

PATENT SPECIFICATION

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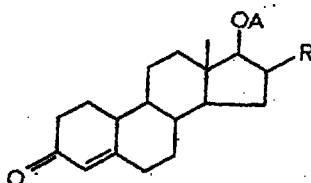
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(54) 16 β -HYDROCARBON SUBSTITUTED ESTRANE COMPOUNDS

(71) We, TAKEDA YAKUHI KOGYO KABUSHIKI KAISHA, also known as TAKEDA CHEMICAL INDUSTRIES LTD of 27, Doshomachi 2-chome, Higashi-ku, Osaka, Japan, a body corporate organised under the laws of Japan, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to novel and useful 16 β -hydrocarbon substituted estrane compounds and methods for producing them, and more particularly to compounds of the formula (I):



(I)

wherein A is hydrogen, an acyl radical or an ether residue and R is a hydrocarbon radical having at least 2 carbon atoms which may optionally be substituted by one or more halogen atoms.

The majority of old men (about 70%) suffer from prostatomegaly. They complain of dysuria (painful or difficult urination) and are caused to suffer anuresis or uremia. However, there has not been developed an effective remedy for prostatomegaly. Although some compounds showing an anti-androgenic activity have been subjected to clinical tests, most of them were concluded to be unqualified as remedies by reason of their severe side-effects such as remarkable atrophy of the adrenal gland, and thymus, as well as serious disorders in the liver.

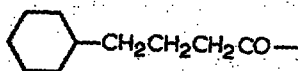
We have now discovered unexpectedly that 16 β -hydrocarbon substituted compounds (I) exhibit a very strong anti-androgenic activity; for example, the efficacy of 17 β -hydroxy-16 β -ethylestr-4-en-3-one is about twice to four times as strong as that of 2-acetyl-7-oxo-1,2,3,4a,4b,5,6,7,9,10,10a-dodecahydrophenanthrene. Furthermore, we have found that the compounds (I) do not produce considerable side-effects in the suprarenal gland, thymus, pituitary gland and liver, etc., even in long-term administration. The acute toxicity of the compounds (I) is also very low, e.g. the LD₅₀ of 17 β -hydroxy-16 β -ethylestr-4-en-3-one is 5—10 g/kg (rat, mouse) by intramuscular and intraperitoneal injection and more than 10 g/kg (rat, mouse) by oral administration.

In the 16 β -hydrocarbon-substituted estrane derivatives (I), the substituent R at the 16 position may be, for example, a straight, branched or cyclic, saturated or unsaturated aliphatic hydrocarbon radical, an aralkyl radical or an aryl radical such as ethyl, isopropyl, butyl, ethynyl, propargyl, vinyl, allyl or phenyl. The radical preferably has up to 6 carbon atoms. These groups may themselves be substituted with lower alkyl groups or by halogen atoms such as chlorine and bromine.

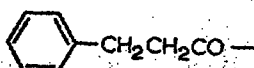
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The symbol A represents hydrogen, an acyl radical such as acetyl, propionyl, valeryl, oenanthoyl, capryloyl, caproyl, lauroyl, decanoyl (of formula $\text{CH}_3(\text{CH}_2)_8\text{CO}-$), cyclohexylbutyryl (of formula



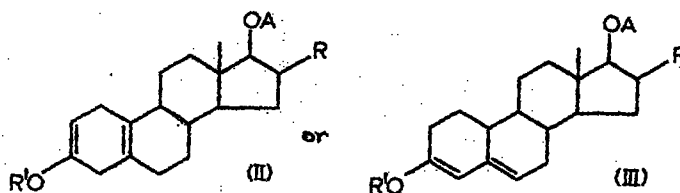
5 phenylpropionyl (of formula



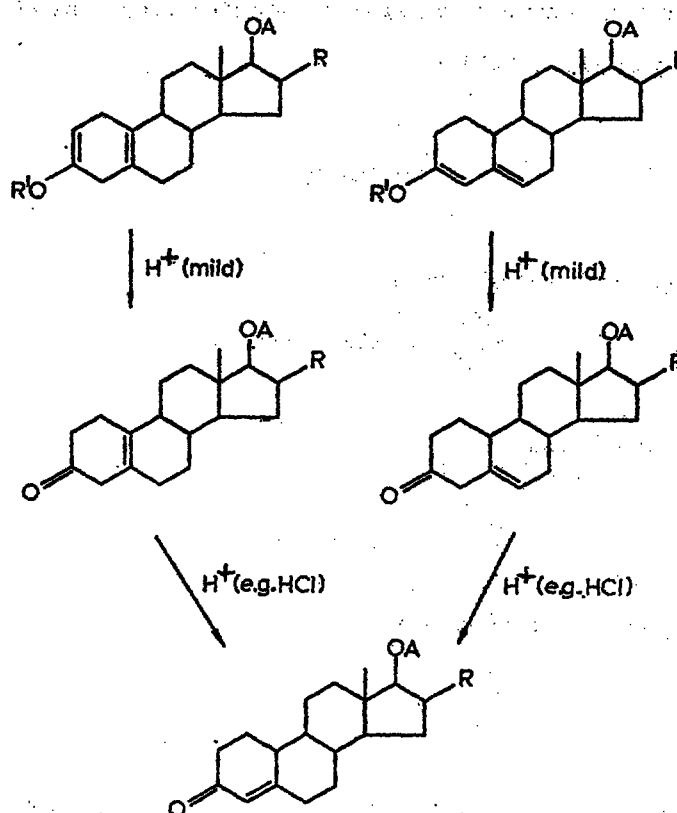
palmitoyl, stearoyl and phenoxyacetyl, or an ether residue such as tetrahydropyranyl, tetrahydrofuryl and tetrahydrothienyl.

10 Particularly preferred compounds of the general formula I are those in which A is hydrogen or an acyl radical having up to 10 carbon atoms and R is a hydrocarbon radical having 2 to 6 carbon atoms.

15 These compounds (I) may be prepared by subjecting 3-protected hydroxy-16 β -hydrocarbon-substituted -estra-2,5(10) or 3,5-dien-17 β -ol compounds or their esters to hydrolysis. The 3-protected hydroxy-16 β -hydrocarbon substituted -estra-2,5(10) or 3,5-dien-17 β -ol compounds or their esters may be represented by the following formulae:



20 wherein R' is a hydrocarbon radical, for example, a straight, branched or cyclic, saturated or unsaturated aliphatic hydrocarbon radical, an aralkyl radical or an aryl radical such as methyl, ethyl, propyl, t-butyl or benzyl or an acyl radical. According to a preferred embodiment of the process according to the invention, the symbol A in the starting compound of formula II or III and in the product of formula I represents hydrogen or an acyl radical having up to 10 carbon atoms and the symbol R represents a hydrocarbon radical having 2 to 6 carbon atoms, while the symbol R' in the starting compound II or III represents an alkyl radical having up to 4 carbon atoms. The hydrolysis of the compound (II) or (III) is preferably conducted in a suitable solvent with the use of an acidic reagent such as an inorganic acid which may, for example, be hydrochloric acid, sulfuric acid, nitric acid or phosphoric acid, or an organic acid which may, for example, be formic acid, acetic acid, oxalic acid or toluenesulfonic acid. The solvent just mentioned is chosen from among various alcohols such as methanol, ethanol or butanol, ethers such as tetrahydrofuran, ether or dioxane, water or other common steroid solvents. The reaction goes to completion within a few hours, giving a 17 β -hydroxy or acyloxy-16 β -hydrocarbon-substituted-estr-4 or 5-en-3-one compound. Where the reaction is conducted under mild conditions, for example when the compound (II) or (III) is hydrolysed with formic acid or oxalic acid, the corresponding $\Delta^{5(6)}$ or $\Delta^{5(10)}$ compound is obtained. On the other hand, hydrolysis with a mineral acid such as hydrochloric acid gives rise to the corresponding Δ^4 compound. The conversion of each of the starting compounds (II) and III to Δ^4 compounds is illustrated in the following reaction scheme.



When R' is an acyl radical, the hydrolysis may also be carried out under alkaline conditions employing e.g. alkali metal hydroxides such as sodium hydroxide, potassium hydroxide, alkali metal carbonates such as sodium carbonate, sodium bicarbonate and potassium carbonate, alkali metal acylates such as sodium acetate and potassium acetate, quaternary ammonium hydroxides such as trimethyl benzyl ammonium hydroxide, tertiary amines such as triethylenediamine, anion-exchange resins such as strongly basic styrene-type copolymer resins, alumina and basic solvents such as dimethylformamide, dimethylacetamide, pyridine, collidine and aldehyde collidine.

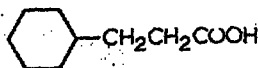
If it is desired to hydrolyse only at the 3-position when both of A and R' are acyl, mild alkaline or acidic conditions should be employed.

The starting compounds (II) where R' is a hydrocarbon radical may be prepared, for example, by the so-called Birch reduction of the corresponding estr-1,3,5(10)-triene compounds, wherein the triene compounds are treated with an alkali metal in liquid ammonia. As the alkali metal, lithium, sodium or potassium may be used. At times, use is made as dissolution aids of such solvents as various ethers, e.g. ether, tetrahydrofuran or dimethoxyethane, or alcohols, e.g. methanol, ethanol or tert-butanol. The reaction is usually conducted at a temperature between the boiling point of ammonia and -80°C . Where R is an unsaturated radical, there may be cases where the hydrocarbon group (e.g. allyl or phenyl) is saturated under the conditions described above. Where it is desired to prevent such saturation, the reaction may be conducted after the 17-hydroxy radical has been converted to a tetrahydropyranyloether, tetrahydrofurylether or tetrahydrothionylether, or to a ketal derivative of the 17-oxo radical.

17 β -acyloxy-16 β -hydrocarbon substituted-estr-4-en-3-ones may be prepared by acylating 17 β -hydroxy-16 β -hydrocarbon substituted-estr-4-en-3-ones. This acylation is carried out with the use of, for example, reactive derivatives of organic acids, such as acid anhydrides, mixed anhydrides, acid halides, ketene or acid azides. Condensing agents such as carbodiimide or phosphorus oxychloride may be used with organic acids. These organic acids are preferably straight-chain fatty acids having up to 10

carbon atoms or cyclic fatty acids having up to 10 carbon atoms. Examples of cyclic fatty acids are:

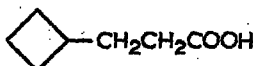
cyclohexyl-propionic acid of formula



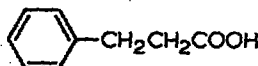
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cyclobutyl-propionic acid of formula

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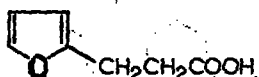
phenoxyacetic acid;
phenyl-propionic acid of formula



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and furyl-propionic acid of formula

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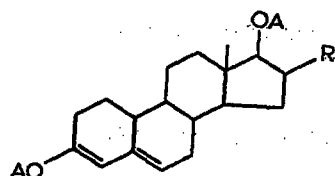
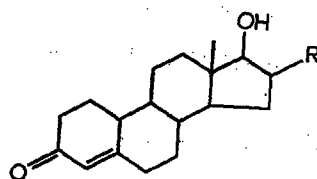


The acylating reaction is conducted in the presence of a catalyst which may be an alkaline catalyst for example, pyridine, picoline, collidine, quinoline or a tertiary amine, e.g. triethylamine, or an acid catalyst, for example, a Lewis acid, e.g. boron trifluoride, zinc chloride or aluminium chloride, para-toluene sulfonic acid or potassium bisulfate. The reaction is generally conducted in one of the common proton-inert solvents for steroids which include, among others, halogenated hydrocarbons, e.g. chloroform or methylene chloride, hydrocarbons, e.g. toluene, benzene or hexane, esters, e.g. ethyl acetate, dimethylformamide, pyridine and picoline. Alternatively, use may be made of a large excess of the acylating agent such as an organic acid anhydride so that the acylating agent will also function as the necessary solvent. The reaction usually proceeds at from 0°C to room temperature, although the reaction may be hastened by heating the system to the neighborhood of 100°C. After the reaction is complete, the reaction mixture may, for example, be treated with a large quantity of water so as to let the 17β-acyloxy derivatives crystallize or, alternatively, subjected to extraction with an organic solvent to obtain the desired compound. A 3-enolether may also be subjected to acylation, in which instance there may be cases in which the 3-position remains unaffected by the acylation, but this product is generally converted to the 4-en-3-one derivatives under acidic conditions. If the acylation of a 4-en-3-one is carried out in the presence of an acid catalyst either under the influence of heat or for an extended period of time, the 3-position is also acylated to give 3,17β-diacylated compounds. These compounds are readily hydrolyzed to the desired 17β-monoacylated compounds by being treated under mildly alkaline or acidic conditions. To establish the alkaline conditions, a solution of alkali hydroxide or alkali carbonate may be conventionally employed, while the acidic conditions are conveniently established with the use of an alcoholic solution of an inorganic acid such as, for example, hydrochloric acid or sulfuric acid.

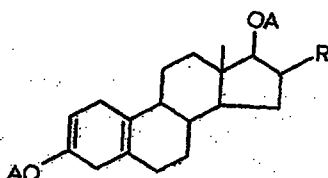
On the other hand, 17β-hydroxy-16β-hydrocarbon substituted-estr-4-en-3-ones may be prepared by subjecting to hydrolysis the compounds represented by the following formulae:

40

40



or



wherein A is an acyl radical and R has the same meaning as above. The reaction may be carried out under rather strong alkaline conditions as described above.

The resulting 16 β -hydrocarbon substituted compounds (I) have a strong anti-androgenic activity and are proved to be less active than the corresponding 16 α -isomers, which have anabolic, androgenic, progestative, ovulation inhibiting and pregnancy-maintaining properties. Therefore, the compounds of formula (I) are useful as drugs for the inhibition of prostatomegaly and are generally administered orally as well as in an injectable form. They may be used for the medical treatment of prostatic cancer, hirsutism, acne, alopecia, Stein-Leventhal syndrome, etc. in suitable form. Injections are prepared, for example, by dissolving or suspending the compounds (I) in vegetable oils (e.g. sesame oil, cottonseed oil, castor oil, olive oil, corn oil or peanut oil) in combination, if desired, with antiseptics (e.g. benzyl alcohol, benzyl benzoate or chlorobutanol), solubilizing agents and surface-active agents. The concentrations of the compounds (I) in oil injections is generally from about 1 to about 200 mg/ml. Among the compounds (I), 17 β -acyl derivatives are readily soluble in oils and exhibit a relatively sustained anti-androgenic action. Taking 17 β -caproyloxy-16 β -ethylestr-4-en-3-one as an example, its anti-androgenic action is retained *in vivo* for longer than about 3 weeks by the administration of 100–600 mg. When the compounds (I) are administered orally, they may be used as powders, tablets, capsules, pills, liquids, syrups, elixirs, buccals or granules. They may be used in the form of an external remedy, e.g. ointments or suppositories. Some examples of practical compositions in which the compounds of this invention are utilized as remedies for prostatomegaly are as follows, in which the relationship of parts by weight to parts by volume is as grams to milliliters:

5	Injections: (1) 16 β -ethylestr-4-en-3-on-17 β -ol	10 weight parts	5
	sesame oil	1000 volume parts	
	(2) 17 β -caproyloxy-16 β -ethylestr-4-en-3-one	200 weight parts	
	benzyl benzoate	20 volume parts	
	sesame oil	1000 volume parts	
10	Capsules: 17 β -caproyloxy-16 β -ethylestr-4-en-3-one	20 weight parts	10
	lactose	140 weight parts	
	corn starch	50 weight parts	
	sugar ester	4 weight parts	
	calcium salt of carboxymethylcellulose	4 weight parts	
15	magnesium stearate	2 weight parts	15
		220 mg/capsule	
	Tablets: 17 β -acetyloxy-16 β -ethylestr-4-en-3-one	20 weight parts	
	lactose	100 weight parts	
	corn starch	90 weight parts	
20	sugar ester	4 weight parts	20
	calcium salt of carboxymethylcellulose	4 weight parts	
	magnesium stearate	2 weight parts	
		220 mg/tablet.	
	An effective dose of the compounds (I) when administered intramuscularly or subcutaneously is usually about 100—600 mg/week for an adult weighing 50 kg. For oral administration, the effective dose is about 50—300 mg/day for an adult weighing 50 kg. However, the dose and the dose interval may vary with the disease and/or the symptom.		
25	It is to be understood that the following examples are solely for the purpose of illustration and not to be construed as limitations of this invention, and that many variations may be resorted to without departing from the scope of this invention. The temperatures are all uncorrected, and the percentages are all on a weight basis.		25
	Example 1.		
	(1) To a solution of 3-methoxy-13 β -methylgona-1,3,5(10)-trien-17-one (2.0 g) in 45 ml. of methanol, there are added 45 ml. acetone and 2 g. potassium hydroxide. The mixture is refluxed for 5 hours. After cooling, the reaction mixture is poured into ice-water, followed by extraction with ether. The ether is removed by distillation under reduced pressure, whereupon 2.0g. of an oily substance are obtained. Recrystallization from ether gives colorless needles of 3-methoxy-16-isopropylidene-13 β -methylgona-1,3,5(10)-trien-17-one (1.8 g). M.p.: 155°C. Elementary analysis: Calcd. for C ₂₂ H ₂₈ O ₂ : C, 81.44; H, 8.70; Found: C, 81.64; H, 8.94; Ultraviolet absorption: λ ^{EtOH} _{max} 248 m μ .		
	(2) To a solution of 3-methoxy-16-isopropylidene-13 β -methylgona-1,3,5(10)-trien-17-one (1.0 g) in 150 ml. of ethanol are added 0.1 g. platinum oxide, whereby the material is catalytically reduced at atmospheric temperature and pressure. The catalyst is removed and then the solvent is distilled off under reduced pressure, whereupon crystals separate out (1.0 g.). Recrystallization from methanol gives colorless needles of 3-methoxy-16 β -isopropyl-13 β -methylgona-1,3,5(10)-trien-17-one. M.p. 109°—111°C; Elementary analysis: Calcd. for C ₂₂ H ₃₀ O ₂ : C, 80.93; H, 9.26; Found: C, 80.70; H, 9.28; Infrared absorption: ν ^{KBr} _{max} 1740 cm ⁻¹ .		
	(3) To a solution of 3-methoxy-16 β -isopropyl-13 β -methylgona-1,3,5(10)-trien-17-one (2.0 g) in 200 ml. of methanol is added 1.0 g. sodium borohydride at room temperature over a period of 30 minutes under constant stirring, and the mixture is allowed to stand for another 30 minutes.		
55	The reaction mixture is poured into water and the crystals separating out are recovered by filtration, washed with water and dried (2.0 g.). Recrystallization from ether- <i>n</i> -hexane (1:1) yields colorless needles of 3-methoxy-16 β -isopropyl-13 β -methylgona-1,3,5(10)-trien-17 β -ol. M.p. 136°C; Elementary analysis: Calcd. for C ₂₂ H ₃₂ O ₂ : C, 80.44; H, 9.83; Found: C, 80.16; H, 9.95; Infrared absorption: ν ^{KBr} _{max} 3400 cm ⁻¹ .		55
	(4) A solution of 3-methoxy-16 β -isopropyl-13 β -methylgona-1,3,5(10)-trien-17 β -ol (2.0 g.) in 80 ml. of anhydrous tetrahydrofuran is dissolved in liquid ammonia (300 ml.) at -70°C, followed by the addition of 20 ml. of dry ethanol.		

Then, lithium metal is added with stirring over a period of 30 minutes.

The reaction mixture is further stirred for an additional 30 minutes, at the end of which time the ammonia is evaporated off. The residue is extracted with ether, which is then removed by distillation under reduced pressure. The procedure yields 2.0 g. of a colorless oil. This oil is dissolved in 80 ml. methanol and while the solution is stirred, 7 ml. of 6N-hydrochloric acid are added. The mixture is left standing for 20 minutes, at the end of which time the solution is poured into ice-water, followed by extraction with ether. The ether is removed by distillation under reduced pressure to recover 1.8 g. of a colorless oil. Recrystallization from ether-*n*-hexane (1:1) yields colorless needles of 17 β -hydroxy-16 β -isopropyl-13 β -methylgon-4-en-3-one (1.6 g.). M.p.: 145°—147°C; Elementary analysis: Calcd. for C₂₁H₃₂O₂: C, 79.70; H, 10.19;

Found: C, 79.80; H, 10.34: Ultra violet absorption $\lambda_{\text{max}}^{\text{EtOH}}$: (0.0951) 0.72 (s) μ

Infra-red absorption $\nu_{\text{max}}^{\text{KBr}}$ 1660, 1615 cm⁻¹; NMR (δ , CDCl₃) 3.76 ppm (17 α -H, 1H,d,J=9HS).

(5) By similar procedures to those described in (1) to (4) above, 17 β -hydroxy-16 β -cyclohexylestra-4-en-3-one is prepared starting from cyclohexanone and 3-methoxy-estra-1,3,5(10)-trien-17-one. M.p.: 148—151°C. Ultraviolet absorption: $\lambda_{\text{max}}^{\text{EtOH}}$ 240 m μ . Elementary analysis: Calculated for C₂₄H₃₆O₂, C, 80.85; H, 10.18; Found: C, 81.12; H, 10.05.

Example 2.

(1) To a mixture of 4.0 g. of metallic magnesium and 150 ml. of dry ether, are added dropwise 10.5 ml. of ethyl iodide. To the resulting ether solution of ethyl magnesium iodide are added with stirring 15 g. of 3-methoxy-16-oxo-estra-1,3,5(10)-trien-17 β -ol suspended in 100 ml. of dried ether. The mixture is left standing for 2 hours and then an aqueous solution saturated with ammonium chloride is added thereto to destroy excess ethyl magnesium iodide. The resulting solution is extracted with ether. The ether layer is washed with water and dried, followed by evaporation of ether to give a colorless oil. The oil is recrystallized from ether to give 15.3 g. of 3-methoxy-16 α -ethyl-estra-1,3,5(10)-trien-16 β ,17 β -diol melting at 131—133°C. Elementary analysis: Calculated for C₂₄H₃₆O₃: C, 76.32; H, 9.15; Found: C, 76.04; H, 8.89.

(2) To a solution of 20g. of 3-methoxy-16 α -ethylestra-1,3,5(10)-trien-16 β ,17 β -diol dissolved in 300 ml. of dry tetrahydrofuran are added 500 ml. of liquid ammonia and then 100 ml. of ethanol under cooling with dry-ice-acetone. To the mixture are added little by little 7.0 g. of metallic lithium in 2 hours.

Then, ammonia is evaporated off from the reaction mixture and to the resulting solution are added 200 ml. of water, followed by extraction with ether. The ether layer is washed with water and dried, followed by evaporating off the solvent to give a colorless oil. The oil is dissolved in 80 ml. of methanol and to the solution is added 1.5 ml. of concentrated hydrochloric acid under stirring. After being left standing for 10 minutes, 200 ml. of water are added to the reaction solution and the mixed solution is extracted with ether. The ether layer is washed with water and dried, followed by evaporation of the solvent to give 17.0 g. of 16 β ,17 β -dihydroxy-16 α -ethylestra-4-en-3-one as a colorless oil. Ultraviolet absorption; λ_{max} 240 m μ (in ethanol).

(3) To a solution of 5.0 g. of 16 β ,17 β -dihydroxy-16 α -ethylestra-4-en-3-one in 100 ml. of methanol 13 ml. of concentrated sulfuric acid are added with stirring. After being left standing for 15 minutes, the reaction solution is gradually poured into 300 ml. of a 10% aqueous solution of sodium bicarbonate. The precipitated crystals are collected by filtration and washed with water. The crystals are recrystallized from ether to yield 3.6 g. of 16 β -ethylestra-4-ene-3,17-dione melting at 79—80°C. Elementary analysis: Calculated for C₂₀H₂₈O₂: C, 79.95; H, 9.39; Found: C, 79.93; H, 9.24.

(4) To a solution of 3.0 g. of 16 β -ethylestra-4-ene-3,17-dione dissolved in 150 ml. of dioxane are added 15 g. of ethyl ortho-formate and 0.1 g. of *p*-toluenesulfonic acid, followed by stirring for 2 hours at room temperature. The reaction solution is poured into 300 ml. of 5% aqueous solution of sodium bicarbonate and the resulting mixture is extracted with ether. The ether layer is washed with water and dried, followed by evaporation of the solvent to give crude crystals of 3-ethoxy-16 β -ethylestra-3,5-dien-17-one. The crystals are recrystallized from ether to give 3.0 g. of the compound melting at 114—115°C. Elementary analysis: Calculated for C₂₂H₃₂O₂: C, 80.44; H, 9.83; Found: C, 80.61; H, 9.56.

(5) To a solution of 3.0 g of the enol-ether compound obtained at (4) above in 50 ml. of methanol, are added 1.5 g. of sodium borohydride. After being left standing for 1.5 hours at room temperature, the reaction solution is poured into 300 ml. of water. The resulting precipitates are collected by filtration and recrystallized from ether to give 2.8 g. of 3-ethoxy-16 β -ethylestra-3,5-dien-17 β -ol melting at 131–133°C. Elementary analysis: Calculated for $C_{28}H_{34}O_2$: C, 79.95; H, 10.37; Found: C, 79.99; H, 10.41.

(6) To a solution of 2.5 g of 3-ethoxy-16 β -ethylestra-3,5-dien-17 β -ol dissolved in 50 ml. of methanol are added 1.2 ml. of concentrated hydrochloric acid, followed by stirring for 10 minutes. The reaction solution is poured into 250 ml. of water. The precipitated crystals are collected by filtration and recrystallized from ether to give 2.3 g. of 17 β -hydroxy-16 β -ethylestr-4-en-3-one melting at 152–153°C. Elementary analysis: Calculated for $C_{28}H_{30}O_2$: C, 79.42; H, 10.00; Found: C, 79.53; H, 10.01 $[\alpha]_D^{25} = +41^\circ$ ($c = 1.0$, ethanol) Ultra-violet absorption; $\lambda_{max} m\mu$ (ϵ) 240 (15800).

Example 3.

(1) In 150 ml. of dioxane are dissolved 3.0 g. of 16 β ,17 β -dihydroxy-16 α -ethylestr-4-en-3-one prepared in step (2) of Example 2 and to the solution are added 7.0 ml. of ethyl orthoformate and 0.5 g. of *p*-toluenesulfonic acid, followed by stirring for 15 minutes. The reaction solution is poured into a 10% aqueous solution of sodium bicarbonate and the resulting solution is extracted with ether. The ether layer is washed with water and subjected to evaporation of the solvent to give 2.7 g. of 3-ethoxy-16 β ,17 β -dihydroxy-16 α -ethylestra-3,5-diene.

(2) To a solution of 3.1 g. of 3-ethoxy-16 β ,17 β -dihydroxy-16 α -ethylestra-3,5-diene in 30 ml. of pyridine, are added little by little 1.3 ml. of phosphoryl trichloride, followed by heating at 80°C. for 5 minutes. The reaction solution is poured into 200 ml. of water and the resulting solution is extracted with ether. The ether layer is washed with water and subjected to evaporation of the solvent to give 1.6 g. of 3-ethoxy-16 β -ethylestra-3,5-dien-17-one melting at 114–115°C. Elementary analysis: Calculated for $C_{22}H_{22}O_2$: C, 80.44; H, 9.83; Found: C, 80.61; H, 9.56.

(3) The resulting 3-ethoxy-16 β -ethylestra-3,5-dien-17-one is reduced in a similar manner to that described in part (5) of Example 2 to yield 3-ethoxy-16 β -ethylestra-3,5-dien-17 β -ol, which is further subjected to hydrolysis in a similar manner to that described in part (6) of Example 1 to yield 17 β -hydroxy-16 β -ethylestr-4-en-3-one.

Example 4.

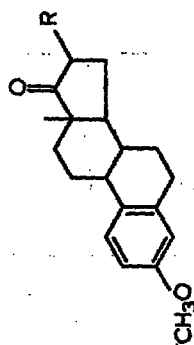
(1) In 100 ml. of methanol are dissolved 10 g. of 3-methoxy-16 β ,17 β -dihydroxy-16 α -ethylestra-1,3,5(10)-trien-17 β -ol obtained in part (1) of Example 2 and to the solution are added 10 ml. of concentrated sulfuric acid with stirring. After being left standing for 10 minutes, the reaction solution is poured into 300 ml. of a 10% aqueous solution of sodium bicarbonate, followed by extraction with ether. The ether layer is washed with water and dried, followed by distillation of the solvent to give a pale yellow oil. The oil is recrystallized from methanol to yield 8.2 g. of 3-methoxy-16 β -ethylestrone melting at 94°C. Elementary analysis: Calculated for $C_{21}H_{22}O_2$: C, 80.73; H, 9.03; Found: C, 80.71; H, 9.09.

(2) To a solution of 5.0 g. of 3-methoxy-16 β -ethylestrone in 140 ml. of methanol are added 20 g. of sodium borohydride with stirring, followed by keeping the same conditions for one hour. The reaction solution is poured into 300 ml. of water and the precipitated crystals are collected by filtration. Recrystallization from ether gives 4.7 g. of 3-methoxy-16 β -ethylestra-1,3,5(10)-trien-17 β -ol melting at 73°C. Elementary analysis: Calculated for $C_{21}H_{26}O_2$: C, 80.21; H, 9.62; Found: C, 79.96; H, 9.83.

(3) To a solution of 10 g. of 3-methoxy-16 β -ethylestra-1,3,5(10)-trien-17 β -ol in 150 ml. of dried tetrahydrofuran are added 300 ml. of liquid ammonia and 30 ml. of ethanol under cooling with dry ice-acetone, and to the resulting solution are added little by little 4.0 g. of metallic lithium for 1.5 hours with stirring. After a deep blue color for the reaction solution is distinguished, ammonia is evaporated off. The resulting solution has added thereto 200 ml. of water and the mixture is extracted with ether. The ether layer is subjected to evaporation of the solvent to give a colorless oil. The oil is dissolved in 30 ml. of methanol and 3 ml. of concentrated hydrochloric acid are added to the solution, followed by stirring for 10 minutes. The reaction solution is poured into 100 ml. of water and precipitated crystals are recovered by filtration. Recrystallization from ether gives 8.6 g. of 17 β -hydroxy-16 β -ethylestr-4-en-3-one melting at 152–153°C. Elementary analysis: Calculated for $C_{20}H_{26}O_2$: C, 79.42; H, 10.00; Found: C, 79.53; H, 10.01.

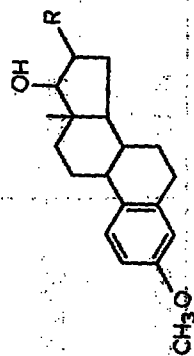
(4) In a similar manner to that described at (1) to (3) above the following compounds are prepared:

TABLE I



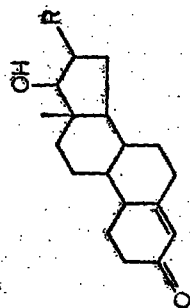
R	M.P. (°C)	Elementary analysis					
		Calculated for			Found		
		formula	C	H	C	H	
$-\text{CH}_2-\text{CH}=\text{CH}_2$	135-137	$\text{C}_{29}\text{H}_{48}\text{O}_2$	81.44	8.70	81.32	8.79	
	150-151	$\text{C}_{29}\text{H}_{48}\text{O}_2$	83.29	7.83	83.14	7.80	
$-\text{n-C}_8\text{H}_7$	—	$\text{C}_{29}\text{H}_{48}\text{O}_2$	80.93	9.26	80.99	9.38	

TABLE 2



R	M.P. (°C)	Elementary analysis					
		Calculated for			Found		
		formula	C	H	C	H	
$-\text{CH}_2-\text{CH}=\text{CH}_2$	138—140	$\text{C}_{23}\text{H}_{30}\text{O}_2$	80.93	9.26	80.85	9.31	
	174—176	$\text{C}_{28}\text{H}_{30}\text{O}_2$	82.83	8.34	83.00	8.28	
$-\text{n-C}_8\text{H}_7$	120—121	$\text{C}_{22}\text{H}_{22}\text{O}_2$	80.44	9.83	80.51	9.63	

TABLE 3



R	M.P. (°C)	Elementary analysis					
		formula	Calculated for		Found		
			C	H	C	H	
$-\text{CH}_2\text{CH}=\text{CH}_2$	137—138	$\text{C}_{31}\text{H}_{50}\text{O}_4$	80.21	9.62	80.01	9.69	
	160	$\text{C}_{31}\text{H}_{50}\text{O}_4$	82.24	8.63	82.19	8.64	
$-\text{n-C}_3\text{H}_7$	149—151	$\text{C}_{31}\text{H}_{53}\text{O}_4$	79.70	10.19	79.80	10.03	

Example 5.

5.0 g. of 17 β -hydroxy-16 β -ethylestr-4-en-3-one are dissolved in dry pyridine (100 ml.), followed by the addition of 15 g. of acetic anhydride with stirring. After the resulting solution is allowed to stand for 6 hours at room temperature, it is poured into a large amount of ice water. The precipitating crystals are collected by filtration and washed with water, whereupon 5.2 g. of 17 β -acetoxy-16 β -ethylstr-4-en-3-one are obtained. M.P.: 113—114°C; Elementary analysis: Calculated for C₂₂H₃₂O₃: C, 76.70; H, 9.36. Found: C, 76.74; H, 9.28; Ultraviolet absorption $\lambda_{\text{max}}^{\text{EtOH}}$ m μ (e) 240 (16300).

Example 6.

20 g. of 17 β -hydroxy-16 β -ethylestr-4-en-3-one are dissolved in caproic anhydride (100 ml.), followed by the addition of 3.0 g. of *p*-toluenesulfonic acid with stirring, and the mixture is allowed to stand for 2 hours at room temperature.

Excess caproic anhydride is removed by steam distillation, and the resulting substance is extracted with ether and then the ether is distilled off, whereupon 25 g. of 16 β -ethylestra-3,5-diene-3,17-diol 3,17 β -dicaproate are obtained, m.p. 62—63°C.

Ultra violet absorption: $\lambda_{\text{max}}^{\text{EtOH}}$ 236 m μ . 24 g. of the above dicaproate are dissolved in methanol (200 ml.), followed by the addition of 5% hydrochloric acid (30 ml.). The mixture is refluxed for 30 minutes. After being cooled, the reaction mixture is poured into water (500 ml.), followed by extraction with ether. Removal of ether by distillation leaves 21 g. of 17 β -caproyloxy-16 β -ethylestr-4-en-3-one, m.p. 70—71°C; Elementary analysis: Calculated for C₂₆H₄₀O₃: C, 77.95; H, 10.07; Found: C, 77.97; H, 10.11; Ultraviolet absorption: $\lambda_{\text{max}}^{\text{EtOH}}$ m μ (e) 240 (15300).

Example 7.

3 g. of 17 β -hydroxy-16 β -ethylestr-4-en-3-one are dissolved in dry pyridine (20 ml.), followed by the addition of 1.5 g. of caproyl chloride under ice-cooling. The mixture is left standing at that temperature for 30 minutes, at the end of which time it is poured into 100 ml. of ice-water. The crystalline powder is recovered by filtration, and washed with water, whereupon 2.7 g. of 17 β -caproyloxy-16 β -ethylestr-4-en-3-one are obtained.

Example 8.

(1) To a solution of 5 g. of 3-ethoxy-16 β -ethylestra-3,5-dien-17 β -ol in 100 ml. of pyridine are added 30 ml. of acetic anhydride, followed by heating at 40°C. for 5 hours. The reaction mixture is poured gradually into 300 ml. of ice-water and the precipitates are collected by filtration, followed by washing with water. The crude crystals (5.0 g.) of 3-ethoxy-17 β -acetoxy-16 β -ethylestra-3,5-diene are dissolved in 150 ml. of methanol and to the resulting solution are added 3 ml. of concentrated hydrochloric acid, followed by standing for 10 minutes. The reaction solution is poured into 400 ml. of water. The precipitating steroid is collected by filtration and washed with water. By recrystallization from ether are obtained 4.7 g. of 17 β -acetoxy-16 β -ethylestr-4-en-3-one melting at 113—114°C. Elementary analysis: Calculated for C₂₂H₃₂O₃: C, 76.70; H, 9.36; Found: C, 76.74; H, 9.28.

Example 9.

To a solution of 4.5 g. of 17 β -acetoxy-16 β -ethylestr-4-en-3-one in 300 ml. of methanol are added 70 ml. of a 5% methanolic solution of sodium hydroxide, followed by heating at 60°C for 1.5 hours. The reaction solution is poured into 300 ml. of water to precipitate crystals which are recovered by filtration. After washing with water, the crystals are recrystallized from ether to give 4.1 g. of 17 β -hydroxy-16 β -ethylestr-4-en-3-one melting at 152—153°C. Ultraviolet absorption: $\lambda_{\text{max}}^{\text{EtOH}}$ 240 m μ (e=14900). Elementary analysis: Calculated for C₂₀H₃₀O₂: C, 79.42; H, 10.00; Found: C, 79.53; H, 10.01.

Example 10.

To 5.0 g. of 17 β -hydroxy-16 β -ethylestr-4-en-3-one in 100 ml. of dry pyridine are added 10 ml. of propionic anhydride, followed by heating at 70°C. for 10 hours. The reaction mixture is poured into 300 ml. of 10% sodium bicarbonate, followed by extraction with ether. The ether is washed with water and dried with anhydrous sodium sulfate. The solvent is distilled off, whereupon a colorless oil is separated out. Recrystal-

lization from hexane gives 3.7 g. of 17 β -propionyloxy-16 β -ethylestr-4-en-3-one melting at 45—47°C. Elementary analysis: Calculated for C₂₅H₃₄O₅: C, 77.05; H, 9.56; Found; C, 77.11; H, 9.59; Ultraviolet absorption; $\lambda_{\max}$ 239 m μ .

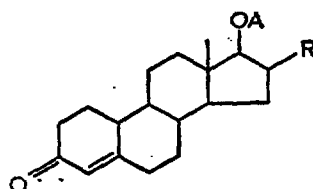
Example 11.

To 3.0 g. of 17 β -hydroxy-16 β -ethylestr-4-en-3-one in 150 ml. of dry pyridine are added 5 ml. of phenoxyacetyl chloride under ice cooling. After being left standing for 10 minutes, the reaction mixture is poured into 300 ml. of water, followed by extraction with ether. The ether layer is washed with a 10% solution of sodium bicarbonate, and then with water, and dried with anhydrous sodium sulfate.

The ether is distilled off, whereupon 2.9 g. of 17 β -hydroxy-16 β -ethylestr-4-en-3-one 17 β -phenoxyacetate are obtained melting at 112—114°C. Elementary analysis; Calculated for C₂₈H₃₆O₄: C, 77.03; H, 8.31; Found: C, 77.12; H, 8.29. Ultraviolet absorption $\lambda_{\max}$ 224, 239, 270, 277 m μ .

WHAT WE CLAIM IS:—

1. A compound of the formula (I)



wherein A is hydrogen, an acyl radical or an ether residue and R is a hydrocarbon radical having at least 2 carbon atoms which may optionally be substituted by one or more halogen atoms.

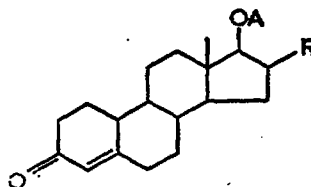
2. A compound of the formula (I) as defined in claim 1 wherein A is hydrogen or an acyl radical having up to 10 carbon atoms and R is a hydrocarbon radical having 2 to 6 carbon atoms.

3. 16 β -ethyl-17 β -hydroxyestr-4-en-3-one.
4. 16 β -n-propyl-17 β -hydroxyestr-4-en-3-one.
5. 16 β -i-propyl-17 β -hydroxyestr-4-en-3-one.
6. 16 β -allyl-17 β -hydroxyestr-4-en-3-one.
7. 16 β -cyclohexyl-17 β -hydroxyestr-4-en-3-one.
8. 16 β -phenyl-17 β -hydroxyestr-4-en-3-one.
9. 17 β -acetyloxy-16 β -ethylestr-4-en-3-one.
10. 17 β -caproyloxy-16 β -ethylestr-4-en-3-one.
11. 17 β -propionyloxy-16 β -ethylestr-4-en-3-one.
12. 17 β -phenoxyacetyloxy-16 β -ethylestr-4-en-3-one.

13. A compound according to claim 1 or 2 substantially as herein described with reference to any of the specific examples.

14. A pharmaceutical composition which comprises a compound as claimed in any of claims 1 to 13 together with a pharmaceutically acceptable carrier or carriers, the composition being administrable in unit dosage form.

15. A process for producing a compound of the formula I:



(I)

wherein A is hydrogen, an acyl radical or an ether residue and R is a hydrocarbon radical having at least 2 carbon atoms which may optionally be substituted by one or more halogen atoms, which comprises subjecting to hydrolysis a compound of the formula:



lization from hexane gives 3.7 g. of 17 β -propionyloxy-16 β -ethylestr-4-en-3-one melting at 45—47°C. Elementary analysis: Calculated for C₂₃H₃₄O₃: C, 77.05; H, 9.56; Found: C, 77.11; H, 9.59; Ultraviolet absorption; $\lambda_{\max}$ 239 m μ .

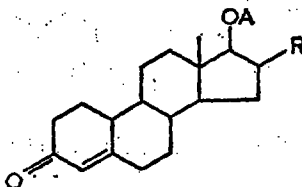
Example 11.

To 3.0 g. of 17 β -hydroxy-16 β -ethylestr-4-en-3-one in 150 ml. of dry pyridine are added 5 ml. of phenoxyacetyl chloride under ice cooling. After being left standing for 10 minutes, the reaction mixture is poured into 300 ml. of water, followed by extraction with ether. The ether layer is washed with a 10% solution of sodium bicarbonate, and then with water, and dried with anhydrous sodium sulfate.

The ether is distilled off, whereupon 2.9 g. of 17 β -hydroxy-16 β -ethylestr-4-en-3-one 17 β -phenoxyacetate are obtained melting at 112—114°C. Elementary analysis: Calculated for C₂₈H₃₈O₄: C, 77.03; H, 8.31; Found: C, 77.12; H, 8.29. Ultraviolet absorption $\lambda_{\max}$ 224, 239, 270, 277 m μ .

WHAT WE CLAIM IS:—

1. A compound of the formula (I)



wherein A is hydrogen, an acyl radical or an ether residue and R is a hydrocarbon radical having at least 2 carbon atoms which may optionally be substituted by one or more halogen atoms.

2. A compound of the formula (I) as defined in claim 1 wherein A is hydrogen or an acyl radical having up to 10 carbon atoms and R is a hydrocarbon radical having 2 to 6 carbon atoms.

3. 16 β -ethyl-17 β -hydroxyestr-4-en-3-one.

4. 16 β -n-propyl-17 β -hydroxyestr-4-en-3-one.

5. 16 β -i-propyl-17 β -hydroxyestr-4-en-3-one.

6. 16 β -allyl-17 β -hydroxyestr-4-en-3-one.

7. 16 β -cyclohexyl-17 β -hydroxyestr-4-en-3-one.

8. 16 β -phenyl-17 β -hydroxyestr-4-en-3-one.

9. 17 β -acetyloxy-16 β -ethylestr-4-en-3-one.

10. 17 β -caproyloxy-16 β -ethylestr-4-en-3-one.

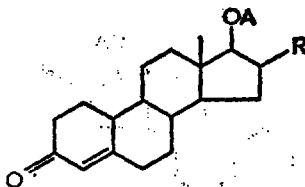
11. 17 β -propionyloxy-16 β -ethylestr-4-en-3-one.

12. 17 β -phenoxyacetyloxy-16 β -ethylestr-4-en-3-one.

13. A compound according to claim 1 or 2 substantially as herein described with reference to any of the specific examples.

14. A pharmaceutical composition which comprises a compound as claimed in any of claims 1 to 13 together with a pharmaceutically acceptable carrier or carriers, the composition being administrable in unit dosage form.

15. A process for producing a compound of the formula I:

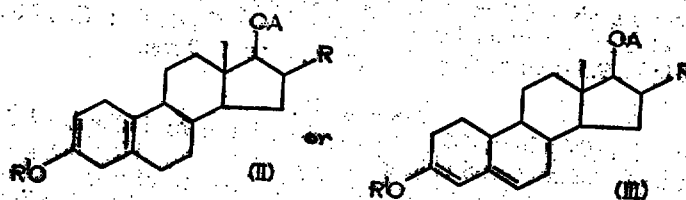


(I)

wherein A is hydrogen, an acyl radical or an ether residue and R is a hydrocarbon radical having at least 2 carbon atoms which may optionally be substituted by one or more halogen atoms, which comprises subjecting to hydrolysis a compound of the formula:

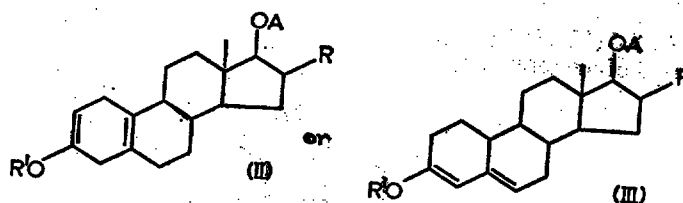


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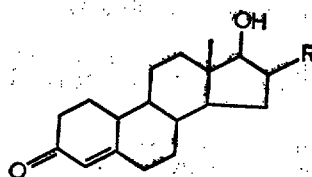
wherein each of A and R has the same meaning as above and R' is a hydrocarbon radical or an acyl radical.

5 16. A process for producing a compound of the formula I as defined in claim 15, wherein A is hydrogen or an acyl radical having up to 10 carbon atoms and R is a hydrocarbon radical having 2 to 6 carbon atoms, which comprises subjecting to hydrolysis under acidic conditions a compound of the formula:

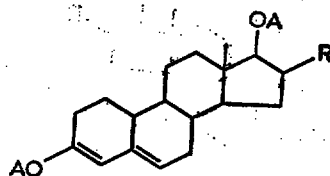
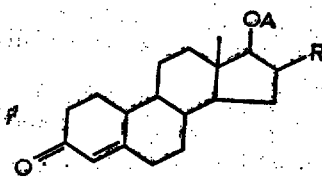


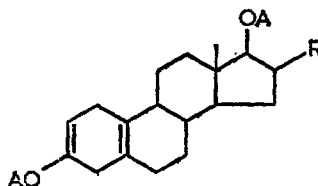
10 wherein each of A and R has the same meaning as above and R' is an alkyl radical having up to 4 carbon atoms.

17. A process for producing a compound of the formula:



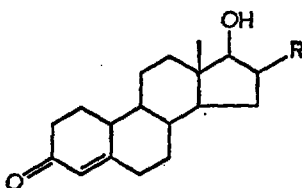
15 wherein R is a hydrocarbon radical having at least 2 carbon atoms which may optionally be substituted by one or more halogen atoms, which comprises subjecting to hydrolysis a compound of the formula:





wherein R has the same meaning as above and A is an acyl radical.

18. A process for producing a compound of the formula (I) as defined in claim 15 wherein A is an acyl radical and R is a hydrocarbon radical having at least 2 carbon atoms which may optionally be substituted by one or more halogen atoms, which comprises acylating a compound of the formula:



and where the resulting product is the corresponding 3,17 β -diacylated compound, hydrolysing the product to form the desired 17 β -monoacylated compound, wherein R is as just defined.

19. A process according to any of claims 15 to 18 substantially as herein described with reference to any of the specific examples.

20. Compounds of the formula (I) as defined in claim 1 when made by a process according to any of claims 15—19.

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