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(54) Title: NOVEL 4- HALOGENATED STEROIDS, PREPARATION METHOD AND INTERMEDIATES, APPLICATION AS MEDICINES AND PHARMACEUTICAL COMPOSITIONS CONTAINING SAME

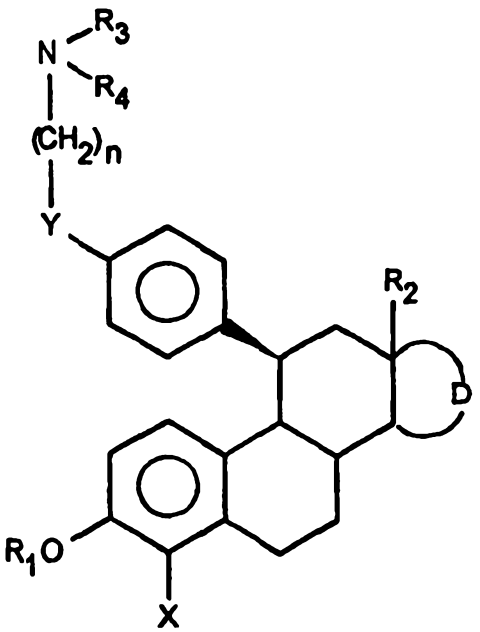
(54) Titre: NOUVEAUX STEROIDES 4-HALOGENES, LEUR PROCEDE ET INTERMEDIAIRES DE PREPARATION, LEUR APPLICATION COMME MEDICAMENTS ET LES COMPOSITIONS PHARMACEUTIQUES LES RENFERMANT

(57) Abstract

The invention concerns compounds of formula (I) in which X is a halogen atom; D represents the residue of a pentagonal or hexagonal cycle, optionally substituted and optionally unsaturated; R_1, R_2, R_3, R_4, Y and n are such as defined in the description. The invention also concerns the preparation method and intermediates thereof, their application as medicine and the pharmaceutical compositions containing them.

(57) Abrégé

L'invention a pour objet les composés de formule (I) dans laquelle X est un atome d'halogène, D représente le reste d'un cycle pentagonal ou hexagonal éventuellement substitué et éventuellement porteur d'insaturation, R_1, R_2, R_3, R_4, y et n sont tels que définis dans la description, leur procédé et intermédiaire de préparation, leur application comme médicament et les compositions pharmaceutiques les renfermant.



(I)

Novel 4-halogenated steroids, process and intermediates for their preparation, their use as medicinal products, and pharmaceutical compositions containing them.

The present invention relates to 4-halogenated steroid compounds, to a process for their preparation, to their use as medicinal products, and to pharmaceutical compositions containing them.

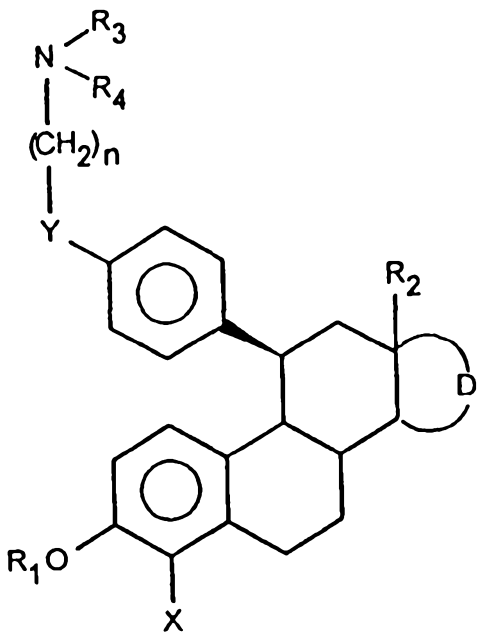
Osteoporosis is a pathology which is characterized by a quantitative and qualitative reduction in bone tissue which is sufficient to result in vertebral or peripheral fractures, either spontaneously or in the event of a minor trauma. Although this complaint has many causal factors, it is the menopause which, in women, is the predominant factor in bone loss or osteopaenia.

This osteopaenia manifests itself by a rarefaction and modification of the architecture of the spongy bone, the consequence of which is to accentuate the fragility of the skeleton and the risk of fractures. Bone loss increases greatly after the menopause, on account of the suppression of ovarian function, and reaches 3 to 5% per year, then slows down after the age of 65.

For therapeutic purposes, post-menopausal hormone deficiency can be compensated by a hormone replacement therapy in which oestrogen plays a major role in preserving the bone mass. However, long-term oestrogen therapy is occasionally accompanied by an undesirable effect on the genital apparatus (endometrial hyperplasia, breast tumour, etc.), which constitutes a major drawback and limits its use.

It is thus desired to find compounds other than oestradiol which have dissociated oestrogen activity, i.e. oestrogen activity on the bones, while at the same time exhibiting little or no endometrial hyperplasia or breast tumour proliferation activity.

The invention thus relates to the compounds of the general formula (I):



(I)

in which:

R_1 represents a hydrogen atom, a $(CH_2)_m$-Ar, (CO)—Ar, $(CH_2)_m$-Alk or (CO)-Alk radical,

R_2 represents a linear or branched, saturated or unsaturated hydrocarbon radical containing 1 to 6 carbon atoms,

D represents a residue of an optionally substituted pentagonal or hexagonal ring optionally bearing an unsaturation,

X represents a halogen atom,

Y is chosen from 0, S, SO, SO_2 and NH,

n is an integer varying from 2 to 8,

either R_3 and R_4, which may be identical or different, represent a hydrogen atom, a $(CH_2)_m$-Ar, $(CH_2)_m$-Het or $(CH_2)_m$Alk group,

or R_3 and R_4 together with the nitrogen atom to which they are attached, form a 3- to 15-membered aromatic or non-aromatic, saturated or unsaturated, monocyclic or polycyclic heterocycle optionally containing 1 to 3 additional heteroatoms chosen from oxygen, sulphur and nitrogen, which is unsubstituted or substituted,

Ar representing a carbocyclic aryl group containing from 6 to 18 carbon atoms, Het representing a saturated or unsaturated aromatic or non-aromatic heterocycle radical

containing from 1 to 9 carbon atoms and from 1 to 5 heteroatoms chosen from oxygen, nitrogen or sulphur atoms, Alk representing a saturated or unsaturated, linear, branched or cyclic, non-aromatic hydrocarbon radical and containing from 1 to 12 carbon atoms, the Ar, Het or Alk radicals being able to be substituted or non-substituted, and m represents 0, 1; 2 or 3, as well as their addition salts with bases or acids.

By the term "halogen" is meant: iodine, bromine, chlorine or fluorine.

By the term "$(CH_2)_m$" is meant the following values: single bond where m is equal to 0, CH_2, $(CH_2)_2$ and $(CH_2)_3$.

The expression "Ar representing the carbocyclic aryl group containing from 6 to 18 carbon atoms" means a cyclic aromatic hydrocarbon derivative, such as the phenyl, naphthyl, phenanthrenyl radical, or alternatively a fused bicyclic or tricyclic hydrocarbon comprising a benzene ring such as indanyl, indenyl, dihydronaphthyl, tetrahydronaphthyl or fluorenyl. The junction is made on the benzene ring. It is preferably phenyl.

The expression "(Het) representing a radical derived from a saturated or unsaturated, aromatic or non-aromatic heterocycle containing from 1 to 9 carbon atoms and from 1 to 5 heteroatoms chosen from oxygen, nitrogen and sulphur atoms", denotes, in particular:

- monocyclic heterocyclic radicals, for example thienyl, furyl, pyranyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, thiazolyl, oxazolyl, furazanyl, pyrrolinyl, imidazolinyl, pyrazolinyl, thiazolinyl, triazolyl and tetrazolyl radicals,
- fused heterocyclic rings, for example benzofuranyl, benzothienyl, benzimidazolyl, benzothiazolyl, naphtho[2, 3-b] thienyl, thianthrenyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathiinyl, indolizinyl, isoindolyl, 3H-indolyl, indolyl, indazolyl, purinyl, quinolizinyl,

isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, carbazolyl, beta-carbolinyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, indolinyl, isoindolinyl, imidazopyridyl or imidazopyrimidinyl, or alternatively fused polycyclic systems consisting of heterocyclic monocyclics as defined above, such as, for example, furo[2,3-b]pyrrole or thieno[2,3-b]furan,

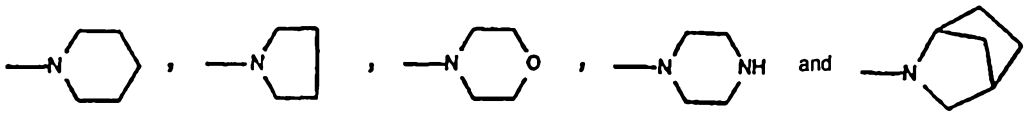
- or saturated heterocycles such as pyrrolidine, piperidine or morpholine.

The expression "(Alk) representing a radical derived from a linear, branched or cyclic, saturated or unsaturated non-aromatic hydrocarbon" means, in the case of acyclic hydrocarbons, alkyl radicals, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, n-pentyl, n-hexyl, 2-methylpentyl, 2,3-dimethylbutyl, n-heptyl, 2-methylhexyl, 2,2-dimethylpentyl, 3,3-dimethylpentyl, 3-ethylpentyl, n-octyl, 2,2-dimethylhexyl, 3,3-dimethylhexyl, 3-methyl-3-ethylpentyl, nonyl, 2,4-dimethylheptyl or n-decyl, alkenyl radicals, such as vinyl, propenyl, isopropenyl, allyl, 2-methylallyl, butenyl or isobutenyl, or alkynyl radicals, such as ethynyl, propynyl, propargyl, butynyl or isobutynyl, and, in the case of cyclic radicals, cycloalkyl radicals, such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

They are preferably methyl or ethyl radicals. The term "CO-Alk" preferably means $COCH_3$ and COEt, the term "CO-Ar" preferably means the benzoyl radical, when m is other than zero, and $(CH_2)_m$-Ar will preferably be a benzyl group.

When R_3 and R_4 form a heterocycle together with the nitrogen atom to which they are attached, these are in particular monocyclic or bicyclic heterocycles optionally containing another hetero atom chosen from oxygen and nitrogen, such as the following unsaturated heterocycles: pyrrolyl, imidazolyl, indolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, thiazolyl, oxazolyl, furazolinyl,

pyrazolinyl or thiazolinyl, or, more particularly, the following saturated heterocycles:



When the various groups Alk, Ar and Het, as well as the residue of a pentagonal or hexagonal ring mentioned above, are substituted, they can be substituted in particular by the following radicals:

- halogen, namely fluorine, chlorine, bromine or iodine, alkoxy, such as methoxy, ethoxy, propoxy, isopropoxy or butoxy, alkylthio, such as methylthio, ethylthio, propylthio, isopropylthio or butylthio, amino, alkylamino, such as methylamino or ethylamino, dialkylamino, such as dimethylamino, diethylamino or methylethylamino, each of these dialkylamino radicals optionally being in oxidized form, aminoalkyl, such as aminomethyl or aminoethyl, dialkylaminoalkyl, such as dimethylaminomethyl or dimethylaminoethyl, dialkylaminoalkyloxy, such as dimethylaminoethyloxy, optionally acylated hydroxyl, acyl, such as acetyl, propionyl, butyryl, benzoyl, free carboxyl, esterified carboxyl, such as alkoxycarbonyl, for example methoxycarbonyl or ethoxycarbonyl, cyano, trifluoromethyl, aryl, such as phenyl, aralkyl, such as benzyl, alkyl, alkenyl or alkynyl, these radicals themselves being optionally substituted by the halogen, alkyl, alkoxy, alkylthio, aminoalkyl or dialkylamino radicals indicated above.

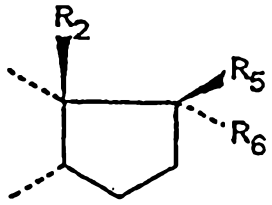
Needless to say, the expression "substituted" indicates the presence of one or more substituents, which may be identical or different. In the case of (Het), the substituents can be on the NH or on a carbon atom.

Needless to say, the values of R_1, R_2, R_3 and R_4 are independent of one another.

The invention naturally covers the salts of the compounds of the formula (I), such as, for example, the

salts formed with inorganic or organic acids on the amine. In this case, they can be hydrochloric acid, hydrobromic acid, nitric acid, sulphuric acid, phosphoric acid, acetic acid, formic acid, propionic acid, benzoic acid, maleic acid, fumaric acid, succinic acid, tartaric acid, citric acid, oxalic acid, glyoxylic acid, aspartic acid, alkanesulphonic acids, such as methanesulphonic acid or ethanesulphonic acid, arylsulphonic acids, such as benzenesulphonic acid or para-toluenesulphonic acid, and arylcarboxylic acids. When the compounds of the formula (I) comprise an acid function, the invention covers the alkali metal, alkaline-earth metal and optionally substituted ammonium salts.

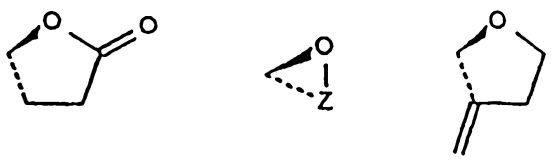
The invention more particularly relates to the compounds of the general formula (I) as defined above in which (D) represents a residue of a pentagonal ring of the formula:



in which R_2 has the same meaning as above,

either R_5 represents an OH, $O-(CH_2)_m-Alk$, $O-(CO)-Alk$, $O-(CH_2)_m-Ar$, $O-(CO)-Ar$, $O-(CH_2)_m-Het$ or $O-(CO)-Het$ radical and R_6 represents a hydrogen atom or a substituted or unsubstituted alkyl, alkenyl or alkynyl radical containing from 1 to 6 carbon atoms, m, Alk, Ar and Het being as defined above,

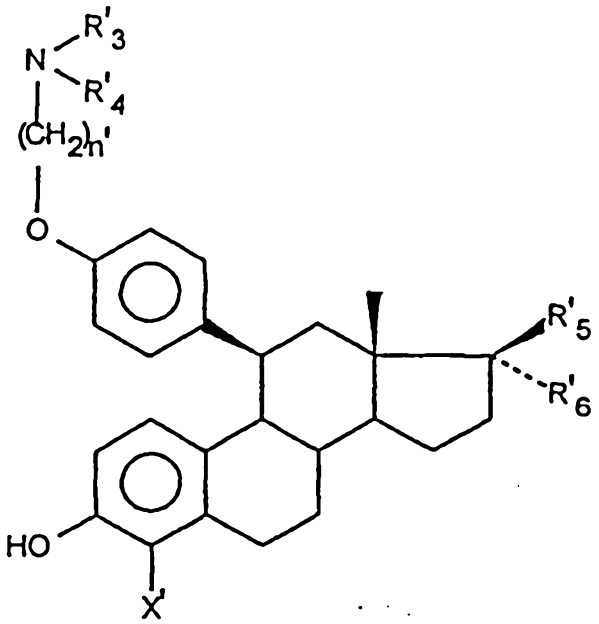
or R_5 and R_6, together with the carbon atom which bears them, form one of the following rings:



in which z represents a $-(CH_2)_l-$ or $-CH=CH-(CH_2)_{l'}$ group; l being an integer between 1 and 4 and l' being an integer equal to 1 or 2,

or R_5 and R_6 together form an oxo group or $=N-OH$, and the addition salts thereof with acids or bases.

The invention most particularly relates to the compounds of the formula (I) as defined above which correspond to the general formula (I'):



(I')

in which:

X' represents a chlorine or bromine atom,

n' is between 2 and 5,

either R'_3 and R'_4, which may be identical or different, represent an alkyl radical containing from 1 to 6 carbon atoms

or R'_3 and R'_4, together with the nitrogen atom to which they are attached, form a 3- to 15-membered saturated monocyclic or polycyclic residue optionally containing an additional hetero atom chosen from oxygen, sulphur and nitrogen,

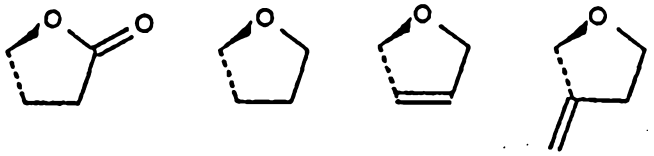
R'_5 and R'_6 are as defined for R_5 and R_6,

and the addition salts thereof with acids and bases.

The invention most particularly relates to the compounds of the formula (I) as defined above which correspond to the general formula (I') in which:

either R'_5 represents an OH radical and R'_6 represents a hydrogen atom or a substituted or unsubstituted alkyl, alkenyl or alkynyl radical containing from 1 to 6 carbon atoms,

or R'_5 and R'_6, together with the carbon atom which bears them, form one of the following rings:



or R'_5 and R'_6 together form an oxo group,

and the addition salts thereof with acids or bases.

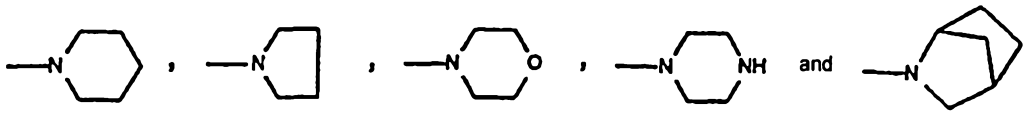
The invention most particularly relates to the compounds of the formula (I) which correspond to the general formula (I') as defined above, in which:

X' represents a chlorine atom

n' is equal to 2,

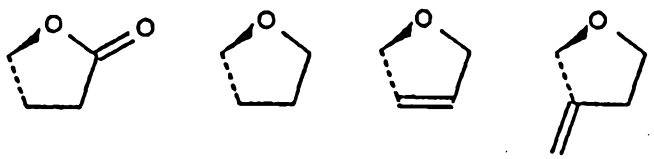
either R'_3 and R'_4, which may be identical or different, represent an alkyl radical containing from 1 to 6 carbon atoms

or R'_3 and R'_4, together with the nitrogen atom, form the following saturated heterocycles:



and either R'_5 represents an OH radical and R'_6 represents a hydrogen atom or a substituted or unsubstituted alkyl, alkenyl or alkynyl radical containing from 1 to 6 carbon atoms,

or R'_5 and R'_6, together with the carbon atom which bears them, form one of the following rings:



or R'_5 and R'_6 together form an oxo group,

and the addition salts thereof with acids or bases.

The invention most particularly relates to the compounds of the formula (I) and the addition salts thereof with acids, of the following names:

- 4-chloro-3-hydroxy-11β-[4-[2-(diethylamino)ethoxy]-phenyl]oestra-1,3,5(10)-trien-17-one,
- 4-chloro-3-hydroxy-11β-[4-[2-(dimethylamino)ethoxy]-phenyl]oestra-1,3,5(10)-trien-17-one,
- 4-chloro-3-hydroxy-11β-[4-[2-(1-piperidyl)ethoxy]-phenyl]oestra-1,3,5(10)-trien-17-one,
- 4-chloro-3-hydroxy-11β-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]oestra-1,3,5(10)-trien-17-one,
- 4-bromo-3-hydroxy-11β-[4-[2-(1-piperidyl)ethoxy]-phenyl]oestra-1,3,5(10)-trien-17-one,
- 4-chloro-11β-[4-[2-(dimethylamino)ethoxy]phenyl]-oestra-1,3,5(10)-triene-3,17beta-diol,
- 4-chloro-11β-[4-[2-(diethylamino)ethoxy]phenyl]-oestra-1,3,5(10)-triene-3,17beta-diol,
- 4-chloro-11β-[4-[2-(1-piperidyl)ethoxy]phenyl]-oestra-1,3,5(10)-triene-3,17beta-diol,
- 4-bromo-11β-[4-[2-(1-piperidyl)ethoxy]phenyl]oestra-1,3,5(10)-triene-3,17beta-diol,
- 4-chloro-11β-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]-oestra-1,3,5(10)-triene-3,17beta-diol,
- 4-chloro-11β-[4-[2-(diethylamino)ethoxy]phenyl]-19-nor-17alpha-pregna-1,3,5(10)-trien-20-yne-3,17beta-diol,
- 4-chloro-11β-[4-[3-(1-piperidyl)propoxy]phenyl]-oestra-1,3,5(10)-triene-3,17beta-diol,
- 4-chloro-11β-[4-[4-(1-piperidyl)butoxy]phenyl]-oestra-1,3,5(10)-triene-3,17beta-diol,
- 4-chloro-11β-[4-[5-(1-piperidyl)pentyloxy]phenyl]-oestra-1,3,5(10)-triene-3,17beta-diol,
- gamma lactone of (17alpha)-4-chloro-3,17beta-dihydroxy-11β-[4-[2-(diethylamino)ethoxy]phenyl]-19-nor-pregna-1,3,5(10)-triene-21-carboxylic acid,

- gamma lactone of (17alpha)-4-chloro-3,17beta-dihydroxy-11β-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]-19-nor-pregna-1,3,5(10)-triene-21-carboxylic acid,

- gamma lactone of (17alpha)-4-chloro-3,17beta-dihydroxy-11β-[4-[2-(1-piperidyl)ethoxy]phenyl]-19-nor-pregna-1,3,5(10)-triene-21-carboxylic acid,

- gamma lactone of (17alpha)-4-chloro-3,17beta-dihydroxy-11β-[4-[3-(1-piperidyl)propoxy]phenyl]-19-nor-pregna-1,3,5(10)-triene-21-carboxylic acid,

- gamma lactone of (17alpha)-4-chloro-3,17beta-dihydroxy-11β-[4-[4-(1-piperidyl)butoxy]phenyl]-19-nor-pregna-1,3,5(10)-triene-21-carboxylic acid,

- gamma lactone of (17alpha)-4-chloro-3,17beta-dihydroxy-11β-[4-[5-(1-piperidyl)pentyloxy]phenyl]-19-nor-pregna-1,3,5(10)-triene-21-carboxylic acid,

- (17beta)-4-chloro-11β-[4-[2-(diethylamino)ethoxy]-phenyl]spiro[oestra-1,3,5(10)-triene-17,2'(5'H)furan]-3-ol,

- (17beta)-4-chloro-11β-[4-[2-(1-piperidyl)ethoxy]-phenyl]spiro[oestra-1,3,5(10)-triene-17,2'(5'H)furan]-3-ol,

- (17beta)-4-chloro-11β-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]spiro[oestra-1,3,5(10)-triene-17,2'(5'H)furan]-3-ol,

- (17beta)-4-chloro-4',5'-dihydro-11β-[4-[2-(1-piperidyl)ethoxy]phenyl]spiro[oestra-1,3,5(10)-triene-17,2'(3'H)furan]-3-ol,

- (17beta)-4-chloro-11β-[4-[3-(1-piperidyl)propoxy]-phenyl]spiro[oestra-1,3,5(10)-triene-17,2'(5'H)furan]-3-ol,

- (17beta)-4-chloro-4',5'-dihydro-11β-[4-[3-(1-piperidyl)propoxy]phenyl]spiro[oestra-1,3,5(10)-triene-17,2'(3'H)furan]-3-ol,

- (17beta)-4-chloro-11β-[4-[4-(1-piperidyl)butoxy]-phenyl]spiro[oestra-1,3,5(10)-triene-17,2'(5'H)furan]-3-ol,

- (17beta)-4-chloro-4',5'-dihydro-11β-[4-[4-(1-piperidyl)butoxy]phenyl]spiro[oestra-1,3,5(10)-triene-17,2'(3'H)furan]-3-ol,

- 4-chloro-11β-[4-[2-(diethylamino)ethoxy]phenyl]-17alpha-methyloestra-1,3,5(10)-triene-3,17beta-diol,

- 4-chloro-17alpha-methyl-11β-[4-[2-(1-piperidyl)-ethoxy]-phenyl]oestra-1,3,5(10)-triene-3,17beta-diol,

- 4-chloro-17alpha-methyl-11β-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]oestra-1,3,5(10)-triene-3,17beta-diol,

- 11β-[4-[2-[2-azabicyclo(2.2.1)hept-2-yl]ethoxy]phenyl]-4-chloro-17alpha-methyloestra-1,3,5(10)-triene-3,17beta-diol,

- 11β-[4-[2-[2-azabicyclo(2.2.1)hept-2-yl]ethoxy]phenyl]-4-chlorooestra-1,3,5(10)-triene-3,17beta-diol,

- 4-chloro-11β-[4-[2-[methyl(1-methylethyl)amino]-ethoxy]-phenyl]oestra-1,3,5(10)-triene-3,17beta-diol,

- 4-chloro-11β-[4-[2-(tetrahydro-(1H)-1,4-thiazin-4-yl)ethoxy]phenyl]oestra-1,3,5(10)-triene-3,17beta-diol,

- 4-chloro-11β-[4-[2-[ethyl(propyl)amino]ethoxy]-phenyl]oestra-1,3,5(10)-triene-3,17beta-diol,

- 4-chloro-11β-[4-[2-[ethyl(methyl)amino]ethoxy]-phenyl]oestra-1,3,5(10)-triene-3,17beta-diol,

- 4-chloro-11β-[4-[2-[(1,1-dimethyl-2-propynyl)amino]-ethoxy]phenyl]oestra-1,3,5(10)-triene-3,17beta-diol,

- 4-chloro-11β-[4-[2-[hexahydro-1H-azepin-1-yl)ethoxy]-phenyl]oestra-1,3,5(10)-triene-3,17beta-diol,

- 4-chloro-11β-[4-[2-[cyclohexyl(methyl)amino]ethoxy]-phenyl]oestra-1,3,5(10)-triene-3,17beta-diol,

- 4-chloro-11β-[4-[2-[butyl(ethyl)amino]ethoxy]-phenyl]oestra-1,3,5(10)-triene-3,17beta-diol,

- 4-chloro-11β-[4-[2-(1-azetidinyl)ethoxy]phenyl]oestra-1,3,5(10)-triene-3,17beta-diol,

- 4-chloro-11β-[4-[2-[ethyl(2-propenyl)amino]ethoxy]-phenyl]oestra-1,3,5(10)-triene-3,17beta-diol,

- 4-chloro-11β-[4-[2-[cyclopentyl(methyl)amino]ethoxy]-phenyl]oestra-1,3,5(10)-triene-3,17beta-diol,

- 4-chloro-11β-[4-[2-(dipropylamino)ethoxy]phenyl]-oestra-1,3,5(10)-triene-3,17beta-diol,

- 4-chloro-11β-[4-[2-(3-thiazolidinyl)ethoxy]phenyl]-oestra-1,3,5(10)-triene-3,17beta-diol,

- 4-chloro-11β-[4-[2-[ethyl(1-methylethyl)amino]-ethoxy]-phenyl]oestra-1,3,5(10)-triene-3,17beta-diol,

- 4-chloro-11β-[4-[2-[methyl(propyl)amino]ethoxy]-phenyl]oestra-1,3,5(10)-triene-3,17beta-diol,

- 4-chloro-11β-[4-[2-[butyl(methyl)amino]ethoxy]-phenyl]oestra-1,3,5(10)-triene-3,17beta-diol,

- 4-chloro-11β-[4-[2-[methyl(2-propynyl)amino]ethoxy]-phenyl]oestra-1,3,5(10)-triene-3,17beta-diol,

- 4-chloro-11β-[4-[2-(4-methyl-1-piperidyl)ethoxy]-phenyl]oestra-1,3,5(10)-triene-3,17beta-diol,

- 4-chloro-11β-[4-[2-(1-piperidyl)ethylthio]phenyl]-oestra-1,3,5(10)-triene-3,17beta-diol,

- 4-chloro-11β-[4-[2-(1-piperidyl)ethylsulphinyl]-phenyl]oestra-1,3,5(10)-triene-3,17beta-diol,

- 4-[4-chloro-11beta-[4-[2-(diethylamino)ethoxy]-phenyl]-17beta-hydroxyoestra-1,3,5(10)-trien-3-yloxy]butanoic acid,

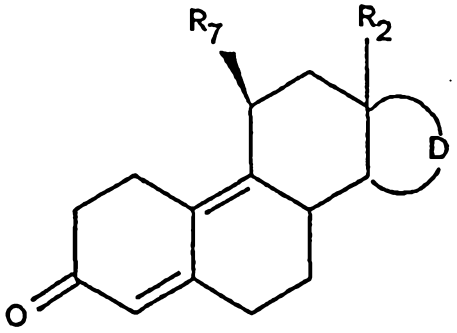
- 4-chloro-3-hydroxy-11beta-[4-[2-(1-piperidyl)ethoxy]-phenyl]oestra-1,3,5(10)-trien-17-one oxime,

- 4-[[2-[4-(4-chloro-3,17beta-dihydroxyoestra-1,3,5(10)-trien-11beta-yl)phenoxy]ethyl]ethylamino]-butanoic acid.

The invention also most particularly relates to the compound of the formula (I) as defined above, of the following name:

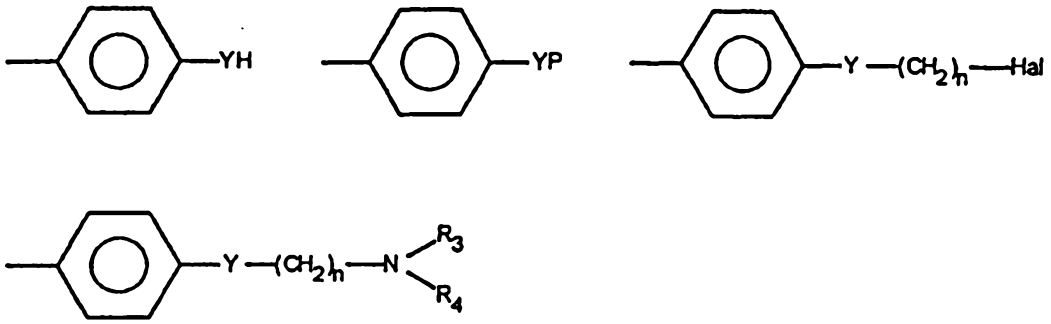
- 4-chloro-11β-[4-[2-(diethylamino)ethoxy]phenyl]-oestra-1,3,5(10)-triene-3,17beta-diol, and the addition salts thereof with acids.

The invention also relates to a process for preparing the compounds of the general formula (I) as defined above, characterized in that a compound of the general formula (II):

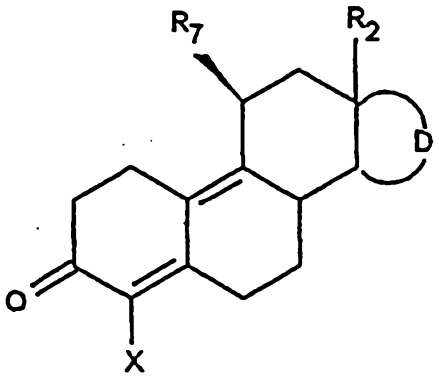


(II)

in which D and R_2 are as defined above, R_7 represents one of the following groups:

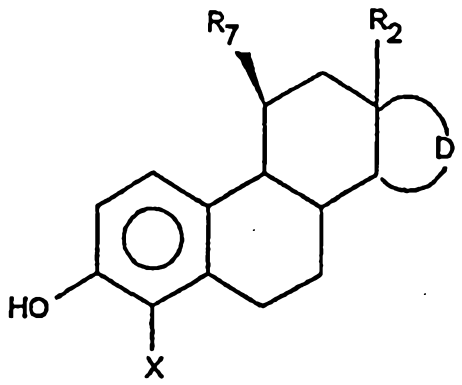


in which n, Y, R_3 and R_4 are as defined above, P is a protecting group and Hal represents a halogen,
is subjected to the action of a halogenating reagent in order to obtain the compound of the formula (III):



(III)

which is subjected to the action of a reagent for aromatizing the ring A, followed by the action of a base in order to obtain the compound of the formula (IV) corresponding to certain compounds of the general formula (I):



(IV)

which compounds of the formula (II), (III) or (IV) are subjected, if so desired and if necessary, in an appropriate order, to one or more of the following reactions:

- protection of the compounds in which R_7 is a -Ph-YH group,
- deprotection of the compounds in which R_7 is a Ph-YP group,
- action of a compound of the formula $Hal_1-(CH_2)_n-Hal_2$ on compounds in which R_7 is a-Ph-YH group, Hal_1 or Hal_2, which may be identical or different, representing a halogen, in order to obtain compounds in which R_7 is a-Ph-Y-$(CH_2)_n$-Hal_2 group,
- action of a compound of the formula R_3-NH-R_4 on compounds in which R_7 is a Ph-Y-$(CH_2)_n$-Hal_2 group in order to obtain compounds in which R_7 is a Ph-Y-$(CH_2)_n$-NR_3R_4 group,
- action of a halide salt ($M-Hal_3$) on compounds in which R_7 is a Ph-Y-$(CH_2)_n$-Hal_2 group in order to obtain compounds in which R_7 is a-Ph-Y-$(CH_2)_n$-Hal_3 group,
- protection of the OH group in position 3 or 17,
- deprotection of the OH group in position 3 or 17,
- alkylation of the OH group in position 3 or 17,
- acylation of the OH group in position 3 or 17,
- action of a reducing agent when D represents a residue of a pentagonal ring as defined above and R_5 and R_6 together form an oxo group,
- action of an organometallic reagent on the compounds of the formula (IV) with D representing a residue of a

pentagonal ring as defined above and R_5 and R_6 together forming an oxo group,

- action of a lactonizing agent on the compounds of the formula (IV) with D representing a residue of a pentagonal ring as defined above and R_5 and R_6 together forming an oxo group,

- action of an agent for reducing the double bond when D represents a residue of a pentagonal ring as defined above and R_5 and R_6, together with the carbon which bears them, form a group $O-(CH_2)_{n'}-CH=CH-$,

- action of an agent for reducing the double bond when D represents a residue of a pentagonal ring as defined above and R_6 is an alkenyl or alkynyl radical containing from 2 to 6 carbon atoms,

- halogenation in position 4, followed by aromatization of ring A, of the compound of the general formula (II),

- aromatization of ring A of the compound of the formula (III),

- salification.

The action of a halogenating reagent, such as N-bromosuccinimide or N-chlorosuccinimide, on the compounds of the formula (II) is carried out in particular in the presence of a dipolar aprotic solvent, such as dimethylformamide.

The aromatization reaction followed by the saponification reaction (action of the base) is carried out according to the standard methods as described in European Patent 0 097 572. A mixture of acetic anhydride and acetyl bromide is preferably used as aromatizing agent, and a base, such as sodium hydroxide in methanol, is then preferably used as saponifying agent.

The protection and deprotection reactions are the standard methods known to persons skilled in the art. A fairly thorough review is found in the following book: Protective Groups in Organic Synthesis, T.W. Greene, John Wiley & Sons (1981).

The protecting group P preferably represents an alkyl radical containing from 1 to 4 carbon atoms, a benzyl group, an $R_CR_DR_ESi$ group, in which R_C, R_D and R_E, which may be identical or different, each represent, independently of each other, an alkyl radical containing from 1 to 4 carbon atoms or a phenyl group. They are most particularly $Si(Me)_2CMe_3$ or $-Si(Ph)_2CMe_3$.

By way of example, the deprotection reactions of the compounds of the formula (II), (III) or (IV) with R_7 = Ph-OP or of the compounds of the formula (IV) in which the 3-OH is protected (3-OP), can be carried out when P is a methyl radical, by the action of tribromoborane in dichloromethane or of hydrochloric acid in pyridine, the deprotection reactions when P is a benzyl group can be carried out by the action of hydrogen in the presence of palladium-on-charcoal in ethyl acetate or by the action of trifluoroacetic acid, and the deprotection reactions when P is a tert-butyldiphenylsilyl group can be carried out by the action of tetrabutylammonium fluoride dissolved in tetrahydrofuran.

When P is a tetrahydropyranyl group, the deprotection is carried out in the presence of an aqueous acid in an alcoholic solvent and preferably by the action of hydrochloric acid in methanol.

The action of a compound of the formula $Hal_1-(CH_2)_n-Hal_2$ on a compound of the formula (II), (III) or (IV) in which R_7 = Ph-YH can be carried out, in particular when Y = O, in the presence of a base in a solvent, such as acetone.

The action of a compound of the formula R_3-NH-R_4 on the compounds in which R_7 is a $Ph-Y-(CH_2)_n-Hal_2$ group [lacuna] under the standard conditions for nucleophilic substitutions, in particular in the presence of an aprotic solvent, such as tetrahydrofuran.

The reaction for substitution of one halogen by another, in particular when R_7 is a $Ph-Y-(CH_2)_n-Cl$ group, is preferably carried out by the action of NaI in methyl ethyl ketone.

The alkylation or acylation reactions of the OH group in position 3 or 17 are carried out by the standard methods known to persons skilled in the art.

The reduction of the 17-keto to the corresponding alcohol (R_5 = OH and R_6 = H) is carried out according to standard methods, in particular by the action of an alkali metal borohydride, such as sodium borohydride, in methanol or ethanol or by the action of lithium aluminium tetrahydride.

The action of an organometallic reagent on the 17-keto gives access to the products of the formula (IV) in which D represents a residue of a pentagonal ring as defined above, R_5 is hydroxyl and R_6 represents an optionally substituted alkyl, alkenyl or alkynyl radical.

The alkyl, alkenyl or alkynyl organometallic derivative is chosen from the magnesium reagents of the formula AlkMgHal and the lithium reagents of the formula AlkLi, in which Alk represents an alkyl, alkenyl or alkynyl group containing not more than 8 carbon atoms and Hal represents a halogen atom. In a preferred embodiment of the process, Hal represents a chlorine, bromine or iodine atom, preferably a bromine atom.

The reaction preferably takes place in the presence of cerium chloride. In a preferred embodiment of the process, Hal represents a chlorine, bromine or iodine atom, preferably a bromine atom.

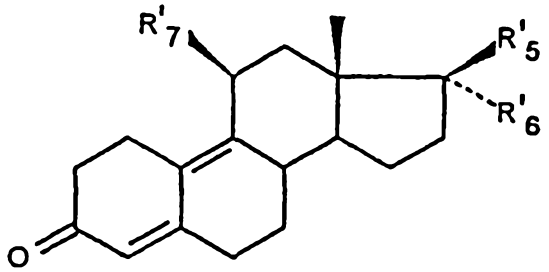
The lactonization reaction starting with the 17-keto is carried out by the Sturtz method (ref: G. Sturtz and J-J. Yaouanc, Synthesis, (1980), 289), in particular in the presence of an alkyl bisdimethylamidophosphate in the presence of an alkyllithium reagent, such as n-butyllithium, in tetrahydrofuran.

The total or partial reduction reaction when R_6 is an alkenyl or alkynyl radical or when R_5 and R_6, together with the carbon atom which bears them, form a group $O-(CH_2)_{m'}-CH=CH-$ can be carried out either totally, by the action of

hydrogen in the presence of a catalyst such as palladium-on-charcoal or a rhodium catalyst, such as Wilkinson's reagent, or partially (alkynyl becomes alkenyl), by the action of a poisoned catalyst, such as palladium on barium sulphate poisoned with pyridine or triethylamine.

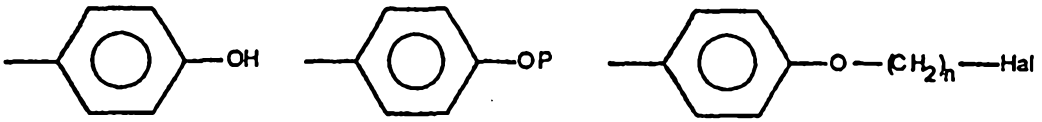
The esterification and salification reactions are carried out by the common methods known to persons skilled in the art.

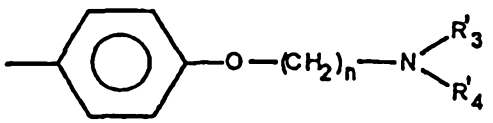
The invention more particularly relates to a process for preparing the compounds of the general formula (I') as described above, characterized in that a compound of the general formula (II'):



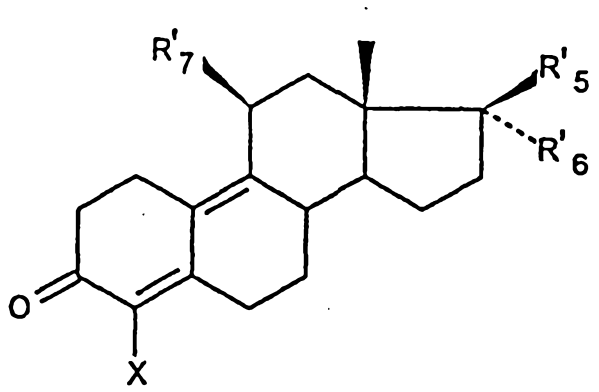
(II')

in which R'_5 and R'_6 are as defined above and R'_7 represents:



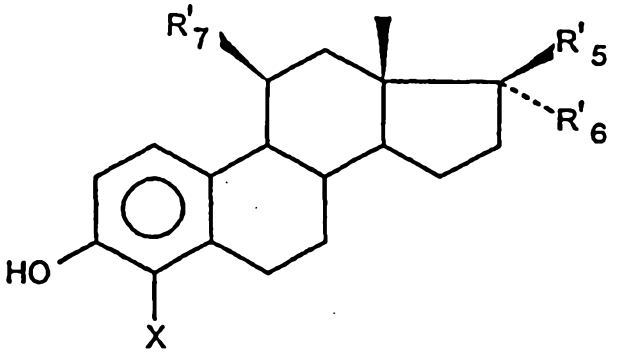


is subjected to the action of a halogenating reagent in order to obtain the compound of the formula (III'):



(III')

which is subjected to the action of a reagent for aromatization of the ring A, followed by the action of a base in order to obtain the compound of the formula (IV') corresponding to certain compounds of the general formula (I'):



(IV')

which compounds of the formula (II'), (III') or (IV') are subjected, if so desired and if necessary, in an appropriate order, to one or more of the following reactions:

- protection of the compounds in which R'_7 is a -Ph-OH group,
- deprotection of the compounds in which R'_7 is a Ph-OP, group
- action of a compound of the formula Hal_1-$(CH_2)_n$-Hal_2 on the compounds in which R'_7 is a -Ph-OH group, Hal_1 or Hal_2, which may be identical or different, representing a halogen, in order to obtain compounds in which R_7 is a-Ph-O-$(CH_2)_n$-Hal_2 group,
- action of a compound of the formula R'_3-NH-R'_4 on the compounds in which R'_7 is a Ph-O-$(CH_2)_n$-Hal_2 group, in order

to obtain compounds in which R'_7 is a $Ph-O-(CH_2)_n-NR'_3R'_4$ group,

- action of a halide salt ($M-Hal_3$) on compounds in which R'_7 is a $Ph-O-(CH_2)_n-Hal_2$ group, in order to obtain compounds in which R_7 is a $Ph-O-(CH_2)_n-Hal_3$ group,
- protection of the OH group in position 3 or 17,
- deprotection of the OH group in position 3 or 17,
- alkylation of the OH group in position 17,
- acylation of the OH group in position 17,
- action of a reducing agent when R'_5 and R'_6 together form an oxo group,
- action of an organometallic reagent on the compounds of the formula (IV') with R'_5 and R'_6 together forming an oxo group,
- action of a lactonizing agent on the compounds of the formula (IV') with R'_5 and R'_6 together forming an oxo group,
- action of an agent for reducing the double bond when R'_5 and R'_6, together with the carbon which bears them, form a group $O-(CH_2)_{1'}-CH=CH-$,
- action of an agent for reducing the double bond when R'_6 is an alkenyl or alkynyl radical containing from 2 to 6 carbon atoms,
- halogenation in position 4, followed by aromatization of ring A, of the compound of the general formula (II'),
- aromatization of the compound of the formula (III'),
- salification.

The compounds of the general formula (I) and the addition salts thereof with pharmaceutically acceptable acids have oestrogen, antioestrogen and antiproliferative activities.

In this respect, the compounds of the formula (I) can be used in the treatment of disorders associated with hypofolliculinia, for example amenorrhoea, dysmenorrhoea, repeated abortions, premenstrual disorders, in the treatment of certain oestrogen-dependent pathologies, such as prostate carcinomas or adenomas, breast carcinomas and its

metastases, or the treatment of benign breast tumours, as an anti-uterotrophic agent and in replacement therapy for the menopause or the perimenopause.

Among the symptoms and consequences associated with the menopause, those more particularly intended are hot flushes, sweats, vaginal atrophy and dryness, urinary symptoms and, in the long term, a decrease in bone mass and an increase in the risk of fractures, as well as loss of the cardiovascular protection afforded by the oestrogens.

In particular, the compounds of the formula (I) and the addition salts thereof with pharmaceutically acceptable acids or bases can thus be used in the prevention or treatment of osteoporosis.

The compounds of the formula (I) and the addition salts thereof with pharmaceutically acceptable acids or bases can also be used in the prevention or treatment of osteoporosis in humans.

They can also be used in the prevention or treatment of secondary osteoporosis (for example those which are cortisone-related associated with immobilization).

The compounds of the formula (I) and the addition salts thereof with pharmaceutically acceptable acids or bases in particular have dissociated oestrogen activity.

The expression "dissociated oestrogen activity" means oestrogen activity on the bones while at the same time exhibiting only minimal uterine activity, thus entailing the absence of endometrial proliferation (activity considerably lower than that of oestradiol).

Moreover, the compounds according to the invention have the following advantages:

- They have anti-oestrogen activity on the breasts. Unlike oestradiol, they do not stimulate the growth of human breast tumour cells and may even inhibit their growth. The compounds according to the invention are thus particularly advantageous for the treatment of the menopause in the case

of women at risk of breast cancer (family history) who are thus excluded from replacement therapy with oestradiol.

They may thus also be usable in the treatment of breast cancers.

- They lead to a lowering in the level of cholesterol in the serum to a level which is equivalent to that induced by oestradiol. They thus reinforce the cardiovascular protection.

- Finally, since the compounds according to the invention have no uterine oestrogen activity, they do not need to be administered in combination with a progestomimetic compound.

The invention thus relates to the compounds of the formula (I) and the addition salts thereof with pharmaceutically acceptable acids or bases as medicinal products.

The invention more particularly relates to the compounds of the formula (I) and the addition salts thereof with pharmaceutically acceptable acids or bases as medicinal products intended for the prevention or treatment of osteoporosis.

The invention covers pharmaceutical compositions comprising, as active principle, at least one of the medicinal products as defined above.

The compounds of the formula (I) are used via the digestive, parenteral or local route, for example via the percutaneous route. They can be prescribed in the form of plain or coated tablets, gel capsules, granules, suppositories, pessaries, injectable preparations, ointments, creams, gels, microspheres, implants, intravaginal rings or patches, which are produced by the usual methods.

The active principle(s) can be incorporated therein with excipients usually used in these pharmaceutical compositions, such as talc, gum arabic, lactose, starch, magnesium stearate, cocoa butter, aqueous or non-aqueous

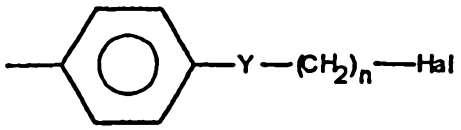
vehicles, fatty substances of animal or plant origin, paraffin derivatives, glycols, various wetting, dispersants or emulsifiers, and preserving agents.

The appropriate dosage varies depending on the complaint to be treated and the route of administration; it can vary, for example, from 1 to 1000 mg per day for an adult via the oral route.

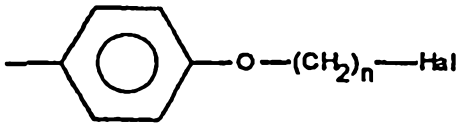
The compounds of the general formula (II) or (II') are known compounds and are described in the following patent: European Patent 0 057 115.

The compounds of the general formula (II) or (II') in which

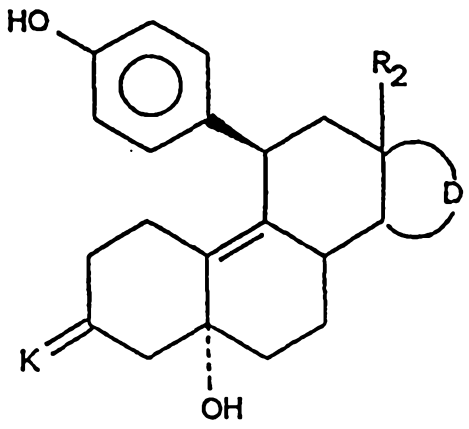
R_7 =



or R'_7 =

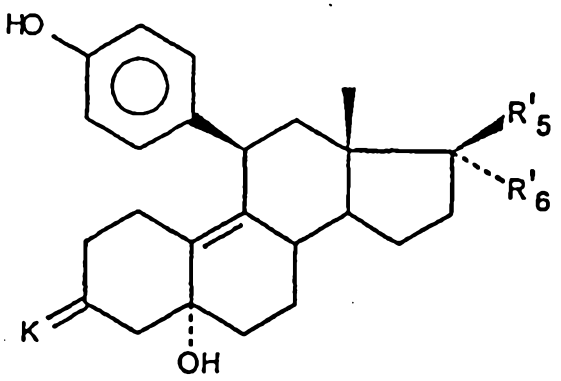


can also be formed from compounds of the formula (IIa):



(IIa)

or (II'a):



(II'a)

in which D, R_2, R'_5 and R'_6 are as defined above and K represents a protecting group for the ketone function,

which compound is subjected to the action of an O-alkylating reagent of the formula Hal-$(CH_2)_n$-Hal and then to the action of a dehydrating reagent which is also capable of releasing the ketone.

The compounds of the formula (IIa) or (II'a) are also known compounds and are described in the following patent:

US Patent No. 5,043,332.

The invention also relates to the compounds of the formulae (III), (III'), (IV) and (IV') as intermediates.

The examples below illustrate the invention, but without limiting it.

Solvents described in the examples: EtOAc (ethyl acetate), TEA (triethylamine), CH_2Cl_2 (dichloromethane), $CHCl_3$ (chloroform), MeOH (methanol), NH_4OH (ammonium hydroxide), iPrOH (isopropyl alcohol).

EXAMPLE 1 : 4-chloro-3-hydroxy-11beta-[4-[2-(1-piperidyl)ethoxy]phenyl]oestra-1,3,5(10)-trien-17-one

Stage A : 11beta-[4-(2-bromoethoxy)phenyl]oestra-4,9-diene-3,17-dione

a) O-alkylation

8.0 g of 5α-hydroxy-11β-(4-hydroxyphenyl)oestr-9-ene-3,17-dione cyclic 3-(1,2-ethanediyl acetal) are dissolved, under inert atmosphere, in 80 ml of 99% 1,2-dibromomethane [sic], 21 ml of 50% sodium hydroxide and 0.800 g of

tetrabutylammonium bromide, and the mixture is stirred under reflux for 1 hour.

b) acid hydrolysis

93 ml of 6M hydrochloric acid are added at room temperature and the mixture is stirred for 45 minutes, followed by extraction, washing, drying and evaporation under reduced pressure to give the crude product (m = 13.17 g), which is recrystallized from a mixture of 50 ml of dichloromethane/50 ml of isopropyl ether. 5.96 g + 7.0 g of the pure expected product are obtained (Rf 70/30 CH_2Cl_2/EtOAc = 0.45). m.p. = 208°C.

IR ($CHCl_3$)

1735 cm^{-1} : 17-keto ; 1658 and 1609 cm^{-1} : conjugated ketone ; 1583 and 1509 : aromatic.

Stage B : 11beta-[4-(2-bromoethoxy)phenyl]-4-chloro-oestra-4,9-diene-3,17-dione (introduction of Cl in position 4)

1.86 g of N-chlorosuccinimide are added to a solution of 5.025 g of the product obtained in Stage A in 67 ml of dimethylformamide under an inert atmosphere at 60°C, and the mixture is stirred for 10 minutes. Saline water is added, followed by extraction, drying and evaporation under reduced pressure to give the crude product (m = 8.149 g), which is purified by chromatography on silica, eluting with a cyclohexane/ethyl acetate mixture (60/40), to give 5.43 g of the pure expected product (Rf 60/40 essence G/EtOAc = 0.35).

IR ($CHCl_3$)

1736 cm^{-1} : 17-keto ; 1677 cm^{-1} : conjugated ketone ; 1609, 1582, 1550 and 1509 cm^{-1} : C=C and aromatic.

Stage C : 11beta-[4-(2-bromoethoxy)phenyl]-4-chloro-3-hydroxyoestra-1,3,5(10)trien-17-one (aromatization of ring A)

a) Aromatization

4.7 ml of acetic anhydride and 4.7 ml of acetyl bromide are added, all a cooling [sic], to a solution of 4.7 g of the product obtained in Stage B in 50 ml of dichloromethane/siliporite under an inert atmosphere at room

temperature, and the mixture is stirred for 5 hours 30 minutes.

b) Saponification of the phenolic acetate

After the dichloromethane has been evaporated off under reduced pressure at room temperature, 47 ml of tetrahydrofuran, 47 ml of methanol and then 47 ml of sodium hydroxide are added under an inert atmosphere with constant cooling, and the mixture is stirred for 1 h at room temperature. Acidification with hydrochloric acid is followed by extraction, washing, drying and evaporation under reduced pressure to give the crude product (m = 4.84 g), which is purified by chromatography on silica, eluting with a cyclohexane/ethyl acetate mixture (70/30). 4.37 g of the expected product are obtained (Rf 70/30 essence G/EtOAc = 0.18).

IR ($CHCl_3$)

3537 cm^{-1} : phenolic OH ; 1733 cm^{-1} : 17-keto ; 1609, 1580, 1511 and 1481 cm^{-1} : aromatic.

Stage D : 4-chloro-3-hydroxy-11beta-[4-(2-iodoethoxy)-phenyl]oestra-1,3,5(10)trien-17-one (iodination)

2.44 g of sodium iodide are added to a solution of 4.11 g of the bromo derivative prepared in Stage C in 80 ml of methyl ethyl ketone under an inert atmosphere at room temperature, and the mixture is stirred under reflux overnight. Water is added, followed by extraction, drying and evaporation under reduced pressure to give 4.184 g of crude expected product (Rf = methanol/water (90/10) = 0.30).

Stage E : 4-chloro-3-hydroxy-11beta-[4-[2-(1-piperidyl)ethoxy]phenyl]oestra-1,3,5(10)trien-17-one (substitution of the iodine with piperidine).

1.248 g of the iodo derivative obtained in Stage D are dissolved in 25 ml of tetrahydrofuran/siliporite under an inert atmosphere at room temperature, 1.35 ml of piperidine are added and the mixture is heated under reflux for 1 hour 30 minutes. After the tetrahydrofuran has been evaporated off under reduced pressure at room temperature, water and

ethyl acetate are added, followed by washing, drying and evaporation under reduced pressure to give 1.185 g of crude amino derivative, which is purified by chromatography on silica, eluting with a 95/5 ethyl acetate/triethylamine mixture. 1.039 g of the pure expected product are obtained (Rf = ethyl acetate/TEA (95/5) = 0.20).

NMR $CDCl_3$

0.45 ppm (s) : CH_3 at 18 ; 2.48 ppm : ring CH_2-N ; 2.71 ppm (t) : CH_2-N of the chain ; 3.99 ppm (t) : CH_2-OAr ; 3.99 ppm : H_{11} ; 6.63 ppm : H_2 ; 6.81 ppm : H_1 ; 6.60 ppm : Ar-O ; 6.91 ppm : Ar-C.

EXAMPLE 2 : 4-chloro-3-hydroxy-11beta-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]oestra-1,3,5(10)-trien-17-one

The process is carried out as in Example 1 Stage E, but starting with 6 g of the iodo derivative obtained in Stage D of Example 1, 60 ml of tetrahydro-furan/siliporite and 4.6 ml of pyrrolidine.

4.2 g of the pure expected product are obtained (Rf : EtOAc/TEA (80/20) = 0.24).

NMR ($CDCl_3$) :

0.45 ppm (s) : CH_3 at 18 ; 1.78 ppm (m) : CH_2 beta to N ; 2.59 ppm (m) : CH_2 alpha to N ; 2.84 ppm (t) : CH_2-N of the chain ; 3.98 ppm (t) : CH_2-OAr ; 3.98 ppm (t): H_{11}, CH_2-O of the chain ; 6.62 ppm : H_2 ; 6.81 ppm : H_1 ; 6.62 ppm : Ar-O ; 6.91 ppm : Ar-C.

EXAMPLE 3 : 4-chloro-3-hydroxy-11beta-[4-[2-diethylamino)ethoxy]phenyl]oestra-1,3,5(10)-trien-17-one

The process is carried as in Example 1 Stage E, but starting with 1.2 g of the iodo derivative obtained in Stage D of Example 1, 25 ml of tetrahydro-furan/siliporite and 1 ml of diethylamine.

0.688 g of the pure expected product is obtained (Rf : EtOAc/TEA (95/5) = 0.22).

NMR ($CDCl_3$) :

0.45 ppm (s) : CH_3 at 18 ; 1.03 ppm (t) : N-CH_2-$\underline{CH_3}$; 2.60 ppm (q) : N-$\underline{CH_2}$-CH_3 ; 2.81 ppm (t) : CH_2-N of the chain ;

3.93 ppm (t) : CH_2-OAr ; 4.00 ppm (t) : H_{11} ; 6.63 ppm : H_2 ; 6.82 ppm : H_1 ; 6.63 ppm : Ar-O ; 6.91 ppm : Ar-C.

EXAMPLE 4 : 4-bromo-3-hydroxy-11beta-[4-[2-(1-piperidyl)ethoxy]phenyl]oestra-1,3,5(10)-trien-17-one

Stage A : 11beta-[4-(2-chloroethoxy)phenyl]oestra-4,9-diene-3,17-dione (O-alkylation)

(7.9 ml x 2) of 1-bromo-2-chloroethane are added to a suspension of 5 g of 11beta-(4-hydroxyphenyl)-oestra-4,9-diene-3,17-dione in 50 ml of acetone, followed by addition of 6 ml of 50% sodium hydroxide and 500 mg of tetrabutylammonium bromide. The mixture is maintained under reflux for 4 h. Water is added, followed by extraction, drying and evaporation under reduced pressure to give a crude product, which is purified in ether.

5.45 g of the expected product are obtained (Rf 90/10 CH_2Cl_2/acetone = 0.82).

NMR ($CDCl_3$) :

0.58 3H (s) : CH_3 at 18 ; 3.80 2H (t) : $C\underline{H}_2Cl$; 4.28 2H (t) : $C\underline{H}_2O$; 4.49 1H (d) : H_{11} ; 5.80 1H (s) : H_4 ; 6.82 2H (d) : 2H arom. ; 7.08 2H (d) : arom. H.

Stage B : 4-bromo-11beta-[4-(2-chloroethoxy)phenyl]-oestra-4,9-diene-3,17-dione (introduction of Br in position 4)

A solution of 2.43 g of N-bromosuccinimide is added to a suspension of 5.35 g of the product from Stage A in 700 ml of dimethylformamide, under a nitrogen atmosphere. After the mixture has been stirred at room temperature for 2 hours, 200 ml of ethyl acetate and 400 ml of saturated NaCl solution are added, followed by extraction, washing, drying and evaporation under reduced pressure to give 8 g of the crude product, which is purified by chromatography, eluting with a 98/2 dichloro-methane/acetone mixture. 4.66 g of the pure expected product are obtained. (Rf 95/5 CH_2Cl_2/acetone = 0.92).

NMR ($CDCl_3$) :

0.57 3H (s) : $C\underline{H}_3$ at 18 ; 3.25 1H (dt) : H_6 ; 3.80 2H (t) : $C\underline{H}_2Cl$; 4.20 2H (t) : $C\underline{H}_2O$; 4.38 1H (broad d) : H_{11} ; 7.07 and 6.83 4H : AA'BB' arom. H.

Stage C : 4-bromo-11beta-[4-(2-chloroethoxy)phenyl]-3-hydroxyoestra-1,3,5(10)-trien-17-one (aromatization of ring A)

The process is carried out as in Stage C of Example 1, starting with 4.5 g of product obtained in the previous stage. 3.05 g of the expected product are obtained. (Rf 90/10 CH_2Cl_2/EtOAc = 0.64).

NMR ($CDCl_3$) :

0.45 3H (s) : $C\underline{H}_3$ at 18 ; 3.75 2H (t) : $C\underline{H}_2Cl$; 4.12 2H (t) : $C\underline{H}_2O$; 4.00 1H (t) : H_{11} ; 5.48 1H (s) : OH ; 6.93 and 6.64 2H : AA'BB' 4H arom. ; 6.85 and 6.64 2H (d) : H_1H_2.

Stage D : 4-bromo-3-hydroxy-11beta-[4-(2-iodoethoxy)-phenyl]oestra-1,3,5(10)-trien-17-one (iodination)

The process is carried out as in Stage D of Example 1, starting with 1 g of the product obtained in the preceding stage. 1.14 g of the expected product are obtained.

Stage E : 4-bromo-3-hydroxy-11beta-[4-[2-(1-piperidyl)-ethoxy]phenyl]oestra-1,3,5(10)-trien-17-one (substitution of the iodine with piperidine)

The process is carried out as in Stage E of Example 1, starting with 1.1 g of the product obtained in the preceding stage. 270 mg of the pure expected product are obtained (Rf 90/10 EtOAc/TEA = 0.43).

NMR ($CDCl_3$) :

0.45 3H (s) : $C\underline{H}_3$ at 18 ; 2.47 4H (m) : ring $C\underline{H}_2N$; 2.70 2H (t) : $C\underline{H}_2$-N ; 3.98 2H (t) : $C\underline{H}_2$-O ; 3.98 1H (broad t) : H_{11} ; 6.88 and 6.62 2H (d) : H_1 and H_2 ; 6.90 and 6.62 4H : AA'BB' aromatic H.

EXAMPLE 5 : 4-chloro-11beta-[4-[3-(1-piperidyl)propoxy]phenyl]oestra-1,3,5(10)-triene-3,17-beta-diol

Stage A : 4-chloro-11beta-[4-(phenylmethoxy)phenyl]-oestra-4,9-diene-3,17-dione (chlorination at 4)

5.295 g of N-chlorosuccinimide are added to a solution of 13.6 g of 11β-[4-(phenylmethoxy)phenyl]oestra-4,9-diene-3,17-dione in 120 ml of dimethylformamide under an inert atmosphere at 60°C, and the mixture is stirred for 10 minutes and then poured into saturated aqueous NaCl solution, followed by extraction, washing, dring and evaporation under reduced pressure to give the crude product (m = 19.128 g). A second test is carried out, and the crude products are combined and purified by chromatography, eluting with a 30/70 ethyl acetate/cyclohexane mixture. 23.28 g of the pure expected product are obtained. (Rf 30/70 EtOAc/cyclohexane = 0.19).

NMR ($CDCl_3$) :

0.58 (s) : $C\underline{H}_3$ at 18 ; 3.25 (dt) : 1H equatorial H_6 ; 4.39 (broad d) : H_{11} ; 5.02 (s) : $C\underline{H}_2Ph$; 6.89 : H ortho to the Ph-O ; 7.06 : H meta to the Ph-O ; 7.29 to 7.45 : aromatic H of the CH_2-Ph.

Stage B : 4-chloro-3-[[(2,2-dimethylethyl)(diphenyl)-silyl]oxy]-11beta-[4-(phenylmethoxy)phenyl]oestra-1,3,5(10)-trien-17-one (aromatization/saponification/-blocking of the phenol)

a) aromatization and saponification

The process is carried out as in Stage C of Example 1, starting with the product obtained in the preceding stage. 13.5 g of the pure expected product (3-OH) are obtained.

b) blocking of the phenol

13.5 g + 5.6 g of product obtained in the preceding stage, 191 mg of dichloromethane/siliporite, 14.5 ml of tert-butyldiphenylchlorosilane and 258 mg of 4-DMAP are dissolved under an inert atmosphere, and the solution is stirred under reflux for 23 hours. It is then poured into water, followed by extraction, washing, drying and evaporation under reduced pressure to give 41.322 g of crude product in the form of an oil, which is purified by chromatography, eluting with a 20/80 and then 40/60 ethyl acetate/petroleum ether mixture. 1.275 g of the pure

expected product are obtained. (Rf 20/80 EtOAc/petroleum ether = 0.27).

NMR ($CDCl_3$):

0.42 (s) : $C\underline{H}_3$ at 18 ; 1.11 (s) : $C(C\underline{H}_3)_3$; 7.25 to 7.40 - 7.60 to 7.75 : SiPh ; 3.85 (t) : H_{11} ; 4.94 (s) : $C\underline{H}_2$-Ph ; 6.65 : H in ortho position (Ph-O) ; 6.84 : H in the para position (Ph-O) ; 6.17 (d) : H_1 ; 6.47 (d) : H_2.

Stage C : 4-chloro-3-[[(2,2-dimethylethyl)(diphenyl)-silyl]oxy]-11beta-[4-(hydroxyphenyl)oestra-1,3,5(10)-trien-17-one (deprotection (debenzylation))

15.6 g of palladium hydroxide on magnesia and 40 ml of 1,4-cyclohexadiene are added to a suspension of 20.82 g of the product obtained in the preceding stage in 420 ml of methanol under an inert atmosphere at room temperature, and the mixture is then maintained under reflux for 8 hours. Filtration and evaporation under reduced pressure give 22 mg of crude product, which is purified by chromatography, eluting with a 7/3 cyclohexane/ethyl acetate mixture. 19.4 g of the pure expected product are obtained. (Rf 7/3 cyclohexane/EtOAc = 0.27).

NMR ($CDCl_3$) :

0.42 (s) : $C\underline{H}_3$ at 18 ; 1.11 (s) : $C(C\underline{H}_3)_3$; 3.83 (broad t) : H_{11} ; 4.56 (s) : $O\underline{H}$; 6.17 (d) - 6.46 (d) : H_1, H_2 ; 7.25 to 7.43 (m) 6H and 7.64 (m) 4H : $SiPh_2$.

Stage D : 4-chloro-3-[[(2,2-dimethylethyl)(diphenyl)-silyl]oxy]-11beta-[4-(3-iodopropoxy)phenyl]oestra-1,3,5(10)-trien-17-one (O-alkylation)

3.18 g of the product obtained in the preceding stage, 15 ml of 1,3-diiodopropane, 800 mg of ground sodium hydroxide and 300 mg of tetrabutylammonium bromide are mixed together for 4 hours at room temperature and acidified with 2N hydrochloric acid, followed by extraction, washing, drying and evaporation under reduced pressure to give the crude product (39.8 g), which is purified by chromatography, eluting with a 75/25 petroleum ether/EtOAc mixture. 2.43 g

of the pure expected product are obtained. (Rf : 80/20 petroleum ether/EtOAc = 0.3).

NMR ($CDCl_3$) :

0.41 (s) : $C\underline{H}_3$ at 18 ; 1.10 (s) : $C(C\underline{H}_3)_3$; 3.34 (t) : $O-CH_2-CH_2-C\underline{H}_2-I$; 3.85 (broad t) : H_{11} ; 3.91 (t) : $O-C\underline{H}_2-CH_2-CH_2-I$; 6.16 (d) - 6.46 (d) : H_1, H_2 ; 7.25 to 7.45 6H and 7.66 4H : $SiPh_2$.

Stage E : 4-chloro-3-[[(2,2-dimethylethyl)(diphenyl)-silyl]oxy]-11beta-[4-[3-(1-piperidyl)propoxy]phenyl]-oestra-1,3,5(10)-trien-17-one (substitution of the iodine with piperidine)

The process is carried out as in Stage E of Example 1, starting with the product obtained in the preceding stage. 2.07 g of the pure expected product are obtained (Rf 98/2 EtOAc/TEA = 0.23).

NMR ($CDCl_3$) :

0.42 (s) : $C\underline{H}_3$ at 18 ; 1.10 (s) : $C(C\underline{H}_3)_3$; 2.52 : ring CH_2-N ; 2.83 : CH_2-N of the chain ; 3.84 (broad t) : H_{11} ; 3.88 (t) : CH_2-O ; 6.16 (d) - 6.47 (d) : H_1, H_2 ; 6.56 - 6.80 : Ph-O ; 7.25 - 7.40 6H and 7.65 4H : $SiPh_2$.

Stage F : 4-chloro-11beta-[4-[3-(1-piperidyl)propoxy]-phenyl]oestra-1,3,5(10)-triene-3,17-beta-diol (reduc-tion of the 17-keto and deprotection)

a) Reduction of the 17-keto

63 mg of 97% sodium borohydride are added, with constant cooling on an ice bath, to a solution of 600 mg of the product obtained in the preceding stage in 4 ml of methanol and 2 ml of tetrahydrofuran under an inert gas at room temperature, and the mixture is stirred for 50 minutes. Ethyl acetate is added, followed by washing with saline water, drying and evaporation under reduced pressure, to give 614 mg of the crude expected product.

b) Deprotection of the phenol at 3

1.6 ml of a solution of tetrabutylammonium fluoride in tetrahydrofuran are added to a solution of 614 mg of the product obtained above in 6 ml of tetrahydrofuran under an

inert gas at room temperature, and the resulting solution is stirred for 50 minutes at room temperature. This mixture is poured into water, followed by extraction, washing, drying and evaporation under reduced pressure, to give 840 mg of crude expected product, which is purified by chromatography, eluting with a 90/10/1 dichloromethane/ methanol/ammonium hydroxyl [sic] mixture. 215 g [sic] of the pure expected product are obtained.

(Rf 90/10/1 CH_2Cl_2/MeOH/NH_4OH = 0.3).

NMR ($CDCl_3$) :

0.38 (s) : CH_3 at 18 ; 2.45 (m) ; CH_2-N ; 3.72 (t) : H_{17} ; 3.86 : H_{11}, CH_2-O ; 6.61 - 6.93 : Ph-O ; 6.61 - 6.75 : H_1, H_2.

EXAMPLE 6 : 4-chloro-11beta-[4-[4-(1-piperidyl)butoxy]-phenyl]oestra-1,3,5(10)-triene-3,17-beta-diol

The process is carried out in the same way as in Example 5, it being possible for the O-alkylation to be carried out:

either with 4-chloro-1-butanol, by the "Mitsunobu" reaction in the presence of triphenylphosphine and diethyl azodicarboxylate in tetrahydrofuran, and the chloro product obtained being converted into the iodo product according to the process described in Example 1 Stage D,

or by direct action with 1,4-diiodobutane (cf. Ex. 6). 189 mg of the pure expected product are obtained (Rf 90/10/1 CH_2Cl_2/MeOH/NH_4OH = 0.24).

EXAMPLE 7 : 4-chloro-11beta-[4-[5-(1-piperidyl)pentyl-oxy]phenyl]oestra-1,3,5(10)-triene-3,17-beta-diol

The process is carried out in the same way as in Example 5, the O-alkylation being carried out with 1,5-diiodopentane. 125 mg of the pure expected product are obtained. (Rf 90/10/1 CH_2Cl_2/MeOH/NH_4OH = 0.30).

EXAMPLE 8 : (17beta)-4-chloro-11beta-[4-[2-(1-piperid-yl)ethoxy]phenyl]spiro[oestra-1,3,5(10)-triene-17,2'(5'H)-furan]-3-ol

Stage A : (17beta)-4-chloro-11beta-(4-hydroxyphenyl)-spiro[oestra-4,9-diene-17,2'(5'H)-furan]-3-one (chlorination)

4.51 g of N-chlorosuccinimide are added to a suspension of 10.46 g of (17beta)-11beta-(4-hydroxyphenyl)spiro[oestra-4,9-diene-17,2'(5'H)-furan]-3-one (WO 87/05908) in 100 ml of dimethylformamide under an inert atmosphere at 60°C, and the mixture is left to react for 10 minutes with stirring. The mixture is then poured into ice-cold sodium chloride solution, followed by extraction, drying and evaporation under reduced pressure, to give 20.85 g of crude product. 8.93 g of product obtained in an additional test, carried out in an identical manner, are added, and the whole is purified by chromatography, eluting with a 95/5 CH_2Cl_2/acetone mixture, followed by recrystallization from ethyl ether. 0.98 g of the pure expected product is obtained. (Rf 95/5 CH_2Cl_2/acetone = 0.2). m.p. = 258°C

Stage B : (17beta)-4-chloro-11beta-[4-(2-bromoethoxy)-phenyl]spiro[oestra-4,9-diene-17,2'(5'H)-furan]-3-one

The process is carried out as in Example 1 Stage A, but starting with 1,2-dibromoethane. 5.34 g of the pure expected product are obtained. (Rf 75/25 essence G/EtOAc = 0.21).

Stage C : Aromatization and saponification

Stage D : Iodination

Stage E : Coupling of the piperidine

Stages C, D and E are carried out in a manner similar to that of Stages C, D and E of Example 1.

0.657 g of the pure expected product is obtained (Rf 92/8 EtOAc/TEA = 0.21).

NMR ($CDCl_3$) :

0.48 (s) : $C\underline{H}_3$ at 18 ; 2.47 (m) : ring CH_2-N ; 2.70 (t) : chain CH_2-N ; 3.89 (broad t) : H_{11} ; 3.99 (t) : chain CH_2-O ; 4.56 : ring CH_2-O ; 5.78 : OH ; 5.87 : H'_3, H'_4 ; 6.60 - 6.80 : H_1 and H_2 ; 6.60 - 6.86 : Ph-O.

EXAMPLE 9 : (17beta)-4-chloro-11beta-[4-[2-(diethylamino)ethoxy]phenyl]spiro[oestra-1,3,5(10)-triene-17,2'(5'H)-furan]-3-ol

The process is carried out as in Example 8, but with final coupling of diethylamine with the iodo derivative. 0.512 g of the pure expected product is obtained. (Rf 93/7/0.2 CH_2Cl_2/MeOH/NH_4OH = 0.29).

NMR ($CDCl_3$) :

0.48 (s) : CH_3 at 18 ; 1.03 (t) : CH_2-CH_3 ; 2.60 (q) : CH_2-CH_3 ; 2.81 (t) : CH_2-N ; 3.89 (broad t) : H_{11} ; 3.93 (t) : chain CH_2-O ; 4.56 : ring CH_2-O (H'_3) ; 5.87 : H'_3, H'_4 ; 6.61 - 6.79 : H_1 and H_2 ; 6.61 - 6.86 : Ph-O.

EXAMPLE 10 : (17beta)-4-chloro-11beta-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]spiro[oestra-1,3,5(10)-triene-17,2'(5'H)-furan]-3-ol

The process is carried out as in Example 8, but with final coupling of pyrrolidine with the iodo derivative. 0.628 g of the expected product is obtained. m.p. = 226-227°C. (Rf 93/7/0.2 CH_2Cl_2/MeOH/NH_4OH = 0.25).

NMR ($CDCl_3$) :

0.48 (s) : CH_3 at 18 ; 2.59 (m) : ring CH_2-N ; 2.80 (m) : chain CH_2-N ; 3.89 (broad t) : H_{11} ; 3.98 (t) : CH_2-O of the chain ; 4.56 (m) : ring CH_2-O (H'_5) ; 5.87 (m) : H'_3, H'_4 ; 6.60 - 6.78 (d) : H_1 and H_2 ; 6.60 - 6.86 AA'BB' : Ph-O.

EXAMPLE 11 : (17beta)-4-chloro-11beta-[4-[3-(1-piperidyl)propoxy]phenyl]spiro[oestra-1,3,5(10)-triene-17,2'(5'H)-furan]-3-ol

The process is carried out as in Example 8, the O-alkylation being carried out directly with 1,3-diiodopropane (avoids Stage D of Example 8). 0.591 g of the pure expected product is obtained. (Rf 92/8 EtOAc/TEA = 0.19).

NMR ($CDCl_3$) :

0.48 (s) : CH_3 at 18 ; 2.30 to 2.50 : CH_2-N ; 3.87 (m) : chain CH_2-O, H_{11} ; 4.56 : ring CH_2-O (H'_5) ; 5.88 : H'_3, H'_4 ; 6.61 - 6.79 : H_1 and H_2 ; 6.61 - 6.86 : Ph-O.

EXAMPLE 12 : (17beta)-4-chloro-11beta-[4-[4-(1-piperidyl)butoxy]phenyl]spiro[oestra-1,3,5(10)-triene-17,2'(5'H)-furan]-3-ol

The process is carried out as in Example 8 Stages A, B, C, D and E, the O-alkylation being carried out with 1-bromo-4-chlorobutane. 0.494 g of the pure product is obtained.

Rf 95/5 EtOAc/TEA = 0.22

m.p. = 154°C

NMR ($CDCl_3$) :

0.50 (s) : CH_3 at 18 ; 2.36 (6H): ring, chain $C\underline{H}_2$-N ; 3.85 (t) : $C\underline{H}_2$-O ; 3.89 (t) : H_{11} ; 4.57 (s) : ring CH_2-O (H'_5) ; 6.60 (m) (3H) - 6.86 (m) (2H) : Ph-O and H_2 ; 6.79 (d) : H_1.

EXAMPLE 13 : 4-chloro-3-hydroxy-11beta-[4-[2-(1-dimethylamino)ethoxy]phenyl]oestra-1,3,5(10)-trien-17-one

Stage A : 4-chloro-11beta-[4-[2-(dimethylamino)ethoxy]-phenyl]oestra-4,9-diene-3,17-dione (introduction of the 4-chloro)

6 ml of 10% sulphuryl chloride in dichloromethane are added to a solution of 1.08 g of 11β-[4-[2-(dimethylamino)-ethoxy]phenyl]oestra-4,9-diene-3,17-dione in 11 ml of pyridine under an inert atmosphere at room temperature, and the mixture is stirred for 30 minutes at about -36°C. This mixture is poured into sodium bicarbonate, followed by extraction, washing, drying and evaporation under reduced pressure, to give 1.84 g of crude product, which is purified by chromatography, eluting with an 80/20 ethyl acetate/triethylamine mixture. 616 mg of the pure expected product are obtained. (Rf 8/2 EtOAc/TEA = 0.35).

Stage B : 4-chloro-11beta-[4-[2-(dimethylamino)ethoxy]-phenyl]-3-hydroxyoestra-1,3,5(10)-trien-17-one (aromatization and saponification)

The aromatization and then saponification reaction are carried out as in Example 1, Stage C, starting with 700 mg of the product obtained in the preceding stage. 360 mg of the pure expected product are obtained. m.p. = 254°C (Rf 93/7/0.7 CH_2Cl_2/iPrOH/NH_4OH = 0.18).

NMR ($CDCl_3$) :

0.44 (s) : CH_3 at 18 ; 2.30 (s) : NMe_2 ; 2.67 (m) : CH_2-N ; 3.94 (m) : CH_2-O ; 4.00 : H_{11} ; 6.62 - 6.91 : Ph-O ; 6.62 - 6.81 (d) : H_1, H_2.

The compound of Example 3 was prepared in the same way.

EXAMPLE 14 : gamma lactone of 4-chloro-3,17beta-di-hydroxy-11beta-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]-19-nor-17alpha-pregna-1,3,5(10)-triene-21-carboxylic acid

6 ml of tetrahydrofuran/siliporite are added to 5.93 ml of n-butyllithium at a concentration of 15% in hexane under inert atmosphere, at room temperature, followed, at -50°C, by addition of 0.921 g of allyl bis-dimethylamidophosphate dissolved in tetrahydro-furan, and finally, at -30°C, 0.586 g of the product obtained in Example 2, and the mixture is stirred at room temperature for 1 hour 45 minutes.

8 ml of 2N hydrochloric acid and 50 ml of saturated sodium bicarbonate solution are added, followed by extraction, washing, drying and evaporation under reduced pressure, to give 0.590 g of crude product, which is purified by chromatography, eluting with a 60/40 ethyl acetate/triethylamine mixture, followed by recrystallization from isobutanol. 0.162 g of the pure expected product is obtained. M.p. = 231°C.

Rf 60/40 EtOAc/TEA = 0.20.

NMR ($CDCl_3$) :

0.51 (s) ; CH_3 at 18 ; 1.79 (m) : CH_2 beta to the ring N ; 2.58 (m) : CH_2 alpha to the ring N ; 2.83 (t) : CH_2-N of the chain ; 3.99 (t) : CH_2-OAr ; 3.99 (t) : H_{11} ; 6.62 : H_2 ; 6.82 : H_1 ; 6.62 : ArO ; 6.82 : ArC.

EXAMPLE 15 : gamma lactone of 4-chloro-3,17beta-di-hydroxy-11beta-[4-[2-(1-piperidyl)ethoxy]phenyl]-19-nor-17alpha-pregna-1,3,5(10)-triene-21-carboxylic acid

The process is carried out as in Example 14, but starting with 1.179 g of the product of Example 1. 0.388 g of the pure expected product is obtained. (Rf 95/5/0.5 CH_2Cl_2/iPrOH/NH_4OH = 0.20).

NMR ($CDCl_3$) :

0.52 (s) : CH_3 at 18 ; 2.50 (m) : ring CH_2-N ; 2.71 (t) : CH_2-N of the chain ; 4.00 (t) : CH_2-OAr ; 4.00 (masked t) : H_{11} ; 6.62 : H_2 ; 6.81 : H_1 ; 6.62 : ArO ; 6.85 : ArC.

EXAMPLE 16 : gamma lactone of 4-chloro-3,17beta-di-hydroxy-11beta-[4-[2-(diethylamino)ethoxy]phenyl]-19-nor-17alpha-pregna-1,3,5(10)-triene-21-carboxylic acid

The process is carried out as in Example 14, but starting with 0.428 g of the product of Example 3. 0.195 g of the pure expected product is obtained. (Rf 50/30/20 EtOAc/TEA/Essence G = 0.25).

NMR ($CDCl_3$) :

0.51 (s) : CH_3 at 18 ; 1.03 (t) : N-CH_2-CH_3 ; 2.60 (q) : N-CH_2-CH_3 ; 2.81 (t) : CH_2-N of the chain ; 3.94 (t) : CH_2-O-Ar ; 3.98 (t) : H_{11} ; 6.59 : H_2 ; 6.79 : H_1 ; 6.59 : ArO ; 6.85 : ArC.

EXAMPLE 17 : gamma lactone of (17-alpha)-4-chloro-3,17beta-dihydroxy-11beta-[4-[3-(1-piperidyl)propoxy]-phenyl]-19-nor-pregna-1,3,5(10)-triene-21-carboxylic acid

Stage A : Lactonization

The process is carried out as in Example 14, but starting with 1.44 g of the compound of Example 5, Stage E, giving 2.36 g of crude product, which is used directly in the reaction for deprotection of the phenol at 3.

Stage B : Deprotection of the phenol at 3.

3.8 ml of a solution of tetrabutylammonium fluoride in tetrahydrofuran are added to a solution of 2.36 g of the product obtained in the preceding stage in 24 ml of tetrahydrofuran, and the resulting solution is stirred for 50 minutes at room temperature. This mixture is poured into water, followed by extraction, drying and evaporation under reduced pressure, to give 695 mg of crude product, which is purified by chromatography, eluting with a 93/7 dichloromethane/methanol mixture followed by recrystallization. 238 mg of the pure expected product are obtained. m.p. = 242°C.

Rf 93/7/0.7 CH_2Cl_2/MeOH/NH_4OH = 0.28

NMR ($CDCl_3$) :

0.51 (s) : CH_3 at 18 ; 2.30 to 2.60 : CH_2-N ; 3.88 : CH_2-O ; 3.98 (broad t) : H_{11} ; 6.61, 6.87 : Ar-O, Ar-C ; 6.61 - 6.76 : H_1, H_2.

EXAMPLE 18 : gamma lactone of 4-chloro-3,17beta-dihydroxy-11beta-[4-[4-(1-piperidyl)butoxy]phenyl]-19-nor-17alpha-pregna-1,3,5(10)-triene-21-carboxylic acid

The process is carried out as in Example 17, but starting with 1.2 g of the product of Example 6, Stage E. 310 mg of the pure expected product are obtained. (Rf 95/5/0.5 CH_2Cl_2/MeOH/NH_4OH = 0.17).

NMR ($CDCl_3$) :

0.51 (s) : CH_3 at 18 ; 3.83 (t) : chain CH_2-O ; 3.99 (broad t) : H_{11} ; 6.61 - 6.85 : Ar-O, Ar-C ; 6.61 - 6.79 : H_1, H_2.

EXAMPLE 19 : gamma lactone of 4-chloro-3,17beta-dihydroxy-11beta-[4-[5-(1-piperidyl)pentyloxy]phenyl]-19-nor-17alpha-pregna-1,3,5(10)-triene-21-carboxylic acid

The process is carried out as in Example 17, but starting with 1.44 g of the product of Example 7, Stage E. 330 mg of the pure expected product are obtained. (Rf 90/10 EtOAc/TEA = 0.22).

NMR ($CDCl_3$) :

0.52 (s) : CH_3 ; 3.83 (t) : CH_2-O ; 3.99 (t) : H_{11} ; 6.60 (m) 3H, 6.67 (d) H_1, 6.85 (d) 2H : H_1, H_2 aromatic.

EXAMPLE 20 : 4-chloro-11beta-[4-[2-(diethylamino)-ethoxy]phenyl]oestra-1,3,5(10)-triene-3,17beta-diol

37 mg of sodium borohydride are added to a solution of 241 mg of the compound from Example 3 in 4 ml of methanol under inert atmosphere,, the mixture is stirred for 1 hour on an ice bath, 2 ml of hydrochloric acid are then added, and the resulting mixture is poured into aqueous sodium bicarbonate solution, followed by extraction with ethyl acetate, washing, drying and evaporation under reduced pressure, to give 245 mg of crude product, which is purified by chromatography, eluting with a 90/10/1 dichloro-methane/methanol/ammonium hydroxide mixture. 195 mg of the

pure expected product are obtained. Rf 90/10/1 CH_2Cl_2/MeOH/NH_4OH = 0.27.

NMR ($CDCl_3$) :

0.32 (s) : CH_3 ; 1.03 (t) : $CH_2\underline{CH_3}$; 2.60 (q) : $\underline{CH_2}CH_3$; 2.81 (t) : CH_2-N ; 3.68 : H_{17} ; 3.93 (t) : CH_2-O ; 6.62 : ArO ; 6.89 : ArC ; 6.80 (d) : H_1 ; 6.62 (d) : H_2.

In a manner similar to that of Example 20, the following products of the formula (I') with R'_5 = OH and R'_6 = H are obtained:

	Starting material	n'	X'	$NR'_3R'_4$	Rf s.
Ex. 21	Ex. 4	2	Br	Piperidino	0.45 90/10 EtOAc/TEA
Ex. 22	Ex. 1	2	Cl	Piperidino	0.13 95/5 EtOAc/TEA
Ex. 23	Ex. 2	2	Cl	Pyrrolidino	0.13 93/7/0.5 CH_2Cl_2/MeOH/NH_4OH
Ex. 24	Ex. 13	2	Cl	NMe_2	0.25 90/10/1 CH_2Cl_2/iPrOH/NH_4OH

EXAMPLE 25 : 4-chloro-11beta-[4-[2-(diethylamino)-ethoxy]phenyl]-19-nor-17alpha-pregna-1,3,5(10)-trien-20-yne-3,17beta-diol

4.7 ml of a 0.43 M/l potassium acetylide solution are added to a solution of 250 mg of the product from Example 3 in 3 ml of tetrahydrofuran/siliporite under an inert atmosphere, the mixture is stirred for 1 hour at room temperature, and 4 ml of hydrochloric acid are then added. The resulting mixture is poured into saturated aqueous sodium bicarbonate solution, followed by extraction, washing, drying and evaporation under reduced pressure, to give 260 mg of crude product, which is purified by chromatography, eluting with a 90/10/0.5 CH_2Cl_2/MeOH/NH_4OH mixture. 215 mg of the pure expected product are obtained.

Rf 90/10/0.5 CH_2Cl_2/MeOH/NH_4OH = 0.31.

NMR ($CDCl_3$) :

0.43 (s) : CH_3 at 18 ; 1.04 (t) : $CH_2\underline{CH_3}$; 2.62 (q) : $\underline{CH_2}CH_3$; 2.64 (s) : C≡C-$\underline{H}$; 2.83 (t) : CH_2-N ; 3.95 (t) : CH_2-O ; 4.00 (broad t) : H_{11} ; 6.62 : Ph-O ; 6.90 : Ph-C ; 6.82 (d) : H_1 ; 6.62 (d) : H_2.

EXAMPLE 26 : (17beta)-4-chloro-4',5'-dihydro-11beta-[4-[2-(1-piperidyl)ethoxy]phenyl]spiro[oestra-1,3,5(10)-triene-17,2'(3'H)furan]-3-ol

0.041 g of 9.5% Pd/C catalyst is added to a solution of 0.411 g of the product of Example 8 in 15 ml of ethanol and 5 ml of tetrahydrofuran, and the mixture is hydrogenated for 2 hours 30 minutes (vol. of H_2 absorbed = 17.5 cm^3). After the catalyst has been filtered off, the filtrate is evaporated under reduced pressure to give 0.42 g of crude product, which is purified by chromatography, eluting with a 92/8 ethyl acetate/triethylamine mixture. 0.33 g of the pure expected product is obtained. m.p. = 170°C. Rf 92/8 EtOAc/TEA = 0.21.

In a manner similar to that of Example 26, the products of the formula (I') given below are obtained in which R'_3 and R'_6, together with the carbon atom which bears them, form the saturated ring

	Starting material	n'	X'	$NR'_3R'_4$	Rf	s.
Ex. 27	Ex. 11	3	Cl	Piperidino	0.19	92/8 EtOAc/TEA
Ex. 28	Ex. 12	4	Cl	Piperidino	0.22	95/5 EtOAc/TEA

EXAMPLE 29 : 4-chloro-11β-[4-[2-(diethylamino)ethoxy]-phenyl]-17alpha-methyloestra-1,3,5(10)-triene-3,17beta-diol

a) Preparation of the cerium reagent

24 ml of anhydrous THF are added to 2.42 g of $CeCl_3 \cdot 7H_2O$, predried under reduced pressure at 140°C for 2 hours and then placed under an inert atmosphere, the suspension is stirred for 2 hours and cooled to -78°C, 4.35 ml of CH_3Li in ether are added and the mixture is stirred for 30 minutes at -78°C.

b) Coupling

0.644 g of the compound prepared in Example 3, dissolved in 8.5 ml of anhydrous THF, is added and the mixture is maintained at this temperature for 1 hour. This mixture is poured into 25 ml of saturated NH_4Cl solution, followed by extraction, washing, drying and evaporation under reduced pressure, to give 0.599 g of crude product, which is purified by chromatography (after addition of 0.192 g of crude product obtained during an additional test carried out in an identical manner), eluting with a $CH_2Cl_2/CH_3OH/NH_4OH$ mixture (92/8/0.2) and then with an EtOAc/TEA mixture (87/13). 0.402 g of the pure expected is obtained.

Rf CH_2Cl_2/MeOH/NH_4OH (92/8/0.2) = 0.18

m.p. = 161-163°C.

NMR ($CDCl_3$) :

0.44 (s) : CH_3 at 18 ; 1.28 (s) : CH_3 at 17 ; 1.03 (t) : $CH_2\underline{CH_3}$; 2.61 (q) : $\underline{CH_2}$-CH_3 ; 2.81 (t) : CH_2-N ; 3.94 (t) : $\underline{CH_2}$-O ; 3.96 : H_{11} ; 6.61-6.80 : H_1 and H_2 ; 6.61-6.83 : Ph-O.

EXAMPLE 30 : 4-chloro-17alpha-methyl-11β-[4-[2-(1-piperidyl)ethoxy]phenyl]oestra-1,3,5(10)-triene-3,17beta-diol

The process is carried out as in Example 28, but starting with 2.79 g of the product obtained in Example 1.

2.12 g of the pure expected product are obtained.

Rf $CH_2Cl_2/CH_3OH/NH_4OH$ (93/7/0.2) = 0.19

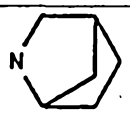
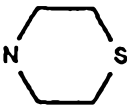
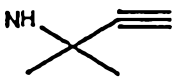
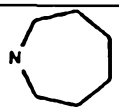
m.p. = 163°C.

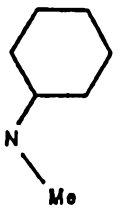
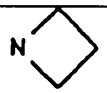
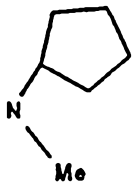
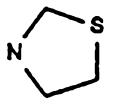
NMR ($CDCl_3$) :

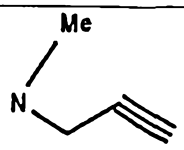
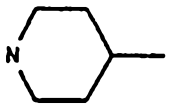
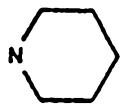
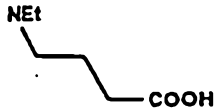
0.44 (s) : CH_3 at 18 ; 1.28 (s) : CH_3 at 17 ; 2.48 (broad t) 4H : ring CH_2N ; 2.71 (t) : CH_2-N chain ; 3.99 (t) : $\underline{CH_2}$-O ;

=4.00 masked : H_{11} ; 6.80 (d) : H_1 ; 6.98 (d) : H_2 ; 6.60-6.88 : Ph-O.

The following compounds were also prepared:

Ex	X	n	R_1	Y	NR_3R_4	R_5	R_6	Rf
31	Cl	2	H	O		OH	Me	(a) 90/10/0.4 0.25
32	Cl	2	H	O		OH	Me	(a) 90/10/0.9 0.25
33	Cl	2	H	O		OH	H	(a) 90/10/1 0.26
34	Cl	2	H	O	NMeiPr	OH	H	(a) 90/10/0.5 0.22
35	Cl	2	H	O		OH	H	(b) 30/70 0.22
36	Cl	2	H	O	NEtPr	OH	H	(a) 90/10/0.5 0.27
37	Cl	2	H	O	NMeEt	OH	H	(b) 30/70 0.22
38	Cl	2	H	O		OH	H	(a) 95/5/0.5 0.28
39	Cl	2	H	O		OH	H	(b) 30/70 0.33

Ex	X	n	R_1	Y	NR_3R_4	R_5	R_6	Rf
40	Cl	2	H	O		OH	H	(b) 30/70 0.32
41	Cl	2	H	O	NEtBu	OH	H	(a) 90/10/0.5 0.37
42	Cl	2	H	O		OH	H	(a) 90/10/0.5 0.20
43	Cl	2	H	O		OH	H	(a) 95/5/0.5 0.25
44	Cl	2	H	O		OH	H	(a) 90/10/0.5 0.30
45	Cl	2	H	O	NPr_2	OH	H	(a) 95/5/0.5 0.20
46	Cl	2	H	O		OH	H	(a) 30/70 0.28
47	Cl	2	H	O	NEtiPr	OH	H	(a) 90/10/0.5 0.22
48	Cl	2	H	O	NMePr	OH	H	(a) 90/10/0.5 0.22
49	Cl	2	H	O	NMeBu	OH	H	(a) 90/10/0.5 0.22

Ex	X	n	R_1	Y	NR_3R_4	R_5	R_6	Rf
50	Cl	2	H	O		OH	H	(a) 95/5/0.5 0.22
51	Cl	2	H	O		OH	H	(a) 90/10/0.5 0.32
52	Cl	2	H	S		OH	H	(a) 93/7/0.5 0.30
53	Cl	2	H	S O		OH	H	(a) 93/7/0.5 0.23
54	Cl	2	$(CH_2)_3$ -COOH	O	NEt_2	OH	H	(a) 80/20/1 0.25
55	Cl	2	H	O		=N-OH		(a) 90/10/0.5 0.18
56	Cl	2	H	O		OH	H	

a) CH_2Cl_2/MeOH/NH_4OH

b) TEA/EtOAc

Pharmacological tests

Effect on the proliferation of breast cells

The proliferative activity of the molecules is studied in comparison with that of oestradiol on human breast cells MCF-7 in culture.

To demonstrate an agonist effect of oestradiol and/or of the test molecules, the culture medium on which the cells are maintained (which is rich in growth factors and steroids) is replaced with a deficient medium, inter alia, which is poor in steroids (DMEM supplemented with 5% of desteroidized serum free of phenol red). The cells undergo this severance two days before the start of the test. After culturing for 7 days in the presence of the test products, the cell proliferation is evaluated by assaying the DNA. In each test, the effect of oestradiol at a concentration of 10^{-10} M (cell growth in the presence of oestradiol minus cell growth in the presence of the solvent) determines the 100% level of the agonist activity. The activity of the molecules is evaluated in comparison to this internal control. The molecules which induce a cell growth which is identical to that observed with the solvent alone are classed as "inactive", and those which induce a cell growth which is less than that observed with the solvent are classed as "inhibiting".

	ACTIVITY
Oestradiol	Agonist
Example 20	Mixed*
Example 22	Inactive
Example 23	Mixed
Example 1	Mixed
Example 30	Mixed

*Mixed : weak agonist activity at very low concentrations and inhibitory activity at higher concentrations.

Study of the effect of a product on the bones of 3-month-old ovariectomized female rats.

Compounds A, B, C, D and E are tested in order to determine their effect on the bone mass and on the activity of formation and resorption in the model of 3-month-old ovariectomized rats. The animals are treated preventively.

Animals:

Species	rat
Strain	Sprague-Dawley
Sex	female
Weight	250 g to 280 g
Number of animals/group	8

Products:

1 - Test product : Product of Examples 20, 22, 23, 30 and 1.

* vehicle(s) : corn oil, 0.5% methylcellulose
* dose(s) : one dose per test product (0.3 mg/kg/day)
* number of administrations : once/day ; 5 days/week for 4 weeks
* route of administration : oral route for the products
* volumes : 5 ml/kg (per os)
* interval between the last injection and sacrifice : 24 hours
* number of administrations : 20.

2 - Reference product : 17β-oestradiol is administered subcutaneously at a dose of 0.1 mg/kg/day as a solution in a mixture of corn germ oil/benzyl alcohol (99/1, v/v) in a volume of 0.2 ml/kg.

Experimental Protocol

Animals

The study is carried out on 3-month-old ovariectomized female rats. The animals are kept in an air-conditioned room (temperature 20°C ± 2°C) and are grouped in boxes, 4 to a box. The animals receive demineralized water and compressed feed ad libitum (pellets: AO4CR-10 UAR).

Surgery

3-month-old female rats weighing about 250 g are ovariectomized under anaesthesia with Imalgene 1000, at a dose of 100 mg/kg via the intraperitoneal (i.p.) route and under a volume of 1 ml/kg. They also receive Nembutal (3 mg/kg i.p. under a volume of 0.3 ml/kg).

After lateral incision, the cutaneous and muscular planes are sectioned. The exeresis of each ovary is carried out after ligature of the oviduct.

The "SHAM" control rats are anaesthetized under the same conditions. After incision of the cutaneous and muscular planes, each ovary is exposed and then replaced in situ.

Treatment

The effects of the products are determined in a preventive treatment. They are administered immediately after the ovariectomy. The animals are divided into groups of 8.

Group 1: "SHAM" control rats receiving the vehicle(s)

Group 2: "OVX" control rats receiving the vehicle(s)

Groups X: "OVX" rats receiving, respectively, the defined doses of the test product(s).

Blood samples

At the end of 4 weeks (duration of the study) the animals are decapitated by guillotine. The sera collected after centrifugation are stored at -20°C.

A lipid balance will be established from the serous assays of total cholesterol, of triglycerides and of phospholipids on a 500 µl aliquot of serum. The lowering of the cholesterol content of the serum is expressed as a percentage relative to the content shown by the ovariectomized animals which receive only the solvent.

Organ samples

After sacrificing the animals, the following organs are removed:

- tractus genitalis

The uteri are removed. The latter are weighed. The increase in weight is expressed as a percentage of the weight of the uterus of the ovariectomized animals which receive only the solvent.

- at the bone level:

The bone mass (BMD or Bone Mineral Density) is measured by biphotonic dual energy X-ray absorptiometry (DEXA). The measurements are carried out on excized bone freed of all soft tissue. The BMD (bone mineral density) is measured on the whole bone as well as on the metaphyseal part at the level of the proximal end for the left tibia. This zone is defined as being the region which is richest in trabecular bone, and consequently is the region which is most sensitive to changes in bone volume and in bone mineral density.

The results are expressed in percentages according to the formula:

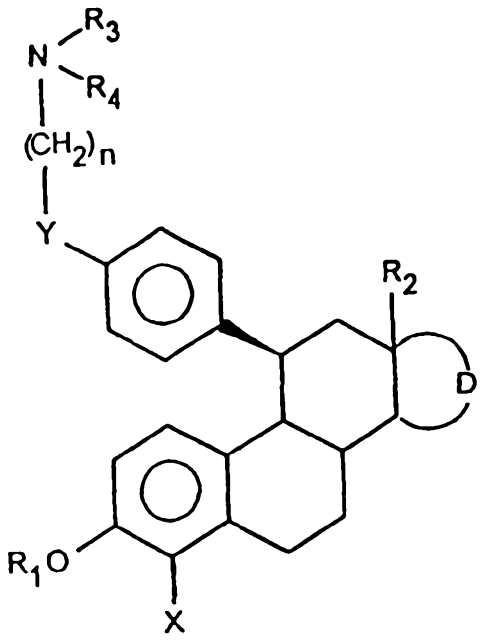
$$\frac{\text{BMD of test product - BMD OVX}}{\text{BMD SHAM - BMD OVX}} \times 100$$

	Dose route mg/kg	TIBIA BONE BMD %	UTERUS Weight %	Cholesterol %
OVX		0		
SHAM		100		
Oestradiol	0.1 s.c.	105	359	-35
Ex. 20	0.3 p.o.	69	60	-43
Ex. 20	1.0 p.o.	74	50	-40
Ex. 22	0.3 p.o.	63	57	-52
Ex. 23	0.3 p.o.	67	64	-53
Ex. 23	1.0 p.o.	71	74	-53
Ex. 1	0.3 p.o.	57	55	-50
Ex. 1	1.0 p.o.	64	55	-48
Ex. 30	0.3 p.o.	52	68	-51
Ex. 30	1.0 p.o.	71	55	-48

Where the terms "comprise", "comprises", "comprised" or "comprising" are used in this specification, they are to be interpreted as specifying the presence of the stated features, integers, steps or components referred to, but not to preclude the presence or addition of one or more other feature, integer, step, component or group thereof.

The claims defining the invention are as follows:

1) Compounds of general formula (I):



(I)

in which:

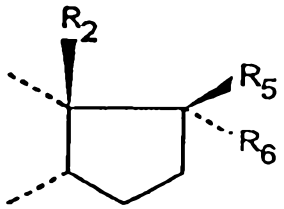
R_1 represents a hydrogen atom, a $(CH_2)_m$-Ar, (CO)-Ar, $(CH_2)_m$-Alk or (CO)-Alk radical,
R_2 represents a linear or branched, saturated or unsaturated hydrocarbon radical containing 1 to 6 carbon atoms,

D represents a residue of an optionally substituted pentagonal or hexagonal ring optionally bearing an unsaturation,

X represents a halogen atom,
Y is chosen from 0, S, SO, SO_2 and NH,
n is an integer ranging from 2 to 8,
either R_3 and R_4, which may be identical or different, represent a hydrogen atom, a $(CH_2)_m$-Ar, $(CH_2)_m$-Het or $(CH_2)_m$Alk group,
or R_3 and R_4, together with the nitrogen atom to which they are attached, form a 3- to 15-membered aromatic or non-aromatic, saturated or unsaturated, monocyclic or polycyclic heterocycle optionally containing 1 to 3 additional heteroatoms chosen from oxygen, sulphur and nitrogen, which is unsubstituted or substituted,

Ar representing a carbocyclic aryl group containing from 6 to 18 carbon atoms, Het representing a saturated or unsaturated aromatic or non-aromatic heterocycle radical containing from 1 to 9 carbon atoms and from 1 to 5 heteroatoms chosen from oxygen, nitrogen or sulphur atoms, Alk representing a saturated or unsaturated, linear, branched or cyclic, non-aromatic hydrocarbon radical and containing from 1 to 12 carbon atoms, the Ar, Het or Alk radicals being able to be substituted or non-substituted, and m represents 0, 1, 2 or 3, as well as their addition salts with bases or acids.

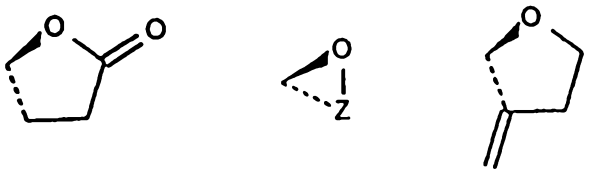
2) Compounds of general formula (I) as defined in claim 1, in which D represents a residue of a pentagonal ring of formula:



in which R_2 is as defined in claim 1,

either R_5 represents an OH, O-$(CH_2)_m$-Alk, O-(CO)-Alk, O-$(CH_2)_m$-Ar, O-(CO)-Ar, O-$(CH_2)_m$-Het, O-(CO)-Het radical and R_6 represents a hydrogen atom or a substituted or unsubstituted alkyl, alkenyl or alkynyl radical containing from 1 to 6 carbon atoms, m, Alk, Ar and Het being as defined in claim 1,

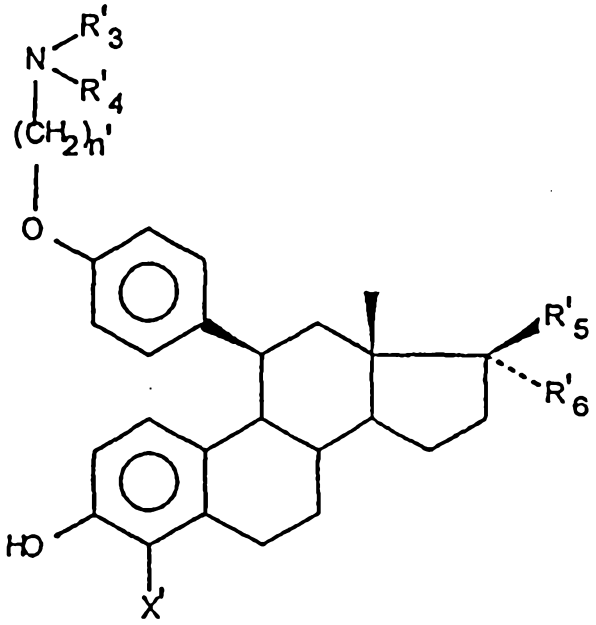
or R_5 and R_6, together with the carbon atom which bears them, form one of the following rings:



in which z represents a $-(CH_2)_l-$ or $-CH=CH-(CH_2)_{l'}$ group; l being an integer between 1 and 4 and l' being an integer equal to 1 or 2,

or R_5 and R_6 together form an oxo group or =N-OH, and the addition salts thereof with acids or bases.

3. Compounds of the general formula (I) as defined in Claim 1, corresponding to the general formula (I'):



(I')

in which:

X' represents a chlorine or bromine atom,

n' is between 2 and 5,

either R'_3 and R'_4, which may be identical or different, represent an alkyl radical containing from 1 to 6 carbon atoms

or R'_3 and R'_4, together with the nitrogen atom to which they are attached, form a 3- to 15-membered saturated monocyclic or polycyclic residue optionally containing an additional hetero atom chosen from oxygen, sulphur and nitrogen,

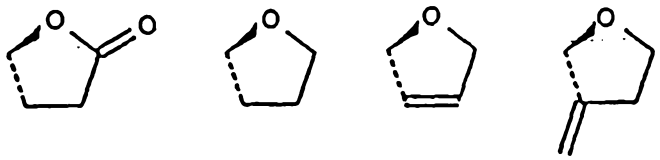
R'_5 and R'_6 are as defined for R_5 and R_6, according to Claim 2, and the addition salts thereof with acids and bases.

4. Compounds of the general formula (I') as defined in Claim 3, in which:

either R'_5 represents an OH radical and R'_6 represents a hydrogen atom or a substituted or unsubstituted alkyl,

alkenyl or alkynyl radical containing from 1 to 6 carbon atoms,

or R'_5 and R'_6, together with the carbon atom which bears them, form one of the following rings:



or R'_5 and R'_6 together form an oxo group,

and the addition salts thereof with acids or bases.

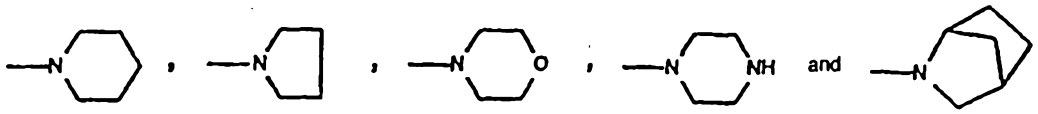
5. Compounds of the general formula (I') as defined in Claim 3 or 4, in which:

X' represents a chlorine atom

n' is equal to 2

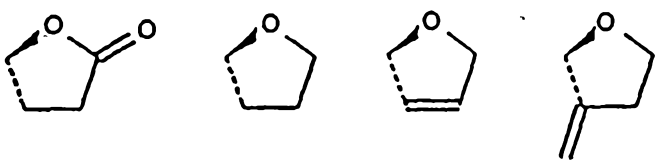
either R'_3 and R'_4, which may be identical or different, represent an alkyl radical containing from 1 to 6 carbon atoms

or R'_3 and R'_4, together with the nitrogen atom, form the following saturated heterocycles:



and either R'_5 represents an OH radical and R'_6 represents a hydrogen atom or a substituted or unsubstituted alkyl, alkenyl or alkynyl radical containing from 1 to 6 carbon atoms,

or R'_5 and R'_6, together with the carbon atom which bears them, form one of the following rings:



or R'_5 and R'_6 together form an oxo group,

and the addition salts thereof with acids or bases.

6. Compounds of the formula (I) or (I') as defined in any one of Claims 1 to 5, of the following names:

- 4-chloro-3-hydroxy-11β-[4-[2-(diethylamino)ethoxy]phenyl]-oestra-1, 3, 5(10)-trien-17-one,
- 4-chloro-3-hydroxy-11β-[4-[2-(dimethylamino)ethoxy]phenyl]-oestra-1, 3, 5(10)-trien-17-one,
- 4-chloro-3-hydroxy-11β-[4-[2-(1-piperidinyl)ethoxy]phenyl]-oestra-1, 3, 5(10)-trien-17-one,
- 4-chloro-3-hydroxy-11β-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]-oestra-1, 3, 5(10)-trien-17-one,
- 4-bromo-3-hydroxy-11β-[4-[2-(1-piperidinyl)ethoxy]phenyl]-oestra-1, 3, 5(10)-trien-17-one,
- 4-chloro-11β-[4-[2-(dimethylamino)ethoxy]phenyl]-oestra-1,3,5(10)-triene-3,17beta-diol,

- 4-chloro-11β-[4-[2-(diethylamino)ethoxy]phenyl]-oestra-1,3,5(10)-triene-3, 17beta-diol,

- 4-chloro-11β-[4-[2-(1-piperidinyl)ethoxy]phenyl]-oestra-1,3,5(10)-triene-3, 17beta-diol,

- 4-bromo-11β-[4-[2-(1-piperidinyl)ethoxy]phenyl]-oestra-1,3,5(10)-triene-3,17beta-diol,

- 4-chloro-11β-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]-oestra-1,3,5(10)-triene-3,17beta-diol,

- 4-chloro-11β-[4-[2-(diethylamino)ethoxy]phenyl]-19-nor-17alpha-pregna-1,3,5(10)-trien-20-yne-3,17beta-diol,

- 4-chloro-11β-[4-[3-(1-piperidinyl)propoxy]phenyl]-oestra-1,3,5(10)-triene-3, 17beta-diol,

- 4-chloro-11β-[4-[4-(1-piperidinyl)butoxy]phenyl]-oestra-1,3,5(10)-triene-3,17beta-diol,

- 4-chloro-11β-[4-(5-(1-piperidinyl)pentyloxy]phenyl]-oestra-1,3,5(10)-triene-3,17beta-diol,
- gamma lactone of (17alpha)-4-chloro-3,17beta-dihydroxy-11β-[4-[2-(diethylamino)ethoxy]phenyl]-19-nor-pregna-1,3,5(10)- triene-21-carboxylic acid,
- gamma lactone of (17alpha)-4-chloro-3,17beta-dihydroxy-11β-[4-[2-(1-pyrrolindinyl) ethoxy]phenyl]-19-nor-pregna-1,3,5(10)-triene-21-carboxylic acid,
- gamma lactone of (17alpha)-4-chloro-3,17beta-dihydroxy-11β-[4[2(1-piperidinyl)ethoxy]phenyl]-19-nor-pregna-1,3,5(10)-triene-21-carboxylic acid,
- gamma lactone of (17alpha)-4-chloro-3,17beta-dihydroxy-11β-[4-[3-(1-piperidinyl)propoxy]phenyl]-l9-nor-pregna-1,3,5(10)-triene-21-carboxylic acid,

- gamma lactone of (17alpha)-4-chloro-3,17beta-dihydroxy-11β-[4-[4-(1-piperidinyl)butoxy]phenyl]-19-nor-pregna-1,3,5(10)-triene-21-carboxylic acid,
- gamma lactone of (17alpha)-4-chloro-3,17beta-dihydroxy-11β-[4-[5-(1-piperidinyl)pentyloxy]phenyl]-19-nor-pregna-1,3,5(10)-triene-21-carboxylic acid,
- (17beta)-4-chloro-11β-[4-[2-(diethylamino)ethoxy]phenyl]-spiro[oestra-1,3,5(10)-triene-17,2'(5'H)furan]-3-o1,
- (17beta)-4-chloro-11β-[4-[2-(1-piperidinyl)ethoxy]phenyl]-spiro[oestra-1,3,5(10)-triene-17,2'(5'H)furan]-3-o1,
- (17beta)-4-chloro-11β-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]-spiro[oestra-1,3,5(10)-triene-17,2'(5'H)furan]-3-o1,
- (17beta)-4-chloro-4',5'-dihydro-11β-[4-[2-(l-piperidinyl)ethoxy]phenyl]-spiro[oestra-1,3,5(10)-triene-17,2'(3'H)furan]-3-o1,
- (17beta)-4-chloro-11β-[4-[3-(1-piperidinyl)propoxy)phenyl]-spiro[oestra-1,3,5(10)-triene-17,2'(5'H)furan]-3-o1,
- (17beta)-4-chloro-4',5'-dihydro-11β-[4-[3-(1-piperidinyl)propoxy] phenyl]-spiro[oestra-1,3,5(10)-triene-17,2'(3'H)furan]-3-o1,
- (17beta)-4-chloro-11β-[4-[4-(1-piperidinyl)butoxy]phenyl]-spiro[oestra-1,3,5(10)-triene-17,2'(5'H)furan]-3-o1,
- (17beta)-4-chloro-4',5'-dihydro-11β-[4-[4-(1-piperidinyl)-butoxy]phenyl]-spiro[oestra-1,3,5(10)-triene-17,2'(3'H)furan]-3-o1,
- 4-chloro-11β-[4-[2-(diethylamino)ethoxy]phenyl]-17alpha-methyl-oestra-1,3,5(10)-triene-3,17beta-diol,
- 4-chloro-17alpha-methyl-11β-[4-[2-(1-piperidinyl)ethoxy]phenyl]-oestra-1,3,5(10)-triene-3,17beta-diol,
- 4-chloro-17alpha-methyl-11β-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]-oestra-1,3,5(10)-triene-3,17beta-diol,
- 11β-[4-[2-[2-aza-bicyclo(2.2.1)hept-2-yl]ethoxy] phenyl]-4-chloro-17alpha-methyl-oestra-1,3,5(10)-triene-3,17beta-diol,
- 11β-[4-[2-[2-aza-bicyclo(2.2.1)hept-2-yl]ethoxy] phenyl]-4-chloro-oestra-1,3,5(10)-triene-3,17beta-diol,
- 4-chloro-11β-(4-[2-[methyl(1-methylethyl)amino]ethoxy]phenyl]-oestra-1,3,5(10)-triene-3,17beta-diol,
- 4-chloro-11β-(4-[2(tetrahydro-(1H)-1,4-thiazin-4-yl)ethoxy]phenyl]-oestra-1,3,5(10)-triene-3,17beta-diol,

- 4-chloro-11β-[4-[2-[ethyl(propyl)amino]ethoxy]phenyl]-oestra-1,3,5(10)-triene-3,17beta-diol,

- 4-chloro-11β-[4-[2-[ethyl(methyl)amino]ethoxy]phenyl]-oestra-1,3,5(10)-triene-3,17beta-diol,

- 4-chloro-11β-[4-[2-[(1,1-dimethyl-2-propynyl)amino]ethoxy]phenyl]-oestra-1,3,5(10)-triene-3,17beta-diol,

- 4-chloro-11β-[4-[2-(hexahydro-1H-azepin-1-yl)ethoxy]phenyl]-oestra-1,3,5(10)-triene-3,17beta-diol,

- 4-chloro-11β-[4-[2-[cyclohexyl(methyl)amino]ethoxy]phenyl]-oestra-1,3,5(10)-triene-3,17beta-diol,

- 4-chloro-11β-[4-[2-[butyl(ethyl)amino]ethoxy]phenyl]-oestra-1,3,5(10)-triene-3,17beta-diol,

- 4-chloro-11β-[4-[2-(1-azetidinyl)ethoxy]phenyl]-oestra-1,3,5(10)-triene-3,17beta-diol,

- 4-chloro-11β-[4-[2-[ethyl(2-propenyl)amino]ethoxy]phenyl]-oestra-1,3,5(10)-triene-3,17beta-diol,

- 4-chloro-11β-[4-[2-[cyclopentyl(methyl)amino]ethoxy]phenyl]-oestra-1,3,5(10)-triene-3,17beta-diol,

- 4-chloro-11β-[4-[2-[dipropylamino)ethoxy]phenyl]-oestra-1,3,5(10)-triene-3,17beta-diol,

- 4-chloro-11β-[4-[2-(3-thiazolidinyl)ethoxy]phenyl]-oestra-1,3,5(10)-triene-3,17beta-diol,

- 4-chloro-11β-[4-[2-[ethyl(1-methylethyl)amino]-ethoxy]-phenyl]oestra-1,3,5(10)-triene-3,17beta-diol,

- 4-chloro-11β-[4-[2-[methyl(propyl)amino]ethoxy]-phenyl]oestra-1,3,5(10)-triene-3,17beta-diol,

- 4-chloro-11β-[4-[2-[butyl(methyl)amino]ethoxy]-phenyl]oestra-1,3,5(10)-triene-3,17beta-diol,

- 4-chloro-11β-[4-[2-[methyl(2-propynyl)amino]ethoxy]-phenyl]oestra-1,3,5(10)-triene-3,17beta-diol,

- 4-chloro-11β-[4-[2-(4-methyl-1-piperidyl)ethoxy]-phenyl]oestra-1,3,5(10)-triene-3,17beta-diol,

- 4-chloro-11β-[4-[2-(1-piperidyl)ethylthio]phenyl]-oestra-1,3,5(10)-triene-3,17beta-diol,

- 4-chloro-11β-[4-[2-(1-piperidyl)ethylsulphinyl]-phenyl]oestra-1,3,5(10)-triene-3,17beta-diol,

- 4-[4-chloro-11beta-[4-[2-(diethylamino)ethoxy]-phenyl]-17beta-hydroxyoestra-1,3,5(10)-trien-3-yloxy]butanoic acid,

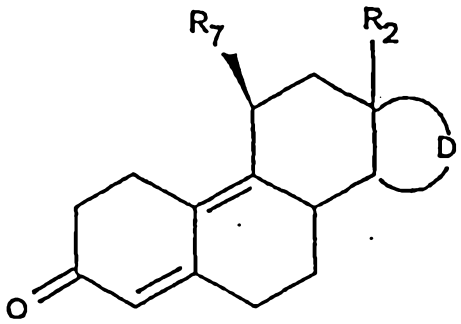
- 4-chloro-3-hydroxy-11beta-[4-[2-(1-piperidyl)ethoxy]-phenyl]oestra-1,3,5(10)-trien-17-one oxime,

- 4-[[2-[4-(4-chloro-3,17beta-dihydroxyoestra-1,3,5(10)-trien-11beta-yl)phenoxy]ethyl]ethylamino]-butanoic acid.

7. Compound of the formula (I) or (I') as defined in any one of Claims 1 to 5, of the following name:

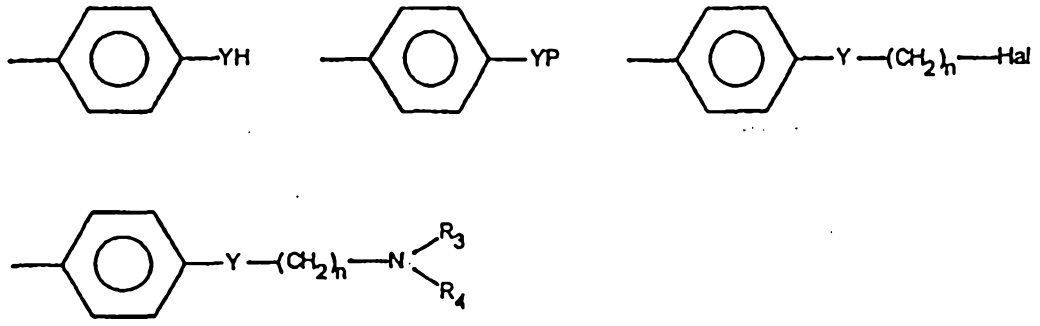
- 4-chloro-11β-[4-[2-(diethylamino)ethoxy]phenyl]-oestra-1,3,5(10)-triene-3,17beta-diol, and the addition salts thereof with acids.

8. Process for preparing the compounds of the general formula (I) as defined in Claim 1 or 2, characterized in that a compound of the general formula (II):



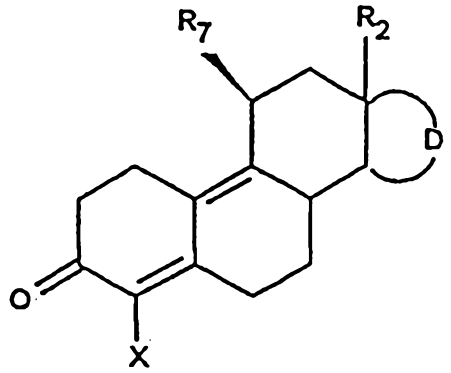
(II)

in which D and R_2 are as defined in Claim 1, R_7 represents one of the following groups:



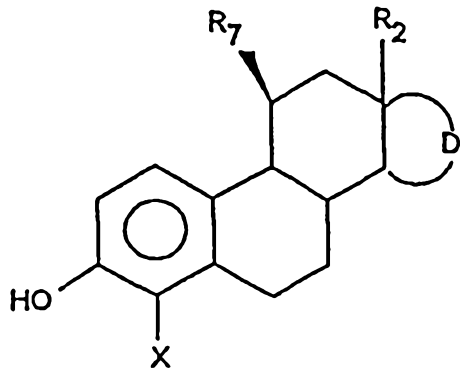
in which n, Y, R_3 and R_4 are as defined in Claim 1, P is a protecting group and Hal represents a halogen,

is subjected to the action of a halogenating reagent in order to obtain the compound of the formula (III):



(III)

which is subjected to the action of a reagent for aromatizing the ring A, followed by the action of a base in order to obtain the compound of the formula (IV) corresponding to certain compounds of the general formula (I):



(IV)

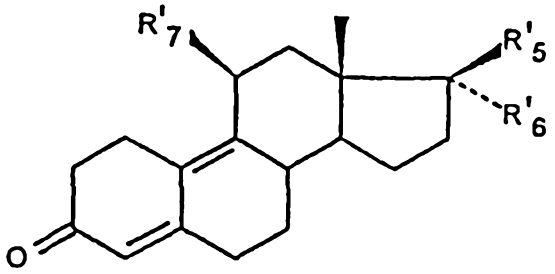
which compounds of the formula (II), (III) or (IV)

are subjected, if so desired and if necessary, in an appropriate order, to one or more of the following reactions:

- protection of the compounds in which R_7 is a -Ph-YH, group
- deprotection of the compounds in which R_7 is a Ph-YP group,
- action of a compound of the formula $Hal_1-(CH_2)_n-Hal_2$ on compounds in which R_7 is a-Ph-YH group, Hal_1 or Hal_2, which may be identical or different, representing a halogen, in order to obtain compounds in which R_7 is a-Ph-Y-$(CH_2)_n$-Hal_2 group,
- action of a compound of the formula R_3-NH-R_4 on compounds in which R_7 is a Ph-Y-$(CH_2)_n$-Hal_2 group in order to obtain compounds in which R_7 is a Ph-Y-$(CH_2)_n$-NR_3R_4 group,
- action of a halide salt ($M-Hal_3$) on compounds in which R_7 is a Ph-Y-$(CH_2)_n$-Hal_2 group in order to obtain compounds in which R_7 is a-Ph-Y-$(CH_2)_n$-Hal_3 group,
- protection of the OH group in position 3 or 17,
- deprotection of the OH group in position 3 or 17,
- alkylation of the OH group in position 3 or 17,
- acylation of the OH group in position 3 or 17,
- action of a reducing agent when D represents a residue of a pentagonal ring as defined in Claim 2 and R_5 and R_6 together form an oxo group,
- action of an organometallic reagent on the compounds of the formula (IV) with D representing a residue of a pentagonal ring as defined in Claim 2 and R_5 and R_6 together form an oxo group,
- action of a lactonizing agent on the compounds of the formula (IV) with D representing a residue of a pentagonal ring as defined in Claim 2 and R_5 and R_6 together forming an oxo group,
- action of an agent for reducing the double bond when D represents a residue of a pentagonal ring as defined in Claim 2 and R_5 and R_6 form, together with the carbon which bears them, a group O-$(CH_2)_{n'}$-CH=CH-,

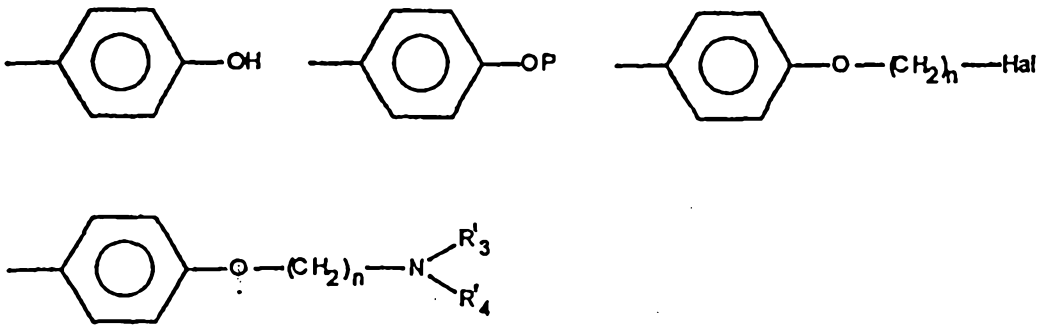
- action of an agent for reducing the double bond when D represents a residue of a pentagonal ring as defined in Claim 2 and R_6 is an alkenyl or alkynyl radical containing from 2 to 6 carbon atoms,
- halogenation in position 4, followed by aromatization of ring A, of the compound of the general formula (II),
- aromatization of ring A of the compound of the formula (III),
- salification.

9. Process according to Claim 8 for preparing the compounds of the general formula (I') as defined in Claim 3, characterized in that a compound of the general formula (II'):

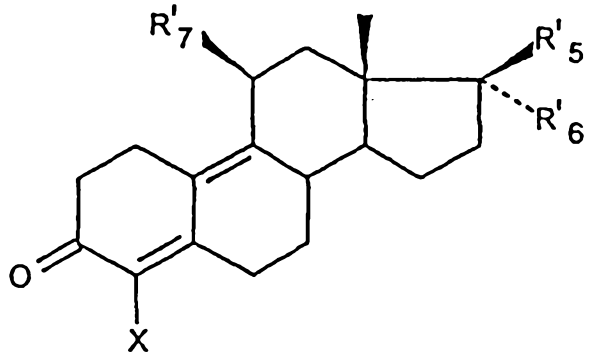


(II')

in which R'_5 and R'_6 are as defined in Claim 3 and R'_7 represents:

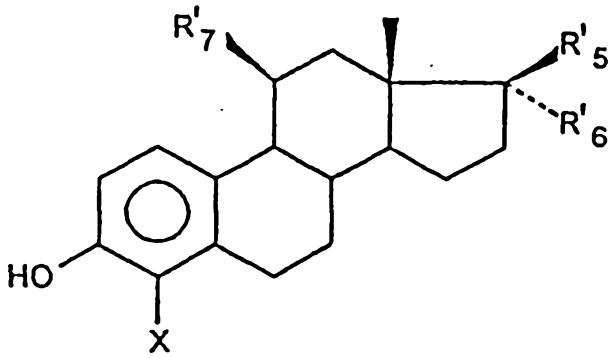


is subjected to the action of a halogenating reagent in order to obtain the compound of the formula (III'):



(III')

which is subjected to the action of a reagent for aromatization of the ring A, followed by the action of a base in order to obtain the compound of the formula (IV') corresponding to certain compounds of the general formula (I'):



(IV')

which compounds of the formula (II'), (III') or (IV') are subjected, if so desired and if necessary, in an appropriate order, to one or more of the following reactions:

- protection of the compounds in which R'_7 is a -Ph-OH group,
- deprotection of the compounds in which R'_7 is a Ph-OP group,
- action of a compound of the formula $Hal_1-(CH_2)_n-Hal_2$ on the compounds in which R'_7 is a -Ph-OH group, Hal_1 or Hal_2, which may be identical or different, representing a halogen, in order to obtain compounds in which R_7 is a $-Ph-O-(CH_2)_n-Hal_2$ group,
- action of a compound of the formula $R'_3-NH-R'_4$ on the compounds in which R'_7 is a $Ph-O-(CH_2)_n-Hal_2$ group in order to obtain compounds in which R'_7 is a $Ph-O-(CH_2)_n-NR'_3R'_4$ group,

- deprotection of the compounds in which R'_7 is a Ph-OP group,
- the action of a compound of formula Hal_1-$(CH_2)_n$-Hal_2 on the compounds in which R'_7 is a -Ph-OH group, Hal_1 or Hal_2, which may be identical or different, representing a halogen in order to obtain the compounds in which R_7 is a -Ph-O-$(CH_2)_n$-Hal_2 group,
- the action of a compound of formula R'_3-NH-R'_4 on the compounds in which R'_7 is a Ph-O-$(CH_2)_n$-Hal_2 group, in order to obtain the compounds in which R'_7 is Ph-O-$(CH_2)_n$-$NR'_3R'_4$ group,
- the action of a halide salt (M-Hal_3) on compounds in which R'_7 is a Ph-O-$(CH_2)_n$-Hal_2 group in order to obtain the compounds in which R_7 is a -Ph-O-$(CH_2)_n$-Hal_3 group,
- protection of the OH group in position 3 or 17,
- deprotection of the OH group in position 3 or 17,
- alkylation of the OH group in position 17,
- acylation of the OH group in position 17,
- the action of a reducing agent when R'_5 and R'_6 together form an oxo group,
- the action of an organometallic reagent on the compounds of formula (IV') with R'_5 and R'_6 together forming an oxo group,
- the action of a lactonizing agent on the compounds of formula (IV') with R'_5 and R'_6 together forming an oxo group,
- the action of an agent for reducing the double bond, when R'_5 and R'_6, together with the carbon which bears them, form a O-$(CH_2)_n$'-CH=CH- group,
- the action of an agent for reducing the double bond, when R'_6 is an alkenyl or alkynyl radical containing 2 to 6 carbon atoms,
- halogenation in position 4, followed by aromatization of ring A, of the compound of formula (II'),
- aromatization of the compound of formula (III'),
- salification.

10 As medicaments the compounds of formula (I) as defined in claim 1, as well as their addition salts with pharmaceutically acceptable acids.

11. As medicaments the compounds of formula (I) or (I') as defined in any one of claims 2 to 5, as well as their addition salts with pharmaceutically acceptable acids.

12. As medicaments the compounds as defined in claim 6 or 7, as well as their addition salts with pharmaceutically acceptable acids.

13. The pharmaceutical compositions containing one or more of the medicaments as defined in any one of claims 10, 11 or 12.

14. As new intermediate products, the compounds of general formula (III), (III'), (IV) or (IV') as defined in claim 8 or 9.

15. Medicament as defined in claims 11 to 13 for the prevention of treatment of osteoporosis.

16. Medicament as defined in claims 11 to 13 for the cardiovascular protection.

17. Compounds of general formula I as defined in claim 1, substantially as herein described with reference to any one of the Examples.

18. Preparation process of claim 8 which process is substantially as herein described with reference to any one of the Examples.

19. The pharmaceutical compositions of claim 13, substantially as herein described with reference to any one of the Examples.

20. Medicaments of any one of claims 10 to 12, 15 or claim 16, substantially as herein described with reference to any one of the Examples.

21. Intermediate products of claim 14, substantially as herein described with reference to any one of the Examples.

Dated this 17th day of May, 2002.

HOECHST MARION ROUSSEL
By their Patent Attorneys:
CALLINAN LAWRIE