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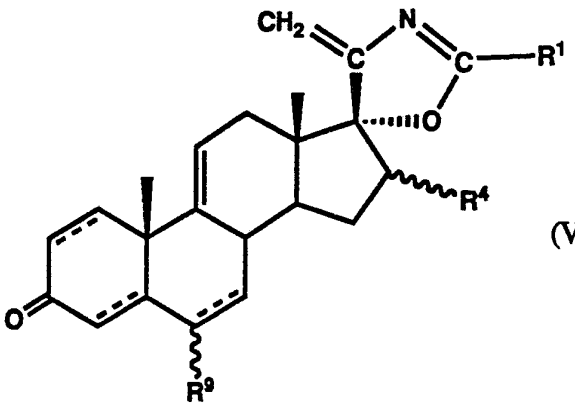
(54) Title: PROCESS FOR DEHYDRATING CORTICOSTEROID INTERMEDIATES



(V)

(57) Abstract

A process for preparing oxazoline corticosteroid intermediates of formula (V) wherein R^1 represents hydrogene (H), loweralkyl, phenyl or phenylalkyl; R^4 represents H or loweralkyl, preferably methyl having either the α or β stereochemistry; and R^9 represents hydrogen, fluoro, chloro or loweralkyl. The process comprises contacting a compound of formula (III) herein, with (A) Vilsmeier reagent, followed by acid hydrolysis to yield the compound of formula (V); or alternatively, (B) an acid having a pK_a of less than 5, to yield the compound of formula (V).

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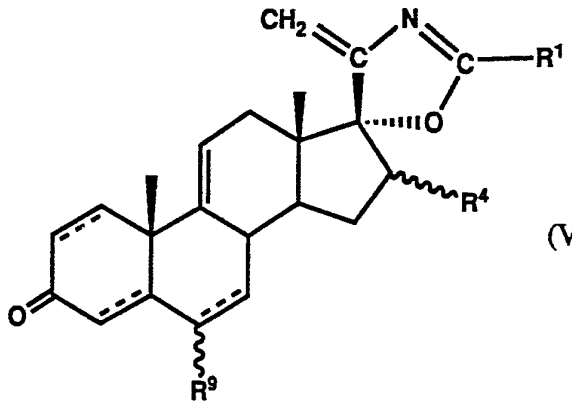
PROCESS FOR DEHYDRATING CORTICOSTEROID INTERMEDIATES

BACKGROUND

The 9α-OH steroids are useful intermediates for preparing corticosteroids. Such corticosteroids are useful for treatment of psoriasis, dermatological diseases and inflammation. U.S. Patent 4,127,596 describes a process for dehydrating 9α–hydroxyandrostenedione type compounds with chlorosulfonic acid to give Δ9,11 steroids. U.S. Patent 4,102,907 and European Patent Application number 87201933.6 teach dehydration of steroid intermediates. United Kingdom (UK) Patent Application GB 2086907A to Barton et al teaches the preparation of oxazoline steroid intermediates by employing a peracid. U.S. Patent 4,585,590 teaches a process for preparing a C_3 protected form of an oxazoline from particular steroid intermediates. However, none of these references teaches the concommittant dehydration and oxazoline formation from a 9α–hydroxysteroid with an acid having a pK_a of about 5 or less or with Vilsmeier Reagent. The oxazoline moiety has been shown in Barton et al to be a useful precursor to pregnanes and corticosteroids. It would be desirable to provide a process for preparing Δ9,11 steroids possessing the requisite oxazoline moiety from 9α-hydroxysteroid starting materials. Steroids containing the Δ9,11 double bond are useful intermediates for the preparation of pharmaceutically active corticosteroids as taught in Louis F. Fieser and Mary Fieser, Steroids, Reinhold Publishing Corporation, New York (1959). Thus, it would be desirable to provide a process for preparing Δ9,11 steroids possessing the requisite oxazoline moiety, and which can also reduce the steps required for their preparation.

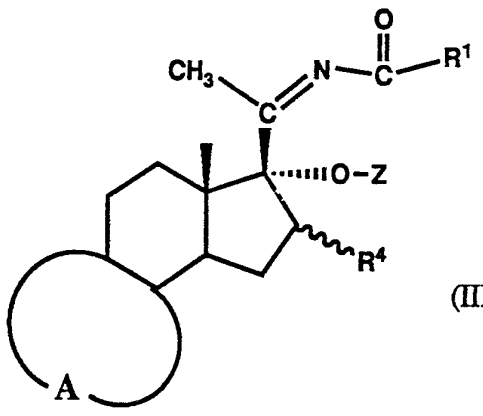
SUMMARY

The present invention is directed towards a process for preparing oxazoline corticosteroid intermediates of formula (V):



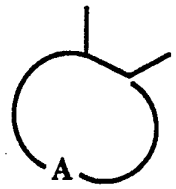
(V)

wherein R^1 represents hydrogen (H), loweralkyl, phenyl or phenylalkyl; R^4 represents H or loweralkyl, preferably methyl having either the α or β stereochemistry; and R^9 represents hydrogen, fluoro, chloro or loweralkyl. The process comprises contacting a 9α-hydroxysteroid of the formula:



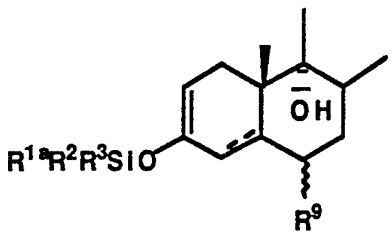
(III)

its tautomer or mixtures thereof, wherein Z represents hydrogen, alkoxyalkyl, trisubstituted silyl of the formula $-SiR^{1a}R^2R^3$ wherein R^{1a}, R^2 and R^3 independently represent loweralkyl, phenyl or phenylalkyl;

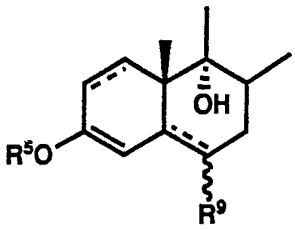


represents

an enol ether of the formula:

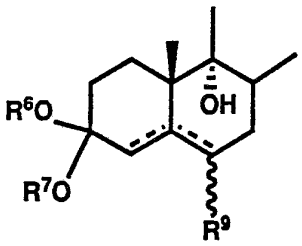


or



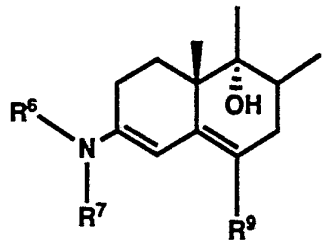
wherein R^5 represents loweralkyl and R^9 is as defined hereinbefore, wherein R^{1a}, R^2 and R^3 are as defined hereinafter;

a ketal of the formula



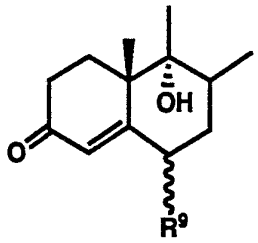
wherein R^6 and R^7 independently represent loweralkyl or -$(CR^{20}R^{21})_v$- and -$(CR^{30}R^{31})_w$-, respectively, wherein R^{20}, R^{21}, R^{30} and R^{31} independently represent H, loweralkyl, or aryl and w and v independently represent an integer from 0 to 6 and v + w is an integer from 2 to 12, preferably 2, and wherein -$(CR^{20}R^{21})_v$- or -$(CR^{30}R^{31})_w$- are connected together in a ring or through an oxygen or nitrogen atom; and R^9 is as defined hereinbefore;

an enamine of the formula



wherein R^6 and R^7 are as defined hereinbefore; or

a ketone of the formula

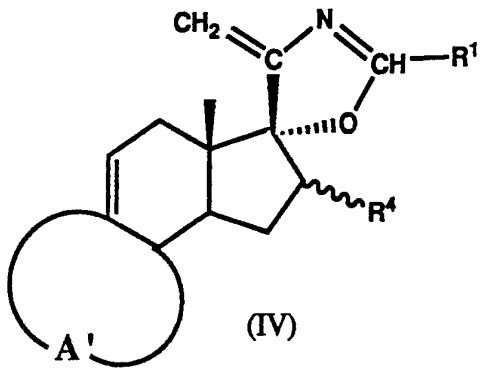


wherein R^9 is as defined hereinbefore; with

(A) Vilsmeier reagent, followed by acid hydrolysis to yield the compound of formula V; or alternatively,

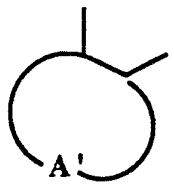
(B) an acid having a pK_a of about 5 or less, to yield the compound of formula V. The acid can be chlorosulfonic acid, sulfuric, phosphoric, methanesulfonic, perchloric, or trifluoracetic acids or mixtures thereof, most preferably chlorosulfonic acid.

In another embodiment, the present invention is directed toward a process for preparing compounds of formula (IV):



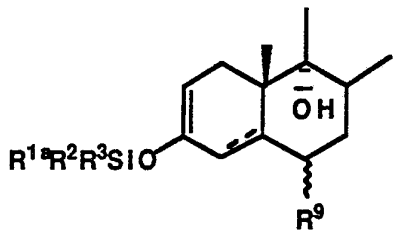
(IV)

wherein R^1 and R^4 are as defined hereinbefore.and

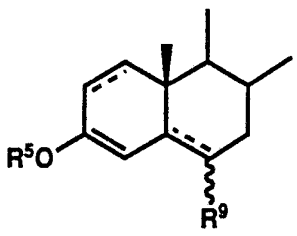


represents

an enol ether of the formula:

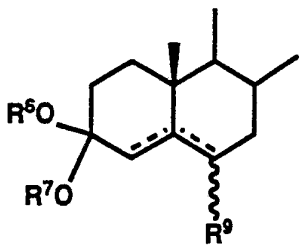


or



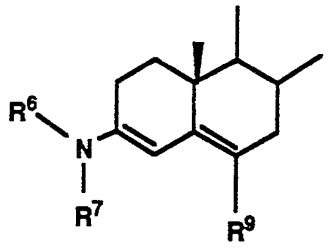
wherein R^5 represents loweralkyl and R^9 is as defined hereinbefore, wherein R^{1a}, R^2 and R^3 are as defined hereinafter;

a ketal of the formula



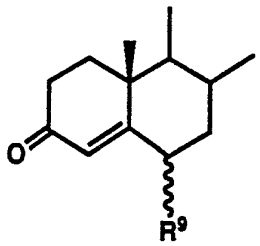
wherein R^6 and R^7 independently represent loweralkyl or -$(CR^{20}R^{21})_v$- and -$(CR^{30}R^{31})_w$-, respectively, wherein R^{20}, R^{21}, R^{30} and R^{31} independently represent H, loweralkyl, or aryl and w and v independently represent an integer from 0 to 6 and v + w is an integer from 2 to 12, preferably 2, and wherein -$(CR^{20}R^{21})_v$- or -$(CR^{30}R^{31})_w$- are connected together in a ring or through an oxygen or nitrogen atom; and R^9 is as defined hereinbefore;

an enamine of the formula



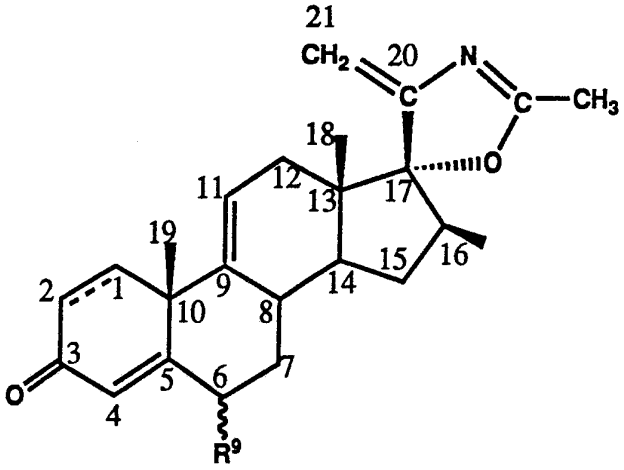
wherein R^6 and R^7 are as defined hereinbefore; or

a ketone of the formula



wherein R^9 is as defined hereinbefore. The process comprises contacting the compound of formula (III) with Vilsmeier Reagent under conditions effective to give the compound of formula (IV).

In one embodiment, the present process gives preferred compounds of formula



(IV')

wherein the dotted line represents an optional double bond and wherein the numbering system is illustrated for those preferred compounds.

The present process has the unexpected and surprising advantage of concommittantly and regio-specifically dehydrating the 9α-OH and forming a Δ9,11 steroid possessing the desired oxazoline moiety for the production of such steroids in a single step or reaction vessel. Such a combination is useful for the production of corticosteroids from the steroid derived compound 9α-hydroxyandrost-4-ene-3,17 dione. The present process also has the advantage of providing a one-step process wherein the product of formula (V) permits convenient attachment of important functional groups at C-21 adjacent to the oxazoline moiety.

DETAILED DESCRIPTION OF THE EMBODIMENTS

When utilized in the present specification and in the appended claims the terms listed hereinbelow, unless otherwise indicated are defined as follows:

The term "alkyl" or "loweralkyl" refers to a straight chain saturated hydrocarbon moiety containing from 1 to 6

carbon atoms, or a branched saturated hydrocarbon moiety of 3 to 6 carbon atoms, such as for example, methyl (ie. -CH_3), ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl and the like.

The term "alkoxy" refers to an alkyl moiety convalently bonded to an adjacent structural element through an oxygen atom, such as for example, methoxy(-OCH_3), ethoxy, propoxy, isopropoxy, butoxy, hexoxy and the like.

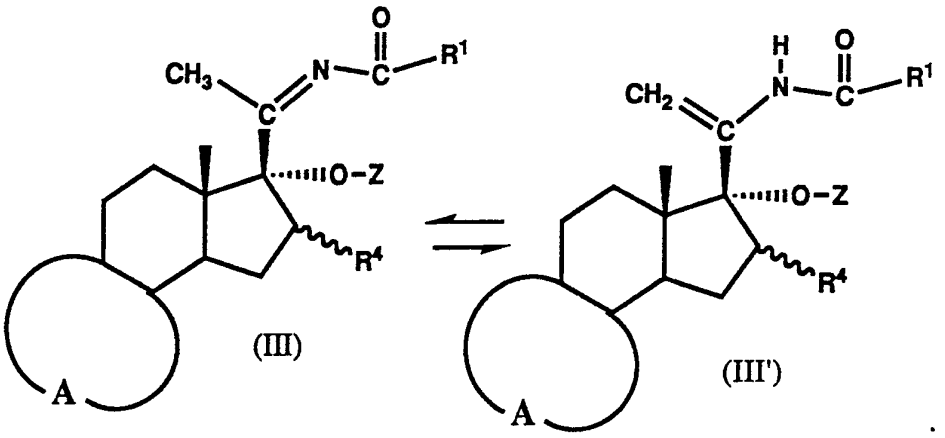
The term "alkoxyalkyl" refers to an alkoxy moiety of 1 to 6 carbon atoms covalently bonded to an alkyl moiety of 1 to 6 carbon atoms.

The term "phenylalkyl" refers to a phenyl moiety convalently bonded to an alkyl moiety of one to six carbon atoms such as, for example, phenylmethyl, 2-phenylethyl and the like.

The term "chlorosulfonic acid" known as sulfuric chlorohydrin, has the empirical formula $ClSO_2OH$. Chlorosulfonic acid is a known compound, formed by treating sulfur trioxide or fuming sulfuric acid with hydrochloric acid.

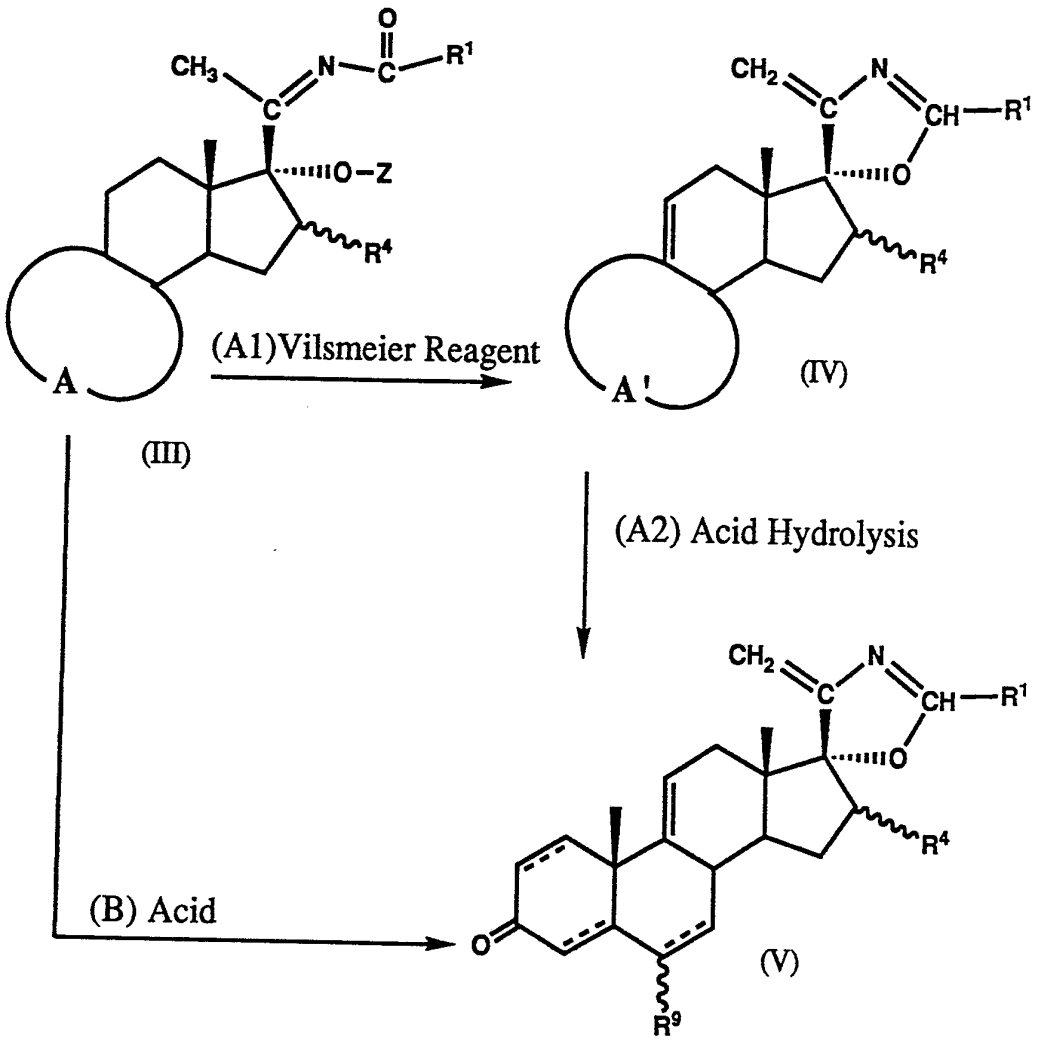
The term for "Z" can represent any group which is sufficiently labile to permit formation of the desired oxazoline. Such groups include but are not limited to hydrogen, alkoxyalkyl, trisubstituted silyl of the formula -$SiR^{1a}R^2R^3$ wherein R^{1a}, R^2 and R^3 independently represents loweralkyl, phenyl or phenylalkyl, preferably -$Si(CH_3)_3$.

One skilled in the art will recognize that the starting materials of formula (III) can exist in tautomeric forms (III) and (III') such as illustrated below:



The present process is intended to encompass the use of either tautomer or mixtures thereof.

The processes of the present invention may be schematically illustrated as follows:



Process (A) is comprised of steps (A1) and (A2). In step (A1), Vilsmeier Reagent or variations thereof can be used to convert the compound of formula (III) to the desired oxazoline corticosteroid of formula (V). Vilsmeier Reagent can be prepared by mixing a formamide of the formula

$$R^{40}R^{41}NCHO \text{ (VI)}$$

wherein $R^{40}$and R^{41} independently represent alkyl or phenyl, with thionyl chloride or phosphoryl chloride, preferably thionyl chloride. A preferred formamide VI is wherein R^{40} and R^{41} are both methyl, known as dimethylformamide(DMF). Vilsmeier Reagent can be prepared according to known methods, such as

described in Louis F. Fieser and Mary Fieser, Reagents for Organic Synthesis, John Wiley and Sons, Inc. New York, (1967), J. March (ed.) Advanced Organic Chemistry, 3rd Edition, John Wiley and Sons, New York, New York, 1985 pp. 487-488, R.S. Kittila "DMF Chemical Uses" (1967) and R.S. Kittila "Supplement to DMF Chemical Uses" E.I. DuPont De Nemours and Co. Inc. (1973). The preparative teachings of these references are incorporated herein by reference. In preparation of Vilsmeier Reagent, from an excess to about equimolar amounts of formamide (VI) can be contacted with one mole of thionyl chloride or phosphoryl chloride to form Vilsmeier Reagent, more preferably from about 3 to about 1.2 moles of formamide (VI). Vilsmeier Reagent can be prepared neat, although preferably it is prepared in the presence of a solvent such as DMF or dichloromethane (CH_2Cl_2) at temperatures ranging from about -25 °C to about 25 °C, preferably about 0 °C. Where DMF is employed in a molar excess, it can serve as both reagent and as solvent.

Optionally and preferably the 9α-hydroxysteroid (III) and Vilsmeier Reagent are contacted in the presence of a base to neutralize acid generated during the reaction. Such bases can include pyridine, collidine, lutidine and mixtures thereof, preferably collidine. The base can be employed in amounts effective to neutralize acid generated during preparation of compounds (IV) or (V) as well as from Vilsmeier Reagent itself. The amounts of base can range from excess to about equimolar amounts of base to one mole thionyl chloride or phosphoryl chloride, preferably from about 10 to 2 moles base, more preferably about 2 moles base.

Vilsmeier Reagent employed in the present process is employed in amounts sufficient to effect the formation of the Δ9,11 double bond on the steroid ring of formula (III) and concommittantly form the desired oxazoline species. Such amounts can range from excess to about equimolar amounts of

Vilsmeier Reagent to one mole of compound of formula (III), preferably from about 5-2 moles Vilsmeier Reagent.

In step (A1) the order of mixing the ingredients is not critical, though preferably the base, where employed, is mixed with the compound of formula III prior to addition of Vilsmeier Reagent. Process (A1) can be conducted at ambient pressures and at temperatures ranging from about -50 degrees Celsius (°C) to about 50 °C, more preferable from about -20 °C to about 25 °C, most preferably from about -20 °C to about 0 °C. The reaction mixture is stirred for a time sufficient to effect the desired completion of the reaction, generally from about 30 minutes to about 2 hours or more. The desired oxazoline corticosteroids of formula (IV) thus prepared can be recovered by adding water to the reaction mixture and diluting the aqueous mix with an organic solvent such as dichloromethane or ethyl acetate. The diluted aqueous/organic mixture can be washed with dilute aqueous alkali such as sodium bicarbonate ($NaHCO_3$), further washed with brine such as saturated sodium chloride (NaCl) and dried with a drying agent such as anhydrous magnesium sulfate ($MgSO_4$) or sodium sulfate (Na_2SO_4) to give the desired oxazoline (IV).

In step (A2) the compound of formula IVcan be contacted with an organic or mineral acid in amounts effective to hydrolyze compound IV to the desired oxazoline (V). Representative mineral acids include hydrochloric, sulfuric, phosphoric and the like, preferably hydrochloric. Representative organic acids include the C-1 to C-10 alkanoic acids such as formic, acetic, propanoic acid, and the like. The acid can be employed in amounts ranging from excess to about 0.1 equivalents acid, preferably from about 2-0.1 equivalents acid. The contacting can be carried out a temperatures ranging from about -20 to 50 °C, preferably about 0°C. The desired oxazoline (V) thus prepared can be recovered by conventional procedures,

such as evaporation of any solvents present, filtration, crystallization, chromatography, distillation and the like.

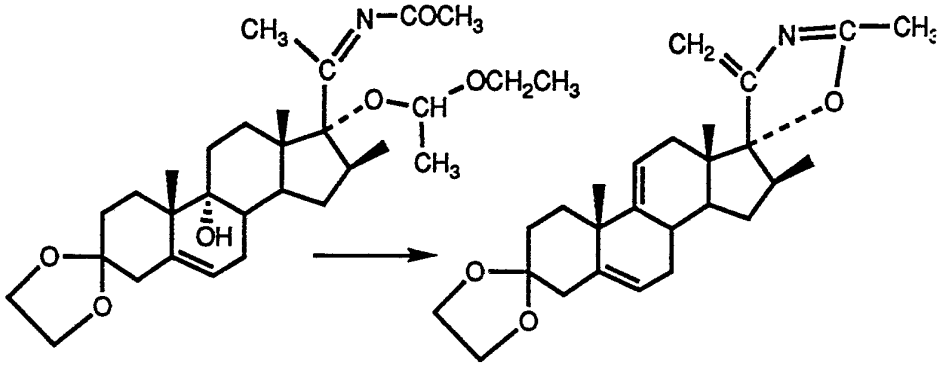
In Process (B), the compounds of formula III are contacted with an acid having a pKa of 5 or less, preferably having a pK_a less than one, such as those described hereinbefore. Where chlorosulfonic acid is employed, the process can be conducted neat, ie. in the absence of a solvent, but a solvent is preferred. Suitable solvents include the chlorinated hydrocarbons such as chloroform, dichloromethane, and carbon tetrachloride; and the alkylated hydrocarbons such as hexane or heptane. The amount of solvent employed should be sufficient to at least dissolve the reactants. The amount of solvent can range from an excess amount to about 10 percent volume basis per reaction mixture.

The acid can be contacted with the compound of formula (III) in amounts ranging from about 10 to about 2 molar equivalents acid to one equivalent 9α-hydroxy steroid of formula III, more preferably from about 5 to about 2 molar equivalents acid. The temperatures, contacting times and recovery procedures for process (B) are similar to those described in process (A).

The following examples illustrate various embodiments by which the present invention can be practised, but as such, should not be limited to the overall scope of the same. All temperatures are in degrees Celsius (°C).

EXAMPLE 1-STEP (A1).

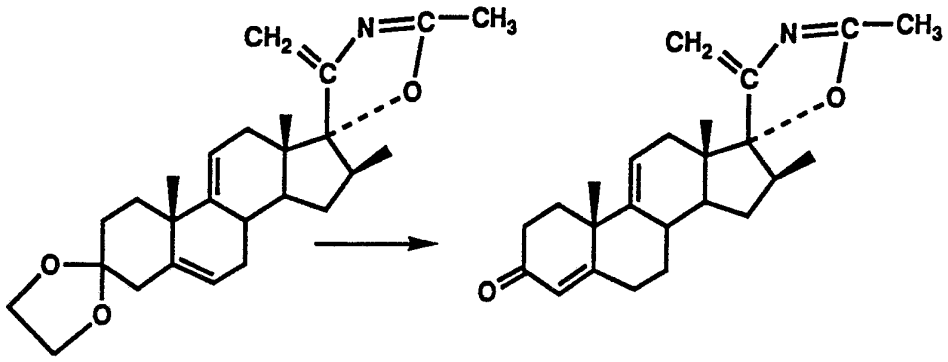
3,3-[1,2-ETHANEDIYLBIS(OXY)]-2',16β-DIMETHYL-4'-METHYLENESPIRO[ANDROSTA-4,9(11)-DIENE-17,5'(4'H)-OXAZOLE



Vilsmeier reagent is prepared by treating a mixture of dimethylformamide (0.56 ml) and dichloromethane (15 ml) at 0° with thionyl chloride (0.5 ml). After 10 minutes this solution is added to a mixture of N-[3,3-[1,2-ethanediylbis(oxy)]-17α-(1-ethoxyethoxy)-9α-hydroxy-16β-methylpregn-5-en-20-ylidene]acetamide (2.49 g), dichloromethane (25 ml) and collidine (1.6 ml) at 0°. After 30 minutes at this temperature water (10 ml) is added and the reaction mixture stirred for 15 minutes. The reaction mixture is diluted with dichloromethane (200 ml), the organic separated, washed with saturated sodium chloride solution (100 ml), dried over sodium sulfate and evaporated to afford the title compound (0.89 g). NMR ($CDCl_3$), δ ppm; 0.78, 1.09, 1.20, 2.0, 3.9, 4.3, 5.22 and 5.42.

EXAMPLE 1-STEP (A2).

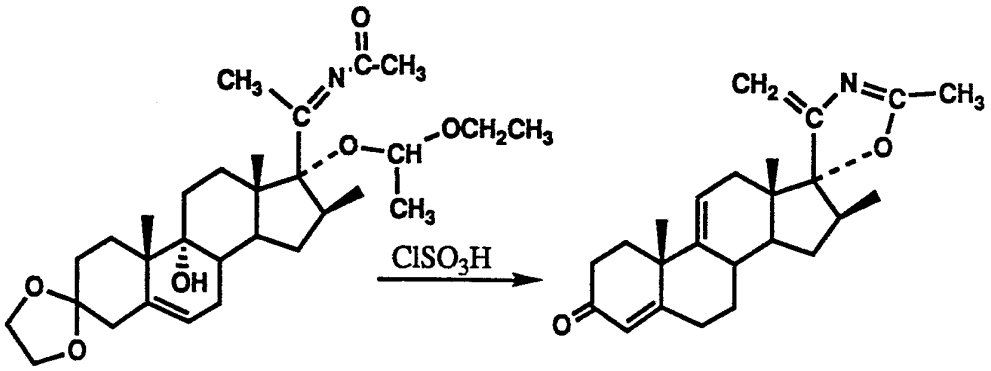
2',16β-DIMETHYL-4'-METHYLENESPIRO[ANDROSTA-4,9(11)-DIENE-17,5'(4'H)-OXAZOL]-3-ONE



3,3-[1,2-ethanediylbis(oxy)]-2',16β–dimethyl-4'-methylenespiro[androsta-4,9(11)-diene-17,5'(4')-oxazole (0.025 g) is dissolved in 10% aqueous methanol (1.5 ml) and treated with 2M hydrochloric acid (0.088 ml). After 2 hours at room temperature evaporation of the solvent afforded the title compound (0.02 g). NMR ($CDCl_3$), δ ppm; 0.8, 1.08, 1.3, 2.05, 4.33, 5.27, 5.5 and 5.71.

EXAMPLE 3.

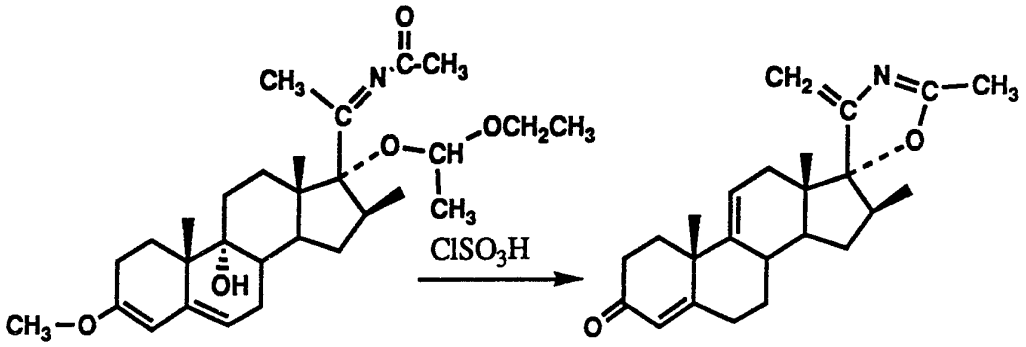
2',16β-DIMETHYL-4'-METHYLENESPIRO[ANDROSTA-4,9(11)-DIENE-17,5'(4'H)-OXAZOL]-3-ONE



A mixture of N-[3,3-[1,2-ethanediylbis(oxy)]-17α–(1-ethoxyethoxy)-9α–hydroxy-16β–methylpregn-5-en-20-ylidene]acetamide (0.52 g) and dichloromethane (8 ml) is cooled to -20° and treated with a solution of chlorosulfonic acid (0.2 ml) in dichloromethane (2 ml) dropwise. After 45 minutes the reaction mixture is treated with water (15 ml) and dichloromethane (100 ml). The organic fraction is separated, washed with saturated sodium bicarbonate solution (100 ml), saturated sodium chloride solution (100 ml), dried over sodium sulfate to give the title compound (0.3 g).

EXAMPLE 4

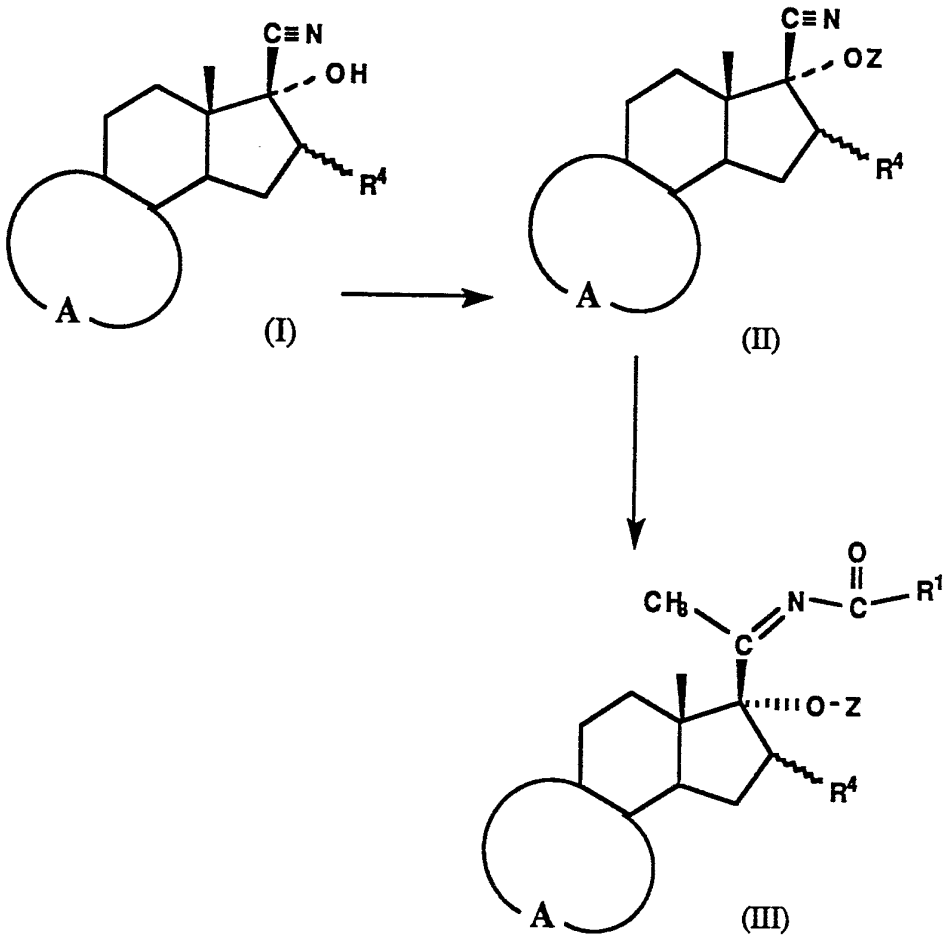
2',16β–DIMETHYL-4'-METHYLENESPIRO[ANDROSTA-4,9(11)-DIENE-17,5'(4'H)OXAZOL]-3-ONE



N-[17α–(1-ethoxyethoxy)-9α–hydroxy-3-methoxy-16β–methylpregna-3,5-diene-20-ylidene]acetamide (0.36 g) in dichloromethane (5 ml) is cooled to -25° and treated with a mixture of chlorosulfonic acid (0.23 ml) and dichloromethane (1.27 ml) dropwise. The mixture is stirred at -25° for 10 minutes then at -25° to -10° for 15 minutes. The reaction mixture is added dropwise to a saturated sodium bicarbonate solution (30 ml), stirred for 30 minutes and the organic fraction separated. The aqueous is re-extracted with ethyl acetate (2 x 50 ml) and the combined organic portions are washed with saturated sodium chloride solution (50 ml), dried over sodium sulfate and evaporated to give the title compound (0.23 g).

Preparation of Starting Materials

The steroids of formula I are known or can be prepared according to known methods such as described in European Patent Application 0263569 whose preparation is schematically illustrated below:



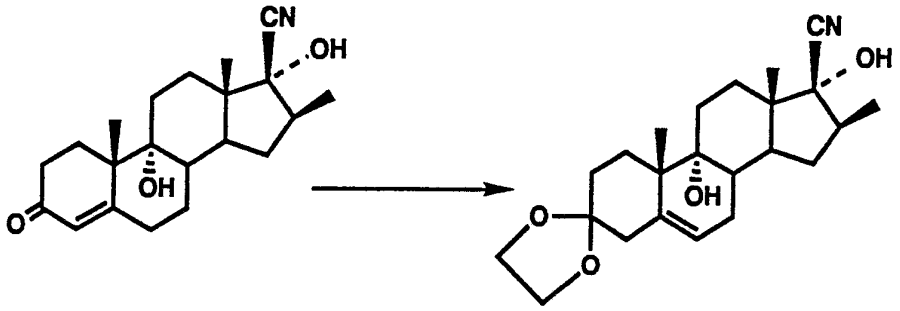
Generally a 17α-hydroxy, 17β cyano compound of formula (I) can be treated with an ether producing reagent such as a lower alkylvinylether as exemplified by ethylvinylether, methylvinyl ether and the like, in the presence of an acid catalyst such as para - toluene sulfonic acid, pyridinium para toluene sulfonate and pyridine hydrochloride to give the compound of formula II, wherein A and R^4 are as defined hereinbefore, and Z is exemplified by $-CH(OR^{50})CH_3$ wherein R^{50} is loweralkyl. The process is carried out under conditions such as those taught in US Patents 4,585,590, whose preparative teachings are incorporated herein by reference.

The ether of formula II can be treated with methyl lithium (CH_3Li) followed by treatment with acetic anhydride $(CH_3CO)_2O$ in the presence of a solvent such as diethylether or

cumene at temperatures ranging from about 0°C to 40°C or the refluxing temperature of the solvent, to give the starting compound of formula (III).

PREPARATIVE EXAMPLE 1

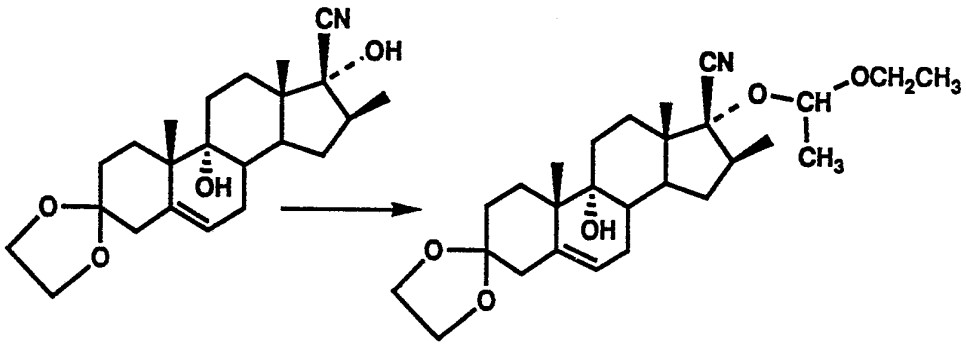
3,3-[1,2-ETHANEDIYLBIS(OXY)]-9α,17α–DIHYDROXY-16β–METHYL ANDROST-5-ENE-17β–CARBONITRILE



A mixture of 9α,17α–dihydroxy-16β–methyl-3-oxoandrost-4-ene-17β–carbonitrile (3.69 g), ethylene glycol (30 ml), trimethylorthoformate (3.8 ml) and benzene (18 ml) is treated with para-toluenesulfonic acid (0.14 g) and stirred at room temperature. After 4 hours diethylether (34 ml), water (34 ml), and pyridine (0.8 ml) are added. After 1 hour the reaction mixture is filtered and the solids washed with water (300 ml) and dried under reduced pressure to afford the title compound (2.0 g). NMR ($CDCl_3$), δ ppm; 0.92, 1.12, 1.28, 3.96 and 5.33.

PREPARATIVE EXAMPLE 2

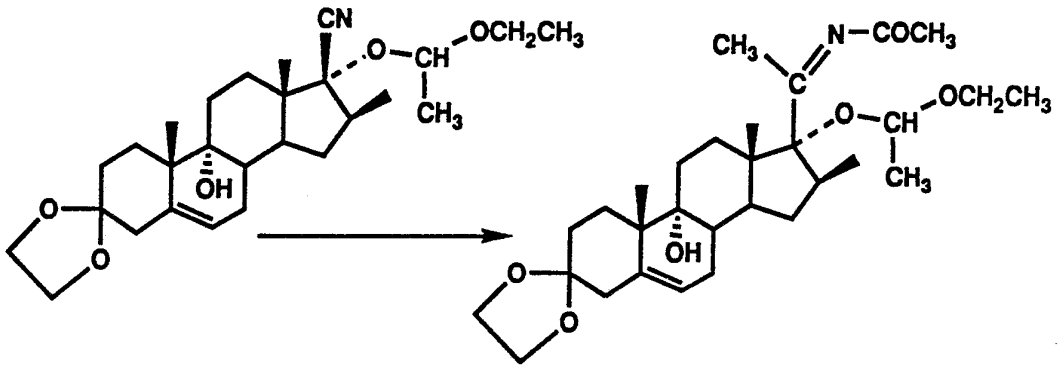
3,3-[1,2-ETHANEDIYLBIS(OXY)]17α-(1-ETHOXYETHOXY)-9α-HYDROXY-16β-METHYLANDROST-5-ENE-17β-CARBONITRILE



A mixture of 3,3-[1,2-ethanediylbis(oxy)]-9α,17α-dihydroxy-16β-methylandrost-5-ene-17β-carbonitrile (15.16 g), dichloromethane (100 ml), ethylvinylether (50 ml) and pyridine hydrochloride (0.5 g) is heated in a sealed flask at 55° for 18 hours. The reaction mixture is vented and the solvent evaporated to give an oil which is filtered through a short column of silica gel to afford the title compound (17 g). NMR ($CDCl_3$), δ ppm; 0.92, 1.12, 1.18, 1.25, 1.30, 3.54, 3.90, 5.01 and 5.36.

PREPARATIVE EXAMPLE 3

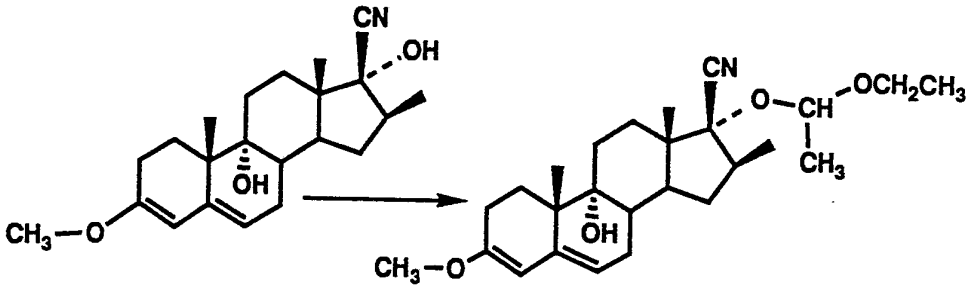
N-[3,3-[1,2-ETHANEDIYLBIS(0XY)]-17α-(1-ETHOXYETHOXY)-9α-HYDROXY-16β-METHYLPREGN-5-EN-20-YLIDENE]ACETAMIDE



A mixture of 3,3-[1,2-ethanediylbis(oxy)]-17α-(1-ethoxyethoxy)-9α-hydroxy-16β-methylandrost-5-ene-17β-carbonitrile (22.63 g) and diethylether (50 ml) is treated with methyllithium in cumene (1.31M, 207 ml) at 0°. Once addition is complete the reaction mixture is heated to 40°. After 5 hours at 40° the reaction mixture is added to a solution of acetic anhydride (38 ml) in toluene (100 ml) pre-cooled to ice/acetone temperature. The combined solutions are washed with pH 7 phosphate buffer (3 x 250 ml), with saturated sodium bicarbonate solution (2 x 250 ml), with phosphate buffer (250 ml), dried over magnesium sulfate and evaporated to give the title compound (25 g). NMR ($CDCl_3$), δ ppm; 0.76, 1.12, 1.20, 1.90, 3.49, 3.92, 4.89 and 5.38.

PREPARATIVE EXAMPLE 4

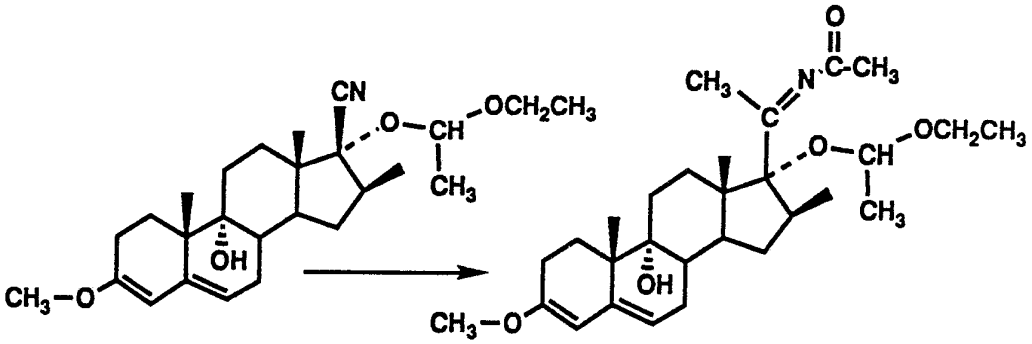
17α-(1-ETHOXYETHOXY-9α-HYDROXY-3-METHOXY-16β-METHYLANDROSTA-3,5-DIENE-17β-CARBONITRILE



A mixture of 9α,17α-dihydroxy-3-methoxy-16β-methylandrosta-3,5-diene-17β-carbonitrile (21.86 g), toluene (180 ml), dichloromethane (20 ml), ethylvinylether (200 ml) and pyridine hydrochloride (2.0 g) is heated in a sealed flask at 80°. After 24 hours the reaction mixture is cooled, treated with triethylamine (10 ml), washed with pH 7 phosphate buffer (3 x 200 ml), saturated sodium chloride solution (200 ml), dried over sodium sulfate and evaporated to afford the title compound (19.25 g). NMR ($CDCl_3$), δ ppm; 0.99, 1.09, 1.19, 1.23, 1.35, 3.58, 5.05, 5.15 and 5.28.

PREPARATIVE EXAMPLE 5

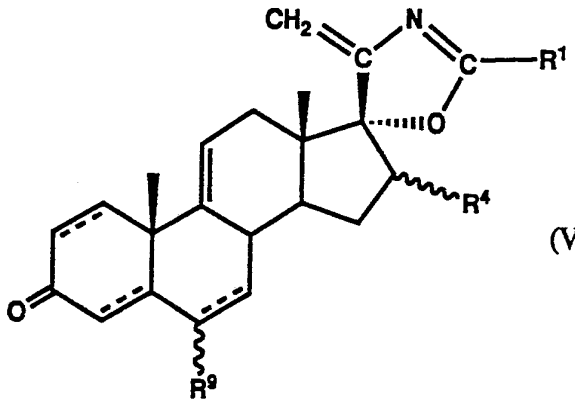
N-[17α-(1-ETHOXYETHOXY)-9α-HYDROXY-3-METHOXY-16β-METHYLPREGNA-3,5-DIENE-20-YLIDENE]ACETAMIDE



A mixture of 17α-(1-ethoxyethoxy)-9α-hydroxy-3-methoxy-16β-methylandrosta-3,5-diene-17β-carbonitrile (1.5 g) and diethyl ether (5 ml) is treated with methyllithium in cumene (1.25 M, 15.4 ml) at 0°. Once addition is complete the reaction mixture is heated to 40°. After 5 hours the reaction mixture is added to a mixture of acetic anhydride (2.7 ml) in toluene (7 ml) pre-cooled to ice/acetone temperature. This solution is warmed to room temperature overnight then treated with pH 7 phosphate buffer (25 ml), stirred for 30 minutes and diluted with ethylacetate (150 ml). The organic portion is separated and the aqueous re-extracted with ethylacetate (150 ml). The combined organic portions are washed with saturated sodium bicarbonate solution (2 x 100 ml), phosphate buffer (100 ml), dried over magnesium sulfate and evaporated to give the title compound (1.58 g). NMR ($CDCl_3$), δ ppm; 0.72, 0.98, 1.12, 2.08, 3.4S, 4.79, 5.08, and S.21.

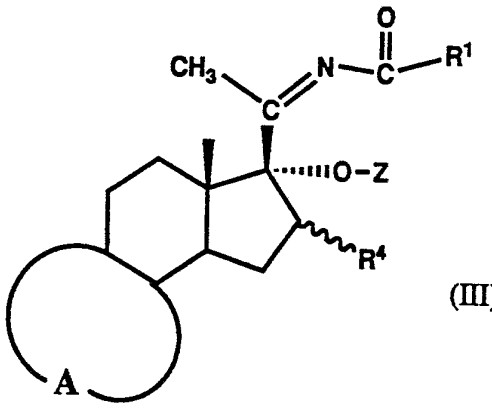
IN THE CLAIMS:

1. A process for preparing oxazoline corticosteroid intermediates of formula (V):



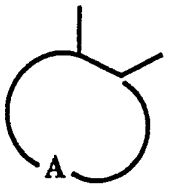
(V)

wherein R^1 represents hydrogen (H), loweralkyl, phenyl or phenylalkyl; R^4 represents H or loweralkyl, preferably methyl having either the α or β stereochemistry; and R^9 represents hydrogen, fluoro, chloro or loweralkyl comprising contacting a compound of the formula:



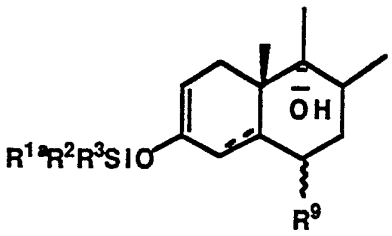
(III)

, its tautomer or mixtures thereof, wherein Z represents hydrogen, alkoxyalkyl, trialkylsilyl of the formula $-SiR^{1a}R^2R^3$ wherein R^1, R^2 and R^3 independently represent loweralkyl, phenyl or phenylalkyl;

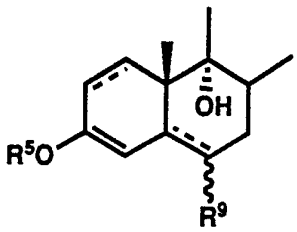


represents

an enol ether of the formula:

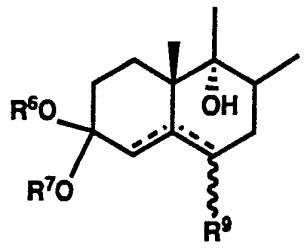


or



wherein R^5 represents loweralkyl and R^9 is as defined hereinbefore, wherein R^{1a}, R^2 and R^3 are as defined hereinbefore;

a ketal of the formula



wherein R^6 and R^7 independently represent loweralkyl or -$(CR^{20}R^{21})_v$- and -$(CR^{30}R^{31})_w$-, respectively, wherein R^{20}, R^{21}, R^{30} and R^{31} independently represent H, loweralkyl, or aryl and w and v independently represent an integer from 0 to 6 and v + w is an integer from 2 to 12, preferably 2, and wherein -$(CR^{20}R^{21})_v$- or -$(CR^{30}R^{31})_w$- are connected together in a ring or through an oxygen or nitrogen atom; and R^9 is as defined hereinbefore;

2. The process of claim 1 wherein the Vilsmeier reagent is prepared by mixing a formamide of the formula

$R^{40}R^{41}NCHO$ (VI)

wherein R^{40} and R^{41} independently represent alkyl or phenyl, with thionyl chloride or phosphoryl chloride.

3. The process of claims 1 or 2 wherein the Vilsmeier Reagent is prepared by mixing formamide (VI) known as dimethylformamide (DMF) with thionyl chloride.

4. The process of claims 1-3 wherein the acid hydrolysis is carried out by contacting compound (IV) with an organic or mineral acid in amounts effective to hydrolyze compound (IV) to compound (V).

5. The process of claims 1-4 wherein the organic acid is formic, acetic or propanoic acid.

6. The process of claims 1-5 wherein the mineral acid is hydrochloric, sulfuric or phosphoric.

7. The process of claims 1-6 wherein the 9α-hydroxysteroid (III) and Vilsmeier Reagent are contacted in the presence of a base.

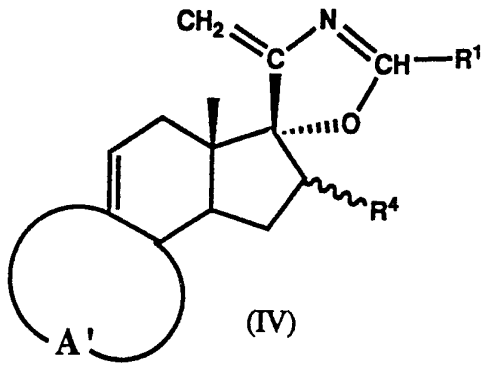
8. The process of claims 1-7 wherein the base is pyridine, collidine, lutidine or mixtures thereof.

9. The process of claim 1 wherein in Process B the compounds of formula III are contacted with an acid having a pKa of 1 or less.

10. The process of claim 9 wherein the acid is chlorosulfonic acid, sulfuric, phosphoric, methanesulfonic, perchloric, trifluoracetic acid or mixtures thereof.

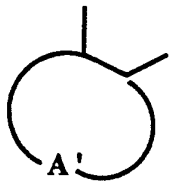
11. The process of claims 1,9 or 10 wherein the acid is chlorosulfonic acid.

12. A process for preparing compounds of formula (IV):



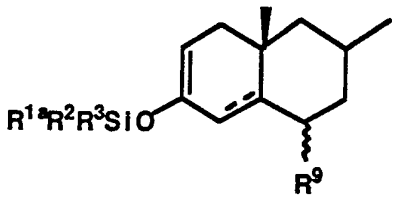
(IV)

wherein R^1 and R^4 are as defined hereinbefore.and

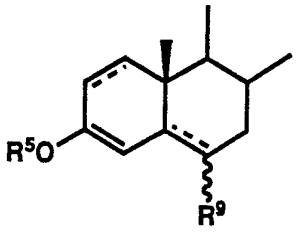


represents

an enol ether of the formula:

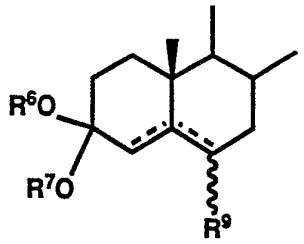


or



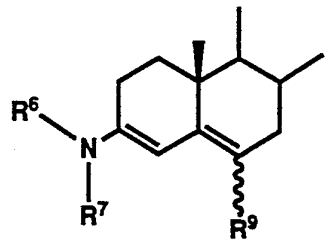
wherein R^5 represents loweralkyl and R^9 is as defined hereinbefore, wherein R^{1a}, R^2 and R^3 are as defined hereinbefore;

a ketal of the formula



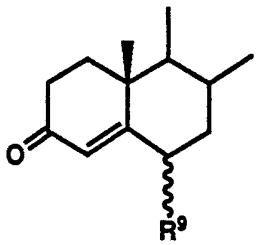
wherein R^6 and R^7 independently represent loweralkyl or -$(CR^{20}R^{21})_v$- and -$(CR^{30}R^{31})_w$-, respectively, wherein R^{20}, R^{21}, R^{30} and R^{31} independently represent H, loweralkyl, or aryl and w and v independently represent an integer from 0 to 6 and v + w is an integer from 2 to 12, preferably 2, and wherein -$(CR^{20}R^{21})_v$- or -$(CR^{30}R^{31})_w$- can be connected together in a ring or through an oxygen or nitrogen atom; and R^9 is as defined hereinbefore;

an enamine of the formula

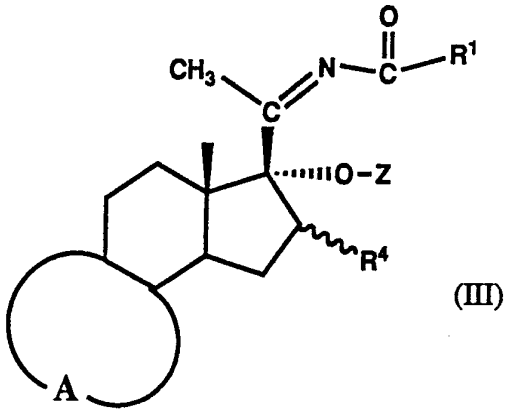


wherein R^6 and R^7 are as defined hereinbefore; or

a ketone of the formula

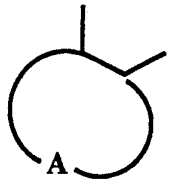


wherein R^9 is as defined hereinbefore;
comprising contacting the compound of formula (III)



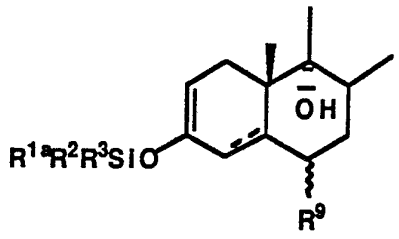
(III)

its tautomer or mixtures thereof, wherein Z represents hydrogen, alkoxyalkyl, trisubstituted silyl of the formula $-SiR^{1a}R^2R^3$ wherein R^{1a}, R^2 and R^3 independently represents loweralkyl, phenyl or phenylalkyl;

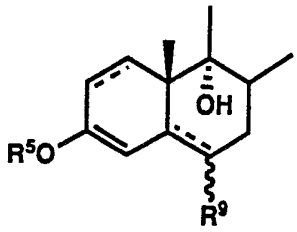


represents

an enol ether of the formula:

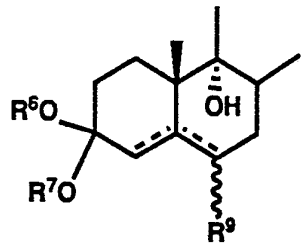


or



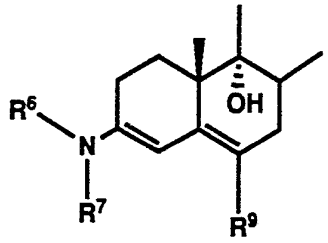
wherein R^5 represents loweralkyl and R^9 is as defined hereinbefore, wherein R^{1a}, R^2 and R^3 are as defined hereinbefore;

a ketal of the formula



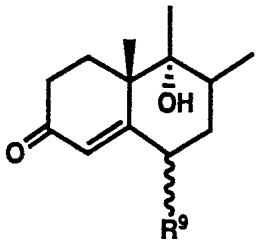
wherein R^6,R^7 and R^9 are as defined hereinbefore;

an enamine of the formula



wherein R^6 and R^7 are as defined hereinbefore; or

a ketone of the formula



wherein R^9 is as defined hereinbefore; with Vilsmeier Reagent under conditions effective to give the compound of formula (IV).

INTERNATIONAL SEARCH REPORT

International Application No PCT/US90/06754

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC (5): C07J 21/00 43/00
U.S. CL US 540/36

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
U.S.	260/379.45 540/36 514/174,177

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

CAS onlines
APS onlines

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
X	US, A, 4,585,590 29 April 1986 (Van Rheenen)	1,18-23
X	US, A, 4,127,596 28 November 1978 (Beaton et al.)	1,18-23
A	US, A, 4,401,596 30 August 1983 (Barton et al.)	1-24
A	N, Chemical Abstract Vol. 92, 1980 92;215325V Kvitko, I. Ya.; Smirnova, V.A.; EL'tsov, A. Study of aminomethylene derivatives of azoles 24. Cyclization of thiohippuric acid in the presence of a Vilsmeier reagent. Khim. Geterotsikl.Soedin. 1980, (1), 36-9 (Russ).	1-24

* Special categories of cited documents: [15]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
January 4, 1991	05 FEB 1991
International Searching Authority [1]	**Signature of Authorized Officer [20]**
ISA/US	for Celia Chang — Ngoc-Ho Nguyen NGUYEN NGOC-HO INTERNATIONAL DIVISION

Form PCT/ISA/210 (second sheet) (May 1986)