PREGNANE 3,20 DIOL MONO- AND DI-SULPHATES

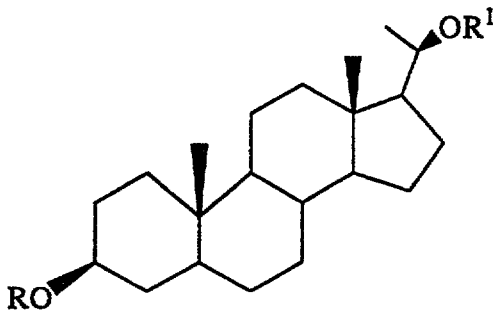
BACKGROUND OF THE INVENTION

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.

Three of the compounds described herein, 5α-pregnan-3β,20β-diol 3-sulfate ester sodium salt, 5α-pregnan-3β,20β-diol 20-sulfate ester sodium salt, and 5α-pregnan-3β,20β-diol 3,20-(bis)sulfate ester (bis)sodium salt, are minor components of PREMARIN (conjugated equine estrogens). The preparation of 3β-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.

DESCRIPTION OF THE INVENTION

In accordance with this invention, there are provided compounds having the formula



I

wherein

R and R^1 are each, independently, hydrogen or $SO_3^- X^+$;

X^+ is alkali metal, alkaline earth metal, ammonium, alkylammonium containing 1-6 carbon atoms, dialkylammonium containing 1-6 carbon atoms in each alkyl group, trialkylammonium containing 1-6 carbon atoms in each alkyl group or tetraalkylammonium salts containing 1-6 carbon atoms in each alkyl group;

with the proviso that R and R^1 are not both hydrogen.

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 trimethyl-ammonium salts and triethylammonium salts.

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

As 5α-pregnan-3β,20β-diol 3-sulfate ester sodium salt, 5α-pregnan-3β,20β-diol 20-sulfate ester sodium salt, and 5α-pregnan-3β,20β-diol 3,20-(bis)sulfate ester (bis)sodium salt are minor components of PREMARIN (conjugated equine estrogens), this invention also provides 5α-pregnan-3β,20β-diol 3-sulfate ester sodium salt in greater than 1 percent purity, 5α-pregnan-3β,20β-diol 20-sulfate ester sodium salt in greater than 1 percent purity, and 5α-pregnan-3β,20β-diol 3,20-(bis)sulfate ester (bis)sodium salt in greater than one percent purity.

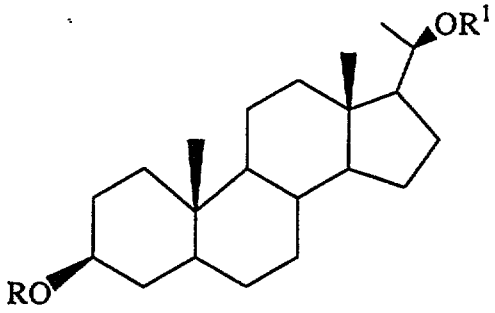
This invention also provides a compound consisting essentially of 5α-pregnan-3β,20β-diol 3-sulfate ester sodium salt, a compound consisting essentially of 5α-pregnan-3β,20β-diol 20-sulfate ester sodium salt, and a compound consisting essentially of 5α-pregnan-3β,20β-diol 3,20-(bis)sulfate ester (bis)sodium salt.

This invention further provides a composition of matter consisting essentially of a compound having the formula

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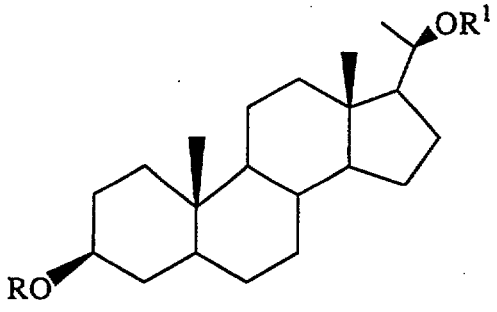
wherein

R and R^1 are each, independently, hydrogen or $SO_3^- X^+$;

X^+ is alkali metal, alkaline earth metal, ammonium, alkylammonium containing 1-6 carbon atoms, dialkylammonium containing 1-6 carbon atoms in each alkyl group, trialkylammonium containing 1-6 carbon atoms in each alkyl group or tetraalkylammonium salts containing 1-6 carbon atoms in each alkyl group;

with the proviso that R and R^1 are not both hydrogen.

This invention additionally provides a method of using a compound having the formula



I

wherein

R and R^1 are each, independently, hydrogen, SO_3H or $SO_3^- X^+$;

X^+ is alkali metal, alkaline earth metal, ammonium, alkylammonium containing 1-6 carbon atoms, dialkylammonium containing 1-6 carbon atoms in each alkyl group, trialkylammonium containing 1-6 carbon atoms in each alkyl group or tetraalkylammonium salts containing 1-6 carbon atoms in each alkyl group;

as a progestational agent.

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The present invention further provides compositions comprising a compound of formula I. In particular it provides compositions comprising at least 1% of a compound of formula I. One aspect of the present invention provides compositions wherein the only progestational agent is a compound of formula I. Embodiments of the present invention include compositions wherein the only active compound is a compound of formula I. 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 the compounds of formula I. It provides processes for the preparation of 5α-pregnan-3,20-diol 3,20-(bis)sulfate ester (bis) salt (i.e. compounds wherein A and B are each independently a sulphate ester salt) which comprise:

a) converting the appropriate 5α-pregnan-3,20-diol 3,20-(bis)sulfate ester to a pharmaceutically acceptable salt,

b) converting a pharmaceutically acceptable salt of the 5α-pregnan-3,20-diol 3,20-(bis)sulfate ester to a different pharmaceutically acceptable salt of the appropriate 5α-pregnan-3,20-diol 3,20-(bis)sulfate ester or

c) directly converting the appropriate 5α-pregnan-3,20-diol to the desired pharmaceutically acceptable salt of 5α-pregnan-3,20-diol 3,20-(bis)sulfate ester.

5α-pregnan-3,20-diol-3,20-(bis)sulfate ester may be converted to pharmaceutically acceptable salts 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.

A pharmaceutically acceptable salt of the appropriate 5α-pregnan-3,20-diol 3,20-(bis)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 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 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 the 5α-pregnan-3,20-diol 3,20-(bis)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 the desired 5α-pregnan-3,20-diol 3,20-(bis)sulfate ester.

A pharmaceutically acceptable salt of the desired 5α-pregnan-3,20-diol-3,20-(bis)sulfate ester may be prepared by directly converting the appropriate 5α-pregnan-3,20-diol. This may be performed by reacting it with the appropriate aminesulfur-trioxide complex, e.g. by reacting it with a trialkylaminesulfurtrioxide (such as triethyl-aminesulfurtrioxide 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.

The invention also provides processes for the preparation of 5α-pregnan-3,20-diol-3-sulfate ester salts or 5α-pregnan-3,20-diol-20-sulfate ester salts (i.e., compounds wherein one of A and B is a sulphate ester salt and the other is hydrogen) which comprise:

a) converting the appropriate 5α-pregnan-3,20–diol-mono sulfate ester to a pharmaceutically acceptable salt,

b) converting a pharmaceutically acceptable salt of the appropriate 5α-pregnan-3,20-diol-mono sulfate ester to a different pharmaceutically acceptable salt of the appropriate the appropriate 5α-pregnan-3,20-diol-mono sulfate ester,

c) converting the corresponding 5α-pregnan-3-ol,20-keto mono sulfate ester salt or 5α-pregnan-3-keto-20-ol mono sulfate ester salt to the desired 5α-pregnan-3,20-diol-3-sulfate ester salt or 5α-pregnan-3,20-diol-20-sulfate ester salt

d) converting 5α-pregnan-3,20-diol to the desired pharmaceutically acceptable salt of the desired 5α-pregnan-3,20-diol-monosulfate ester,

e) deprotecting the corresponding 20 protected 5α-pregnan-3,20-diol-3-sulfate ester salt or 3 protected 5α-pregnan-3,20-diol-20-sulfate ester salt or

f) converting one stereo isomer of the pharmaceutically acceptable salt of the appropriate 5α-pregnan-3,20-diol-mono sulfate ester to another by inversion.

The conversion of the appropriate 5α-pregnan-3,20-diol-mono sulfate ester to a pharmaceutically acceptable salt and the conversion of a pharmaceutically acceptable salt of the appropriate 5α-pregnan-3,20-diol-mono sulfate ester to a different pharmaceutically acceptable salt of the appropriate the appropriate 5α-pregnan-3,20-diol-mono sulfate ester may be performed by analogy to the methods described above.

5α-pregnan-3-ol,20-keto mono sulfate ester salt or 5α-pregnan-3-keto-20-ol mono sulfate ester salt may be converted to the desired 5α-pregnan-3,20-diol-mono-sulfate ester salt by reduction with a suitable reducing agent, e.g. $LiBH_4$. If desired one steroisomer may be converted another by inversion, e.g. by a MITSUNOBU inversion.

5α-pregnan-3,20-diol may be converted directly to the desired pharmaceutically acceptable salt of the desired 5α-pregnan-3,20-diol-monosulfate ester by analogy to the methods described above.

In order to prepare the desired 5α-pregnan-3-ol,20-keto mono sulfate ester salt it may be necessary to protect the second hydroxy group. This may be achieved by conventional means using a suitable protecting group which will finally be removed to provide the product.

The invention also provides processes for the preparation of the free sulfate acids esters of formula I (i.e. compounds wherein at least one of A and B is a free sulphate acid) which comprises sulphonating the corresponding hydroxy compounds using, e.g. sulphuric acid, chloro-sulphuric acid or an amidosulfonic acid. Alternatively the pH of a salt of the corresponding mono or bis sulfate may be adjusted to provide the desired free acid.

The invention also provides processes for the preparation of 5α-pregnan-3,20-diol (i.e. compounds wherein both A and B are hydroxy groups) which comprises the reduction of the corresponding 3,20-di-keto compound using a suitable reducing agent, e.g. $LiBH_4$.

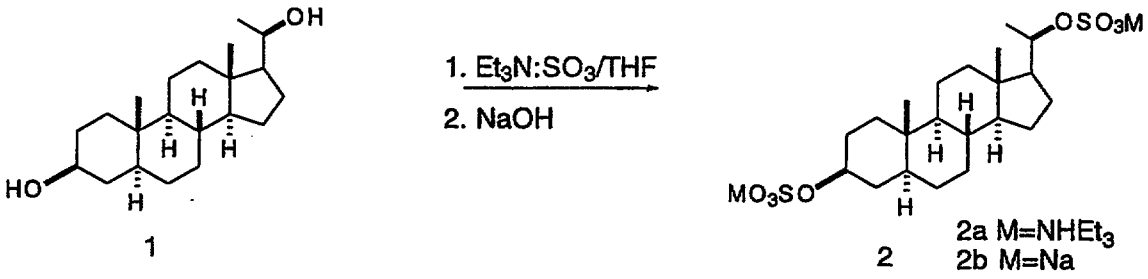
The present invention also provides a compound of formula I prepared by a chemical process, particularly those prepared according to the processes described above. The invention also provides a compound of formula I obtainable by such processes.

The compounds of this invention can be prepared from readily available starting materials according to the processes in Scheme I-III. For example, according to Scheme I, commercially available 5α-pregnane-3β, 20β-diol (1) [D.M. Glick and H. Hirschmann, J. Org. Chem. 27, 3212 (1962)] is treated with two or more equivalents of triethylamine:sulfur trioxide reagent in a suitable solvent such as tetrahydrofuran at room temperature to afford 5α-pregnan-3β, 20β-diol (bis)sulfate, (bis)triethylammonium salt (2a). The triethylammonium salt (2a) is converted to the sodium salt (2b) by ion exchange chromotography (Dowex 50X8, Na+form).

According to Scheme II, commercially available 5α-pregnan-3β, 20β-diol-3-acetate (3) [W. Klyne and D.H.R. Barton, J. Am. Chem Soc. 71, 1500 (1949)] is treated with one or more equivalents of triethylamine:sulfur trioxide reagent to afford 5-α-pregnan-3β,20β-diol-3-acetate-20-sulfate, triethylammonium salt (4). The triethylammonium salt (4) is treated with methanol/aqueous sodium hydroxide to afford the 5-α-pregnan-3β,20β-diol-20-sulfate sodium salt (5).

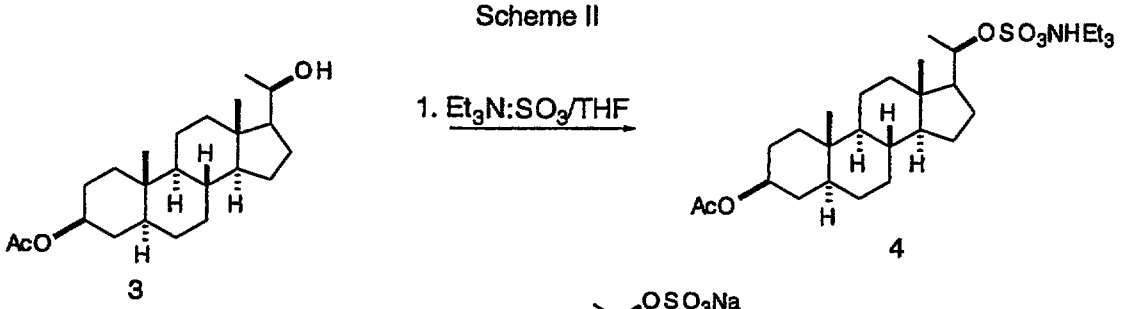
According to Scheme III, 5α-pregnane-3β,20b-diol-20-acetate (6) [prepared from 5α-pregnan-3β, 20β-diol-diacetate according to the procedure of A. Butenandt and J. Schmidt, Chem. Ber. 67, 1893 (1934)] is treated with one or more equivalents of triethylamine:sulfur trioxide reagent to afford 5α-pregnan-3β, 20β-diol-20-acetate-3-sulfate, triethylammonium salt (7). The triethylammonium salt (7) is treated with methanol/aqueous sodium hydroxide to afford 5α-pregnan-3β,20β-diol-3-sulfate, sodium salt (8).

Scheme I

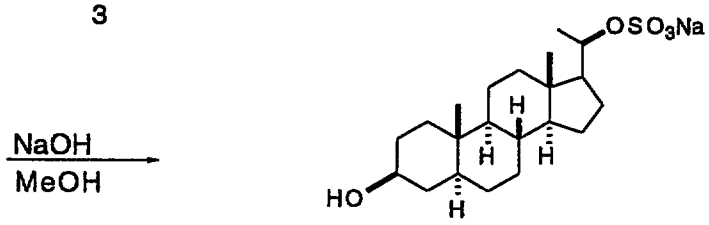


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Scheme II

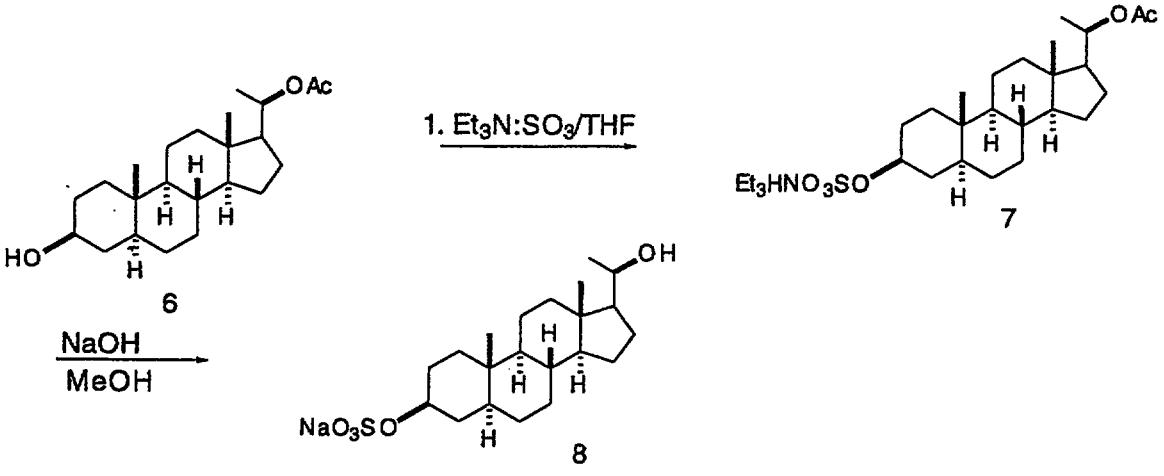


3 4



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Scheme III



6 7 8

The progestational activity of a representative compound of this invention (5α-pregnan-3β,20β-diol) was evaluated in an in vitro standard pharmacological test procedure. The procedure used and results obtained are briefly described below.

The results of these standard pharmacological test procedures demonstrate that the compounds of this invention are progestational. In this test procedure, the progestational activity of a compound is quantified based on its stimulation of alkaline phosphatase enzyme activity in T47D cells, a human breast cancer cell line which expresses high levels of progesterone receptors. This is a well established test procedure in which both the progestin receptors and the response stimulated by activated progestin receptors are endogenous to the cells. Cells are pre-conditioned in low serum medium for one day and then treated with test compounds. Alkaline phosphatase activity is measured 24 hr after treatment. Reference progestins, such as progesterone and medroxyprogesterone acetate, induce a 30 - 60 fold induction of alkaline phosphatase requiring only low nanomolar concentrations for activity. The alkaline phosphatase activity induced by progestins is blocked or inhibited by progestin receptor antagonists such as RU486 indicating the specificity of the response. When evaluated in this test procedure, 5α-pregnan-3β,20β-diol, had an IC_{50} of 5 $x10^{-5}$ demonstrating progestational activity.

The neuroprotective and cognition enhancing effects of the compounds of this invention were evaluated in an in vitro standard pharmacological test procedure which measured the effects of 5α-pregnan-3β,20β-diol, as a representative compound of this invention, on calcium and potassium channel currents. Briefly, the following procedure was used.

Whole cell recording techniques were used to record calcium and potassium currents from cultured hippocampal neurons. The compounds to be evaluated were made fresh each day in a 400 μM ethanol stock solution. The test compounds were diluted in saline to obtain a final concentration of 2 μM. The amplitude of calcium or potassium currents in control, test compound, and washout solutions was measured from at least 10 current traces for each condition. To compensate for rundown of the calcium current with time, control and washout currents were averaged. The current amplitude with drug was divided by the averaged control and washout current to determine the percent change. The means, standard deviations and errors for each test compound were calculated and significance from control was determined using the paired T-Test. 5α-Pregnan-3β,20β-diol enhanced increased potassium channel currents

versus control by 19.95 ± 3.46 % (p = 0.0005), indicating that 5α-pregnan-3β,20β-diol hyperpolarizes neurons, thereby allowing them to respond more readily to other stimuli. Calcium channel currents were not significantly changed from control (increased by 2.20 ± 0.97 % versus control). These results show that the compounds are useful in protecting against epileptic seizures and in cognition enhancement.

The compounds of this invention are progestational agents. Based on the results obained in the standard pharmacological test procedures, the compounds of the invention are useful as oral contraceptives (male and female), in hormone replacement therapy (particularly when combined with an estrogen), in the treatment of endometriosis luteal phase defects, benign breast and prostatic diseases and prostatic and endometrial cancers. The compounds of this invention are also useful in protecting against epileptic seizures, in cognition enhancement, in treating Alzheimer's disease, dementias, vasomotor symtpoms related to menopause, and other central nervous system disorders The compounds of this invention are futher useful in stimulating erythropoises.

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 and 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.

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 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 cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidine, 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 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 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 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 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 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 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 semipermiable 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 μg/kg - 750 μg/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 representative compounds of this invention.

Example 1

5α-Pregnane-3β, 20β-diol-3, 20-(bis)sulfate, (bis)triethylammonium salt **(2a)**

5α-Pregnane-3β, 20β-diol (1) (3.0g, 9.375 mmol) was dissolved in 360 ml of tetrahydrofuran and 100 ml of dichloromethane. Sulfur trioxide triethylamine complex (10.8 g, 39.6 mmol) was added and the solution was stirred at room temperature for 20 hours. The dichloromethane was removed in vacuo. The residue was filtered on a Buchner funnel, washed with tetrahydrofuran and dried for 20 hours to provide the title compound as a white solid (4.98g, 78%).

^{1}H NMR (300 MHz, DMSO-d_6)

δ 0.70 (s, 3H), 0.75 (s, 3H), 1.18 (t, 18H), 1.55 (m, 4H), 1.79 (m, 1H), 2.15 (d, J=12.3 Hz, 1H), 3.09 (m, 12H), 3.93 (m, 1H), 4.06 (m, 1H);

m/z (ES negative) 479(M-H).

5α-Pregnan-3β, 20β-diol-3, 20-(bis)sulfate, (bis)sodium salt **(2b)**

Crude triethylammonium salt (2a) was dissolved in 250 ml of distilled water and the solution was passed through an ion exchange column (Dowex 50X8 Na^+-form). The column was rinsed with 100ml of distilled water, and the eluent was lyophilized; 6.8g (82.9%). The product was stirred in 100 ml of methanol and filtered. The filtrate was concentrated in vacuo and the solid product was collected with ether, filtered on a Buchner funnel and dried to provide the title compound as a white solid(6.1g 74%).

^{1}H NMR (300 MHz, DMSO-d_6)

δ 0.69 (s, 3H), 0.74 (s, 3H), 1.54 (m, 5H), 1.80 (d, J=9.7Hz, 1H), 2.17 (d, J=12.6Hz, 1H), 3.08 (m, 1H), 3.9 (m, 1H), 4.05 (m, 1H)

m/z (ES negative) 479 (M-H).

Example 2

5α-Pregnan-3β–acetoxy–20β-ol-20-sulfate, triethylammonium salt **(4)**

5α -Pregnan-3β–acetoxy–20β-ol (3) (7.5g, 20.63 mmol) was dissolved in 700 mL of tetrahydrofuran and sulfur trioxide triethylamine complex (13g, 47.7 mmol) was added. The mixture was stirred at room temperature for 20 hours, and filtered. The filtrate was concentrated in vacuo and the residue was triturated with ether. The precipitate was collected on a Buchner funnel washed with ether and dried to provide the title compound as a white solid (9.6g 86%).

^{1}H NMR (300 MHz, DMSO-d_6)

δ 0.70 (s, 3H), 0.78 (s, 3H), 1.18 (t, 9H), 1.96 (s, 3H), 2.16 (d, J=12.7 Hz, 1H), 3.10 (q, 6H), 4.06 (m, 1H), 4.56 (m, 1H);

m/z (ES negative) 441 (M-H).

5α-Pregnane-3β, 20β-diol-20-sulfate, sodium salt **(5)**

The crude triethylammonium salt (4) was dissolved in 300 ml of methanol and 100 ml of 1N sodium hydroxide was added. The mixture was stirred 72 hours and the crude product was filtered on a Buchner funnel and dried in vacuo for 20 hours. The material was stirred in 100 ml of methanol and filtered. The filtrate was diluted with 400 ml of ether, stirred 18 hours and filtered on a Buchner funnel to provide the title compound as a white solid (3.6g, 48%).

^{1}H NMR (300 MHz, DMSO-d_6)

δ 0.69 (s, 3H), 0.74 (s, 3H), 2.17 (d, J=12.7 Hz, 1H), 4.08 (m, 1H), 4.41 (d, J=4.6 Hz, 1H);

m/z (ES negative) 399 (M-H);

Anal. ($C_{21}H_{35}O_5SNa$): calcd. C 59.69; H 8.35; found C 59.28; H 8.07.

Example 3

5α-Pregnan-3β, 20-β-diol-20-acetate -3-sulfate, triethylammonium salt (7).

5α-Pregnan-3β, 20-β-diol-20-acetate (6) (prepared from commercially available 5α-Pregnan-3β, 20β-diol diacetate according to A. Butenandt, J. Schmidt, Chem. Ber. 67. 1893 (1934) (.75g, 21mmol) was dissolved in 10 ml of tetrahydrofuran and triethylamine sulfur trioxide complex (0.45g, 25 mmol) was added. The mixture was stirred at room temperature for 20 hours. After addition of 30 ml of ether, a precipitate was formed which was collected on a Buchner funnel, washed with ether and dried to provide the title compound as a white solid (0.8g, 70%).

^{1}H NMR (300 MHz, DMSO-d_6)

δ 0.54 (s, 3H), 0.76 (s, 3H), 1.08 (d, 3H), 1.20 (t, 9H), 1.96 (s, 3H), 3.10 (q, 6H), 3.90 (m, 1H) 4.71 (m, 1H) 8.90 (s, 1H);

m/z (ES negative) 441 (M-H).

5α-Pregnan-3β, 20β-diol 3-sulfate, sodium salt (8)

5α-Pregnan-3β, 20β-diol-20-acetate-3 sulfate, triethylammonium salt (7) (1.3g, 24 mmol) was dissolved in a mixture of 50 ml of 20% aqueous sodium hydroxide and 50 ml of methanol. The mixture was stirred at room temperature for 30 hours. The methanol was removed in vacuo and the aqueous solution was extracted with 300 ml of n-butanol. The butanol solution was filtered through Celite and concentrated in vacuo to obtain a glassy residue. The residue was dissolved in ethanol, and charcoal was added. The mixture was filtered through Celite and concentrated in vacuo to obtain a solid residue. The residue was triturated with 500 ml of ether, collected on a Buchner funnel, and dried to provide the title compound as a white solid (0.8 g, 79%)

^{1}H NMR (300 MHz DMSO-d_6)

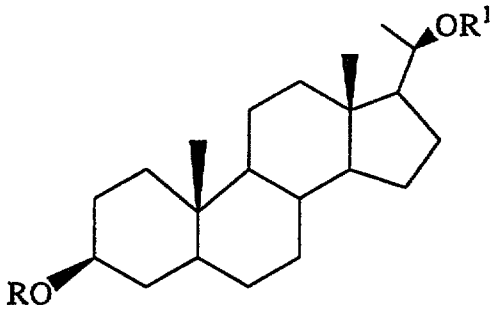
δ 0.68 (s, 3H), 0.78 (s, 3H), 1.10 (d, 3H), 1.83 (d, 1H) 2.11 (d, 1H) 3.48 (q, 1H), 3.93 (m, 1H), 4.06 (m, 1H) 4.34 (m, 1H)

m/z (ES negative) 399 (M).

* C L M S *

WHAT IS CLAIMED IS:

1. A compound having the formula



I

wherein

R and R^1 are each, independently, hydrogen or $SO_3^- X^+$;

X^+ is alkali metal, alkaline earth metal, ammonium, alkylammonium containing 1-6 carbon atoms, dialkylammonium containing 1-6 carbon atoms in each alkyl group, trialkylammonium containing 1-6 carbon atoms in each alkyl group or tetraalkylammonium salts containing 1-6 carbon atoms in each alkyl group;

with the proviso that R and R^1 are not both hydrogen.

2. The compound according to claim 1 which is 5α-pregnan-3β,20β-diol 3-sulfate ester sodium salt, where said compound is in greater than 1 percent purity.

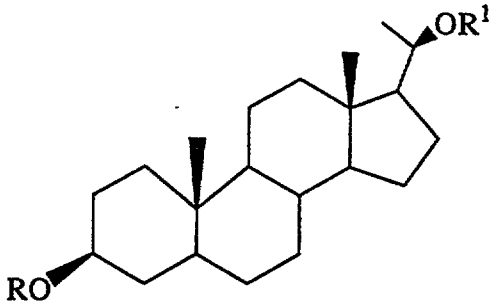
3. The compound according to claim 1 which is 5α-pregnan-3β,20β-diol 20-sulfate ester sodium salt, where said compound is in greater than 1 percent purity.

4. The compound according to claim 1 which is 5α-pregnan-3β,20β-diol 3,20-(bis)sulfate ester (bis)sodium salt, where said compound is in greater than 1 percent purity.

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5. A composition of matter consisting essentially of a compound having the formula



I

wherein

R and R^1 are each, independently, hydrogen or $SO_3^- X^+$;

X^+ is alkali metal, alkaline earth metal, ammonium, alkylammonium containing 1-6 carbon atoms, dialkylammonium containing 1-6 carbon atoms in each alkyl group, trialkylammonium containing 1-6 carbon atoms in each alkyl group or tetraalkylammonium salts containing 1-6 carbon atoms in each alkyl group;

with the proviso that R and R^1 are not both hydrogen.

6. The composition of matter according to claim 5, which is 5α-pregnan-3β,20β-diol 3-sulfate ester sodium salt.

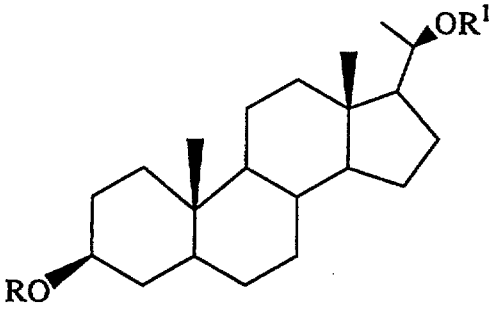
7. The composition of matter according to claim 5, which is 5α-pregnan-3β,20β-diol 20-sulfate ester sodium salt.

8. The composition of matter according to claim 5, which is 5α-pregnan-3β,20β-diol 3,20-(bis)sulfate ester (bis)sodium salt.

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9. A pharmaceutical composition which comprises compound having the formula



I

wherein

R and R^1 are each, independently, hydrogen, SO_3H or $SO_3^- X^+$;

X^+ is alkali metal, alkaline earth metal, ammonium, alkylammonium containing 1-6 carbon atoms, dialkylammonium containing 1-6 carbon atoms in each alkyl group, trialkylammonium containing 1-6 carbon atoms in each alkyl group or tetraalkylammonium salts containing 1-6 carbon atoms in each alkyl group;

with the proviso that R and R^1 are not both hydrogen, and a pharmaceutical carrier.

10. A pharmaceutical composition which comprises at least 1% of a compound as defined in any one of Claim 1 to 4.

11. A method of providing progestational therapy to a mammal in need thereof which comprises administering a progestationally effective amount of a compound as defined in any one of Claim 1 to 4 to said mammal.

12. A method of treating or inhibiting cancers, central nervous system disorders, dementias, or Alzheimer's disease in a mammal in need thereof, which comprises administering an effective amount of a compound as defined in any one of Claim 1 to 4 to said mammal.

13. Use of a compound as defined in any one of Claim 1 to 4 as a medicament.

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14. Use of a compound as defined in any one of Claim 1 to 4 in the preparation of a medicament for providing progestational therapy to a mammal or for treating or inhibiting cancers, central nervous system disorders, dementias, or Alzheimer's disease in a mammal.

15. A process for the preparation of compounds of formula I wherein A and B are each independently a sulphate ester salt which comprises:

a) converting the appropriate 5α-pregnan-3,20-diol 3,20-(bis)sulfate ester to a pharmaceutically acceptable salt,

b) converting a pharmaceutically acceptable salt of the 5α-pregnan-3,20-diol 3,20-(bis)sulfate ester to a different pharmaceutically acceptable salt of the appropriate 5α-pregnan-3,20-diol 3,20-(bis)sulfate ester or

c) directly converting the appropriate 5α-pregnan-3,20-diol to the desired pharmaceutically acceptable salt of 5α-pregnan-3,20-diol 3,20-(bis)-sulfate ester.

16. A process for the preparation of compounds of formula I wherein one of A and B is a sulphate ester salt and the other is hydrogen which comprise:

a) converting the appropriate 5α-pregnan-3,20–diol-mono sulfate ester to a pharmaceutically acceptable salt,

b) converting a pharmaceutically acceptable salt of the appropriate 5α-pregnan-3,20-diol-mono sulfate ester to a different pharmaceutically acceptable salt of the appropriate the appropriate 5α-pregnan-3,20-diol-mono sulfate ester,

c) converting the corresponding 5α-pregnan-3-ol,20-keto mono sulfate ester salt or 5α-pregnan-3-keto-20-ol mono sulfate ester salt to the desired 5α-pregnan-3,20-diol-3-sulfate ester salt or 5α-pregnan-3,20-diol-20-sulfate ester salt

d) converting 5α-pregnan-3,20-diol to the desired pharmaceutically acceptable salt of the desired 5α-pregnan-3,20-diol-monosulfate ester,

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e) deprotecting the corresponding 20 protected 5α-pregnan-3,20-diol-3-sulfate ester salt or 3 protected 5α-pregnan-3,20-diol-20-sulfate ester salt or

f) converting one stereo isomer of the pharmaceutically acceptable salt of the appropriate 5α-pregnan-3,20-diol-mono sulfate ester to another by inversion.

17. A process for the preparation of compounds of formula I wherein at least one of A and B is a free sulphate acid which comprises sulphonating the corresponding hydroxy compound.

18. A process for the preparation of compounds of formula I wherein A and B are both hydroxy groups which comprises the reduction of the corresponding 3,20-di-keto compound.

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