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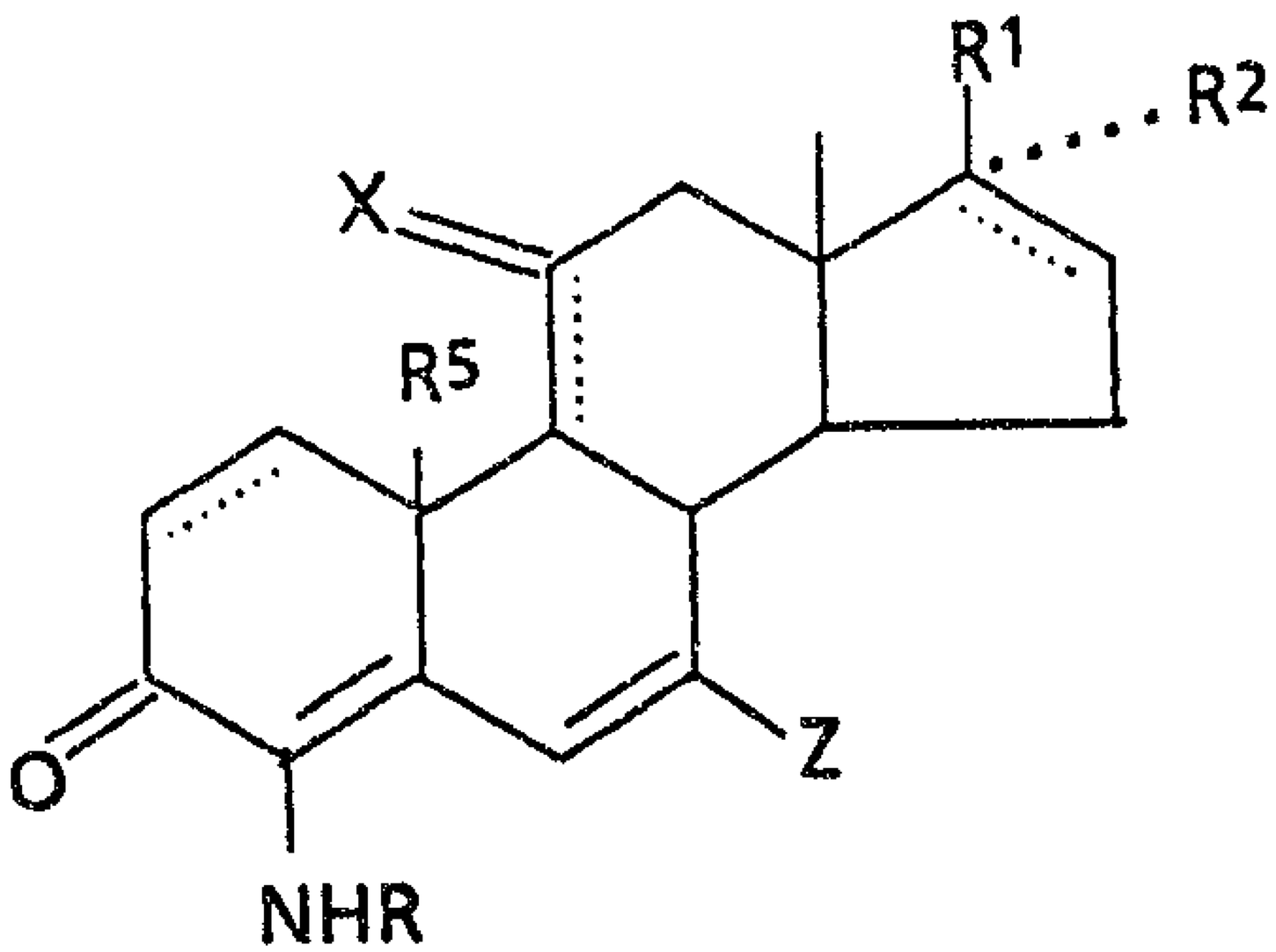
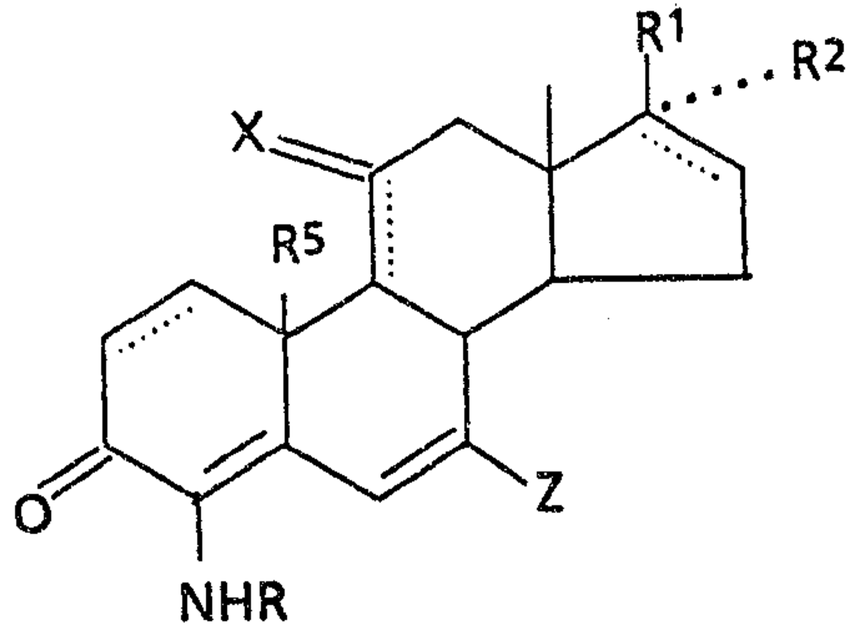
(54) Titre : LES 4-AMINO-4,6-STEROIDES ET LEUR UTILISATION COMME INHIBITEURS DE LA 5-α-REDUCTASE
(54) Title: 4-AMINO- 4,6-STEROIDS AND THEIR USE AS 5-α-REDUCTASE INHIBITORS



(57) Abrégé/Abstract:
The present invention relates to 4-amino-$\Delta^{4,6}$-steroids of the formula: (see formula I) which are useful as inhibitors of 5α-reductase, for example for treating a patient afflicted with a dihydrotestosterone - mediated disease or condition or for treating benign prostatic hypertrophy in a patient. The compounds are prepared by the reaction of an appropriate 4,5-epoxy steroid with sodium azide in an inert solvent in the presence of a strong acid such as sulfuric acid at about 100°C.

ABSTRACT OF THE DISCLOSURE

The present invention relates to 4-amino-$\Delta^{4,6}$-steroids of the formula:



which are useful as inhibitors of 5α-reductase, for example for treating a patient afflicted with a dihydrotestosterone - mediated disease or condition or for treating benign prostatic hypertrophy in a patient. The compounds are prepared by the reaction of an appropriate 4,5-epoxy steroid with sodium azide in an inert solvent in the presence of a strong acid such as sulfuric acid at about 100°C.

4-AMINO-$\Delta^{4,6}$-STEROIDS AND THEIR USE AS 5α-REDUCTASE INHIBITORS

BACKGROUND OF INVENTION

Mammalian steroid 5α-reductase, an enzyme present in mammalian tissues including skin, male genitalia and prostate gland, catalyzes the conversion of the steroidal hormone testosterone to the steroidal hormone dihydrotestosterone (17β-hydroxy-5α-androstan-3-one). Testosterone and dihydrotestosterone (DHT) are both androgenic hormones and they are the primary androgenic steroids in males. These steroids are responsible for the physical characteristics which differentiate males from females. DHT, however, is much more potent than testosterone as an androgen and it acts as an end-organ effector in certain tissues, particularly in mediating growth. Furthermore, the formation of DHT occurs primarily in the target cells themselves as a result of the reduction of testosterone by 5α-reductase.

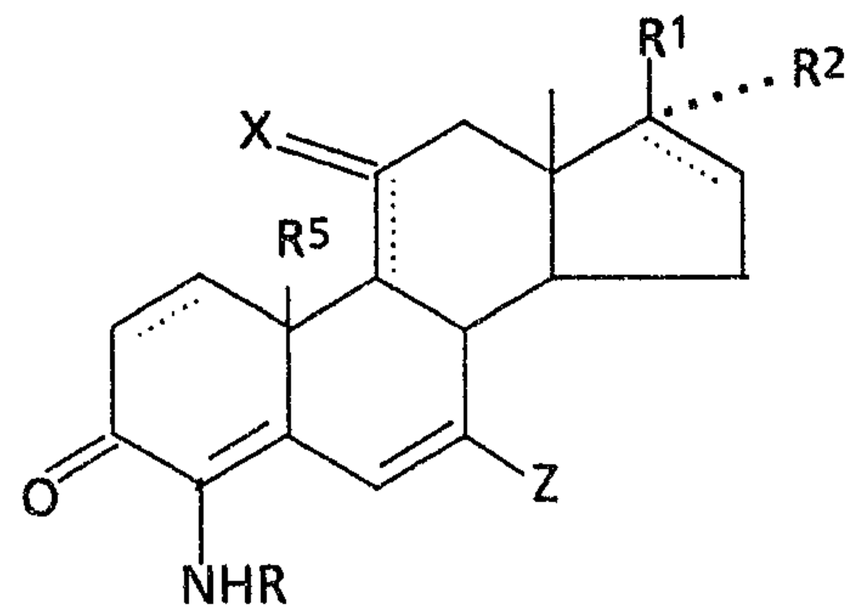
It is known that skin responds to androgens and is an active site of androgen metabolism. In particular, testosterone is converted to DHT in the skin by the action of 5α-reductase. Testosterone metabolism in the skin may at times be abnormally excessive and have undesirable effects as a result of the DHT formed. Thus, there is considerable evidence that DHT is involved in the pathogenesis of acne,

including acne vulgaris, as well as other androgen associated conditions [See Price, *Arch. Dermatol.* 111, 1496 (1975)]. Agents which are capable of blocking the formation of DHT from testosterone in skin, such as by inhibiting the activity of 5α-reductase, would therefore be useful in the treatment of acne.

In addition, other physical conditions and disease states, including benign prostatic hypertrophy, androgenic alopecia (common baldness caused by androgen in genetically susceptible men and women), seborrhea and female hirsutism, are also associated with elevated androgen activity and could be treated by the administration of 5α-reductase inhibitors. [See T. Liang et al., Endocrinology 117, 571 (1985); J.R. Brooks et al., Steroids 47, 1 (1986); J.R. Carlin et al., Journal of Chromatography, 427, 79 (1988).] Thus, agents which are capable of blocking the formation of DHT from testosterone by inhibiting the effects of 5α-reductase would also be effective in the treatment of these conditions.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates a group of compounds which are 4-amino-$\Delta^{4,6}$-steroids and to the use of these compounds as inhibitors of 5α-reductase. More particularly, the present invention relates to aminosteroid compounds having the following general formula:



wherein R is hydrogen or C_{1-4} alkyl; R^1 is C_{2-6} alkanoyl, $-(C_{1-6}$ alkyl$)-OZ^1$, $-(C_{2-6}$ alkyl$)-(OZ^1)_2$ or -A-C(O)-Y; Z^1 is hydrogen, C_{1-6} alkyl, phenyl-(C_{1-4} alkyl), Y^1-substituted phenyl)-(C_{1-4} alkyl), C_{1-6} alkanoyl, benzoyl or Y^1-substituted benzoyl wherein Y^1 is methyl, halogen or methoxy; A is absent or is present as an alkylene of 1 to 6 carbon atoms; Y is -OH, -O(C_{1-6} alkyl) or NR^3R^4; R^2 is hydrogen or R^1 and R^2 can be combined to give $-O-CH_2CH_2CH_2---$; R^3 and R^4 are each independently hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl or they can be combined to give $-(CH_2)_n-$ wherein n is 4 to 6; R^5 is hydrogen or methyl; X is O or (H)(H); Z is hydrogen or C_{1-6} alkyl; and each of the dotted lines in the ring indicates the optional presence of a double bond with the proviso that a 9,11-double bond can only be present when X is (H) and the proviso that, when a 16,17-double bond is present then R^2 is absent.

The various alkyl groups referred to above can be straight or branched-chain and can be exemplified, with the carbon limitations as provided, by methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tert-butyl, pentyl and hexyl. When the alkyl groups are substituted by two $-OZ^1$ groups, the two OZ^1 groups are situated on different carbon atoms. Some examples of the two types of HO-substituted alkyl groups referred to above are hydroxymethyl, 1-hydroxyethyl, 1,2-dihydroxyethyl, 1-methyl-2-hydroxyethyl, 1-hydroxypropyl and 3-hydroxypropyl. Examples of etherified R^1 groups (i.e., Z^1 is alkyl or phenylalkyl) are 2-methoxy-1-methyl-ethyl and 2-(phenylmethoxy)-1-methylethyl. Examples of esterified R^1 groups (i.e., Z^1 is alkanoyl, benzoyl or substituted benzoyl) are 2-acetoxy-1-methylethyl and 2-benzoyl-1-methylethyl. In those case where optical isomerism is possible in the R^1-substituent, the individual pure optical isomers are each part of this invention. Examples of the halogen substituents referred to above are fluorine, chlorine and bromine. The C_{2-6} alkanoyl groups referred to above can be straight or branched-chained and can be exemplified by acetyl, propionyl, butyryl, isobutyryl and

hexanoyl. The C_{1-6} alkanoyl, groups can be exemplified similarly and also include formyl. The C_{3-6} cycloalkyl groups can exemplified by cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. When R^3 and R^4 are combined to give $-(CH_2)n-$, then $-NR^3R^4$ can be exemplified by 1-pyrrolidinyl, 1-piperidinyl or hexahydro-1H-azepin-1-yl. When R^1 is -A-C(O)-Y and A is absent, then the carbonyl function is attached directly to the steroid ring; when A is alkylene of 1 to 6 carbon atoms examples of A are methylene, ethylene, ethylidene, propylene and tetramethylene. When R^1 and R^2 are combined as $-O-CH_2CH_2CH_2---$, a spiro-tetrahydrofuran structure results.

A preferred group of compounds are those in which R^2 is hydrogen and X is (H)(H). Further preferred are those compounds in which R^2 is hydrogen and R^5 is methyl. Still further preferred as potent 5α-reductase inhibitors are those compounds in which R^1 is $-C(O)NR^3R^4$, wherein R^3 and R^4 are each independently hydrogen or C_{1-6} alkyl. In addition, those compounds wherein R^1 is $-(C_{1-6}$ alkyl$)-OZ^1$ wherein Z^1 is defined as above and, particularly, where R^1 is $-CH(CH_3)-CH_2OZ^1$, are further useful because, in addition to their activity as inhibitors of 5α-reductase, they also inhibit C_{17-20} lyase.

Acid addition salts of the aforesaid compounds wherein R is hydrogen or C_{1-6} alkyl, with pharmaceutically acceptable acids, are equivalent to the above amines for the purposes of this invention. Illustrative of such salts are the salts with inorganic acids such as, for example, hydrochloric, hydrobromic, sulfuric, phosphoric and like acids; with organic carboxylic acids such as, for example, acetic, propionic, glycolic, lactic, pyruvic, malonic, succinic, fumaric, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic and dihydroxymaleic, benzoic, phenylacetic, 4-aminobenzoic, 4-hydroxybenzoic, anthranilic, cinnamic, salicylic, 4-aminosalicylic, 2-phenoxybenzoic, 2-acetoxybenzoic, mandelic and like acids; and with organic sulfonic acids such as methanesulfonic acid and p-toluenesulfonic acids.

Examples of compounds of the present invention are the following:

4-Aminopregna-4,6-diene-3,20-dione.
4-Aminopregna-1,4,6-triene-3,20-dione.
4-Aminopregna-4,6,9(11)-trien-3,20-dione.
4-Amino-7-methylpregna-4,6-diene-3,20-dione.
4-Amino-19-norpregna-4,6-diene-3,20-dione.
4-Amino-3-oxoandrosta-4,6-diene-17β-carboxamide.
4-Amino-N-(1,1-dimethylethyl)-3-oxoandrosta-4,6-diene-17β-carboxamide.
4-Amino-N,N-diethyl-3-oxoandrosta-4,6-diene-17β-carboxamide.
4-Amino-N-cyclohexyl-3-oxoandrosta-4,6-diene-17β-carboxamide.
4-Amino-N,N-pentamethylene-3-oxoandrosta-4,6-diene-17β-carboxamide.
2-[4-Amino-N-(1,1-dimethylethyl)-3-oxoandrosta-4,6-dien-17β-yl]acetamide.
4-Amino-3-oxopregna-4,6-diene-20-carboxylic acid.
4-Amino-3-oxopregna-4,6-diene-20-carboxylic acide methyl ester.
4-Amino-N,N-diethyl-3-oxopregna-4,6-diene-20-carboxamide.
4-Aminopregna-4,6-diene-3,11,20-trione.
4-Amino-21-hydroxy-20-methylpregna-4,6-dien-3-one.
4-Amino-20-hydroxypregna-4,6-dien-3-one.
4-Amino-17β-hydroxymethylandrosta-4,6-dien-3-one.
4',5'-Dihydrospiro[4-aminoandrosta-4,6-diene-17,2'(3'H)-furan]-3-one.
4-Amino-N,N-bis(1-methylethyl)-3-oxoandrosta-1,4,6-triene-17β-carboxamide.
4-Amino-N-(1,1-dimethylethyl)-7-methyl-3-oxoandrosta-4,6-diene-17β-carboxamide.
4-(Methylamino)-N-(1,1-dimethylethyl)-3-oxoandrosta-4,6-diene-17β-carboxamide.

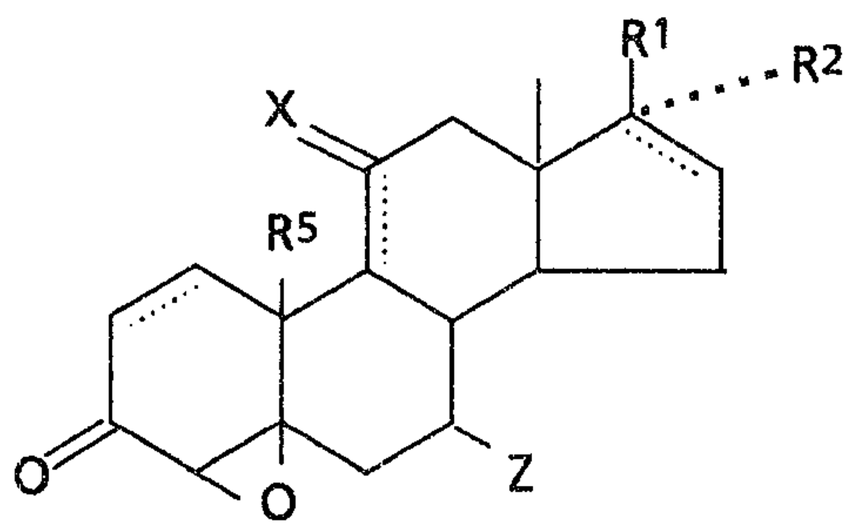
(20S)-4-(Methylamino)-21-hydroxy-20-methylpregna-4,6-dien-3-one.

(20S)-4-Amino-21-methoxy-20-methylpregna-4,6-dien-3-one.

(20S)-4-Amino-21-(phenylmethoxy)-20-methylpregna-4,6-dien-3-one.

The present invention further provides a method for treating a patient afflicted with a DHT-mediated disease or condition which comprises administering to said patient an effective 5α-reductase inhibitory amount of a compound of the present invention. As used herein, the term "patient" refers to a warm-blooded animal, such as a human, which is afflicted with a DHT-mediated disease or condition. DHT-mediated diseases or conditions are those which are associated with elevated androgen activity due to the excessive formation of DHT. Such DHT-mediated diseases or conditions include acne, acne vulgaris, benign prostatic hypertrophy, androgenic alopecia (common baldness caused by androgen in genetically susceptible men and women), seborrhea and female hirsutism. The present invention further relates to the treatment of the particular DHT-mediated diseases and conditions described above.

The 4-amino-4,6-diene compounds of the present invention are obtained by the reaction of a 4,5-epoxy compound of the formula:



wherein R^1, R^2, R^5, X, Z and the dotted lines are defined as above, with sodium azide in an inert solvent such as dimethyl sulfoxide. The reaction is carried out in the presence of a catalytic amount of a strong acid, such as sulfuric acid, with heating at 100°C. No effort is made to isolate

any intermediates but it appears that the epoxide is first opened to give the 4-azido-4-ene. Under the reaction conditions used, the azido compound loses nitrogen, a putative azirine forms, and this opens to give the desired 4-amino-4,6-diene. The amino compound obtained in this way can be further reacted with an appropriate anhydride to give the corresponding 4-amido compound. In the case of the form-amido compound, mixed formic acetic anhydride, prepared in situ, is used as the anhydride.

The 4,5-epoxy compound, used as the starting material above, is itself obtained by the base catalyzed epoxidation of the appropriate corresponding 4-ene using 30% aqueous hydrogen peroxide. For those compounds containing a double bond at the 1-position, it is more convenient to introduce that unsaturation after the epoxide is formed. Thus, for example, treatment of a 4,5-epoxy 3-ketone with dichlorodicyanoquinone gives the corresponding Δ^1 epoxide compound. The epoxide product obtained is generally a mixture of the α and β-epoxides with the β-epoxide being the preponderant product. In some instances, a single isomer is obtained. In any case, further reaction of the epoxides with sodium azide as described earlier gives the desired 4-amino-4,6-diene.

The starting materials used in the above syntheses are known compounds and/or they can be prepared by standard known procedures. For example, for those compounds in which R^5 is hydrogen, estrone 3-methyl ether can be used as the starting material. The desired substitution at the 17-position is introduced by standard procedures. Birch reduction of the aromatic A-ring followed by acidification gives the corresponding 3-oxo-Δ^4-19-norsteroid which is then converted to the epoxide and further reacted as described earlier. Variations in this procedure and the order in which the reactions are carried out are also possible. Thus, starting with the appropriately substituted steroid, it is possible to carry out a Birch reduction and obtain 20-hydroxy-19-nor-

pregn-4-en-3-one. Treatment of this compound with hydrogen peroxide then gives the corresponding 4,5-epoxide and oxidation of the 20-hydroxy group gives 4,5-epoxy-19-norpregnane-3,20-dione which is then reacted as described earlier.

The steroid 4-enes, which are used as starting materials above, are themselves known compounds or they can be prepared by known standard chemical procedures. The starting materials containing an ether group in the 17-substituent can be prepared from the corresponding alcohol. Thus, for example, a 17-(hydroxyalkyl substituted) steroid-4-en-3-one is first converted to the corresponding 3-methoxysteroid-3,5-diene by reaction with trimethyl orthoformate and a trace of p-toluenesulfonic acid in dioxane as the solvent. Pyridine is used to work up this reaction mixture. Alternatively, the 3-ketone can be protected as the ethylene ketal. In either case, the resulting alcohol is then reacted with sodium hydride in dimethylformamide to give the corresponding sodium salt which is then reacted with the appropriate halide, such as methyl iodide or benzyl bromide, to give the corresponding compound containing an ether group as part of the 17-substituent. This ether is then treated with 10% hydrochloric acid, either as part of the general isolation procedure or after isolation of the crude product, to convert the 3-enol ether structure back to the desired steroid-4-en-3-one.

The 4-amino-compounds of the present invention in which R^1 is -COOH or a similar acid group can be obtained by the alkaline hydrolysis of the corresponding alkyl ester. Those 4-amino-compounds in which R is C_{1-4} alkyl are obtained from the corresponding compounds in which R is hydrogen by standard reactions.

The foregoing syntheses are illustrative of the preparation of the present compounds and many other conventional reactions and combinations of these reactions may be used to produce or to interconvert the compounds of the invention.

These conventional reactions and conditions may be found, e.g., in Fieser et al., "Steroids" (Reinhold, New York, 1959); Djerassi, Ed., "Steroid Reactions" (Holden-Day, San Francisco, 1963); Kirk et al., "Steroid Reaction Mechanisms" (Elsevier, Amsterdam, 1968); Carruthers, "Some Modern Methods of Organic Synthesis" (Cambridge U. Press, Cambridge, 1971); and Harrison et al., "Compendium of Organic Synthetic Methods" (Wiley-Interscience, New York, 1971).

The compounds of the present invention are useful as 5α-reductase inhibitors. Accordingly, they are useful in the treatment of the various diseases and conditions which would be affected by such inhibitors as described above.

The activity of the present compounds as 5α-reductase inhibitors can be demonstrated by the following standard test procedure. Microsomal preparations of the steroid 5α-reductase enzyme (protein) were obtained from human prostate tissue and stored in aliquots. Protein concentration was determined prior to use of the samples. In the method itself, individual assays for 5α-reductase activity contained 0.1M phosphate citrate buffer, pH 5.6, 1mM EDTA, 7 to 22 µg of microsomal protein, 1mM NADPH, 5 mM glucose-6-phosphate, 1 IU/ml glucose-6-phosphate dehydrogenase, 1,2-^{3}H-testosterone, and test compound, dissolved in dimethyl sulfoxide and then diluted in phosphate-citrate buffer to yield a final assay concentration of 0.1% (v/v) dimethyl sulfoxide. The same buffer and the same quantity of dimethyl sulfoxide, without any test compound is used for the control assays. The total assay volume was 100 µl and assays were performed in duplicate. The reaction was initiated by the addition of the testosterone, and incubated for 30 minutes at 25°C. The assay is linear with time to 30 minutes.

Depending on the nature of the inhibition, testosterone concentration was typically varied from 0.15 µM (approximately 0.5 K_m) to 10 K_m with radioactive label constant at 0.15 µCi per assay. The amount of test compound added was

varied to provide final concentrations of 1 nM to 100 μM. The reaction was quenched by the addition of 50 volumes of chloroform:methanol (2:1). The steroids were then extracted and separated by high pressure liquid chromatography and the amounts of testosterone and dihydrotestosterone present were determined to determine the percent conversion of testosterone to dihydrotestosterone and to calculate the 5α-reductase activity. The activity of the test compound was then expressed as the IC_{50}, or the concentration of test compound that produced a 50% inhibition of the testosterone conversion. When compounds of the present invention were tested in this way, the following results were observed:

Test Compound	IC_{50}(nM)
4-Aminopregna-4,6-diene-3,20-dione	25
N,N-Diisopropyl-4-amino-3-oxoandrosta-4,6-diene-17β-carboxamide	16
N-(t-Butyl)-4-amino-3-oxoandrosta-4,6-diene-17β-carboxamide	8

To achieve the desired anti-acne or anti-seborrheic effect the compounds employed in the present invention can be administered orally, parenterally, for example, intramuscularly and subcutaneously, and topically to a patient in need of treatment. Topical administration is preferred. As used herein in association with the treatment of acne or oily skin, the term patient is taken to mean a warm-blooded mammal, for example, primates, human males and females having an acne condition or an oily skin condition in need of treatment. The compounds of the invention can be administered alone or suitably admixed in the form of a pharmaceutical preparation to the patient being treated. The amount of compound administered will vary with the severity of the acne condition or oily skin condition and repetitive treatment may be desired. For oral and parenteral administration, the amount of compound administered, that is, the anti-acne or anti-seborrheic effective amount, is from 0.001 to 10 mg/kg of body weight per day and preferably from 0.01

to 1.0 mg/kg of body weight per day. Unit dosages for oral or parenteral administration may contain, for example, from 0.2 to 100 mg of the active ingredient. For topical administration the anti-acne or anti-seborrheic effective amount of the compounds of the invention on a percent basis can vary from 0.001% to 5% and preferably from 0.005% to 1%. For topical administration the formulated active ingredient, that is, a compound of the invention can be applied directly to the site requiring treatment or can be applied to the oral or nasal mucosa. Applicator sticks carrying the formulation may be employed in administering the compounds.

In the treatment of benign prostatic hypertrophy (BPH) the compounds of the invention may be administered in various manners to the patient being treated to achieve the desired effect. As used herein in the treatment of BPH, the term patient is taken to mean male warm blooded animals, such as male dogs and human males. The compounds can be administered alone or in combination with one another. Also, the compounds can be administered in the form of a pharmaceutical preparation. The compounds may be administered orally, parenterally, for example, intravenously, intraperitoneally, intramuscularly or subcutaneously, including injection of the active ingredient directly into the prostate. Slow release implants can also be used. The amount of compound administered will vary over a wide range and can be any effective amount. Depending on the patient to be treated, the condition being treated and the mode of administration, the effective amount of compound administered will vary from about 0.001 to 10 mg/kg of body weight per day and preferably from 0.01 to 1.0 mg/kg of body weight per day. Unit dosages for oral or parenteral administration may contain, for example, from 0.2 to 100 mg of a compound of the invention.

These dosage ranges represent the amount of compound that will be effective in reducing the size of the prostate, i.e., the amount of compound effective in treating BPH. The

compounds can be administered from onset of hypertrophy of the prostate to regression of the symptoms, and may be used as a preventive measure.

The compounds of the present invention may be administered either as individual therapeutic agents or as mixtures with other therapeutic agents. They may be administered alone but are generally administered in the form of pharmaceutical compositions, i.e., mixtures of the active agents with suitable pharmaceutical carriers or diluents. Examples of such compositions include tablets, lozenges, capsules, powders, aerosol sprays, aqueous or oily suspensions, syrups, elixirs and aqueous solutions for injection. The compounds are most preferably administered in oral dosage forms.

The nature of the pharmaceutical composition and the pharmaceutical carrier or diluent will, of course, depend on the desired route of administration, i.e., orally or parenterally. Oral compositions may be in the form of tablets or capsules and may contain conventional excipients such as binding agents (e.g., syrup, acacia, gelatin, sorbitol, tragacanth or polyvinylpyrrolidone), fillers (e.g., lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine), lubricants (e.g., magnesium stearate, talc, polyethylene glycol or silica), disintegrants (e.g., starch) or wetting agents (e.g., sodium lauryl sulfate). Oral liquid preparations may be in the form of aqueous or oily suspensions, solutions, emulsions, syrups, elixirs, etc., or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, flavoring agents, diluents or emulsifying agents. For parenteral administration, solutions or suspensions of a compound of the present invention with conventional pharmaceutical vehicles may be employed, e.g., as an aqueous solution for intravenous injection or as an oily suspension for intramuscular injection. Procedures for the preparation of

compositions as discussed above are described in standard texts, such as Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pennsylvania.

The following are illustrative pharmaceutical formulations suitable for oral administration which may be employed in practicing the present invention:

TABLET

(a)	N-(t-Butyl)-4-amino-3-oxoandrosta-4,6-diene-17β-carboxamide	75 g
(b)	Lactose	1.216 Kg
(c)	Corn starch	0.3 Kg

Mix the active ingredient, lactose and corn starch uniformly. Granulate with 10% starch paste. Dry to a moisture content of about 2.5%. Screen through a No. 12 mesh screen. Add and mix the following:

(a)	Magnesium stearate	0.015 Kg
(b)	Corn starch qs ad	1.725 Kg

Compress on a suitable tablet machine to a weight of 0.115 g/tablet.

SOFT GELATIN CAPSULE

(a)	N-(t-Butyl)-4-amino-3-oxoandrosta-4,6-diene-17β-carboxamide	0.25 Kg
(b)	Polysorbate 80	0.25 Kg
(c)	Corn oil qs ad	25.0 Kg

Mix and fill into 50,000 soft gelatin capsules.

The following examples are presented to illustrate the present invention but they should not be construed as limiting it in any way.

EXAMPLE 1

N-(1,1-Dimethylethyl)-4,5-epoxy-3-oxoandrostane-17β-carboxamide

A solution of N-(1,1-dimethylethyl)-3-oxoandrost-4-ene-17β-carboxamide (4.77 g, 12.8 mmole) in methanol (55 mL) and dichloromethane (11 mL) was cooled to 12°C and treated in one portion with 30% aqueous hydrogen peroxide (3.3 mL) followed by dropwise addition of an aqueous sodium hydroxide solution prepared by dissolving sodium hydroxide (0.38 g) in water (2.2 mL). After one hour, the cooling bath was removed and the reaction was stirred for an additional 3 hours. Most of the solvent was then removed in vacuo. The residue was dissolved in dichloromethane and purified by flash chromatography (hexane-20% ethyl acetate and hexane-40% ethyl acetate) to give N-(1,1-Dimethylethyl)-4,5-epoxy-3-oxoandrostane-17β-carboxamide (3.3 g, 66.2%) as a solid foam. This material was a mixture of the 4α,5α- and 4β,5β-isomers and it was used as is in further reactions.

EXAMPLE 1A

When the procedure of Example 1 was repeated using the appropriate starting materials, the following compounds were obtained, usually as a mixture of the two isomeric epoxides:

N,N-Bis(1-methylethyl)-4,5-epoxy-3-oxoandrostane-17β-carboxamide (73.5%).

(20S)-4,5-Epoxy-3-oxopregnane-20-carboxylic acid methyl ester (61.3%).

4,5-Epoxypregnane-3,20-dione (87.6%).

4,5-Epoxy-17α-hydroxypregnane-3,20-dione (79.1%).

4,5-Epoxypregnane-3,11,20-trione (41.8%).

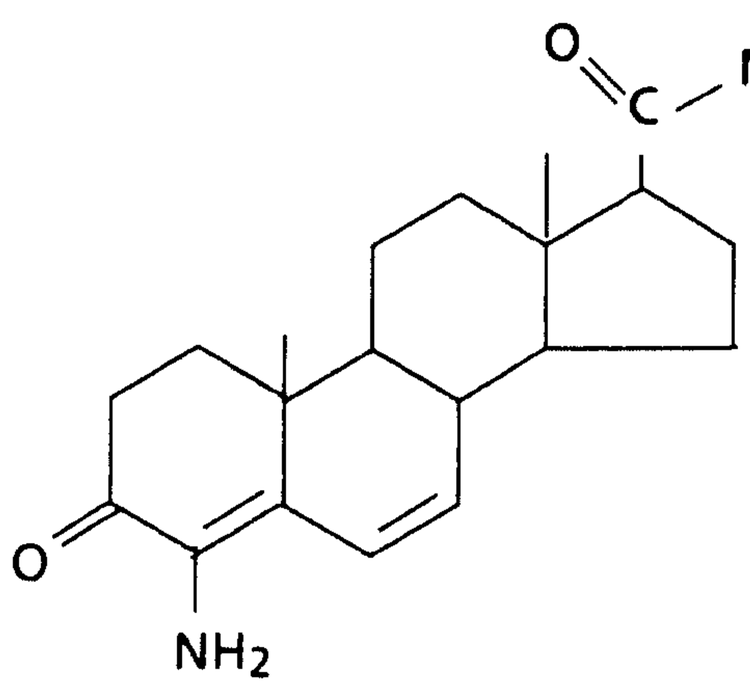
(20S)-4,5-Epoxy-21-hydroxy-20-methylpregnan-3-one (73.1%).

4,5-Epoxypregn-9(11)-ene-3,20-dione (75.5%).

EXAMPLE 2

4-Amino-N-(1,1-dimethylethyl)-3-oxoandrosta-4,6-diene-17β-carboxamide

A solution of 4,5-epoxy-N-(1,1-dimethylethyl)-3-oxo-androstane-17β-carboxamide (3.0 g, 7.7 mmole) in dimethyl sulfoxide (40 mL), under a nitrogen atmosphere, was placed in an oil bath heated at 60°C. The solution was stirred vigorously as sodium azide (8.11 g, 0.338 mole) was slowly added. After the addition of the azide was complete, concentrated sulfuric acid (0.54 mL) was added. The bath temperature was raised to 100°C and the reaction was stirred at this temperature for 90 minutes. The reaction was removed from the oil bath and cooled to room temperature and the resulting solid mass was broken up and poured into cold water (550 mL). The mixture was stirred for 30 min and the solids were collected by filtration, washed with water and dried to a yellow solid. The crude product was purified by flash chromatography (hexane-30% ethyl acetate) to give 4-amino-N-(1,1-dimethylethyl)-3-oxoandrosta-4,6-diene-17β-carboxamide as a crystalline, yellow solid (0.90 g, 30%) (aq methanol). IR 3442, 3372, 1662, 1616, 1592, 1570, 1512 cm^{-1}; MS (CI) m/z 385 (100%, $M^+ + 1$); (EI) m/z 384 (35%, M^+), 150 (100%); ^1H NMR ($CDCl_3$) δ 0.77 (3H, s, C_{18}-Me), 1.06 (3H, s, C_{19}-Me), 1.37 (s, ^tBu-Me's), 2.44-2.54 (1H, pr dd), 2.58-2.72 (1H, pr dd), 3.70 (1.6H, br, NH_2), 5.13 (1H, s, NH), 5.97 (1H, dd), 6.30 (1H, dd); ^{13}C NMR ($CDCl_3$) δ 132.27, 132.44, 135.90, 171.51, 194.27. This compound has the following structure:



EXAMPLE 2A

When the procedure of Example 2 was repeated using the appropriate starting materials, the following compounds were obtained:

4-Amino-N,N-bis(1-methylethyl)-3-oxoandrosta-4,6-diene-17β-carboxamide, IR 3446, 3372, 1662, 1634, 1592 cm^{-1}; MS (CI) m/z 413 (100%, $M^+ + 1$); (EI) m/z 412 (100%, M^+); ^1H NMR ($CDCl_3$) δ 0.84 (3H, s, C_{18}-Me), 1.06 (3H, s, C_{19}-Me), 1.14 (d, ^iPr-Me), 1.21 (d, ^iPr-Me), 1.39 + 1.42 (pr d, 2 x ^iPr-Me), 3.40 (1H, hept ^iPr-CH), 3.71 (2H, br s, NH_2), 4.20 (1H, hept ^iPr-CH), 5.98 (1H, dd) 6.31 (1H, dd); ^{13}C NMR ($CDCl_3$) δ 121.83, 132.16, 132.64, 136.23, 173.63, 194.29.

(20S)-4-Amino-3-oxopregna-4,6-diene-20-carboxylic acid methyl ester, IR 3478, 3374, 1728, 1666, 1616, 1596, 1572 cm^{-1}; MS (CI) m/z 372 (100%, $M^+ + 1$); (EI) m/z 371 (100%, M^+); ^1H NMR ($CDCl_3$) δ 0.77 (3H, s, C_{18}-Me), 1.05 (3H, s, C_{19}-Me), 1.19 (d, C_{21}-Me), 3.64 (5H, s over br s, $CH_3O + NH_2$), 5.94 (1H, dd), 6.29 (1H, dd); ^{13}C NMR ($CDCl_3$) δ 121.88, 132.14, 132.68, 136.14, 177.12, 194.32.

4-Aminopregna-4,6-diene-3,20-dione, IR 3450, 3365, 1695, 1660, 1620, 1595, 1575 cm^{-1}; MS (CI) m/z 328 (100%, $M^+ + 1$); (EI) m/z 327 (40%, M^+), 150 (100%); ^1H NMR ($CDCl_3$) δ 0.71 (3H, s, C_{18}-Me), 1.06 (3H, s, C_{19}-Me), 2.15 (s, C_{21}-Me), 3.72 (2H, br s, NH_2), 5.95 (1H, dd), 6.31 (1H, dd); ^{13}C NMR ($CDCl_3$) δ 122.04, 132.24, 132.28, 135.61, 194.25, 209.16.

4-Amino-17α-hydroxypregna-4,6-diene-3,20-dione, IR 3442, 1704, 1660, 1614, 1590 cm^{-1}; MS (CI) m/z 344 (100%, $M^+ + 1$); (EI) m/z 343 (75%, M^+), 150 (100%); ^1H NMR ($CDCl_3$) δ 0.78 (s, C_{18}-Me), 1.06 (3H, s, C_{19}-Me), 2.28 (3H, s, C_{21}-Me), 2.7-3.7 (2.5H, br m, NH_2), 5.97 (1H, dd); ^{13}C NMR ($CDCl_3$) δ 89.62, 122.08, 132.25, 132.51, 135.69, 178.91, 194.32, 211.39.

4-Aminopregna-4,6-diene-3,11,20-trione, IR 3454, 3362, 1706, 1694, 1620, 1600, 1570 cm^{-1}; MS (CI) m/z 342 (100%, M^+

+ 1); (EI) m/z 341 (80%, M^+), 43 (100%); ^{1}H-NMR ($CDCl_3$) 0.70 (3H, s, C_{18}-Me), 1.27 (3H, s, C_{19}-Me), 2.12 (3H, s, C_{21}-Me), 3.28 (2H br s, NH_2), 5.93 (1H,dd), 6.36 (1H,dd); ^{13}C NMR ($CDCl_3$) 122.73, 129.56, 132.64, 133.04, 194.60, 207.60, 208.40.

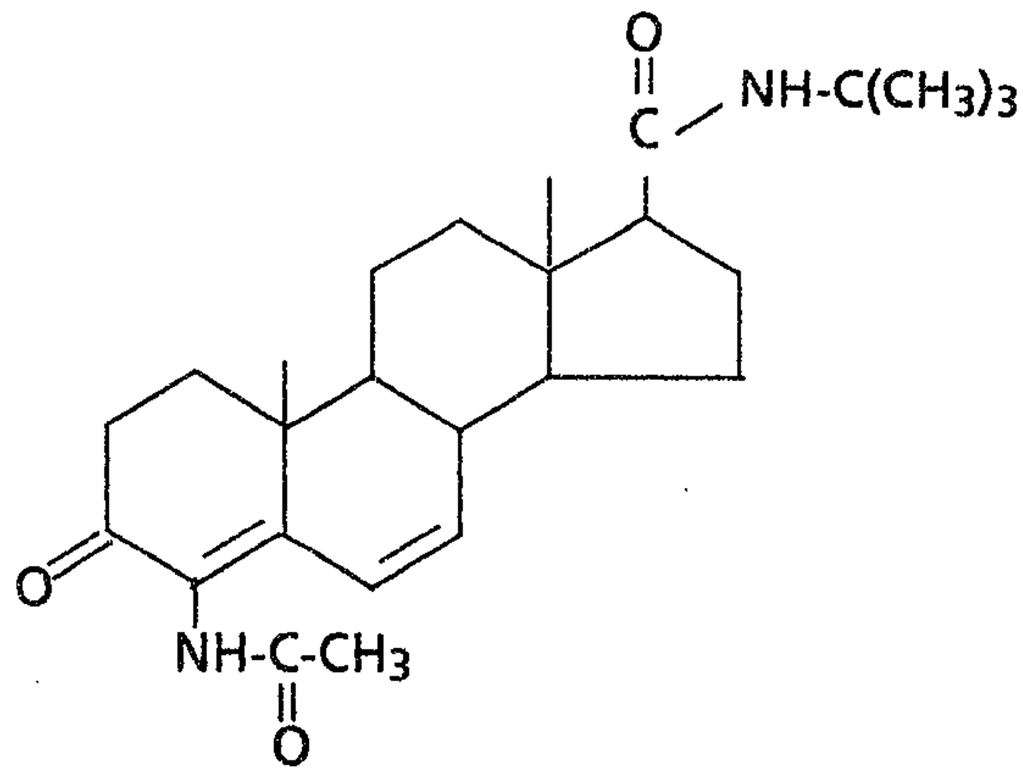
(20S)-4-Amino-21-hydroxy-20-methylpregna-4,6-dien-3-one, IR 3462, 3390, 3346, 1652, 1616, 1592, 1564 cm^{-1}; MS (CI) m/z 344 (100%, M^+ + 1); (EI) m/z 343 (60%, M^+), 150 (100%); ^{1}H NMR ($CDCl_3$) δ 0.76 (3H, s, C_{18}-Me), 1.04 + 1.05 (6H, s + d, C_{19}-Me + C_{21}-Me) 2.48 (1H, dq), 2.63 (1H, dq), 3.38 (1H, dd, 1/2 C_{21}-CH_2), 3.64(dd + v br, 1/2 C_{21}-CH_2 + NH_2), 5.97 (1H, dd) 6.30 (1H, dd); ^{13}C NMR ($CDCl_3$) δ 121.77, 132.08, 132.98, 136.55, 194.40.

EXAMPLE 3

4-Acetamido-N-(1,1-dimethylethyl)-3-oxoandrosta-4,6-diene-17β-carboxamide

A solution of 4-amino-N-(1,1-dimethylethyl)-3-oxoandrosta-4,6-diene-17β-carboxamide (0.9 g, 2.34 mmole) in acetic anhydride (3 mL) and pyridine (6 mL) was stirred overnight at room temperature. Water was added and the mixture was stirred for 3 hours. The solids were collected by filtration to give a brown solid which was purified by flash chromatography (hexane-50% ethyl acetate, ethyl acetate) to give 4-acetamido-N-(1,1-dimethylethyl)-3-oxoandrosta-4,6-diene-17β-carboxamide (0.29 g, 30.4%, diethyl ether-hexane). IR 3442, 3382, 1664, 1616 cm^{-1}; MS (CI) m/z 427 (100%, M^+ + 1); (EI) m/z 426 (65%, M^+), 57 (100%); ^{1}H NMR ($CDCl_3$) δ 0.78 (3H, s, C_{18}-Me), 1.13 (3H, s, C_{19}-Me), 1.35 (s, 3 x ^{t}Bu-Me's), 2.14 (s, Ac-Me), 5.13 (1H, s, NHCOBu), 6.16 (2H, s, C_6-H + C_7-H), 7.12 (1H, NHAc); ^{13}C NMR ($CDCl_3$) δ 124.65, 124.89, 139.95, 153.20, 168.74, 171.44, 194.93.

This compound has the following structure:



EXAMPLE 3A

When the procedure of Example 3 was repeated using the appropriate starting materials, the following compound was obtained:

4-Acetamidopregna-4,6-diene-3,20-dione, IR 3295, 1700, 1665, 1615(m) cm^{-1}; MS (CI) m/z 370 (100%, M^+ + 1); (EI) m/z 369 (10%, M^+), 43 (100%); ^1H NMR ($CDCl_3$) δ 0.71 (3H, s, C_{18}-Me), 1.13 (3H, s, C_{19}-Me), 2.13 (s, C_{21}-Me + Ac-Me), 6.12 (2H, s, C_6-H + C_7-H), 7.03 (1H, br s, NH); ^{13}C NMR ($CDCl_3$) δ 124.83, 139.63, 152.95, 195.92, 209.14.

(20S)-4-Acetamido-21-acetoxy-20-methylpregna-4,6-dien-3-one is obtained in a similar manner.

EXAMPLE 4

4-Formamido-N-(1,1-dimethylethyl)-3-oxoandrosta-4,6-diene-17β-carboxamide

A solution of formic acid (0.22 mL, 5.84 mmole) and acetic anhydride (0.46 mL, 4.76 mmole) was heated at reflux temperature for 2 hours under a nitrogen atmosphere. The cooled solution was diluted with tetrahydrofuran (5 mL) and a solution of 4-amino-N-(1,1-dimethylethyl)-3-oxoandrosta-4,6-diene-17β-carboxamide, (0.35 g, 0.91 mmole) in tetrahydrofuran (10 mL) was added. The reaction was stirred overnight at room temperature and then diluted with water (25 mL). A gummy material separated which was extracted into diethyl ether-dichloromethane and washed with saturated

aqueous sodium bicarbonate. The dried solution was concentrated to a yellow foam which was purified by flash chromatography (hexane-50% ethyl acetate, ethyl acetate) to give 4-formamido-N-(1,1-dimethylethyl)-3-oxoandrosta-4,6-diene-17β-carboxamide (0.25 g, 67.6%, diethyl ether). IR 3440, 3304, 3246, 1684, 1670, 1650 cm^{-1}; MS (CI) m/z 413 (100%, M^+ + 1); (EI) m/z 412 (18%, M^+), 57 (100%); ^1H NMR ($CDCl_3$) δ 0.78 (3H, s, C_{18}-Me), 1.14 (3H, s, C_{19}-Me), 1.37 (s, 3 x ^{t}Bu-Me's), 5.11 (1H, s, NHCOBu), 6.15-6.45 (2H, m, C_6-H+C_7-H), 7.07-7.20 (1H, d + s, NHCO), 8.12+8.29 (1H, d + s, CHO).

EXAMPLE 4A

When the procedure of Example 4 was repeated using the appropriate starting material, the following compound was obtained:

4-Formamidopregna-4,6-diene-3,20-dione, IR 3325, 1710, 1690, 1650, 1615, 1585, 1475; MS (CI) m/z 356 (100%, M^+ + 1); (EI) m/z 355 (25%, M^+), 43 (100%); ^1H NMR ($CDCl_3$) δ 0.73 + 0.74 (pr s, C_{18}-Me), 1.13 + 1.15 (pr s, C_{19}-Me), 2.12 (s, C_{21}-Me), 6.14-6.25 (m + s) 6.38-6.45 (m, 3 parts), 7.00-7.08 (m, 3 parts + 8 parts), 7.16 (br s, 4 parts), 7.59 (d, 3 parts), 8.02 s, 4 parts).

EXAMPLE 5

(20S)-4-Amino-N,N-diethyl-3-oxopregna-4,6-diene-20-carboxamide

A stirred suspension of 3-oxopregn-4-ene-20-carboxylic acid (2.0 g, 5.8 mmole) in benzene (40 mL) was mixed with pyridine (0.59 mL, 7.3 mmole), cooled in an ice-water bath and treated with oxalyl chloride (0.65 mL, 7.5 mmole). The cooling bath was removed and the reaction mixture was stirred for one hour at room temperature. The mixture was then cooled in an ice-water bath and treated with diethylamine (3.48 mL, 33.7 mmole). After 45 minutes, the reaction was diluted with methylene chloride (100 mL) and extracted with 7% hydrochloric acid (100mL). The organic layer was separated, dried over magnesium sulfate, treated with char-

coal and filtered. The solvent was then removed to leave a white solid which was redissolved in methylene chloride and purified by flash chromatography (ethyl acetate-50% hexane). The resulting solid was recrystallized from aqueous methanol to give (20S)-N,N-diethyl-3-oxopregn-4-ene-20-carboxamide melting at about 198-199°C.

When the product obtained by the above reaction is reacted with 30% aqueous hydrogen peroxide according to the procedure described in Example 1, the corresponding 4,5-epoxide is obtained. This epoxide is then reacted with sodium azide and sulfuric acid according to the procedure described in Example 2 to give (20S)-4-amino-N,N-diethyl-3-oxopregna-4,6-diene-20-carboxamide.

EXAMPLE 6

(20S)-4-Amino-N-(1,1-dimethylethyl)-3-oxopregna-4,6-diene-20-carboxamide

A stirred suspension of 3-oxopregn-4-ene-20-carboxylic acid (1.7 g, 5.0 mmole) in benzene (35 mL) was mixed with pyridine (0.56 mL, 6.25 mmole), cooled in an ice-water bath and treated with oxalyl chloride (0.56 mL, 6.45 mmole). The cooling bath was removed and the reaction mixture was stirred for 1.5 hours. The resulting mixture was then cooled in ice and treated slowly with tert-butylamine (2.9 mL, 29 mmole). After thirty minutes, the mixture was diluted with methylene chloride (100 mL), extracted with 5% hydrochloric acid, dried over magnesium sulfate, treated with charcoal, and filtered. The resulting filtrate was concentrated to give a yellow solid which was dissolved in methylene chloride and purified by flash chromatography (hexane-40% ethyl acetate). The product obtained in this way was subjected to flash chromatography again (hexane-30% ethyl acetate) and the resulting product was recrystallized from acetone to give (20S)-N-(1,1-dimethylethyl)-3-oxopregn-4-ene-20-carboxamide. IR 3445, 3375, 1670 cm^{-1}.

When the product obtained by the above reaction is reacted with 30% aqueous hydrogen peroxide according to the procedure described in Example 1, the corresponding 4,5-epoxide is obtained. This epoxide is then reacted with sodium azide and sulfuric acid according to the procedure described in Example 2 to give (20S)-4-amino-N-(1,1-dimethylethyl)-3-oxopregna-4,6-diene-20-carboxamide.

EXAMPLE 7

(20S)-4,5-Epoxy-21-hydroxy-20-methylpregnan-3-one Acetate

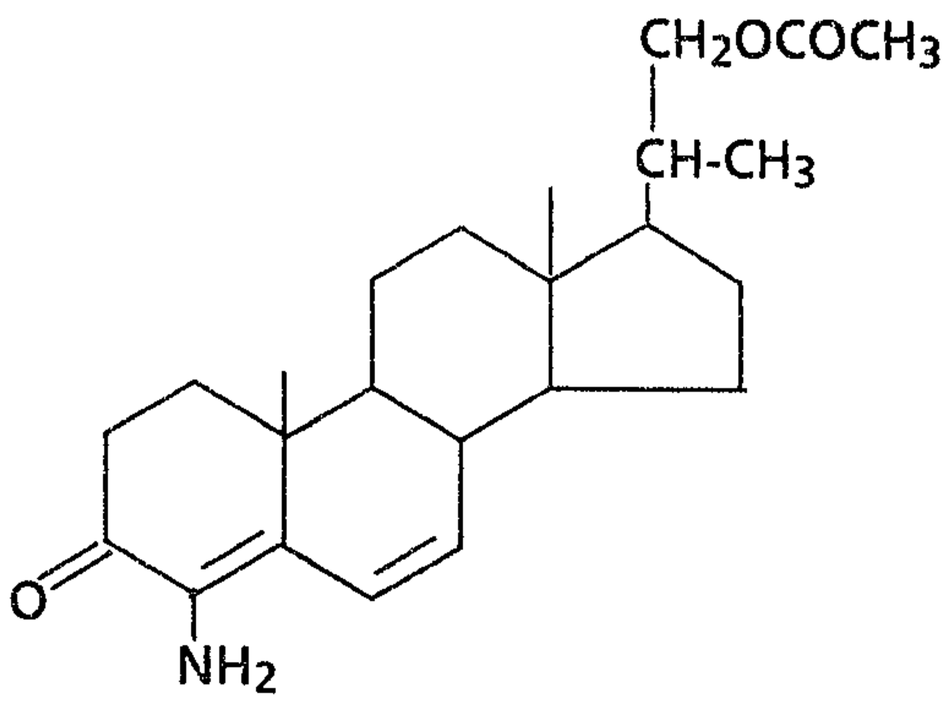
To a solution of (20S)-21-hydroxy-20-methylpregn-4-en-3-one acetate (10.6 g, 28.3 mmole) in methanol (60 mL) and dichloromethane (15 mL) cooled to 15°C in a cold water bath there was added 30% hydrogen peroxide (6.8 mL) and then, dropwise, a solution of sodium hydroxide (0.49 g) in water (3.2 mL). After 30 minutes, the cold bath was removed and the reaction was stirred for 4 hours at room temperature. The solvents were then removed under reduced pressure and the residue was dissolved in dichloromethane (300 mL) and extracted with brine (100 mL). The organic layer was separated, dried over magnesium sulfate, filtered and concentrated to a solid which was purified by flash chromatography on silica gel to give (20S)-4,5-epoxy-21-hydroxy-20-methylpregnan-3-one acetate (6.1 g, 55.6%) as a mixture of the 4α,5α- and 4β,5β-isomers.

EXAMPLE 8

(20S)-4-Amino-21-hydroxy-20-methylpregna-4,6-dien-3-one Acetate

To a vigorously stirred solution of the (20S)-4,5-epoxy-21-hydroxy-20-methylpregnan-3-one acetate (2.0 g, 5.15 mmole) obtained in Example 7, in dimethyl sulfoxide (70 mL) and heated to 60°C, there was added sodium azide (5.4 g) and then concentrated sulfuric acid (0.37 mL). The mixture was quickly brought to a temperature of 100°C and held at that temperature for 1 hour. The cooled mixture was then poured into cold water (450 mL). The solids were collected by filtration, washed with water, and dried by suction to give

a yellow solid which was purified by flash chromatography to give (20S)-4-amino-21-hydroxy-20-methylpregna-4,6-dien-3-one acetate (1.04 g, 52.5%). IR 3488, 3446, 3360, 1740, 1668, 1612 (m), 1592 (m), 1562 (m), 1252 cm^{-1}; MS (CI) 386 (20%, M + 1), 326 (100%, M + 1 - AcOH); ^1H NMR ($CDCl_3$) δ 0.78 (3H, s, C_{18}-Me), 1.03 (d, C_{22}-Me), 1.06 (s, C_{19}-Me), 2.07 (s, Ac-Me), 3.69 + 3.78 (3H, v br + dd, NH_2 + 1/2 C_{21}-CH_2), 4.09 (1H, dd, 1/2 C_{21}-CH_2), 5.97 (1H, dd), 6.30 (1H, dd). This compound has the following structure:



EXAMPLE 9

(20S)-21-Hydroxy-20-methylpregn-4-en-3-one Benzoate

A solution of (20S)-21-hydroxy-20-methylpregn-4-en-3-one (8.0 g, 24.2 mmole) in dichloromethane (200 mL) was cooled in an ice-water bath and treated sequentially with triethylamine (3.69 mL, 26.6 mmole) and benzoyl chloride (3.09 mL, 26.6 mmole) and stirred for 16 hours at room temperature. After the reaction mixture was diluted with dichloromethane (200 mL), it was extracted with ether, dried over magnesium sulfate and filtered and the filtrate was concentrated to a solid which was purified by flash chromatography to give (20S)-21-hydroxy-20-methylpregn-4-en-3-one benzoate (9.4 g, 89.5%) melting at 193-195°C after recrystallization from acetone. IR 1716, 1676, 1614 (m), 1284 cm^{-1}; MS (CI) 435 (100%, M + 1), 313 (70%, M + 1 - PhCOOH); ^1H NMR ($CDCl_3$) δ 0.77 (3H, s, C_{18}-Me), 1.04 (d, C_{22}-Me), 1.19 (s, C_{19}-Me), 4.05 (1H, dd, 1/2 C_{21}-CH_2), 4.34 (1H, dd, 1/2 C_{21}-CH_2), 5.72 (1H, s, C_4-H), 7.45 (2H, t), 7.56 (1H, t), 8.04 (2H, dd).

EXAMPLE 10

(20S)-4,5-Epoxy-21-hydroxy-20-methylpregnan-3-one Benzoate

A solution of (20S)-21-hydroxy-20-methylpregn-4-en-3-one benzoate (8.9 g, 20.5 mmole) in methanol (80 mL) and dichloromethane (80mL) was cooled to 15°C and treated sequentially with 30% hydrogen peroxide (5.0 mL) and sodium hydroxide (1.09 g) in water (6.7 mL). After 4 hours at room temperature, the product was isolated from the reaction mixture by the same procedure as described in Example 7 to give (20S)-4,5-epoxy-21-hydroxy-20-methylpregnan-3-one benzoate (1.6 g, 17.3%). IR 1720, 1280 cm^{-1}; MS (CI) 451 (95%, M + 1), 329 (100%, M + 1 - PhCOOH); ^1H NMR ($CDCl_3$) δ 0.76 (3H, s, C_{18}-Me), 1.13 (d, C_{22}-Me), 1.16 (s, C_{19}-Me), 2.98 + 3.04 (1H, s + s, C_4-H), 4.04 (1H, dd, 1/2 C_{21}-CH_2), 4.32 (1H, dd, 1/2 C_{21}-CH_2), 7.46 (2H, t), 7.57 (1H, t), 8.04 (1H, dd).

EXAMPLE 11

(20S)-4-Amino-21-hydroxy-20-methylpregna-4,6-dien-3-one Benzoate

To a vigorously stirred solution of (20S)-4,5-epoxy-21-hydroxy-20-methylpregnan-3-one benzoate (1.0 g, 2.22 mmole) in dimethyl sulfoxide (35 mL), heated to 60°C, there was added sodium azide (2.7 g) and the concentrated sulfuric acid (0.2 mL). The mixture was quickly brought to a temperature of 100°C and held at that temperature for 1 hour. The cooled mixture was then poured onto cold water (250 mL). The resulting mixture was extracted with ether (300 mL) and the ether solution was washed with brine, dried over magnesium sulfate and filtrate and the filtrate was concentrated to give a yellow solid which was purified by chromatography to give (20S)-4-amino-21-hydroxy-20-methylpregna-4,6-dien-3-one benzoate (0.8 g, 80.1%) melting at 163-167°C with decomposition. IR 3470, 3366, 1718, 1682 (m), 1656, 1608 (m), 1586 (m), 1567 (m), 1274, 1268, 718 cm^{-1}; MS (CI) 448 (100%, M + 1), 326 (35%, M + 1 - PhCOOH); ^1H NMR ($CDCl_3$) δ 0.82 (3H, s, C_{18}-Me), 1.07 (s, C_{19}-Me), 1.15 (d, C_{22}-Me), 3.71 (2H, v br, NH_2), 4.07 (1H, dd, 1/2 C_{21}-CH_2), 4.35 (1H, dd, 1/2 C_{21}-

CH_2), 5.98 (1H dd), 6.30 (1H dd), 7.35 (2H, t), 7.57 (1H, t), 8.04 (2H, dd).

EXAMPLE 12

If the procedures as described in Examples 1 and 2 are repeated using the appropriate starting materials, the following compounds are obtained:

4-Amino-17β-hydroxymethylandrosta-4,6-dien-3-one.

(20S)-4-Amino-20-hydroxypregna-4,6-dien-3-one.

(20R)-4-Amino-20-hydroxypregna-4,6-dien-3-one.

(20S)-4-Amino-20-hydroxypregna-4,6,16-trien-3-one.

(20R)-4-Amino-20-hydroxypregna-4,6,16-trien-3-one.

(20R)-4-Amino-20,21-dihydroxypregna-4,6-dien-3-one.

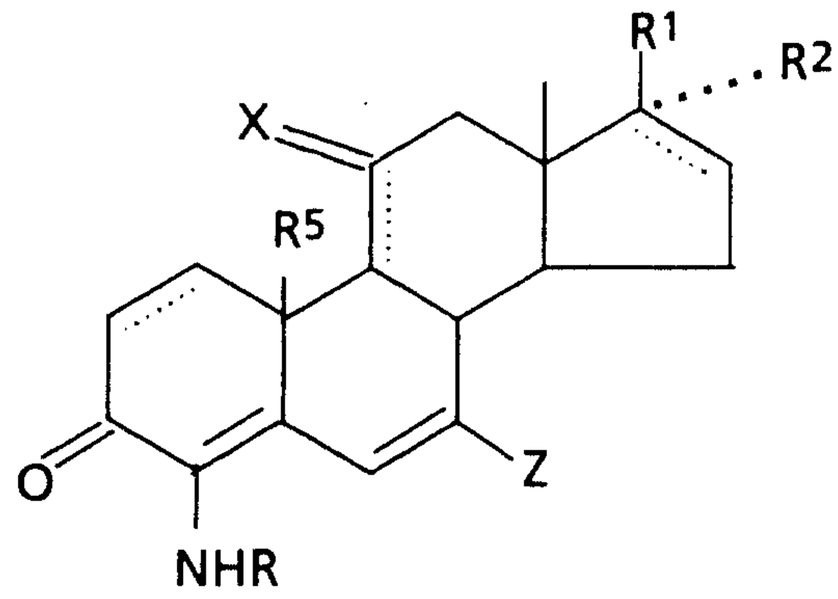
4-Amino-21-hydroxypregna-4,6-dien-3-one.

(20S)-4-Amino-21-methoxy-20-methylpregna-4,6-dien-3-one.

(20S)-4-Amino-21-(phenylmethoxy)-20-methylpregna-4,6-dien-3-one.

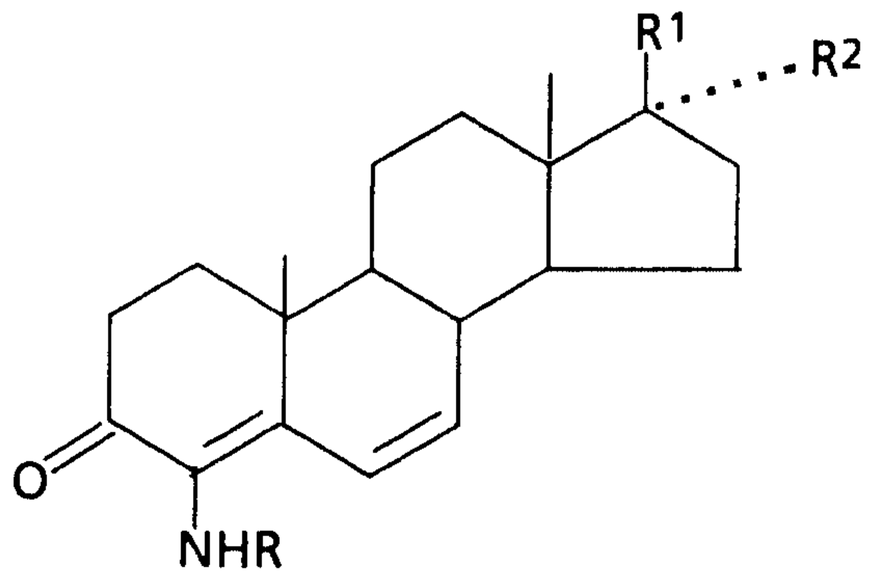
WHAT IS CLAIMED IS:

1. A compound of the formula:



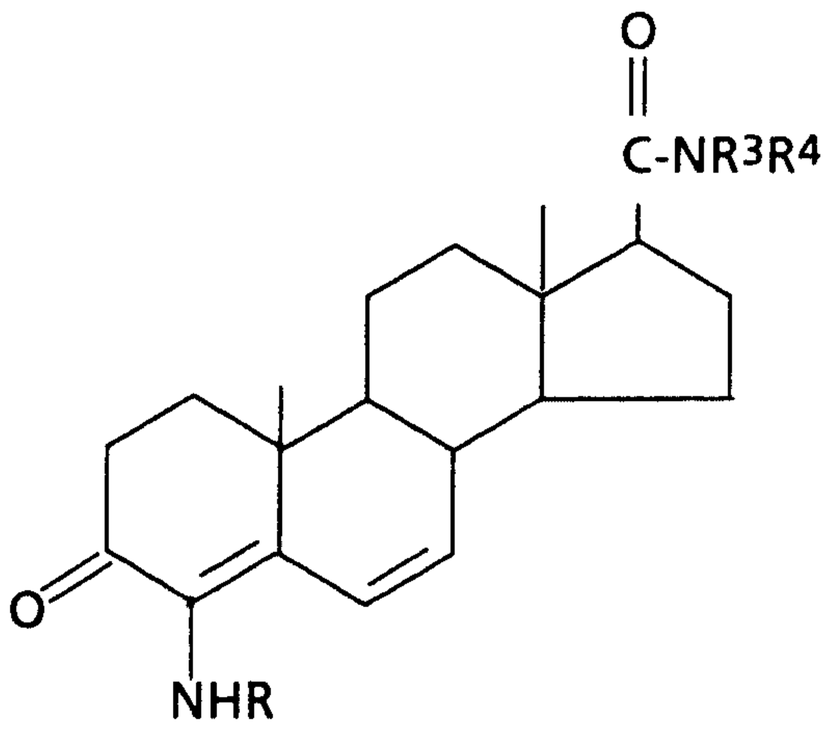
wherein R is hydrogen or C_{1-4} alkyl; R^1 is C_{2-6} alkanoyl, $-(C_{1-6}$ alkyl$)-OZ^1$, $-(C_{2-6}$ alkyl$)-(OZ^1)_2$ or -A-C(O)-Y; Z^1 is hydrogen, C_{1-6} alkyl, phenyl-(C_{1-4} alkyl), (Y^1-substituted phenyl)-(C_{1-4} alkyl), C_{1-6} alkanoyl, benzoyl or Y^1-substituted benzoyl wherein Y^1 is methyl, halogen or methoxy; A is absent or is present as an alkylene of 1 to 6 carbon atoms; Y is -OH, -O(C_{1-6} alkyl) or NR^3R^4; R^2 is hydrogen or R^1 and R^2 can be combined to give $-O-CH_2CH_2CH_2---$; R^3 and R^4 are each independently hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl or they can be combined to give $-(CH_2)_n-$ wherein n is 4 to 6; R^5 is hydrogen or methyl; X is O or (H); Z is hydrogen or C_{1-6} alkyl; and each of the dotted lines in the rings indicates the optional presence of a double bond with the proviso that a 9,11-double bond can only be present when X is (H) and the proviso that, when a 16,17-double bond is present, then R^2 is absent.

2. A compound according to Claim 1 which has the formula:



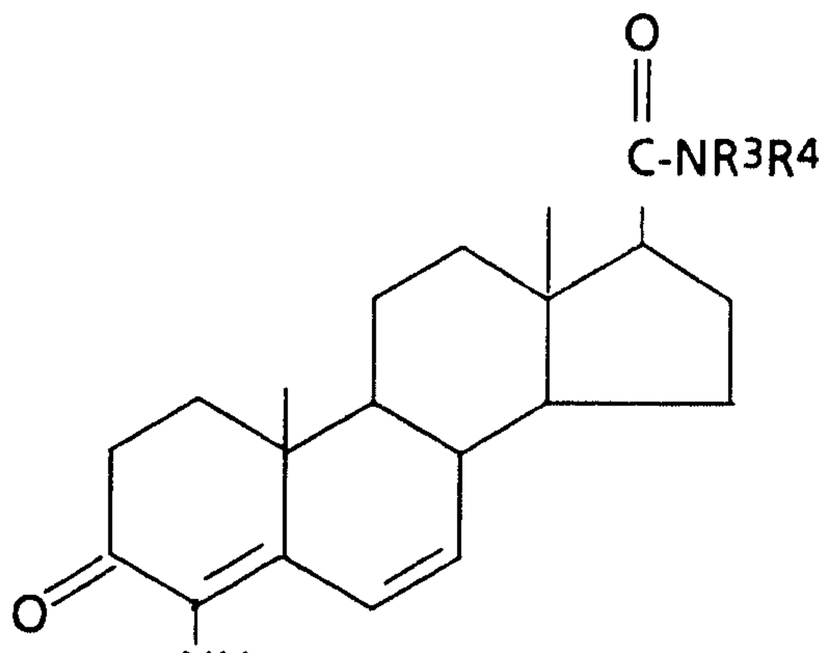
wherein R is hydrogen or C_{1-4} alkyl; R^1 is C_{2-6} alkanoyl, $-CH(CH_3)-CH_2OZ^1$, $-CH(CH_3)-COO(C_{1-6}$ alkyl) or $-C(O)-NR^3R^4$; R^2 is hydrogen or R^1 and R^2 can be combined to give $-O-CH_2CH_2CH_2---$; Z^1 is hydrogen, C_{1-6} alkyl or C_{1-6} alkanoyl; R^3 and R^4 are each independently hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl or they can be combined to give $-(CH_2)_n-$ wherein n is 4 to 6.

3. A compound according to Claim 2 which has the formula:



wherein R is hydrogen or C_{1-4} alkyl; R^3 and R^4 are each independently hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl or they can be combined to give $-(CH_2)_n-$ wherein n is 4 to 6.

4. A compound according to Claim 3 which has the formula:

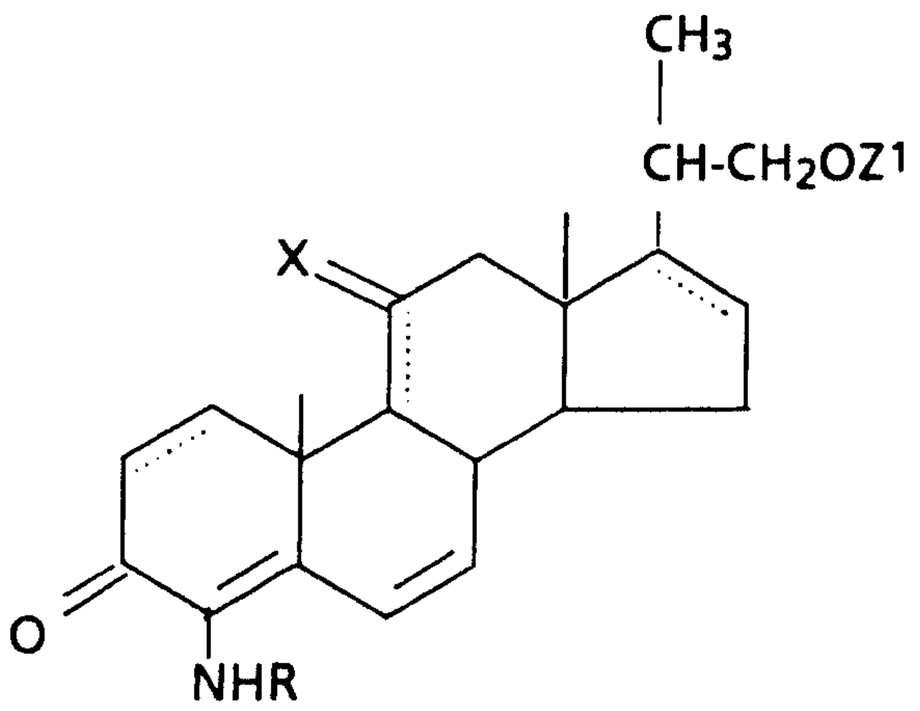


wherein R^3 and R^4 are each independently hydrogen or C_{1-6} alkyl.

5. A compound according to Claim 4 which is 4-amino-N-(1,1-dimethylethyl)-3-oxoandrosta-4,6-diene-17β-carboxamide.

6. A compound according to Claim 4 which is 4-amino-N,N-bis(1-methylethyl)-3-oxoandrosta-4,6-diene-17β-carboxamide.

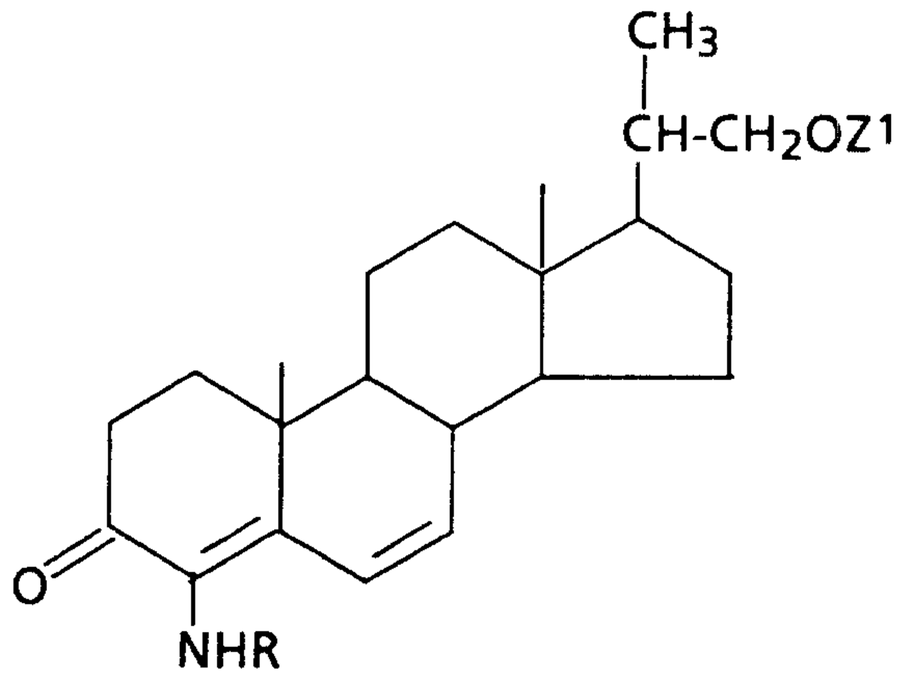
7. A compound according to Claim 1 which has the formula:



wherein R is hydrogen or C_{1-4} alkyl; X is O or (H); Z^1 is hydrogen, C_{1-6} alkyl, phenyl-(C_{1-4} alkyl), Y^1-substituted phenyl)-(C_{1-4} alkyl), C_{1-6} alkanoyl, benzoyl or Y^1-substi-

tuted benzoyl wherein Y^1 is methyl, halogen or methoxy; and each of the dotted lines indicates the optional presence of a double bond with the proviso that a 9,11-double bond can only be present when X is (H)(H) and the proviso that, when a 16,17-double bond is present, then R^2 is absent.

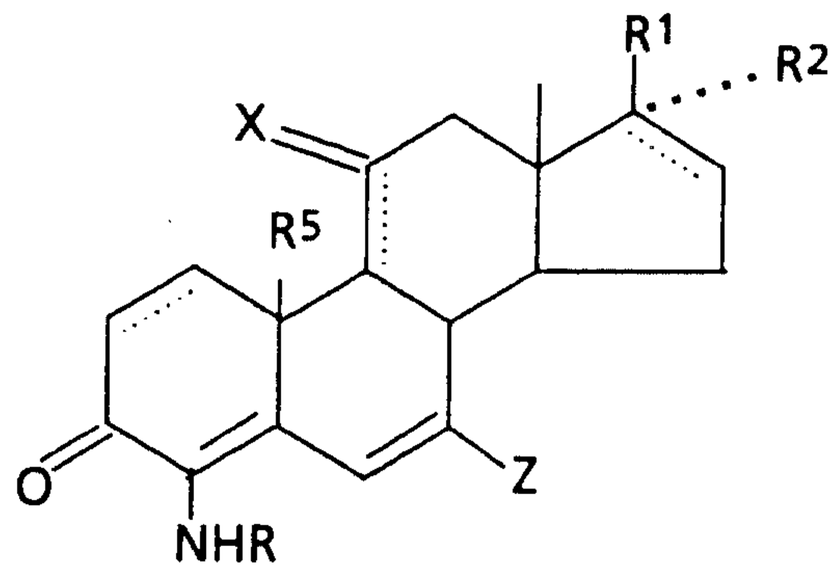
8. A compound according to Claim 7 which has the formula:



wherein R is hydrogen or C_{1-4} alkyl; and Z^1 is hydrogen, C_{1-6} alkyl or C_{1-6} alkanoyl.

9. A compound according to Claim 7 which is (20S)-4-amino-21-hydroxy-20-methylpregna-4,6-dien-3-one.

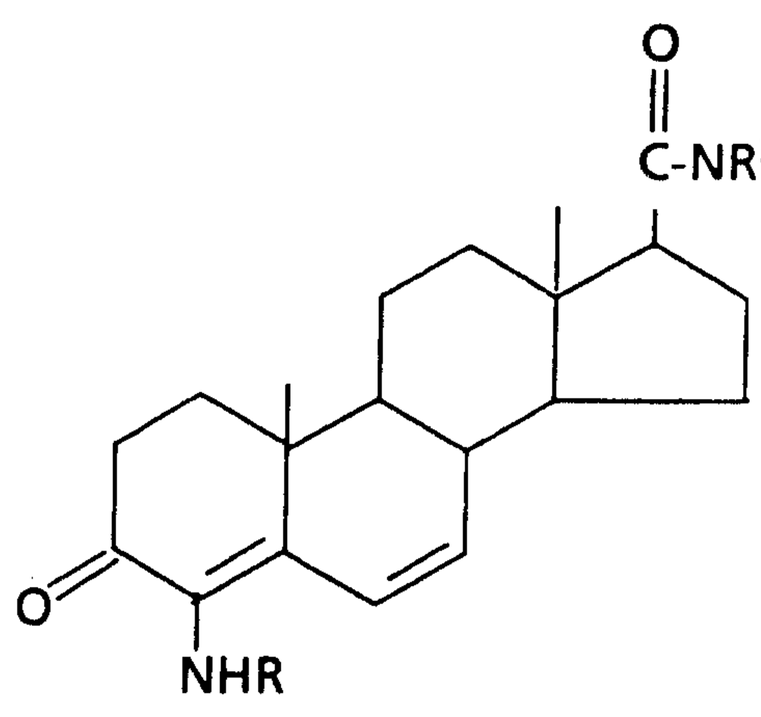
10. A use of an effective 5α-reductase inhibitory amount of a compound of the formula:



wherein R is hydrogen or C_{1-4} alkyl; R^1 is C_{2-6} alkanoyl, $-(C_{1-6}$ alkyl$)-OZ^1$, $-(C_{2-6}$ alkyl$)-(OZ^1)_2$ or -A-C(O)-Y; Z^1 is hydrogen, C_{1-6} alkyl, phenyl-(C_{1-4} alkyl), (Y^1-substituted phenyl)-(C_{1-4} alkyl), C_{1-6} alkanoyl, benzoyl or Y^1-substi-

tuted benzoyl wherein Y^1 is methyl, halogen or methoxy; A is absent or is present as an alkylene of 1 to 6 carbon atoms; Y is -OH, -O(C_{1-6} alkyl) or NR^3R^4; R^2 is hydrogen or R^1 and R^2 can be combined to give $-O-CH_2CH_2CH_2---$; R^3 and R^4 are each independently hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl or they can be combined to give $-(CH_2)_n-$ wherein n is 4 to 6; R^5 is hydrogen or methyl; X is O or (H); Z is hydrogen or C_{1-6} alkyl; and each of the dotted lines in the rings indicates the optional presence of a double bond with the proviso that a 9,11-double bond can only be present when X is (H) and the proviso that, when a 16,17-double bond is present, then R^2 is absent; for treating a patient afflicted with a DHT-mediated disease or condition in need of such treatment.

11. A use of an effective 5α-reductase inhibitory amount of a compound of the formula:

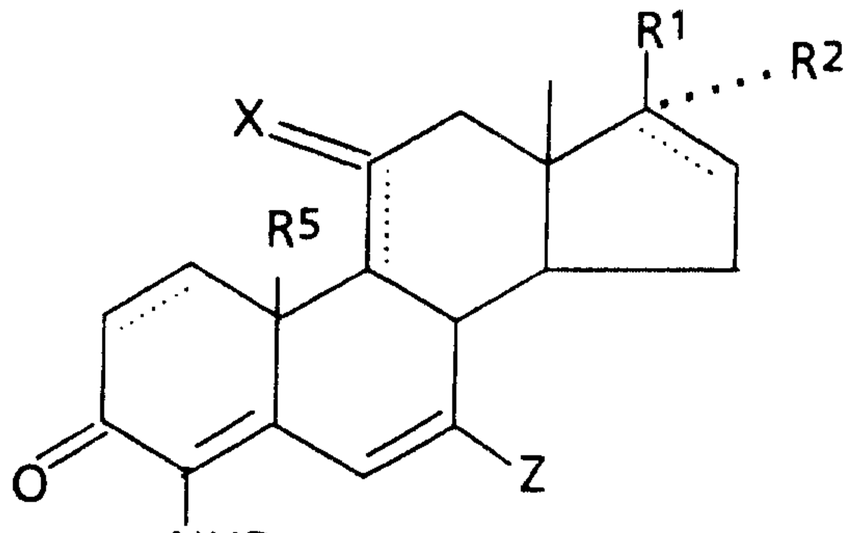


wherein R is hydrogen or C_{1-4} alkyl; R^3 and R^4 are each independently hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl or they can be combined to give $-(CH_2)_n-$ wherein n is 4 to 6; for treating a patient afflicted with a DHT-mediated disease or condition in need of such treatment.

12. The use according to Claim 11 wherein the compound is 4-amino-N-(1,1-dimethylethyl)-3-oxoandrosta-4,6-diene-17β-carboxamide.

13. A use of an effective 5α-reductase inhibitory amount of a compound of the formula:

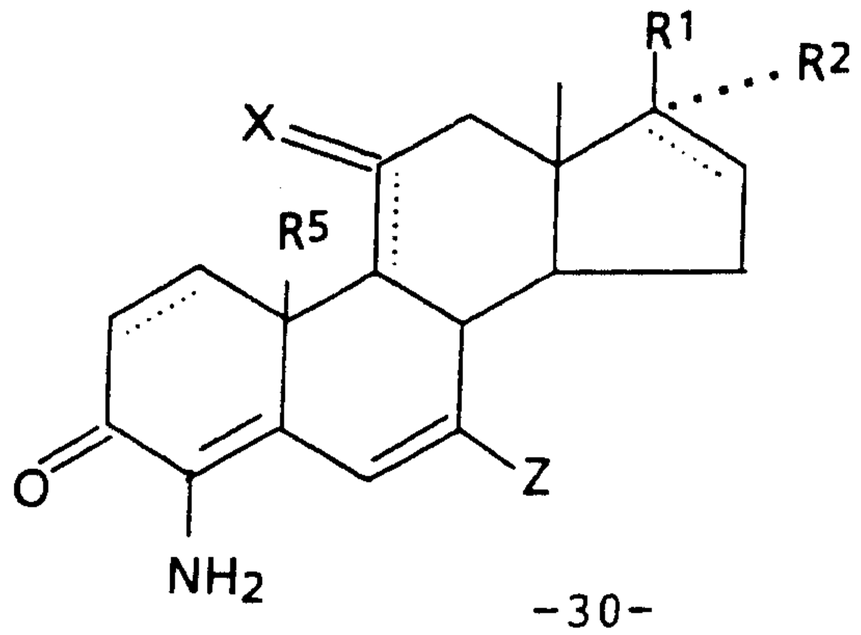
3



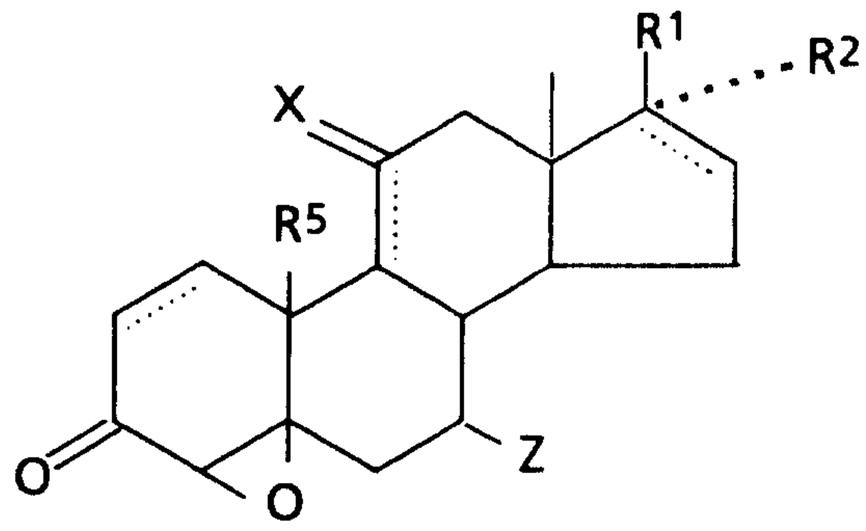
wherein R is hydrogen or C_{1-4} alkyl; R^1 is C_{2-6} alkanoyl, $-(C_{1-6}$ alkyl$)-OZ^1$, $-(C_{2-6}$ alkyl$)-(OZ^1)_2$ or -A-C(O)-Y; Z^1 is hydrogen, C_{1-6} alkyl, phenyl-(C_{1-4} alkyl), (Y^1-substituted phenyl)-(C_{1-4} alkyl), C_{1-6} alkanoyl, benzoyl or Y^1-substituted benzoyl wherein Y^1 is methyl, halogen or methoxy; A is absent or is present as an alkylene of 1 to 6 carbon atoms; Y is -OH, -O(C_{1-6} alkyl) or NR^3R^4; R^2 is hydrogen or R^1 and R^2 can be combined to give $-O-CH_2CH_2CH_2-$---; R^3 and R^4 are each independently hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl or they can be combined to give $-(CH_2)_n-$ wherein n is 4 to 6; R^5 is hydrogen or methyl; X is O or (H); Z is hydrogen or C_{1-6} alkyl; and each of the dotted lines in the rings indicates the optional presence of a double bond with the proviso that a 9,11-double bond can only be present when X is (H) and the proviso that, when a 16,17-double bond is present, then R^2 is absent; for treating benign prostatic hypertrophy in a patient in need of such treatment.

14. The use according to Claim 13 wherein the compound is (20S)-4-amino-21-hydroxy-20-methylpregna-4,6-dien-3-one.

15. A process for preparing a compound of the formula:



wherein R^1 is C_{2-6} alkanoyl, -(C_{1-6} alkyl)-OZ^1, -(C_{2-6} alkyl)-$(OZ^1)_2$ or -A-C(O)-Y; Z^1 is hydrogen, C_{1-6} alkyl, phenyl-(C_{1-4} alkyl), (Y^1-substituted phenyl)-(C_{1-4} alkyl), C_{1-6} alkanoyl, benzoyl or Y^1-substituted benzoyl wherein Y^1 is methyl, halogen or methoxy; A is absent or is present as an alkylene of 1 to 6 carbon atoms; Y is -OH, -O(C_{1-6} alkyl) or NR^3R^4; R^2 is hydrogen or R^1 and R^2 can be combined to give -O-$CH_2CH_2CH_2$---; R^3 and R^4 are each independently hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl or they can be combined to give -$(CH_2)_n$- wherein n is 4 to 6; R^5 is hydrogen or methyl; X is O or (H); Z is hydrogen or C_{1-6} alkyl; and each of the dotted lines in the rings indicates the optional presence of a double bond with the proviso that a 9,11-double bond can only be present when X is (H) and the proviso that, when a 16,17-double bond is present, then R^2 is absent; which comprises reacting a compound of the formula:



with sodium azide in an inert solvent in the presence of sulfuric acid at 100°C.

16. A process according to Claim 15 for the preparation of 4-amino-N-(1,1-dimethylethyl)-3-oxoandrosta-4,6-diene-17β-carboxamide which comprises reacting N-(1,1-dimethyl-ethyl)-4,5-epoxy-3-oxoandrostane-17β-carboxamide with sodium azide.

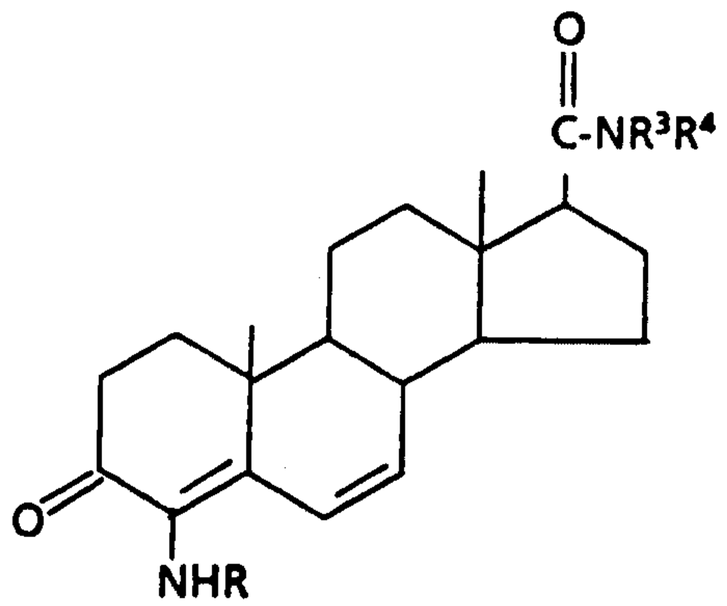
17. A process according to Claim 15 for the preparation of (20S)-4-amino-21-hydroxy-20-methylpregna-4,6-dien-3-one which comprises reacting (20S)-4,5-epoxy-21-hydroxy-20-methylpregnan-3-one with sodium azide.

18. A pharmaceutical composition comprising an effective amount of a compound, as defined in claim 1, 2, 3, 4, 5, 6, 7, 8 or 9, together with a pharmaceutically acceptable carrier therefor.

19. A composition, as claimed in claim 18, wherein said compound is selected from the group consisting of 4-amino-N-(1,1-dimethylethyl)-3-oxoandrosta-4,6-diene-17β-carboxamide; 4-amino-N,N-bis(1,1-methylethyl)-3-oxoandrosta-4,6-diene-17β-carboxamide; acetamido-N-(1,1-dimethylethyl)-3-oxoandrosta-4,6-diene-17β-carboxamide, and (20S)-4-amino-21-hydroxy-20-methylpregen-4,6-diene-3-one.

20. A pharmaceutical composition for use in treating a patient afflicted with a dihydrotestosterone - mediated disease or condition which comprises an effective 5α-reductase inhibitory amount of a compound, as defined in claim 1, 2, 3, 4, 5, 6, 7, 8 or 9, together with a pharmaceutically acceptable carrier therefor.

21. A composition, as claimed in claim 20, wherein said compound is a compound of the formula:



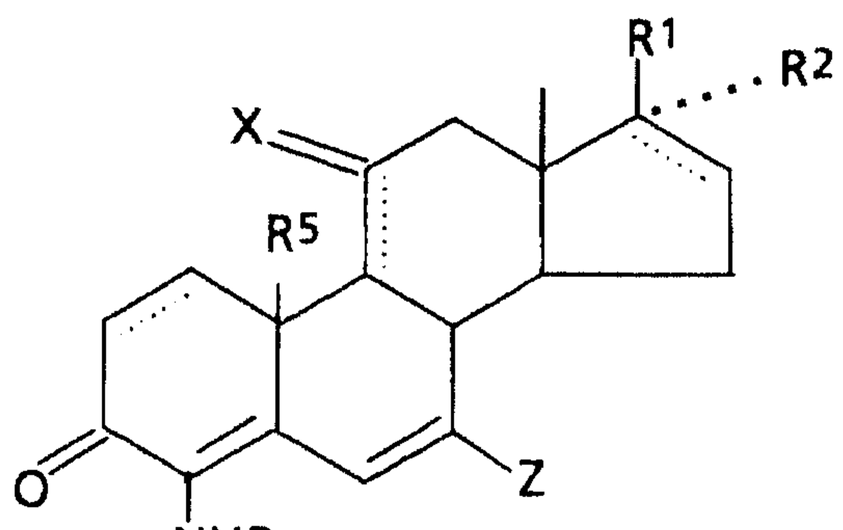
wherein R is hydrogen or C_{1-4} alkyl; R^3 and R^4 are each independently hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl or they can be combined to give $-(CH_2)_n-$ wherein n is 4 to 6.

22. A composition, as claimed in claim 20, wherein said compound is 4-amino-N-(1,1-dimethylethyl)-3-oxoandrosta-4,6-diene-17β-carboxamide.

23. A pharmaceutical composition for use in treating benign prostatic hypertrophy in a patient which comprises an effective 5α-reductase inhibitory amount of a compound, as defined in claim 1, 2, 3, 4, 5, 6, 7, 8 or 9, together with a pharmaceutically acceptable carrier therefor.

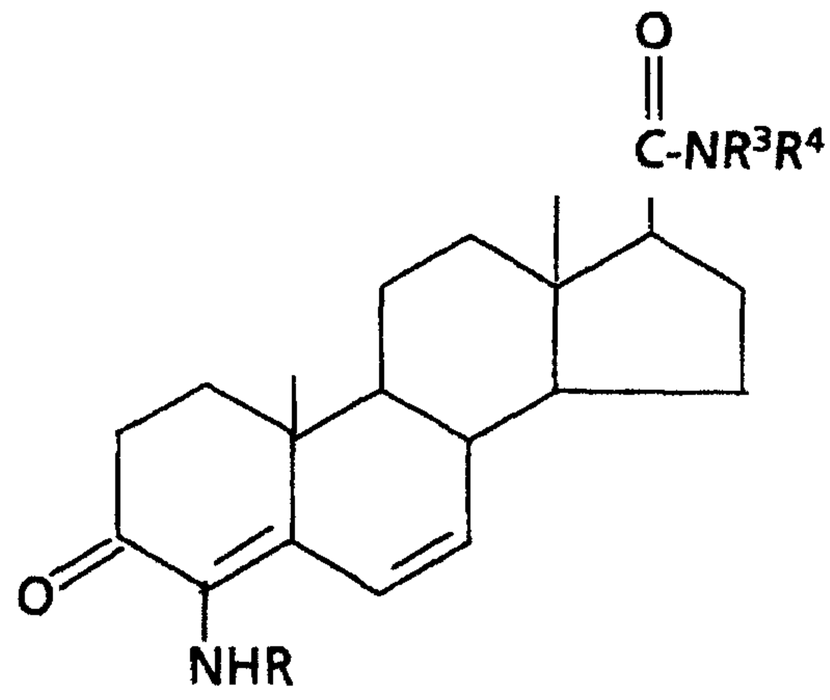
24. A composition, as claimed in claim 23, wherein said compound is (20S)-4-amino-21-hydroxy-20-methylpregna-4,6-diene-3-one.

25. A use of an effective 5α-reductase inhibitory amount of a compound of the formula:



wherein R is hydrogen or C_{1-4} alkyl; R^1 is C_{2-6} alkanoyl, -(C_{1-6} alkyl)-OZ^1, -(C_{2-6} alkyl)-$(OZ^1)_2$ or -A-C(O)-Y; Z^1 is hydrogen, C_{1-6} alkyl, phenyl-(C_{1-4} alkyl), (Y^1-substituted phenyl)-(C_{1-4} alkyl), C_{1-6} alkanoyl, benzoyl or Y^1-substituted benzoyl wherein Y^1 is methyl, halogen or methoxy; A is absent or is present as an alkylene of 1 to 6 carbon atoms; Y is -OH, -O(C_{1-6} alkyl) or NR^3R^4; R^2 is hydrogen or R^1 and R^2 can be combined to give -O-$CH_2CH_2CH_2$---; R^3 and R^4 are each independently hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl or they can be combined to give -$(CH_2)_n$- wherein n is 4 to 6; R^5 is hydrogen or methyl; X is O or (H); Z is hydrogen or C_{1-6} alkyl; and each of the dotted lines in the rings indicates the optional presence of a double bond with the proviso that a 9,11-double bond can only be present when X is (H) and the proviso that, when a 16,17-double bond is present, then R^2 is absent, in the manufacture of a medicament for the treatment of a DHT-mediated disease or condition.

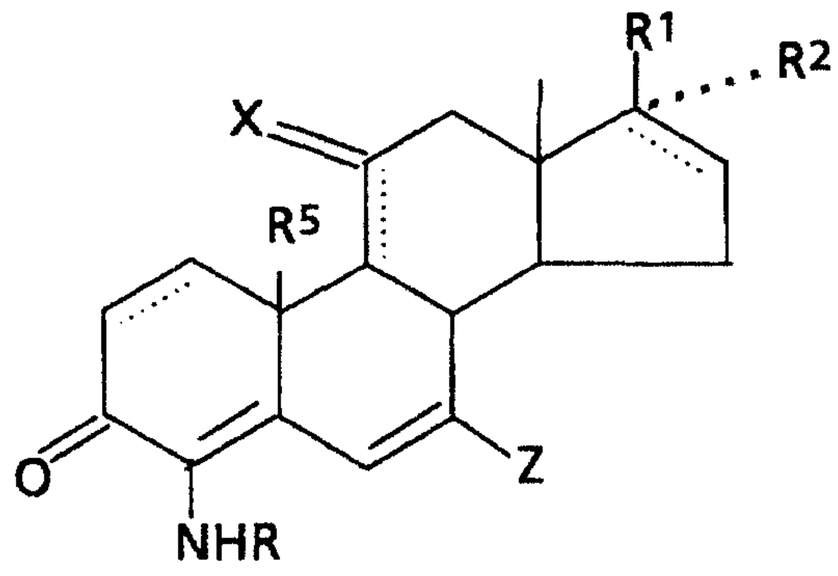
26. A use of an effective 5α-reductase inhibitory amount of a compound of the formula:



wherein R is hydrogen or C_{1-4} alkyl; R^3 and R^4 are each independently hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl or they can be combined to give $-(CH_2)_n-$ wherein n is 4 to 6, in the manufacture of a medicament for the treatment of a DHT-mediated disease or condition.

27. The use according to claim 26 wherein the compound comprises 4-amino-N-(1,1-dimethylethyl)-3-oxoandrosta-4,6-diene-17β-carboxamide.

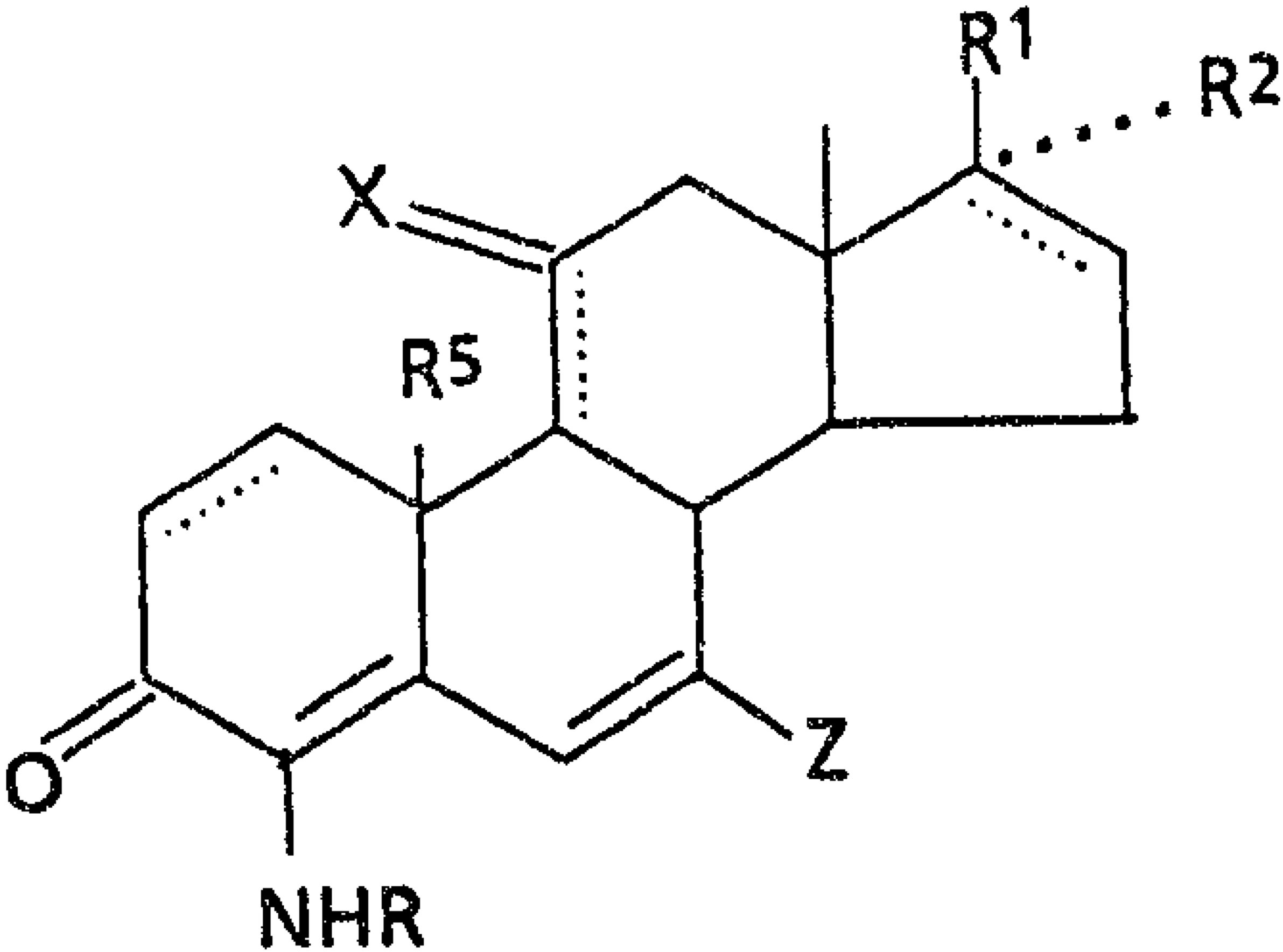
28. A use of an effective 5α-reductase inhibitory amount of a compound of the formula:



wherein R is hydrogen or C_{1-4} alkyl; R^1 is C_{2-6} alkanoyl, $-(C_{1-6}$ alkyl$)-OZ^1$, $-(C_{2-6}$ alkyl$)-(OZ^1)_2$ or -A-C(O)-Y; Z^1 is hydrogen, C_{1-6} alkyl, phenyl-$(C_{1-4}$ alkyl), (Y^1-substituted phenyl)-$(C_{1-4}$ alkyl), C_{1-6} alkanoyl, benzoyl or Y^1-substituted benzoyl wherein Y^1 is methyl, halogen or methoxy; A is absent or is present as an alkylene of 1 to 6 carbon atoms;

Y is -OH, -O(C_{1-6} alkyl) or NR^3R^4; R^2 is hydrogen or R^1 and R^2 can be combined to give -O-$CH_2CH_2CH_2$---; R^3 and R^4 are each independently hydrogen, C_{1-6} alkyl, C_{3-6} cycloalkyl or they can be combined to give -$(CH_2)_n$- wherein n is 4 to 6; R^5 is hydrogen or methyl; X is O or (H); Z is hydrogen or C_{1-6} alkyl; and each of the dotted lines in the rings indicates the optional presence of a double bond with the proviso that a 9,11-double bond can only be present when X is (H) and the proviso that, when a 16,17-double bond is present, then R^2 is absent, in the manufacture of a medicament for the treatment of benign prostatic hypertrophy.

29. The use according to claim 28 wherein the compound is (20S)-4-amino-21-hydroxy-20-methylpregna-4,6-dien-3-one.


R1
R2
X
R5
Z
O
NHR