

Description

The present invention is concerned with novel oxidized analogs of 17β -N-monosubstituted carbamoyl-4-aza- 5α -androst-1-en-3-one compounds and the use of such compounds as testosterone- 5α -reductase inhibitors.

It is well known in the art that certain undesirable physiological manifestations, such as acne vulgaris, seborrhea, female hirsutism, and male pattern baldness and benign prostatic hypertrophy, are the result of hyperandrogenic stimulation caused by an excessive accumulation of testosterone or similar androgenic hormones in the metabolic system. Early attempts to provide a chemotherapeutic agent to counter the undesirable results of hyperandrogenicity resulted in the discovery of several steroidal antiandrogens having undesirable hormonal activities of their own. The estrogens, for example, not only counteract the effect of the androgens but have a feminizing effect as well. Non-steroidal antiandrogens have also been developed, for example, 4'-nitro-3'-trifluoromethylisobutyranilide. See Neri et al., *Endo.*, Vol. 91, No. 2 (1972). However, these products, though devoid of hormonal effects, are peripherally active, competing with the natural androgens for receptor sites, and hence have a tendency to feminize a male host or the male fetus of a female host.

It more recently became known in the art that the principal mediator of androgenic activity in some target organs is 5α -dihydrotestosterone, and that it is formed locally in the target organ by the action of testosterone- 5α -reductase. It therefore has been postulated and demonstrated that inhibitors of testosterone- 5α -reductase will serve to prevent or lessen symptoms of hyperandrogenic stimulation. Nayfeh et al., *Steroids*, 14, 269 (1969) demonstrated in vitro that methyl 4-androsten-3-one- 17β -carboxylate was a testosterone- 5α -reductase inhibitor. Then Voigt and Hsia, *Endocrinology*, 92, 1216 (1973), Canadian Pat. No. 970,692, demonstrated that the above ester and the parent free acid, 4-androsten-3-one- 17β -carboxylic acid are both active inhibitors of testosterone- 5α -reductase in vitro. They further demonstrated that topical application of either testosterone or 5α -dihydrotestosterone caused enlargement of the female hamster flank organ, an androgen dependent sebaceous structure. However, concomitant administration of 4-androsten-3-one- 17β -carboxylic acid or its methyl ester inhibited the response elicited by testosterone but did not inhibit the response elicited by 5α -dihydrotestosterone. These results were interpreted as indicating that the compounds were antiandrogenic by virtue of their ability to inhibit testosterone- 5α -reductase.

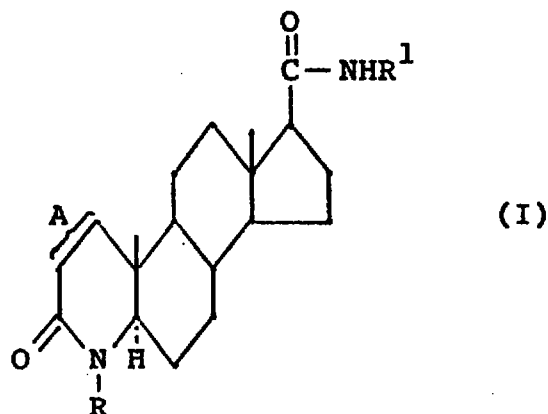
A number of 4-aza steroid compounds are known. See, for example, U.S. Pat. Nos. 2,227,876; 3,239,417; 3,264,301; and 3,285,918; French Pat. No. 1,465,544; Doorenbos and Solomons, *J. Pharm. Sci.* 62, 4, pp. 638-640 (1973); Doorenbos and Brown, *J. Pharm. Sci.*, 60 8, pp. 1234-1235 (1971); and Doorenbos and Kim, *J. Pharm. Sci.* 63, 4, pp. 620-622 (1974).

In addition U.S. Patent 4,377,584 and 4,220,775 and EP Appln. 4949 of Rasmusson et al. describe a group of 4-aza- 17β -substituted- 5α -androstan-3-ones which are useful in the treatment of hyperandrogenic conditions. Recently, a number of investigators from Merck & Co., Inc. have published regarding the biological activity of 5α -reductase inhibitors. See for example, Rasmusson et al., *J. Med. Chem.* 29: 2298-2315 (1986), Brooks et al., *The Prostate* 9: 65-75 (1986), Liang et al., *Endocrinology* 117, No. 2, pp. 571-579 (1985), Rasmusson et al., *J. Med. Chem.* 27: 1690-1701 (1984), Liang et al., *J. Biol. Chem.* 259, No. 2, pp. 734-739 (1984). The biological activity of 17β -(N-t-butylcarbamoyl)-4-aza-androst-1-en-3-one has also been reported. However, only the Rasmusson et al. (1986) reference teaches or suggests that any of the novel oxidized analogs of 17β N-(monosubstituted)carbamoyl-4-aza- 5α -androstan-3-ones of the present invention would have utility as highly potent testosterone- 5α -reductase inhibitors.

In addition to being 5α -reductase inhibitors and thus useful for the treatment of benign prostatic hypertrophy, acne vulgaris, seborrhea and hirsutism, certain of the compounds of the present invention are metabolites resulting from in vivo administration of 17β -(N-t-butylcarbamoyl)-4-aza- 5α -androst-1-en-3-one. In many cases, metabolism of active drug result in deactivation and/or excretion, however, in this case the compounds of the present invention maintain a sustained high level of bioactivity in treated animals and have prolonged half-lives.

The present invention is concerned with novel oxidized analogs of 17β -N-(monosubstituted)-carbamoyl-4-aza- 5α -androst-1-en-3-one compounds, pharmaceutical formulations comprising the novel compounds as active ingredients and methods of inhibiting testosterone- 5α -reductase and of treating hyperandrogenic conditions with the novel compounds or their pharmaceutical formulations.

The present invention is concerned with compounds of the formula:



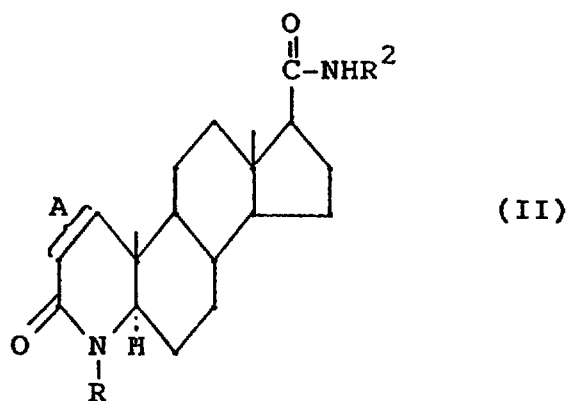
wherein R is hydrogen, methyl or ethyl;

R¹ is C₁₋₁₂ straight or branched chain alkyl wherein one of the hydrogens is substituted by hydroxy, carboxylic acid or C₁₋₄ alkyl ester; and

A is -CH=CH-,

or the pharmaceutically acceptable salts thereof.

A preferred embodiment of the novel compounds of our invention is represented by the formula:



wherein R is hydrogen, methyl or ethyl; and

R² is C₃₋₈ branched chain alkyl wherein one of the hydrogens is substituted by hydroxy, carboxylic acid or C₁₋₄ alkyl ester; and

A is -CH=CH-.

A more preferred embodiment is represented by the formula II compounds wherein R is hydrogen or methyl, R² is C₃₋₈ branched chain alkyl wherein one of the hydrogens is substituted by hydroxy, carboxylic acid or C₁₋₄ alkyl ester.

Representative compounds of the present invention include the following:

17β-N-(2-hydroxymethyl-2-propyl)carbamoyl-4-aza-5α-androst-1-en-3-one;

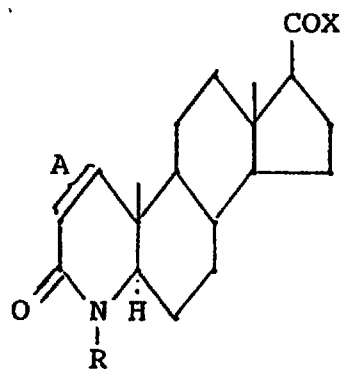
17β-N-(2-carboxy-2-propyl)carbamoyl-4-aza-5α-androst-1-en-3-one;

17β-N-(2-carbomethoxy-2-propyl)carbamoyl-4-aza-5α-androst-1-en-3-one;

and the corresponding compounds wherein the 4-hydrogen substituent is replaced in each of the above named compounds by a methyl radical.

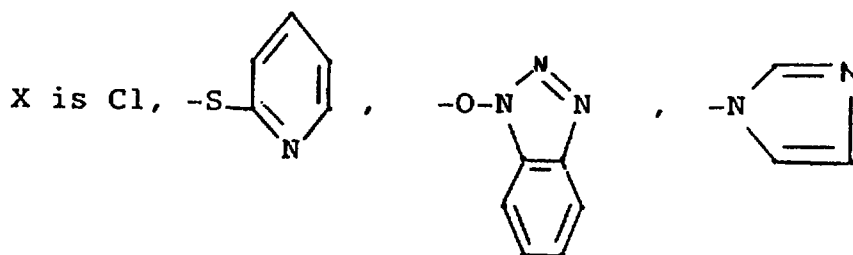
Also included as representative compounds are any of the above indicated compounds where the side chain alkyl substituent is replaced by a branched chain, such as i-butyl, s-butyl, t-butyl, i-pentyl, s-pentyl, t-pentyl, etc.

The novel compounds of formula I of the present invention are prepared by a method starting with the steroid ester of the formula shown in Rasmusson *et al.*, J. Med. Chem., 29: 2298-2315 (1986):

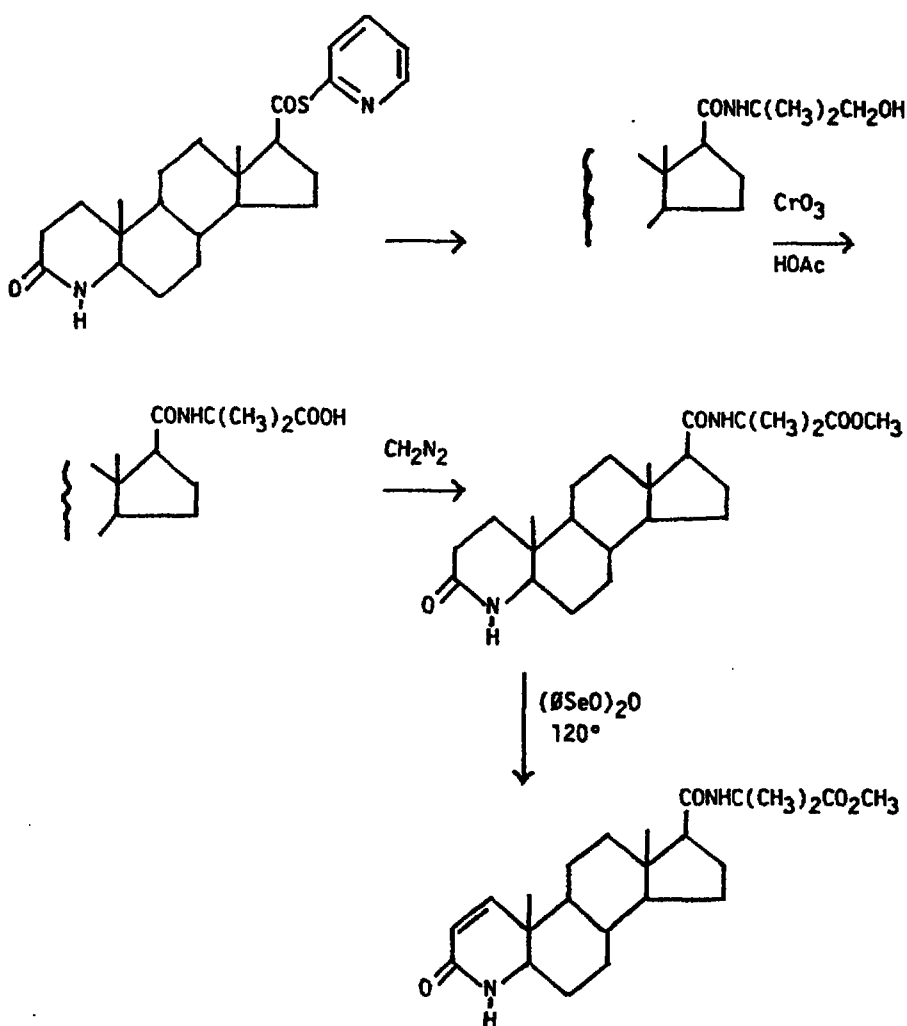
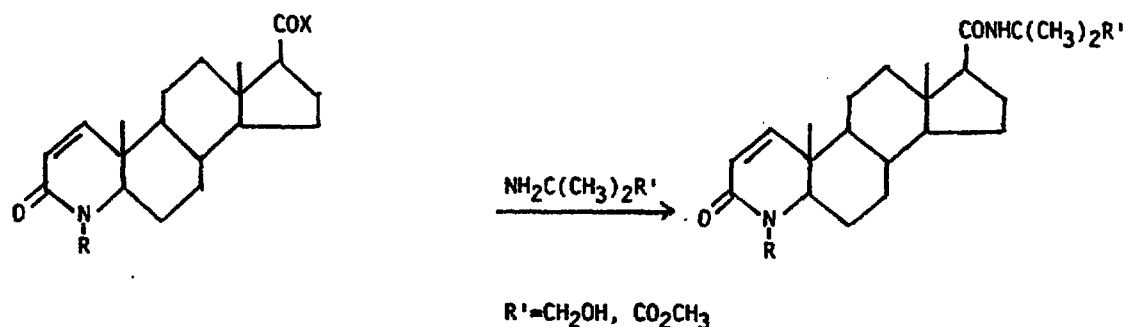


(III)

A is $-\text{CH}=\text{CH}_2$,
R is H, CH_3 , C_2H_5 ,



The above reactions are schematically represented in the following structural formula outline.



In general, a functionalized alkyl amine is reacted with a suitably reactive derivative of the 17β-carboxyazasteroid to form the corresponding 17β-carboxamide. The side-chain or nucleus of the steroid can be further modified by standard synthetic reactions.

The compounds of the present invention, prepared in accordance with the method described above, are, as already described, potent antiandrogens by virtue of their ability to specifically inhibit testosterone-5α-reductase.

Additionally, certain of the compounds of the present invention are metabolites resulting from *in vivo* administration of 17β-(N-t-butylcarbonyl)-4-aza-androst-1-en-3-one. Thus, a major plasma metabolite is the sidechain hydroxylated (monohydroxymethyl) species of Example 1. An acidic metabolite resulting from further oxidation of the monohydroxymethyl species was identified as the compound of Example 2. An additional metabolite was identified as the compound of Example 3. Thus, these metabolic products in

17 β -N-(2-carbomethoxy-2-propyl)carbamoyl-4-aza-androst-1-en-3-one

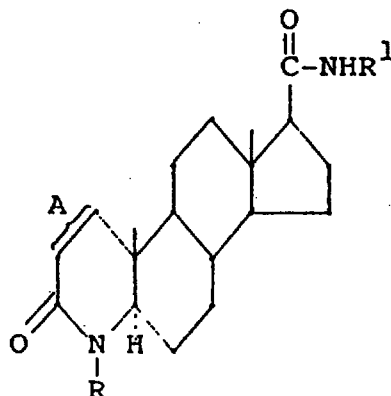
To a solution of 22 mg of the product of Example 2 in 3.0 ml of tetrahydrofuran was added a slight excess of diazomethane as a solution in diethyl ether. After 10 minutes at room temperature sufficient glacial acetic acid was added to consume all the diazomethane. The solution was concentrated and the residue was crystallized from ethyl acetate to give 15 mg of the product.

Alternately, this product can be prepared by the following procedure: A solution of 20 mg of 17 β -N-(2-carbomethoxy-2-propyl)carbamoyl-4-aza-5 α -androst-3-one (Example 9 below) and 50 mg of benzeneseleninic anhydride in 0.8 ml of chlorobenzene is heated at reflux for 3 hours. After cooling ethyl acetate and water are added and the phases are separated. The organic layer is washed with dilute sodium bicarbonate solution and then dried and concentrated. The product is isolated by thin layer chromatography on silica eluted with chloroform-acetone (2:1) and is identified by its mass spectrum (molecular ion, 416).

Claims

15 **Claims for the following contracting states : AT, BE, FR, DE, GB, NL, IT, LU, SE, CH**

1. A compound of the formula:

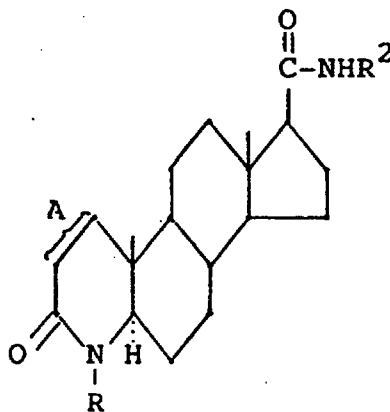


wherein R is hydrogen, methyl or ethyl;

R¹ is C₁₋₁₂ straight or branched chain alkyl wherein one of the hydrogens is substituted by hydroxy, carboxylic acid or C₁₋₄ alkyl ester; and

A is -CH=CH-,
or the pharmaceutically acceptable salts thereof.

2. A compound of Claim 1 of the formula:



wherein R is hydrogen, methyl or ethyl; and

R² is C₃₋₈ branched chain alkyl wherein one of the hydrogens is substituted by hydroxy, carboxylic acid or C₁₋₄ alkyl ester; and

17 β -N-(2-carbomethoxy-2-propyl)carbamoyl-4-aza-androst-1-en-3-one

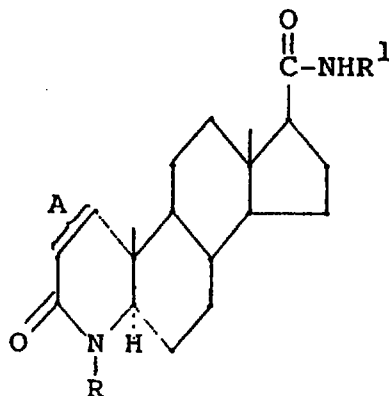
To a solution of 22 mg of the product of Example 2 in 3.0 ml of tetrahydrofuran was added a slight excess of diazomethane as a solution in diethyl ether. After 10 minutes at room temperature sufficient
5 glacial acetic acid was added to consume all the diazomethane. The solution was concentrated and the residue was crystallized from ethyl acetate to give 15 mg of the product.

Alternately, this product can be prepared by the following procedure: A solution of 20 mg of 17 β -N-(2-carbomethoxy-2-propyl)carbamoyl-4-aza-5 α -androst-3-one (Example 9 below) and 50 mg of benzeneseleninic anhydride in 0.8 ml of chlorobenzene is heated at reflux for 3 hours. After cooling ethyl
10 acetate and water are added and the phases are separated. The organic layer is washed with dilute sodium bicarbonate solution and then dried and concentrated. The product is isolated by thin layer chromatography on silica eluted with chloroform-acetone (2:1) and is identified by its mass spectrum (molecular ion, 416).

Claims

15 **Claims for the following contracting states : AT, BE, FR, DE, GB, NL, IT, LU, SE, CH**

1. A compound of the formula:

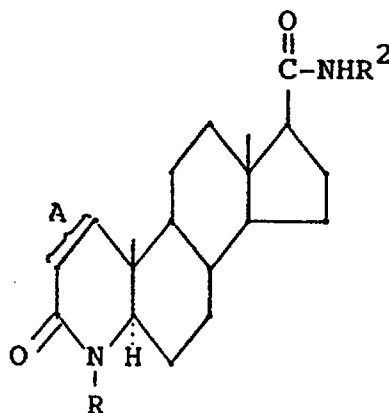


wherein R is hydrogen, methyl or ethyl;

R¹ is C₁₋₁₂ straight or branched chain alkyl wherein one of the hydrogens is substituted by
35 hydroxy, carboxylic acid or C₁₋₄ alkyl ester; and

A is -CH=CH-,
or the pharmaceutically acceptable salts thereof.

2. A compound of Claim 1 of the formula:



wherein R is hydrogen, methyl or ethyl; and

R² is C₃₋₈ branched chain alkyl wherein one of the hydrogens is substituted by hydroxy,
carboxylic acid or C₁₋₄ alkyl ester; and

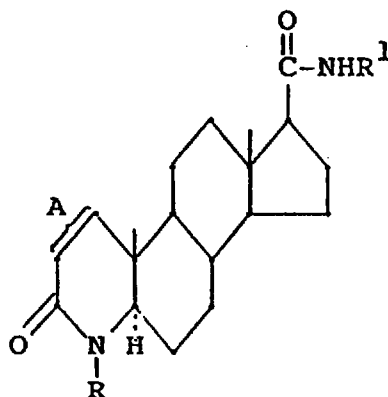


A is -CH=CH-.

3. A compound of Claim 2 wherein R is hydrogen or methyl, R² is C₃₋₈ branched chain alkyl having one of the hydrogens substituted by hydroxy, carboxylic acid or C₁₋₄ alkyl ester.
4. A compound of Claim 1 which is
 17β-N-(2-hydroxymethyl-2-propyl)carbamoyl-4-aza-5α-androst-1-en-3-one;
 17β-N-(2-carboxy-2-propyl)carbamoyl-4-aza-5α-androst-1-en-3-one;
 17β-N-(2-carbomethoxy-2-propyl)carbamoyl-4-aza-5α-androst-1-en-3-one.
5. A compound of Claim 4 in substantially pure form.
6. The use of a compound as claimed in Claim 1 for the preparation of a medicament useful for treating the hyperandrogenic condition of acne vulgaris, seborrhea, female hirsutism, and benign prostatic hypertrophy.
7. The use of a compound as claimed in Claim 1 for the preparation of a medicament useful for inhibiting testosterone 5α-reductase.
8. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of a compound of Claim 1.

Claims for the following contracting state : ES

1. A process for the preparation of a compound of the formula:



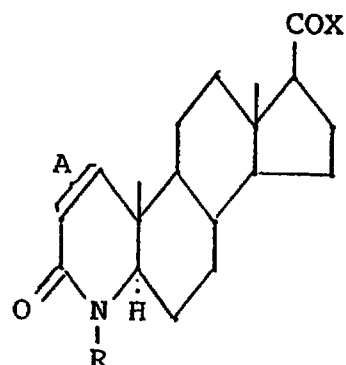
wherein R is hydrogen, methyl or ethyl;

R¹ is C₁₋₁₂ straight or branched chain alkyl wherein one of the hydrogens is substituted by hydroxy, carboxylic acid or C₁₋₄ alkyl ester; and

A is -CH=CH-.

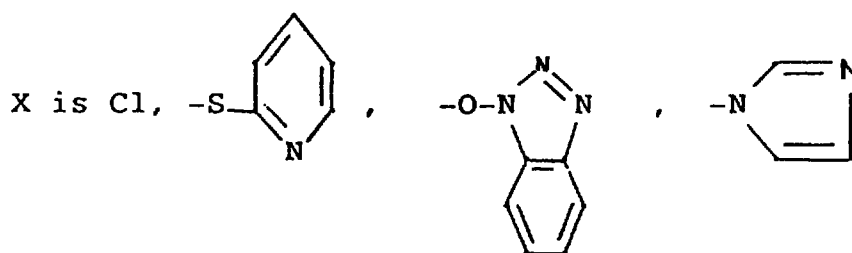
or the pharmaceutically acceptable salts thereof; which process comprises reacting a compound of formula (III)





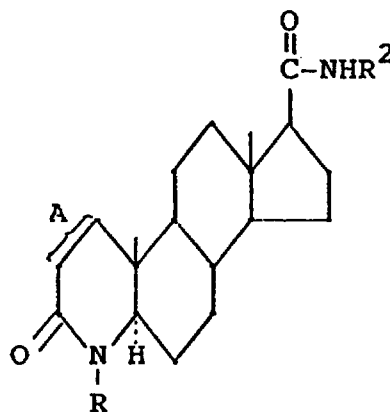
(III)

A is $-\text{CH}=\text{CH}-$,
 R is H, CH_3 , C_2H_5 ,



with a functionalised alkyl amine of formula NH_2R^1 ; and optionally thereafter modifying the side-chain or nucleus.

2. A process of Claim 1 for the preparation of a compound of the formula:



wherein R is hydrogen, methyl or ethyl; and

R^2 is C_3 - 8 branched chain alkyl wherein one of the hydrogens is substituted by hydroxy, carboxylic acid or C_1 - 4 alkyl ester; and

A is $-\text{CH}=\text{CH}-$.

3. A process of Claims 2 wherein R is hydrogen or methyl, R^2 is C_3 - 8 branched chain alkyl having one of the hydrogens substituted by hydroxy, carboxylic acid or C_1 - 4 alkyl ester.

4. A process of Claim 1 for the preparation of a compound which is
 17β -N-(2-hydroxymethyl-2-propyl)carbamoyl-4-aza- 5α -androst-1-en-3-one;
 17β -N-(2-carboxy-2-propyl)carbamoyl-4-aza- 5α -androst-1-en-3-one;
 17β -N-(2-carbomethoxy-2-propyl)carbamoyl-4-aza- 5α -androst-1-en-3-one.

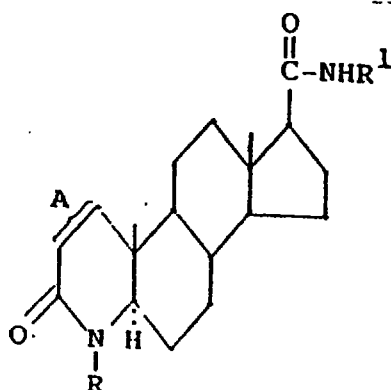


5. A process of Claim 4 for the preparation of the compound in substantially pure form.
6. A process for preparing a pharmaceutical composition comprising mixing a pharmaceutically acceptable carrier and an effective amount of a compound prepared as claim in Claim 1.

Revendications

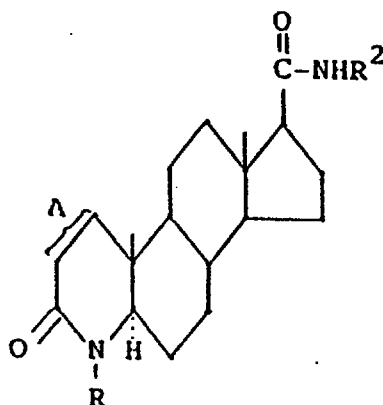
Revendications pour les Etats contractants suivants : AT, BE, FR, DE, GB, NL, IT, LU, SE, CH

1. Composé de formule :



dans laquelle R est un atome d'hydrogène ou un radical méthyle ou éthyle ;
R¹ est un radical alkyle à chaîne droite ou ramifiée en C₁₋₁₂ dont l'un des atomes d'hydrogène est substitué par un groupe hydroxy, acide carboxylique ou ester alkylque en C₁₋₄ ; et A représente -CH=CH-, ou ses sels pharmaceutiquement acceptables.

2. Composé selon la revendication 1, répondant à la formule :



dans laquelle R est un atome d'hydrogène, un radical méthyle ou éthyle ; et R² est un radical alkyle à chaîne ramifiée en C₃₋₈ dont l'un des atomes d'hydrogène est substitué par un groupe hydroxy, acide carboxylique ou ester alkylque en C₁₋₄ ; et A représente -CH=CH-.

3. Composé selon la revendication 2, dans lequel R est un atome d'hydrogène ou un radical méthyle, R² est un radical alkyle à chaîne ramifiée en C₃₋₈ dont l'un des atomes d'hydrogène est substitué par un groupe hydroxy, acide carboxylique ou ester alkylque en C₁₋₄.

4. Composé selon la revendication 1, qui est :
17bêta-N-(2-hydroxyméthyl-2-propyl)carbamoyl-4-aza-5alpha-androst-1-en-3-one ;
17bêta-N-(2-carboxy-2-propyl)carbamoyl-4-aza-5alpha-androst-1-en-3-one ;

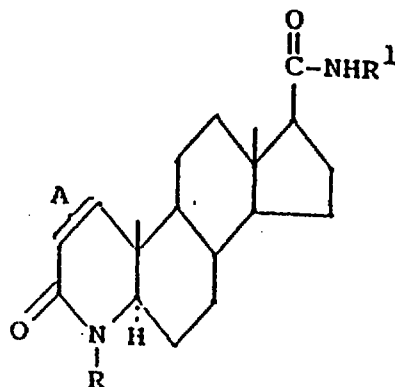


17bêta-N-(2-carbométhoxy-2-propyl)carbamoyl-4-aza-5alpha-androst-1-en-3-one

5. Composé selon la revendication 4, sous une forme sensiblement pure.
6. Utilisation d'un composé selon la revendication 1, pour la préparation d'un médicament servant à traiter un état hyperandrogène de l'acné vulgaris, de la séborrhée, de l'hirsutisme féminin et de l'hypertrophie prostatique bénigne.
7. Utilisation d'un composé selon la revendication 1, pour la préparation d'un médicament utile pour inhiber la testostérone-5alpha-réductase.
8. Composition pharmaceutique comprenant un véhicule pharmaceutiquement acceptable et une quantité efficace d'un composé selon la revendication 1.

Revendications pour l'Etat contractant suivant : ES

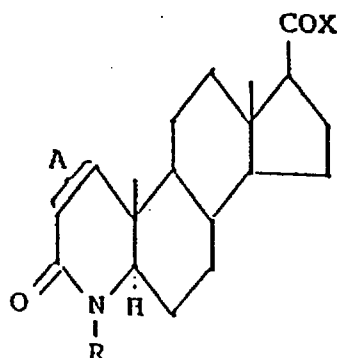
1. Procédé de préparation d'un composé de formule:



dans laquelle R est un atome d'hydrogène ou un radical méthyle ou éthyle ; R¹ est un radical alkyle à chaîne droite ou ramifiée en C₁₋₁₂ dont l'un des atomes d'hydrogène est substitué par un groupe hydroxy, acide carboxylique ou ester alkyle en C₁₋₄ ; et

A est -CH=CH-,

ou ses sels pharmaceutiquement acceptables, procédé qui consiste à faire réagir un composé de formule (III) :



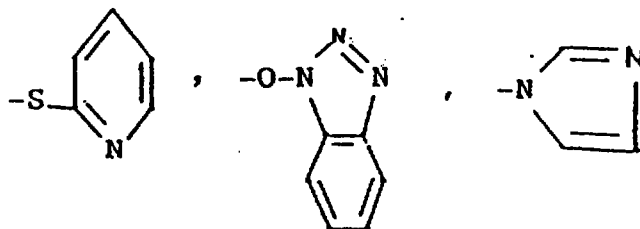
(III)

dans laquelle : A est -CH=CH-,

R représente H, CH₃, C₂H₅,

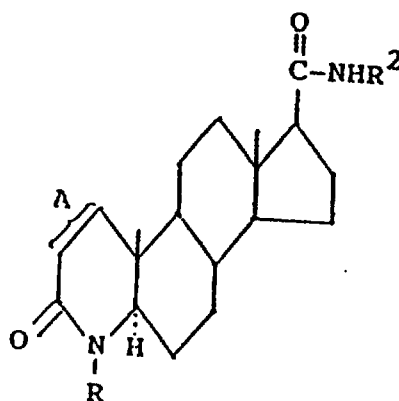


X représente Cl,



avec une alkylamine fonctionnalisée de formule NH_2R^1 ; et facultativement, à modifier ensuite la chaîne latérale ou le noyau.

2. Procédé selon la revendication 1, pour la préparation d'un composé de formule :



dans laquelle R est un atome d'hydrogène ou un radical méthyle ou éthyle ; et R^2 est un radical alkyle à chaîne ramifiée en C_3-8 dont l'un des atomes d'hydrogène est substitué par un groupe hydroxy, acide carboxylique ou ester alkylique en C_1-4 ; et A est $-\text{CH}=\text{CH}-$.

3. Procédé selon la revendication 2, dans lequel R est un atome d'hydrogène ou un radical méthyle, R^2 est un radical alkyle à chaîne ramifiée en C_3-8 dont l'un des atomes d'hydrogène est substitué par un groupe hydroxy, acide carboxylique ou ester alkylique en C_1-4 .

4. Procédé selon la revendication 1, pour la préparation d'un composé qui est :
 17bêta-N-(2-hydroxyméthyl-2-propyl)carbamoyle-4-aza-5alpha-androst-1-en-3-one ;
 17bêta-N-(2-carboxy-2-propyl)carbamoyle-4-aza-5alpha-androst-1-en-3-one ;
 17bêta-N-(2-carbométhoxy-2-propyl)carbamoyle-4-aza-5alpha-androst-1-en-3-one.

5. Procédé selon la revendication 4, pour la préparation du composé sous une forme sensiblement pure.

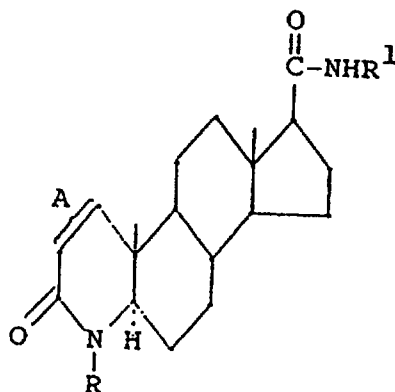
6. Procédé de préparation d'une composition pharmaceutique, qui consiste à mélanger un véhicule pharmaceutiquement acceptable avec une proportion efficace d'un composé préparé selon la revendication 1.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten: AT, BE, FR, DE, GB, NL, IT, LU, SE, CH

1. Verbindung der Formel





15 worin

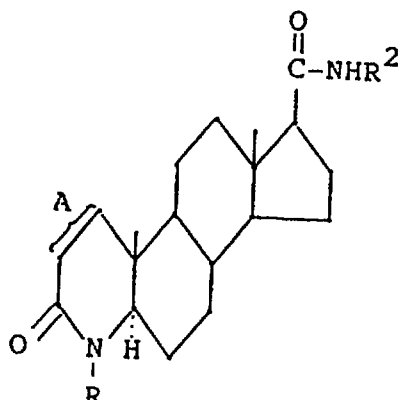
R Wasserstoff, Methyl oder Ethyl ist;

R¹ geradkettiges oder verzweigtes C₁₋₁₂-Alkyl ist, worin einer der Wasserstoffe durch Hydroxy, eine Carboxylgruppe oder einen C₁₋₄-Alkylester substituiert ist, und

A -CH=CH ist,

20 oder pharmazeutisch annehmbare Salze davon.

2. Verbindung nach Anspruch 1 der Formel



40 worin

R Wasserstoff, Methyl oder Ethyl ist und

R² verzweigtes C₃₋₈-Alkyl ist, worin einer der Wasserstoffe durch Hydroxy, eine Carbonsäuregruppe oder eine C₁₋₄-Alkylestergruppe substituiert ist; und

A -CH=CH- ist.

45 3. Verbindung nach Anspruch 2, worin R Wasserstoff oder Methyl ist, R² verzweigtes C₃₋₈-Alkyl mit einem durch Hydroxy, eine Carbonsäuregruppe oder eine C₁₋₄-Alkylestergruppe substituierten Wasserstoff ist.

4. Verbindung nach Anspruch 1, welche

50 17β-N-(2-Hydroxymethyl-2-propyl)carbamoyl-4-aza-5α-androst-1-en-3-on;

17β-N-(2-Carboxy-2-propyl)carbamoyl-4-aza-5α-androst-1-en-3-on;

17β-N-(2-Carbomethoxy-2-propyl)carbamoyl-4-aza-5α-androst-1-en-3-on ist.

5. Verbindung nach Anspruch 4 in im wesentlichen reiner Form.

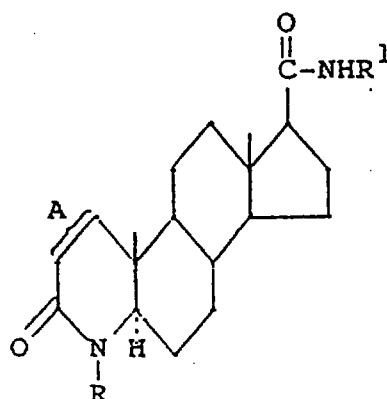
6. Verwendung einer Verbindung nach Anspruch 1 zur Herstellung eines zur Behandlung von hyperandrogenen Zuständen von Akne vulgaris, Seborrhöe, weiblichem Hirsutismus und gutartiger Prostatahypertrophie geeigneten Medikaments.



7. Verwendung einer Verbindung nach Anspruch 1 zur Herstellung eines zur Inhibierung der Testosteron-5 α -reduktase geeigneten Medikaments.
8. Pharmazeutische Zusammensetzung, welche einen pharmazeutisch annehmbaren Träger und eine wirksame Menge einer Verbindung nach Anspruch 1 enthält.

Patentansprüche für folgenden Vertragsstaat : ES

1. Verfahren zur Herstellung einer Verbindung der Formel



worin

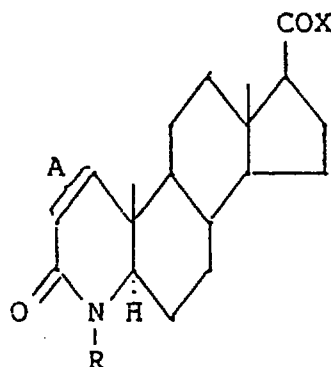
R Wasserstoff, Methyl oder Ethyl ist;

R¹ geradkettiges oder verzweigtes C₁₋₁₂-Alkyl ist, worin einer der Wasserstoffe durch Hydroxy, eine Carbonsäuregruppe oder eine C₁₋₄-Alkylestergruppe substituiert ist; und

A -CH=CH- ist,

oder pharmazeutisch annehmbarer Salze davon,

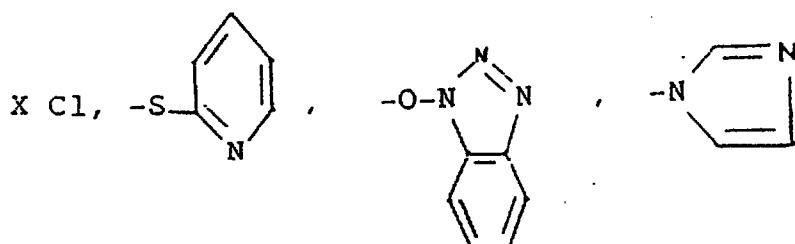
welches Verfahren das Umsetzen einer Verbindung der Formel (III)



worin

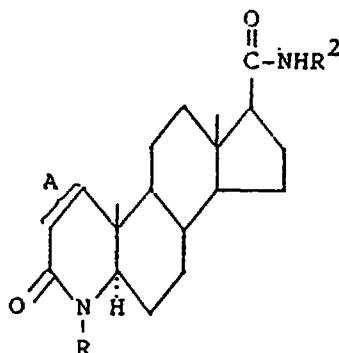
A -CH=CH- ist,

R H, CH₃, C₂H₅ ist,



ist, mit einem funktionalisierten Alkylamin der Formel NH_2R^1 ; sowie gegebenenfalls anschließende Modifizierung der Seitenkette oder des Kerns umfaßt.

2. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung der Formel



worin

- R Wasserstoff, Methyl oder Ethyl ist; und
 R² verzweigtes C₃₋₈-Alkyl ist, worin einer der Wasserstoffe durch Hydroxy, eine Carbonsäuregruppe oder eine C₁₋₄-Alkylestergruppe substituiert ist; und
 A -CH=CH- ist.

3. Verfahren nach Anspruch 2, worin R Wasserstoff oder Methyl ist, R² verzweigtes C₃₋₈-Alkyl mit einem durch Hydroxy, eine Carbonsäuregruppe oder eine C₁₋₄-Alkylestergruppe substituierten Wasserstoff ist.
4. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung, welche
 17β-N-(2-Hydroxymethyl-2-propyl)carbamoyl-4-aza-5α-androst-1-en-3-on;
 17β-N-(2-Carboxy-2-propyl)carbamoyl-4-aza-5α-androst-1-en-3-on;
 17β-N-(2-Carbomethoxy-2-propyl)carbamoyl-4-aza-5α-androst-1-en-3-on ist.
5. Verfahren nach Anspruch 4 zur Herstellung der Verbindung in im wesentlichen reiner Form.
6. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung durch Mischen eines pharmazeutisch annemmbaren Trägers und einer wirksamen Menge einer nach Anspruch 1 hergestellten Verbindung.

