C-H
0		CH ₃	-OH	-C≡C-CH ₃
0		CH ₃	-OH	-CH ₂ -C≡C-H
0		CH ₃	-OH	-C≡C-H
0		CH ₃	-OH	-C≡C-CH ₃
0		CH ₃	-OH	-CH ₂ -C≡C-H
0		CH ₃	-OH	-C≡C-H
0		CH ₃	-OH	-C≡C-CH ₃
0		CH ₃	-OH	-CH ₂ -C≡C-H
0		CH ₃	-OH	-C≡C-H
0		CH ₃	-OH	-C≡C-CH ₃
0		CH ₃	-OH	-CH ₂ -C≡C-H
0		CH ₃	-OH	-C≡C-H
0		CH ₃	-OH	-C≡C-CH ₃
0		CH ₃	-OH	-CH ₂ -C≡C-H
0		CH ₃	-OH	-C≡C-H
0		CH ₃	-OH	-C≡C-CH ₃
0		CH ₃	-OH	-CH ₂ -C≡C-H
0		CH ₃	-OH	-C≡C-H
0		CH ₃	-OH	-C≡C-CH ₃
0		CH ₃	-OH	-CH ₂ -C≡C-H
0		CH ₃	-OH	-C≡C-H
0		CH ₃	-OH	-C≡C-CH ₃
0		CH ₃	-OH	-CH ₂ -C≡C-H
0		CH ₃	-OH	-C≡C-H
0		CH ₃	-OH	-C≡C-CH ₃
0		CH ₃	-OH	-CH ₂ -C≡C-H
0		CH ₃	-OH	-C≡C-H
0		CH ₃	-OH	-C≡C-CH ₃
0		CH ₃	-OH	-CH ₂ -C≡C-H
0		CH ₃	-OH	-C≡C-H
0		CH ₃	-OH	-C≡C-CH ₃
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0		CH ₃	-OH	-C≡C-H
0		CH ₃	-OH	-C≡C-CH ₃
0		CH ₃	-OH	-CH ₂ -C≡C-H
0		CH ₃	-OH	-C≡C-H
0		CH ₃	-OH	-C≡C-CH ₃
0		CH ₃	-OH	-CH ₂ -C≡C-H
0		CH ₃	-OH	-C≡C-H
0		CH ₃	-OH	-C≡C-CH ₃
0		CH ₃	-OH	-CH ₂ -C≡C-H
0		CH ₃	-OH	-C≡C-H
0		CH ₃	-OH	-C≡C-CH ₃
0		CH ₃	-OH	-CH ₂ -C≡C-H
0		CH ₃	-OH	-C≡C-H
0		CH ₃	-OH	-C≡C-CH ₃
0		CH ₃	-OH	-CH ₂ -C≡C-H
0		CH ₃	-OH	-C≡C-H
0		CH ₃	-OH	-C≡C-CH ₃
0		CH ₃	-OH	-CH ₂ -C≡C-H
0		CH ₃	-OH	-C≡C-H
0		CH ₃	-OH	-C≡C-CH ₃
0		CH ₃	-OH	-CH ₂ -C≡C-H
0		CH ₃	-OH	-C≡C-H
0		CH ₃	-OH	-C≡C-CH ₃
0		CH ₃	-OH	-CH ₂ -C≡C-H
0		CH ₃	-OH	-C≡C-H
0		CH ₃	-OH	-C≡C-CH ₃
0		CH ₃	-OH	-CH ₂ -C≡C-H
0		CH ₃	-OH	-C≡C-H
0		CH ₃	-OH	-C≡C-CH ₃
0		CH ₃	-OH	-CH ₂ -C≡C-H
0		CH ₃	-OH	-C≡C-H
0		CH ₃	-OH	-C≡C-CH ₃
0		CH ₃	-OH	-CH ₂ -C≡C-H
0		CH ₃	-OH	-C≡C-H
0		CH ₃	-OH	-C≡C-CH ₃
0		CH ₃	-OH	-CH ₂ -C≡C-H
0		CH ₃	-OH	-C≡C-H
0		CH ₃	-OH	-C≡C-CH ₃
0		CH ₃	-OH	-CH ₂ -C≡C-H
0		CH ₃	-OH	-C≡C-H
0		CH ₃	-OH	-C≡C-CH ₃
0		CH ₃	-OH	-CH ₂ -C≡C-H
0		CH ₃	-OH	-C≡C-H
0		CH ₃	-OH	-C≡C-CH ₃
0				

A	R ₁	R ₂	R ₃	R ₄
O		CH ₃	OH	-C≡C-CF ₃
O		CH ₃	OH	-C≡C-H
O		CH ₃	OH	-CH ₂ -CH=CH ₂
O		CH ₃	OH	-CH ₂ -C≡C-H
O		CH ₃	OH	-CH ₂
O		CH ₃		-CH ₃
b		CH ₃	OH	-CH ₂ -CN
HO-N=(E)		CH ₃	OH	-C≡C-H
HO-N=(E)		CH ₃	OH	-C≡C-CH ₃
HO-N=(E)		CH ₃	OH	-C≡C-CH ₂ CH ₃
HO-N=(E)		CH ₃	OH	-C≡C-Cl
HO-N=(E)		CH ₃	OH	-CH ₂ -C≡C-
HO-N=(E)		CH ₃	-C≡C-H	-OH
HO-N=(E)		CH ₃		-H
HO-N=(Z)		CH ₃		-H
HO-N=(Z)		CH ₃	-C≡C-H	-OH
HO-N=(Z)		CH ₃	OH	-C≡C-H
HO-N=(Z)		CH ₃	OH	-C≡C-CH ₃
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50

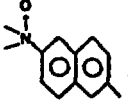
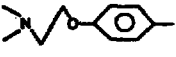
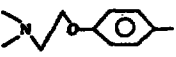
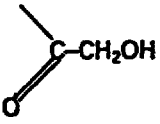
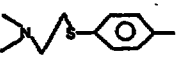
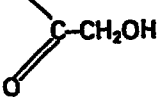
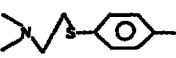
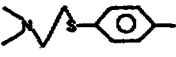
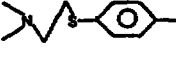
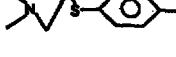
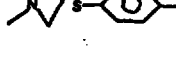
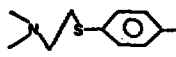
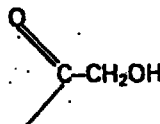
A	R ₁	R ₂	R ₃	R ₄
HO-N=(Z)		CH ₃	OH	-CH ₂ -C≡C-H
O		CH ₂ CH ₃	OH	-C≡C-H
O		CH ₂ CH ₃	OH	-C≡C-CH ₃
O		CH ₂ CH ₃	OH	-CH ₂ -C≡C-H
O		CH ₂ CH ₃	OH	-CH ₂ -CH=CH ₂
O		CH ₂ CH ₃		-CH ₃
O		CH ₂ CH ₃		-H
O		CH ₂ CH ₃	-C≡C-H	-OH
O		CH ₃	OH	-C≡C-H
O		CH ₃	OH	-C≡C-CH ₃
O		CH ₃	OH	-C≡C-Cl
O		CH ₃	OH	-C≡C-CH ₂ CH ₃
O		CH ₃	OH	-CH ₂ -C≡C-H
O		CH ₃	OH	-CH ₂ -CH=CH ₂
O		CH ₃	-C≡C-H	-OH
O		CH ₃		-H
O		CH ₃		-CH ₃
O		CH ₃		-H
O		CH ₃		-H

51

A	R ₁	R ₂	R ₃	R ₄
O		CH ₃		-CH ₃
O		CH ₃		-H
O		CH ₃	-C≡C-H	-OH
O		CH ₃	OH	-C≡C-H
O		CH ₃	OH	-C≡C-CH ₃
O		CH ₃	OH	-C≡C-Cl
O		CH ₃	OH	-C≡C-CH ₂ CH ₃
O		CH ₃	OH	-CH ₂ -C≡C-H
O		CH ₃	OH	-CH ₂ -CH=CH ₂
O		CH ₃	OH	-C≡C-H
O		CH ₃	OH	-C≡C-CH ₃
O		CH ₃	OH	-CH ₂ -C≡C-H
O		CH ₃	-C≡C-H	-OH
O		CH ₃	O	-H
O		CH ₃	C-CH ₂ OH	-H
O		CH ₃	OH	-C≡C-H
O		CH ₃	OH	-C≡C-CH ₃
O		CH ₃	OH	-CH ₂ -C≡C-H

52

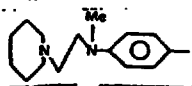
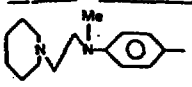
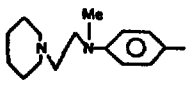
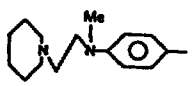
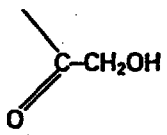
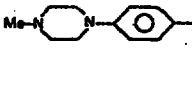
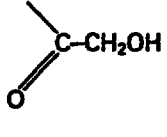
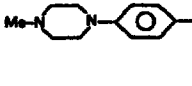
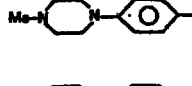
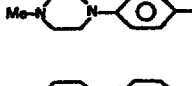
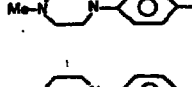
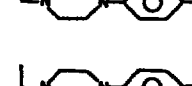
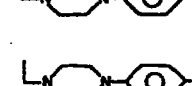
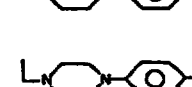
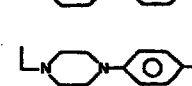
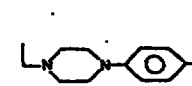
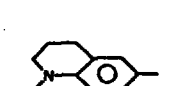
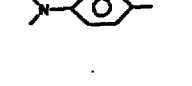
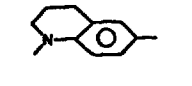
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O		CH ₃	-C≡C-H	-OH
O		CH ₃		-H
O		CH ₃	OH	-C≡C-CH ₃
O		CH ₃	OH	-CH ₂ -C≡C-H
O		CH ₃	OH	-C≡C-H
O		CH ₃	OH	-C≡C-CH ₃
O		CH ₃	OH	-C≡C-Cl
O		CH ₃	OH	-CH ₂ -C≡C-H
O		CH ₃	-C≡C-H	-OH
O		CH ₃		-H
O		CH ₃		-H
O		CH ₃	-C≡C-H	-OH
O		CH ₃	-OH	-C≡C-H
O		CH ₃	-OH	-C≡C-CH ₃
O		CH ₃	-OH	-C≡C-Cl

A	R ₁	R ₂	R ₃	R ₄
O		CH ₃	-OH	-CH ₂ -C≡C-H
O	Me ₃ Si CH ₂ -	CH ₃	-OH	-C≡C-H
O	Me ₃ Si CH ₂ -	CH ₃	-OH	-C≡C-CH ₃
O	Me ₃ Si CH ₂ -	CH ₃	-OH	-CH ₂ -C≡C-H
O	Me ₃ Si CH ₂ -	CH ₃	-C≡C-H	-OH
HO-N=(E)	Me ₃ Si CH ₂ -	CH ₃	-C≡C-H	-OH
HO-N=(E)	Me ₃ Si CH ₂ -	CH ₃	OH	-C≡C-H
HO-N=(E)	Me ₃ Si CH ₂ -	CH ₃	OH	-C≡C-CH ₃
HO-N=(E)	Me ₃ Si CH ₂ -	CH ₃	OH	-CH ₂ -C≡C-H
HO-N=(Z)	Me ₃ Si CH ₂ -	CH ₃	-C≡C-H	-OH
HO-N=(Z)	Me ₃ Si CH ₂ -	CH ₃	OH	-C≡C-H
HO-N=(Z)	Me ₃ Si CH ₂ -	CH ₃	OH	-C≡C-CH ₃
HO-N=(Z)	Me ₃ Si CH ₂ -	CH ₃	OH	-CH ₂ -C≡C-H
O		CH ₃	OH	-C≡C-CH ₃
O		CH ₃		-H
O		CH ₃		-H
O		CH ₃	OH	-C≡C-H
O		CH ₃	OH	-C≡C-CH ₃
O		CH ₃	OH	-CH ₂ -C≡C-H
O		CH ₃	OH	-CH ₂ -CH=CH ₂
O		CH ₃	OH	-CH ₂ CN
O		CH ₃	-C≡C-H	-OH
O		CH ₃		-H

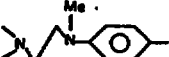
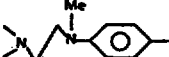
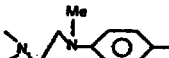
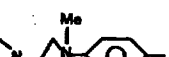
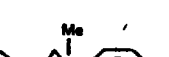
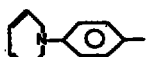
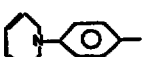
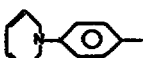
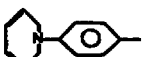
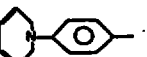
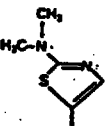
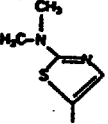
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A	R ₁	R ₂	R ₃	R ₄
0		CH ₃		-CH ₃
0		CH ₃	OH	-H
0		CH ₃	OH	-C≡C-H
0		CH ₃	OH	-C≡C-CF ₃
0		CH ₃	OH	-C≡C-CH ₂ CH ₃
0		CH ₃	OH	-C≡C-Cl
0		CH ₃	OH	-CH ₂ -C≡C-H
0		CH ₃	-C≡C-H	-OH
0		CH ₃		-H
0		CH ₃		-CH ₃
0		CH ₂ CH ₃	OH	-C≡C-H
0		CH ₂ CH ₃	OH	-C≡C-CH ₃
0		CH ₂ CH ₃	OH	-CH ₂ -C≡C-H
0		CH ₂ CH ₃	-C≡C-H	-OH
0		CH ₂ CH ₃		-H
0		CH ₃	OH	-C≡C-H

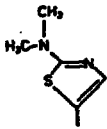
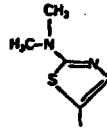
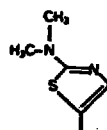
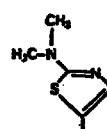
55

A	R ₁	R ₂	R ₃	R ₄
0		CH ₃	OH	-C≡C-CH ₃
0		CH ₃	OH	-CH ₂ -C≡C-H
0		CH ₃	-C≡C-H	-OH
0		CH ₃		-H
0		CH ₃		-H
0		CH ₃	-C≡C-H	-OH
0		CH ₃	OH	-C≡C-H
0		CH ₃	OH	-CH ₂ -C≡C-H
0		CH ₃	OH	-CH ₂ -CH=CH ₂
0		CH ₃	OH	-CH ₂ CN
0		CH ₃	OH	-C≡C-H
0		CH ₃	OH	-C≡C-CH ₃
0		CH ₃	OH	-CH ₂ -C≡C-H
0		CH ₃	OH	-CH ₂ -CH=CH ₂
0		CH ₃	OH	-CH ₂ -CN
0		CH ₃	-C≡C-H	-OH
0		CH ₃	-OH	-C≡C-H
0		CH ₃	-OH	-C≡C-CH ₃
0		CH ₃	-OH	-CH ₂ -C≡C-H

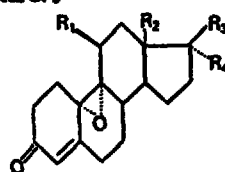
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A	R ₁	R ₂	R ₃	R ₄
0		CH ₃	-C≡C-H	-OH
0		CH ₃	C-CH ₂ OH	-H
0		CH ₃	C-CH ₂ OH	-H
0		CH ₃	-C≡C-H	OH
0		CH ₃	OH	-C≡C-H
0		CH ₃	OH	-C≡C-CH ₃
0		CH ₃	OH	-CH ₂ -C≡C-H
0		CH ₃	OH	-H
0		CH ₃	OH	-CH ₃
0		CH ₃	OH	-C≡C-H
0		CH ₃	OH	-C≡C-CH ₃
0		CH ₃	OH	-C≡C-CF ₃
0		CH ₃	OH	-CH ₂ -C≡C-H
0		CH ₃	-C≡C-H	-OH
0		CH ₃	OH	-C≡C-H
0		CH ₃	OH	-C≡C-CH ₃

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A	R ₁	R ₂	R ₃	R ₄
O		CH ₃	OH	-C≡C-CF ₃
O		CH ₃	OH	-CH ₂ -C≡C-H
O		CH ₃	-C≡C-H	-OH
O		CH ₃	-C≡C-CH ₃	-OH

B) The products of formula:



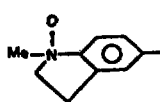
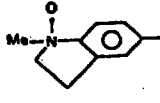
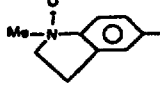
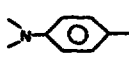
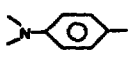
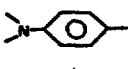
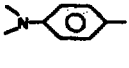
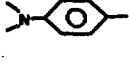
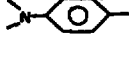
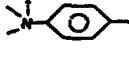
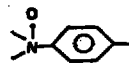
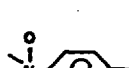
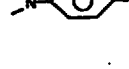
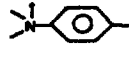
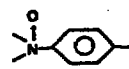
in which R₁, R₂, R₃ and R₄ have the following meanings:

R ₁	R ₂	R ₃	R ₄
	CH ₃	OH	-C≡C-H
	CH ₃	OH	-C≡C-CH ₃
	CH ₃	OH	-C≡C-CF ₃
	CH ₃	OH	-CH ₂ CH ₃
	CH ₃	OH	-CH ₂ -C≡C-H
	CH ₃	-C≡C-H	-OH
	CH ₃	OH	-C≡C-H

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R ₁	R ₂	R ₃	R ₄
	CH ₃	OH	-C≡C-CH ₃
	CH ₃	OH	-C≡C-CF ₃
	CH ₃	OH	-C≡C-CH ₂ CH ₃
	CH ₃	OH	-CH ₂ -C≡C-H
	CH ₃	OH	-H
	CH ₃	OH	-CH ₂ CH ₃
	CH ₃	-C≡C-H	-OH
	CH ₃		-H
	CH ₃		-CH ₃
	CH ₃		-CH ₃
	CH ₃	OH	-C≡C-H
	CH ₃	OH	-C≡C-CH ₃
	CH ₃	OH	-C≡C-CF ₃
	CH ₃	OH	-CH ₂ CH ₃

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R ₁	R ₂	R ₃	R ₄
	CH ₃	OH	-CH ₂ -C≡C-H
	CH ₃	-C≡C-H	-OH
	CH ₃	OH	H
	CH ₃	$\begin{array}{c} \text{-C-CH}_3 \\ \parallel \\ \text{O} \end{array}$	CH ₃
	CH ₃	OH	-C≡C-H
	CH ₃	OH	-C≡C-CH ₃
	CH ₃	OH	-C≡C-CF ₃
	CH ₃	OH	-CH ₂ CH ₃
	CH ₃	OH	-CH ₂ -C≡C-H
	CH ₃	OH	-C≡C-H
	CH ₃	OH	-C≡C-CH ₃
	CH ₃	OH	-C≡C-CF ₃
	CH ₃	OH	-CH ₂ -CH ₃
	CH ₃	OH	-CH ₂ -C≡C-H
	CH ₃	OH	H
	CH ₃	OH	CH ₃
	CH ₃	-C≡C-H	OH

It is also possible to prepare the epoxides corresponding to the other products appearing in list A above.

Example 1: 17 β -hydroxy 17 α -(prop-1-ynyl) 11 β -(4-pyridyl) estr-4,9-dien-3-one.

5 Stage A : 11 β -(4-pyridyl) 3,3-[1,2-ethanediyl bis(oxy)] 17 α -[prop-1-ynyl] estr-9-en 5 α 17 β -diol.

At 20° C, 100 cm³ of a solution of 4-chloropyridinyl magnesium bromide in tetrahydrofuran (0.5 - 0.6 M solution prepared from 15 g of 4-chloropyridine and 6g of magnesium) are added to a solution containing 6.16 g of dimethyl sulphide / copper bromide complex in 40 cm³ of tetrahydrofuran.

[The whole] is agitated for 20 minutes at ambient temperature under inert atmosphere and over 10 minutes a solution containing 3.7 g of 3,3-[1,2-ethanediyl bis (oxy)] 5 α 10 α -epoxy 17 α -(prop-1-ynyl) estr-9(11)-en 17 β -ol is added. [The whole] is agitated for one hour at ambient temperature and poured into a mixture of cold water and ammonium chloride. The reaction mixture is agitated for half an hour at ambient temperature and extracted with ether. [The extract] is washed with a saturated solution of sodium chloride, dried and concentrated to dryness under reduced pressure. 6 g are obtained of a product which is chromatographed on silica, elution being carried out with the methylene chloride / acetone mixture, 1:1 containing 1 per thousand of triethylamine. 3.15 g are thus isolated of [a] product which is dried under a vacuum of 0.1 mm of mercury at about 60° C. The product sought is thus obtained $\alpha_D = -52^\circ \pm 1.5$ (c=1% CHCl₃).

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Stage B : 17 β -hydroxy 17 α -(prop-1-ynyl) 11 α -(4-pyridyl) estra
4,9-dien-3-one.

For 3 hours at ambient temperature under inert atmosphere
a solution containing 2.9 g of the product prepared in Stage A,
14 cm³ of methanol and 7 cm³ of 2N hydrochloric acid is agitated.
A solution containing 200 cm³ of ether and 90cm³ of a
saturated solution of sodium acid carbonate is then added.
[The whole] is agitated for 15 minutes at ambient temperature,
decanted and extracted with ether. The extracts are washed
with a saturated solution of sodium chloride then dried and
concentrated to dryness under reduced pressure. 2.3 g are
obtained of a product which is chromatographed on silica,
elution being carried out with the methylene chloride / acetone
mixture : 6 : 4. 1.7 g of product are isolated and dried under
pressure of 0.1 mm of mercury for 24 hours of which 8 hours
[are] at 80° C. The product sought is thus obtained $[\alpha]_D =$
 $+ 30.5^\circ - 1^\circ$ (c = 1% CHCl₃)

In the same manner, 17 β -hydroxy, 17 α -(prop-1-ynyl)
11 β -(3-pyridyl) estra 4,9-dien 3-one ($[\alpha]_D = +14^\circ$ c = CHCl₃)
and 17 β -hydroxy 17 α -(prop-1-ynyl) 11 β -(2-pyridyl) estra-4,9-
dien 3-one ($[\alpha]_D = -2^\circ$ c = 1% CHCl₃) were prepared.

Example 2 : 17 β -hydroxy 11 β [3-(N,N-dimethyl amino)propyl]
17 α -(prop-1-ynyl) estra-4,9-dien 3-one.

Stage A : 11 β -[3-(N,N-dimethylamino) propyl] 3,3-[1,2-ethane
diyl bis (oxy)] 17 α -(prop-1-ynyl) estr-9-en 5 α 17 β -diol.

Over 5 minutes at 0° C, 12.33 g of dimethyl sulphide
/ copper bromide complex are added to 141 cm³ of 3-(N,N
dimethylamino) propyl magnesium chloride (0.85 M solution

*Translator's note: The French "a" = "has" is clearly a misprint
for "à" = "at".

(62)

prepared from 42 g of chloro 3-N,N dimethylamino propane and 10.5 g of magnesium). [The whole] is kept under agitation for 25 minutes at 0° C and, drop by drop, 3.70 g of 3,3[1,2-ethanediyl bis (oxy)] 5 α 10 α epoxy 17 α -(1-propynyl) estr-9(11)-en -17 β -ol in solution in 50 cm³ of tetrahydrofuran are introduced. The reaction mixture is kept under agitation for 3 hours at 0° C and poured into a mixture containing 40 g of ammonium chloride and 200 cm³ of iced water.

[The whole] is agitated for 15 minutes at ambient temperature then extracted with ether. [The extract] is washed with a saturated solution of sodium chloride, dried and concentrated to dryness under reduced pressure. 4.6 g of a product are obtained and chromatographed on silica, elution being carried out with a methylene chloride / methanol mixture (8 : 2). 2.55 g of product are isolated.

$[\alpha]_D = -86^\circ \pm 1.5^\circ$ (c = 1% in chloroform)

Stage B : 17 β -hydroxy 11 β [3-(N,N-dimethylamino) propyl] 17 α (prop-1-ynyl) estra 4,9-dien-3-one.

2.4 g of the product prepared in Stage A, 14 cm³ of methanol and 7 cm³ of 2N hydrochloric acid are agitated at ambient temperature for 4 hours under inert atmosphere. 200 cm³ of isopropyl ether and 90 cm³ of a saturated solution of sodium acid carbonate are then added. [The whole] is agitated for half an hour at ambient temperature, decanted and extracted with ether. [The extract] is washed with a saturated solution of sodium chloride and dried. [It] is concentrated to dryness under reduced pressure and 1.8 g of a product are obtained and

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chromatographed on silica, elution being carried out with the chloroform / methanol mixture, 8:2. 1.30 g of a product are thus obtained and dried at about 30° - 40° C under reduced pressure of 0.1 mm of mercury. 1.25 g of product sought are thus obtained, $[\alpha]_D = -114^\circ + 2.5^\circ \text{C} (c = 1\% \text{CHCl}_3)$.

Example 3 : 11 β -[4-(N,N-dimethyl amino ethyloxy) phenyl] 17 β -hydroxy 17 α -(prop-1-ynyl) estra 4,9-dien-3-one.

Stage A : 3,3-ethane-diyl bis(oxy) 11 β -[4-(N,N-dimethyl amino ethyloxy) phenyl] 17 α -(prop-1-ynyl) estra-9-en 5 α , 17 β -diol.

10 a) magnesium derivative of 4-(N,N-dimethylamino ethyloxy) bromobenzene.

Drop by drop over 45 minutes a solution containing 24 g of 4-(N,N-dimethylamino ethyloxy) bromobenzene in 90 cm³ of anhydrous tetrahydrofuran is introduced. The reaction is catalysed by the addition of 0.2 cm³ of 1,2-dibromoethane. 15 When the introduction is finished, [the whole] is agitated again for 1 hour at 25° C. A 0.7 M solution is thus obtained and used as it is.

b) condensation.

20 The solution prepared above is added to a solution containing 6.16 g of dimethyl sulphide / copper bromide complex in 20 cm³ of tetrahydrofuran. [The whole] is agitated for 20 minutes at ambient temperature and, drop by drop, over a few minutes, 3.7 g of 3,3[1,2-(ethanediyl bis (oxy))] 25 5 α , 10 α -epoxy 17 α -(prop-1-ynyl) estr - 9(11)-en 17 β -ol in 50 cm³ of tetrahydrofuran are added. [The whole] is then

*Translator's note: The French "(propy-1-ynyl)" is clearly a misprint for "(prop-1-ynyl)".

(34)

agitated for one hour under inert atmosphere, then the reaction mixture is poured into a solution containing 15 g of ammonium chloride in 200 cm³ of iced water. [The whole] is extracted with ether and [the extract] is washed with a saturated aqueous solution of sodium chloride. [It] is dried and concentrated under reduced pressure. 18.3 g of an oil are thus obtained and chromatographed on alumina [and] ^{*}eluted with chloroform and 4.5 g of the product sought are thus obtained.

10 $[\alpha]_D = -44^\circ \pm 1.5^\circ$ (c = 1% CHCl₃)

Stage B : 118[4-(N,N-dimethylamino ethyloxy) phenyl] 178-hydroxy 17a-(prop-1-ynyl) estra 4,9-dien-3-one.

9.5 cm³ of 2N hydrochloric acid are added to a solution containing 4.5 g of the product prepared in Stage A in 20 cm³ of methanol. The solution is kept under agitation for 2 hours at ambient temperature and 260 cm³ of ether and 110 cm³ of a saturated solution of sodium acid carbonate are added.

[The whole] is kept under agitation for 15 minutes at ambient temperature, decanted and extracted with ether. [The extract] is dried and concentrated to dryness under reduced pressure. 3.3 g of a product are obtained and chromatographed on silica, elution being carried out with the methylene chloride / methanol mixture (92.5 : 7.5). 1.8 g of amorphous expected product are thus obtained.

25 $[\alpha]_D = + 71^\circ$ (c=1% CHCl₃)

*Translator's note: The French "élui" would appear to be a misprint for "éluit".

(65)

Example 4 : 17 β -hydroxy 11 β -(4-dimethylamino phenyl) 17 α -(prop-1-ynyl) estro 4,9-dien-3-one.

Stage A : 11 β -(4-dimethylamino phenyl) 3,3[1,2-ethanediyl bis (oxy)] 17 α -(prop-1-ynyl) estr 9-en 5 α ,17 β -diol.

5 A solution containing 38 m.moles of p-dimethylamino phenyl magnesium bromide in tetrahydrofuran is added to a suspension containing 4.1 g of copper bromide / dimethyl sulphide complex in 20 cm³ of tetrahydrofuran. 2.45 g of 3,3-[1,2-ethanediyl bis (oxy)] 5 α , 10 α epoxy 17 α -(propyl-10 1-ynyl) estr 9(11) en 17 β -ol in solution in tetrahydrofuran are then added. The reaction mixture is kept under agitation for 10 minutes[and] hydrolysed with 50 cm³ of a saturated solution of ammonium chloride. [The whole]is decanted [and] extracted with ether and the organic phase is washed with 15 water and dried. The solvents are evaporated under reduced pressure and 11 g of crude product sought are obtained and chromatographed on silica, elution being carried out with the cyclohexane / ethyl acetate mixture, 6:40. 1.8 g 20 of the product sought (11 β) and 750 mg of the product 11 α are thus obtained. [The products]are recrystallised from isopropyl ether and ethyl acetate.

M.Pt. = 210° C $[\alpha]_D = -66.5^\circ$ (1% CHCl₃).

(66)

Stage B : 17 β -hydroxy 11 β -(dimethylamino phenyl) 17 α -(prop-1-ynyl) estro-4,9-dien-3-one.

2 cm³ of a solution of concentrated hydrochloric acid are added to a solution containing 1.53 g of the product prepared in Stage A in 60 cm³ of methanol. [The whole] is agitated for 30 minutes at ambient temperature and 150 cm³ of ether are added, then 50 cm³ of a N aqueous solution of sodium hydroxide. The reaction medium is agitated for 15 minutes and decanted [and] the organic phase is dried.

The solvents are evaporated under reduced pressure and 1.4 g of crude product are obtained and purified on silica, elution being carried out with the cyclohexane / ethyl acetate mixture (7:3). 0.932g of the product sought are obtained with M. Pt. = 150° C $[\alpha]_D = + 138.5^\circ$ (c = 0.5% CHCl₃)

Example 5 : 17 β -hydroxy 17 α -(prop-1-ynyl) 11 β [(4-trimethylsilyl) phenyl] estro-4,9-dien-3-one.

Stage A : 11 β [(4-trimethylsilyl)phenyl] 3,3-[1,2-ethanediyl bis (oxy)] 17 α -(prop-1-ynyl) estr-9-en-5 α , 17 β -diol.

At -30° C under inert atmosphere there are added to 45 cm³ of a 0.65 M solution of 4-trimethylsilyl phenyl magnesium bromide in tetrahydrofuran, 200 mg of copper chloride then, drop by drop, the temperature being kept at -20° C, a solution of 3.3 g of 3,3-[1,2-ethanediyl bis (oxy)] 5 α , 10 α -epoxy 17 α -(prop-1-ynyl) estr 9(11)-en 17 β -ol in 25 cm³ of tetrahydrofuran. After one hour [the whole] is hydrolysed by means of an aqueous solution of ammonium chloride, extracted with ether [and] dried and the solvents

(7)

are evaporated under reduced pressure. [The residue] is chromatographed on silica, elution being carried out with the methylene chloride / acetone mixture (94:6) containing 0.1 % of triethylamine. 2.087 g of the product sought are isolated and purified by recrystallisation from isopropyl ether then from ethyl acetate, M.Pt = 226° C

$[\alpha]_D = -60^\circ \pm 1.5^\circ$ (c = 0.9% CHCl₃)

Stage B: 17 β -hydroxy-17 α -(prop-1-ynyl)-11 β [(4-trimethylsilyl)phenyl]estra-4,9-dien-3-one.

1.7 g of Redex sulphonic resin are added to a solution containing 1.68 g of the product prepared in Stage A in 17 cm³ of boiling 90° alcohol. [The whole] is heated to reflux for 30 minutes, the resin is separated [and] rinsed with methylene chloride and the filtrate is evaporated under reduced pressure. The residue thus obtained is taken up with methylene chloride [and] dried and the solvent is driven off under reduced pressure. The residue obtained is chromatographed on silica, elution being carried out with the benzene / ethyl acetate mixture (85:15). 1.217 g of the product sought are thus obtained, melting at 212° C.

$[\alpha]_D = + 94^\circ$ (c = 0.9% CHCl₃)

In the same manner, 17 β -hydroxy-17 α -(prop-1-ynyl)-11 β -[(3-trimethylsilyl) phenyl] estra-4,9-dien-3-one was prepared.

$[\alpha]_D = + 52.5^\circ \pm 2^\circ$ (c = 1% CHCl₃).

Preparation: 3,3-[1,2-ethanediyl bis (oxy)] 17 α -(prop-1-ynyl) estr- 9(11)-en 5,10-epoxy 17 β -ol.

Stage A: 3,3-[1,2-ethanediyl bis (oxy)] 17 α -(prop-1-ynyl) estra 5(10)-9(11)-dien-17 β -ol.

Translator's note: *The French "(pro-1-ynyl)" is clearly a misprint for "(prop-1-ynyl)".
** The French "-éthanediyl.." should read "-éthanediyl..".

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Under agitation, 207 cm³ of a 1.15% solution of ethyl magnesium bromide in tetrahydrofuran are cooled to 0° C [and] propyne gas previously dried on calcium chloride is bubbled in for 1 hour 30 minutes at 0° C. [The whole] is allowed to return to ambient temperature and agitated again for 1 hour, the bubbling-in being maintained. Then at 20~25° C over half an hour a solution containing 30 g of 3,3-[1,2-ethanediyl bis (oxy)] estra 5(10) 9(11)-dien 17-one in 120 cm³ of anhydrous tetrahydrofuran and one drop of anhydrous triethylamine are added. [The whole] is agitated at ambient temperature for two hours and poured into a mixture of distilled water, ammonium chloride and ice. [The whole] is agitated and extracted three times with ethyl ether. The organic phase is washed with water, dried and concentrated under reduced pressure. The residue is dried under vacuum. 35.25 g of the product sought are obtained.

N.M.R. Spectrum CDCl₃ ppm

0.83	H of the methyl at 18
1.85	H of the methyl at c= C CH ₃
5.65	H of the carbon at 11
4	H of the ethylene ketal

Stage B : 3,3-[1,2-ethylenedioxy bis (oxy)] 17α-(prop-1-vnyl)
estr 9(11)-en 5α, 10α-epoxy 17β-ol

Under agitation and bubbling-in of nitrogen, 30 g of the product prepared in Stage A are introduced into 150 cm³ of methylene chloride. [The whole] is cooled to 0° C

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then, all at once, 1.8 cm³ of hexafluoroacetone sesquihydrate are added then, under agitation, 4.35 cm³ of 85% hydrogen peroxide. The reaction mixture is kept under agitation and bubbling-in of nitrogen at 0° C for 72 hours. The reaction solution is then poured into a mixture containing 250 g of ice and 500 cm³ of 0.2N sodium thiosulphate. [The whole] is agitated for a few moments then extracted with methylene chloride. The organic phase is washed with distilled water, dried on sodium sulphate in the presence of pyridine, then concentrated under reduced pressure. The residue is dried under reduced pressure. 31.6 g of a product are obtained and chromatographed on silica, eluant: benzene / ethyl acetate, 90:10 . The product sought is thus obtained.

NMR Spectrum CDCl₃ ppm

15	0.82	H of the methyl at 18
	1.83	H of the methyl of the radical c ≡ C -CH ₃
	6.1	H of the carbon at 11
	3.92	H of the ketal

20 Example 6 : 17β-ethynyl 17α-hydroxy 11β-(4-dimethylaminophenyl) estra 4,9-dien 3-one.

Stage A : 3,3-dimethoxy 5α-17α-hydroxy 11β-(4-dimethylamino-phenyl) 17β-ethynyl estr-9-ene.

Under inert gas 2.8 g of 3,3-dimethoxy 5α- 10α-epoxy

*Translator's note: The French "interte" is clearly a misprint for "inerte" = "inert".

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17 β -ethynyl 17 α -hydroxy estr-9(11)-ene, 56 cm³ of anhydrous tetrahydrofuran and 80 mg of anhydrous copper chloride are mixed. [The mixture] is agitated for 5 minutes at ambient temperature then placed in a bath of iced water and, drop by drop, 33 cm³ of a 0.95 M solution of (4-dimethylamino-phenyl) magnesium bromide in tetrahydrofuran are added.

[The whole] is then allowed to rise again to ambient temperature.

To a suspension of the copper bromide / dimethyl sulphide complex (6.15g) in 30cm³ of anhydrous tetrahydrofuran are added 63 cm³ of (4-dimethylaminophenyl) magnesium bromide so that the temperature remains below 28.5°. [The whole] is left for 30 minutes under agitation then, drop by drop, the solution obtained above is added. [The whole] is kept for 18 hours under agitation at ambient temperature, poured into a saturated solution of ammonium chloride, agitated for 10 minutes [and] extracted with chloroform, the organic phase is washed with water [and] dried and the solvent is evaporated. The residue is chromatographed on silica, elution being carried out with the petroleum ether / ethyl acetate mixture (1:1) containing 0.5 per thousand of triethylamine [and] 1.28 g of product are obtained. This product is purified again by chromatography on silica, elution being carried out with the same mixture, and 0.84 g of expected product is obtained.

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Stage B : 17 β -ethynyl 17 α -hydroxy 11 β -(4-dimethylaminophenyl) estra 4,9-dien-3-one.

0.76 g of the product obtained in Stage A is mixed with 15 cm³ of methanol and 1.6 cm³ of 2N hydrochloric acid. [The mixture] is agitated for an hour and a half then poured into a saturated aqueous solution of sodium bicarbonate [and] extracted with chloroform, the organic phase is dried and the solvent is evaporated. 0.76 g of crude product is obtained and chromatographed on silica, elution being carried out with the petroleum ether / ethyl acetate mixture (1:1) then with the ethyl ether / petroleum ether mixture (3:1). 0.435 g of expected product is obtained, which is crystallised from isopropyl ether.

M.Pt. = 142° C

15 $[\alpha]_D = + 235.5^\circ \pm 4.5^\circ$ (c = 0.45% chloroform)

The starting product of Stage A was prepared as follows:

Stage a : 3,3-dimethoxy 17 α -hydroxy 17 β -ethynyl estra 5(10) 9 (11)diene.

A mixture of 16.8 g of 3,3-dimethoxy 17 β -hydroxy 17 β -ethynyl estra 5 (10) 9 (11) diene, 175 cm³ of anhydrous tetrahydrofuran [and] 4.35 g of lithium bromide is agitated for 5 minutes at ambient temperature then cooled to - 60° C and 37 cm³ of a 1.35M solution of butyllithium in hexane are added. [The whole] is left for 30 minutes under agitation then 3.9 cm³

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of methane sulphonyl chloride are added and [the whole] is left for 1 hour at -60°C under agitation. [It] is then poured into 500 cm^3 of a saturated aqueous solution of ammonium chloride, agitated for 10 minutes [and] extracted with methylene chloride, the organic phase is dried, 2.5 cm^3 of pyridine are added then [the whole] is evaporated to dryness under reduced pressure at 0°C . 75 cm^3 of tetrahydrofuran are added to the residue obtained, then 12.5 cm^3 of water containing 0.75 g of silver nitrate. [The whole] is kept for 18 hours at -30°C , then for 4 hours at ambient temperature. [It] is poured into 500 cm^3 of a half-saturated aqueous solution of ammonium chloride, containing 5 g of sodium cyanide. [The whole] is agitated for 30 minutes at 20°C , extracted with chloroform, washed with a saturated aqueous solution of sodium chloride [and] dried and the solvent is evaporated. [The residue] is chromatographed on silica, elution being carried out with the petroleum ether / ethyl acetate mixture (9:1). 3 g of expected product are obtained.

M. Pt. $\sim 150^{\circ}\text{C}$

$[\alpha]_{\text{D}} = + 125^{\circ} \pm 2.5^{\circ}$ (c = 1% chloroform)

Stage b : 3,3-dimethoxy 5 α -10 α -epoxy 17 β -ethynyl 17 α -hydroxy estr-9(11)-ene.

2.6 g of the product obtained in Stage a, 12 cm^3 of methylene chloride and one drop of pyridine are mixed. [The mixture] is cooled to 0°C , and 0.12 cm^3 of hexachloroacetone and 0.65 cm^3 of hydrogen peroxide (200 volumes) are added.

After one hour under agitation, 13 cm³ of chloroform are added then the agitation is continued for 18 hours. [The whole] is poured into 100 cm³ of a saturated solution of sodium thiosulphate, agitated for 10 minutes [and] extracted with chloroform, the organic phase is washed with a saturated aqueous solution of sodium chloride [and] dried and the solvent is evaporated. 2.8 g of expected product are obtained, [which is] used as it is for the following stage. (The product contains a small proportion of β epoxide).

10 Example 7 : 17 β -hydroxy 17 α -phenyl 11 β (4-dimethylaminophenyl) estr-4,9-dien-3-one.

Stage A : 3,3-[1,2-ethane diyl bis (oxy)] 11 β -dimethylamino-phenyl) estr-9-ene 5 α -hydroxy 17-one.

a) preparation of the magnesium derivative.

15 Under inert gas 29 g of magnesium turnings and 50 cm³ of anhydrous tetrahydrofuran are mixed. Over two and a half hours, the temperature being kept at 35° C $\pm$ 5° C, there is introduced a mixture of 200 g of 4-dimethylamino bromo benzene in 950 cm³ of anhydrous tetrahydrofuran. A 0.8 M solution of expected magnesium derivative is thus obtained.

b) addition of the magnesium derivative.

25 Under inert gas 25 g of 3,3-[1,2-ethane diyl bis (oxy)] 5 α -10 α -epoxy estr-9(11)-en 17-one, 500 cm³ of anhydrous tetrahydrofuran and 0.757 g of copper chloride are mixed. [The mixture] is cooled to 0° [to] +5° C and , drop by drop, over 1 hour 15 minutes, there are added 284 cm³ of the solution of magnesium derivative prepared above. [The whole] is then agitated for 15 minutes, poured into a saturated solution of ammonium

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chloride [and] extracted with ethyl acetate [and] the organic phase is washed with a saturated solution of ammonium chloride then with a saturated solution of sodium chloride. The organic phase is dried and evaporated to dryness under reduced pressure. 46 g of crude product are obtained and chromatographed on silica, elution being carried out with the petroleum ether / ethyl acetate mixture (1:1) containing 1 per thousand of triethylamine [and] 17.76 g of expected product are obtained. M. Pt. = 178° C.

The impure fractions of product obtained are again chromatographed on silica, elution being carried out with the petroleum ether / acetone mixture (8:2) containing 1 per thousand of triethylamine. 6.35 g of expected product are again obtained. M.Pt. = 176° C. The product thus obtained is used as it is for the following stage.

Stage B : 3,3-[1,2-ethane diyl bis (oxy)] 5 α ,17 β -dihydroxy 11 β -(4-dimethylaminophenyl) 17 α -phenyl estr-9-ene.

Over 30 minutes at +25° C there is added to a solution of 33.3 cm³ of phenyllithium (1.5 M), a solution of 4.51 g of the product obtained in Stage A in 45.1 cm³ of anhydrous tetrahydrofuran. [The whole] is agitated for 4 hours at ambient temperature, poured into a saturated aqueous solution of ammonium chloride [and] extracted with ether, the organic phase is washed with a saturated aqueous solution of sodium chloride [and] dried and the solvent is evaporated. 5.6 g of crude product are obtained and chromatographed on silica, elution being carried out with the methylene chloride / acetone mixture

(9:1) containing 1 per thousand of triethylamine. 1.16 g of expected product are obtained and crystallised from the methylene chloride / isopropyl ether mixture.

M.Pt. = 240° C

5 $[\alpha]_D = +53^{\circ} \pm 2.5^{\circ}$ (c = 0.5% chloroform)

Stage C : 17 β -hydroxy 17 α -phenyl 11 β -(4-dimethylaminophenyl) estr-4,9-dien-3-one.

Under inert gas 1.5 g of the product obtained in Stage B are mixed into 45 cm³ of methanol. [The mixture] is cooled to 10 0 [to] +5^o C and 3 cm³ of 2N hydrochloric acid are introduced. [The whole] is agitated for 1 hour at 0^o [to] +5^o C, then 90 cm³ of ether and 90 cm³ of a 0.25 M aqueous solution of sodium bicarbonate are added. [The whole] is agitated for 5 minutes, decanted [and] extracted with ether, the organic phase is washed 15 with a saturated aqueous solution of sodium chloride [and] dried and the solvent is evaporated. 1.30 g of product are obtained and purified by chromatography on silica, elution being carried out with the petroleum ether / ethyl acetate mixture (1:1). 0.93 g of expected product is obtained and crystallised 20 from the methylene chloride / isopropyl ether mixture.

M.Pt. = 226° C

$[\alpha]_D = +151.5^{\circ}$ (c = 0.4% chloroform).

The starting product of Stage A was prepared as follows.

11.18 g of 3,3-[1,2-ethane diyl bis (oxy)] estr-5 (10) 25 9 (11) dien-17-one and 56 cm³ of methylene chloride are mixed, two drops of pyridine are added, [the whole] is cooled to 0^o C

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and 4.3 cm³ of hexafluoroacetone sesquihydrate are introduced,
then 1.6 cm³ of 85% hydrogen peroxide are added. [The whole]
is kept under agitation and under inert gas at 0° C for 23
hours. [It] is then poured into a mixture containing 200 cm³
5 of 0.5 M solution of sodium thiosulphate and 200 g of ice.
[The whole] is kept for 30 minutes under agitation then extracted
with methylene chloride containing a trace of pyridine. The
organic phase is washed with water [and] dried and the solvent
is evaporated. 11.4 g of expected product are obtained,
10 [which is] used as it is for the following stage.

Example 8 : 11β-(4-dimethylaminophenyl) 17β-hydroxy 23-methyl
(17α) 19,21-dinorchola-4,9,23-trien-20-yn-3-one.

Stage A : 3,3-[1,2-ethane diyl bis (oxy)] 11β-(4-dimethylamino-
phenyl) 23-methyl (17α) 19,21-dinorchola-9,23-dien-20-yn -5α-
15 17β-diol.

Under inert gas 4.5 g of potassium tert-butyrate are
mixed with 90 cm³ of anhydrous tetrahydrofuran. [The mixture]
is cooled to -10° C and 10.61 cm³ of 2-methyl 1-buten 3-yne
are added. [The whole] is agitated for 15 minutes at -10° C,
20 then, over 15 minutes, a solution of 4.5 g of product obtained
in Stage A of Example 7 in 45 cm³ of anhydrous tetrahydrofuran
is added. [The whole] is agitated for 30 minutes at - 10° C
then for 4 hours at 0 [to] +5° C. [It] is poured into 500 cm³
of a saturated aqueous solution of ammonium chloride [and]
25 extracted with ethyl acetate [and] the organic phase is washed

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with a saturated aqueous solution of sodium chloride, dried and evaporated to dryness. 5.56 g of crude expected product are obtained. M. Pt. = 205° C. The product is used as it is for the next part of the synthesis.

5 The crude product [is] chromatographed on silica, elution being carried out with the methylene chloride / ethyl acetate mixture (9:1) containing 1 per thousand of triethylamine, then recrystallised from ethyl acetate, melting at 215° C.
Stage B : 11 β -(4-dimethylaminophenyl)-17 β -hydroxy-2 β -methyl
10 (17 α)-19,21-dinorchola-4,9,2 β -trien-20-yn-3-one.

Under inert gas 5 g of the product obtained in Stage A are mixed with 300 cm³ of methanol and 10 cm³ of 2N hydrochloric acid. [The mixture] is agitated for 15 minutes at 20° C, 300 cm³ of methylene chloride are added then
15 300 cm³ of a 0.25 M aqueous solution of sodium bicarbonate. After 10 minutes under agitation, [the whole] is decanted [and] extracted with methylene chloride [and] the organic phase is washed with water, dried and evaporated to dryness.
4,5 g of crude expected product are obtained and chroma-
20 tographed on silica, elution being carried out with the petroleum ether / ethyl acetate mixture (1:1). After recrystallisation of the product from diisopropyl oxide, 2.01 g of expected product are obtained.
M.Pt = 185° C
25 $[\alpha]_D = +88.5^\circ \pm 1.5^\circ$ (c = 1% chloroform).

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Example 9 : 11 β (4-dimethylaminophenyl) 17 β -methoxy
23-methyl (17 α) 19,21-dinorchola -4,9,23-trien-20-
yn-3-one.

5 Under inert gas 4.5 g of potassium tert-butyrate
are mixed into 90 cm³ of anhydrous tetrahydrofuran.
The suspension is cooled to -10° C then, drop by
drop, 10.61 cm³ of 2-methyl 1-buten-3-yne are added.
[The whole] is agitated for 15 minutes at -10° C,
then, over 15 minutes, 4.5 g of the product obtained
10 in Stage A of Example 7 in 45 cm³ of anhydrous
tetrahydrofuran are added. [The whole] is agitated
for 30 minutes at -10° C, then for 4 hours at
0° [to] +5° C. 7.5 cm³ of methyl iodide are then
added then [the whole] is kept for 30 minutes under
15 agitation in an ice bath. The mixture is then poured
into 500 cm³ of 0.1 N hydrochloric acid. [The whole]
is agitated for 30 minutes at ambient temperature
[and] extracted with ethyl acetate [and] the organic
phase is washed with a saturated aqueous solution
20 of sodium bicarbonate, then with a saturated aqueous
solution of sodium chloride.

[It] is dried and the solvent is evaporated. The
residue is chromatographed on silica, elution being
carried out with the methylene chloride / ethyl acetate



mixture (95:5). 2.7 g of expected product are obtained and recrystallised from methanol. M.Pt. = 105° C.

Example 10 : 21-chloro 17 β -hydroxy 11 β (4-dimethyl-aminophenyl) (17a) 19-nor pregna-4,9-dien-20-yn 3-one.

5 Stage A : 21-chloro 3,3[1,2-ethane diyl bis (oxy)] 11 β (4-dimethylaminophenyl) (17a) 19-nor pregn-9-en 20-yn 5a, 17 β -diol.

Preparation of the lithium derivative

10 Under inert gas 77.5 cm³ of a 1M solution of butyllithium in hexane are mixed with 310 cm³ of anhydrous ethyl ether. [The mixture] is cooled to 0 [to] +5° C and, over 45 minutes, a solution of 7 cm³ of trichlorethylene in 28 cm³ of anhydrous ethyl ether is added. [The whole] is agitated for 1 hour,
15 the temperature being allowed to return to 20° C.

Condensation.

The mixture obtained above is cooled to 0 [to] +5° C and added to it, drop by drop, over thirty minutes, is a solution of 7 g of the product obtained in Stage A
20 of Example 7 in 70 cm³ of tetrahydrofuran. [The whole] is agitated for thirty minutes at 0 [to] +5° C then the temperature is allowed to return to 20° C, [the whole] is poured slowly into a saturated aqueous solution of ammonium chloride, decanted [and] extracted with methylene

chloride, the organic phase is washed with water [and] dried and the solvent is evaporated. 8.5 g of crude product are obtained (M.Pt. = 220° C) and introduced into 42.5 cm^3 of diisopropyl oxide. [The whole] is
5 agitated for thirty minutes [and] separated and 6.38 g of expected product are obtained. M.Pt. = 230° C.

The product can be purified by chromatography on silica, elution being carried out with the benzene / ethyl acetate mixture (7:3) containing 1 per thousand
10 of triethylamine. By dissolution of this product in methylene chloride and the addition of diisopropyl oxide, a crystalline product is obtained melting at 240° C.

$[\alpha]_D = -85.5^{\circ} \pm 1.5^{\circ}$ (c = 1% chloroform)

15 Stage B: 21-chloro-17 β -hydroxy-11 β -(dimethylaminophenyl)
(17 α)-19-nor-pregna-4,9-dien-20-yn-3-one.

Under inert gas 6.38 g of the product obtained in the previous stage and 191.4 cm^3 of 95% ethanol are mixed. 15 cm^3 of 2N hydrochloric acid are added,
20 [the whole] is agitated for one hour [and] 300 cm^3 of methylene chloride are added then 200 cm^3 of a 0.25 M aqueous solution of sodium bicarbonate. [The whole] is decanted [and] extracted with methylene chloride, the organic phase is washed with water [and] dried and
25 the solvent is evaporated. 6 g of crude product are

*Translator's note; The French " dm^3 " would appear to be a misprint for " cm^3 ".

obtained and chromatographed on silica, elution being carried out with the benzene / ethyl acetate mixture (7:3). 3.95 g of expected product are obtained and crystallised from ethyl acetate.

5 M.Pt = 240° C.

$[\alpha]_D = +111^{\circ} \pm 2^{\circ}$ (c = 1% chloroform).

Example 11 : 21-chloro 17 β -hydroxy 11 β -(4-dimethyl-aminophenyl) (17a) 19-nor pregna 4,9-dien-20-yn-3-one N-oxide.

10 Under inert gas 1.2 g of the product obtained in Example 10 are mixed into 24 cm³ of methylene chloride. [The mixture] is cooled to 0 [to] $+5^{\circ}$ C and a mixture of 0.54 g of metachloroperbenzoic acid (at 85%) in 10.8 cm³ of methylene chloride is added.

15 [The whole] is agitated for one hour at 0 [to] $+5^{\circ}$ C, poured into a 0.2 N solution of sodium thiosulphate [and] extracted with methylene chloride, the organic phase is washed with a saturated aqueous solution of sodium bicarbonate then with water [and] dried and
20 the solvent is evaporated. 1.3 g of crude product are obtained. This product is purified by chromatography on silica, elution being carried out with the methylene chloride / methanol mixture (7:3).

1.15 g of expected product are obtained.

25 $[\alpha]_D = +47.5^{\circ} \pm 2.5^{\circ}$ (c = 0.7% chloroform).

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Example 12 : 21-chloro 9 α -10 α -epoxy 17 β -hydroxy 11 β -(4-dimethylaminophenyl) (17 α) 19-nor pregn-4-en-20-yn-3-one N-oxide.

5 1.18 g of product obtained in Example 10 are dissolved in 23.6 cm³ of methylene chloride, [the solution] is cooled to 0° [to] +5° C and, over 15 minutes, a mixture of 1.17 g of metachloroperbenzoic acid (at 85%) in 23.4 cm³ of methylene chloride is added. [The whole] is agitated for 2 hours at 20° C,

10 0.117 g of metachloroperbenzoic are added again [the whole] is agitated again for one hour, the mixture is poured into a 0.2 N solution of sodium thiosulphate [and] extracted with methylene chloride. [and] the organic phase is washed with a saturated aqueous solution
15 of sodium bicarbonate, then with water, dried and evaporated to dryness. 1.14 g of crude product are obtained. M.Pt. = 220° C.

The product is purified by chromatography on silica, elution being carried out with the methylene
20 chloride / methanol mixture (8:2) and 1 g of expected product is obtained. M.Pt. = 270° C.

$[\alpha]_D = +39.5^\circ \pm 2.5^\circ$ (c = 0.5% chloroform).

Example 13 : 21-chloro 9 α -10 α -epoxy 17 β -hydroxy 11 β -(4-dimethylaminophenyl) (17 α) 19-nor pregn-4-en-20-yn-3-one.

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Under inert gas 0.63 g of the product obtained

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in Example 12 is mixed with 6.3 cm³ of acetic acid.
0.34 g of triphenylphosphine is added, [the whole] is
agitated for 45 minutes at ambient temperature,
poured into water [and] extracted with methylene chloride,
5 the organic phase is washed with water [and] dried
and the solvent is evaporated. 0.9 g of product is
obtained and chromatographed on silica, elution
being carried out with the petroleum ether / ethyl
acetate mixture (1:1). The product thus obtained
10 is recrystallised from a methylene chloride /
isopropyl ether mixture and 0.346 g of expected
product is obtained. M.Pt. = 265° C.

$[\alpha]_D = +45^\circ \pm 2^\circ$ (c = 0.8% chloroform)

Example 14 : 17 β -hydroxy 11 β -(4-dimethylaminophenyl)
15 21-phenyl (17 α) 19-nor-pregna-4,9-dien-20-yn-3-one.
Stage A : 21-phenyl 3,3-[1,2-ethane diyl bis (oxy)]
11 β -(4-dimethylaminophenyl) 5 α -17 β -dihydroxy (17 α)
19-nor-pregn-9-en-20-yne.

Under inert gas 4.17 g of potassium tert-butyrate
20 are mixed into 83 cm³ of anhydrous tetrahydrofuran.
[The mixture] is agitated for 5 minutes then cooled
to -10° C and, drop by drop, 4.5 cm³ of phenyl
acetylene are added. The suspension is agitated for
5 minutes then, drop by drop at -10° C, a solution of
25 4.17 g of product obtained in Stage A of Example 7

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in 41 cm³ of anhydrous tetrahydrofuran is added. At the end of the introduction the temperature is brought to 0° C, then after 1 hour the mixture is poured into a saturated solution of ammonium chloride. [The whole] is extracted with ether, the organic phase is washed with the aid of a saturated aqueous solution of sodium chloride, dried [and] concentrated to dryness and 4.7 g of product are obtained and chromatographed on silica, elution being carried out with the methylene chloride / acetone mixture (95:5). 3.71 g of expected product are obtained. M.Pt. = 168° C
[α]_D = -119.5° ± 2° (c = 1% chloroform).

Stage B : 17β-hydroxy 11β-(4-dimethylaminophenyl) 21-phenyl (17α) 19-nor-pregna-4,9-dien-20-yn-3-one.

3.49 g of product obtained as described in the previous stage are dissolved in 68 cm³ of methanol, then 6.3 cm³ of 2N hydrochloric acid are added. After thirty minutes under agitation, [the whole] is poured into a mixture of 180 cm³ of ethyl ether and 90 cm³ of a 0.25 M solution of sodium bicarbonate. [The whole] is agitated for five minutes, decanted [and] extracted with ether [and] the organic phases are washed with a 0.25 M solution of sodium bicarbonate then with a saturated solution of sodium chloride. [They] are dried, the solvent is evaporated and 4.35 g of product are obtained and purified by chromatography on silica,

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elution being carried out with the methylene chloride / acetone mixture (95:5). 2.13 g of expected product are obtained after crystallisation from isopropyl ether. $[\alpha]_D = +22.5^\circ \pm 1^\circ$ (c = 1% chloroform).

5 Example 15 : 17 β -hydroxy 11 β -(4-dimethylaminophenyl) 17 α -(propa-1,2-dienyl) estra-4,9-dien-3-one.

10 Stage A : 11 β -(4-dimethylaminophenyl) 3,3-[1,2-ethane diyl bis (oxy)] 17 α -(propa-1,2-dienyl) estr-9-en-5 α -17 β -diol and 11 β -(4-dimethylaminophenyl) 3,3-[1,2-ethane diyl bis (oxy)] 17 α -(prop-2-ynyl) estr-9-en-5 α -17 β -diol.

Preparation of the lithium derivative.

Into 50 cm³ of anhydrous tetrahydrofuran at 0 [to] +5° C is bubbled Allene until absorbtion of 2,1 g.
15 [The whole] is cooled to -70° C and, over 15 minutes, 23.9 cm³ of a 1.3 M solution of butyllithium in hexane are added. The mixture obtained is agitated for 15 minutes at -70° C.

Condensation

20 To the solution of lithium derivative obtained above is added, at -70° C over 25 minutes, a solution of 3.5g of the product obtained in Stage A of Example 7 in 35 cm³ of anhydrous tetrahydrofuran. [The whole] is agitated for one hour at -70° C [and] poured slowly into a chilled
25 saturated aqueous solution of ammonium chloride. [The whole] is extracted with ether, the organic phase is washed

with a saturated solution of sodium chloride [and]
dried and the solvent is evaporated. 3.4 g of product
are obtained and chromatographed on silica, elution
being carried out with the petroleum ether / ethyl acetate
mixture (1:1) containing one per thousand of triethylamine.
There are thus isolated:

a) 1.73 g of 17 α -(propa-1,2-dienyl) isomer

M.Pt. = 178° C $[\alpha]_D = -32^\circ \pm 2^\circ$ (c = 0.7% chloroform);

b) 1.5 g of 17 α (prop-2-ynyl) isomer

M.Pt. = 150° C $[\alpha]_D = -15^\circ \pm 2^\circ$ (c = 0.9% chloroform).

Stage B : 17 β -hydroxy 11 β -(4-dimethylaminophenyl) 17 α -
(propa-1,2-dienyl) estra-4,9-dien-3-one.

Under inert gas 1.73 g of 17 α -(propa-1,2-dienyl)
isomer obtained in Stage A, 51.8 cm³ of 95% ethanol
and 3.5 cm³ of 2N hydrochloric acid are mixed. [The
mixture] is agitated at 20° C for one hour, 50 cm³
of methylene chloride are added, then 50 cm³ of a
0.25 M solution of sodium bicarbonate; [the whole] is
decanted, extracted with methylene chloride, washed
with water [and] dried and the solvent is evaporated.

1.51 g of product are obtained and dissolved in 10 cm³
of methylene chloride with heating. To this are added
15 cm³ of isopropyl ether [and the whole] is concentrated
and left to stand. 1.23 g of expected product are thus
isolated and crystallised again from the methylene chloride
/ isopropyl ether mixture. Finally 1.11 g of expected
product are obtained. M.Pt. = 228° C.

$[\alpha]_D = +139.5^\circ \pm 3^\circ$ (c = 0.8% chloroform).

Example 16 : 17 β -hydroxy 11 β -(4-dimethylaminophenyl)
17 α -(prop-2-ynyl) estra-4,9-dien-3-one.

5 0.94 g of 17 α -(prop-2-ynyl) isomer obtained in Stage
A of Example 15, 28.2 cm³ of 95% ethanol and 2 cm³ of
2N hydrochloric acid are mixed. [The mixture] is agitated at
20° C for one hour, 50 cm³ of methylene chloride and
50 cm³ of a 0.25 M solution of sodium bicarbonate are
added [and the whole] is agitated for 5 minutes, decanted
10 and extracted with methylene chloride. The organic phase
is washed with water [and] dried and the solvent is evaporated.
The product obtained is chromatographed on silica,
elution being carried out with the petroleum ether /
ethyl acetate mixture (1:1). 0.42 g of amorphous expected
15 product is thus obtained.

$[\alpha]_D = +143^\circ \pm 3^\circ$ (c = 0.8% chloroform).

Example 17 : 17 α -ethynyl 17 β -hydroxy 11 β -(4-dimethyl-
aminophenyl) estra 4,9-dien-3-one.

20 Stage A : 17 β -cyano 11 β -(4-dimethylaminophenyl) 3,3-[1,2-
ethane diyl bis (oxy)] 17 α -trimethyl silyloxy) estr-9-en-
5 α -ol.

25 Under inert gas at ambient temperature, a solution
of 18 m/moles of (4-dimethylaminophenyl) magnesium bromide
in anhydrous tetrahydrofuran is added to a suspension of
2.05 g of copper bromide / dimethyl sulphide complex in
10 cm³ of anhydrous tetrahydrofuran, then [the whole]

*Translator's note: The French "17 β -cynao" is clearly a
misprint for "17 β -cyano".

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is agitated for 20 minutes and 20 cm³ of anhydrous triethylamine are added. 0.95 g of 17 β -cyano 17 α -(trimethyl silyloxy) 3,3-[1,2-ethane diyl bis (oxy)] 5 α -10 α -epoxy estr-9-(11) ene in solution in anhydrous tetrahydrofuran is then added, [the whole] is agitated for 15 hours at ambient temperature, poured into 50 cm³ of a saturated solution of ammonium chloride, decanted [and] extracted with ether, the organic phase is washed with water [and] dried and the solvent is evaporated.

10 The residue is purified by chromatography on silica, elution being carried out with the benzene / ethyl acetate mixture(8:2). 1.1 g of expected product are obtained and recrystallised from isopropyl ether.

M.Pt. = 247° C.

15 [α]_D = -12.5° (c = 1% chloroform)

Stage B : 17 α -ethynyl 3,3-ethane diyl bis (oxy)]
11 β -(4-dimethylaminophenyl) estr-9-en-5 α -17 β -diol.

To 0.8 g of product obtained in Stage A in 8 cm³ of ethylene diamine is added 1 g of lithium acetylide / ethylene diamine complex, then [the whole] is kept under agitation and under inert gas at ~50° C for an hour and a half. [It] is cooled to 20° C then poured into a solution of ammonium chloride. [The whole] is extracted with ether and with methylene chloride.

25 The organic phase is dried and the solvent

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is evaporated. The residue is chromatographed on silica, elution being carried out with the benzene / ethyl acetate mixture (7:3), the product obtained is recrystallised from isopropyl ether and 0.43 g of expected product is obtained.

M.Pt = 199° C.

$[\alpha]_D = -43^{\circ} \pm 1.5^{\circ}$ (c = 1% chloroform).

Stage C : 17 α -ethynyl 17 β -hydroxy 11 β -(4-dimethylamino-phenyl) estro-4,9-dien-3-one.

To a solution of 0.25 g of product obtained in Stage B, in 6 cm³ of methanol, is added 1 cm³ of 2N hydrochloric acid. [The whole] is agitated for 40 minutes at 20° C, poured into water containing 2.5 cm³ of 1N sodium hydroxide [and] extracted with ether, the organic phase is dried and the solvent is evaporated. The residue is chromatographed on silica, elution being carried out with the benzene / ethyl acetate mixture (7:3) and 0.25 g of expected product is obtained.

Analysis : C₂₈H₃₃NO₂ (415.54)

Calculated : C% 80.92 H% 8.00 N% 3.37

Found : C% 80.7 H% 8.1 N% 3.1

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Example 18 : 17 α -ethynyl 17 β -hydroxy 11 β -(4-dimethylaminophenyl) estra 4,9-dien-3-one.

Stage A : 11 β -(4-dimethylaminophenyl) 3,3-[1,2-ethane diyl bis (oxy)] 5 α -17 β -dihydroxy 17 α -ethynyl estr-9-ene.

5 Under inert gas 6 g of product obtained in Stage A of Example 7 are dissolved in 180 cm³ of tetrahydrofuran then 12.25 g of lithium acetylide / ethylene diamine complex are added. The temperature is taken to 55° C [and the whole] is agitated for 4 hours, cooled, then
10 poured into 600 cm³ of a chilled saturated solution of ammonium chloride. [The whole] is extracted with ether, the organic phase is washed with a saturated solution of sodium chloride [and] dried and the solvent is evaporated. The residue obtained is purified by chromatography on
15 silica, elution being carried out with the benzene / ethyl acetate mixture (7:3) containing 1 per thousand of triethylamine and 4.5 g of expected product are obtained and recrystallised from the methylene chloride / diisopropyl oxide mixture. M.Pt. = 202° C.

20 $[\alpha]_D = -47.5^\circ \pm 1.5^\circ$ (c= 1% chloroform)

Stage B : 17 α -ethynyl 17 β -hydroxy 11 β -(4-dimethylaminophenyl) estra 4,9-dien-3-one.

2 g of the product obtained in Stage A are mixed into 50 cm³ of 95% ethanol. To the suspension are
25 added 5 cm³ of 2N hydrochloric acid. [The whole] is kept under agitation for 1 hour at 20° C and 100 cm³ of ethyl

*Translator's note: The French "ocyde" would appear to be a misprint for "oxyde" = "oxide".

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ether are added then 100 cm³ of a 0.25 M solution of sodium bicarbonate. [The whole] is decanted [and] extracted with ether, the organic phase is washed with a saturated aqueous solution of sodium chloride, dried and
5 evaporated* to dryness. The residue is chromatographed on silica, elution being carried out with the petroleum ether / ethyl acetate mixture (6:4) and 1.52 g of expected product are isolated and recrystallised from diisopropyl oxide. M.Pt. = 172° C.

10 $[\alpha]_D^{20} = +182^\circ \pm 2.5^\circ$ (c = 1% chloroform)

Example 19 : 17 β -hydroxy 11 β -(3-dimethylaminophenyl) 17 α -(prop-1-ynyl) estr-4,9-dien-3-one.

Stage A : 11 β -(3-dimethylaminophenyl) 3,3-[1,2-ethane diyl bis (oxy)] 17 α -(prop-1-ynyl) estr-9-en-5 α -17 β -diol.

15 Preparation of the magnesium derivative.

Under inert gas 1.46 g of magnesium and 5 cm³ of anhydrous tetrahydrofuran are mixed. Over 45 minutes, the temperature being kept at about 50° C, 10 g of metabromodimethylaniline in 45 cm³ of anhydrous
20 tetrahydrofuran are introduced. (The reaction was initiated by the addition of dibromomethane). [The whole] is kept for one hour under agitation and a 0.95 M solution of the expected magnesium derivative is obtained.

Condensation

25 Under inert gas 3.7 g of 3,3-[1,2-ethylene dioxy bis (oxy)] 17 α -(prop-1-ynyl) estr-9 (11) en-5 α -10 α -epoxy 17 β -ol, 74 cm³ of anhydrous tetrahydrofuran and 99 mg

*Translator's note: The French "évaopre" is clearly a misprint for "évapore".

of copper chloride are mixed. [The mixture] is cooled to 0 [to] +5° C then, over thirty minutes, 42.2 cm³ of the solution of magnesium derivative obtained above are added. [The whole] is agitated for thirty minutes at 0 [to] +5° C, poured into a saturated aqueous solution of ammonium chloride [and] extracted with ether, the organic phase is washed with a saturated aqueous solution of sodium chloride [and] dried and the solvent is evaporated. The residue is chromatographed on silica, elution being carried out with the methylene chloride / acetone mixture (9:1) containing 1 per thousand of triethylamine. 3.5 g * of expected product are obtained. M.Pt = 262° C.

$[\alpha]_D = -64^\circ \pm 1.5^\circ$ (c = 1% chloroform).

0.66 g of the corresponding 5 β OH isomer is also isolated. M.Pt. = 210° C.

$[\alpha]_D = +32.5^\circ \pm 1^\circ$ (c = 0.8% chloroform).

Stage B : 17 β -hydroxy 11 β -(3-dimethylaminophenyl) 17 α -(prop-1-ynyl) estra 4,9-dien-3-one.

Under inert gas 3.3 g of the product obtained in Stage A are mixed with 100 cm³ of methanol [and] cooled to 0 [to] +5° C and 10 cm³ of 2N hydrochloric acid are added. [The whole] is agitated for 1 hour at 0 [to] +5° C [and] 200 cm³ of diethyl oxide are added, then 200 cm³ of a 0.25 M solution of sodium bicarbonate. [The whole] is agitated for 5 minutes, decanted [and] extracted with diethyl oxide, the organic phase is washed with a

*Translator's note: The French "den" would appear to be a misprint for "de" = "of".

saturated solution of sodium chloride [and] dried and the solvent is evaporated. 3 g of product are obtained and chromatographed on silica, elution being carried out with the benzene / ethyl acetate mixture (7:3).

5 1.43 g of amorphous expected product are isolated.

$[\alpha]_D = +43^\circ \pm 2.5^\circ$ (c = 1% chloroform).

Example 20 : 17 β -hydroxy 11 β -(4-dimethylaminophenyl)
17 α -(prop-1-ynyl) estra 4,9-dien-3-one N-oxide.

10 1.5 g of product obtained in Example 4 are mixed with 30 cm³ of methylene chloride. [The mixture] is cooled to 0 [to] +5° C and, over 10 minutes, a solution of 0.71 g of metachloroperbenzoic acid (at 85%) in 14.2 cm³ of methylene chloride is added. [The whole] is agitated at 0 [to] +5° C for 1 hour, poured into 100 cm³
15 of a 0.2 N solution of sodium thiosulphate, decanted [and] extracted with methylene chloride, the organic phase is washed with a 0.5 M solution of sodium bicarbonate [and] dried and the solvent is evaporated. The residue is dissolved in 20 cm³ of methylene chloride and 20 cm³
20 of diisopropyl oxide are added. Crystallisation is initiated, [the whole] is left to stand [and] the crystals formed are separated and dried. 1.4 g of expected product are obtained. M.Pt. = 210° C.

$[\alpha]_D = +73.5^\circ \pm 2^\circ$ (c = 1% chloroform).

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Example 21 : 11 β -(4-dimethylaminophenyl) 17 β -hydroxy
estra 4,9-dien-3-one.

1 g of the product obtained in Stage A of Example 7
is mixed into 20 cm³ of tetrahydrofuran containing
5 10% of water. After dissolution, 106 mg of sodium
borohydride are added, [the whole] is agitated for 1
hour, poured into 200 cm³ of water [and] extracted with
methylene chloride, the organic phase is washed with a
saturated solution of sodium chloride [and] dried and
10 the solvent is evaporated. 1.3 g of 5 α -17 β -dihydroxy
product are obtained.

0.63 g of product obtained above is introduced
into a mixture of 12 cm³ of methanol and 2.4 cm³ of
2N hydrochloric acid. [The whole] is agitated for one
15 hour thirty minutes at ambient temperature, poured
into a solution of sodium bicarbonate [and] extracted
with ether, the organic phase is washed with a
saturated solution of sodium chloride [and] dried and
the solvent is evaporated. The residue is chroma-
20 tographed on silica, elution being carried out with
the petroleum ether / ethyl acetate mixture (6:4).
The residue is triturated in petroleum ether [and]
separated and 0.38 g of expected product is obtained.
M.Pt. = 130° C.
25 $[\alpha]_D = +277^\circ \pm 5^\circ$ (c = 0.5% chloroform).

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Example 22 : 17 β -hydroxy 11 β -(4-dimethylaminophenyl)
17 α -(prop-2-enyl) estra 4,9-dien-3-one.

Stage A : 3,3[1,2-ethane diyl bis (oxy)] 11 β -(4-dimethyl-
aminophenyl) 17 α -(prop-2-enyl) estr-9-ene 5 α -17 β -diol.

5 Into 55.5 cm³ of a 0.7 M solution of allyl magnesium
bromide in ether is introduced, under inert gas at 20° C
over 15 minutes, a solution of 3.5 g of the product
obtained in Stage A of Example 7 in 35 cm³ of tetrahydro-
furan. [The whole] is agitated at 20° C for 1 hour,
10 poured into a saturated aqueous solution of ammonium
chloride [and] extracted with ether, the organic phase is
washed with a saturated aqueous solution of sodium chloride
[and] dried and the solvent is evaporated. The residue
obtained is dissolved in 10 cm³ of methylene chloride.
15 To this are added 15 cm³ of diisopropyl oxide [and the whole]
is concentrated then left to stand. The crystals formed
are separated, rinsed with diisopropyl oxide [and] dried
and 2.76 g of expected product are obtained.
M.Pt. = 198° C.

20 Analysis : C₃₁ H₄₃ NO₄ (493.69)
Calculated : C% 74.42 H% 8.78 N% 2.83
Found : C% 74.0 H% 8.7 N% 2.9

Stage B : 17 β -hydroxy 11 β -(4-dimethylaminophenyl)
17 α -prop-2-enyl) estra 4,9-dien-3-one.

25 2.2 g of the product obtained in Stage A are put
into suspension in 66 cm³ of methanol, then 4.5 cm³ of 2N

*Translator's note: The French "diisoporpyle" is clearly
a misprint for "diisopropyle"

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hydrochloric acid are added. [The whole] is agitated for thirty minutes at 20° C [and] 132 cm³ of diethyl oxide are added, then 132 cm³ of a 0.25 M aqueous solution of sodium bicarbonate. [The whole] is decanted, extracted with diethyl oxide, washed with a saturated aqueous solution of sodium chloride [and] dried and the solvent is evaporated. The residue is chromatographed on silica, elution being carried out with the benzene / ethyl acetate mixture (7:3) the product obtained is taken up in a mixture of 15 cm³ of diisopropyl oxide and 7.5 cm³ of methylene chloride [and the whole] is concentrated then left to stand. [It] is separated and the crystals obtained are rinsed with diisopropyl oxide and 1.365 g of expected product are obtained. M.Pt. = 182° C

$[\alpha]_D = +206.5^\circ \pm 3^\circ$ (c = 1% chloroform)

Example 23 : 17 β -hydroxy 11 β -[4-(N,N-dimethylaminomethyl) phenyl] 17 α -(prop-1-ynyl) estro 4,9-dien-3-one.

Stage A : 3,3[1,2-ethane diyl bis (oxy)] 11 β -[4-(N,N-dimethylaminomethyl) phenyl] 17 α -(prop-1-ynyl) estr-9-en-5 α -17 β -diol.

Preparation of the magnesium derivative.

Under inert gas 5.5 g of magnesium and 10 cm³ of anhydrous tetrahydrofuran are mixed. Over 1 hour 30 minutes, the temperature being kept at 45° - 50° C,

*Translator's note: The French "aus" is clearly a misprint for "au".

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42.8 g of 4-(N,N-dimethylaminomethyl) bromo benzene in 190 cm³ of anhydrous tetrahydrofuran are introduced. The reaction was initiated by the addition of dibromoethane. After the end of the introduction, [the whole] is kept under agitation for 1 hour. The expected 0.85 M solution of magnesium derivative is thus obtained.

5

Addition on to the epoxide.

Under inert gas 10 g of 3,3-[1,2-ethane diyl bis (oxy)] 17 α -(prop-1-ynyl) estr-9, (11)-en-5 α -10 α -epoxy 17 β -ol, 200 cm³ of anhydrous tetrahydrofuran and 0.27 g of copper chloride are mixed. [The mixture] is cooled to 0 [to] +5° C and, over one hour, 127 cm³ of the solution of magnesium derivative prepared above are introduced. [The whole] is then agitated for 15 minutes, poured into a saturated aqueous solution of ammonium chloride [and] extracted with ether, the organic phase is washed with a saturated aqueous solution of sodium chloride [and] dried and the solvent is evaporated. The residue is chromatographed on silica, elution being carried out with the methylene chloride / methanol mixture (9:1) containing 1 per thousand of triethylamine. 10.1 g of product are obtained and crystallised by dissolution in methylene chloride and the addition of a few cm³ of methanol then of diisopropyl oxide. After concentration and keeping standing for six hours, the product obtained is separated and 7.37 g of expected product are obtained.

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M.Pt. = 186° C.

$[\alpha]_D = -63^\circ \pm 2.5^\circ$ (c = 0.5% chloroform).

Stage B : 17 β -hydroxy 11 β -[4-(N,N-dimethylaminomethyl) phenyl] 17 α -(prop-1-ynyl) estro 4,9-dien-3-one.

5 Under inert gas 7.37 g of the product obtained in Stage A are mixed into 147.4 cm³ of methanol and 15 cm³ of 2N hydrochloric acid. [The mixture] is agitated at 20° C for one hour, 300 cm³ of diethyl oxide and 300 cm³ of a 0.25 M aqueous solution of sodium bicarbonate are
10 added, [the whole] is decanted [and] extracted with diethyl oxide, the organic phase is washed with a saturated aqueous solution of sodium chloride [and] dried and the solvent is evaporated. The product obtained is recrystall-
15 ised by being dissolved in a mixture of diisopropyl oxide and methylene chloride, then by concentrating the solution and leaving it to stand. It is separated and the crystals formed are dried. 3.74 g of expected product are thus obtained. M.Pt. = 190° C.

$[\alpha]_D = +84.5^\circ \pm 2^\circ$ (c = 0.8% chloroform).

20 Example 24 : 17 β -hydroxy 11 β -(4-pyrrolidinyl phenyl) 17 α -(prop-1-ynyl) estro 4,9-dien-3-one.

Stage A : 3,3-[1,2-ethane diyl bis (oxy)] 11 β -(4-pyrrolidinyl phenyl) 17 α -(prop-1-ynyl) estr-9-en-5 α -17 β -diol.

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Preparation of the magnesium derivative.

Under inert gas 4 g of magnesium and 10 cm³ of anhydrous tetrahydrofuran are mixed. Over one hour, the temperature being maintained at 45 - 50° C, 34 g of 4-pyrrolidinyl bromo benzene in 140 cm³ of anhydrous tetrahydrofuran are introduced. The reaction was initiated by the addition of dibromoethane. A 1 M solution of expected magnesium derivative is thus obtained.

Condensation on to the epoxide.

Under inert gas 8 g of 3,3-[1,2-ethane diyl bis (oxy)] 5α-10α-epoxy 17α-(prop-1-ynyl) estr-9 (11) en-17β-ol, 160 cm³ of anhydrous tetrahydrofuran and 216 mg of copper chloride are mixed. [The mixture] is cooled to 0 [to] +5° C and, over one hour thirty minutes, 86.4 cm³ of the solution of magnesium derivative prepared above are introduced. [The whole] is agitated for one hour, poured into a saturated aqueous solution of ammonium chloride [and] extracted with diethyl oxide, the organic phase is washed with a saturated aqueous solution of ammonium chloride then with a saturated aqueous solution of sodium chloride [and] dried and the solvent is evaporated. The residue is purified by chromatography on silica, elution being carried out with the methylene chloride / acetone mixture (95:5) containing 1 per thousand of triethylamine. 8.3 g of

expected product are thus obtained and recrystallised from a methylene chloride / isopropyl ether mixture.

M.Pt. = 185°C

$[\alpha]_{\text{D}} = -67^{\circ} \pm 1.5^{\circ}$ (c = chloroform).

5 Stage B: 17 β -hydroxy 11 β -(4-pyrrolidinylphenyl)
17 α -(prop-1-ynyl) estro 4,9-dien-3-one.

6.4 g of product obtained in Stage A are dissolved in 128 cm³ of methanol then 13 cm³ of 2N hydrochloric acid are added. [The whole] is agitated at 20°C for
10 one hour, then 256 cm³ of diethyl oxide and 256 cm³ of a 0.25 M aqueous solution of sodium bicarbonate are added. [The whole] is decanted [and] extracted with diethyl oxide, the organic phase is washed with a 0.25 M
15 aqueous solution of sodium bicarbonate, then with a saturated aqueous solution of sodium chloride [and] dried and the solvent is evaporated. The residue is chromatographed on silica, elution being carried out with the petroleum ether / ethyl acetate mixture (1:1) and 5.25 g of expected product are obtained and
20 recrystallised from a methylene chloride / diisopropyl oxide mixture.

M.Ft. = 190.

$[\alpha]_{\text{D}} = +120^{\circ} \pm 2.5^{\circ}$ (c = 1.2% chloroform).

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Example 25 : 17 β -hydroxy 11 β -(4-dimethylaminophenyl)
17 α -ethenyl estro 4,9-dien-3-one.

Stage A : 3,3-[1,2-ethane diyl bis (oxy)] 11 β -
(4-dimethylaminophenyl) 17 α -ethenyl estr-9-en-5 α -17 β
-diol.

3 g of product obtained in Stage B of Example 17
are mixed with 60 cm³ of anhydrous pyridine and 0.6 g
of 5% palladium on calcium carbonate is added. A
current of hydrogen is passed into the mixture at
ambient temperature for one hour. The catalyst is
separated, the filtrate is evaporated to dryness [and]
the residue is taken up with toluene and again
evaporated to dryness. 2.94 g of expected product
are thus obtained, [which is] used as it is for the next
part of the synthesis. M.Pt = 181° C. The product
can be recrystallised from a methylene chloride /
diisopropyl oxide mixture. M. Pt. = 182° C.

$[\alpha]_D = -6.5^\circ \pm 2^\circ$ (c = 0.7% chloroform)

Stage B : 17 β -hydroxy 11 β -(4-dimethylaminophenyl) 17 α -
-ethenyl estro 4,9-dien-3-one.

Under inert gas 2.94 g of the product obtained in
Stage A are mixed with 60 cm³ of methanol, then 6.2 cm³
of 2N hydrochloric acid are added. The solution is
agitated at 20° C for one hour, 120 cm³ of ether and
120 cm³ of a 0.25 M aqueous solution of sodium bicarbon-
ate are added [and the whole] is kept under agitation

*Translator's note: The French "maintint" is clearly a
misprint for "maintient" = "is kept".

for 10 minutes, decanted and extracted with ether.
The organic phase is washed with a 0.25 M aqueous
solution of sodium bicarbonate then with a saturated
aqueous solution of sodium chloride. [It] is dried and
the solvent is evaporated. 2.65 g of product are
obtained and chromatographed on silica, elution being
carried out with the benzene / ethyl acetate mixture
(7:3), and then crystallised from a diisopropyl oxide
/ methylene chloride mixture. 1.51 g of expected
product are finally obtained. M.Pt. = 150° C

$[\alpha]_D = +243^\circ \pm 3^\circ$ (c = 0.8% chloroform)

Example 26 : 17 β -hydroxy 11 β -(4-diethylaminophenyl)
17 α -(prop-1-ynyl) estro 4,9-dien-3-one.

Stage A : 3,3-[1,2-ethane diyl bis (oxy)] 11 β -
(4-diethylaminophenyl) 17 α -(prop-1-ynyl) estr-9-en
5 α -17 β -diol.

Formation of the magnesium derivative.

Under inert gas 3.9 g of magnesium are mixed into
10 cm³ of tetrahydrofuran. Drop by drop, 34.2 g of
4-(N,N-diethylamino) bromo benzene in 110 cm³ of
tetrahydrofuran are added, the temperature being kept
at about 35° C. A 1 M solution of the expected magnesium
derivative is obtained.

Condensation.

7.4 g of 3,3-[1,2-ethane diyl bis (oxy)] 5 α - 10 α -
epoxy 17 α -(prop-1-ynyl) estr-9 (11) en 17 β -ol are
dissolved in 150 cm³ of anhydrous tetrahydrofuran.

0.25 g of copper chloride are added. [The whole] is
agitated at 0 [to] +5° C under inert gas and 80 cm³
of the solution of magnesium derivative prepared
above are added slowly. [The whole] is kept for 17
5 hours under agitation at 20° C, poured into an
aqueous solution of ammonium chloride [and] extracted
with ether, the organic phase is washed with an
aqueous solution of sodium bicarbonate [and] dried
and the solvent is evaporated. The residue is
10 made into a paste with petroleum ether then treated
with active charcoal in ether and recrystallised
from isopropyl ether. 4 g of expected product are
thus obtained.

$[\alpha]_D = -61^\circ \pm 2.5^\circ$ (c = 0.7% chloroform)

15 Stage B : 17 β -hydroxy 11 β -(4-diethylaminophenyl)
17 α -(prop-1-ynyl) estro 4,9-dien-3-one.

To a solution of 3.12 g of product obtained in
Stage A in 45 cm³ of methanol are added 8 cm³ of
2N hydrochloric acid and [the whole] is agitated at
20 20° C under inert gas for 45 minutes. [It] is
poured into water, neutralised by the addition of
2N sodium hydroxide, extracted with methylene chloride
[and] dried and the solvent is evaporated. The residue
is chromatographed on silica, elution being carried out
25 with the benzene / ethyl acetate mixture (1:1) and

*Translator's note: The French "carbon" could be a misprint
for either "carbone" = "carbon" or "charbon" = "charcoal"
and the latter would appear to be more appropriate here.

(A)

1.34 g of expected product are obtained.

$[\alpha]_D = +144.5^\circ \pm 3^\circ$ (c = 0.8% chloroform)

Analysis : $C_{31} H_{39} NO_2$ (457.63)

Calculated : C% 81.36 H% 8.59 N% 3.06

5 Found : C% 81.7 H% 8.8 N% 2.09

The 4-(N,N-diethylamino) bromo benzene used at the start of Stage A was prepared as follows.

To a solution of 86 g of N,N-diethylaniline in 400 cm³ of acetic acid are added, drop by drop, 93 g of bromine. After the end of the introduction, [the whole] is poured into a water / ice mixture [and] extracted with methylene chloride, the organic phase is washed with an aqueous solution of sodium bicarbonate [and] dried and the solvent is evaporated. 125 g of expected product are obtained. B.Pt. : 0.6 = 97° C.

Example 27 : 17 β -hydroxy 11 β -[4-[methyl(3-methylbutyl) amino]phenyl] 17 α -(prop-1-ynyl) estro 4,9-dien-3-one.

Stage A : 3,3-[1,2-ethane diyl bis (oxy)] 11 β -[4-[methyl(3-methylbutyl) amino] phenyl] 17 α -(prop-1-ynyl) estr-9-en 5 α -17 β -diol.

Preparation of the magnesium derivative.

Under inert gas 4.12 g of magnesium and 10 cm³ of tetrahydrofuran are mixed. A few cm³ of N-methyl N-(3-methylbutyl) 4-bromo benzenamine in solution in tetrahydrofuran are introduced and the reaction is initiated by the addition of 0.2 cm³ of 1,2-dibromoethane.

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Then over 40 minutes, the rest of the solution of N-methyl
N-(3-methylbutyl) 4-bromo benzenamine in
anhydrous tetrahydrofuran (32.6 g in 90 cm³) is
added. [The whole] is then allowed to return to ambient
5 temperature then kept under agitation for 1 hour.
A 0.9 M solution of the expected magnesium derivative
is thus obtained.

Condensation.

8 g of 3,3-[1,2-ethane diyl bis (oxy)] 5 α -10 α -
10 epoxy 17 α -(prop-1-ynyl) estr-9 (11) en 17 β -ol are
mixed with 90 cm³ of anhydrous tetrahydrofuran and
3.77 g of copper chloride. [The mixture] is agitated for
20 minutes at 0 [to] +5° C under inert gas, then 100 cm³
of the solution of magnesium derivative prepared
15 above are added. The mixture is then poured into an
aqueous solution of ammonium chloride [and] extracted
with ether mixed with triethylamine then with methylene
chloride mixed with triethylamine. The combined organic
phases are washed with a saturated aqueous solution of
20 sodium chloride, dried and evaporated to dryness.
31.2 g of expected product are obtained, [which is] used
as it is for the following stage. The product can be
purified by chromatography on silica, elution being
carried out with the methylene chloride / acetone /
25 triethylamine mixture (96.5 : 4.5 : 0.5).
[α]_D = -59.5° $\pm$ 2.5° (c = 0.7% chloroform).

*Translator's note: The French "M-méthyl" would appear
to be a misprint for "N-méthyl".

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Stage B : 17 β -hydroxy 11 β -[4-(methyl (3-methylbutyl) amino]phenyl] 17 α -(prop-1-ynyl) estro 4,9-dien-3-one.

26 g of product obtained in Stage A are dissolved in 200 cm³ of methanol, then 52 cm³ of 2N hydrochloric acid are added. After one hour under agitation, the mixture is poured into an aqueous solution of sodium bicarbonate [and] extracted with ether, then with methylene chloride, the combined organic phases are washed with a saturated aqueous solution of sodium chloride [and] dried and the solvent is evaporated.

The product is purified by chromatography on silica, elution being carried out with the toluene / ethyl acetate mixture (92:8) and 3.23 g of expected product are obtained.

[α]_D = +125° $\pm$ 3.5° (c = 0.6% chloroform)

Analysis : C₃₃ H₄₃ NO₂ (485.71)

Calculated: C% 81.6 H% 8.92 N% 2.88

Found: 81.4 9.0 2.7

The amine used at the start of Stage A was prepared as follows.

Stage a : N-methyl N-(3-methylbutyl) aniline.

86 g of N-methyl aniline, 500 cm³ of anhydrous benzene and 81 g of anhydrous triethylamine are mixed. Drop by drop, 121 g of isoamyl bromide are added and [the whole] is taken to reflux for 100 hours. The mixture is filtered, the filtrate is washed with water [and] dried and the solvent is evaporated. The residue is distilled and 90 g of

(07)

expected product are obtained. B.Pt. 18 = 132° C.

Stage b : N-methyl N-(3-methylbutyl) 4-bromo aniline

64 g of product obtained in Stage a are mixed with 300 cm³ of acetic acid then, drop by drop, over 1 hour at about 15° C, 58 g of ^{*}bromine in solution in 60 cm³ of acetic acid are added. The temperature is taken to 80° C, [the whole] is agitated for 8 hours, then poured into iced water [and] extracted with methylene chloride, the organic phase is washed with a solution of sodium bicarbonate then with water [and] dried and the solvent is evaporated. The residue is distilled and 70 g of expected product are obtained. B.Pt 0.5 = 119° C.

Example 28 : 17β-hydroxy 11β-[4-(N,N-dimethylaminoethylthio) phenyl] 17α-(prop-1-vnyl) estra 4,9-dien-3-one.

Stage A : 3,3[1,2-ethane diyl bis (oxy)] 11β-[4-(N,N-dimethylaminoethylthio) phenyl] 17α-(prop-1-vnyl) estr-9-en 5α-17β-diol.

Preparation of the magnesium derivative.

Under inert gas 2g of magnesium and 15 cm³ of anhydrous tetrahydrofuran are mixed. Then, over 45 minutes, the temperature being allowed to rise to 56° C, a solution of 20 g of 4-(N,N-dimethylaminoethylthio) 1-bromo benzene in 40 cm³ of anhydrous tetrahydrofuran is introduced. The reaction ^{**}was initiated by the addition of 1,2-dibromoethane. [The whole] is then allowed to return to 20° C, then kept under agitation for 45 minutes under inert

*Translator's note: The French "bromo" would appear to be a misprint for "brome" = "bromine".

** The French should apparently read "On a amorcé la réaction.." = "The reaction was initiated.."



gas. A 1.05 M solution of the expected magnesium derivative is thus obtained.

Condensation

Under inert gas 38 cm³ of the solution of magnesium derivative obtained above is cooled to -20° C. To this are added 1.730 g of copper chloride, [the whole] is kept under agitation for 20 minutes, then 5 g of 3,3-[1,2-ethane diyl bis (oxy)] 5α-10α-epoxy 17α-(prop-1-ynyl estr-9 (11) en 17β-ol in 50 cm³ of anhydrous tetrahydrofuran are added. [The whole] is kept at 20° C under inert gas for 2 hours 45 minutes. The mixture is poured into 600 cm³ of iced water containing 60 g of ammonium chloride. [The whole] is kept under agitation for 45 minutes [and] decanted, the aqueous phase is extracted with diethyl oxide mixed with triethylamine, the combined organic phases are washed with a saturated aqueous solution of sodium chloride [and] dried and the solvent is evaporated. The residue is chromatographed on alumina, elution being carried out with the methylene chloride / acetone mixture (95:5) and 10.3 g of expected product are obtained.

I.R.Spectrum.

Absorption at 3600 cm⁻¹ (OH), 2240 cm⁻¹ (C≡C), 1705 and 1670 cm⁻¹ (CO and conjugated CO), 1615 and 1490 cm⁻¹ (aromatic bands).

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Stage B : 17 β -hydroxy 11 β -[4-(N,N-dimethylaminoethylthio) phenyl] 17 α -prop-1-ynyl) estra 4,9-dien-3-one.

Under inert gas 10.3 g of product obtained in Stage A are mixed with 72 cm³ of methanol, then 20.6 cm³ of 2N
5 hydrochloric acid are added. [The whole] is kept under agitation at 20°C for 1 hour 15 minutes [and] neutralized by the addition of a saturated aqueous solution of sodium bicarbonate, 200 cm³ of diethyl oxide are added, [the whole] is decanted [and] extracted with diethyl oxide,
10 [and] the combined organic phases are washed with a saturated aqueous solution of sodium chloride, dried and concentrated to dryness, The residue is chromatographed on silica, elution being carried out with the methylene chloride / methanol mixture (9:1) and 3 g of expected
15 product are obtained and crystallized by making into a paste in diisopropyl oxide. M.Pt. = 145°C.

$[\alpha]_D = +125^\circ \pm 2^\circ$ ($[c] = 1\%$ chloroform).

The amine used at the start of Stage A was prepared as follows.

20 20 g of sodium hydroxide in pellets are dissolved in 500 cm³ of ethanol. Elsewhere, 23.5 g of chloroethyl-dimethylamine hydrochloride are dissolved in 75 cm³ of ethanol, then 160 cm³ of the sodium hydroxide solution prepared above are added. Elsewhere, 30 g of parabromo-
25 thiophenol are dissolved in 100 cm³ of ethanol, then 160 cm³ of the sodium hydroxide solution prepared above are added. Then, over 2 minutes, at 20°C, the amine solution prepared above _____

*Translator's note: The French "diisoprpyle" would appear to be a misprint for "diisopropyle".

**It would appear that "c" has been omitted at this point from the French text.

(110)

is added. [The whole] is taken to reflux for 3 hours, the solvent is evaporated, water is added, [the whole] is extracted with methylene chloride, the organic phase is washed with a 0.1 N aqueous solution of sodium hydroxide then with water [and] dried and the solvent is evaporated. The residue is distilled and 35.5 g of expected product are obtained. B.Pt. 0.1 = 110°C.

Example 29 : 11 β -(4-dimethylaminophenyl) 17 β -hydroxy 21-(trimethylsilyl) (17 α) 19-nor pregna 4,9-dien-20-yn-3-one.

10 Stage A : 11 β -(4-dimethylaminophenyl) 3,3-[1,2-ethane diyl bis (oxy)] 21-(trimethylsilyl) (17 α) 19-nor pregn-9-en-20-yn 5 α -17 β -diol.

Under inert gas 13 cm³ of a 1.6 M solution of ethyl magnesium bromide in tetrahydrofuran are mixed with 13 cm³ of anhydrous tetrahydrofuran. [The mixture] is agitated for 5 minutes at 0 [to] +5°C, then, drop by drop, 3.4 cm³ of trimethylsilyl acetylene are added. The temperature is allowed to rise again to 20°C and the agitation is continued for 20 minutes then, drop by drop, a solution of 1.12 g of the product obtained in Stage A of Example 7 in 10 cm³ of anhydrous tetrahydrofuran is introduced. [The whole] is kept for 16 hours at ambient temperature under agitation, poured into an aqueous solution of ammonium chloride, agitated for 10 minutes at ambient temperature [and] extracted with methylene chloride, the organic phase is washed with a saturated aqueous solution of sodium chloride [and] dried and the solvent is evaporated. The

*Translator's note: The French: "diméthylaminophenyl" is clearly a misprint for "diméthylaminophenyl".

(111)

residue is chromatographed on silica, elution being carried out with the petroleum ether / ethyl acetate mixture (6:4) and 690 mg of expected product are obtained. $[\alpha]_D = -76.5^\circ \pm 3^\circ$ (c = 0.5% chloroform).

5 Stage B : 11 β -(4-dimethylaminophenyl) 17 β -hydroxy 21-(trimethylsilyl) (17 α) 19-nor pregna 4,9-dien-20-yn-3-one.

562 mg of the product obtained in Stage A are mixed with 15 cm³ of methanol and 1 cm³ of 2N hydrochloric acid. [The mixture] is kept under agitation at ambient temperature
10 for 40 minutes, poured into an aqueous solution of sodium bicarbonate [and] extracted with ether, the organic phase is washed with a saturated solution of sodium chloride [and] dried and the solvent is evaporated. The residue is chromatographed on silica, elution being carried
15 out with the petroleum ether / ethyl acetate mixture (6:4) and 364 mg of expected product are obtained.

$[\alpha]_D = +97.5^\circ \pm 3^\circ$ (c = 0.35% chloroform).

Analysis : C₃₁ H₄₁ NO₂ Si (487.76)

Calculated : C% 76.33 H% 8.47 N% 2.87

20 Found : C% 76.4 H% 8.7 N% 2.8

Example 30 : 17 β -hydroxy 11 β -[4-(N,N-dimethylaminomethyl) phenyl] 17 α -(prop-1-ynyl) estra 4,9-dien-3-one N-oxide.

1.4 g of product obtained in Example 23 are dissolved in 28 cm³ of methylene chloride then, over 15 minutes at
25 0 [to] +5°C, a solution of 0.64 g of metachloroperbenzoic acid in 12.8 cm³ of methylene chloride is introduced. [The whole] is agitated for 1 hour at 0 [to] +5°C then poured into

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a 0.2 N aqueous solution of sodium thiosulphate, decanted,
extracted with methylene chloride, washed with an aqueous
solution of sodium bicarbonate, dried and evaporated to
dryness. The residue is chromatographed on silica,
5 elution being carried out with the methylene chloride /
methanol mixture (8:2) and 1.28 g of expected product are
obtained and dissolved in a methylene chloride / diisopropyl
oxide mixture. The crystals formed are separated [and] dried
and 1.075 g of expected product are obtained. M.Pt. = 215°C.
10 $[\alpha]_D = +74.5^\circ \pm 2.5^\circ$ (c = 0.7% chloroform).

Example 31 : Hemifumarate of 17 β -hydroxy 11 β -[4-(N,N-
dimethylaminomethyl) phenyl] 17 α -(prop-1-ynyl) estra 4,9-
-dien-3-one.

1.44 g of the product obtained in Example 23 are
15 mixed into 2.88 cm³ of ethanol then a mixture of 0.378 g
of fumaric acid in 4.54 cm³ of ethanol is added. The
suspension is agitated for 30 minutes at 60°C, the
temperature is allowed to return to 20°C and [the whole] is
kept under agitation. The solvent is evaporated, the
20 residue is taken up with ether, separated [and] dried and
1.70 g of expected product are obtained. M.Pt. = 160°C.
 $[\alpha]_D = +70.5^\circ \pm 2.5^\circ$ (c=0.8% chloroform).

Example 32 : 17 β -hydroxy 11 β -[4-(N,N-dipropylamino)
phenyl] 17 α -(prop-1-ynyl) estra 4,9-dien-3-one.

25 Stage A : 3,3-[1,2-ethane diyl bis (oxy)] 11 β -[4-(N,N-
-dipropylamino) phenyl] 17 α -(prop-1-ynyl) estr-9-en 5 α -
-17 β -diol.

Preparation of the magnesium derivative.

Under inert gas 5 g of magnesium are mixed with 15 cm³ of anhydrous tetrahydrofuran. Drop by drop, a solution of 52 g of 4-bromo N,N-dipropylaniline in 110 cm³ of tetrahydrofuran is added, the temperature being kept at 40°C. A 1.1 M solution of expected magnesium derivative is thus obtained.

Condensation.

Under inert gas a solution of 5.55 g of 3,3-[1,2-ethane diyl bis (oxy)] 5 α -10 α -epoxy 17 α -(prop-1-ynyl) estr-9 (11)-en 17 β -ol obtained in Stage A of Example 7 is mixed with 200 mg of copper chloride. [The mixture] is agitated at 0 [to] +5°C then, over 15 minutes, 50 cm³ of the solution of magnesium derivative obtained above are added. [The whole] is then agitated for 1 hour at 20°C, poured into a saturated aqueous solution of ammonium chloride [and] extracted with ether, the organic phase is dried and the solvent is evaporated. The residue is chromatographed on silica, elution being carried out with the toluene / ethyl acetate mixture (7:3) and 6.3 g of expected product are obtained.

$[\alpha]_D = -56^\circ \pm 2^\circ$ (c. = 0.8% chloroform).

Analysis : C₃₅ H₄₉ NO₄ (547.75)

Calculated : C% 76.74 H% 9.02 N% 2.56

Found : C% 76.6 H% 9.2 N% 2.5

Stage B : 17 β -hydroxy 11 β -[4-(N,N-dipropylamino) phenyl] 17 α -(prop-1-ynyl) estra 4,9-dien-3-one.

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To a solution of 5.83 g of product obtained in Stage A in 80 cm³ of methanol are added 10 cm³ of 2N hydrochloric acid and [the whole] is agitated at 20°C for 50 minutes. [It] is neutralised by the addition of 5 N sodium hydroxide, the solvent is evaporated under reduced pressure and the residue is taken up with methylene chloride. The organic phase is washed with water [and] dried and the solvent is evaporated. The residue is chromatographed on silica, elution being 10 carried out with the toluene / ethyl acetate mixture (75:25) and 3.81 g of expected product are obtained.

IR Spectrum (chloroform)

Absorption at 3600 cm⁻¹ (OH), 1654 cm⁻¹ (C=O), 1610-1595-1558 and 1517 cm⁻¹ (4.9 + aromatic bands), 15 2240 cm⁻¹ (C≡C).

The products below constitute examples of other products which can be obtained by the process of the invention :

- 11β-[4-(N-ethyl N-methylamino) phenyl] 17β-hydroxy 20 17α-(prop-1-ynyl) estra 4,9-dien-3-one (M.Pt. = 174°C; α_D = +149° ± 2.5°, c = 1% CHCl₃);
- 17β-hydroxy 11β-[N-methyl 2,3-dihydro 1H-indol-5-yl] 17α-(prop-1-ynyl) estra 4,9-dien-3-one (M.Pt. = 176°C; α_D = +133° ± 3°, c = 0.8% CHCl₃);
- 25 - 11β-(4-dimethylaminophenyl) 3-hydroxyimino 17α-(prop-1-ynyl) estra 4,9-dien-17β-ol, isomer Z (M.Pt. = 260°C; α_D = 141° ± 3.5°, c = 0.8% CHCl₃);

- 11 β -(4-dimethylaminophenyl) 3-hydroxyimino 17 α -(prop-1-ynyl) estra 4,9-dien-17 β -ol, isomer E (M.Pt. = 220°C; $\alpha_D = +164^\circ \pm 3.5^\circ$, c = 0.8% CHCl₃);
- 5 - 17 β -hydroxy 11 β -(4-pyrrolidylphenyl) 17 α -(prop-1-ynyl) estra 4,9-dien-3-one N-oxide, (M.Pt. = 220°C; $\alpha_D = +88^\circ \pm 2.5^\circ$, c = 0.75% CHCl₃);
- 17 β -hydroxy 11 β -[4-N-methyl N-(1-methylethyl) aminophenyl] 17 α -(prop-1-ynyl) estra 4,9-dien-3-one ($\alpha_D = +140^\circ \pm 3.5^\circ$, c = 0.5% CHCl₃);
- 10 - 11 β -[4-(N,N-dimethylaminoethoxy) phenyl] 17 β -hydroxy 17 α -(prop-1-ynyl) estra 4,9-dien-3-one N-oxide, ($\alpha_D = +60.5^\circ$, c = 1.2% CHCl₃);
- 17 β -hydroxy 11 β -[(N-methyl) 2,3-dihydro 1H-indol-5-yl] 17 α -(prop-1-ynyl) estra 4,9-dien-3-one N-oxide,
- 15 ($\alpha_D = +103^\circ \pm 2.5^\circ$, c = 0.8% CHCl₃);
- 17 β -hydroxy 11 β -[4-(N-methyl N-trimethylsilylmethyl) aminophenyl] 17 α -(prop-1-ynyl) estra 4,9-dien-3-one;
- 17 β -hydroxy 11 β -[4-(N-methyl N-dimethylaminoethyl) aminophenyl] 17 α -(prop-1-ynyl) estra 4,9-dien-3-one;
- 20 - 17 β -hydroxy 11 β -[4-(N-methyl piperazin-1-yl) phenyl] 17 α -(prop-1-ynyl) estra 4,9-dien-3-one;
- 17-hydroxyimino 11 β -(4-dimethylaminophenyl) estra 4,9-dien-3-one, [α]_D = +207.5° $\pm$ 3.5°, (c = 1% CHCl₃);
- 3(E)-hydroxyimino 17-hydroxyimino 11 β -(4-dimethylamino-
- 25 phenyl) estra 4,9-dien-3-one, ($\alpha_D = +195^\circ \pm 3^\circ$, c = 1% CHCl₃); [and]
- 3(Z)-hydroxyimino 17-hydroxyimino 11 β -(4-dimethylamino-phenyl) estra 4,9-dien-3-one, ($\alpha_D = +163^\circ \pm 2.5^\circ$, c = 0.6% CHCl₃).

*Translator's note: The French "CHCl₃" is clearly a misprint for "CHCl₃".

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Pharmacological Study

Study of the activity of the products on hormone receptors.
Mineralocorticoid receptor of the rat kidney.

Male Sprague-Dawley EOPS rats, weighing 140 to 160 g,
5 from which the suprarenal glands have been removed 4 to 8
days previously, are sacrificed and their kidneys are
perfused in situ with 50 ml of a buffer [of] 10 mM Tris,
0.25 M saccharose [and] HCl [at] pH 7.4. The kidneys are
then removed, decapsulated and homogenized at 0°C using
10 a Potter polytetrafluoroethylene glass (1 g of tissue to
3 ml of buffer). The homogenate is centrifuged for 10
minutes at 800 g, at 0°C.

So as to eliminate the fixing of tritiated aldosterone
on the glucocorticoid receptor, the 11 β , 17 β -dihydroxy
15 21-methyl pregna 1,4,6-trien 20-yn 3-one steroid adhering
solely to the glucocorticoid receptor is mixed with the
supernatant liquid at the final concentration of 10⁻⁶M.
This supernatant liquid is ultracentrifuged at 105,000 g
for 60 minutes at 0°C. Aliquot parts of the supernatant
20 liquid thus obtained are incubated at 0°C with a constant
concentration (T) of tritiated aldosterone in the presence
of increasing concentrations (0 - 2,500 . 10⁻⁹M) of cold
aldosterone or of the cold product to be studied. After
a period (t) of incubation, the concentration of bonded,
25 tritiated aldosterone (B) is measured by the technique of
adsorption to charcoal-dextran.

Androgen receptor of the rat prostate gland.

Male Sprague-Dawley EOPS rats of 160 to 200 g are castrated. 24 hours after castration, the animals are sacrificed; the prostate glands are removed, weighed and homogenized at 0°C using a Potter polytetrafluoroethylene glass in a TS^{*} buffered solution (10 mM Tris, 0.25 M saccharose [and] HCl [at] pH 7.4) (1 g of tissue to 5 ml of TS).

The homogenate is then ultracentrifuged (105,000 g x 60 minutes) at 0°C. Aliquot parts of the supernatant liquid thus obtained are incubated at 0°C for two hours with a constant concentration (T) of product P (17β-hydroxy-17α-methyl-estra-4,9,11-trien-3-one) in the presence of increasing concentrations (0 - 1,000 . 10⁻⁹M) either of cold P, or of cold testosterone, or of the product to be tested. The concentration of bonded tritiated P (B) is then measured in each incubate by the technique of adsorption to charcoal-dextran.

Progestogen receptor of the rabbit uterus.

Impubic female rabbits of about 1 kg receive a cutaneous application of 25 µg of estradiol. 5 days after this treatment, the animals are sacrificed; the uteri are removed, weighed and homogenized at 0°C using a Potter polytetrafluoroethylene glass in a TS buffered solution (10 mM Tris, 0.25 M saccharose [and] HCl [at] 7.4) (1 g of tissue to 50 ml of TS).

The homogenate is then ultracentrifuged (105,000 g

*Translator's note: The French "t_{em}ponnée" is clearly a misprint for "t_amponnée" = "buffered".

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5 x 90 minutes) at 0°C. Aliquot parts of the supernatant liquid thus obtained are incubated at 0°C for a period (t) with a constant concentration (T) of tritiated product R (17,21-dimethyl 19-nor-4,9-pregnadiene-3,20-
5 -dione) in the presence of increasing concentrations (0 - 2,500 . 10⁻⁹M) either of cold R, or of cold progesterone, or of the cold product to be tested. The concentration of bonded tritiated R (B) is then measured in each incubate by the technique of adsorption to charcoal-dextran.
10

Glucocorticoid receptor of the rat thymus.

Male Sprague-Dawley EOPS rats of 160 to 200 g have their suprarenal glands removed. 4 to 8 days after this removal, the animals are sacrificed and the thymi are
15 removed and homogenized at 0°C in a buffer [of] 10 mM Tris, 0.25 saccharose, 2 mM dithiothreitol [and] HCl [at] *** pH 7.4, using a Potter polytetrafluoroethylene glass (1 g of * tissue to 10 ml of TS). The homogenate is then ultracentrifuged (105,000 g x 90 minutes) at 0°C.

20 Aliquot parts of the supernatant liquid thus obtained are incubated at 0°C for a period (t) with a constant concentration (T) of tritiated dexamethasone in the presence of increasing concentrations (0 - 2,500 . 10⁻⁹M) either of cold dexamethasone, or of the cold product to
25 be tested. The concentration of the bonded tritiated dexamethasone (B) is then measured in each incubate by the technique of adsorption** to charcoal-dextran.

*Translator's note: The French "issu" is clearly a misprint for "tissu" = "tissue".

** The French "absorption" would appear to be a misprint for "adsorption".

***The French "ph" should clearly read "pH".

Estrogen receptor of the mouse uterus.

Impubic female mice, 18 to 21 days old, are sacrificed; the uteri are removed, then homogenized at 0°C using a Potter polytetrafluoroethylene glass in a TS buffered solution (10 mM Tris, 0.25 M saccharose [and] HCl [at] pH 7.4) (1 g of tissue to 25 ml of TS). The homogenate is then ultracentrifuged (105,000 g x 90 minutes) at 0°C. Aliquot parts of the supernatant liquid thus obtained are incubated at 0°C for a period (t) with a constant concentration (T) of tritiated estradiol in the presence of increasing concentrations (0 - 1,000 . 10⁻⁹M) either of cold estradiol, or of the cold product to be tested. The concentration of bonded tritiated estradiol (B) is then measured in each incubate by the technique of adsorption to charcoal-dextran. Calculation of the relative affinity of bonding.

The calculation of the relative affinity of bonding (RAB) is identical for all the receptors.

The following two curves are traced : the percentage of bonded tritiated hormone $\frac{B}{T}$ as a function of the

logarithm of the concentration of the cold reference hormone and $\frac{B}{T}$ as a function of the logarithm of the

concentration of the cold product tested.

The straight line of the equation

25
$$I_{50} = \left\{ \frac{B}{T} \text{ max} + \frac{B}{T} \text{ min} \right\} / 2 \text{ is determined.}$$

$\frac{B}{T} \text{ max}$ = percentage of the tritiated hormone bonded for

one incubation of this tritiated hormone at the concentration (T).

$\frac{B}{T} \text{ min}$ = percentage of the tritiated hormone bonded for

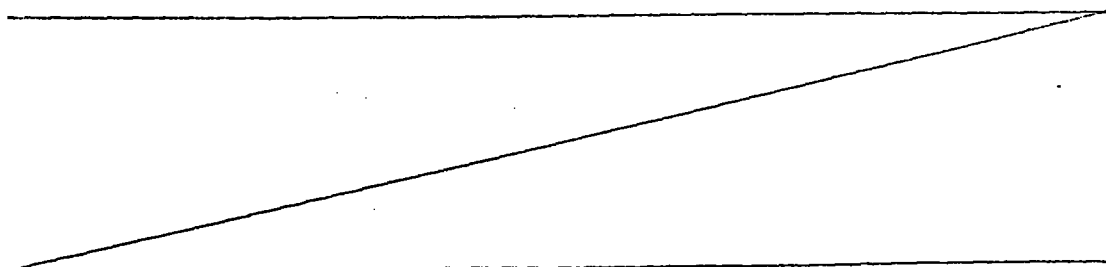
- 5 one incubation of this tritiated hormone at the concentration (T) in the presence of a large excess of cold hormone ($2,500 \cdot 10^{-9} \text{ M}$).

The intersections of the straight line I_{50} and of the curves enable the concentrations of the cold reference hormone (CH) and of the cold product tested (CX), which inhibit by 50% the bonding of the tritiated hormone to the receptor, to be evaluated.

The relative affinity of bonding (RAB) of the product tested is determined by the equation

15
$$\text{RAB} = 100 \frac{(\text{CH})}{(\text{CX})} .$$

The results obtained are as follows:



*Translator's note: The French "relaitve" is clearly a misprint for "relative".

Product of example	Incubation period at 0°C	Mineralo corticoid			Androgen			Progesterogen			Glucocorticoid			Estrogen		
		2H	4H	24H	2H	4H	24H	2H	4H	24H	2H	4H	24H	2H	4H	24H
4		-	-	0	-	-	20	74	-	640	-	270	265	0	-	-
17		-	-	0	-	-	68	81	-	351	-	279	235	0	-	-
14		-	-	-	-	-	0	41	-	250	-	46	94	0	-	-
8		-	-	0	-	-	14.7	81	-	268	-	212	167	0	-	-
10		-	-	0	-	-	32	78	-	467	-	254	292	0	-	-
11		-	-	0	-	-	9.8	6.3	-	8.3	-	9	14	0	-	-
16		-	-	1.7	-	-	29	129	-	166	-	283	259	0	-	-
12		-	-	0	-	-	2.8	0.6	-	0.4	-	5.3	6.2	0	-	-
6		-	-	0.8	-	-	7.3	10	-	4.3	-	171	118	0	-	-
20		-	-	-	-	-	2.2	1.1	-	2.5	-	7.8	5	0	-	-
22		-	-	0.3	-	-	8	175	-	843	-	178	221	0	-	-
29		-	-	0	-	-	4.6	15.2	-	38	-	79	104	0	-	-

Conclusion:

The products studied and more particularly the products of Examples 4, 17, 10, 16 and 22 show a very marked affinity for the glucocorticoid and progestogen receptors, as well as a slight affinity for the androgen receptor. On the other hand, these products do not show any activity with regard to the mineralocorticoid and estrogen receptors.

From the results obtained, it may be concluded that the products can show agonist or antagonist activity towards glucocorticoids, progestogens and androgens. II - Study of the anti-inflammatory activity of the product of Example 4.

The anti-inflammatory activity was investigated according to the standard granuloma test.

In the technique used, a modification of the method of R. MEIER and colleagues (Experientia, 1950, 6, 469), conventional female Wistar rats, weighing from 100 to 110 g, receive an implant of two cotton-wool pellets, each of 10 mg, under the skin of the thorax. The subcutaneous treatment, which begins immediately after this implantation, lasts 2 days at the rate of 2 injections per day; sixteen hours after the last injection, that is on the third day, the animals are sacrificed.

The pellets, surrounded with granuloma tissue formed, are weighed while fresh, then after standing for eighteen hours at 60°C : the weight of the granuloma is obtained by

Translator's notes: * The French "acitivté" is clearly a misprint for "activité";
** The French "antogoniste" should read "antagoniste";
*** The French "granaulome" should read "granulome".
****The French "rest" would appear to be a misprint for "test".

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deducting the initial weight of the cotton-wool.

The thymi are also removed and weighed so as to determine the thymolytic activity of the product.

At the dose of 50 mg/kg administered by sub-cutaneous route, the product of Example 4 does not show any anti-inflammatory glucocorticoid or thymolytic effect.

III - Antigluccorticoid activity.

The technique used comes from the method described by Daune and colleagues in Molecular Pharmacology 13, 948 - 955 (1977) "The relationship between glucocorticoid structure and effects upon thymocytes", for mice thymocytes.

Thymocytes from rats, from which the suprarenal glands have been removed, are incubated at 37°C for 3 hours, in a nutrient medium containing $5 \cdot 10^{-8}$ M of dexamethasone, in the presence or absence of a product to be studied at different concentrations. Tritiated uridine is added and the incubation is continued for one hour. The incubates are cooled, treated with a 5% solution of trichloroacetic acid, filtered on Whatman GF/A paper [and] washed three times with a 5% solution of trichloroacetic acid. The radioactivity retained by the filter is determined.

The glucocorticoids and in particular dexamethasone cause a reduction in the incorporation of tritiated uridine. The products tested and, more particularly, the products of Examples 4, 14, 8, 10, [11], 16, 6, 20 and 22 are contrary to this effect.

*Translator's note: The French "l'incunbation" is clearly a misprint for "l'incubation".

** The French "filtres" should clearly read "filtre".

***I believe that "11" should appear in the French text at this point.

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Product of example	$5 \cdot 10^{-8}$ Dexamethasone + Product tested	% inhibition of the effect of Dexamethasone
4	$10^{-8}M$	30
	$10^{-7}M$	70
	$10^{-6}M$	90
14	$10^{-8}M$	18
	$10^{-7}M$	57
	$10^{-6}M$	*
8	$10^{-8}M$	22
	$10^{-7}M$	53
	$10^{-6}M$	*
10	$10^{-8}M$	57
	$10^{-7}M$	85
	$10^{-6}M$	*
11	$10^{-8}M$	14
	$10^{-7}M$	34
	$10^{-6}M$	75
16	$10^{-8}M$	28
	$10^{-7}M$	60
	$10^{-6}M$	99
6	$10^{-8}M$	5
	$10^{-7}M$	15
	$10^{-6}M$	83
20	$10^{-8}M$	4
	$10^{-7}M$	21
	$10^{-6}M$	50
22	$10^{-8}M$	16
	$10^{-7}M$	69
	$10^{-6}M$	*

* At the dose of $10^{-6}M$, the inhibition of the effect of the dexamethasone was total.

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It has, moreover, been established that, ^{*}used alone, the products tested do not cause any effect of the glucocorticoid type.

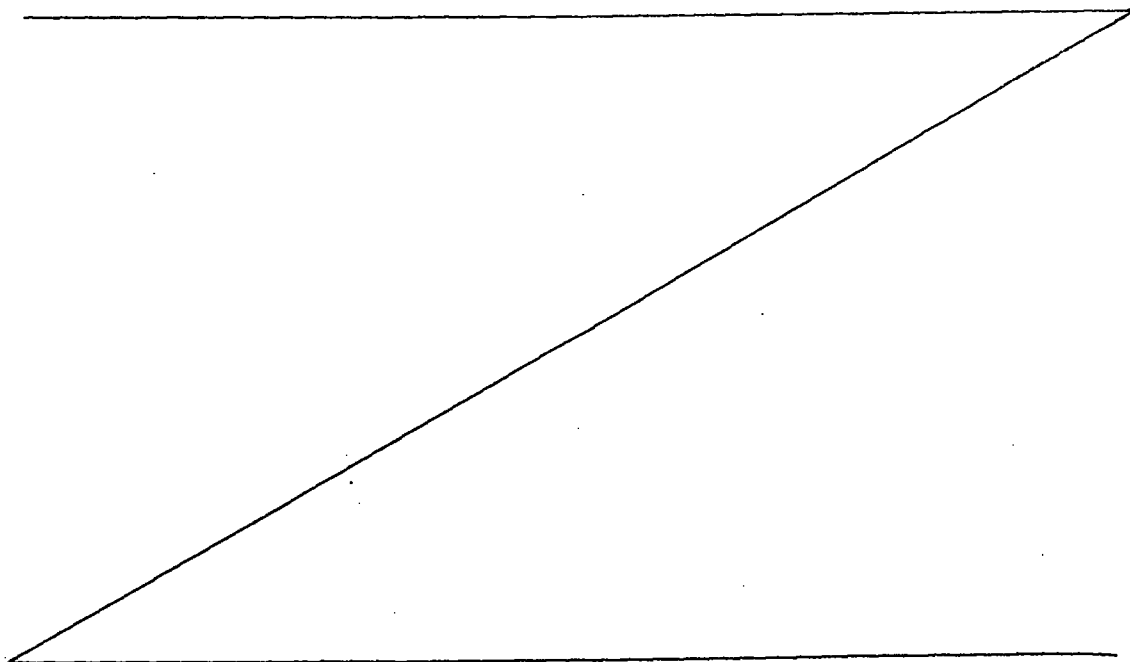
Conclusion:

- 5 The products studied show a very marked antiglucocorticoid activity, whilst being devoid of glucocorticoid activity.

Pharmaceutical compositions.

- 10 Compressed tablets were prepared, corresponding to the following formula:

Product of Example 4 50 mg
Excipient (talc, starch, magnesium stearate)
q.s. for one compressed tablet up to 120 mg.



*Translator's note: It would appear that the French "utilisé seul" is here intended to describe "produits testés" (= "products tested") and should, therefore, read "utilisés seuls".

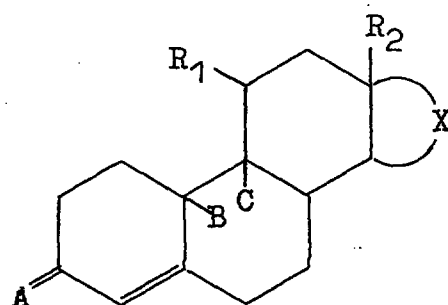


(26)

Claims for the Contracting States

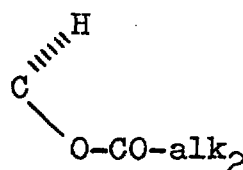
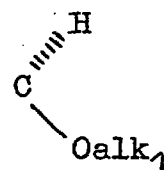
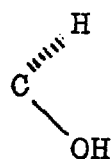
BE CH DE FR GB IT LI LU NL SE

1. The compounds of formula (I') :



(I')

in which R_1 represents an organic radical containing
 5 from 1 to 18 carbon atoms, containing at least one
 nitrogen, phosphorus or silicon atom, the atom immediately
 adjacent the carbon at [position] 11 being a carbon atom,
 R_2 represents a hydrocarbon radical containing from 1 to 8
 carbon atoms, X represents the residue of a pentagonal or
 10 hexagonal ring, possibly substituted and possibly bearing
 an unsaturation, the group $C = A$ at position 3 represents
 an oxo group, free or blocked in ketal form, a group

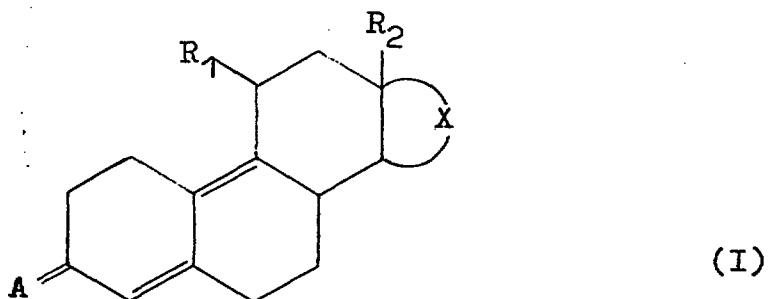


a group $C=NOH$, a group $C=NO-alk_3$ or a group CH_2 , alk_1 ,
 15 alk_2 and alk_3 representing an alkyl radical containing
 from 1 to 8 carbon atoms or an aralkyl group containing
 from 7 to 15 carbon atoms and B and C together form a
 double bond or an epoxide bridge, as well as their salts
 of addition with acids.



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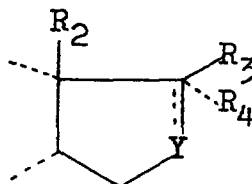
2. The compounds of formula (I'), as defined in Claim 1, corresponding to the formula (I) :



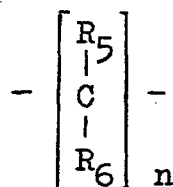
in which R_1 , R_2 , X and A are defined as in Claim 1.

3. The compounds of formula (I'), as defined in Claim 1 or 2, for which R_2 represents a methyl radical.

4. The compounds of formula (I'), as defined in Claim 1, 2 or 3, for which X represents the residue of a ring of formula :



in which R_2 keeps the same meaning as in Claim 1, 2 or 3, the dotted line at [position] 16-17 symbolizes the possible presence of a double bond, Y represents a radical

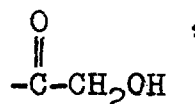


in which n represents the number 1 or 2, R_5 represents a hydrogen atom, an alkyl radical containing from 1 to 8 carbon atoms, an alkenyl or alkynyl radical containing

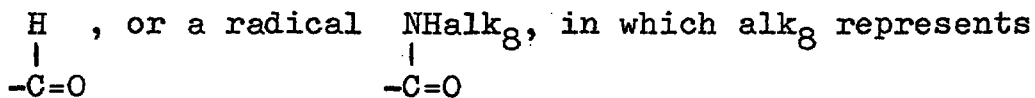


(28)

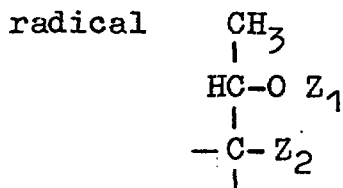
from 2 to 8 carbon atoms, an aryl radical containing
 from 6 to 14 carbon atoms or an aralkyl radical
 containing from 7 to 15 carbon atoms [and] R_6 , being
 the same as or different from R_5 , can take one of the
 5 values indicated for R_5 and can also represent a
 hydroxyl radical, [and] R_3 and R_4 , being the same or
 different, represent either a hydrogen atom or a radical
 OH, Oalk₄ [or] O-CO-alk₅, alk₄ and alk₅ representing an
 alkyl radical containing from 1 to 8 carbon atoms or
 10 [an] aralkyl [radical] containing from 7 to 15 carbon
 atoms, or an alkenyl or alkynyl radical containing from
 2 to 8 carbon atoms, or a radical



or a radical -COCH₂OCOalk₆, in which alk₆ represents an
 alkyl radical containing from 1 to 8 carbon atoms,
 15 possibly substituted, or an aralkyl radical containing
 from 7 to 15 carbon atoms, or a radical CO-CO₂H or
 CO-CO₂-alk₇ in which alk₇ represents an alkyl radical
 containing from 1 to 8 carbon atoms, or a radical



20 an alkyl radical containing from 1 to 8 carbon atoms
 or an aralkyl radical containing from 7 to 15 carbon
 atoms, or a radical -C≡N, or R_3 and R_4 together form a



in which Z_1 represents a hydrogen atom, an alkyl radical



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or an acyl radical containing from 1 to 8 carbon atoms and Z_2 [represents] an alkyl radical containing from 1 to 8 carbon atoms.

5 The compounds of formula (I'), as defined in Claim 4, for which the ring D does not bear any ethylenic unsaturation*, R_5 and R_6 represent a hydrogen atom and n is equal to 1.

6. The compounds of formula (I'), as defined in any one of Claims 1 to 5, for which C = A represents an oxo group,

10 7. The compounds of formula (I'), as defined in any one of Claims 1 to 6, for which R_1 represents a hydrocarbon radical containing from 1 to 8 carbon atoms and containing at least one nitrogen atom.

8. The compounds of formula (I'), as defined in Claim 7, for which R_1 represents a primary, secondary or tertiary alkyl radical containing from 1 to 8 carbon atoms, containing one or more heteroatoms selected from the group constituted by oxygen, nitrogen and sulphur, of which at least one [is] a nitrogen atom, or** substituted
20 by a heterocycle containing at least one nitrogen atom.

9. The compounds of formula (I'), as defined in Claim 7, for which R_1 represents a heterocyclic radical containing at least one nitrogen atom, possibly substituted by an alkyl radical containing from 1 to 8 carbon atoms.

25 10. The compounds of formula (I'), as defined in Claim 7, for which R_1 represents an aryl or aralkyl radical

Translator's notes: * The French "insaturatin" would appear to be a misprint for "insaturation"
= "unsaturation".

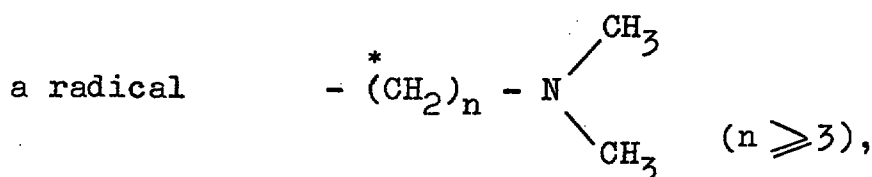
** The French "on" would appear to be a misprint for "ou"
= "or".



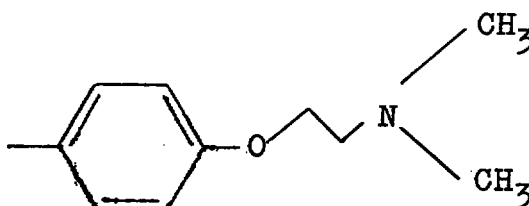
bearing an amine function $-N \begin{matrix} R_7 \\ R_8 \end{matrix}$, in which R_7 and R_8

represent an alkyl radical containing from 1 to 8 carbon atoms or a primary, secondary or tertiary alkyl radical containing from 1 to 8 carbon atoms, containing one or more heteroatoms selected from the group constituted by oxygen, nitrogen and sulphur, of which at least one [is] a nitrogen atom, or substituted by a heterocycle containing at least one nitrogen atom.

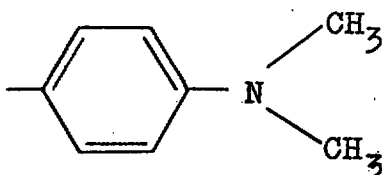
11. The compounds of formula (I'), as defined in any one of Claims 1 to 10, for which R_1 represents a 2-, 3- or 4-pyridyl radical,



a radical



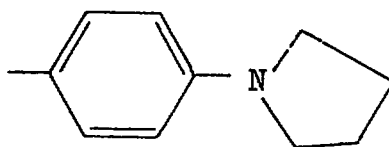
a radical



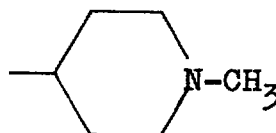
*Translator's note: It would appear that, in the French text, " $-(CH_2)_n$ " has been duplicated in error.



a radical



or a radical



12. The compounds of formula (I'), as defined in any one of Claims 1 to 11, in which R₁ contains an oxidized nitrogen atom.

13. Any one of the compounds of formula (I'), of which the names are as follows :

- 11β-[4-N,N-dimethylaminoethoxy) phenyl] 17β-hydroxy 17α-(prop-1-ynyl) estra 4,9-dien-3-one;

- 11β-(4-dimethylaminophenyl) 17β-hydroxy 17α-prop-1-ynyl) estra 4,9-dien-3-one;

- 21-chloro 17β-hydroxy 11β-(4-dimethylaminophenyl) (17α) 19-nor pregna 4,9-dien-20-yn-3-one N-oxide;

- 21-chloro 9α,10α-epoxy 17β-hydroxy 11β-(4-dimethylaminophenyl) (17α) 19-nor pregn-4,9-en-20-yn-3-one N-oxide;

- 17β-hydroxy 11β-(4-dimethylaminophenyl) 17α-(prop-2-ynyl) estra 4,9-dien-3-one [and]

- 17β-hydroxy 11β-(4-dimethylaminophenyl) 17α-(prop-1-ynyl) estra 4,9-dien-3-one N-oxide.

14. As medicaments, the pharmaceutically-acceptable compounds defined in any one of Claims 1 to 13, as well as their salts of addition with the pharmaceutically-acceptable acids.

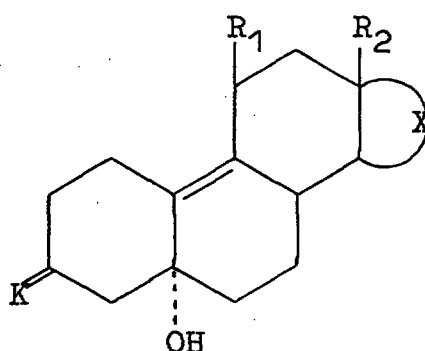


(132)

15. Pharmaceutical compositions containing, as active principle, at least one medicament defined in Claim 14.

16. Process for preparing the compounds of formula (I'), as defined in any one of Claims 1 to 13, characterized

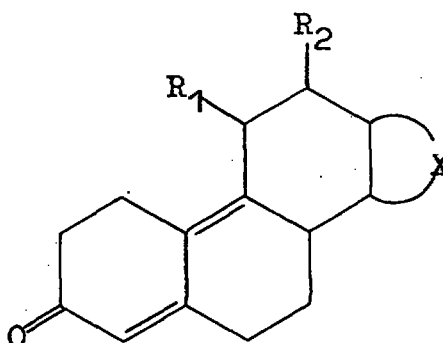
5 in that a compound of general formula (II) :



(II)

in which K represents a ketone group blocked in [the] form of [a] ketal, thioketal, oxime or methyloxime, [and] R_1 , R_2 and X keep the same meaning as in Claim 1,

10 is subjected to the action of a dehydrating agent capable of releasing the ketone function, to obtain a compound of formula (I'_A) :



(I'_A)

which is subjected, if necessary,

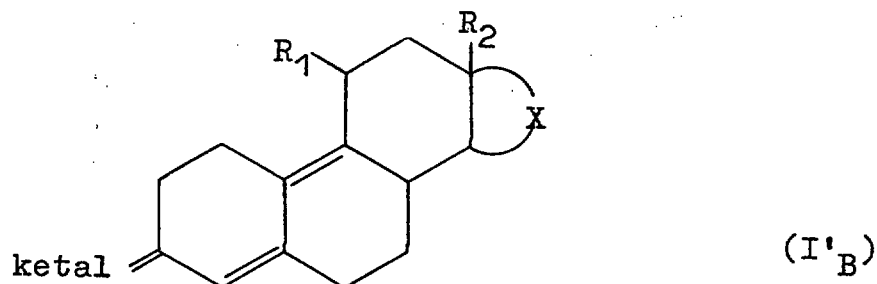
* either to the action of a ketalizing agent to obtain

*Translator's note: The French "sont" would appear to be a misprint for "soit" = "either".

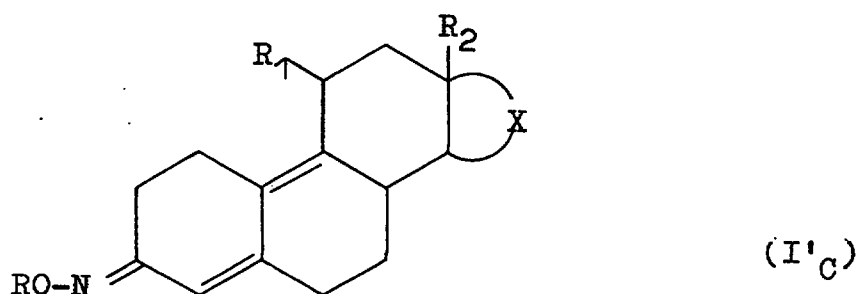


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the compound of formula (I'_B) in which the ketone function at [position] 3 is blocked in ketal form :



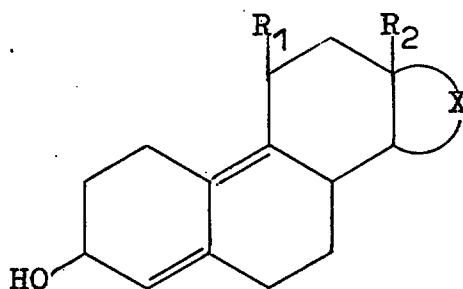
5 or to the action of the free hydroxylamine NH_2OH or [the hydroxylamine] blocked in the form [of] $\text{NH}_2\text{O-alk}_3$ in which alk_3 keeps its meaning of Claim 1, to obtain the compound of formula (I'_C) :



10 in which R represents a hydrogen atom or a group alk_3 , or to the action of a reducing agent capable of reducing selectively the ketone function to obtain the compound of formula (I'_D) :

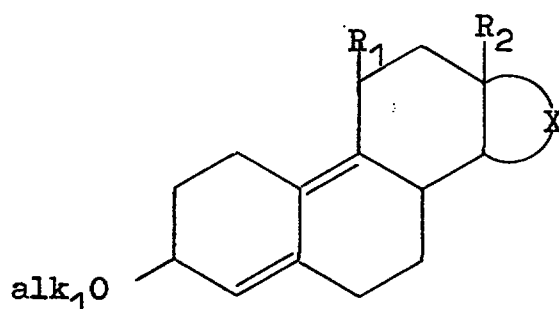


(3)



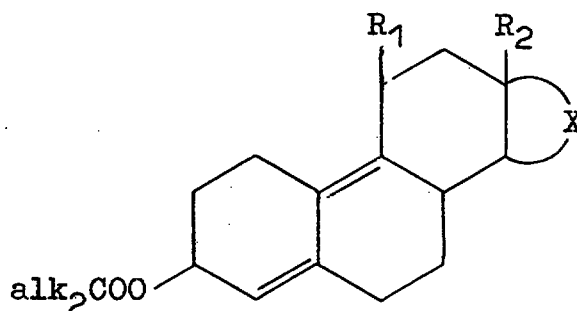
(I'D)

which is subjected, if necessary, either to the action of an etherifying agent capable of introducing the radical alk_1 to obtain a compound of formula (I'E) :



(I'E)

5 or to the action of an esterifying agent capable of introducing the group CO alk_2 in which alk_2 keeps the meaning of Claim 1, to obtain a compound of formula (I'F) :





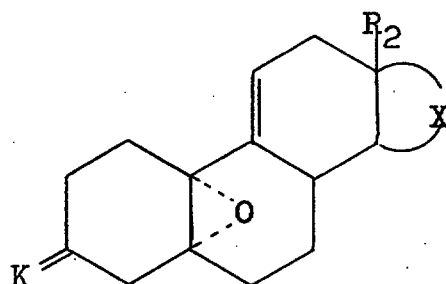
(135)

- or which compound of formula (I'_A) is converted, if necessary, according to known methods, into a derivative for which C=A represents a group CH₂ and which compound of formula (I'_A), (I'_B), (I'_C), (I'_D), (I'_E) or (I'_F), if necessary, is subjected to the action of an acid to obtain a salt, or to the action of an oxidizing agent to obtain either, if the radical R₁ contains a nitrogen atom, a derivative containing at [position] 11β a radical of which the nitrogen atom is oxidized and in which the radicals B and C form possibly an epoxide bridge, or, if the radical R₁ does not contain a nitrogen atom, a derivative in which the radicals B and C form an epoxide bridge, and in which compound at the same time the radical R₁ contains an oxidized nitrogen atom and B and C together form an epoxide bridge which, if necessary, is reduced selectively at the level of the oxidized nitrogen atom contained in the radical R₁ and which, if necessary, is subjected to the action of an acid to obtain a salt.
17. Preparation process according to Claim 16, characterized in that the starting compound used is a compound in which X is defined as in Claim 4.
18. Process according to Claim 16 or 17, characterized in that the starting product of formula (II) is prepared by subjecting a compound of formula (III) :

*Translator's note: The French "aome" would appear to be a misprint for "atome".



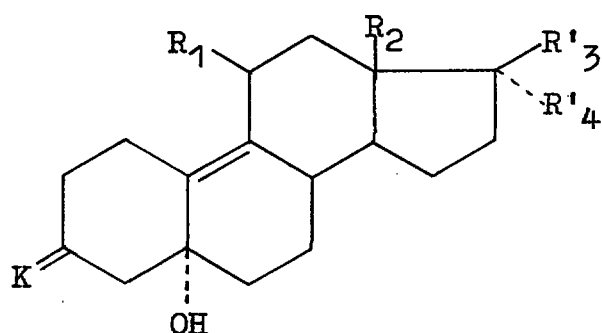
(136)



(III)

to the action of a compound selected from the group constituted by the compounds of formula $(R_1)_2CuLi$, of formula R_1MgHal and of formula R_1Li , in which R_1 keeps the same meaning as in Claim 1 and Hal represents a halogen atom, if necessary in the presence of copper halide, to obtain the corresponding compound of formula (II).

19. Process according to Claim 16 or 17, characterized in that the starting product, corresponding to the formula (II') :



(II')

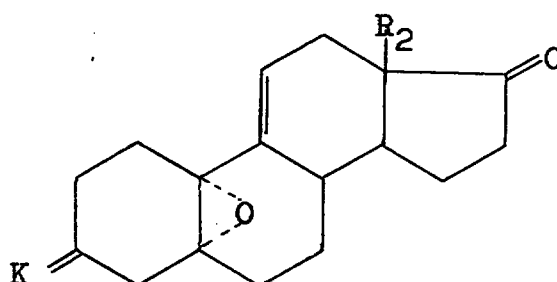
in which R_1 , R_2 and K are defined as in Claim 16, R'_3 represents a hydroxy radical or a radical OR_e , in which R_e represents the residue alk_4 of an ether group or



(37)

COalk₅ of an ester group, alk₄ and alk₅ being defined as in Claim 4 and R'₄ represents a hydrogen atom or an alkenyl or alkynyl radical containing from 2 to 8 carbon atoms, is prepared by subjecting a compound of

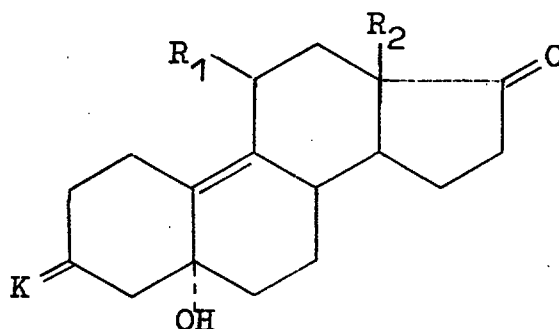
5 formula (IV) :



(IV)

to the action of a compound selected from the group constituted by the compounds of formula (R₁)₂CuLi, of formula R₁MgHal and of formula R₁Li, in which R₁ and Hal are defined as in Claim 18, if necessary in the presence of copper halide, to obtain the compound of formula (V) :

10



(V)

which is subjected either to the action of a reducing agent, to obtain the corresponding 17-hydroxy compound,



or to the action of an appropriate magnesium derivative,
to obtain the corresponding 17β -hydroxy 17α -substituted
compound, or to the action of an organometallic derivative
such as a lithium derivative or a potassium derivative,
5 to obtain the corresponding 17β -hydroxy 17α -substituted
compound, or to the action of a cyaniding agent, to
obtain the corresponding 17β -cyano 17α -hydroxy compound,
of which the hydroxy function is protected, then to the
action of an organometallic derivative as described
10 before, to obtain the corresponding 17β -hydroxy
 17α -substituted compound, and in that, if necessary,
one or other of the 17-hydroxy compounds obtained above
is subjected to the action of an esterifying or
etherifying agent and in that, if necessary, one or
15 other of the 17-substituted compounds obtained above,
in which the substituent at [position] 17 contains a
triple bond, is subjected to the action of a reducing
agent, to obtain the corresponding ethylenic [compound].

