P213600/HC/LW/6958T.3

PATENT APPLICATION FORM

COMMONWEALTH OF AUSTRALIA

Regulation 9

Patents Act 1952

617140

We, SCHERING AKTIENGESELLSCHAFT

of MullerstraBe 170-178, D-1000 Berlin 65, Germany

hereby apply for the grant of a Standard Patent for an invention entitled 17-HALOMETHYLENE ESTRATRIENES

which is described in the accompanying complete specification.

For a Convention application - details of basic application-

Number	Country	Date of Application
37 41 800.9	Germany	December 7, 1987

Our address for service is ARTHUR S. CAVE & CO., Patent and Trade Mark Attorneys, Level 10, 10 Barrack Street, Sydney, New South Wales, Australia 2000.

Dated this 7th day of December, 1988.

SCHERING
AKTIENGESELLSCHAFT
By Its Patent Attorneys,
ARTHUR S. CAVE & CO.

P.R. TAYLOR F.I.P.A.A.

To:
Commissioner of Patents

ARTHUR S. CAVE & CO.
PATENT AND TRADE MARK ATTORNEYS
SYDNEY

ASC 1

S004111 07/12/88

P213600/MAH

Regulation 12(2)

PATENT DECLARATION FORM (CONVENTION)

COMMONWEALTH OF AUSTRALIA

Patents Act 1952

DECLARATION IN SUPPORT OF A CONVENTION APPLICATION FOR A PATENT

In support of the Convention application made for a patent for an invention entitled: 17-Halogenmethylen-estratrienes

I/We Jürgen Schönherr, Horst Kosmol ..... (full name of declarant)
of .Grieg.Str..20,.D-1000.Berlin 33,.Eggepfad 29,.D-1000 Berlin 37..... (full address)
do solemnly and sincerely declare as follows:-

1. I am/We are authorised by SCHERING AKTIENGESELLSCHAFT the applicant for the patent to make this declaration on its behalf.

2. The basic Application(s) as defined by Section 141 of the Act was/were made in the following country or countries on the following date namely:-
in Germany on 7 December 1987 by SCHERING AKTIENGESELLSCHAFT

3. Prof. Dr. Pater Jungblut, D-3057 Neustadt-Buren, Kampweg 4, Biochemiker; Prof. Dr. Dr.h.c. Rudolf Wiechert, D-1000 Berlin 39, Petzower Strabe 8 A, Chemiker; Dr. Rolf Bohlmann, D-1000 Berlin 21, Melanchtonstrabe 23, Chemiker are the actual inventors of the invention and the facts upon which the applicant(s) are entitled to make the application are as follows:

The Applicant is the Assignee of the said invention from the actual inventors.

4. The basic application(s) referred to in paragraph 2 of this Declaration was the first application(s) made in a Convention country in respect of the invention the subject of the application.

Declared at Berlin this 29th day of January , 1991.

SCHERING AKTIENGESELLSCHAFT
i.V. ppa.

Kosmol

Dr. Kosmol Dr. Schönherr
Signature of Declarant(s)

To:
The Commissioner of Patents

ARTHUR S. CAVE & CO.
PATENT AND TRADE MARK ATTORNEYS

(12) PATENT ABRIDGMENT (11) Document No. AU-B-26652/88
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 617140

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17-HALOMETHYLENE ESTRATRIENES

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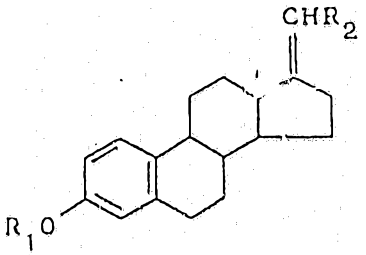
(57) Claim

1. A 17-halomethylene estratriene of the formula



(I),

wherein R_1 is hydrogen, methyl or the acyl group of a C_{1-12} hydrocarbon carboxylic acid, optionally substituted by C_{1-4} alkyl, hydroxy, C_{1-4}-alkoxy, oxo, amino or halogen, or of a mineral acid, and

R_2 is halogen.

13. A method of treating estrogen deficiency symptoms, comprising administering a compound of claim 1.

14. A method of treating a hormone-dependent tumor, comprising administering a compound of claim 1.

15. A method of contraception, comprising of administering to a female mammal a contraceptively effective amount of a compound of claim 1.

AUSTRALIA

PATENTS ACT 1952

COMPLETE SPECIFICATION

(ORIGINAL)

FOR OFFICE USE

617140

Application Number:
Lodged:

Complete Specification Lodged:
Accepted:
Published:

Priority:
Related Art:

TO BE COMPLETED BY APPLICANT

Name of Applicant:	SCHERING AKTIENGESELLSCHAFT
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Complete Specification for the invention entitled
17-HALOMETHYLENE ESTRATRIENES.

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

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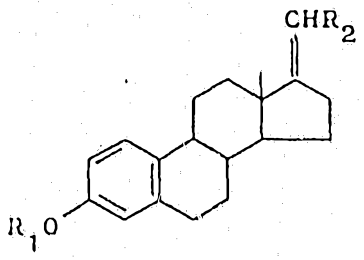
ASC 49

17-HALOMETHYLENE ESTRATRIENES

Summary of the Invention

The invention relates to novel 17-halomethylene estratrienes, processes for their production, pharmaceutical preparations containing these compounds, methods of treating estrogen deficiency symptoms and hormone-dependent tumors, and methods of contraception.

The novel 17-halomethylene estratrienes are characterized by Formula I



(I),

wherein

R_1 is a hydrogen atom, a methyl or acyl group, and

R_2 is a halogen atom.

Suitable acyl groups are physiologically compatible groups derived from acids customarily used for the esterification of hydroxy steroids. The identity and structure of the acyl moiety are not critical. Suitable acyl groups include organic carboxylic acids of 1-12 carbon atoms, e.g., hydrocarbon acids, pertaining to the aliphatic, cycloaliphatic, aromatic or aromatic-aliphatic series which can be saturated or unsaturated, mono- or poly-basic and/or substituted. Examples that can be mentioned for the substituents are alkyl (e.g.,

of 1-4 C atoms), hydroxy, alkoxy (e.g., of 1-4 C atoms), oxo or amino groups (e.g., amino and mono- or dialkylamino (1-4 C-alkyl groups)) and halogen atoms. Among these are also the usual inorganic acids.

Examples of such carboxylic acids of 1-12 carbon atoms include alkanoyl groups from formic acid, acetic acid, propionic acid, butyric acid, isobutyric acid, valeric acid, isovaleric acid, caproic acid, enanthic acid, caprylic acid, pelargonic acid, capric acid, undecylic acid, lauric acid, trimethylacetic acid, tert-butylacetic acid, cyclopentylacetic acid, diethylaminoacetic acid, lactic acid, succinic acid, adipic acid; other preferred groups include benzoic acid, nicotinic acid, morpholinoacetic acid, etc.

Examples of inorganic acids include sulfuric and phosphoric acids.

The esters of succinic acid, adipic acid, sulfuric acid, and phosphoric acid can optionally be converted with an alkali into the water-soluble salts.

Hetero acyl groups can be derived from heterocyclic acids comprising 1-2 fused rings, wherein each ring contains 4-7 ring atoms and 1-2 hetero atoms, the hetero atoms comprising O, N and/or S. Suitable acyl groups include that from pyrrolidino-, piperidino-, piperazino-, morpholinosulfonic acid.

Suitable halogen atoms throughout the foregoing are fluorine, chlorine, bromine and iodine, preferably fluorine and chlorine.

It has been found that the estratrienes substituted by halomethylene in the 17-position differ markedly from the estrones. As compared with the estrones, from which they are produced, the compounds of general Formula I show a lower affinity to the estrogen receptors than estradiol and, as compared with estradiol, bring about

increased cellular membrane and blood/lymphatic vessel permeability.

In the estrogen receptor binding test for estrogenic activity with the use of cytosol from pig uterus homogenate and of 6,7^{3}H estradiol as the reference compound, the compounds of Formula I show a lower affinity for the estrogen receptor.

The following table indicates the competition at the receptor in percent.

T A B L E

Estrogen Receptor Binding Test

Compound	Mol	% Competition
	2×10^{-8}	49
Estradiol	2×10^{-7}	88
	2×10^{-6}	96
17-Fluoro-methylene-1,3,5(10)-estratrien-3-ol	2×10^{-8}	12
	2×10^{-7}	23
	2×10^{-6}	78

In a uterus growth test with immature, 23-day-old Sprague-Dawley rats, for example, 17-fluoromethylene-1,3,5(10)-estratrien-3-ol exhibits 1/40 of the uterotropic activity of estradiol, based on moist uterus weights including intrauterine fluid. When DNA content is employed as a measure of the uterus cell number, then approximately 1/70 of estradiol activity is found for 17-fluoromethylene-1,3,5(10)-estratriene.

For performing the test, the immature female rats receive once daily over 3 days estradiol or 17-fluoromethylene-1,3,5(10)-estratrien-3-ol subcutaneously. On the 4th day, the animals are sacrificed, and the uterus weight or the DNA content per uterus is determined.

A uterus weight of 67 mg is obtained with 0.1 ug of estradiol or with 4.2 ug of 17-fluoromethylene-1,3,5(10)-estratrien-3-ol. A DNA content of 381 ug is the result with 0.1 ug of estradiol or with 7.3 ug of 17-fluoromethylene-1,3,5(10)-estratrien-3-ol.

Upon local administration of estradiol or 17-fluoromethylene-1,3,5(10)-estratrien-3-ol into the uterine lumen of a pig, a uterine edema is produced which is more strongly pronounced in case of the 17-fluoromethylene compound than in case of estradiol. The extent of edema can be determined by ascertaining the albumin and DNA content of the uterus.

Intrauterine injection of 1 x 10^{-6}-molar solutions (20-50 ml/uterus) of the compounds to be tested leads, after 120 minutes, in case of estradiol, to an increase in the albumin content of about 17 mg of albumin/1 mg of DNA and, in case of the corresponding 17-fluoromethylene compound, to an increase of 36 mg albumin/1 mg DNA.

Introduction of the test compound into a uterine horn of a female pig brings about edema formation only at that location; the untreated horn is not affected. The compound is bound to the receptor without subsequent renewed synthesis of receptor.

Accordingly, the finding for the compounds of Formula I is an activity disproportionation indicating a lower activity in the cell nucleus by way of the estrogen receptor, with an edema formation that is unchanged as compared with estradiol.

The compounds of Formula I are substrates for intracellular enzymes, the products of which lead to an increase in cellular membrane and blood/lymphatic vessel permeability, which can be demonstrated as so-called "water imbibition" in the form of a massive edema in the target organ, the uterus. These compounds are especially suitable for the treatment of climacteric

complaints, as well as generally for the treatment of symptoms occurring due to defunctionalization of the second activity segment of estradiol.

The active compounds are preferably administered orally, e.g. to mammals including humans, but they can also be administered locally and parenterally. For this purpose, the active compounds are processed according to conventional methods for the customary forms of administration together with the additives, excipients and/or solubilizers customary in galenic pharmacy. For the preferred oral administration, especially suitable are tablets, dragees, capsules, pills, aqueous suspensions or alcoholic solutions, and for local and parenteral administration, especially ointments and, respectively, oily solutions, such as, for example, sesame oil or castor oil solutions which can additionally contain, if desired, a solubilizer, e.g., benzyl benzoate.

The concentration of active compound in the pharmaceutical preparations depends on the type of administration and the field of usage. Thus, for example, tablets, dragees, capsules or pills can contain 10-150 µg of active compound per dosage unit, and oily solutions or ointments can contain 1-20 µg of active compound per milliliter.

In a preferred embodiment, the oral form of administration contains 10-100 ug of active agent.

After treating therapeutically castrated women, as well as women in the climacteric, all of whom suffered from hot flashes and moodiness, with daily 10-100 µg of active compound according to Formula I, a marked decrease in discomfort occurred as early as after 2 days.

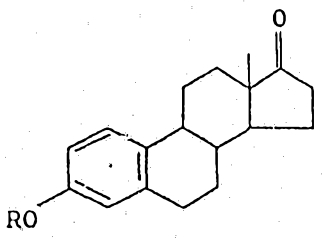
The systemic administration of compounds of Formula I to Sprague-Daley rats with mammary tumors induced by 7,12-dimethylbenzanthracene leads to cessation of tumor

growth without any marked effect on the estrous cycle. The compounds are thus likewise suitable for the treatment of hormone-dependent tumors analogously to the known compound Tamoxifen . With the use of the compounds in daily amounts of 0.1-5 µg per kg, stimulation of growth of existing hormone-dependent tumors is prevented.

This antitumor activity can be demonstrated using any conventional protocol, e.g., as described in Science 137 (1962), 257-262.

The compounds of Formula I, being substances with a selective estrogenic activity, can also be utilized in preparations for contraception, preferably in combination with a progestationally active hormone component, e.g., levonorgestrel, gestodene, or desogestrel. Forms of administration that can be given orally contain preferably 10-100 µg of a compound of Formula I and 50-500 µg of a strongly effective gestagen per day . The compounds are administered analogously to the known compound Microgynon (R).

The novel 17-halomethylene estratrienes of Formula I can be prepared according to this invention by reacting an estrone of Formula II



(II),

wherein R is a hydrogen atom or a methyl group, with a halomethylenylide, and optionally acylating a free hydroxy group.

The reaction with halomethylenylide takes place according to conventional methods, for example in an

aprotic solvent, such as dimethyl sulfoxide, dimethylformamide, dioxane, tetrahydrofuran, or a mixture of these solvents at temperatures of between 20° and 40°C, a protective gas, such as nitrogen or argon being preferably employed during the reaction. (Pure and Applied Chemistry 52 (1980) 771).

The halomethylenylide is suitably prepared in the reaction solution from halomethyltriphenylphosphonium salt with a base, such as sodium hydride, sodium hydroxide, potassium tert-butylate, sodium methylate or butyllithium. (Journal Flourine Chemistry 27 (1985) 85).

Especially suitable halomethyltriphenylphosphonium salts are fluoromethyltriphenylphosphonium tetrafluoroborate and chloromethyltriphenylphosphonium chloride.

The subsequent optional acylation takes place according to conventional methods for esterification of phenolic hydroxy groups, preferably with pyridine/acid anhydride or pyridine/acid chloride, at room temperature. (Ang. Chemie 90 (1978) 602).

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

In the foregoing and in the following examples, all temperatures are set forth uncorrected in degrees Celsius and unless otherwise indicated, all parts and percentages are by weight.

The entire texts of all applications, patents and publications, if any, cited above and below, and of corresponding application, West German P. 37 41 800.9,

filed December 7, 1987, are hereby incorporated by reference.

EXAMPLES

Example 1

17.2 g of fluoromethyltriphenylphosphonium tetrafluoroborate [J. Fluorine Chem. 27: 85-89 (1985)] is suspended in 150 ml of dioxane and combined at 20°C with 6.7 g of potassium tert-butylate in incremental portions, and further agitated for 0.5 hour. To this solution is added 2.0 g of 1,3,5(10)-estratrien-3-ol-17-one in 30 ml of dioxane, and the mixture is stirred for 30 minutes. For working-up purposes, the mixture is poured on water, dried over sodium sulfate, and concentrated to dryness under vacuum. After purification by chromatography on silica gel with hexane/ethyl acetate, 1.63 g of 17-fluoromethylene-1,3,5(10)-estratrien-3-ol is obtained as an E/Z mixture, mp 125-129°C. $[\alpha]_D$ +68.1° (chloroform).

Example 2

17.2 g of chloromethyltriphenylphosphonium chloride is suspended in 150 ml of dioxane and combined at 20°C with 6.7 g of potassium tert-butylate in incremental portions, and further stirred for 0.5 hour. To this solution is added 2 g of 3-[(tetrahydropyran-2-yl)oxy]-1,3,5(10)-estratrien-17-one in 30 ml of dioxane, and the mixture is stirred for 30 minutes. For working-up purposes, the mixture is poured on water, dried over sodium sulfate, and concentrated to dryness under vacuum, thus obtaining 17-chloromethylene-3-[(tetrahydropyran-2-yl)oxy]-1,3,5(10)-estratriene which, as a crude product, is dissolved in 50 ml of methanol and heated under reflux for one hour with 2 g of oxalic acid. Then the product is precipitated with ice water/sodium chloride, taken up in ethyl acetate, dried over sodium sulfate, and concentrated to dryness under vacuum. After purification by chromatography on silica

gel with hexane/ethyl acetate, 1.74 g of 17-chloromethylene-1,3,5(10)-estratrien-3-ol is obtained as an E/Z mixture having a melting point of 130-133°C.

$[\alpha]_D$ +52.8° (chloroform).

Example 3

Analogously to Example 1, 2.0 g of 3-methoxyestrone is reacted to 1.67 g of 17-fluoromethylene-3-methoxy-1,3,5(10)-estratriene as an oil.

Example 4

1.0 g of 17-fluoromethylene-1,3,5(10)-estratrien-3-ol in 10 ml of pyridine is agitated with 5 ml of acetic anhydride for 2 hours at 20°C. Then the mixture is precipitated with sulfuric acid ice water, taken up in dichloromethane, washed neutral with sodium bicarbonate solution, dried over magnesium sulfate, and freed of solvent under vacuum. After chromatography on silica gel with hexane/ethyl acetate, 955 mg of 3-acetoxy-17-fluoromethylene-1,3,5(10)-estratriene is obtained.

Example 5

Analogously to Example 4, 1.0 g of 17-fluoromethylene-1,3,5(10)-estratrien-3-ol is reacted with 5 ml of butyric acid anhydride to form 1.03 g of 3-butyryloxy-17-fluoromethylene-1,3,5(10)-estratriene.

Example 6

Analogously to Example 4, 1.0 g of 17-fluoromethylene-1,3,5(10)-estratrien-3-ol is reacted with 5 ml of undecylic acid anhydride to produce 1.06 g of 17-fluoromethylene-3-undecyloxy-1,3,5(10)-estratriene.

Example 7

Analogously to Example 2, 2.0 g of 3-methoxyestrone is reacted to 1.59 g of 17-chloromethylene-3-methoxy-1,3,5(10)-estratriene as an oil.

Example 8

1.0 g of 17-chloromethylene-1,3,5(10)-estratrien-3-ol in 10 ml of pyridine is stirred with 5 ml of acetic anhydride for 2 hours at 20°C. Then the product is precipitated with sulfuric acid ice water, taken up in dichloromethane, washed neutral with sodium bicarbonate solution, dried over magnesium sulfate, and freed of solvent under vacuum. After chromatography on silica gel with hexane/ethyl acetate, 955 mg of 3-acetoxy-17-chloromethylene-1,3,5(10)-estratriene is obtained.

Example 9

Analogously to Example 8, 1.0 g of 17-chloromethylene-1,3,5(10)-estratrien-3-ol is reacted with 5 ml of butyric acid anhydride to 1.03 g of 3-butyryloxy-17-chloromethylene-1,3,5(10)-estratriene.

Example 10

Analogously to Example 8, 1.0 g of 17-chloromethylene-1,3,5((10)-estratrien-3-ol is reacted with 5 ml of undecylic acid anhydride to 1.06 g of 17-chloromethylene-3-undecyloxy-1,3,5(10)-estratriene.

Example 11

Composition of a Dragee

0.010 mg 17-Fluoromethylene-1,3,5(10)-estratrien-3-ol
46.490 mg Lactose
26.800 mg Cornstarch
3.000 mg Poly(1-vinyl-2-pyrrolidone) average MW 25,000
3.700 mg Talc
80.000 mg Total weight, supplemented to about 140 mg with the usual sugar mixture.

Example 12

Composition of an Alcoholic Solution

1 mg of 17-chloromethylene-1,3,5(10)-estratrien-3-ol is dissolved in 10 ml of 46% strength ethyl alcohol.

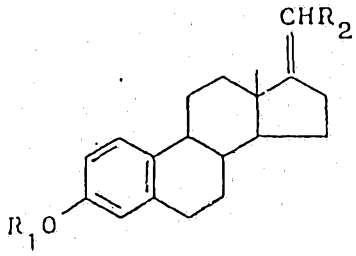
Ten drops (0.5 ml) contain 50 µg of active compound.

The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

The Claims defining the invention are as follows:

1. A 17-halomethylene estratriene of the formula



(I),

wherein R_1 is hydrogen, methyl or the acyl group of a C_{1-12} hydrocarbon carboxylic acid, optionally substituted by C_{1-4} alkyl, hydroxy, C_{1-4}-alkoxy, oxo, amino or halogen, or of a mineral acid, and

R_2 is halogen.

2. A compound of claim 1, wherein R_1 is C_{1-12} alkanoyl.

3. A compound of claim 1, wherein R_1 is H.

4. A compound of claim 1, wherein R_1 is CH_3.

5. A compound of claim 1, wherein R_2 is fluorine.

6. 17-Fluoromethylene-1,3,5(10)-estratrien-3-ol, 17-fluoromethylene-3-methoxy-1,3,5(10)-estratriene, 3-butyryloxy-17-fluoromethylene-1,3,5(10)-estratriene, and

17-fluoromethylene-3-undecyloxy-1,3,5(10)-estratriene, each a compound of claim 5.

7. A compound of claim 1, wherein R_2 is chlo[illegible].

8. 17-Chloromethylene-1,3,5(10)-estratrien-3-ol, 17-chloromethylene-3-methoxy-1,3,5(10)-estratriene, 3-acetoxy-17-chloromethylene-1,3,5(10)-estratriene, 3-butyryloxy-17-chloromethylene-1,3,5(10)-estratriene, and 17-chloromethylene-3-undecyloxy-1,3,5(10)-estratriene, each a compound of claim 7.

9. A pharmaceutical preparation comprising an amount of a compound according to claim 1 and a pharmaceutically acceptable excipient.

10. A pharmaceutical preparation comprising an amount of a compound according to claim 6 and a pharmaceutically acceptable excipient.

11. A pharmaceutical preparation comprising an amount of a compound according to claim 8 and a pharmaceutically acceptable excipient.

12. A pharmaceutical preparation of claim 9, wherein said amount is 10-150 µg per dosage unit.

13. A method of treating estrogen deficiency symptoms, comprising administering a compound of claim 1.

14. A method of treating a hormone-dependent tumor, comprising administering a compound of claim 1.

15. A method of contraception, comprising of administering to a female mammal a contraceptively effective amount of a compound of claim 1.

16. A method of contraception comprising of administering, in combination, contraceptively effective amounts of a compound of claim 1 and a progestationally active compound.

17. A 17-halomethylene estratriene of the formula I substantially as herein described with reference to anyone of the examples.

DATED this 5th day of September, 1991

SCHERING AKTIENGESELLSCHAFT
By Its Patent Attorneys,
Arthur S Cave & Co

1036T/LFP