

PATENT REQUEST: STANDARD PATENT

We, the Applicant/Nominated Person specified below, request we be granted a patent for the invention disclosed in the accompanying standard complete specification.

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[54] Invention Title:

17-Spirofurane-3-ylidene Steroids

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Basic Convention Application Details

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Basic Applicant:	Akzo N.V.	

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Registered Patent Attorney



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SPRUSON & FERGUSON

Australia

Patents Act 1990

NOTICE OF ENTITLEMENT

I, John Gordon Hinde, of Spruson & Ferguson, St Martins Tower, 31 Market Street, Sydney, New South Wales 2000, Australia, being the patent attorney for the Applicant(s)/Nominated Person(s) in respect of an application entitled:

17-Spirofuran-3'-ylidene Steroids

state the following:-

The Applicant(s)/Nominated Person(s) has/have entitlement from the actual inventor(s) as follows:-

The Applicant(s)/Nominated Person(s), by virtue of a Contract of Employment between the actual inventor(s) as employee(s) and the Applicant(s)/Nominated Person(s) as employer(s), is a person entitled to have the patent assigned to it if a patent were granted on an application made by the actual inventor(s).

The Applicant(s)/Nominated Person(s) is/are the applicant(s) of the basic application(s) listed on the Patent Request. The basic application(s) listed on the Patent Request is/are the application(s) first made in a Convention Country in respect of the invention.

DATED this 21st day of January 19 93


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John Gordon Hinde

IRN:

INSTR CODE:

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KRS/665P

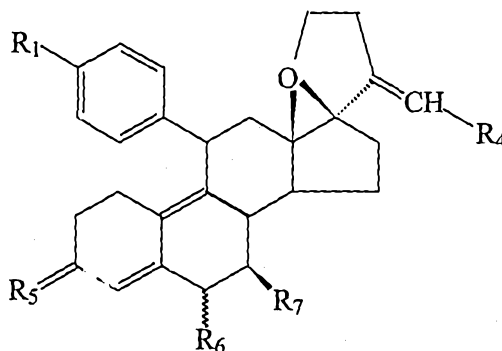


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- (57) Claim

1. A 17-spirofuran-3'-ylidene steroid having the formula



I

R_1 is NR_2R_3 , lower acyl, OH, SH, O-lower alkyl or $S(O)_n$ -lower alkyl wherein n is 0-2;
 R_2 and R_3 are independently selected from hydrogen and lower alkyl;
 R_4 is hydrogen or lower alkyl;
 R_5 is O, (H,H), (H,OH), (H, O-lower acyl), or NOH;
 R_6 and R_7 are both hydrogen, or one is hydrogen and the other lower alkyl; and
the twiched line represents an α or β bond.

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4. A method of treating a human for conditions in which the progesterone receptor is involved, comprising administering to said human an antiprogestin effective amount of a steroid of any one of claims 1 to 3.

10. A pharmaceutical composition having antiprogestin activity, comprising a compound of claim 8 together with a pharmaceutically acceptable carrier, diluent, excipient or adjuvant.

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COMPLETE SPECIFICATION

FOR A STANDARD PATENT

ORIGINAL

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Invention Title:

17-Spirofuran-3'-ylidene Steroids

The following statement is a full description of this invention, including the
best method of performing it known to me/us:-

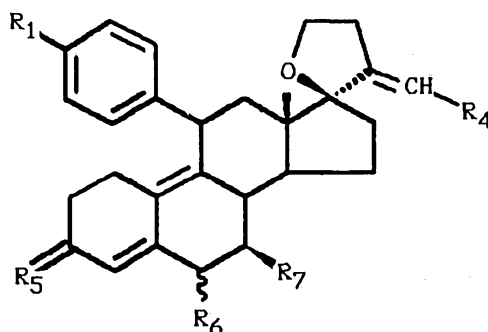
17-SPIROFURAN-3'-YLIDENE STEROIDS

The invention relates to novel 17-spirofuran-3'-ylidene steroids, to methods of preparation thereof, a pharmaceutical composition containing the same, and a use of these steroids for the manufacture of a medicament having antiprogesterin activity.

Antiprogestins, i.e. compounds which show affinity for the progesterone receptor, are known. One of the best known compounds in this respect is RU 486, which is disclosed in European patent 0,057,115.

It has now been found that steroids having a 17-spirofuran-3'-ylidene ring show surprisingly strong affinity to the progesterone receptor, and, moreover, have at the same time decreased affinity to the glucocorticoid receptor. Further, the novel compounds have virtually no affinity to the mineralocorticoid receptor. The present steroids, therefore, show an improved selectivity and are more suitable for therapeutic use.

The 17-spirofuran-3'-ylidene steroids of the invention have a formula



wherein

R_1 is NR_2R_3 , lower acyl, OH, SH, O-lower alkyl or $S(O)_n$ -lower alkyl wherein n is 0-2;

R_2 and R_3 are independently selected from hydrogen and lower alkyl;

R_4 is hydrogen or lower alkyl;

R_5 is O, (H,H), (H,OH), (H,O-lower acyl), or NOH;

R_6 and R_7 are both hydrogen, or one is hydrogen and the other lower alkyl; and

the twitched line represents an α or β bond.

Preferred steroids according to the invention have formula I, wherein

R_1 is $N(CH_3)_2$, acetyl, S-lower alkyl, or SO_2 -lower alkyl;

R_4 is hydrogen or methyl;

R_5 is O;

R_6 and R_7 are both hydrogen, or one is hydrogen and the other methyl.

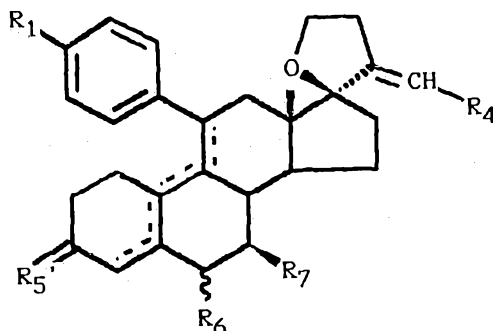
Most preferred is the 17-spirofuran-3'-ylidene steroid, wherein R_1 is acetyl, R_4 is hydrogen, R_5 is O, and R_6 and R_7 are both hydrogen.

The term lower alkyl means a branched or unbranched alkyl group having 1-6 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, pentyl, hexyl and the like. Preferred alkyl groups have 1-4 carbon atoms, and most preferred is the methyl group.

The term lower acyl means an acyl group derived from an aliphatic carboxylic acid having 2-6 carbon atoms. Acetyl is the preferred acyl group.

When R_4 is an alkyl group Z- and E-isomers are possible. Both isomeric forms are considered to belong to this invention.

The 17-spirofuran-3'-ylidene steroids of this invention can be prepared in various ways. A convenient method is the cleavage of a protective group of a corresponding steroid in which the 3-keto or 3-oxim is protected, which steroid has the formula



II

wherein

R_1 is NR_2R_3 , lower acyl, OH, SH, O-lower alkyl, or $S(O)_n$ -lower alkyl wherein n is 0-2;

R_2 and R_3 are independently selected from hydrogen and lower alkyl;

R_4 is hydrogen or lower alkyl;

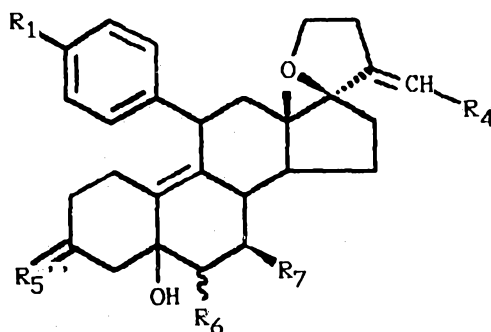
R_5' is a protected O or protected NOH;

R_6 and R_7 are both hydrogen, or one is hydrogen and the other lower alkyl; the dotted line represents two conjugated bonds, and

the twitched line represents an α or β bond.

Suitable protective groups are known in the art, for instance, from T.W. Green: Protective Groups in Organic Synthesis (Wiley, NY, 1981), which is included by reference. Particularly suitable are acetals for the protection of keto groups, for example 1,2-ethylene ketal. In this respect, also a dithioketal should be mentioned, which easily can be converted into a keto group by treatment with silver nitrate.

Another suitable method is the dehydration of a compound having formula



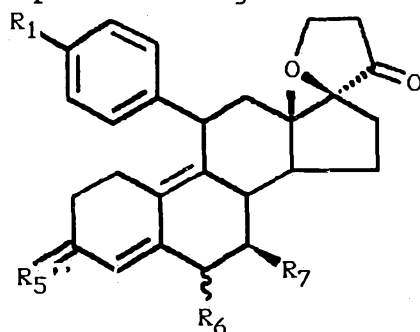
III

wherein

R_5'' is protected O, (H,H), (H,protected OH), (H,O-lower acyl), or protected NOH, and R_1 - R_4 , R_6 - R_7 , and the

twitched line have the previously given meanings. The protective groups, if present, are simultaneously cleaved or cleaved after the dehydration step. Dehydration is normally performed under acidic conditions, but also catalytic dehydration (for example using aluminum oxide), and indirect dehydration by converting the 5-hydroxy group into a suitable leaving group, which is removed together with an adjacent hydrogen atom, are possible. An example of the latter method is the conversion of the 5-hydroxy group into a halogen like iodide, followed by dehydrohalogenation under alkaline conditions.

Yet another method is a Wittig, Wittig-like, or Peterson reaction using a compound having the formula

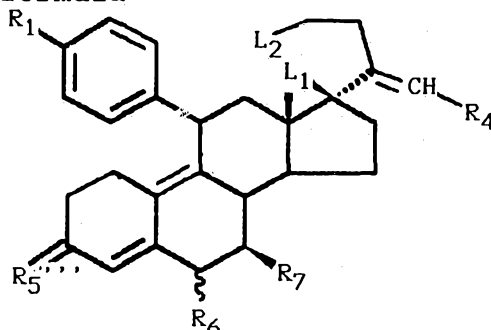


IV

wherein R_5'' is protected O, (H,H), (H,protected OH), (H,O-lower acyl), protected NOH, and R_1 - R_3 , R_6 - R_7 , and the twitched line have the previously given meanings, and a R_4 -CH₂-Wittig, R_4 -CH₂-Wittig-like, or R_4 -CH₂-Peterson reagent, wherein R_4 has the previously given meaning. This reaction is followed by deprotection of an optionally present protective group into the 17-spiro-furan-3'-ylidene steroid of this invention. Suitable Wittig or Wittig-like reagents are triphenylphosphoranes such as R_4 -CH₂-P(Hal)Ph₃, and the like, and suitable Peterson reagents are, for example, trimethylsilane reagents like R_4 -CH(MgHal)Si(CH₃)₃, wherein Hal denotes a halogen like chlorine or bromine.

Alternatively, the 17-spirofuran-3'-ylidene steroids of this invention can also be prepared by ring closure to

the 17-spirofuran-3'-ylidene ring. In this method a compound having the formula



V

wherein R_5''' is R_5 or protected O, (H,H), (H,protected OH), or protected NOH, and R_1 - R_7 , and the twatched line have the previously given meanings, and one of L_1 and L_2 is OH and the other is a leaving group, is converted into a 17-spirofuran-3'-ylidene steroid, which after deprotection of an optionally present protective group affords the desired 17-spirofuran-3'-ylidene steroid. Leaving groups are known in the art. Suitable leaving groups are, for instance, hydroxy, halogen (particularly chlorine and bromine), and sulfonates such as *para*-toluene sulfonate and mesylate groups.

It is possible to convert the products obtained by one of the previously mentioned procedures into another product according to the invention. Using generally known methods it is, for instance, possible to convert steroids wherein R_2 and/or R_3 is hydrogen, for example, by a Leuckart-Wallach reaction, to afford steroids wherein R_2 and/or R_3 is alkyl. Steroids having R_5 is O can easily be converted into steroids having R_5 is NOH, for example, by condensation with hydroxylamine, or to steroids having R_5 is (H,OH), for example, by sodium borohydride reduction. Steroids having R_5 is (H,OH) can be acylated to steroids having R_5 is (H,O-lower acyl).

The compounds of the invention may be administered enterally or parenterally, and for humans preferably in a daily dosage of 0,001-10 mg per kg body weight. Mixed with pharmaceutically suitable auxiliaries, e.g. as

described in the standard reference, Gennaro et al.,
 Remington's Pharmaceutical Sciences, (18th ed., Mack
 Publishing Company, 1990, see especially Part 8:
 Pharmaceutical Preparations and Their Manufacture) the
 compounds may be compressed into solid dosage units,
 such as pills, tablets, or be processed into capsules or
 suppositories. By means of pharmaceutically suitable
 liquids the compounds can also be applied as an
 injection preparation in the form of a solution,
 suspension, emulsion, or as a spray, e.g. a nasal spray.
 For making dosage units, e.g. tablets, the use of
 conventional additives such as fillers, colorants, poly-
 meric binders and the like is contemplated. In general
 any pharmaceutically acceptable additive which does not
 interfere with the function of the active compounds can
 be used.

Suitable carriers with which the compositions can be
 administered include lactose, starch, cellulose
 derivatives and the like, or mixtures thereof, used in
 suitable amounts.

The invention is further illustrated by the following
 examples.

EXAMPLE 1

(11 β ,17 α)-17,23-epoxy-11-[(4-dimethylamino)phenyl]-
19,24-dinorchola-4,9,20-trien-3-one

- a. To a solution of 25.6 g of (17 β)-3-methoxyspiro-
 [estra-1,3,5(10)-triene-17,2'(3'H)-furan]-3'-one (see
 D. Gange and Ph. Magnus, J. Am. Chem. Soc., 100
 (1978), 7746-7747) in 200 ml of ethanol and 200 ml of
 toluene were added 2.85 g of sodium borohydride, and
 the mixture was stirred at room temperature for 16
 hours. Acetic acid was added until pH 7, followed by
 addition of water, and the mixture was extracted with

toluene. Removal of the solvent under reduced pressure afforded the crude alcohol, which was crystallized from methanol to yield 24 g of (17 β ,3'S)-4',5'-dihydro-3-methoxyspiro[estra-1,3,5(10)-triene-17,2'(3'H)-furan]-3'-ol, m.p. 130 °C

b. (i) A solution of 9 g of (17 β ,3'S)-4',5'-dihydro-3-methoxyspiro[estra-1,3,5(10)-triene-17,2'(3'H)-furan]-3'-ol in 150 ml of tetrahydrofuran was added to a solution of 4 g of lithium in 450 ml of liquid ammonia at -33 °C. After stirring for 3 hours at this temperature 60 ml of ethanol were added and the ammonia was allowed to evaporate. The residue was partitioned between water and ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and concentrated under reduced pressure, affording after trituration with diisopropyl ether 8.9 g of (17 β ,3'S)-4',5'-dihydro-3-methoxyspiro[estra-2,5(10)-diene-17,2'(3'H)-furan]-3'-ol.

(ii) 8.9 g of the above-mentioned diene were dissolved in 65 ml of methanol and 65 ml of tetrahydrofuran. At 5 °C a solution of 4.6 g of oxalic acid in 45 ml of water and 22 ml of methanol was added. After stirring for 6 hours at ambient temperature the mixture was poured into an ice-cold 1% sodium hydrogen carbonate solution and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and concentrated under reduced pressure to give 8.5 g of the crude (17 β ,3'S)-4',5'-dihydro-3'-hydroxyspiro[estr-5(10)-ene-17,2'(3'H)-furan]-3-one.

(iii) 8.5 g of this ketone were dissolved in 90 ml of pyridine. To this solution were added portionwise 10 g of phenyltrimethylammonium tribromide during 15 min at 0 °C. After stirring for 3 hours at room temperature the mixture was poured into 800 ml of ice-water and the product was extracted with ethyl acetate. The organic layer was washed with 2M

hydrochloric acid, brine and dried over magnesium sulfate. The residue was chromatographed after evaporation of the solvent to yield 4.7 g of (17 β ,3'S)-4',5'-dihydro-3'-hydroxyspiro[estra-4,9-diene-17,2'(3'H)-furan]-3-one, m.p. 180 °C.

c. (i) A mixture of 4.1 g of (17 β ,3'S)-4',5'-dihydro-3'-hydroxyspiro[estra-4,9-diene-17,2'(3'H)-furan]-3-one, 30 ml of dichloromethane, 30 ml of ethylene glycol, 10 ml of triethyl orthoformate, and 200 mg of para-toluenesulphonic acid was stirred for 2 hours at room temperature. The reaction was stopped by the addition of water and sodium hydrogen carbonate, the layers were separated and the organic layer was washed with water. After drying over magnesium sulfate and concentration under reduced pressure 5.1 g of the crude (17 β ,3'S)-4',5'-dihydro-3'-hydroxyspiro[estra-4,9-diene-17,2'(3'H)-furan]-3-one 3-cyclic 1,2-ethanediyl acetal were obtained, which was used in the next step without further purification.

(ii) A mixture of 5.1 g of the above-mentioned compound, 200 ml of toluene, 36 ml of cyclohexanone and 3.6 g of aluminum iso-propoxide was refluxed for 3 hours. After cooling to room temperature, ethyl acetate was added and the mixture was washed repeatedly with a 75 % w/v solution of Seignette salt. The organic layer was washed with water, brine, and dried over magnesium sulfate. Evaporation of the solvent under reduced pressure followed by chromatography afforded 4 g of (17 β)-4',5'-dihydrospiro[estra-5(10),9(11)-diene-17,2'(3'H)-furan]-3,3'-dione 3-cyclic 1,2-ethane-diyl acetal, m.p. 146 °C.

d. To a suspension of 3.09 g of methyltriphenylphosphonium bromide in 25 ml of toluene were added 0.83 g of potassium tert-butoxide. The mixture was refluxed for 45 min, and then cooled, after which a solution of 1.10 g of the acetal of c(ii) in 2 ml of toluene were

added and the mixture was refluxed for 1 hour. The suspension was subsequently poured into ice-water, the toluene layer separated, washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was chromatographed to afford 0.95 g of (17 α)-17,23-epoxy-19,24-dinorchola-5(10),9(11),20-trien-3-one 3-cyclic 1,2-ethanediyl acetal, m.p. 132 °C.

e. (i) To a solution of 3.7 g of 17 α)-17,23-epoxy-19,24-dinorchola-5(10),9(11),20-trien-3-one 3-cyclic 1,2-ethanediyl acetal in 25 ml of dichloromethane were added 5 g of sodium hydrogen carbonate. To this mixture was added at -40 °C a solution of 2.5 g of meta-chloroperbenzoic acid in 15 ml of dichloromethane. After stirring for 30 min at 0 °C, the mixture was poured into ice-water and extracted with dichloromethane. The organic layer was washed with a sodium hydrogen carbonate solution and with water, dried over magnesium sulfate and concentrated under reduced pressure. The residue was chromatographed to give 1.8 g of the intermediate 5 α ,10 α -epoxide.

(ii) To a solution of [4-N,N-(dimethylamino)phenyl]-magnesium bromide (prepared from 4.4 g of 4-bromo-N,N-dimethylaniline and 0.6 g of magnesium) in 40 ml of tetrahydrofuran were added 0.5 g of copper(I) chloride at room temperature. Subsequently, 1.8 g of the 5 α ,10 α -epoxide of e(i) in 10 ml of tetrahydrofuran were added and stirring was continued for 30 min. The mixture was poured into an ammonium chloride solution and extracted with ethyl acetate. After washing with water, the organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The residue was chromatographed to afford 1.4 g of the intermediate (5 α ,11 β ,17 α)-17,23-epoxy-5-hydroxy-11-[(4-dimethylamino)phenyl]-19,24-dinorchola-9,20-dien-3-one 3-cyclic 1,2-ethanediyl acetal.

(iii) 1.4 g of the acetal of e(ii) in 15 ml of 70% acetic acid were heated for 2 hours at 50 °C. After cooling to room temperature the mixture was neutralized with sodium hydrogen carbonate and extracted with ethyl acetate. After drying over magnesium sulfate, the solvent was evaporated and the residue chromatographed to give 0.9 g of (11 β ,17 α)-17,23-epoxy-11-[(4-dimethylamino)phenyl]-19,24-dinorchola-4,9,20-trien-3-one, m.p. 168 °C, $[\alpha]_D^{20} = +125^\circ$ (c = 1.135, dioxane).

EXAMPLE 2

In an analogous manner as described in Example 1 were prepared:

(7 β ,11 β ,17 α)-17,23-epoxy-7-methyl-11-[(4-dimethylamino)phenyl]-19,24-dinorchola-4,9,20-triene-3-one, m.p. 100 °C, $[\alpha]_D^{20} = +368^\circ$ (c = 1.02, dioxane).

(11 β ,17 α)-11-(4-acetylphenyl)-17,23-epoxy-19,24-dinorchola-4,9,20-trien-3-one, m.p. 126 °C, $[\alpha]_D^{20} = +82^\circ$ (c = 0.955, dioxane).

(11 β ,17 α)-11-(4-methoxyphenyl)-17,23-epoxy-19,24-dinorchola-4,9,20-trien-3-one, m.p. 185 °C.

(6 β ,11 β ,17 α)-17,23-epoxy-6-methyl-11-(4-dimethylaminophenyl)-19,24-dinorchola-4,9,20-trien-3-one, m.p. 89 °C, $[\alpha]_D^{20} = +128^\circ$ (c = 1.03, dioxane).

(11 β ,17 α)-17,23-epoxy-11-(4-ethenylphenyl)-19,24-dinorchola-4,9,20-trien-3-one. m.p. 191 °C; $[\alpha]_D^{20} = +128^\circ$ (c = 0.94, dioxane).

(11 β ,17 α)-17,23-epoxy-11-(4-methylthiophenyl)-19,24-dinorchola-4,9,20-trien-3-one. m.p. 186 °C; $[\alpha]_D^{20} = +121^\circ$ (c = 1.155, dioxane).

5 The E and Z-ethylidene derivatives were prepared analogously to the preparation of (11 β ,17 α)-11-[(4-dimethylamino)phenyl]-17,23-epoxy-19,24-dinorchola-4,9,20-trien-3-one by using ethyl triphenylphosphonium bromide. Separation by chromatography afforded:

10 (3'E,11 β ,17 β)-11-[(4-dimethylamino)phenyl]-3'-ethylidene-4',5'-dihydrospiro[estra-4,9-diene-17,2'(3'H)-furan]-3-one. m.p. 175 °C; $[\alpha]_D^{20} = +128^\circ$ (c = 0.885, dioxane).

15 (3'Z,11 β ,17 β)-11-[(4-dimethylamino)phenyl]-3'-ethylidene-4',5'-dihydrospiro[estra-4,9-diene-17,2'(3'H)-furan]-3-one. m.p. 172 °C.

20 EXAMPLE 3

The intermediate of Example 1d can also be prepared by treatment of (17 β)-4',5'-dihydrospiro[estra-5(10),9(11)-diene-17,2'(3'H)-furan]-3,3'-dione 3-cyclic 1,2-ethanediy l acetal with trimethylsilylmethylmagnesium chloride, followed by acid treatment.

30 EXAMPLE 4

35 The intermediate of Example 1c(ii) can also be prepared by converting the known estra-5(10),9(11)-dien-3,17-dione 3-cyclic 1,2-ethanediy l acetal (A. Belanger, D. Philibert, and G. Teutsch, *Steroids*, 37 (1981), 361-383) in a similar manner as described by D. Gange and Ph. Magnus, *J. Am. Chem. Soc.*, 100 (1978), 7747-7748:

(i) To 65 ml of n-butyllithium (1.6 M solution in hexane) in 48 ml of tetrahydrofuran were added 9.3 ml

of 1-methoxy-1,2-propadiene at -78°C . After stirring for 45 min at this temperature 10.6 g of estra-5(10),9(11)-diene-3,17-dione 3-cyclic 1,2-ethanediyl acetal were added. Subsequently, the mixture was stirred at -40°C for 30 min and poured into an ice-cold ammonium chloride solution. Ethyl acetate was added and the layers were separated. The organic layer was washed with brine, dried over magnesium sulfate and the solvent was removed under reduced pressure.

(ii) The crude 1,2-propadiene was mixed with 230 ml of *tert*-butanol, 3.75 g of potassium *tert*-butoxide and 0.3 g of dicyclohexano-18-crown-6. After refluxing for 8 hours, the mixture was poured into water and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, evaporated, and the residue was chromatographed to afford 9.1 g of the methyl enol ether of (17 β)-4',5'-dihydrospiro[estra-5(10),9(11)-diene-17,2'(3'H)-furan]-3,3'-dione 3-cyclic 1,2-ethanediyl acetal.

(iii) This enol ether was dissolved in 70 ml of acetone and a 1 M hydrochloric acid solution was added until pH 2. The mixture was stirred for 3 h, subsequently poured into a sodium hydrogen carbonate solution, and extracted with ethyl acetate. After drying over magnesium sulfate and removal of the solvent, the residue was subjected to chromatography to yield 6.4 g of (17 β)-4',5'-dihydro-spiro[estra-5(10),9(11)-diene-17,2'(3'H)-furan]-3,3'-dione 3-cyclic 1,2-ethanediyl acetal.

EXAMPLE 5

The intermediate of Example 1d can also be prepared in one step by reaction of estra-5(10),9(11)-dien-3,17-dione 3-cyclic 1,2-ethanediyl acetal with 4-chloro-2-lithio-1-butene. Finally introduction of the 20-21

double bond into the cholane system could also be effected by an elimination reaction of an (17 α ,20xi)-17,23-epoxy-24-norcholane precursor possessing a suitable leaving group in either the 20- or the 21-position.

EXAMPLE 6

(i) 520 mg of (5 α ,11 β ,17 α)-17,23-epoxy-5-hydroxy-11-[(4-(methylthio)phenyl]-19,24-dinorchola-9,20-dien-3-one 3-cyclic 1,2-ethanediyl acetal [prepared analogously to EXAMPLE 1e(ii)], 5 ml of acetone and 0.1 ml of 30% hydrogen peroxide were refluxed for 2 h. After cooling to room temperature, water was added and the mixture was extracted with ethyl acetate. The organic layer was washed with a sodium thiosulfate solution and with water, dried over magnesium sulfate and concentrated under reduced pressure.

(ii) The residue (515 mg) was dissolved in 5 ml of 70% acetic acid and heated for 3 h at 50 °C. After cooling to room temperature water was added and the mixture was neutralized with sodium hydrogen carbonate and extracted with ethyl acetate. After drying over magnesium sulfate the solution was filtered over silicagel to give 250 mg of a mixture of diastereomeric sulfoxides of (11 β ,17 α)-17,23-epoxy-11-[4-(methylsulfinyl)phenyl]-19,24-dinorchola-4,9,20-trien-3-one. m.p. 115 °C.

EXAMPLE 7

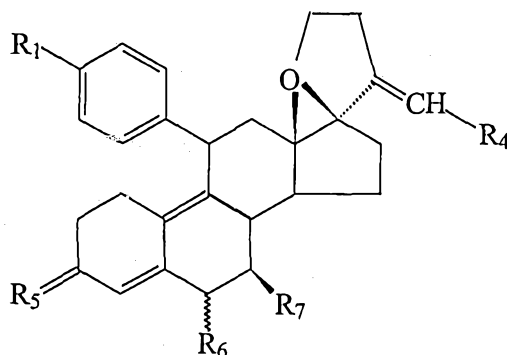
(i) To a solution of 520 mg of a diastereomeric mixture of (5 α ,11 β ,17 α)-17,23-epoxy-5-hydroxy-11-[4-(methylsulfinyl)phenyl]-19,24-dinorchola-9,20-dien-3-one 3-cyclic 1,2-ethanediyl acetal [EXAMPLE 6(i)], in 5 ml of methyl alcohol was added at 5 °C a solution of 615

mg of oxone (KHSO_5) in 6 ml of water. After stirring for 3 h at this temperature the mixture was extracted with dichloromethane. The organic layer was washed with water, dried over magnesium sulfate and concentrated under reduced pressure.

(ii) The residue (520 mg) was dissolved in 5 ml of 70% acetic acid and heated for 3 h at 50 °C. After cooling to room temperature the mixture was neutralized with sodium hydrogen carbonate and extracted with ethyl acetate. After drying over magnesium sulfate the solvent was removed and the residue was chromatographed to give 510 mg of (11 β ,17 α)-17,23-epoxy-11-[4-(methylsulfonyl)phenyl]-19,24-dinorchola-4,9,20-trien-3-one. m.p. 142 °C.

The claims defining the invention are as follows:-

1. A 17-spirofuran-3'-ylidene steroid having the formula



I

R_1 is NR_2R_3 , lower acyl, OH, SH, O-lower alkyl or $S(O)_n$ -lower alkyl wherein n is 0-2;

R_2 and R_3 are independently selected from hydrogen and lower alkyl;

R_4 is hydrogen or lower alkyl;

R_5 is O, (H,H), (H,OH), (H, O-lower acyl), or NOH;

R_6 and R_7 are both hydrogen, or one is hydrogen and the other lower alkyl; and the wavy line represents an α or β bond.

2. The 17-spirofuran-3'-ylidene steroid of claim 1, wherein

R_1 is $N(CH_3)_2$, acetyl, S-lower alkyl, or SO_2 -lower alkyl;

R_4 is hydrogen or methyl;

R_5 is O;

R_6 and R_7 are both hydrogen or one is hydrogen and the other methyl.

3. The 17-spirofuran-3'-ylidene steroid of claim 2, wherein R_1 acetyl, R_4 is hydrogen, R_5 is O, R_6 and R_7 are both hydrogen.

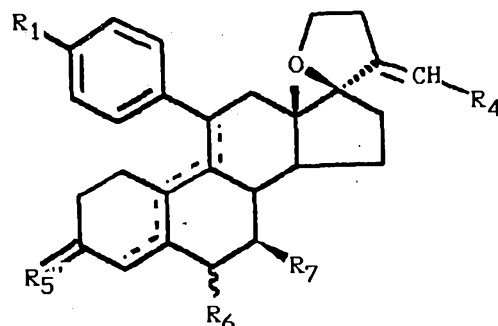
4. A method of treating a human for conditions in which the progesterone receptor is involved, comprising administering to said human an antiprogestin effective amount of a steroid of any one of claims 1 to 3.



5. A pharmaceutical composition comprising the 17-spiro-furan-3'-ylidene steroid of any one of claims 1-3 and pharmaceutically acceptable auxiliaries.

6. A use of the the 17-spirofuran-3'-ylidene steroid of any one of claims 1-3 for the manufacture of a medicament having antiprogestin activity.

7. A process for the preparation of the 17-spirofuran-3'-ylidene steroid of claim 1, characterized in that
a) a 3-keto or 3-oxim protective group in a compound having the formula



II

wherein

R_1 is NR_2R_3 , lower acyl, OH, SH, O-lower alkyl, or $S(O)_n$ -lower alkyl wherein n is 0-2;

R_2 and R_3 are independently selected from hydrogen and lower alkyl;

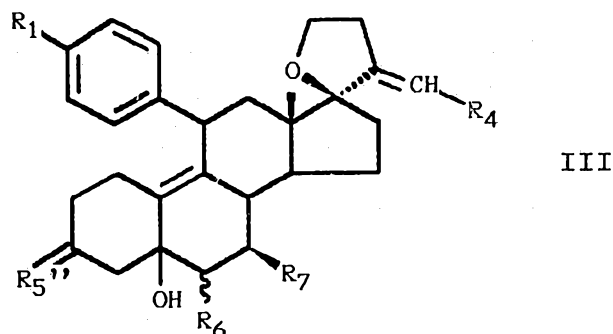
R_4 is hydrogen or lower alkyl;

$R_{5'}$ is a protected O or protected NOH;

R_6 and R_7 are both hydrogen, or one is hydrogen and the other lower alkyl; the dotted line represents two conjugated bonds, and

the twatched line represents an α or β bond, is removed; or

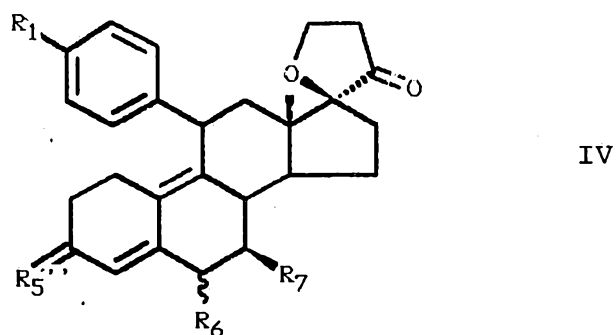
b) a compound having formula



wherein

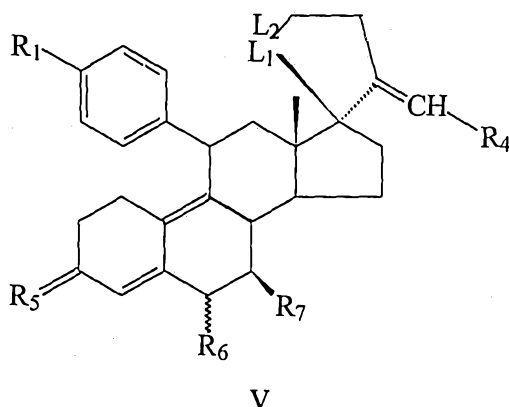
$R_{5''}$ is protected O, (H,H), (H,protected OH), (H,O-lower acyl), or protected NOH, and R_1 - R_4 , R_6 - R_7 , and the twitched line have the previously given meanings, is dehydrated and simultaneously cleaved or followed by cleavage of an optionally present protective group; or

c) a compound having the formula



wherein $R_{5''}$ is protected O, (H,H), (H,protected OH), (H,O-lower acyl), protected NOH, and R_1 - R_3 , R_6 - R_7 , and the twitched line have the previously given meanings, is condensed with an R_4 -CH₂-Wittig, R_4 -CH₂-Wittig-like, or R_4 -CH₂-Peterson reagent, wherein R_4 has the previously given meaning, followed by deprotection of an optionally present protective group into the 17-spirofuran-3'-ylidene steroid of claim 1; or

d) a compound having the formula



5

wherein R_5'' is R_5 or protected O, (H,H), (H, protected OH), or protected NOH, and R_1 - R_7 and the twiched line have the previously given meanings, and one of L_1 and L_2 is OH and the other is a leaving group, is converted into a 17-spirofuran-3'-ylidene steroid, which after deprotection of an optionally present protective group affords the 17-spirofuran-3'-ylidene steroid of claim 1.

8. A 17,23-epoxy-11-phenyl-19,24-dinorchola-4,9,20-triene derivative substantially as hereinbefore described with reference to any one of the Examples.

9. A process for the preparation of a 17,23-epoxy-11-phenyl-19,24-dinorchola-4,9,20-triene derivative substantially as hereinbefore described with reference to any one of the Examples.

10. A pharmaceutical composition having antiprogestin activity, comprising a compound of claim 8 together with a pharmaceutically acceptable carrier, diluent, excipient or adjuvant.

11. A method of treating a human for conditions in which the progesterone receptor is involved, comprising administering to said human an antiprogestin effective amount of a steroid of claim 8 or a composition of claim 10.

Dated 26 October, 1994

Akzo N.V.

Patent Attorneys for the Applicant/Nominated Person

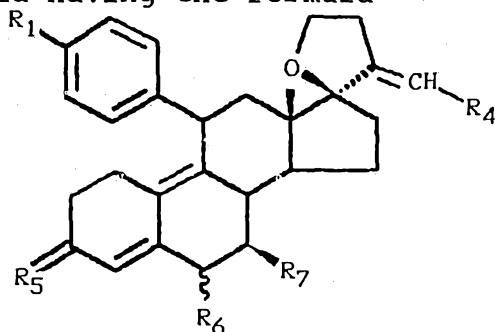
SPRUSON & FERGUSON



17-Spirofuran-3'-ylidene Steroids

Abstract

The invention relates to an antiprogestin 17-spirofuran-3'-ylidene steroid having the formula



wherein

R_1 is NR_2R_3 , lower acyl, OH, SH, O-lower alkyl or $S(O)_n$ -lower alkyl wherein n is 0-2;

R_2 and R_3 are independently selected from hydrogen and lower alkyl;

R_4 is hydrogen or lower alkyl;

R_5 is O, (H,H), (H,OH), (H,O-lower acyl), or NOH;

R_6 and R_7 are both hydrogen, or one is hydrogen and the other lower alkyl; and

the twitched line represents an α or β bond.