

- 1 -

ESTROGENIC 19-NORADNROST-17-ONE DERIVATIVES WITH AN AROMATIC B-RING

BACKGROUND OF THE INVENTION

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The use of naturally occurring estrogenic compositions of substantial purity and low toxicity such as PREMARIN (conjugated equine estrogens) has become a preferred medical treatment for alleviating the symptoms of menopausal syndrome, osteoporosis/osteopenia in estrogen deficient women and in other hormone related disorders. The estrogenic components of the naturally occurring estrogenic compositions have been generally identified as sulfate esters of estrone, equilin, equilenin, 17- β -estradiol, dihydroequilenin and 17- β -dihydroequilenin (U.S. Patent 2,834,712). The estrogenic compositions are usually buffered or stabilized with alkali metal salts of organic or inorganic acids at a substantially neutral pH of about 6.5 to 7.5. Urea has also been used as a stabilizer (U.S. 3,608,077). The incorporation of antioxidants to stabilize synthetic conjugated estrogens and the failure of pH control with tris(hydroxymethyl)aminomethane (TRIS) to prevent hydrolysis is discussed in U.S. 4,154,820.

One of the compounds described herein, 3 β -hydroxy-5,7,9-estratriene-17-one 3-sulfate ester sodium salt is a minor component of PREMARIN (conjugated equine estrogens). The preparation of 3 β -hydroxy-5,7,9-estratriene-17-one is been disclosed by D. Banerjee in Ind. Chim. Belge. Suppl. 2: 435 (1959); however, no utility is provided for this compound.

25 DESCRIPTION OF THE INVENTION

In accordance with this invention, there is provided 3 β -hydroxy-5,7,9-estratriene-17-one or a pharmaceutically acceptable salt of its 3-sulfate ester. The structure of 3 β -hydroxy-5,7,9-estratriene-17-one is shown below as compound I.

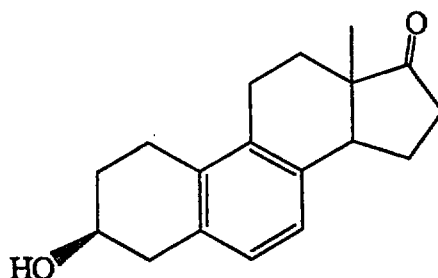
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- 2 -



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Pharmaceutically acceptable salts of 3 β -hydroxy-5,7,9-estratriene-17-one 3-sulfate ester include, but are not limited to, the alkali metal salts, alkaline earth metal salts, ammonium salts, alkylammonium salts containing 1-6 carbon atoms or dialkylammonium salts containing 1-6 carbon atoms in each alkyl group, trialkylammonium salts containing 1-6 carbon atoms in each alkyl group and tetraalkylammonium salts containing 1-6 carbon atoms in each alkyl group.

Alkali metal salts include sodium and potassium salts, particularly preferred are sodium salts. Alkaline earth metal salts include calcium and magnesium salts. Suitable alkyl groups include methyl, ethyl, propyl, butyl, pentyl and hexyl, preferred alkyl groups being methyl and ethyl. Where more than one alkyl group is present the groups may be the same or different. Preferred trialkylammonium salts are trimethylammonium salts and triethylammonium salts.

The salts of the invention are preferably in greater than 1 percent purity.

As 3 β -hydroxy-5,7,9-estratriene-17-one 3-sulfate ester sodium salt is a minor component of PREMARIN (conjugated equine estrogens), this invention also provides 3 β -hydroxy-5,7,9-estratriene-17-one 3-sulfate sodium salt in greater than one percent purity. This invention further provides a compound consisting essentially of a pharmaceutically acceptable salt of 3 β -hydroxy-5,7,9-estratriene-17-one 3-sulfate ester; a compound consisting essentially of 3 β -hydroxy-5,7,9-estratriene-17-one 3-sulfate ester sodium salt; and a compound consisting essentially of 3 β -hydroxy-5,7,9-estratriene-17-one or a pharmaceutically acceptable salt of its 3-sulfate ester.

As used in accordance with this invention, treating covers treatment of an existing condition, ameliorating the condition, or providing palliation of the condition

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and inhibiting includes inhibiting or preventing the progress or development of the condition.

5 The present invention further provides compositions comprising 3β -hydroxy-5,7,9-estratriene-17-one, 3β -hydroxy-5,7,9-estratriene-17-one 3-sulfate ester or pharmaceutically acceptable salts or a mixture of these. In particular it provides compositions comprising at least 1% of 3β -hydroxy-5,7,9-estratriene-17-one, 3β -hydroxy-5,7,9-estratriene-17-one 3-sulfate ester or pharmaceutically acceptable salts or a mixture of these. One aspect of the present invention provides compositions wherein
10 the only estrogenic agent is 3β -hydroxy-5,7,9-estratriene-17-one, 3β -hydroxy-5,7,9-estratriene-17-one 3-sulfate ester or pharmaceutically acceptable salts or a mixture of these. Embodiments of the present invention include compositions wherein the only active compound is 3β -hydroxy-5,7,9-estratriene-17-one, 3β -hydroxy-5,7,9-estratriene-17-one 3-sulfate ester or pharmaceutically acceptable salts or a mixture of
15 these. In these embodiments other excipients and carriers may be included but no further active materials are included.

The present invention also provides processes for the preparation of 3β -hydroxy-5,7,9-estratriene-17-one, 3β -hydroxy-5,7,9-estratriene-17-one 3-sulfate ester
20 and pharmaceutically acceptable salts of these.

3β -hydroxy-5,7,9-estratriene-17-one or a pharmaceutically acceptable salt thereof may be prepared by the oxidative aromatisation of estra-5(10),7-dien- 3β -ol-17-one or estra-5(10),7-dien- 3α -ol-17-one using a suitable oxidising agent, such as DEAD
25 (diethyldiazodicarboxylate), DDQ or Pd/C. Alternatively equilenin (or a partially hydrogenated derivative thereof) may be reduced e.g. by metal alcohol reduction (e.g. by the Birch reaction), by metal ammonium reduction or by electrolytic reduction.

3β -hydroxy-5,7,9-estratriene-17-one 3-sulfate ester may be prepared by
30 sulphonating 3β -hydroxy-5,7,9-estratriene-17-one using, e.g. sulphuric acid, chlorosulphuric acid or an amidosulfonic acid.

Alternatively the pH of a salt of 3β -hydroxy-5,7,9-estratriene-17-one or its 3-sulfate ester may be adjusted to provide the free acid.

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A pharmaceutically acceptable salt of 3β -hydroxy-5,7,9-estratriene-17-one or its 3-sulfate ester may be prepared by:

- 4 -

- a) converting 3β -hydroxy-5,7,9-estratriene-17-one or its 3-sulfate ester to a pharmaceutically acceptable salt or
- 5 b) converting a pharmaceutically acceptable salt of 3β -hydroxy-5,7,9-estratriene-17-one or its 3-sulfate ester to a different pharmaceutically acceptable salt of 3β -hydroxy-5,7,9-estratriene-17-one or its 3-sulfate ester.

10 3β -hydroxy-5,7,9-estratriene-17-one or its 3-sulfate ester may be converted to a pharmaceutically acceptable salt by neutralising the acid with an appropriate base, e.g. with an alkali metal carbonate, an alkaline earth metal carbonate or a primary, secondary, tertiary or quaternary amine carbonate. Alkali metal or alkaline earth metal salts may be prepared by using the appropriate alkali metal hydride e.g. sodium hydride, potassium hydride or lithium hydride.

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A pharmaceutically acceptable salt of 3β -hydroxy-5,7,9-estratriene-17-one or its 3-sulfate ester may be converted to a different pharmaceutically acceptable salt by displacement, by using an ion exchange resin or by double decomposition (metastasis). Displacement of a weak base with a stronger one may be utilised to convert, e.g. an

20 amine salt to an alkali metal salt or an alkaline earth metal salt using an appropriate base, e.g. a hydroxide. For example a trialkylamine salt such as a triethylamine salt may be converted to an alkali metal salt such as a sodium salt by treating it with an alkali metal hydroxide such as aqueous sodium hydroxide. The displacement may be carried out using an ion exchange resin. Alternatively one salt may be converted to another by

25 double decomposition, e.g. an alkaline earth metal salt such as the calcium salt may be replaced with an alkali metal salt. E.g. the calcium salt of 3β -hydroxy-5,7,9-estratriene-17-one or its 3-sulfate ester may be dissolved in water followed by the addition of e.g. sodium carbonate. Insoluble calcium carbonate would then precipitate out to provide the sodium salt of 3β -hydroxy-5,7,9-estratriene-17-one or its 3-sulfate

30 ester.

A pharmaceutically acceptable salt of 3β -hydroxy-5,7,9-estratriene-17-one 3-sulfate ester may be prepared by directly converting 3β -hydroxy-5,7,9-estratriene-17-one to a pharmaceutically acceptable salt of 3β -hydroxy-5,7,9-estratriene-17-one 3-sulfate ester. This may be performed by reacting it with the appropriate aminesulfurtrioxide complex, e.g. by reacting it with a trialkylaminesulfurtrioxide (such as triethylaminesulfurtrioxide complex) to provide the corresponding trialkylamine salt

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- 5 -

(such as the triethylamine salt). If desired the salt may then be converted to another salt of the invention as described above. Alkali metal or alkaline earth metal salts may be prepared by treating 3 β -hydroxy-5,7,9-estratriene-17-one with the appropriate alkali metal hydride e.g. sodium hydride, potassium hydride or lithium hydride to produce the corresponding alkoxide *in situ* and then adding a trialkylaminesulfurtrioxide (such as triethylaminesulfurtrioxide complex) to provide the corresponding trialkylamine salt (such as the triethylamine salt). If desired the salt may then be converted to another salt of the invention as described above.

10 The present invention also provides 3 β -hydroxy-5,7,9-estratriene-17-one 3-sulfate ester and its pharmaceutically acceptable salts prepared by a chemical process, particularly those prepared according to the processes described above. The invention also provides 3 β -hydroxy-5,7,9-estratriene-17-one 3-sulfate ester and its pharmaceutically acceptable salts obtainable by such processes.

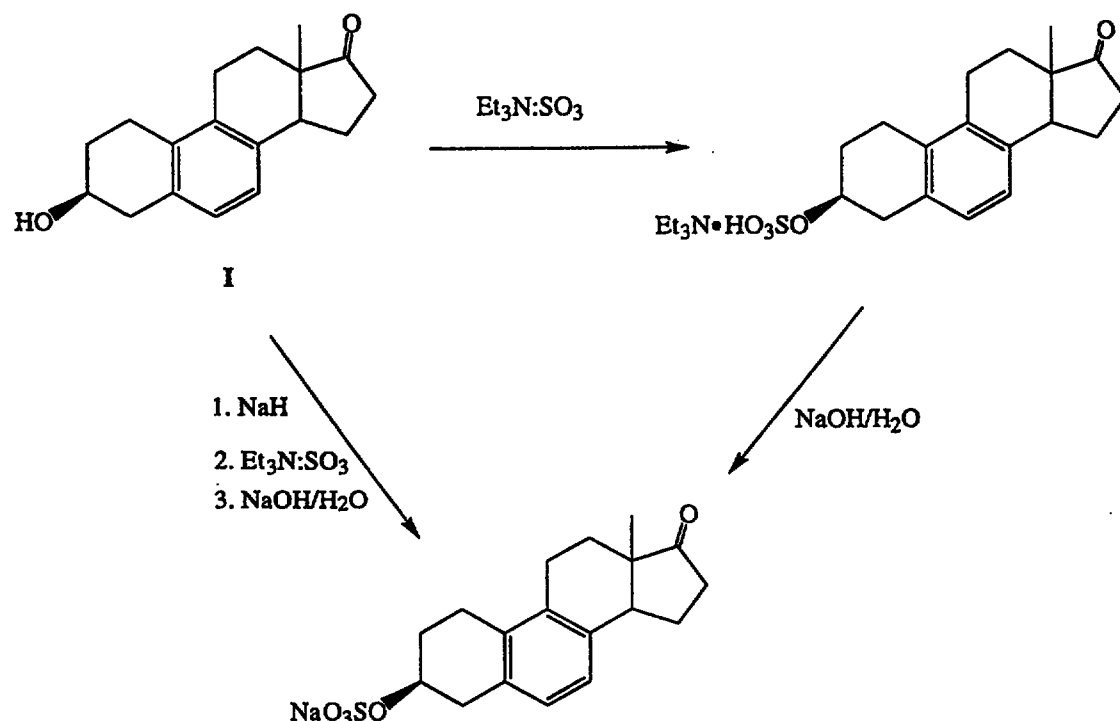
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 The compounds of this invention can be prepared from readily available starting materials. For example, the preparation of 3 β -hydroxy-5,7,9-estratriene-17-one 3-sulfate ester sodium salt can be prepared from 3 β -hydroxy-5,7,9-estratriene-17-one according to Scheme I. 3 β -Hydroxy-5,7,9-estratriene-17-one can be prepared according to D. Banerjee in Ind. Chim. Belge. Suppl. 2: 435 (1959).

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- 6 -

Scheme I



The compounds of this invention are estrogenic, as shown in the *in vitro* and *in vivo* standard pharmacological test procedures described below in which 3β-hydroxy-5,7,9-estratriene-17-one was evaluated as a representative compound of this invention.

Estrogen Receptor Binding

An initial evaluation examined the competitive binding properties of 3β-hydroxy-5,7,9-estratriene-17-one to the human estrogen receptor (hER-α) prepared as a soluble cell extract (cytosol). In this standard pharmacological test procedure, 3β-hydroxy-5,7,9-estratriene-17-one demonstrated no specific binding activity. However, when estrogen receptor binding was analyzed using a whole cell test procedure, specific binding was clearly demonstrated. This test procedure indicated an IC_{50} of 7.9×10^{-9} M for 3β-hydroxy-5,7,9-estratriene-17-one. This would be compared with a K_i for estrone, equilin and equilinen of 51, 67 and 375nM, respectively.

In Vitro Cotransfection Test Procedure

In this standard pharmacological test procedure, hER-α over-expressed in Chinese hamster ovary (CHO) cells infected with adeno-2x-ERE-tk-luciferase, an

- 7 -

estrogen responsive reporter gene construct, cells were exposed to varying concentrations (10^{-12} - 10^{-5} M) of 3 β -hydroxy-5,7,9-estratriene-17-one for 24 hours. Cells were also exposed to 17 β -estradiol at 10^{-9} M. Following the 24-hour treatment, cells were lysed and cell extracts assayed for luciferase activity. The results provided
5 that 3 β -hydroxy-5,7,9-estratriene-17-one had an EC₅₀ of approximately 50 nM. Using a similar test procedure, previous data indicate a 5.6nM EC₅₀ for estrone.

In Vivo Uterotropic Activity

Immature rats were treated with 100 μ g 3 β -hydroxy-5,7,9-estratriene-17-one
10 for three days (S.C.) as well as additional groups (n=6) of rats treated with 0.5 μ g ethinyl estradiol and vehicle as positive and negative controls, respectively. Rats treated with 3 β -hydroxy-5,7,9-estratriene-17-one had a uterine weight of 54.63 ± 5.2 mg, whereas control rats had uterine weight of 29.78 ± 1.84 mg demonstrating that 3 β -hydroxy-5,7,9-estratriene-17-one was estrogenic. Rats treated with ethinyl estradiol
15 (0.5 μ g) had a uterine weight of 92.68 ± 7.6 mg.

The results of these standard pharmacological test procedures demonstrate that the compounds of this invention are estrogenic.

20 A representative compound of this invention (3 β -hydroxy-5,7,9-estratriene-17-one) was evaluated in a standard pharmacological test procedure which measured the cardioprotective effects of the compound tested.

Briefly, Female rats, weighing 180-200 g, were pretreated with DES (0.25 mg/kg, i.p.) 18 hr prior to the study. Uterine horns and aortae were removed from
25 pentobarbital-overdosed animals, cleaned of adherences and cut into 1 cm and 2-3 mm segments, respectively. The preparations were mounted in organ baths containing Jalon solution at 30° C and Krebs solution at 37° C, respectively, and aerated with 95%O₂ and 5% CO₂. The contractions were monitored with force-displacement transducers on a Grass polygraph recorder. DMSO produced no effects on the tissues
30 in the present study and thus, was used as a vehicle for dissolving the test compounds.

Both uterine and aortic smooth muscles were contracted with 60 mM KCl. When potassium-induced contraction reached steady-state, cumulative-concentration response curves were determined for test drug or vehicle. Increasing concentrations of the compound to be evaluated were added when the effect of the previous concentration
35 reached steady state (not longer than 20 min). The EC₅₀ was defined as the concentration of test compound which produced 50% relaxation.

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- 8 -

EC₅₀ values of 3.9×10^{-5} and 4.0×10^{-5} were obtained in uterine muscle and thoracic aorta, respectively, for 3 β -hydroxy-5,7,9-estratriene-17-one. These results demonstrate that the compounds of this invention provide cardioprotective protection, particularly in the treatment of ischemic disease and hypertension.

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Based on the results obtained in the standard pharmacological test procedures, the compounds of this invention are useful in providing estrogen replacement therapy following ovariectomy or menopause, and in relieving symptoms related to estrogen deficiency, including vasomotor symptoms, such as hot flushes, and other menopausal related conditions, such as vaginal atrophy, vaginitis, and atrophic changes of the lower urinary tract which may cause increased urinary frequency, incontinence, and dysuria. The compounds of this invention are useful in preventing bone loss and in the inhibition or treatment of osteoporosis. The compounds of this invention are cardioprotective and they are useful in the treatment of atherosclerosis, ischemic disease, and hypertension. These cardiovascular protective properties are of great importance when treating postmenopausal patients with estrogens to prevent osteoporosis and in the male when estrogen therapy is indicated. The compounds of this invention are also antioxidants, and are therefore useful in treating or inhibiting free radical induced disease states. Specific situations in which antioxidant therapy is indicated to be warranted are with cancers, central nervous system disorders, Alzheimer's disease, bone disease, aging, inflammatory disorders, peripheral vascular disease, rheumatoid arthritis, autoimmune diseases, respiratory distress, emphysema, prevention of reperfusion injury, viral hepatitis, chronic active hepatitis, tuberculosis, psoriasis, systemic lupus erythematosus, adult respiratory distress syndrome, central nervous system trauma and stroke. Additionally, the compounds of this invention are useful in the suppression of lactation, and in the prophylaxis and treatment of mumps orchitis.

The compounds of this invention can be used alone as a sole therapeutic agent or can be used in combination with other agents, such as other estrogens, progestins, or androgens.

The compounds of this invention can be formulated neat or with a pharmaceutical carrier for administration, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of administration and standard pharmacological practice. The pharmaceutical carrier may be solid or liquid.

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- 9 -

A solid carrier can include one or more substances which may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents; it can also be an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the
5 finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl
10 cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidone, low melting waxes and ion exchange resins.

Liquid carriers are used in preparing solutions, suspensions, emulsions, syrups, elixirs and pressurized compositions. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic
15 solvent, a mixture of both or pharmaceutically acceptable oils or fats. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (partially
20 containing additives as above, e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g. glycols) and their derivatives, lethicins, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration, the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers
25 are useful in sterile liquid form compositions for parenteral administration. The liquid carrier for pressurized compositions can be halogenated hydrocarbon or other pharmaceutically acceptable propellant.

Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by, for example, intramuscular, intraperitoneal or subcutaneous
30 injection. Sterile solutions can also be administered intravenously. The compounds of this invention can also be administered orally either in liquid or solid composition form.

The compounds of this invention may be administered rectally or vaginally in the form of a conventional suppository. For administration by intranasal or intrabronchial inhalation or insufflation, the compounds of this invention may be
35 formulated into an aqueous or partially aqueous solution, which can then be utilized in the form of an aerosol. The compounds of this invention may also be administered transdermally through the use of a transdermal patch containing the active compound

- 10 -

and a carrier that is inert to the active compound, is non toxic to the skin, and allows delivery of the agent for systemic absorption into the blood stream via the skin. The carrier may take any number of forms such as creams and ointments, pastes, gels, and occlusive devices. The creams and ointments may be viscous liquid or semisolid emulsions of either the oil-in-water or water-in-oil type. Pastes comprised of absorptive powders dispersed in petroleum or hydrophilic petroleum containing the active ingredient may also be suitable. A variety of occlusive devices may be used to release the active ingredient into the blood stream such as a semipermeable membrane covering a reservoir containing the active ingredient with or without a carrier, or a matrix containing the active ingredient. Other occlusive devices are known in the literature.

The dosage requirements vary with the particular compositions employed, the route of administration, the severity of the symptoms presented and the particular subject being treated. Based on the results obtained in the standard pharmacological test procedures, projected daily dosages of active compound would be 0.02 $\mu\text{g/kg}$ - 750 $\mu\text{g/kg}$. Treatment will generally be initiated with small dosages less than the optimum dose of the compound. Thereafter the dosage is increased until the optimum effect under the circumstances is reached; precise dosages for oral, parenteral, nasal, or intrabronchial administration will be determined by the administering physician based on experience with the individual subject treated. Preferably, the pharmaceutical composition is in unit dosage form, e.g. as tablets or capsules. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions, for example, packeted powders, vials, ampoules, prefilled syringes or sachets containing liquids. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form.

The following provides the preparation of 3 β -hydroxy-5,7,9-estratriene-17-one 3-sulfate ester sodium salt as a representative compound of this invention.

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- 11 -

EXAMPLE 1**3 β -Hydroxy-5,7,9-estratriene-17-one 3-sulfate ester sodium salt****Method A:**

To a slurry of sodium hydride (60% dispersion in oil, 0.011 g) in THF (6 mL) was added, under nitrogen, at room temperature, 3 β -hydroxy-5,7,9-estratriene-17-one (0.06 g, 0.2 mmol). After stirring for 5 min, triethylamine-sulfur trioxide complex (0.04 g, 0.21 mmol) was added and stirring continued for 18 h. Solvent was evaporated off and the residue obtained partitioned between water and diethyl ether (6 mL each). The aqueous solution was separated and lyophilized to provide 0.06 g of the desired product.

Method B:

To a solution of 3 β -hydroxy-5,7,9-estratriene-17-one (0.58 g, 2.1 mmol) in THF (15 mL) at RT, under nitrogen, was added triethylamine-sulfur trioxide complex (0.4 g, 2.3 mmol) and stirred for 48 h. The precipitate formed was filtered off and washed with THF (3X3 mL) and dried to provide 3 β -hydroxy-5(10),6, 8-estratriene-17-one-3-triethylammonium sulfate (0.71 g, 73.9%).

To a solution of the triethylammonium salt (0.68 g, 1.5 mmol) was added aqueous sodium hydroxide (1N, 1.6 mL). The solution was stirred for 1h at RT and repeatedly washed with ether (4X10 mL). The aqueous portion was separated and lyophilized to provide 0.56 g of the desired product.

IR (KBr)

3450, 2930, 1734, 1634, 1238, 1189, 1117, 1069, 980, 978, 810, 620 cm⁻¹

¹H NMR (DMSO-d₆)

6.88 (s, 2H, aromatic), 4.74 (m, 1H, 3-H), 0.64 (s, 3H, 18-Me)

¹³C NMR (DMSO-d₆)

219.14, 134.80, 133.74, 133.43, 132.25, 126.77, 122.48, 70.45, 46.28, 45.77, 36.02, 35.85, 28.72, 28.39, 23.57, 23.45, 21.28, 12.89



WHAT IS CLAIMED IS:

1. A compound which is a pharmaceutically acceptable salt of 3 β -hydroxy-5,7,9-estratriene-17-one 3-sulfate ester.
- 5 2. The compound of claim 1 wherein the pharmaceutically acceptable salt of the 3-sulfate ester is an alkali metal salt, alkaline earth metal salt, ammonium salt, alkylammonium salt containing 1-6 carbon atoms, dialkylammonium salt containing 1-6 carbon atoms in each alkyl group, trialkylammonium salt containing 1-6 carbon atoms
10 in each alkyl group or tetraalkylammonium salt containing 1-6 carbon atoms in each alkyl group.
3. 3 β -Hydroxy-5,7,9-estratriene-17-one 3-sulfate ester sodium salt, which is at least 1 percent pure.
- 15 4. A compound which consists essentially of a pharmaceutically acceptable salt of 3 β -hydroxy-5,7,9-estratriene-17-one 3-sulfate ester.
5. The compound of claim 4 wherein the pharmaceutically acceptable salt of the 3-sulfate ester is an alkali metal salt, alkaline earth metal salt, ammonium salt,
20 alkylammonium salt containing 1-6 carbon atoms, or dialkylammonium salt containing 1-6 carbon atoms in each alkyl group, trialkylammonium salt containing 1-6 carbon atoms in each alkyl group or tetraalkylammonium salt containing 1-6 carbon atoms in each alkyl group.
- 25 6. A compound which is 3 β -hydroxy-5,7,9-estratriene-17-one or a pharmaceutically acceptable salt thereof.
7. The compound of claim 6 wherein the pharmaceutically acceptable salt is an
30 alkali metal salt, alkaline earth metal salt, ammonium salt, alkylammonium salt containing 1-6 carbon atoms, or dialkylammonium salt containing 1-6 carbon atoms in each alkyl group, trialkylammonium salt containing 1-6 carbon atoms in each alkyl group or tetraalkylammonium salt containing 1-6 carbon atoms in each alkyl group.
- 35 8. A compound which consists essentially of 3 β -hydroxy-5,7,9-estratriene-17-one or a pharmaceutically acceptable thereof.

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9. The compound of claim 8 wherein the pharmaceutically acceptable salt is an alkali metal salt, alkaline earth metal salt, ammonium salt, alkylammonium salt containing 1-6 carbon atoms, dialkylammonium salt containing 1-6 carbon atoms in each alkyl group, trialkylammonium salt containing 1-6 carbon atoms in each alkyl group or tetraalkylammonium salt containing 1-6 carbon atoms in each alkyl group.

10. A method of inhibiting or treating free radical induced disease states in a mammal in need thereof which comprises administering to said mammal an antioxidant amount of 3β -hydroxy-5,7,9-estratriene-17-one, a pharmaceutically acceptable salt thereof, 3β -hydroxy-5,7,9-estratriene-17-one 3-sulfate ester or a pharmaceutically acceptable salt of to a mammal in need thereof.

11. A method of inhibiting endogenous free radical involvement in disease development of cancers, central nervous system disorders, dementias, Alzheimer's disease, bone disease, aging, inflammatory disorders, peripheral vascular disease, rheumatoid arthritis, autoimmune diseases, respiratory distress, emphysema, prevention of reperfusion injury, viral hepatitis, chronic active hepatitis, tuberculosis, psoriasis, systemic lupus erythematosus, adult respiratory distress syndrome, central nervous system trauma and stroke, or injury during reperfusion procedures in a mammal in need thereof which comprises administering an effective amount of 3β -hydroxy-5,7,9-estratriene-17-one, a pharmaceutically acceptable salt thereof, 3β -hydroxy-5,7,9-estratriene-17-one 3-sulfate ester or a pharmaceutically acceptable salt of to said mammal.

12. A method of providing estrogen replacement therapy or treating estrogen deficiency in a mammal in need thereof, which comprises administering an estrogenic amount of 3β -hydroxy-5,7,9-estratriene-17-one, a pharmaceutically acceptable salt thereof, 3β -hydroxy-5,7,9-estratriene-17-one 3-sulfate ester or a pharmaceutically acceptable salt of to said mammal.

13. A method of treating vasomotor symptoms related to estrogen deficiency in a mammal in need thereof, which comprises administering an effective amount of 3β -hydroxy-5,7,9-estratriene-17-one, a pharmaceutically acceptable salt thereof, 3β -hydroxy-5,7,9-estratriene-17-one 3-sulfate ester or a pharmaceutically acceptable salt of to said mammal.

14. The method of claim 13, wherein the vasomotor symptom is hot flushes.





15. A method of treating or inhibiting osteoporosis in a mammal in need thereof which comprises administering an anti-osteoporosis effective amount of 3β -hydroxy-5,7,9-estratriene-17-one, a pharmaceutically acceptable salt thereof, 3β -hydroxy-5,7,9-estratriene-17-one 3-sulfate ester or a pharmaceutically acceptable salt of to said mammal.
16. A method of treating or inhibiting atherosclerosis in a mammal in need thereof which comprises administering an anti-atherosclerosis effective amount of 3β -hydroxy-5,7,9-estratriene-17-one, a pharmaceutically acceptable salt thereof, 3β -hydroxy-5,7,9-estratriene-17-one 3-sulfate ester or a pharmaceutically acceptable salt of to said mammal.
17. A pharmaceutical composition which comprises 3β -hydroxy-5,7,9-estratriene-17-one, a pharmaceutically acceptable salt thereof, 3β -hydroxy-5,7,9-estratriene-17-one 3-sulfate ester or a pharmaceutically acceptable salt of and a pharmaceutical carrier.
18. A pharmaceutical composition which comprises a pharmaceutically acceptable salt of 3β -hydroxy-5,7,9-estratriene-17-one 3-sulfate ester and a pharmaceutical carrier.
19. Use of a compound as defined in any one of claims 1 to 9 as a medicament.
20. Use of a compound as defined in any one of claims 1 to 9 in the preparation of a medicament for:
- a) inhibiting or treating free radical induced disease states,
- b) inhibiting endogenous free radical involvement in disease development of cancers, central nervous system disorders, dementias, Alzheimer's disease, bone disease, aging, inflammatory disorders, peripheral vascular disease, rheumatoid arthritis, autoimmune diseases, respiratory distress, emphysema, prevention of reperfusion injury, viral hepatitis, chronic active hepatitis, tuberculosis, psoriasis, systemic lupus erythematosus, adult respiratory distress syndrome, central nervous system trauma and stroke, or injury during reperfusion procedures,
- c) providing estrogen replacement therapy or treating estrogen deficiency,



- 15 -

d) treating vasomotor symptoms related to estrogen deficiency,

e) treating or inhibiting osteoporosis or

5 f) treating or inhibiting atherosclerosis



in a mammal.

21. A composition comprising at least 1% of a compound as defined in any one of
10 claims 1 to 9.

22. A process for the preparation of 3 β -hydroxy-5,7,9-estratriene-17-one which
comprises:

15 a) the oxidative aromatisation of estra-5(10),7-dien-3 β -ol-17-one or estra-5(10),7-dien-
3 α -ol-17-one or

b) the reduction of equilenin or a partially hydrogenated derivative thereof.

20 23. A process for the preparation of 3 β -hydroxy-5,7,9-estratriene-17-one 3-sulfate
ester which comprises sulphonating 3 β -hydroxy-5,7,9-estratriene-17-one using a
sulphonating agent.

24. A process for the preparation of a pharmaceutically acceptable salt of 3 β -
25 hydroxy-5,7,9-estratriene-17-one or its 3-sulfate ester which comprises:

a) converting 3 β -hydroxy-5,7,9-estratriene-17-one or its 3-sulfate ester to a
pharmaceutically acceptable salt or

30 b) converting a pharmaceutically acceptable salt of 3 β -hydroxy-5,7,9-estratriene-
17-one or its 3-sulfate ester to a different pharmaceutically acceptable salt of 3 β -
hydroxy-5,7,9-estratriene-17-one or its 3-sulfate ester.

25. A process for the preparation of a pharmaceutically acceptable salt of 3 β -
35 hydroxy-5,7,9-estratriene-17-one 3-sulfate ester which comprises the direct conversion
of 3 β -hydroxy-5,7,9-estratriene-17-one.

This Sheet Has Been Replaced



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REPLACED