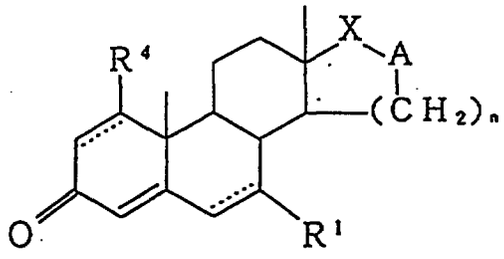
DESCRIPTION

NOVEL 7-SUBSTITUTED OXA- OR AZASTEROID COMPOUND

Technical Field

This invention relates to novel 7-substituted oxa- or azasteroid compounds having an aromatase-inhibiting action, and more detailedly relates to a steroid compound represented by the formula



(I)

wherein

R^1 denotes $-S-R^2$, $-S(O)m-R^3$ or an aralkyl group,

wherein

R^2 denotes a hydrogen atom; a lower alkyl group optionally substituted with a hydroxyl, amino or lower alkoxycarbonyl group; a lower alkenyl group; an aralkyl group; an aryl group optionally substituted with halogen atom(s), or amino, di-(lower alkyl)amino, lower alkoxy or lower alkyl group(s); an acyl group; or a lower alkoxycarbonyl group,

R^3 denotes a lower alkyl group,

m denotes 1 or 2,

R^4 denotes a hydrogen atom or $-S-R^5$, wherein

R^5 denotes a lower alkyl group optionally substituted with a hydroxyl, amino or lower alkoxycarbonyl group; a lower alkenyl group; an aralkyl group; an aryl group optionally substituted with halogen atom(s), or amino, di-(lower alkyl)amino, lower alkoxy or lower alkyl group(s); or an acyl group,

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X denotes C=O or CH_2,

A denotes O or NH,

n denotes 1 or 2, and

the broken lines between the 1- and 2-positions and between the 6- and 7-positions of the steroid skeleton mean that a double bond can exist there, provided that

(a) when A denotes NH, X is assumed to denote C=O,

(b) when R^1 denotes $-S-R^2$ or $-S(O)m-R^3$, the bond between the 6- and 7-positions is assumed to denote a single bond, and

(c) when R^4 denotes $-S-R^5$, the bond between the 1- and 2-positions is assumed to denote a single bond.

Background Technique

Biosynthesis of estrogens can be carried out by that androgens are subjected to oxidation and elimination of formic acid by an enzyme called aromatase, and aromatized. Therefore, if the action of aromatase can effectively be inhibited, it is expected to be useful for treatment of diseases caused by estrogens, and in line with this expectation, several aromatase inhibitors have already been found to be effective for treatment of breast cancer and prostatic hypertrophy.

Aromatase inhibitors are also effective for treatment of other diseases caused by estrogens, for example uterine cancer, ovarian cancer, endometriosis, male gynecomastia, male infertility related to oligospermia, etc.

As known compounds as steroid aromatase inhibitors, there have, for example, been known testolactone (Merck Index, 10th edition, 8999), 4-hydroxy-4-androstene-3,17-dione and its esters (US Patent No. 4,235,893), 1-alkylandrosta-1,4-diene-3,17-dione derivatives (Japanese Laid-Open Patent Publi-

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cation No. 13796/1985), 4-substituted androstene-3,17-dione derivatives (Japanese Laid-Open Patent Publication No. 189295/1986), 6-methyleneandrosta-1,4-diene-3,17-dione derivatives (Japanese Laid-Open Patent Publication No. 12797/1987), 16-oxaandrosta-1,4-diene-3,17-dione (Journal of Medicinal Chemistry, 32, 651, (1989)), 7α-substituted thioandrostenedione derivatives (Journal of Medicinal Chemistry, 21, 1007, (1978)), etc.

However, these steroid aromatase inhibitors, when administered into living bodies, are liable to be inactivated through metabolism, and were still not those satisfactory for clinical use.

The present inventors found that a series of steroid compounds wherein a hetero atom is introduced into the ring D part and the 7-position of the steroid skeleton is substituted with a specific substituent have a very excellent aromatase-inhibiting activity, and moreover, are slow to undergo inactivation through metabolism.

DISCLOSURE OF INVENTION

In this description, the term "lower" means that the carbon atom number of groups or compounds to which this term is attached is 6 or less, preferably 4 or less.

In the above formula (I), the "lower alkyl group" includes, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, n-pentyl, n-hexyl groups, etc., the "lower alkoxy group" includes, for example, methoxy, ethoxy, n-propoxy, n-butoxy groups, etc., the "lower alkenyl group" includes, for example, vinyl, allyl groups, etc., the "lower alkoxycarbonyl group" includes, for example, methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl groups, etc., and the "aralkyl group" includes, for

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example, benzyl, 4-methoxybenzyl, phenethyl groups, etc.

The "lower alkyl group optionally substituted with a hydroxyl, amino or lower alkoxycarbonyl group" includes, for example, besides the above-mentioned unsubstituted lower alkyl groups, 2-hydroxyethyl, 3-hydroxypropyl, 2-aminoethyl, 3-aminopropyl, methoxycarbonylmethyl, methoxycarbonylethyl, ethoxycarbonylmethyl, ethoxycarbonylethyl, groups, etc., and the "aryl group optionally substituted with halogen atom(s), or amino, di-(lower alkyl)amino, lower alkoxy or lower alkyl group(s) includes, for example, phenyl, 1-naphthyl, 2-naphthyl, 4-chlorophenyl, 2-aminophenyl, 4-aminophenyl, 4-amino-1-naphthyl, 4-dimethylaminophenyl, 4-alkoxyphenyl, 4-alkylphenyl groups, etc.

The "acyl group" is the residue part remaining after at least one OH was removed from an organic acid such as a mono- or polycarboxylic acid, and specifically includes groups of the formula $-COR^6$. Herein, R^6 means a hydrogen atom; a lower alkyl group optionally substituted with a halogen atom, an amino group, a carboxyl group, a lower alkoxycarbonyl group, a lower alkanoyloxy group, a carbamoyl group or an aryl group; a lower alkenyl group optionally substituted with an aryl group; a lower cycloalkyl group; an aryl group optionally substituted with lower alkyl group(s), lower alkoxy group(s) or halogen atom(s); an amino group optionally substituted with one or two lower alkyl groups; etc.

Specific examples of the "acyl group" includes formyl, acetyl, propionyl, butyryl, trifluoroacetyl, glycyl, 3-carboxypropionyl, 3-ethoxycarbonylpropionyl, acetoxyacetyl, phenylacetyl, acryloyl, benzoyl, p-methoxybenzoyl, p-methylbenzoyl, p-chlorobenzoyl, carbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, etc.

A preferred group of compounds in the above

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formula (I) are compounds of the formula (I) wherein R^1 denotes $-S-R^2$ or $-S(O)m-R^3$.

Another preferred group of compounds are compounds of the formula (I) wherein A denotes O and n denotes 2.

In the compounds of the above formula (I) of this invention, when the bonds between the 1- and 2-positions and/or between the 6- and 7-positions denote single bonds, the substituents R^1 and $-S-R^5$ may bind to any of the α-position and the β-position, but in view of pharmacological activities, compounds wherein the substituents bind to the α-positions are particularly preferable (all the chemical formulae described in this description, regardless of whether the substituents at the 1- and 7-positions bind to the α-position or the β-position, are expressed by solid lines).

As representative examples of the compounds of the above formula (I) provided by this invention, the following ones, besides those described in the later-described examples, can be mentioned.

7α-mercapto-D-homo-17-oxaandrost-4-en-3-one,

7α-(methylthio)-D-homo-17-oxaandrost-4-ene-3,17a-dione,

7α-(butylthio)-D-homo-17-oxaandrosta-1,4-diene-3,17a-dione,

7α-[(2-hydroxyethyl)thio]-D-homo-17-oxaandrosta-1,4-dien-3-one,

7α-(benzylthio)-D-homo-17-oxaandrosta-1,4-diene-3,17a-dione,

7α-[(1-naphthyl)thio]-D-homo-17-oxaandrost-4-ene-3,17a-dione,

7α-[(4-chlorophenyl)thio]-D-homo-17-oxaandrosta-1,4-diene-3,17a-dione,

7α-[(2-aminophenyl)thio]-D-homo-17-oxaandrost-4-ene-3,17a-dione,

7α-[(4-aminophenyl)thio]-D-homo-17-

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oxaandrosta-1,4-diene-3,17a-dione,

7α-[(4-dimethylaminophenyl)thio]-D-homo-17-oxaandrosta-1,4-dien-3-one,

7α-[(4-methoxyphenyl)thio]-D-homo-17-oxaandrosta-1,4-diene-3,17a-dione,

7α-[(4-methylphenyl)thio]-D-homo-17-oxaandrost-4-ene-3,17a-dione,

7α-(propionylthio)-D-homo-17-oxaandrosta-1,4-dien-3-one,

7α-(ethylsulfinyl)-D-homo-17-oxaandrosta-1,4-diene-3,17a-dione,

7α-mercapto-16-oxaandrosta-1,4-diene-3,17-dione,

7α-mercapto-16-oxaandrosta-1,4-dien-3-one,

7α-(ethylthio)-16-oxaandrosta-1,4-diene-3,17-dione,

7α-[(2-hydroxyethyl)thio)-16-oxaandrost-4-ene-3,17-dione,

7α-[(4-aminophenyl)thio)-16-oxaandrost-4-en-3-one,

7α-[(4-methoxyphenyl)thio)-16-oxaandrosta-1,4-diene-3,17-dione,

7α-(acetylthio)-16-oxaandrost-4-ene-3,17-dione,

7α-(acetylthio)-16-oxaandrosta-1,4-dien-3-one,

7α-(N,N-dimethylcarbamoylthio)-16-oxaandrosta-1,4-diene-3,17-dione,

7α-(methylsulfinyl)-16-oxaandrosta-1,4-diene-3,17-dione,

1α-(acetylthio)-7α-mercapto-D-homo-17-oxaandrost-4-ene-3,17a-dione,

1α-(acetylthio)-7α-[(4-aminophenyl)thio]-D-homo-17-oxaandrost-4-en-3-one,

1α,7α-bis[(2-hydroxyethyl)thio]-D-homo-17-oxaandrost-4-ene-3,17a-dione,

1α,7α-bis[(2-aminoethyl)thio]-D-homo-17-oxaandrost-4-en-3-one,

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1α,7α-bis(ethoxycarbonylmethylthio)-D-homo-17-oxaandrost-4-ene-3,17a-dione,

1α,7α-bis[(4-dimethylaminophenyl)thio]-D-homo-17-oxaandrost-4-en-3-one,

1α,7α-bis[(4-methoxyphenyl)thio]-D-homo-17-oxaandrost-4-ene-3,17a-dione,

1α,7α-bis(N,N-dimethylcarbamoylthio)-D-homo-17-oxaandrost-4-en-3-one,

7α-mercapto-16-azaandrosta-1,4-diene-3,17-dione,

7α-(methylthio)-16-azaandrosta-1,4-diene-3,17-dione,

7α-[(4-aminophenyl)thio]-16-azaandrost-4-ene-3,17-dione,

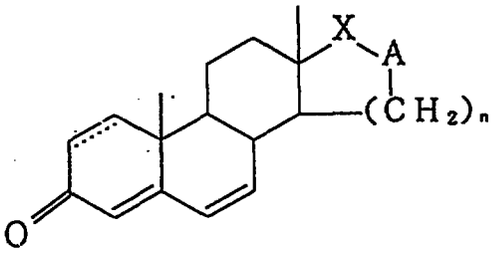
7α-(acetylthio)-16-azaandrosta-1,4-diene-3,17-dione,

7α-(benzoylthio)-16-azaandrost-4-ene-3,17-dione,

7α-mercapto-17-aza-D-homoandrosta-1,4-diene-3,17a-dione,

7α-(acetylthio)-17-aza-D-homoandrost-4-ene-3,17a-dione.

According to this invention, a compound of the above formula (I) wherein the symbol R^1 denotes $-S-R^2$ (a) can be prepared by reacting a compound of the formula



(II)

wherein, X, A and n have the same meanings as defined above,

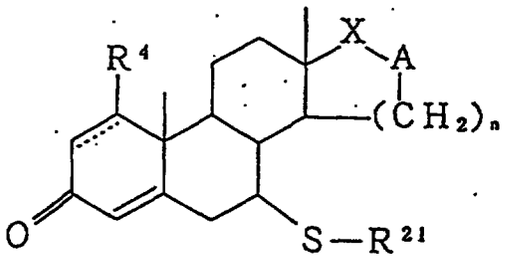
with a compound of the formula

$$HS-R^{21} \qquad \text{(III)}$$

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wherein, R^{21} denotes a lower alkyl group optionally substituted with a hydroxy, amino or lower alkoxycarbonyl group; a lower alkenyl group; an aralkyl group; an aryl group optionally substituted with halogen atom(s), or amino, di-(lower alkyl) amino, lower alkoxy or lower alkyl group(s); or an acyl group,

and, if desired, subjecting the resultant compound of the formula



(I-a)

wherein, R^{21}, R^4, X, A and n have the same meanings as defined above,

to any reaction selected from

(i) a reaction to convert the 7-position to a mercapto group

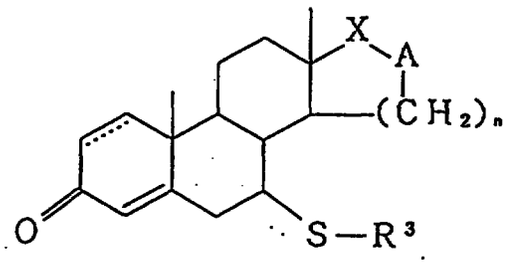
(ii) a reaction to convert the 7-position to a mercapto group, and then further convert it to an optionally substituted lower alkylthio group, an acylthio group or a lower alkoxycarbonylthio group, and

(iii) a reaction to eliminate the group R^4 at the 1-position to introduce a double bond between the 1- and 2-positions.

Further according to this invention, a compound of the above formula (I) wherein the symbol R^1 denotes $-S(O)m-R^3$

(b) can be prepared by oxidizing a compound represented by the formula

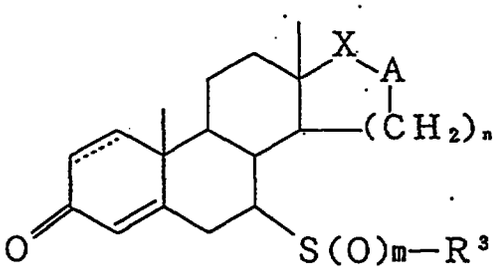
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(I - b)

wherein, R^3, X, A and n have the same meanings as defined above,

and, if desired, subjecting the resultant compound of the formula



(I - c)

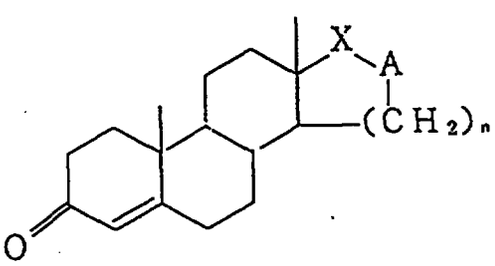
wherein, R^3, m, X, A and n have the same meanings as defined above,

to

(iv) a reaction to convert the 1-position to $-S-R^5$.

Further according to this invention, a compound of the above formula (I) wherein the symbol R^1 denotes an aralkyl group

(c) can be prepared by subjecting a compound of the formula



(IV)

wherein, X, A and n have the same meanings as defined above,

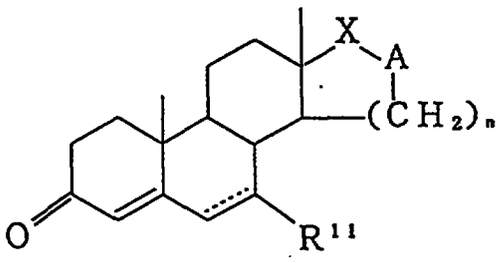
to any reaction selected from

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(v) a reaction to introduce an aralkyl group to the 7-position, and

(vi) a reaction to introduce an aralkyl group to the 7-position and introduce a double bond between the 6- and 7-positions,

and, if desired, subjecting the resultant compound of the formula



(I - d)

wherein, R^{11} denotes an aralkyl group, and X, A and n have the same meanings as defined above, to any reaction selected from

(vii) a reaction to introduce a double bond between the 1- and 2-positions, and

(viii) a reaction to introduce a double bond between the 1- and 2-positions, and convert the 1-position to a group $-S-R^5$.

In the above process (a), the reaction of the compound of the formula (II) with the compound of the formula (III), when R^{21} denotes an acyl group, can, usually, be carried out, in the absence of solvents or in a solvent such as acetic acid, at room temperature to the reflux temperature of the reaction mixture, preferably at the reflux temperature of the reaction mixture. On the other hand, when R^{21} denotes a group other than an acyl group, the reaction can, usually, be carried out, in an inert solvent such as dioxane, tetrahydrofuran, methanol or ethanol, in the presence of an alkali metal alkoxide such as sodium methoxide or sodium ethoxide; an alkali metal such as sodium metal or potassium metal; an alkali metal hydride such as sodium

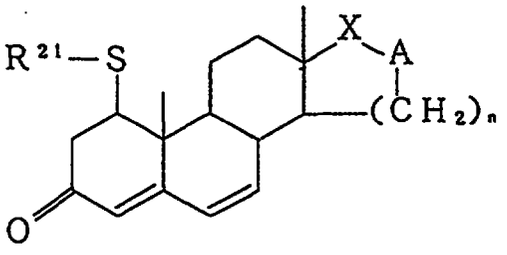
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hydride or potassium hydride. Proper reaction temperature in this case is, generally, 0℃ to the reflux temperature of the reaction mixture.

As to the use ratio of the compound of the formula (III) to the compound of the formula (II), it is generally advantageous to use the formula (III) in an amount of at least one mol, usually of the order of 2 to 20 mols per mol of the compound of the formula (II). It is suitable to use about 1.5 to 15 mols of the alkali metals per mol of the compound of the formula (III).

Thus, a compound of the above formula (I-a) aimed at by this invention is formed.

When this reaction is performed under a mild condition, for example at a reaction temperature of 0℃ to around room temperature, using as a starting material a compound of the formula (II) wherein a double bond exists between the 1- and 2-positions, a compound of the following formula



(V)

wherein, R^{21}, X, A and n have the same meanings as defined above,

is also formed, besides the compound of the above formula (I-a).

The obtained compound of the formula (I-a) can, if desired, be converted to another compound aimed at by this invention, by subjecting the former compound to any reaction selected from the above-mentioned reactions of (i), (ii) and (iii).

The conversion of the 7-position to a mercapto group in the reaction of the above (i) can readily be

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performed by subjecting a compound whose 7-position is an acylthio group to hydrolysis. The hydrolysis can be performed by a process known per se, for example by treating the compound with an alkali such as sodium hydroxide or potassium hydroxide in a solvent such as tetrahydrofuran, methanol or ethanol.

The conversion of the 7-position from a mercapto group to an optionally substituted lower alkylthio group in the reaction of the above (ii) can readily be performed, for example by treating the raw material compound with a lower alkylating reagent such as an optionally substituted lower alkyl halide, in an inert solvent such as dimethylformamide, dimethyl sulfoxide or tetrahydrofuran, in the presence of an alkali such as sodium hydride or sodium methoxide. The conversion of the 7-position from a mercapto group to an acylthio group or a lower alkoxycarbonylthio group can readily be performed, for example by treating the raw material compound with an acid halide, a lower alkyl halogenocarbonate, an acid anhydride or the like, in an inert solvent such as chloroform, dichloromethane or dioxane, in the presence of an alkali such as pyridine, sodium hydride or sodium methoxide.

In the reaction of introduction of a double bond between the 1- and 2-positions in the (iii), different reaction conditions are used between the case where the substituent R^4 at the 1-position denotes a hydrogen atom and the case where R^4 denotes $-S-R^5$.

Namely, when the substituent R^4 at the 1-position denotes a hydrogen atom, the reaction can, usually, be performed by dehydrogenating a compound of the formula (I-a) in an inert solvent such as dioxane or benzene under reflux, using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).

On the other hand, when the substituent R^4 at the 1-position denotes $-S-R^5$, the group $-S-R^5$

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at the 1-position can be eliminated by heating a compound of the formula (I-a) or treating it with an alkali.

The treatment with heating can, for example, be performed in an inert solvent such as dimethyl formamide, dimethyl sulfoxide or toluene under reflux, if desired in the presence of an acid such as acetic acid or p-toluenesulfonic acid.

The treatment with an alkali can, for example, be performed in an inert solvent such as tetrahydrofuran, dioxane or methanol, in the presence of an alkali such as sodium methoxide or sodium hydroxide. In this reaction, when a compound of the formula (I-a) wherein R^{21} denotes an acyl group is used, not only the group $-S-R^5$ at the 1-position is eliminated, but also the acylthio group at the 7-position is converted to a mercapto group through hydrolysis with the alkali.

According to the above mentioned process (b), the oxidation of the compound of the formula (I-b) can usually be performed by treating it with an oxidizing agent such as m-chloroperbenzoic acid or peracetic acid, in an inert solvent such as benzene, toluene or chloroform.

Proper reaction temperature is generally on the order of 0 to 50℃ , preferably from under ice cooling to around room temperature, and it is usually suitable to make the use rate of the oxidizing agent on the order of 0.5 to 3 mols per mol of the compound of the above formula (I-b).

Thus, a compound of the above formula (I-c) aimed at by this invention is formed.

It is possible in this invention to prepare a desired compound of the formula (I-c) wherein m is 1 and/or 2, by appropriately select the amount of the oxidizing agent to be used and reaction conditions.

The resultant compound of the formula (I-c) can,

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if desired, be converted to another compound aimed at by this invention by subjecting it to the reaction of the above (iv).

The conversion of the hydrogen atom at the 1-position to the group $-S-R^5$ in the above reaction of (iv) can be performed in the same manner as in the reaction of the compound of the formula (II) with the compound of the formula (III) in the above process (a).

According to the above-mentioned process (c), a compound of the above formula (I-d) of this invention wherein the 7-position is substituted with an aralkyl group can be prepared by subjecting a compound of the above formula (IV) to either the reaction of (v) or the reaction of (vi).

The introduction of an aralkyl group into the 7-position in the above reaction of (v) can be performed by first introducing a double bond between the 6- and 7-positions of the compound of the above formula (IV), and then aralkylating the resultant compound.

The introduction of a double bond between the 6- and 7-positions can, usually, be performed by dehydrogenating the compound of the above formula (IV) in t-butanol or xylene under reflux, using 2,3,5,6-tetrachloro-1,4-benzoquinone (chloranil). The succeeding aralkylation can readily be performed, for example by treating the resultant compound with an aralkylmagnesium halide, e.g., benzylmagnesium chloride, in an inert solvent such as tetrahydrofuran, dioxane or diethyl ether, in the presence of cuprous chloride.

When a compound of the formula (IV) wherein X denotes C=O is used as a starting material in this reaction, it is preferable either to previously protect the oxo group at the 17- or 17a-position with an ethylenedioxy group, etc. in the aralkylation, or to first convert the oxo group to a hydroxyl group by reduction with lithium tri-tert-butoxyaluminohydride,

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etc. in an inert solvent such as tetrahydrofuran, protect the resultant hydroxy compound with an acetyl group, a methoxymethyl group, a tetrahydropyranyl group, t-butyldimethylsilyl group, etc., and then perform the aralkylation. In the above case, after the introduction of the aralkyl group, the 17- or 17a-position is restored to an oxo group by removing the protective group or by removing the protective group and then performing oxidation with Jones reagent.

In the above reaction of (vi), the reaction to introduce an aralkyl group at the 7-position and introduce a double bond between the 6- and 7-positions can be performed by first subjecting a compound of the above formula (IV) to a reaction to protect the oxo group and an isomerization reaction, subjecting the resultant compound to oxidation reaction to introduce an oxo group at the 7-position and then subjecting the resultant compound to aralkylation reaction. In this occasion, after introduction of the aralkyl group, the protective group of the oxo group is eliminated, for example by treating the aralkylated compound with sulfuric acid in dioxane.

Thereby, a compound of the above formula (I-d) aimed at by this invention is formed.

The resultant compound of the above formula (I-d) can, if desired, be converted to another compound aimed at by this invention by subjecting it to the reaction of (vii) or (viii).

The introduction of a double bond between the 1- and 2-positions in the reaction of the above (vii) can, usually, be performed by dehydrogenating the compound of the formula (I-d) in dioxane or benzene under reflux, using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).

The conversion of the hydrogen atom at the 1-position to the group $-S-R^5$ in the reaction of the above (viii) can be performed in the same manner as in

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the reaction of the compound of the formula (II) with the compound of the formula (III) in the above method (a).

A compound of the formula (I) of this invention wherein X denotes CH_2 can also be prepared by reducing a compound of the formula (I) wherein X denotes C=O with lithium tri-tert-butoxyaluminohydride, diisobutylaluminum hydride, etc. in an inert solvent such as tetrahydrofuran, dioxane or toluene to convert the group X to a hydroxyl group, and further reducing the resultant hydroxy compound with triethylsilane and boron trifluoride-diethyl ether complex in methylene chloride.

Compounds of the above formula (I) prepared according to the processes of this invention can be isolated and purified from the reaction mixtures according to methods known per se, for example by methods such as recrystallization, distillation, column chromatography and/or thin layer chromatography.

Effect of Invention

The above-descrived 7-substituted oxa- or azasteroid compounds of this invention represented by the formula (I) have an excellent aromatase-inhibiting action, and effective for treatment of diseases caused by estrogens, for example, breast cancer, uterine cancer, ovarian cancer, endometriosis, male gynecomastia, prostatic hypertrophy, male infertility related to oligospermia, etc.

The results of in vitro and in vivo tests on an aromatase-inhibiting action of compounds of the formula (I) of this invention are set forth below.

(1) Assay of aromatase-inhibiting action (in vitro)

Human placental microsome (centrifuged at

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105,000 X g for 60 minutes) was prepared, according to the method of Ryan (The Journal of Biological Chemistry, 234, 268-272, (1959)). The microsome was used after it was washed twice with 0.5mM dithiothreitol solution, freeze dried, and stored at -20℃ .

The aromatase-inhibiting action was assayed according to the method developed by Tompson and Siiteri (Journal of Steroid Biological Chemistry, 249, 5373-5378, (1974)). Namely, the method comprises quantitatively determine $^{3}H_2O$ released through aromatization of [1,2-^{3}H]androstenedione. The experiment using the enzyme was performed in 67mM phosphate buffer (pH 7.5) so that the final amount of the incubation solution could be 0.5ml. The incubation solution contained 180μM of NADPH, 2μM of [1,2-^{3}H]androstenedione, 150μg of freeze dried human placental microsome, 25μl of methanol and a test compound in various concentrations. Incubation was performed in the air at 37℃ for 20 minutes, the reaction was ceased with addition of 3ml of chloroform, and the mixture was stirred for 40 seconds. The mixture was centrifuged at 700 X g for 10 minutes, 0.3ml of the aqueous solution was taken from the supernatant, the scintillation mixture was added, and the amount of $^{3}H_2O$ formed was measured.

The results are shown in the following Table 1.

Table 1

Compound	IC_{50} (μM)
Example 1	2.3
Example 8	0.4
Example 16	0.5

(2) Assay of aromatase-inhibiting action (in vivo)

Aromatase-inhibiting action was assayed ac-

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cording to the method developed by G.H. Deckers and A.H.W.M. Schuurs (Journal of Steroid Biochemistry, 32, 625-631, (1989)).

Namely, groups of mature female rats at one week after enucleation of the pituitary gland were used, each group consisting of 8 to 10 animals. 16mg/kg of dehydroepiandrosterone sulfate (DHEAS) and 5ml/kg of a solvent (physiological saline containing 2% polysorbate 80), or DHEAS and 2mg/kg of a test compound suspended in the solvent were orally administered to each rat once a day for the succeeding 4 days. For 6 days starting from the next day of the first administration, vaginal smear was sampled and observed by a microscope after being stained with Giemsa staining solution. Cornification of the vaginal smear with DHEAS was observed from 3 days after the first administration, and its action disappeared 6 days thereafter. Therefore, the cornification smear number was assumed to be the total of 3 days from the third day to fifth day after the initiation of administration. A cornification- inhibiting action with a test compound was expressed as the rate against cornification in the solvent administration group.

In this connection, the cornification of vaginal smear is caused by estrogens biosynthesized from DHEAS by aromatase, and therefore, when aromatase is inhibited, inhibition of cornification is observed.

The results are shown in the following Table 2.

Table 2

Compound	Inhibition rate (%)
Example 8	68.2± 13.6
Example 16	70.6± 15.6
Example 43	70.6± 15.6

Thus, the compounds of this invention represented by the formula (I) can orally administered or

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parenterally administered (e.g., intramuscularly injected, intravenouly injected, rectally administered, percutaneously administered, etc.) as an agent for inhibiting biosynthesis of estrogens, for treatment of human beings or other mammals.

The compounds of this invention, when used as pharmaceuticals, can be formulated, together with pharmaceutically acceptable nontoxic additives, into any of dosage forms of solid forms (e.g., tablets, hard gelatin capsules, soft capsules, granules, powders, fine granules, pills, troches, etc.), semisolid forms (e.g., suppositories, ointments, etc.) and liquid forms (e.g., injections, emulsions, suspensions, lotions, sprays, etc.), in accordance with their uses.

Nontoxic additives usable for the above preparations include, for example, starches, gelatin, glucose, lactose, fructose, maltose, magnesium carbonate, talc, magnesium stearate, methylcellulose, carboxymethylcellulose or its salts, gum arabic, polyethylene glycol, p-hydroxybenzoic acid alkyl esters, syrups, ethanol, propylene glycol, Vaselines, Carbowaxes, glycerol, sodium chloride, sodium sulfite, sodium phosphate, citric acid, etc. The pharmaceuticals can also contain another therapeutically useful pharmaceutical. The contents of the compounds of this invention in the pharmaceuticals vary depending on their dosage forms, etc., but, generally, it is desirable to contain the compounds of this invention at concentrations of 0.1 to 50 weight% in the case of solid and semisolid forms, and at concentrations of 0.05 to 10 weight% in the case of liquid forms.

The doses of the compounds of this invention can be widely varied in accordance with the kind of mammals including human beings as subjects, administration routes, the seriousness of symptoms, diagnoses of doctors, etc., but, generally, the doses can be within

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the range of 0.1 to 100mg/kg, preferably 1 to 50mg/kg. However, it is of course possible to administer an amount smaller than the lower limit of the above range or an amount larger than the upper limit in accordance with the seriousness of the symptoms of patients, diagnoses of doctors, etc. The above doses can be administered once a day or several times in divisions per day.

Example

This invention is further specifically described below by examples and preparation examples.

Example 1

To a mixture of 100mg of D-homo-17-oxaandrosta-4,6-diene-3,17a-dione, 0.15ml of 4-aminothiophenol and 1.5ml of dioxane was added 5mg of sodium metal, and the mixture was stirred in an atmosphere of nitrogen at room temperature for 5 days. Water was added to the reaction mixture, and the product was extracted with ethyl acetate. The extract was washed with saturated saline, and dried over anhydrous magnesium sulfate. The solvent was distilled off, and the resultant crude product was purified by TLC [developing solvent, chloroform : acetone (19 : 1)] to give 42mg of 7α-[(4-aminophenyl)thio]-D-homo-17-oxaandrost-4-ene-3,17a-dione.

^{1}H-NMR ($CDCl_3$, δ) : 1.20 (3H, s), 1.26 (3H, s), 3.43 (1H, m), 4.0~4.7 (2H, m), 5.67 (1H, s), 6.8~7.5 (4H, m)

MS (m/z) : 425 (M^+), 409

Example 2

0.13ml of Jones reagent was added dropwise at 0℃ to a mixture of 100mg of 7α-benzyl-17aξ-hydroxy-D-homo-17-oxaandrost-4-en-3-one and 8.5ml of acetone, and the mixture was stirred for 10 minutes. Water was added

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to the reaction mixture, and the product was extracted with ethyl acetate. The extract was washed with aqueous 5% sodium bicarbonate solution and saturated saline, and dried over anhydrous magnesium sulfate. The solvent was distilled off, and the resultant crude product was purified by TLC [developing solvent, chloroform : acetone (19 : 1)] to give 48mg of α-benzyl-D-homo-17-oxaandrost-4-ene-3,17a-dione.

^{1}H-NMR ($CDCl_3$, δ) : 1.22 (3H, s), 1.30 (3H, s), 4.0~4.7 (2H, m), 5.72 (1H, s), 6.9~7.5 (5H, m)

MS (m/z) : 392 (M^+), 377, 301

Example 3

A mixture of 50mg of D-homo-17-oxaandrosta-4,6-dien-3-one and 0.2ml of thioacetic acid was refluxed for 3 hours. The solvent was distilled off, and the resultant crude product was purified by TLC [developing solvent, hexane : ethyl acetate (2 : 1)] to give 62mg of 7α-(acetylthio)-D-homo-17-oxaandrost-4-en-3-one.

^{1}H-NMR ($CDCl_3$, δ) : 1.03 (3H, s), 1.21 (3H, s), 2.33 (3H, s), 3.00, 3.39 (2H, ABq, J=11Hz), 3.33 (1H, m), 4.00 (2H, m), 5.71 (1H, d, J=2Hz)

MS (m/z) : 362 (M^+), 320, 305, 287

Example 4

The same operation as in Example 1 was made using benzylmercaptan in place of 4-aminothiophenol, 1N sulfuric acid was added to the resultant reaction mixture, and the mixture was stirred overnight at room temperature. The product was extracted with ethyl ace-

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tate, and the extract was washed with saturated saline and dried over anhydrous sodium sulfate. The solvent was distilled off, and the resultant crude product was purified by TLC [developing solvent, chloroform : acetone (39 : 1)] to give 7α-(benzylthio)-D-homo-17-oxaandrost-4-ene-3,17a-dione.

^{1}H-NMR ($CDCl_3$, δ) : 1.16 (3H, s), 1.17 (3H, s), 2.83 (1H, m), 3.55, 3.70 (2H, ABq, J=14Hz), 3.8~4.5 (2H, m), 5.78 (1H, br s), 7.1~7.4 (5H, m)

MS (m/z) : 424 (M^+), 409, 333, 302, 287

Example 5

To a mixture of 68mg of D-homo-17-oxaandrosta-4,6-dien-3-one, 150mg of 4-aminothiophenol and 2.5ml of dioxane was added 15mg of potassium metal, and the mixture was subjected to supersonic wave at room temperature for one hour in an atmosphere of nitrogen. Potassium metal was removed, water was added to the reaction mixture, and the product was extracted with ethyl acetate. The extract was washed with saturated saline, and dried over anhydrous magnesium sulfate. The solvent was distilled off, and the resultant crude product was purified by TLC [developing solvent, benzene : ethyl acetate (4 : 1)] to give 32mg of 7α-[(4-aminophenyl)thio]-D-homo-17-oxaandrost-4-en-3-one.

^{1}H-NMR ($CDCl_3$, δ) : 1.04 (3H, s), 1.20 (3H, s), 3.05 (1H, d, J=11Hz), 3.2~3.6 (3H, m), 4.05 (1H, m), 5.62 (1H, s), 7.0~7.4 (4H, m)

MS (m/z) : 411 (M^+), 395, 393

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Example 6

A mixture of 6ml of 2.0M benzylmagnesium chloride tetrahydrofuran solution, 400mg of cuprous chloride and 15ml of tetrahydrofuran was stirred at 0℃ for 10 minutes in an atmosphere of nitrogen. To this mixture was added a mixture of 38mg of D-homo-17-oxaandrosta-4,6-dien-3-one, 5mg of cuprous chloride and 2.5ml of tetrahydrofuran, and the mixture was stirred at room temperature for one hour. Diethyl ether, water and 5% hydrochloric acid were added to the reaction mixture, and the organic layer was washed with aqueous 5% sodium bicarbonate solution and saturated saline and dried over anhydrous sodium sulfate. The solvent was distilled off, and the resultant crude product was purified by TLC [developing solvent, chloroform : acetone (19 : 1)] to give 28mg of 7α-benzyl-D-homo-17-oxaandrost-4-en-3-one.

^{1}H-NMR ($CDCl_3$, δ) : 1.07 (3H, s), 1.22 (3H, s), 3.05, 3.44 (2H, ABq, J=11Hz), 3.42 (1H, m), 4.11 (1H, m), 5.72 (1H, s), 6.9~7.5 (5H, m)

Example 7

The same operations as in Example 3 were made using 50mg of D-homo-17-oxaandrosta-1,4,6-trien-3-one in place of D-homo-17-oxaandrosta-4,6-dien-3-one, and the resultant crude product was purified by TLC [developing solvent, hexane : ethyl acetate (1 : 1)] to give 38mg of 7α-(acetylthio)-D-homo-17-oxaandrosta-1,4-dien-3-one as the more polar product.

^{1}H-NMR ($CDCl_3$, δ) : 1.06 (3H, s), 1.26 (3H, s), 2.32 (3H, s), 2.92 (1H, m), 2.99, 3.39 (2H, ABq, J=11Hz), 3.30 (1H, m),

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4.05 (2H, m), 6.03 (1H, br t, J=2Hz), 6.27 (1H, dd, J=2, 10Hz), 7.00 (1H, d, J=10Hz).

MS (m/z) : 361 (MH^+), 318, 284

Further, 12mg of 1α,7α-bis(acetylthio)-D-homo-17-oxaandrost-4-en-3-one was obtained as the less polar product.

^{1}H-NMR ($CDCl_3$, δ) : 1.02 (3H, s), 1.41 (3H, s), 2.3~3.6 (7H, m), 2.36 (3H, s), 2.37 (3H, s), 3.9~4.2 (3H, m), 5.72 (1H, br s)

MS (m/z) : 393 (M^+-COCH_3), 361, 360, 318

Further, 15mg of 1α-(acetylthio)-D-homo-17-oxaandrosta-4,6-dien-3-one was obtained as the further less polar product.

^{1}H-NMR ($CDCl_3$, δ) : 1.06 (3H, s), 1.30 (3H, s), 2.32 (3H, s), 2.3~3.6 (5H, m), 3.9~4.3 (2H, m), 5.72 (1H, br s), 6.20 (2H, br s)

Example 8

A mixture of 42mg of 1α,7α-bis(acetylthio)-D-homo-17-oxaandrost-4-en-3-one, 0.5ml of 28% sodium methylate methanol solution and 3ml of methanol was stirred at room temperature for 40 minutes in an atmosphere of nitrogen. Acetic acid was added to the reaction mixture, the solvent was distilled off, chloroform

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was added to the residue, and the insoluble matter was filtered off under a stream of nitrogen. The filtrate was concentrated, and the resultant crude product was purified by TLC [developing solvent, hexane : ethyl acetate (1 : 1)] to give 24mg of 7α-mercapto-D-homo-17-oxaandrosta-1,4-dien-3-one.

Melting point: 225-229℃ (dichloromethane-ethyl acetate)

^{1}H-NMR ($CDCl_3$, δ) : 1.07 (3H, s), 1.24 (3H, s), 2.50 (1H, dd, J=2, 13Hz), 3.02, 3.40 (2H, ABq, J=11Hz), 3.03 (1H, m), 3.40 (2H, m), 4.05 (1H, m), 6.13 (1H, brt, J=2Hz), 6.29 (1H, dd, J=2, 10Hz), 7.03 (1H, d, J=10Hz)

MS (m/z) : 318 (M^+), 284

Elementary analysis:

Calculated for $C_{19}H_{26}O_2S$: C,71.66; H,8.23

Found : C,71.87; H,8.39

Example 9

The same operations as in Example 5 were made using 136mg of D-homo-17-oxaandrosta-1,4,6-trien-3-one in place of D-homo-17-oxaandrosta-4,6-dien-3-one, and the resultant crude product was purified by TLC [developing solvent, benzene : ethyl acetate (1 : 1)] to give 68mg of 1α,7α-bis[(4-aminophenyl)thio]-D-homo-17-oxaandrost-4-en-3-one as the more polar product.

^{1}H-NMR ($CDCl_3$, δ) : 1.05 (3H, s), 1.32 (3H, s), 3.10 (1H, d, J=11Hz), 3.2~4.3 (7H, m), 5.74 (1H, s), 6.5~7.4 (8H, m)

Further, a mixture of 7α-[(4-aminophenyl)-

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thio]-D-homo-17-oxaandrosta-1,4-dien-3-one and 1α-[(4-aminophenyl)thio]-D-homo-17-oxaandrosta-4,6-dien-3-one was obtained from the less polar part. This mixture was purified by TLC [developing solvent, chloroform : acetone (9 : 1)] to give 5mg of 7α-[(4-aminophenyl)thio]-D-homo-17-oxaandrosta-1,4-dien-3-one as the more polar product.

^{1}H-NMR ($CDCl_3$, δ) : 1.06 (3H, s), 1.23 (3H, s), 3.04, 3.40 (2H, ABq, J=11Hz), 3.2~4.2 (3H, m), 6.05 (1H, br s), 6.29 (1H, dd, J=2, 10Hz), 7.03 (1H, d, J=10Hz), 6.4~7.3 (4H, m)

MS (m/z) : 409 (M^+), 285

Further, 9mg of 1α-[(4-aminophenyl)thio]-D-homo-17-oxaandrosta-4,6-dien-3-one was obtained as the less polar product.

^{1}H-NMR ($CDCl_3$, δ) : 1.10 (3H, s), 1.25 (3H, s), 3.08, 3.44 (2H, ABq, J=11Hz), 3.2~4.3 (3H, m), 5.76 (1H, s), 6.20 (2H, s), 6.4~7.4 (4H, m)

MS (m/z) : 409 (M^+), 285, 284, 248

Example 10

A mixture of 715mg of 7ξ-benzyl-3,3:17a,17a-bis(ethylenedioxy)-D-homo-17-oxaandrost-5-en-7ξ-ol, 1.8ml of 5% sulfuric acid and 11ml of dioxane was stirred at room temperature for 3 hours. Water and aqueous 5% sodium bicarbonate solution were added to the reaction mixture, and the product was extracted with ethyl acetate. The extract was washed

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with saturated saline, and dried over anhydrous magnesium sulfate. The solvent was distilled off, and the resultant crude product was purified by TLC [developing solvent, chloroform : acetone (9 : 1)] to give 140mg of 7-benzyl-D-homo-17-oxaandrosta-4,6-diene-3,17a-dione.

^{1}H-NMR ($CDCl_3$, δ) : 1.03 (3H, s), 1.28 (3H, s), 3.66 (2H, s), 3.8~4.6 (2H, m), 5.63 (1H, s), 6.06 (1H, br s), 7.0~7.5 (5H, m)

MS (m/z) : 390 (M^+), 299

Example 11

A mixture of 30mg of 7-benzyl-17aξ-hydroxy-D-homo-17-oxaandrosta-4,6-dien-3-one, 0.03ml of triethylsilane, 0.02ml of boron trifluoride-diethyl ether complex and 0.8ml of methylene chloride was stirred at 0℃ for 2 minutes under a stream of nitrogen. Aqueous 5% sodium bicarbonate solution was added to the reaction mixture, and the mixture was stirred at room temperature for 10 minutes. The product was extracted with ethyl acetate, and the extract was washed with saturated saline and dried over anhydrous magnesium sulfate. The solvent was distilled off, and the resultant crude product was purified by TLC [developing solvent, chloroform : acetone (19 : 1)] to give 10mg of 7-benzyl-D-homo-17-oxaandrosta-4,6-dien-3-one.

^{1}H-NMR ($CDCl_3$, δ) : 0.95 (3H, s), 1.07 (3H, s), 3.02, 3.41 (2H, ABq, J=11Hz), 3.30 (1H, m), 3.59 (2H, s), 4.02 (1H, m), 5.59 (1H, s), 5.99 (1H, br s), 7.0~7.5 (5H, m)

MS (m/z) : 376 (M^+), 285

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Example 12

To a mixture of 6mg of 7α-mercapto-D-homo-17-oxaandrosta-1,4-dien-3-one, 4μl of 28% sodium methylate methanol solution and 0.3ml of dimethylformamide was added 4μl of methyl iodide, and the mixture was stirred at room temperature for 5 minutes in an atmosphere of nitrogen. Water was added to the reaction mixture, and the product was extracted with ethyl acetate. The extract was washed with saturated saline, and dried over anhydrous magnesium sulfate. The solvent was distilled off, and the resultant crude product was purified by TLC [developing solvent, chloroform : acetone (100 : 1)] to give 5mg of 7α-(methylthio)-D-homo-17-oxaandrosta-1,4-dien-3-one.

^{1}H-NMR ($CDCl_3$, δ) : 1.05 (3H, s), 1.25 (3H, s), 2.01 (3H, s), 2.4~2.9 (2H, m), 3.00, 3.39 (2H, ABq, J=11Hz), 3.06 (1H, m), 3.40 (1H, m), 4.05 (1H, m,), 6.11 (1H, br s), 6.27 (1H, dd, J=2, 10Hz), 7.01 (1H, d, J=10Hz)

MS (m/z) : 332 (M^+), 284

Example 13

The same operations as in Example 3 were made using 100mg of D-homo-17-oxaandrosta-4,6-diene-3,17a-dione in place of D-homo-17-oxaandrosta-4,6-dien-3-one, and the resultant crude product was purified by TLC [developing solvent, chloroform : acetone (39 : 1)] to give 71mg of 7α-(acetylthio)-D-homo-17-oxaandrost-4-ene-3,17a-dione.

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^{1}H-NMR ($CDCl_3$, δ) : 1.22 (3H, s), 1.26 (3H, s), 2.35 (3H, s), 2.83 (1H, m), 4.0~4.6 (3H, m), 5.73 (1H, d, J=2Hz)

MS (m/z) : 376 (M^+), 334, 319, 301, 285

Example 14

A mixture of 33mg of 7α-(acetylthio)-D-homo-17-oxaandrost-4-ene-3,17a-dione, 1ml of 1.4N aqueous sodium hydroxide solution and 1ml of tetrahydrofuran was stirred at 0℃ for 25 minutes. 10% hydrochloric acid was added to the reaction mixture, and the mixture was stirred for one hour. The product was extracted with ethyl acetate, and the extract was washed with saturated saline and dried over anhydrous sodium sulfate. The solvent was distilled off, and the resultant crude crystals were recrystallized from acetone to give 27mg of 7α-mercapto-D-homo-17-oxaandrost-4-ene-3,17a-dione.

^{1}H-NMR ($CDCl_3$, δ) : 1.20 (3H, s), 1.27 (3H, s), 2.93 (1H, m), 3.40 (1H, m), 4.1~4.7 (2H, m), 5.81 (1H, d, J=2Hz)

MS (m/z) : 334 (M^+), 319, 301, 285

Example 15

The same operations as in Example 3 were made using 20mg of D-homo-17-oxaandrosta-1,4,6-triene-3,17a-dione in place of D-homo-17-oxaandrosta-4,6-dien-3-one, and the resultant crude product was purified by TLC [developing solvent, chloroform : acetone (50 : 1)] and then by TLC [developing solvent, benzene : ethylacetate (3 : 1)] to give 7mg of 7α-(acetylthio)-D-homo-17-oxaandrosta-1,4-diene-3,17a-dione.

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^{1}H-NMR ($CDCl_3$, δ) : 1.26 (3H, s), 1.29 (3H, s), 2.35 (3H, s), 2.93 (1H, m), 4.0~4.6 (3H, m), 6.05 (1H, br t, J=2Hz), 6.29 (1H, dd, J=2, 10Hz), 7.01 (1H, d, J=10Hz)

MS (m/z) : 374 (M^+), 359, 332, 298, 283.

Example 16

The same operations as in Example 14 were made using 5mg of 7α-(acetylthio)-D-homo-17-oxaandrosta-1,4-diene-3,17a-dione in place of 7α-(acetylthio)-D-homo-17-oxaandrost-4-ene-3,17a-dione, and the resultant crude product was purified by TLC [developing solvent, benzene : ethyl acetate (3 : 1)] to give 1mg of 7α-mercapto-D-homo-17-oxaandrosta-1,4-diene-3,17a-dione.

^{1}H-NMR ($CDCl_3$, δ) : 1.24 (3H, s), 1.30 (3H, s), 2.54 (1H, dd, J=2, 14Hz), 3.04 (1H, m), 3.43 (1H, m), 4.0~4.6 (2H, m), 6.15 (1H, br t, J=2Hz), 6.30 (1H, dd, J=2, 10Hz), 7.03 (1H, d, J=10Hz)

MS (m/z) : 332 (M^+), 317, 298, 283

Example 17

A mixture of 8mg of 7α-mercapto-D-homo-17-oxaandrost-4-ene-3,17a-dione, 0.04ml of pyridine, 0.02ml of benzoyl chloride and 0.2ml of methylene chloride was stirred under ice cooling for 60 minutes. Water and aqueous 5% hydrochloric acid solution were added to the reaction mixture, and the product was extracted with ethyl acetate. The extract was washed with water and

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dried over anhydrous magnesium sulfate. The solvent was distilled off, and the resultant crude product was purified by TLC [developing solvent, benzene : ethyl acetate (3 : 1)] to give 8mg of 7α-(benzoylthio)-D-homo-17-oxaandrost-4-ene-3,17a-dione.

^{1}H-NMR ($CDCl_3$, δ) : 1.26 (3H, s), 1.28 (3H, s), 2.9 (1H, m), 3.9~4.6 (3H, m), 5.73 (1H, d, J=2Hz), 7.3~8.2 (5H, m)

Example 18

To a mixture of 50mg of D-homo-17-oxaandrosta-1,4,6-trien-3-one, 0.05ml of 28% sodium methylate methanol solution and 2ml of dioxane was added 0.1ml of thiophenol, and the mixture was stirred at room temperature for 5 minutes in an atmosphere of nitrogen. Water was added to the reaction mixture, and the product was extracted with ethyl acetate. The extract was washed with saturated saline and dried over anhydrous magnesium sulfate. The solvent was distilled off, and the resultant crude product was purified by TLC [developing solvent, benzene : ethyl acetate (4 : 1)] to give 8mg of 7α-(phenylthio)-D-homo-17-oxaandrosta-1,4-dien-3-one as the more polar product.

^{1}H-NMR ($CDCl_3$, δ) : 1.07 (3H, s), 1.24 (3H, s), 2.2~2.9 (2H, m), 3.03 (1H, d, J=11Hz), 3.2~3.7 (3H, m), 4.00 (1H, m), 6.00 (1H, br s), 6.29 (1H, dd, J=2, 10Hz), 7.04 (1H, d, J=10Hz), 7.2~7.5 (5H, m)

MS (m/z) : 394 (M^+), 284

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Further, 80mg of 1α,7α-bis(phenylthio)-D-homo-17-oxaandrost-4-en-3-one was obtained as the less polar product.

^{1}H-NMR (CDCl$_3$, δ) : 1.06 (3H, s), 1.37 (3H, s), 2.4~2.8 (4H, m), 3.07 (1H, d, J=11Hz), 3.2~3.7 (4H, m), 4.01 (1H, m), 5.71 (1H, br s), 7.1~7.6 (10H, m)

MS (m/z) : 504 (M^+), 394, 284

Example 19

The same operations as in Example 18 were made using ethanethiol in place of thiophenol and a dioxane-dimethylformamide mixed solvent in place of dioxane, and the resultant crude product was purified by TLC [developing solvent, hexane : ethyl acetate (1 : 1)] to give 12mg of 1α-(ethylthio)-D-homo-17-oxaandrosta-4,6-dien-3-one as the less polar product.

^{1}H-NMR (CDCl$_3$, δ) : 1.08 (3H, s), 1.23 (3H, t, J=7Hz), 1.26 (3H, s), 2.3~3.6 (8H, m), 4.07 (1H, m), 5.72 (1H, s), 6.17 (2H, s)

Further, the more polar part was purified by TLC [developing solvent, chloroform : acetone (19 : 1)] to give 30mg of 1α,7α-bis(ethylthio)-D-homo-17-oxaandrost-4-en-3-one as the less polar product.

^{1}H-NMR (CDCl$_3$, δ) : 1.03 (3H, s), 1.23 (6H, t, J=7Hz), 1.35 (3H, s), 2.2~3.7 (13H, m), 4.03 (1H, m), 5.79 (1H, s)

MS (m/z) : 408 (M^+), 379, 346, 320, 284

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Further, 19mg of 7α-(ethylthio)-D-homo-17-oxaandrosta-1,4-dien-3-one was obtained as the more polar product.

^{1}H-NMR ($CDCl_3$, δ) : 1.05 (3H, s), 1.22 (3H, t, J=7Hz), 1.24 (3H, s), 2.3~3.6 (8H, m), 4.02 (1H, m), 6.10 (1H, br s), 6.26 (1H, dd, J=2, 10Hz), 7.01 (1H, d, J=10Hz)

MS (m/z) : 346 (M^+), 284

Example 20

The same operations as in Example 19 were made using 2-aminoethanethiol in place of ethanethiol, and the resultant crude product was purified by TLC [developing solvent, chloroform : methanol (9 : 1)] to give 10mg of 7α-[(2-aminoethyl)thio]-D-homo-17-oxaandrosta-1,4-dien-3-one.

^{1}H-NMR ($CDCl_3$, δ) : 1.05 (3H, s), 1.24 (3H, s), 2.4~3.6 (12H, m), 4.00 (1H, m), 6.15 (1H, br s), 6.27 (1H, dd, J=2, 10Hz), 7.02 (1H, d, J=10Hz)

Example 21

The same operations as in Example 18 were made using methyl thioglycolate in place of thiophenol and dimethylformamide in place of dioxane, and the resultant crude product was purified by TLC [developing solvent, hexane : ethyl acetate (1 : 1)] and then TLC [developing solvent, chloroform : acetone (19 : 1)] to give 7α-(methoxycarbonylmethylthio)-D-homo-17-oxaandrosta-1,4-dien-3-one.

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^{1}H-NMR ($CDCl_3$, δ) : 1.05 (3H, s), 1.25 (3H, s), 2.6~2.8 (2H, m), 3.00 (1H, d, J=11Hz), 3.16 (2H, d, J=1Hz), 3.2~3.6 (3H, m), 3.71 (3H, s), 4.01 (1H, m), 6.08 (1H, br s), 6.27 (1H, dd, J=2, 10Hz), 7.00 (1H, d, J=10Hz)

MS (m/z) : 390 (M^+), 331, 284

Example 22

A mixture of 50mg of D-homo-17-oxaandrosta-1,4,6-trien-3-one and 1ml of thiobenzoic acid was heated to 60℃ in an atmosphere of nitrogen. Water was added to the reaction mixture, and the product was extracted with ethyl acetate. The extract was washed with aqueous 5% sodium bicarbonate solution and saturated saline, and dried over anhydrous magnesium sulfate. The solvent was distilled off, and the resultant crude product was purified by TLC [developing solvent, hexane : ethyl acetate (2 : 1)] to give 95mg of 1α,7α-bis(benzoylthio)-D-homo-17-oxaandrost-4-en-3-one as the more polar product.

^{1}H-NMR ($CDCl_3$, δ) : 1.04 (3H, s), 1.51 (3H, s), 2.5~3.5 (7H, m), 3.8~4.5 (3H, m), 5.77 (1H, s), 7.3~8.1 (10H, m)

MS (m/z) : 422 ($M^+-C_6H_5COSH$), 284

Further, 4mg of 1α-(benzoylthio)-D-homo-17-oxaandrosta-4,6-dien-3-one was obtained as the less polar product.

^{1}H-NMR ($CDCl_3$, δ) : 1.06 (3H, s), 1.36 (3H, s), 2.5~3.6 (5H, m), 3.9~4.4 (2H, m),

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5.77 (1H, s), 6.24 (2H, s), 7.3~8.0 (5H, m)

MS (m/z) : 422 (M^+), 284

Example 23

A mixture of 50mg of 7α-mercapto-D-homo-17-oxaandrosta-1,4-dien-3-one, 0.4ml of pyridine and 0.2ml of benzoyl chloride was stirred overnight at room temperature. Water and aqueous 5% hydrochloric acid solution were added to the reaction mixture, and the product was extracted with ethyl acetate. The extract was washed with water, and dried over anhydrous magnesium sulfate. The solvent was distilled off, and the resultant crude product was purified by TLC [developing solvent, hexane : ethyl acetate (1 : 1)] to give 57mg of 7α-(benzoylthio)-D-homo-17-oxaandrosta-1,4-dien-3-one.

^{1}H-NMR ($CDCl_3$, δ) : 1.08 (3H, s), 1.30 (3H, s), 2.55 (1H, dd, J=3, 14Hz), 2.8~3.5 (4H, m), 3.94 (1H, m), 4.34 (1H, m), 6.04 (1H, br s), 6.30 (1H, dd, J=2, 10Hz), 7.04 (1H, d, J=10Hz), 7.3~8.2 (5H, m)

MS (m/z) : 422 (M^+), 284

Example 24

A mixture of 10mg of 7α-(methylthio)-D-homo-17-oxaandrosta-1,4-dien-3-one, 5mg of m-chloroperbenzoic acid and 0.6ml of benzene was stirred at 10℃ for 10 minutes. Water was added to the reaction mixture, and the product was extracted with ethyl acetate. The extract was washed with aqueous 5% sodium bicarbonate solution and saturated saline, and dried over anhydrous sodium sulfate. The solvent was distilled off, and the resultant crude product was purified by TLC [developing solvent, chloroform : methanol (15 : 1)] to give 3mg of 7α-(methylsulfinyl)-D-homo-17-oxaandrosta-1,4-dien-3-one

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as the more polar product.

^{1}H-NMR ($CDCl_3$, δ) : 1.05 (3H, s), 1.30 (3H, s), 2.66 (3H, s), 2.4~3.7 (6H, m), 3.97 (1H, m), 5.94 (1H, br s), 6.29 (1H, dd, J=2, 10Hz), 7.10 (1H, d, J=10Hz)

MS (m/z) : 348 (M^+), 285

Further, 1mg of 7α-(methylsulfonyl)-D-homo-17-oxaandrosta-1,4-dien-3-one was obtained as the less polar product.

^{1}H-NMR ($CDCl_3$, δ) : 1.05 (3H, s), 1.26 (3H, s), 2.89 (3H, s), 2.7~3.8 (5H, m), 4.03 (1H, m), 6.17 (1H, br s), 6.29 (1H, dd, J=2, 10Hz), 7.07 (1H, d, J=10Hz)

MS (m/z) : 364 (M^+), 284

Example 25

A mixture of 10mg of 7α-(methylthio)-D-homo-17-oxaandrosta-1,4-dien-3-one and 0.2ml of thioacetic acid was stirred at room temperature for one hour in an atmosphere of nitrogen. Water was added to the reaction mixture, and the product was extracted with ethyl acetate. The extract was washed with aqueous 5% sodium bicarbonate solution and saturated saline, and dried over anhydrous magnesium sulfate. The solvent was distilled off, and the resultant crude product was purified by TLC [developing solvent, chloroform : acetone (19 : 1)] to give 12mg of 1α-(acetylthio)-7α-(methylthio)-D-homo-17-oxaandrost-4-en-3-one.

^{1}H-NMR ($CDCl_3$, δ) : 1.01 (3H, s), 1.40 (3H, s), 2.05 (3H, s), 2.34 (3H, s), 2.4~3.6

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(8H, m), 3.9～4.2 (2H, m), 5.80 (1H, br s)

MS (m/z) : 408 (M^+), 284

Example 26

A mixture of 15mg of 7α-mercapto-D-homo-17-oxaandrost-4-ene-3,17a-dione, 0.75ml of pyridine and 0.05ml of propionic anhydride was stirred overnight under N_2 at room temperature. Water and aqueous 5% hydrochloric acid solution were added to the reaction mixture, and the product was extracted with ethyl acetate. The extract was washed with aqueous 5% sodium bicarbonate solution and saturated saline, and dried over anhydrous sodium sulfate. The solvent was distilled off, and the resultant crude product was purified by TLC [developing solvent, hexane : ethyl acetate (1 : 1)] to give 3mg of 7α-(propionylthio)-D-homo-17-oxaandrost-4-ene-3,17a-dione.

^{1}H-NMR ($CDCl_3$, δ) : 1.17 (3H, t, J=7.5Hz), 1.22 (3H, s), 1.26 (3H, s), 2.58 (2H, q, J=7.5Hz), 2.9 (1H, m), 4.0～4.6 (3H, m), 5.72 (1H, d, J=2Hz)

MS (m/z) : 390 (M^+), 357, 334

Example 27

The same operations as in Example 26 were made using dimethylcarbamoyl chloride in place of propionic anhydride to give 17mg of 7α-(N,N-dimethylcarbamoylthio)-D-homo-17-oxaandrost-4-ene-3,17a-dione.

^{1}H-NMR ($CDCl_3$, δ) : 1.22 (3H, s), 1.27 (3H, s), 3.00 (6H, s), 4.0～4.6 (3H, m), 5.76 (1H, d, J=1.5Hz)

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MS (m/z) : 405 (M^+), 390, 372, 333

Example 28

The same operations as in Example 26 were made using ethyl chlorocarbonate in place of propionic anhydride to give 9mg of 7α-(ethoxycarbonylthio)-D-homo-17-oxaandrost-4-ene-3,17a-dione.

^{1}H-NMR ($CDCl_3$, δ) : 1.22 (3H, s), 1.27 (3H, s), 1.31 (3H, t, J=7Hz), 2.57 (1H, dd, J=3, 10Hz), 2.88 (1H, ddd, J=1.8, 4, 15Hz), 3.8~4.0 (1H, m), 4.26 (2H, q, J=7Hz), 4.0~4.6 (2H, m), 5.78 (1H, m)

MS (m/z) : 406 (M^+), 391, 362, 347

Example 29

A mixture of 15mg of D-homo-17-oxaandrosta-4,6-diene-3,17a-dione, 1μl of 28% sodium methylate methanol solution, 30μl of allylmercaptan and 0.23ml of dioxane was stirred under N_2 at room temperature for 3 days. Water and aqueous 5% hydrochloric acid solution were added to the reaction mixture, and the product was extracted with ethyl acetate. The extract was washed with aqueous 5% sodium bicarbonate solution and saturated saline, and dried over anhydrous sodium sulfate. The solvent was distilled off, and the resultant crude product was purified by TLC [developing solvent, hexane : ethyl acetate (1 : 1)] to give 10mg of 7α-(allylthio)-D-homo-17-oxaandrost-4-ene-3,17a-dione.

^{1}H-NMR ($CDCl_3$, δ) : 1.20 (3H, s), 1.25 (3H, s), 3.0~3.2 (3H, m), 4.1~4.7 (2H, m), 5.08 (1H, dd, J=1. 3, 15Hz), 5.11 (1H, dd,

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J=1.8, 11Hz), 5.4~6.1 (1H, m), 5.78 (1H, br s)

MS (m/z) : 374 (M^+), 359, 341, 333

Example 30

The same operations as in Example 29 were made using ethanethiol in place of allylmercaptan, and the resultant crude product was purified by TLC [developing solvent, hexane : ethyl acetate (2 : 1)] to give 6mg of 7α-(ethylthio)-D-homo-17-oxaandrost-4-ene-3,17a-dione.

^{1}H-NMR ($CDCl_3$, δ) : 1.21 (3H, s), 1.24 (3H, t, J=7Hz), 1.26 (3H, s), 2.3~2.7 (4H, m), 3.1~3.2 (1H, m), 4.1~4.6 (2H, m), 5.78 (1H, br s)

MS (m/z) : 362 (M^+), 347, 333

Example 31

The same operations as in Example 29 were made using 2-mercaptoethanol in place of allylmercaptan, and the resultant crude product was purified by TLC [developing solvent, chloroform : methanol (9 : 1)] to give 4mg of 7α-[(2-hydroxyethyl)thio]-D-homo-17-oxaandrost-4-ene-3,17a-dione.

^{1}H-NMR ($CDCl_3$, δ) : 1.21 (3H, s), 1.26 (3H, s), 2.70 (2H, t, J=6Hz), 3.1~3.3 (1H, m), 3.74 (2H, t, J=6Hz), 4.1~4.7 (2H, m), 5.79 (1H, br s)

MS (m/z) : 378 (M^+), 363, 360, 348

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Example 32

A mixture of 15mg of 7α-mercapto-D-homo-17-oxaandrosta-1,4-diene-3,17a-dione, 0.75ml of pyridine and 0.05ml of benzoyl chloride was stirred overnight under N_2 at room temperature. Water and aqueous 5% hydrochloric acid solution were added to the reaction mixture, and the product was extracted with ethyl acetate. The extract was washed with aqueous 5% sodium bicarbonate solution and saturated saline, and dried over anhydrous sodium sulfate. The solvent was distilled off, and the resultant crude product was purified by TLC [developing solvent, chloroform : acetone (19 : 1)] and then TLC [developing solvent, hexane : ethyl acetate (1 : 1)] to give 12mg of 7α-(benzoylthio)-D-homo-17-oxaandrosta-1,4-diene-3,17a-dione.

^{1}H-NMR ($CDCl_3$, δ) : 1.30 (3H, s), 1.31 (3H, s), 2.55 (1H, dd, J=2.9, 14Hz), 3.05 (1H, ddd, J=1.5, 4, 14Hz), 2.9~3.6 (3H, m), 6.07 (1H, br s), 6.30 (1H, dd, J=2, 10Hz), 7.06 (1H, d, J=10Hz), 7.3~7.7 (3H, m), 7.8~8.0 (2H, m)

MS (m/z) : 436 (M^+), 421, 403

Example 33

The same operations as in Example 32 were made using propionic anhydride in place of benzoyl chloride to give 11mg of 7α-(propionylthio)-D-homo-17-oxaandrosta-1,4-diene-3,17a-dione.

^{1}H-NMR ($CDCl_3$, δ) : 1.17 (3H, t, J=8Hz), 1.26 (3H, s), 1.29 (3H, s), 2.58 (2H, q, J=8Hz), 2.97 (1H, ddd, J=1.5, 4, 14Hz),

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4.0～4.6 (3H, m), 6.05 (1H, t, J=1.5Hz, 6.27 (1H, dd, J=2, 10Hz), 7.02 (1H, d, J=10Hz)

MS (m/z) : 389 (MH^+), 360, 332

Example 34

The same operations as in Example 32 were made using dimethylcarbamoyl chloride in place of benzoyl chloride to give 17mg of 7α-(N,N-dimethylcarbamoylthio)-D-homo-17-oxaandrosta-1,4-diene-3,17a-dione.

^{1}H-NMR ($CDCl_3$, δ) : 1.26 (3H, s), 1.30 (3H, s), 2.99 (6H, s), 4.0～4.6 (3H, m), 6.09 (1H, t, J=1.5Hz), 6.27 (1H, dd, J=2, 10Hz), 7.04 (1H, d, J=10Hz)

MS (m/z) : 403 (M^+), 388, 370, 332

Example 35

The same operations as in Example 32 were made using ethyl chlorocarbonate in place of benzoyl chloride to give 14mg of 7α-(ethoxycarbonylthio)-D-homo-17-oxaandrosta-1,4-diene-3,17a-dione.

^{1}H-NMR ($CDCl_3$, δ) : 1.26 (3H, s), 1.30 (3H, s), 1.31 (3H, t, J=7Hz), 2.61 (1H, dd, J=3, 14Hz), 2.97 (1H, ddd, J=1.3, 4, 14), 3.8～4.6 (3H, m), 4.28 (2H, q, J=7Hz), 6.11 (1H, t, J=1.5Hz), 6.27 (1H, dd, J=2, 10Hz), 7.02 (1H, d, J=10Hz)

MS (m/z) : 405 (MH^+), 375, 360

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Example 36

The same operations as in Example 29 were made using D-homo-17-oxaandrosta-1,4,6-triene-3,17a-dione in place of D-homo-17-oxaandrosta-4,6-diene-3,17a-dione, and the resultant crude product was purified by TLC [developing solvent, hexane : ethyl acetate (1 : 1)] to give 1mg of 7α-(allylthio)-D-homo-17-oxaandrosta-1,4-diene-3,17a-dione as the more polar product.

^{1}H-NMR ($CDCl_3$, δ) : 1.24 (3H, s), 1.27 (3H, s), 2.53 (1H, dd, J=3, 14Hz), 2.80 (1H, ddd, J=1.3, 4, 14Hz), 3.0~3.3 (3H, m), 4.1~4.6 (2H, m), 4.9~5.2 (2H, m), 5.5~6.1 (1H, m), 6.12 (1H, t, J=1.3Hz), 6.27 (1H, dd, J=2, 10Hz), 7.02 (1H, d, J=10Hz)

MS (m/z) : 372 (M^+), 358, 339, 331

Further, the less polar part was purified by TLC [developing solvent, benzene:ethyl acetate (4:1)] to give 14mg of 1α,7α-bis(allylthio)-D-homo-17-oxaandrost-4-ene-3,17a-dione as the more polar product.

^{1}H-NMR ($CDCl_3$, δ) : 1.25 (3H, s), 1.34 (3H, s), 2.5~3.2 (10H, m), 4.1~4.7 (2H, m), 4.9~5.2 (4H, m), 5.4~6.0 (2H, m), 5.81 (1H, br s)

Further, 4mg of 1α-(allylthio)-D-homo-17-oxaandrosta-4,6-diene-3,17a-dione was obtained as the less polar product.

^{1}H-NMR ($CDCl_3$, δ) : 1.25 (3H, s), 1.31 (3H, s), 2.5~3.0 (2H, m), 3.0~3.2 (3H, m),

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4.1～4.7 (2H, m), 4.9～5.3 (2H, m), 5.5～6.1 (1H, m), 5.74 (1H, s), 6.18 (2H, br s)

Example 37

To a mixture of 21mg of 7α-mercapto-D-homo-17-oxaandrosta-1,4-diene-3,17a-dione, 19μl of 28% sodium methylate methanol solution and 0.45ml of methanol was added 4μl of ethyl bromide, and the mixture was stirred at room temperature for 5 minutes in an atmosphere of nitrogen. Aqueous 3.6% hydrochloric acid solution was added to the reaction mixture, and the product was extracted with ethyl acetate. The extract was washed with aqueous 5% sodium bicarbonate solution and saturated saline, and dried over anhydrous magnesium sulfate. The solvent was distilled off, and the resultant crude product was purified by TLC [developing solvent, chloroform : acetone (19 : 1)] to give 8mg of 7α-(ethylthio)-D-homo-17-oxaandrosta-1,4-diene-3,17a-dione.

^{1}H-NMR ($CDCl_3$, δ) : 1.24 (3H, s), 1.28 (3H, s), 2.3～3.0 (4H, m), 3.1～3.3 (1H, m), 4.1～4.7 (2H, m), 6.11 (1H, t, J=1.5Hz), 6.26 (1H, dd, J=2, 10Hz), 7.03 (1H, d, J=10Hz)

MS (m/z) : 360 (M^+), 345, 332

Example 38

To a mixture of 21mg of 7α-mercapto-D-homo-17-oxaandrosta-1,4-diene-3,17a-dione, 14μl of 28% sodium methylate methanol solution and 1ml of dimethylformamide was added 30μl of ethylenebromohydrine, and the mixture was stirred at room temperature for 5 minutes in an atmosphere of nitrogen. Aqueous 3.6% hydrochloric acid

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solution was added to the reaction mixture, and the product was extracted with ethyl acetate. The extract was washed with aqueous 5% sodium bicarbonate solution and saturated saline, and dried over anhydrous magnesium sulfate. The solvent was distilled off, and the resultant crude product was purified by TLC [developing solvent, chloroform : acetone (4 : 1)]to give 12mg of 7α-[(2-hydroxyethyl)thio]-D-homo-17-oxaandrosta-1,4-diene-3,17a-dione.

^{1}H-NMR ($CDCl_3$, δ) : 1.25 (3H, s), 1.28 (3H, s), 2.70 (2H, t, J=6Hz), 2.5~3.0 (2H, m), 3.2~3.4 (2H, m), 3.6~3.9 (2H, br m), 4.1~4.7 (2H, m), 6.12 (1H, t, J=1. 3Hz), 6.27 (1H, dd, J=2, 10Hz), 7.04 (1H, d, J=10Hz)

MS (m/z) : 376 (M^+), 361, 346, 331

Example 39

The same operations as in Example 38 were made using ethyl bromoacetate in place of ethylenebromohydrine, and the resultant crude product was purified by TLC [developing solvent, chloroform : acetone (19 : 1)] to give 2mg of 7α-(ethoxycarbonylmethylthio)-D-homo-17-oxaandrosta-1,4-diene-3,17a-dione.

^{1}H-NMR ($CDCl_3$, δ) : 1.25 (3H, s), 1.28 (3H, s), 2.61 (1H, dd, J=3, 14Hz), 2.86 (1H, ddd, J=1.5, 3, 14Hz), 3.18, 3.21 (2H, AB q J=15Hz), 3.4~3.6 (1H, m), 3.73 (3H, s), 4.1~4.7 (2H, m), 6.10 (1H, br m), 6.27 (1

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H, dd, J=1.8, 10Hz), 7.02 (1H, d, J=10Hz)

MS (m/z) : 404 (M^+), 389, 372, 345

Example 40

The same operations as in Example 38 were made using methyl iodide in place of ethylenebromohydrine, and the resultant crude product was purified by TLC [developing solvent, hexane : ethyl acetate (1 : 1)] to give 15mg of 7α-(methylthio)-D-homo-17-oxaandrosta-1,4-diene-3,17a-dione.

^{1}H-NMR ($CDCl_3$, δ) : 1.25 (3H, s), 1.28 (3H, s), 2.04 (3H, s), 2.5~2.9 (2H, m), 3.0~3.2 (1H, m), 4.0~4.6 (2H, m), 6.12 (1H, br s), 6.27 (1H, dd, J=1.8, 10Hz), 7.03 (1H, d, J=10Hz)

MS (m/z) : 346 (M^+), 331, 300, 298

Example 41

A mixture of 13mg of 7α-(methylthio)-D-homo-17-oxaandrosta-1,4-diene-3,17a-dione, 6.5mg of m-chloroperbenzoic acid and 0.8ml of anhydrous benzene was stirred at room temperature for 20 minutes. The solvent was distilled off from the reaction mixture, and the resultant crude product was purified by TLC [developing solvent, chloroform : methanol (9 : 1)] to give 7mg of 7α-(methylsulfinyl)-D-homo-17-oxaandrosta-1,4-diene-3,17a-dione.

^{1}H-NMR ($CDCl_3$, δ) : 1.28 (3H, s), 1.30 (3H, s), 2.69 (3H, s), 3.2~3.4 (1H, m), 4.2~4.5 (2H, m), 5.9~6.0 (1H, m), 6.29 (1H, dd, J=1.8, 10Hz), 7.11 (1H, d, J=10Hz)

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MS (m/z) : 362 (M^+), 346, 344

Example 42

A mixture of 14µl of 28% sodium methylate methanol solution and 1ml of dimethylformamide was cooled to -20℃, and under N_2, a largely excess amount of methanethiol was added and the mixture was stirred for 5 minutes. To this reaction mixture was added 15mg of D-homo-17-oxaandrosta-1,4,6-triene-3,17a-dione, and the mixture was stirred at room temperature for 3 days. Water and aqueous 5% hydrochloric acid solution were added to the reaction mixture, and the product was extracted with ethyl acetate. The extract was washed with aqueous 5% sodium bicarbonate solution and saturated saline, and dried over anhydrous sodium sulfate. The solvent was distilled off, and the resultant crude product was purified by TLC [developing solvent, hexane : ethyl acetate (1 : 1)] to give 20mg of 1α,7α-bis(methylthio)-D-homo-17-oxaandrost-4-ene-3,17a-dione.

^{1}H-NMR ($CDCl_3$, δ) : 1.26 (3H, s), 1.36 (3H, s), 2.07 (3H, s), 2.09 (3H, s), 2.4~3.2 (6H, m), 4.1~4.6 (2H, m), 5.82 (1H, br s)

MS (m/z) : 394 (M^+), 379, 347, 320

Example 43

A mixture of 2g of D-homo-17-oxaandrosta-1,4,6-triene-3,17a-dione and 8ml of thioacetic acid was refluxed for 4 hours. The reaction mixture was left to cool and poured into ice water wherein 4.8g of sodium hydroxide had been dissolved, and the product was extracted with ethyl acetate. The extract was washed with aqueous 5% sodium bicarbonate solution and saturated saline, and dried over anhydrous magnesium sulfate. The

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solvent was distilled off, and the resultant crude product was crystallized from diethy ether-ethyl acetate to give 2.45g of 1α,7α-bis(acetylthio)-D-homo-17-oxaandrost-4-ene-3,17a-dione.

^{1}H-NMR ($CDCl_3$, δ) : 1.25 (3H, s), 1.40 (3H, s), 2.36 (3H, s), 2.39 (3H, s), 4.0~4.7 (4H, m), 5.74 (1H, br s)

MS (m/z) : 451 (MH^+), 407, 390, 375

The resultant mother liquor was purified by TLC [developing solvent, hexane : ethyl acetate (1 : 1)] to give 106mg of 1α-(acetylthio)-D-homo-17-oxaandrosta-4,6-diene-3,17a-dione.

^{1}H-NMR ($CDCl_3$, δ) : 1.30 (6H, s), 2.32 (3H, s), 2.67 (1H, ddd, J=1, 2.6, 18Hz), 3.12 (1H, dd, J=4, 18Hz), 4.0~4.2 (1H, m), 4.2~4.7 (2H, m), 5.74 (1H, s), 6.20 (2H, s)

MS (m/z) : 374 (M^+), 346, 341, 332

Example 44

A mixture of 1g of 1α,7α-bis(acetylthio)-D-homo-17-oxaandrost-4-ene-3,17a-dione, 1.8ml of 28% sodium methylate methanol solution and 10ml of methanol was stirred at room temperature for 30 minutes in an atmosphere of nitrogen. The reaction mixture was poured into aqueous 3.6% hydrochloric acid solution, and the product was extracted with ethyl acetate. The extract was washed with aqueous 5% sodium bicarbonate solution and saturated saline, and dried over anhydrous magnesium sulfate. The solvent was distilled off, and the resultant crude product was purified by silica gel column chromatography [eluting solvent, chloroform] to give

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694mg of 7α-mercapto-D-homo-17-oxaandrosta-1,4-diene-3,17a-dione.

Melting point: 207-211℃ (dichloromethane-ethyl acetate)

^{1}H-NMR ($CDCl_3$, δ) : 1.24 (3H, s), 1.30 (3H, s), 2.54 (1H, dd, J=2, 14Hz), 3.04 (1H, m), 3.43 (1H, m), 4.0～4.6 (2H, m), 6.15 (1H, br t, J=2Hz), 6.30 (1H, dd, J=2, 10Hz), 7.03 (1H, d, J=10Hz)

MS (m/z) : 332 (M^+), 317, 298, 283

Elementary analysis:

Calculated for $C_{19}H_{24}O_3S$: C, 68.64: H, 7.28
Found : C, 68.60: H, 7.34

Preparation example 1

A mixture of 2.0g of D-homo-17-oxaandrosta-4,6-diene-3,17a-dione, 4.6g of lithium tri-tert-butoxyaluminohydride and 100ml of tetrahydrofuran was stirred at 0℃ for 20 minutes. Water and 5% hydrochloric acid were added to the reaction mixture, and the product was extracted with ethyl acetate. The extract was washed with aqueous 5% sodium bicarbonate solution and saturated saline, and dried over anhydrous magnesium sulfate. The solvent was distilled off to give 1.8g of 17aξ-hydroxy-D-homo-17-oxaandrosta-4,6-dien-3-one.

Preparation example 2

A mixture of 1.8g of 17aξ-hydroxy-D-homo-17-oxaandrosta-4,6-dien-3-one, 12ml of pyridine and 6ml of acetic anhydride was stirred at room temperature for 15 hours. Water was added to the reaction mixture, and the product was extracted with ethyl acetate. The extract

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was washed with 3% hydrochloric acid, aqueous 5% sodium bicarbonate solution and saturated saline, and dried over anhydrous magnesium sulfate. The solvent was distilled off, and the resultant crude product was purified by TLC [developing solvent, chloroform : acetone (39 : 1)] to give 1.73g of 17aξ-acetoxy-D-homo-17-oxaandrosta-4,6-dien-3-one.

Preparation example 3

The same operations as in Example 6 were made using 800mg of 17aξ-acetoxy-D-homo-17-oxaandrosta-4,6-dien-3-one in place of D-homo-17-oxaandrosta-4,6-dien-3-one, and the resultant crude product was purified by TLC [developing solvent, benzene : ethyl acetate (1 : 1)] to give 106mg of 7α-benzyl-17aξ-hydroxy-D-homo-17-oxaandrost-4-en-3-one.

Preparation example 4

Water was gradually azeotropically removed from a mixture of 2.0g of D-homo-17-oxaandrost-4-en-3-one, 100ml of ethylene glycol, 500mg of p-toluenesulfonic acid and 400ml of benzene using a Dean-Stark apparatus. Aqueous 5% sodium bicarbonate solution was added to the reaction mixture, and the product was extracted with ethyl acetate. The extract was washed with saturated saline, and dried over anhydrous magnesium sulfate. The solvent was distilled off to give 2.4g of 3,3:17a,17a-bis(ethylenedioxy)-D-homo-17-oxaandrost-5-ene.

^{1}H-NMR ($CDCl_3$, δ) : 1.02 (3H, s), 1.11 (3H, s), 3.6~4.3 (10H, m), 5.33 (1H, m)

MS (m/z) : 390 (M^+), 345, 302

Preparation example 5

A mixture of 13.3g of chromium oxide, 22ml of pyridine and 210ml of methylene chloride was stirred at room temperature for 20 minutes in an atmosphere of

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nitrogen. To the mixture was added a mixture of 2.4g of 3,3:17a,17a-bis(ethylenedioxy)-D-homo-17-oxaandrost-5-ene and 88ml of methylene chloride, and the mixture was stirred for 5 days. Diethyl ether was added to the reaction mixture, the insoluble matter was filtered off, and the filtrate was washed with 3% hydrochloric acid, aqueous 5% sodium bicarbonate solution and saturated saline, and dried over anhydrous sodium sulfate. The solvent was distilled off, and the residue was recrystallized from acetone-diethyl ether to give 870mg of 3,3:17a,17a-bis(ethylenedioxy)-D-homo-17-oxaandrost-5-en-7-one.

^{1}H-NMR ($CDCl_3$, δ) : 1.11 (3H, s), 1.22 (3H, s), 3.5~4.4 (10H, m), 5.63 (1H, br s)

Preparation example 6

1.25ml of 2.0M benzylmagnesium chloride tetrahydrofuran solution was added dropwise over a period of 20 minutes to a mixture of 200mg of 3,3:17a,17a-bis(ethylenedioxy)-D-homo-17-oxaandrost-5-en-7-one and 17.6ml of tetrahydrofuran at room temperature in an atmosphere of nitrogen. The reaction mixture was poured into aqueous saturated ammonium chloride solution, and the product was extracted with diethyl ether. The extract was washed with saturated saline, and dried over anhydrous sodium sulfate. The solvent was distilled off to give 240mg of 7ξ-benzyl-3,3:17a,17a-bis(ethylenedioxy)-D-homo-17-oxaandrost-5-en-7ξ-ol.

Preparation example 7

The same operations as in Preparation example 1 were made using 30mg of 7-benzyl-D-homo-17-oxaandrosta-4,6-diene-3,17a-dione in place of D-homo-17-oxaandrosta-4,6-diene-3,17a-dione to give 30mg of 7-benzyl-17aξ-hydroxy-D-homo-17-oxaandrosta-4,6-dien-3-one.

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A preparation example of a pharmaceutical containing a compound of this invention is shown below.

Preparation example A: Tablet	mg/tablet
Active ingredient	100
Starch	20
Lactose	105.5
Carboxymethylcellulose calcium	20
Talc	3
Magnesium stearate	1.5
	250mg

The active ingredient is pulverized into a particle size of 70 microns or less, and to this were added starch, lactose and carboxymethylcellulose calcium, and the mixture is sufficiently mixed. 10% of starch paste is added to the mixed fine particles, the mixture is mixed, and granules are prepared. After being dried, the granules are gradede into a particle size of around 1,000 microns, talc and magnesium stearate are mixed therewith, and the mixture is tableted.

Industrial Applicability

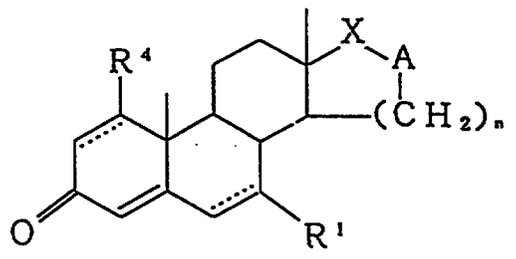
The compounds of the abovementioned formula (I) of this invention have an aromatase-inhibiting action, and are useful for prophylaxis and treatment of diseases caused by estrogens, for example breast cancer, uterine cancer, prostatic hypertrophy, etc.

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CLAIMS

1. A steroid compound represented by the formula



wherein

R^1 denotes $-S-R^2$, $-S(O)m-R^3$ or an aralkyl group, wherein

R^2 denotes a hydrogen atom; a lower alkyl group optionally substituted with a hydroxyl, amino or lower alkoxycarbonyl group; a lower alkenyl group; an aralkyl group; an aryl group optionally substituted with halogen atom(s), or amino, di-(lower alkyl)amino, lower alkoxy or lower alkyl group(s); an acyl group; or a lower alkoxycarbonyl group,

R^3 denotes a lower alkyl group,

m denotes 1 or 2,

R^4 denotes a hydrogen atom or $-S-R^5$, wherein

R^5 denotes a lower alkyl group optionally substituted with a hydroxyl, amino or lower alkoxycarbonyl group; a lower alkenyl group; an aralkyl group; an aryl group optionally substituted with halogen atom(s), or amino, di-(lower alkyl)amino, lower alkoxy or lower alkyl group(s); or an acyl group,

X denotes C=O or CH_2,

A denotes O or NH,

n denotes 1 or 2, and

the broken lines between the 1- and 2-positions and between the 6- and 7-positions of the steroid skeleton mean that a double bond can exist there, provided that

(a) when A denotes NH, X is assumed to denote

* C L M S *

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C=O,

(b) when R^1 denotes -S-R^2 or -S(O)m-R^3, the bond between the 6- and 7-positions is assumed to denote a single bond, and

(c) when R^4 denotes -S-R^5, the bond between the 1- and 2-positions is assumed to denote a single bond.

2. The steroid compound according to claim 1 wherein R^1 denotes -S-R^2 or -S(O)m-R^3.

3. The steroid compound according to claim 1 wherein the substituent R^1 binds to the α-position.

4. The steroid compound according to claim 1 wherein A denotes O and n denotes 2.

5. An aromatase inhibitor which contains a compound according to claim 1.

6. A pharmaceutical composition which comprises a compound according to claim 1 and pharmaceutically acceptable additive(s).

7. Use of the composition according to claim 6 for prophylaxis or treatment of diseases caused by estrogens.

8. A method for prophylaxis or treatment of diseases in human beings or other mammals caused by estrogens, which comprises administering to the human beings or other mammals an effective amount of a compound according to claim 1.

CLMS

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