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(54) Title: NEW DELTA-17 AND DELTA-20 OLEFINIC AND SATURATED 17β-SUBSTITUTED-4-AZA-5α-ANDROSTAN-3-ONES AS 5α-REDUCTASE INHIBITORS

(57) Abstract

Described are new delta-17 and delta-20 olefinic and saturated 17β-substituted 4-aza-5α-androstan-3-ones and related compounds and the use of such compounds as 5α-reductase inhibitors for treatment of benign prostatic hyperplasia and other hyperandrogenic related disorders.

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TITLE OF THE INVENTION

NEW DELTA-17 AND DELTA-20 OLEFINIC AND SATURATED 17β-SUBSTITUTED 4-AZA-5α-ANDROSTAN-ONES AS 5α-REDUCTASE INHIBITORS

BACKGROUND OF THE INVENTION

The present invention is directed to new delta-17 and delta-20 olefinic and saturated 17β-substituted 4-aza-5α-androstan-3-ones and related compounds and the use of such compounds as 5α-reductase inhibitors.

DESCRIPTION OF THE PRIOR ART

The art reveals that certain undesirable physiological manifestations, such as acne vulgaris, seborrhea, female hirsutism, male pattern baldness and benign prostatic hyperplasia, 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'-trifluoromethyl-isobutyranilide. 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 is now known in the art that the principal mediator of androgenic activity in some target organs, e.g. the prostate, is 5α-dihydrotestosterone, and that it is formed locally in the target organ by the action of testosterone-5α-reductase. It is also known that inhibitors of testosterone-5α-reductase will serve to prevent or lessen symptoms of hyperandrogenic stimulation. For example, a number of 4-aza

steroid compounds are known which are 5α-reductase inhibitors.

See the following Merck & Co., Inc. patents, U.S. Patent Nos. 4,377,584, 4,220,775, 4,859,681, 4,760,071 and the articles J. Med. Chem. 27, p. 1690-1701 (1984) and J. Med. Chem. 29, 2998-2315 (1986) of Rasmusson, et al., and U.S. Patent 4,845,104 to Carlin, et al., and U.S. Patent 4,732,897 to Cainelli, et al. which describe 4-aza-17β-substituted-5α-androstan-3-ones said to be useful in the treatment of DHT-related hyperandrogenic conditions.

Further there is the suggestion in the early prior art that hyperandrogenic diseases are the result of a single 5α-reductase. However, there are later reports regarding the presence of other 5α-reductase isozymes in both rats and humans. For example, in human prostate, Bruchovsky, et al. (See J. Clin. Endocrinol. Metab. 67, 806-816, 1988) and Hudson (see J. Steroid Biochem. 26, p 349-353, 1987) found different 5α-reductase activities in the stromal and epithelial fractions. Additionally, Moore and Wilson described two distinct human reductases with peaks of activities at either pH 5.5 or pH 7-9. (See J. Biol. Chem. 251, 19, p. 5895-5900, 1976.)

Recently, Andersson and Russell isolated a cDNA which encodes a rat liver 5α-reductase (see J. Biol. Chem. 264 pp. 16249-55 (1989). They found a single mRNA which encodes both the liver and prostatic reductases in rats. This rat gene was later used to identify a human prostatic cDNA encoding a 5α-reductase termed "5α-reductase 1". (See Proc. Nat'l. Acad. Sci. 87, p. 3640-3644, 1990.)

More recently, a second, human prostatic reductase (5α-reductase 2) has been cloned with properties identified with the more abundant form found in crude human prostatic extracts. (See Nature, 354, p. 159-161, 1991.)

Further,-"Syndromes of Androgen Resistance" - The Biology of Reproduction, Vol. 46, p. 168-173 (1992) by Jean O. Wilson suggests that the 5α-reductase 1 enzyme is associated with hair follicles.

Thus, the art supports the existence of at least two genes for 5α-reductase and two distinct isozymes of 5α-reductase in humans. Both isozymes are believed to be present in prostatic tissue in which,

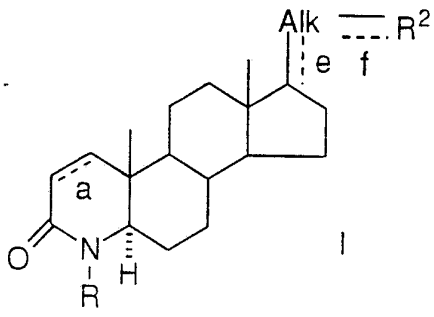
5α-reductase 2, is the more abundant, while the other isozyme, 5α-reductase 1, is believed to be more abundant in scalp tissue.

In the treatment of hyperandrogenic disease conditions, e.g. benign prostatic hyperplasia (BPH) it would be desirable to have one drug entity which is dually active against both enzymes 1 and 2 in the prostate to substantially inhibit dihydrotesterone (DHT) production. Alternatively, it would be desirable to have a drug entity which is highly selective for inhibiting the scalp-associated enzyme 5α-reductase 2. The drug could also be used in combination with PROSCAR® (finasteride) which is highly selective for the prostatic enzyme 5α-reductase 2 for combination therapy in the treatment of BPH.

SUMMARY OF THE INVENTION

The present invention discloses novel delta-17 and delta-20 olefinic-and saturated 17β-substituted-4-aza-5α-androstan-3-one compounds which are useful for inhibiting the 5α-reductase enzyme and isozymes thereof in prostatic tissue. They are also particularly effective in selectively inhibiting the 5α-reductase 1 associated with the scalp and/or dually inhibiting both isozymes 1 and 2 in the oral, parenteral or topical treatment of benign prostatic hyperplasia, acne, female hirsutism, androgenic alopecia, i.e., male pattern baldness, alopecia areata, alopecia senilis, prostatitis, and the prevention and treatment of prostatic carcinoma.

In accordance with the present invention there is provided novel 17β-substituted olefinic and saturated 4-aza-5α-androstan-3-one and related compounds of the formula:



I

wherein:

Alk is C_1-C_4 straight or branched chain alkyl or alkenyl; dashed lines a, e and f each can independently represent a double bond when present, with the proviso that double bonds formed by e and f are not both present concurrently;

R is selected from hydrogen, methyl or ethyl;

R^2 is (a) C_6-C_{10} aryl, cyano, a 5-6 membered heteroaryl radical, which can contain 1-4 nitrogen atom, one oxygen or sulfur atoms or combinations thereof with 1-2 nitrogen atoms, providing that where R^2 is cyano, double bonds e and f are not present;

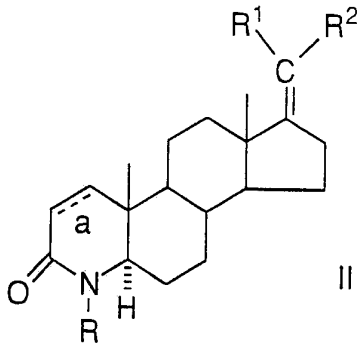
(b) COR_1, where R_1 is C_6-C_{10} aryl, substituted C_6-C_{10} aryl, and heteroaryl;

(c) $CONHR_2$, where R_2 is substituted phenyl, heteroaryl, substituted heteroaryl, or C_7 to C_{12} cycloalkyl;

(d) CO_2R_3, where R_3 is C_1-C_{18} linear or branched alkyl, C_6-C_{10} aryl, substituted C_6-C_{10} aryl, or C_7-C_{12} cycloalkyl; providing that in (b), (c) and (d), Alk can only be alkenyl;

wherein the above aryl or heteroaryl radicals can also be fused with a benzo or another heteroraryl ring and can further be substituted with one or more substitutents; and pharmaceutically acceptable salts and esters thereof.

Further provided is a compound of the formula:



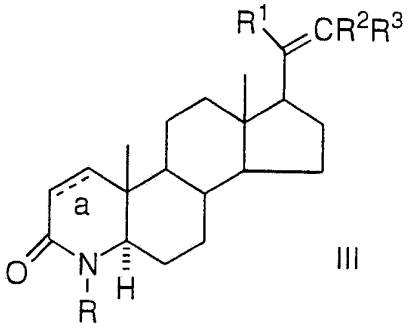
II

wherein the dashed line a represents a double bond when present;

R and R1 are selected from hydrogen, methyl and ethyl; and

R2 is as defined above, including both (E) and (Z) forms, and mixtures thereof.

Also provided is a compound of Claim 1 of the formula:



III

wherein the dashed line a can represent a double bond when present,

R, R1 and R3 are independently selected from hydrogen, methyl and ethyl, with the proviso that at least one of R1 and R3 is hydrogen.

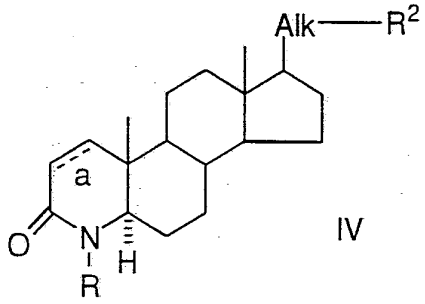
R^2 is (a) C_6-C_{10} aryl or heteroaryl as defined above,
and R^2 and R^3 can be in a E or Z bond configuration;

(b) COR_1, where R_1 is C_6-C_{10} aryl, substituted C_6-C_{10} aryl, and heteroaryl;

(c) $CONHR_2$, where R_2 is substituted phenyl, heteroaryl, substituted heteroaryl, or C_7 to C_{12} cycloalkyl;

(d) CO_2R_3, where R_3 is C_1-C_{18} linear or branched alkyl, C_6-C_{10} aryl, substituted C_6-C_{10} aryl, or C_7-C_{12} cycloalkyl; providing that in (b), (c) and (d), Alk can only be alkenyl; and mixed thereof.

Additionally, there is provided a compound of the formula:



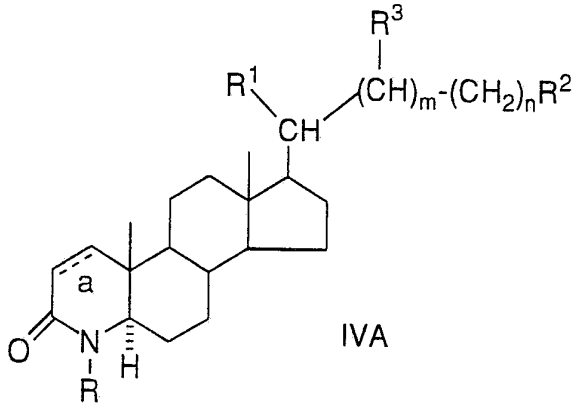
IV

wherein:
Alk is C_1-C_4 straight or branched chain alkyl; dashed line a can represent a double bond when present;

R is selected from hydrogen, methyl or ethyl; and

R^2 is as defined above.

Also specifically provided is a compound of structure IVA of the formula:



IVA

wherein the dashed line a can represent a double bond when present, and

m is 0-1,

n is 0-3; and

R, R^1 and R^3 are independently selected from hydrogen, methyl and ethyl, with the proviso that at least one of R^1 and R^3 is hydrogen,

R^2 is C_6-C_{10} aryl, cyano, or heteroaryl as defined above.

Also disclosed are processes for their preparation, pharmaceutical formulations comprising the novel compounds as active ingredients and methods of inhibiting 5α-reductases 1 and/or 2 in diseases which occur under hyperandrogenic conditions, e.g., benign prostatic hyperplasia.

DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

The structures I-IV above encompass all the 5α-reductase inhibitor compounds of this invention.

By the term "Alk" is meant C_1-C_4 or branched alkyl or alkenyl; e.g. methyl, ethyl, isopropyl, propyl, n-butyl, isobutyl. sec-butyl, ethenyl, propenyl, isopropenyl, 1- and 2-butenyl and the like.

Where the double bond "e" is present, the compounds are delta-17 olefins and where the double bond "f" is present, the compounds are delta-20 olefins. Note that dashed lines "e" and "f" both cannot be double bonds concurrently.

Dashed line "a" can independently be a double bond and when present, the compound is a 1-ene.

R^2 is a C_6-C_{10} aryl including phenyl, benzyl, 1- and 2-phenethyl and naphthyl, and also cyano.

Preferred is where R^2 aryl is phenyl or cyano.

R^2 can also be 5-6 membered heteroaryl radical being fully unsaturated containing 1-4 nitrogen atoms, e.g. pyridyl, pyrryl, imidazolyl, tetrazolyl, pyrazinyl, pyrimidinyl, pyrazolyl, or triazolyl: containing 1-2 oxygen or sulfur atoms, e.g. thienyl, furanyl; or in combination with 1-2 nitrogen atoms, e.g. isothiazolyl, thiazolyl, isoxazolyl, oxazolyl or thiadiazolyl; or fused with a benzo ring, e.g. quinolyl, isoquinolyl, benzothienyl, isobenzofuryl, indolyl, carbazolyl: or fused with another heteroaryl ring, e.g. purinyl, and the like.

Preferred examples are 2-, 3-, and 4-pyridyl, 2-thienyl; 2-pyrazinyl, 2-, 4-, and 5-thiazolyl.

The R^2 aryl or heteroaryl ring can be unsubstituted or substituted with one or more of the following substituents providing the substitution leads to a chemically inert, but biologically active 5α reductase inhibitor.

The R^2 ring substituents include:

C_1-C_{18} straight or branched alkyl; e.g. methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, isobutyl, t-butyl, n-pentyl, n-hexyl, iso-hexyl, n-butyl, n-octyl, iso-octyl, t-octyl, n-decyl, n-dodecyl.

isooctodecyl, and the like;

C_2-C_8 straight or branched alkenyl, e.g. ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-pentenyl, 1-hexenyl, 1-heptenyl, 1-octenyl, 2-octenyl, and the like;

C_3-C_8 cycloalkyl e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 1-methylcyclobutyl, cyclopentyl, cyclohexyl, 1-methylcyclohexyl, 2-methylcyclohexyl, 2-ethylcyclohexyl, and the like;

C_2-C_8 alkynyl e.g., 1-ethynyl; 1-propynyl, 2-propynyl, 2-butynyl, 2-pentynyl, 1-hexynyl, 1-heptynyl, 1-octynyl;

$CONR^4R^5$ where R^4 and R^5 independently are H, C_1-C_8 alkyl, as defined above, C_3-C_8 cycloalkyl as defined above, C_1-C_4 perhaloalkyl e.g., trifluoromethyl, perfluoromethyl, trichloromethyl, preferably perfluoroalkyl; phenyl, or substituted phenyl, as described below;

COR^4, where R^4 is defined above, including acetyl, isobutylcarbonyl, benzoyl and the like;

$S(O)_n R^4$, where n is 0-2 and R^4 is defined above, including methylsulfinyl, methylsulfonyl, phenylsulfonyl, 4-chlorophenylsulfinyl and the like;

$OCOR^4$, where R^4 is defined above, including acetoxy, propionyloxy, benzoyloxy, 4-chlorobenzoyloxy and the like.

$SO_2NR^4R^5$ where R^4 and R^5 are described above, including sulfonamido, N-methylsulfonamido, N-phenylsulfonamido, N,N-dimethylsulfonamido and the like;

$NR^4(CO)R^5$, wherein R^4 and R^5 are defined above, including; acetylamino, benzoylamino, N-methylbenzoylamino and the like;

$NR^4(CO)NHR^5$, wherein R^4 and R^5 are described above, including; ureido, N-methylureido, N-methyl-N1-phenylureido and the like;

$NHSO_2R^4$, R^4 being defined above, including methylsulfonylamino, phenylsulfonylamino and the like;

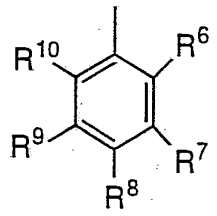
OR^4, where R^4 is defined above, including methoxy, phenoxy, 4-chlorophenoxy and the like.

NR^4R^5, wherein R^4 and R^5 are described above, including amino, methylamino, dimethylamino, anilino and the like;

Cyano, nitro, halo, including: fluoro, chloro, bromo and iodo;

Perhalo C_1-C_4 alkyl, including: trifluoromethyl, perfluoroethyl, trichloromethyl and the like.

CO_2R^4, wherein R^4 is defined above, including CO_2CH_3, CO_2Ph, CO_2-(1-adamantyl) and the like; phenyl and substituted phenyl of the formula:



wherein the radicals R^6-R^{10} each can represent one or more of the substituents defined above, including; hydrogen, 4-chlorophenyl, 4-fluorophenyl, 4-methoxyphenyl, 4-phenoxy and the like.

Unless otherwise indicated, the 17-position substituent is in the beta configuration.

Representative compounds of the present invention include the following:

(17E)-17-[phenyl)methylene]-4-methyl-4-aza-5α-androstan-3-one,

(17E)-17-[(4-chlorophenyl)methylene]-4-methyl-4-aza-5α-androstan-3-one,

(17E)-17-[(3-chlorophenyl)methylene]-4-methyl-4-aza-5α-androstan-3-one,

(17E)-17-[(2-chlorophenyl)methylene]-4-methyl-4-aza-5α-androstan-3-one,

(17E)-17-[(4-ethoxycarbonylphenyl)methyl-ene]-4-methyl-4-aza-5α-androstan-one,

(17E)-17-[(4-carboxyphenyl)methylene]-4-methyl-4-aza-5α-androstan-3-one,

(17E)-17-[4-[[(1,1-dimethylethyl)amino)carbonyl]phenyl]-methylene]-4-methyl-4-aza-5α-androstan-3-one,

(17E)-17-[(3,4,5-trimethoxyphenyl)methyl-ene]-4-aza-5α-androstan-3-one,

(17E)-17-[(2-methoxyphenyl)methylene]-4-methyl-4-aza-5α-androstan-3-one,

(17E)-17-[(4-methylsulfonylphenyl)methyl-ene]-4-methyl-4-aza-5α-androstan-3-one,

(17E)-17-[(4-biphenyl)methylene]-4-aza-5α-androstan-3-one,

(17E)-17-[(4-nitrophenyl)methylene]-4-methyl-4-aza-5α-androstan-3-one,

(17E)-17-[(4-aminophenyl)methylene]-4-aza-5α-androstan-3-one,

(17E)-17-[(4-acetylaminophenyl)methylene]-4-methyl-4-aza-5α-androstan-3-one,

(17E)-17-(4-pivaloylaminophenyl)methylene)-4-methyl-4-aza-5α-androstan-3-one,

(17E)-17-[(4-phenoxyphenyl)methylene]-4-aza-5α-androstan-3-one,

(17E)-17-[(2-imidazolyl)methylene]-4-methyl-4-aza-5α-androst-1-en-3-one,

(17E)-17-[(2-thiazolyl)methylene]-4-aza-5α-androst-1-en-3-one,

(17E)-17-[(2-pyrazinyl)methylene]-4-methyl-4-aza-5α-androstan-3-one,

(17E)-20-phenyl-4-methyl-4-aza-5α-pregn-17-en-3-one,

(17E)-20-[(4-chloro)phenyl]-4-aza-5α-pregn-17-en-3-one,

(20E)-4-methyl-21-[(4-methoxy)phenyl]-4-aza-5α-pregn-20-en-3-one,

(20E)-4-methyl-21-phenyl-4-aza-5α-pregn-20-en-3-one,

(20E)-4-methyl-21-[(4-methyl)phenyl]-4-aza-5α-pregn-20-en-3-one,

(20E)-4-methyl-21-[(4-chloro)phenyl]-4-aza-5α-pregn-20-en-3-one,

(20E)-4-methyl-21-(4-pyridyl)-4-aza-5α-pregn-20-en-3-one,

(20E)-4-methyl-21-[(3-chloro)phenyl]-4-aza-5α-pregn-20-en-3-one,

(20E)-4-methyl-21-[(2-chloro)phenyl]-4-aza-5α-pregn-20-en-3-one,

(20E)-4-methyl-21-(2-pyridyl)-4-aza-5α-pregn-20-en-3-one,

(20E)-4-methyl-21-(2-thienyl)-4-aza-5α-pregn-20-en-3-one,

(20E)-21-[(4-methoxy)phenyl]-4-aza-5α-pregn-20-en-3-one,

(20E)-4-methyl-21-(3-thienyl)-4-aza-5α-pregn-20-en-3-one,

(20E)-4-methyl-21-(2-furanyl)-4-aza-5α-pregn-20-en-3-one,

(20E)-4-methyl-21-[(2-fluoro)phenyl]-4-aza-5α-pregn-20-en-3-one,

(20E)-21-(4-pyridyl)-4-aza-5α-pregn-1,20-dien-3-one,

(20E)-21-(4-pyridyl)-4-aza-5α-pregn-20-en-3-one,

(20E)-21-[(4-methoxy)phenyl]-4-aza-5α-pregn-1,20-dien-3-one,

(20E)-21-(2-furanyl)-4-aza-5α-pregn-1,20-dien-3-one,

(20E)-21-(2-pyridyl)-4-aza-5α-pregn-1,20-dien-3-one,

(20E)-21-(3-pyridyl)-4-aza-5α-pregn-1,20-dien-3-one

(20E)-21-[(4-ethoxycarbonyl)phenyl]-4-aza-5α-pregn-1,20-dien-3-one,

(20E)-21-4-[N-phenyl]benzamido-4-aza-5α-pregn-1,20-dien-3-one,

(20E)-21-(2-pyridyl)-4-aza-5α-pregn-20-en-3-one,

(20E)-21-(3-pyridyl)-4-aza-5α-pregn-20-en-3-one,

(20E)-21-(2-thienyl)-4-aza-5α-pregn-20-en-3-one,

(20E)-4,20-dimethyl-21-phenyl-4-aza-5α-pregn-20-en-3-one,

(20E)-4,20-dimethyl-21-(4-chlorophenyl)-4-aza-5α-pregn-20-en-3-one,

(20E)-4,20-dimethyl-21-(2-thienyl)-4-aza-5α-pregn-20-en-3-one,

(20E)-4,20-dimethyl-21-(2-pyridyl)-4-aza-5α-pregn-20-en-3-one,

(20E)-20-methyl-21-(4-pyridyl)-4-aza-5α-pregna-1,20-dien-3-one,

(20E)-4,20-dimethyl-21-(4-pyridyl)-4-aza-5α-pregn-20-en-3-one,

(20E)-20-methyl-21-(2-furyl)-4-aza-5α-pregna-1,20-dien-3-one,

(20E)-20-methyl-21-(2-pyridyl)-4-aza-5α-pregna-1,20-dien-3-one,

(20E)-20-ethyl-21-phenyl-4-aza-5α-pregna-1,20-dien-3-one,

(20E)-20-ethyl-21-(2-pyridyl)-4-aza-5α-pregna-1,20-dien-3-one,

20(E,Z)-4,21-dimethyl-21-phenyl-4-aza-5α-pregn-20-en-3-one,

20(E,Z)-21-methyl-21-(4-chlorophenyl)-4-aza-5α-pregn-20-en-3-one,

20(E,Z)-4,21-dimethyl-21-(2-pyridyl)-4-aza-5α-pregn-1,20-dien-3-one,

17β-[(4-chlorophenyl)methyl]-4-methyl-4-aza-5α-androstan-3-one,

17β-[(phenyl)methyl]-4-aza-5α-androstan-3-one,

17β-[(2-pyridyl)methyl]-4-methyl-4-aza-5α-androst-1-en-3-one,

17β-[(2-thienyl)methyl]-4-aza-5α-androst-1-en-3-one,

20-phenyl-4-methyl-4-aza-5α-pregnan-3-one,

20-(4-chloro)phenyl-4-aza-5α-pregnan-3-one,

20-(2-pyridyl)-4-methyl-4-aza-5α-pregn-1-en-3-one,

20-(2-thienyl)-4-aza-5α-pregn-1-en-3-one,

21-phenyl-4-aza-5α-pregnan-3-one,

21-(2-pyridyl)-4-methyl-4-aza-5α-pregnan-3-one,

21-[(4-methoxy)phenyl]-4-methyl-4-aza-5α-pregnan-3-one,

21-(2-thienyl)-4-methyl-4-aza-5α-pregnan-3-one,

21-[(4-chlorophenyl]-4-aza-5α-pregn-1-en-3-one,

4-methyl-17ß-[3-(phenyl)propyl]-4-aza-5α-androstan-3-one,

17β-[3-(2-pyridyl)propyl]-4-aza-5α-androst-1-en-3-one,

17β-[3-(4-chlorophenyl)propyl]-4-aza-5α-androstan-3-one,

4-methyl-17β-[2-(thienyl)propyl]-4-aza-5α-androst-1-en-3-one,

4-methyl-17β-[4-(phenyl)butyl]-4-aza-5α-androstan-3-one,

17β-[3-(2-pyridyl)butyl]-4-aza-5α-androst-1-en-3-one,

17β-[3-(4-chlorophenyl)butyl]-4-aza-5α-androstan-3-one,

4-methyl-17β-[2-(thienyl)butyl]-4-aza-5α-androst-1-en-3-one,

20-ethyl-21-(2-pyridyl)-4-aza-5α-pregnan-3-one,

20-ethyl-21-phenyl-4-aza-5α-pregnan-3-one,

20-ethyl-21-(2-methoxyphenyl)-4-aza-5α-pregnan-3-one,

4,21-dimethyl-21-(2-pyridyl)-4-aza-5α-pregnan-3-one,

4,21-dimethyl-21-[(4-benzoylamino)phenyl]-4-aza-5α-pregnan-3-one,

4,21-dimethyl-21-(2-thiazolyl)-4-aza-5α-preganan-3-one,

21-phenyl-4-aza-5α-pregnan-3-one,

21-(2-pyridyl)-4-aza-5α-pregnan-3-one,

21-(2-thienyl)-4-aza-5α-pregnan-3-one,

21-(2-methoxyphenyl)-4-aza-5α-pregn-1-en-3-one,

21-(3-pyridyl)-4-aza-5α-pregn-1-en-3-one,

21-(2-thiazolyl)-4-aza-5α-pregn-1-en-3-one,

4-methyl-21-[4-(methylsulfonyl)phenyl]-4-aza-5α-pregn-1-en-3-one,

4-ethyl-21-(4-fluorophenyl)-4-aza-5α-pregn-1-en-3-one,

4-methyl-21-(4-carboxyphenyl)-4-aza-5α-pregn-1,20-dien-3-one,

4-ethyl-21-(4-carbamoylphenyl)-4-aza-5α-pregn-1,20-dien-3-one,

20-(3-pyridyl)-4-aza-5α-pregna-1,17-dien-3-one,

4-methyl-20-(2-pyrazinyl)-4-aza-5α-pregn-1,17-dien-3-one,

20-ethyl-4-methyl-21-phenyl-4-aza-5α-pregn-20-en-3-one,

4,20-dimethyl-21-(2,6-dimethoxyphenyl)-4-aza-5α-pregna-1,20-dien-3-one,

20-ethyl-4-methyl-21-(s-triazinyl)-4-aza-5α-pregna-1,20-dien-3-one,

4-methyl-20-(phenylmethyl)-4-aza-5α-pregnan-3-one,

20-ethyl-4-methyl-21-(2-pyridyl)-4-aza-5α-pregnan-3-one,

20-(2-thiazolyl)-4-aza-5α-pregnan-3-one,

20-ethyl-21-(3-pyridyl)-4-aza-5α-pregnan-3-one,

20-(4-methylsulfonylphenyl)-4-aza-5α-pregn-1-en-3-one,

20-ethyl-21-(4-methoxyphenyl)-4-aza-5α-pregn-1-en-3-one,

4-methyl-20-(3,4-dimethoxyphenyl)-4-aza-5α-pregn-1-en-3-one,

20-ethyl-4-methyl-21-(2-pyrimidinyl)-4-aza-5α-pregn-1-en-3-one,

4,21-dimethyl-21-(4-pyridyl)-4-aza-5α-pregna-1,20-dien-3-one,

21-methyl-21-(2-thienyl)-4-aza-5α-pregn-1-en-3-one,

21-methyl-21-(1-imidazolyl)-4-aza-5α-pregnan-3-one,

4,21-dimethyl-21-(4-carbamoylphenyl)-4-aza-5α-pregn-1-en-3-one,

4-methyl-21-(4-methoxyphenyl)-4-aza-5α-pregnan-3-one,

4-methyl-17-((4-chloro)phenylmethyl)-4-aza-5α-androstan-3-one,

N-(1,1-dimethylethyl)-4-(4-methyl-3-oxo-4-aza-5α-pregn-21-yl)benzamide,

4-methyl-21-(3-pyridyl)-4-aza-5α-pregn-20-en-3-one,

21-(2-pyrazinyl)-4-methyl-4-aza-5α-preg-20-en-3-one,

4-methyl-21-(2-pyrazinyl)-4-aza-5α-pregnan-3-one,

4-methyl-24-nor-4-aza-5α-cholane-23-nitrile,

4-methyl-3-oxo-4-aza-5α-pregnane-21-carbon-nitrile,

24-nor-4-aza-5α-chol-1-ene-23-nitrile,

24-nor-4-aza-5α-cholane-23-nitrile,

4-methyl-24-nor-4-aza-5α-chol-1-ene-23-nitrile,

3-oxo-4-aza-5α-pregn-1-ene-21-carbonitrile,

3-oxo-4-aza-5α-pregnane-21-carbonitrile,

4-methyl-3-oxo-4-aza-5α-pregnane-21-nitrile,

4-methyl-3-oxo-4-aza-5α-cholane-24-nitrile,

3-oxo-4-aza-5α-chol-1-ene-24-nitrile,

4-methyl-3-oxo-21-nor-4-aza-5α-cholane-24-nitrile,

3-oxo-21-nor-4-aza-5α-cholane-24-nitrile,

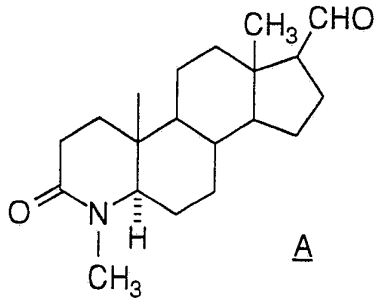
and also including the corresponding compounds wherein the 4-hydrogen substituent is replaced by a methyl or an ethyl radical, and/or a delta-one double bond is present.

Also included within the scope of this invention are pharmaceutically acceptable salts, i.e. hydrochloride, hydrobromide, acetate, pamoate, and the like, of the compound where a basic heteroaryl radical is present, e.g. 4-pyridyl, which can be used as the dosage form for modifying solubility or hydrolysis characteristics or for use as sustained release or prodrug formulations.

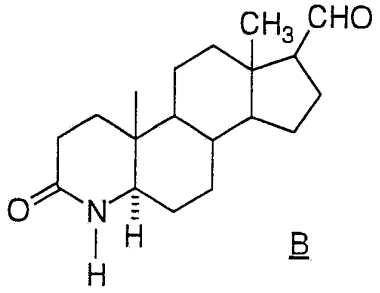
The novel compounds of formula I of the present invention are prepared by methods starting with appropriate steroid 17-carboxaldehydes and ketones of the following formulae:

CHART A

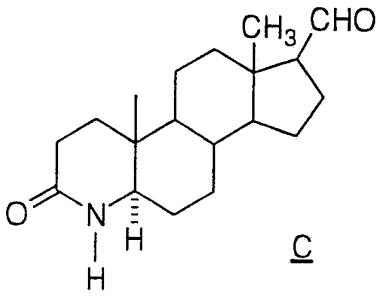
Carboxaldehydes



A



B



C

Carboxaldehyde A can be prepared from 17-(2-pyridylthio) carboxylate-4-methyl-5α-androstan-3-one by reaction with Raney nickel to the 17β-carbinol followed by oxidation to the aldehyde with pyridinium chlorochromate. (See J. Med. Chem. 1986, Vol. 29, No. 11, p. 2299, Compound 10bg) The starting 2-pyri- dylthio ester can be made by hydrolyzing the 17-COOMe derivative to the acid and reacting the acid with 2,2'-dipyridyl disulfide in an inert solvent, e.g. chlorobenzene.

Carboxaldehyde B can be prepared from the lithum aluminum hydride reduction of 17β-(N-methyl- N-methoxy)-carboxamide-5α-4-aza-androst-1-en-3-one (see USP 5,061,801 for its preparation, as also described in the following section "Preparation of Starting Materials".

Carboxaldehyde C can be concurrently prepared from the same procedure, as a secondary reaction product, as described above for Carboxaldehyde B (See preparation in "Preparation of Starting Materials").

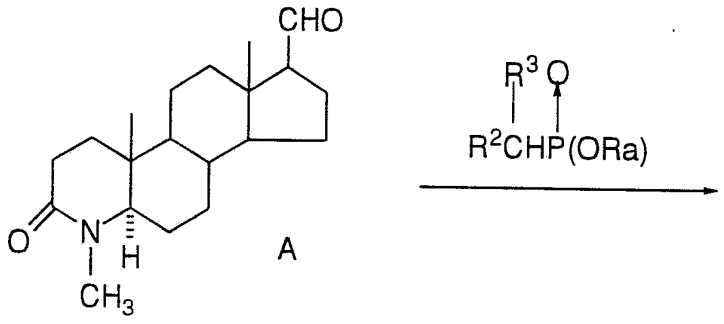
Note that the corresponding 4-ethyl analogs are also available through conventional alkylation of the 4-NH derivative via, e.g. ethyl iodide, sodium hydride in dry DMF at room temperature.

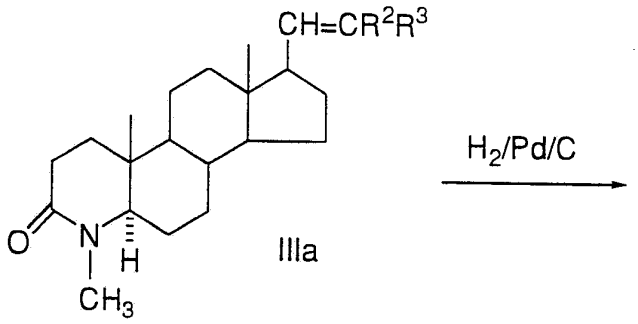
As seen in Flowsheet A, the carboxaldehydes A, B, or C can be reacted with the phosphonate reagent as shown, where R^2 is defined above, R^3 is hydrogen or methyl and R_a is a conventional ester alkyl radical, e.g. methyl or ethyl, to yield the Δ-20 olefins IIIa, IIIb & IIIc.

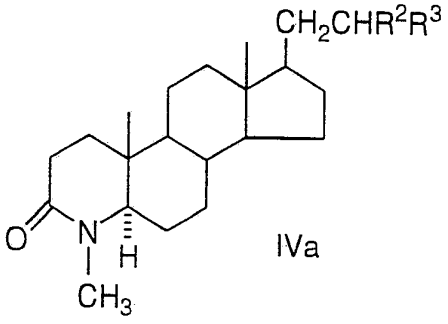
In general, the procedure for reacting the carboxaldehyde with the phosphonate ylid reagent is analogous to the conditions as described for the Wadsworth-Emmons modification of the Wittig reaction (See Chem. Rev. 74, p. 87, 1974 and JACS Vol. 83, p. 1733, 1961). The phosphonate ylid is reacted under anhydrous conditions with the carboxaldehyde in about a 1:1 molar ratio together with a hydride reagent, e.g. sodium hydride, also in a 1:1 molar ratio with the phosphonate reagent in a dry solvent, e.g. dimethylformamide, dimethylacetamide, tetrahydrofuran, dioxane, DMSO and the like, under anhydrous conditions, usually a nitrogen atmosphere, at a temperature of about 50-100°C, preferably 80-85°C for about 1-4 hours. Workup is conventional, e.g. organic liquid extraction followed by drying, evaporating off solvent, followed by chromatography, distillation or recrystallization of the crude material to yield the desired product, being a species of Formula I.

The starting phosphonates can be prepared by known procedures in the art. One procedure that can be used is the modified Arbuzov reaction in which a chloromethyl-aryl or heteroaryl compound, e.g. thienylmethyl chloride, is reacted with an alkyl phosphite, e.g triethyl phosphite, at 125-175°C for 1-10 hours. Conventional workup yields the desired starting phosphonate, e.g. diethyl 2-thienylmethylphosphonate.

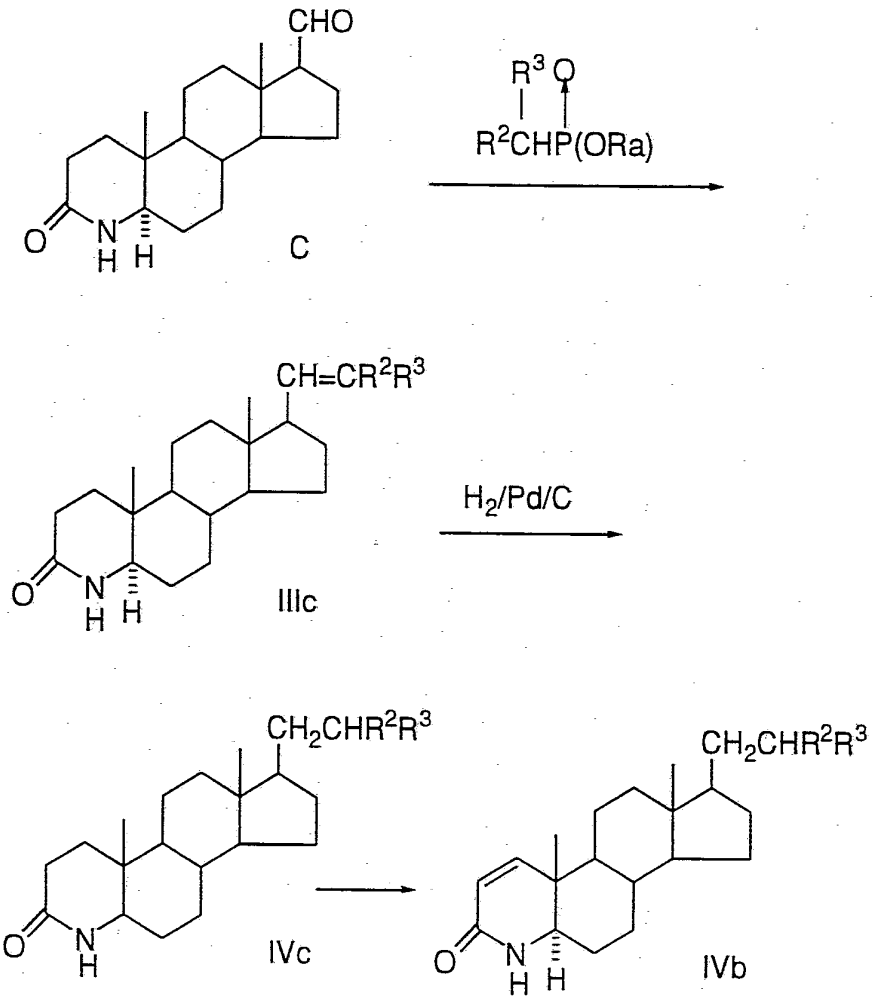
FLOWSHEET A


CHO
R3 O
R2CHP(ORa)
O
N
H
CH3
A

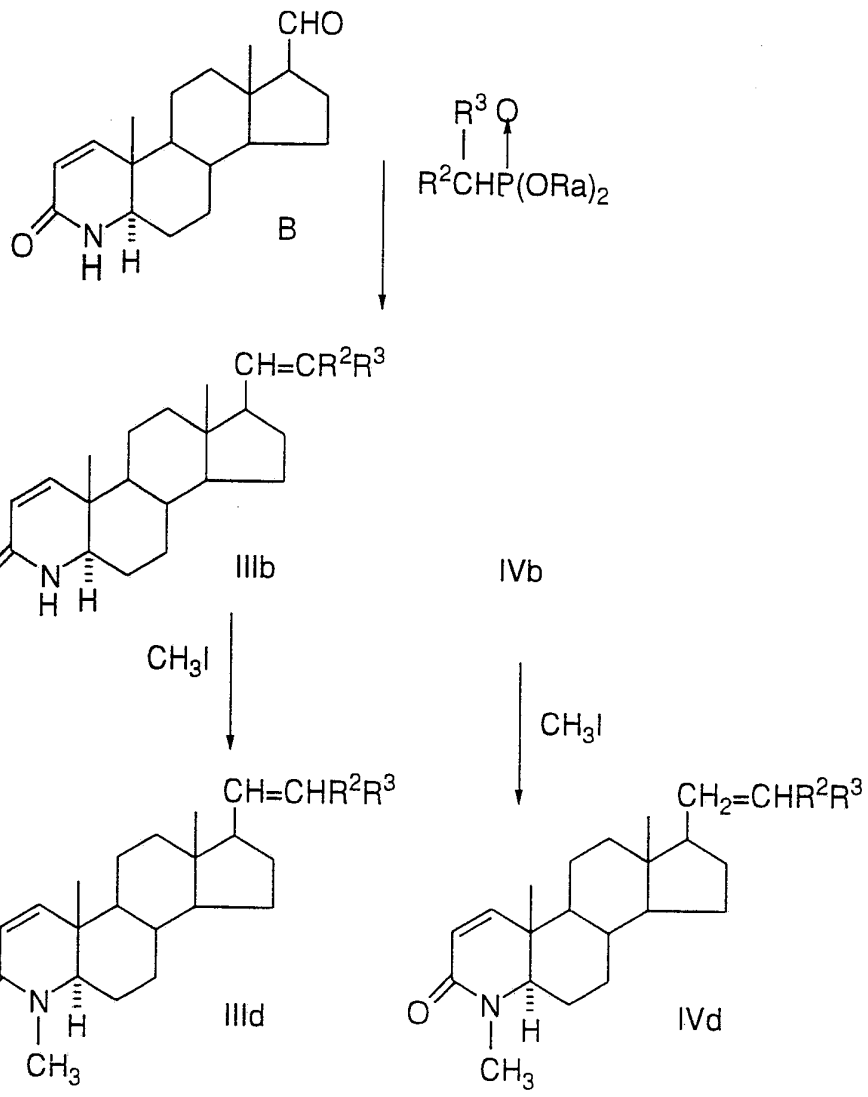

CH=CR2R3
H2/Pd/C
O
N
H
CH3
IIIa


CH2CHR2R3
O
N
H
CH3
IVa

FLOWSHEET A (Cont'd)



FLOWSHEET A (Cont'd)



Alternately, the chloromethyl heteroaryl compound, e.g. 4-chloromethylpyridine, can be reacted with diethylphosphite and sodium hydride at about 80-100°C for several hours to also produce the desired phosphonate starting materials.

Representative syntheses are given in the "Preparation of Starting Materials" section and representative examples of phosphonate starting materials are:

diethyl 2-thienylmethylphosphonate.

diethyl 4-pyridylmethylphosphonate,
diethyl 4-methylbenzylphosphonate,
diethyl benzylphosphonate,
diethyl 4-chlorobenzylphosphonate,
diethyl 3-chlorobenzylphosphonate,
diethyl 2-chlorobenzylphosphonate,
diethyl 2-pyridylmethylphosphonate,
diethyl 3-thienylmethylphosphonate,
diethyl 2-furanylmethylphosphonate,
diethyl 2-fluorobenzylphosphonate,
diethyl 3-pyridylmethylphosphonate,
diethyl 4-ethoxycarbonylbenzylphosphonate,
diethyl 4-(phenylaminocarbonyl)benzylphosphonate,

As outlined on Flowsheet A, the Δ^{20} olefins IIIa and IIIc can be reduced with e.g. 10% palladium on carbon in a suitable solvent, e.g. methanol, ethanol, dioxane, acetic acid and the like, at room temperature under 1-50 psig hydrogen atmosphere to form IVa and IVc. Compound IVc can be further reacted to form the Δ' olefin IVb by the procedure of Dolling et al using dichlorodicyanobenzoquinone, see JACS (1988), Vol 110, pp 3318-3319. Compound 52f (Example 8) was prepared by this procedure. Alternatively IVb can be formed by reacting IVc with benzeneselenic anhydride in refluxing chlorobenzene. The 4-nitrogen in IIIb and IVb can be alkylated with methyl iodide in the presence of sodium hydride in e.g. dry dimethylformamide solvent to give IIId and IVd.

Note that the 4-methyl group in the appropriate compounds in Flowsheet A can be replaced with a 4-ethyl group to prepare the corresponding 4-ethyl analogs of IIIa, IVa, IIId, and IVd.

The aldehydes A, B and C can be reacted with diethyl α-methyl-benzylphosphonate (US 4,515,883) in the Wadsworth-Emmons modification of the Wittig reaction and the corresponding products hydrogenated, alkylated on the 4-nitrogen and dehydrogenated as outlined in Flowsheet A to give compounds IIIa-d and IVa-d with R^2 =

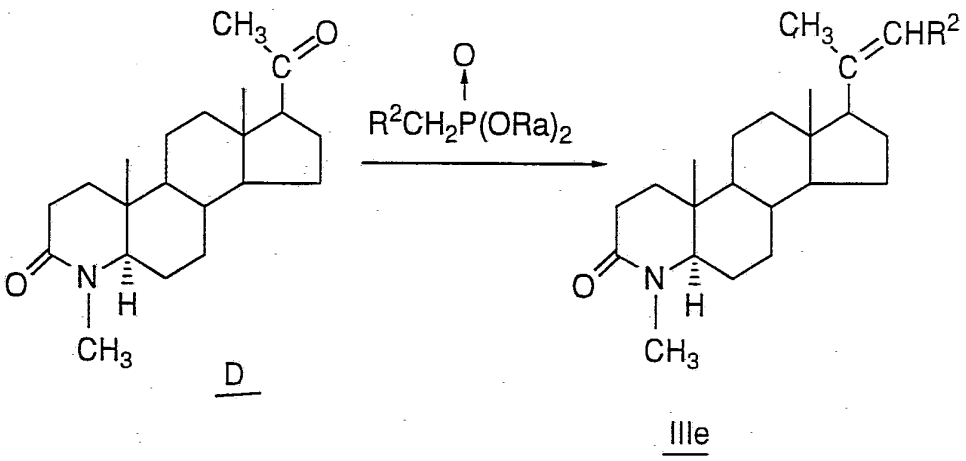
phenyl and R^3 = methyl.

Methyl ketone D (see Chart B) and its preparation is described in J. Med. Chem., 1984, Vol. 27, p. 1690-1701, by G. H. Rasmusson et. al (see Compound 4d.) These compounds can be prepared by reacting the S-(2-pyridyl)androstan-3-one-17β-thio-carboxylate with methylmagnesium chloride under appropriate Grignard conditions.

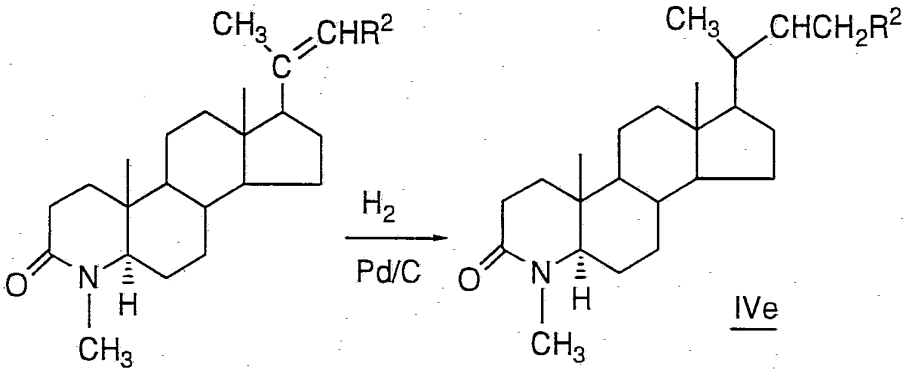
Methyl Ketone E can be prepared by reacting N-methoxy-N-methyl-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide (4) with excess methylmagnesium bromide in tetrahydrofuran.

The above 17-methylketones D and E can be reacted with the phosphonate ylids described above in an analogous manner to achieve the 20-methyl pregn-20-en-3-one compounds IIIi and IIIj as illustrated in the following Flowchart B.

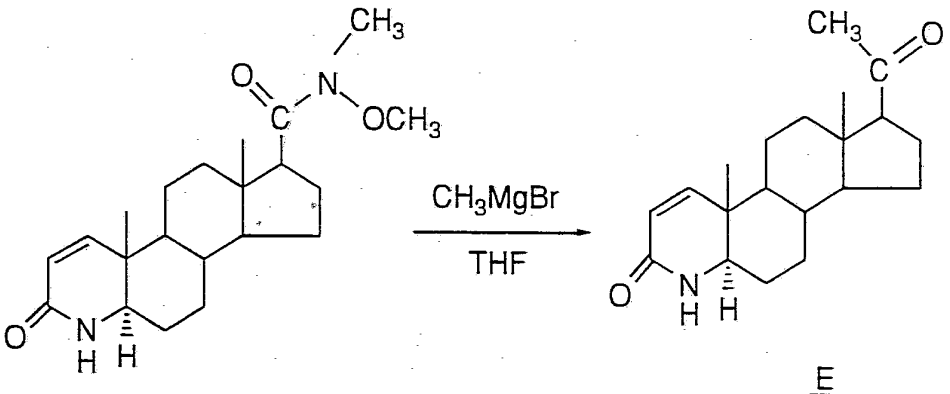
FLOWCHART B



D IIIe

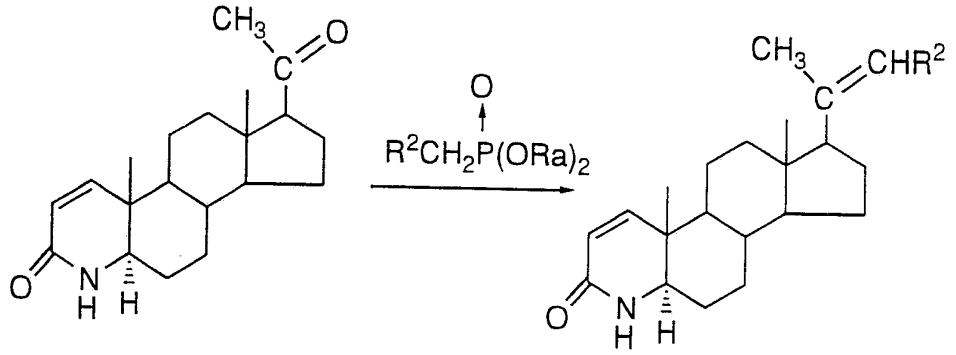


IIIe IVe

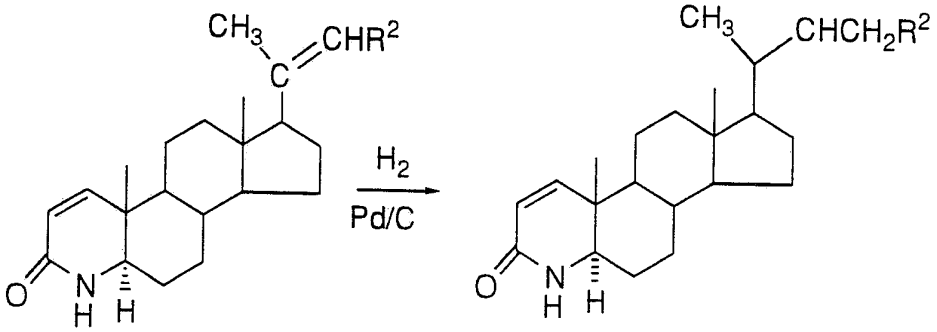


4 E

FLOWCHART B (Cont'd.)

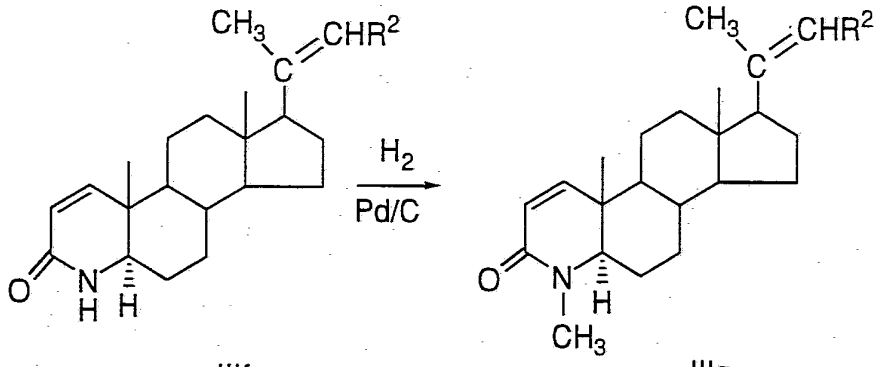


E IIIf

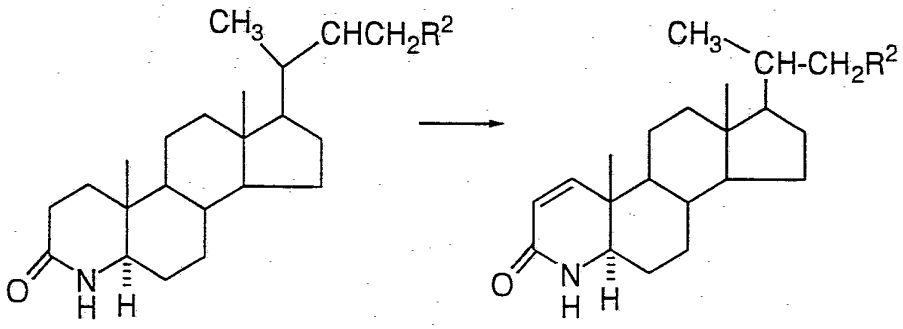


IIIf IVf

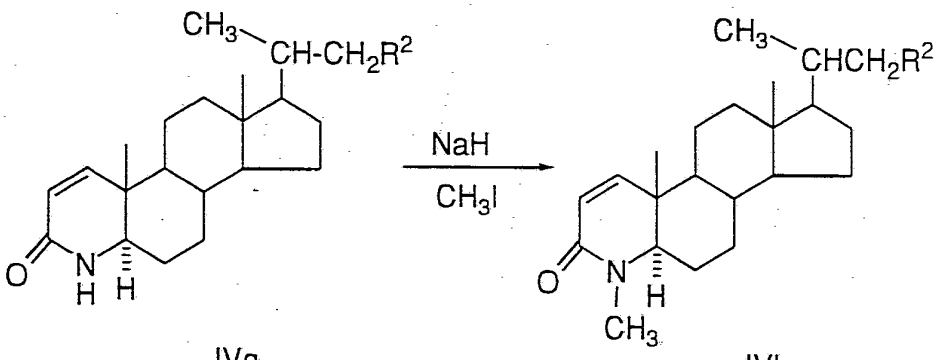
FLOWCHART B (Cont'd.)



IIIf IIIg



IVf IVg



IVg IVh

As outlined in Flowsheet B, IIIe and IIIf can be hydrogenated as above to give IVe and IVf. Compound IVf can be dehydrogenated as described above to the Δ'-compound IVg. Compounds IIIf and IVg can be methylated on the 4-nitrogen to give IIIg and IVh.

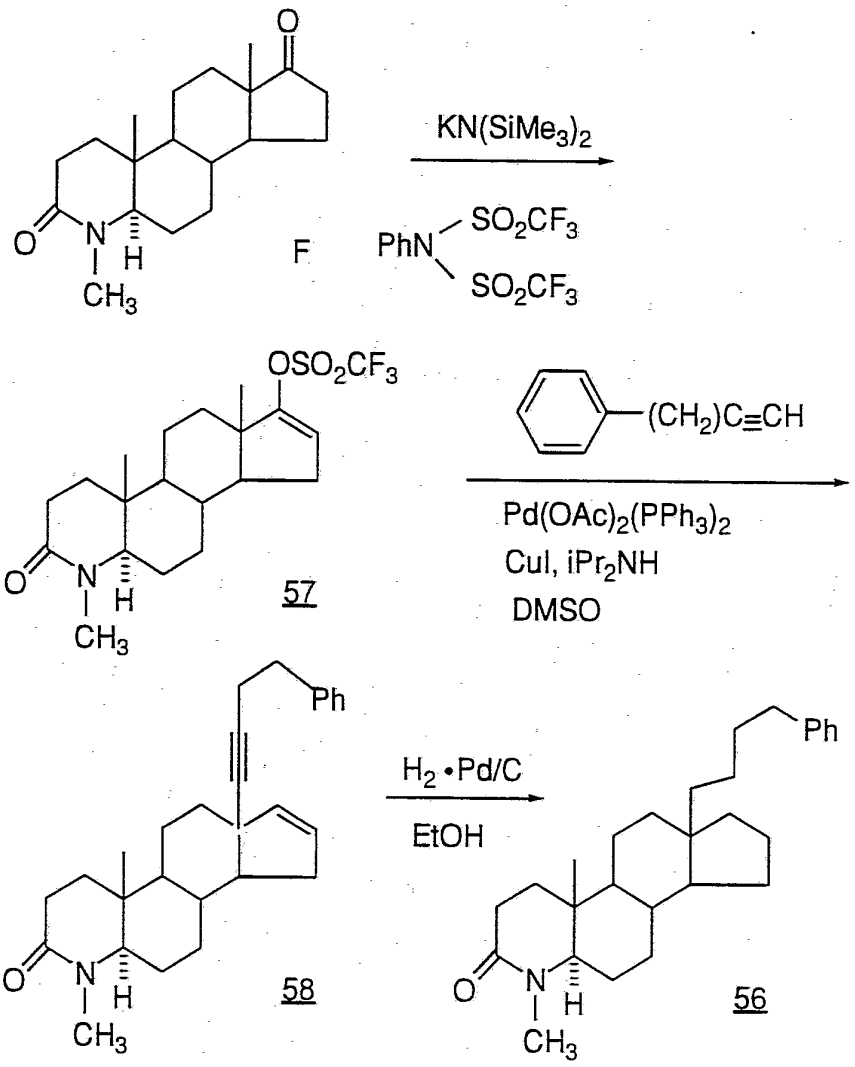
Also the amide 4 can be reacted with ethyl- magnesium bromide to give ethyl ketone versions of D and E. Using the reactions outlined in Flowsheet B compounds IIIe-g and IVe-h with the 20-methyl replaced by a 20-ethyl can be prepared.

Ketone F (Flowchart C) can be prepared by conventional techniques, including oxidation of the corresponding 17-β-ol with e.g. Jones reagent, and is known in the art in J. Med. Chem. 1984, Vol. 27, p. 1690-1701 by G. H. Rasmusson et. al., (see Compound 22 on p. 1693).

Ketones G and H can be prepared by Jones reagent oxidation of the corresponding 17 β-alcohols described in the above reference. Using the reactions shown in Flowsheet A, the ketones F, G, and H are converted into compounds IIIh-k and IVh-l as seen in Flowsheet C.

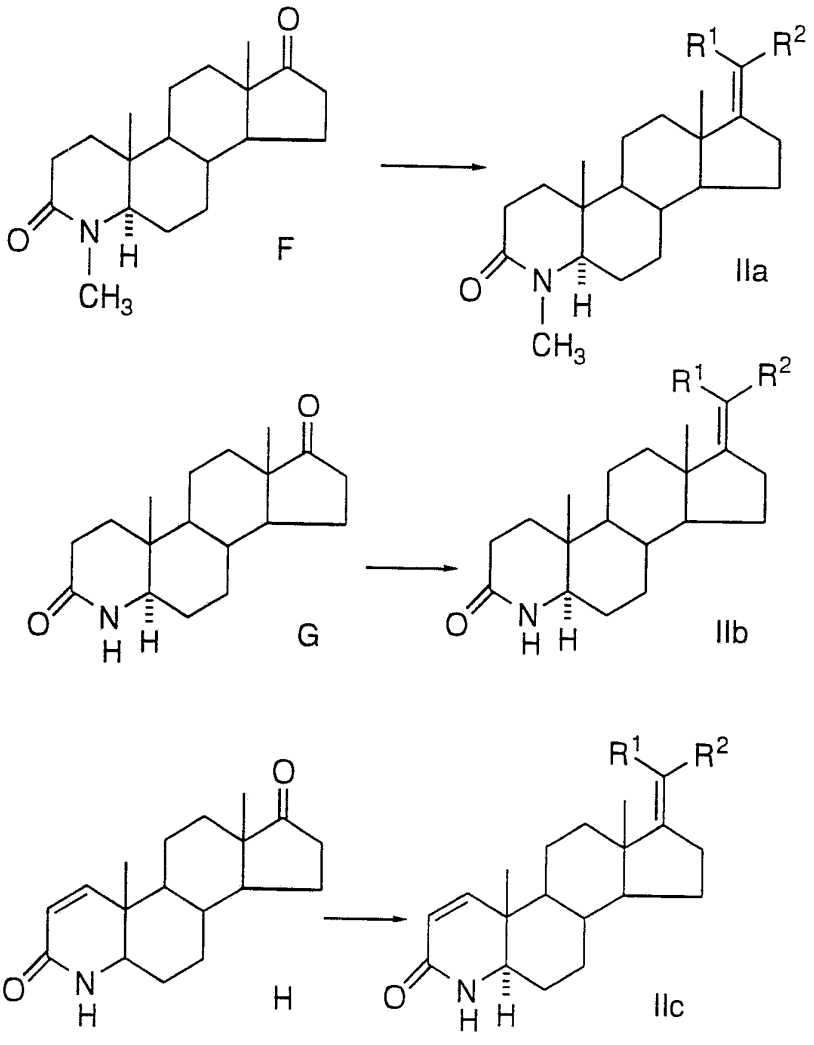
As indicated in Example 9, the 17β-3-phenylpropyl compound (53) can be prepared from aldehyde A by a phosphonate olefination with diethyl benzoylmethylphosphonate followed by reduction of the ketone and double-bond by hydrogenation with palladium on carbon catalyst in ethanol. Using the reaction sequences outlined in Flowsheet A, the 4-H, Δ'-4-H, and 4-CH_3-Δ' analogs can be prepared starting from aldehydes A or B.

FLOWSHEET B-1

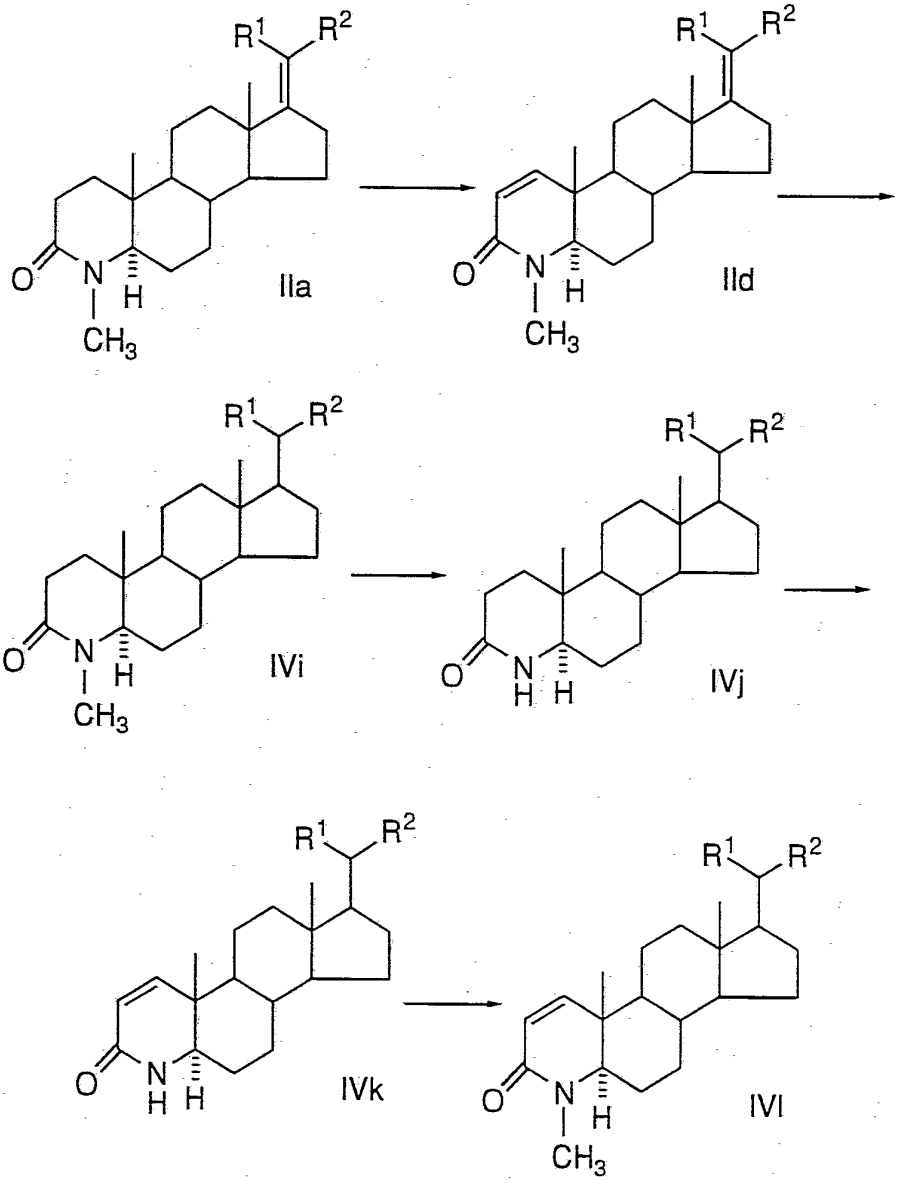


As shown in Flowsheet B-1, the 17β-3-phenyl- butyl compound 56 can be prepared from the ketone F by conversion of the latter to the Δ16-17-trifluoromethylsulfonate 57 with potassium hexamethyldisilazide and N-phenyltrifluoromethanesulfinimide (Tetrahedron Lett. 24, 979 (1983)). Palladium-catalyzed coupling of 57 with 4-phenyl-1-butyne (Synthesis, 320 (1986)) can give the en-yne 58 which can be hydrogenated to the desired 17β-3-phenylbutyl compound 56.

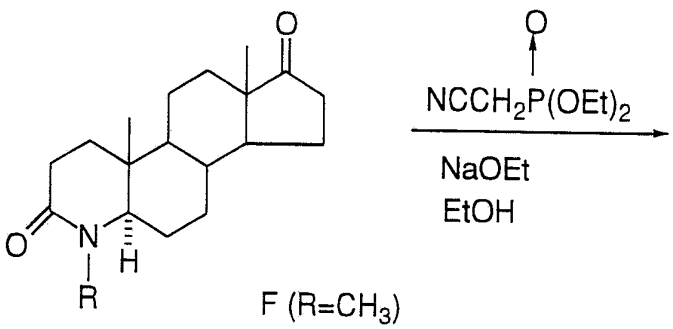
FLOWSHEET C



FLOWSHEET C (Cont'd)

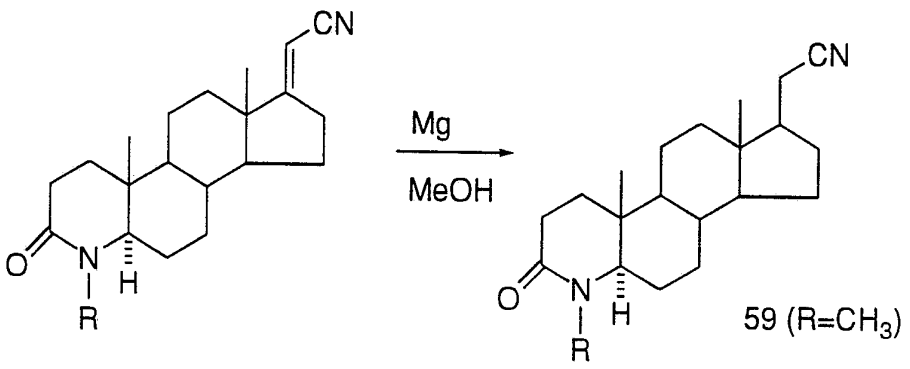


FLOWSHEET D



F (R=CH_3)

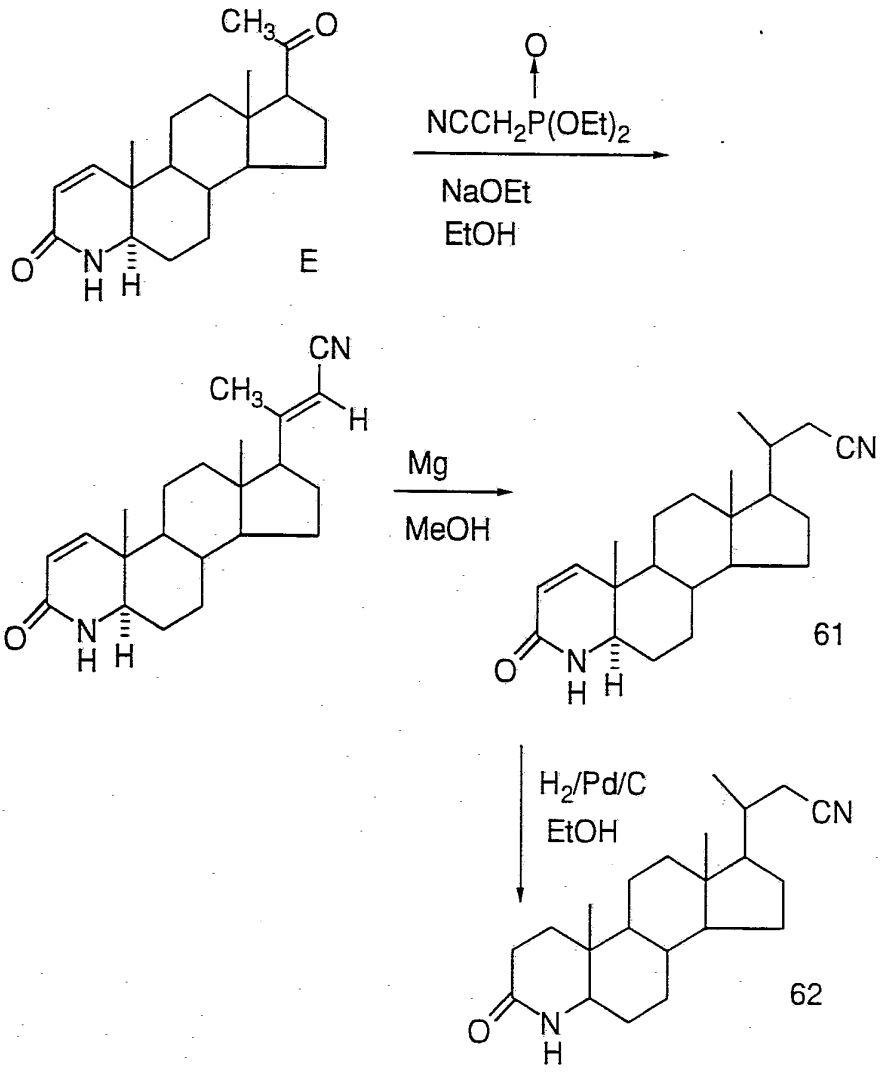
G (R=H)



59 (R=CH_3)

60 (R=H)

FLOWSHEET D (Cont'd)



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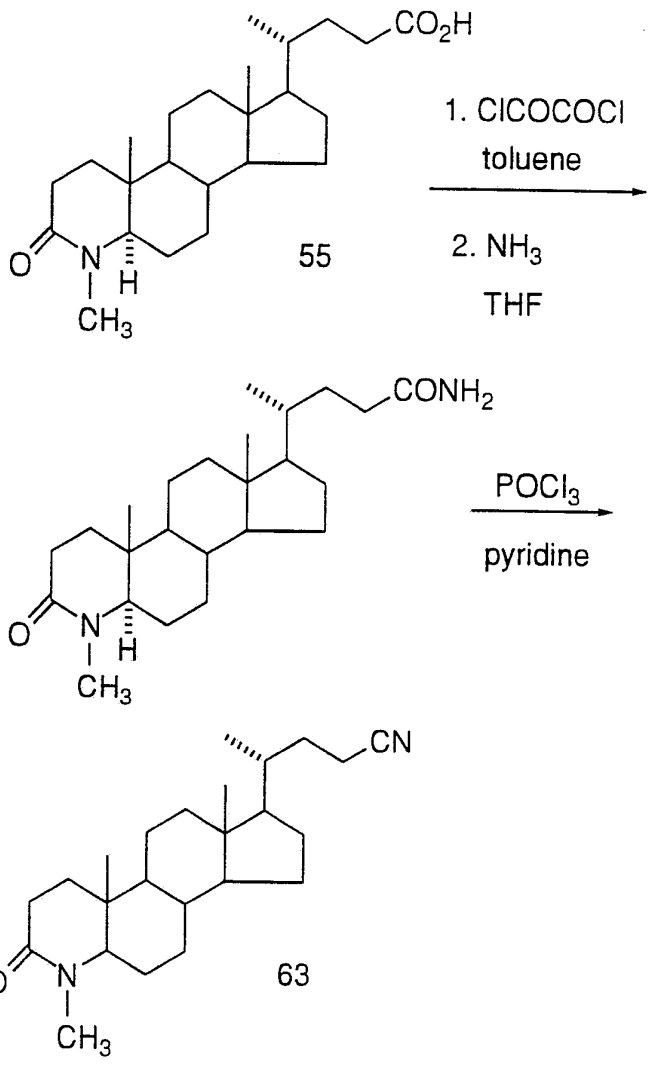

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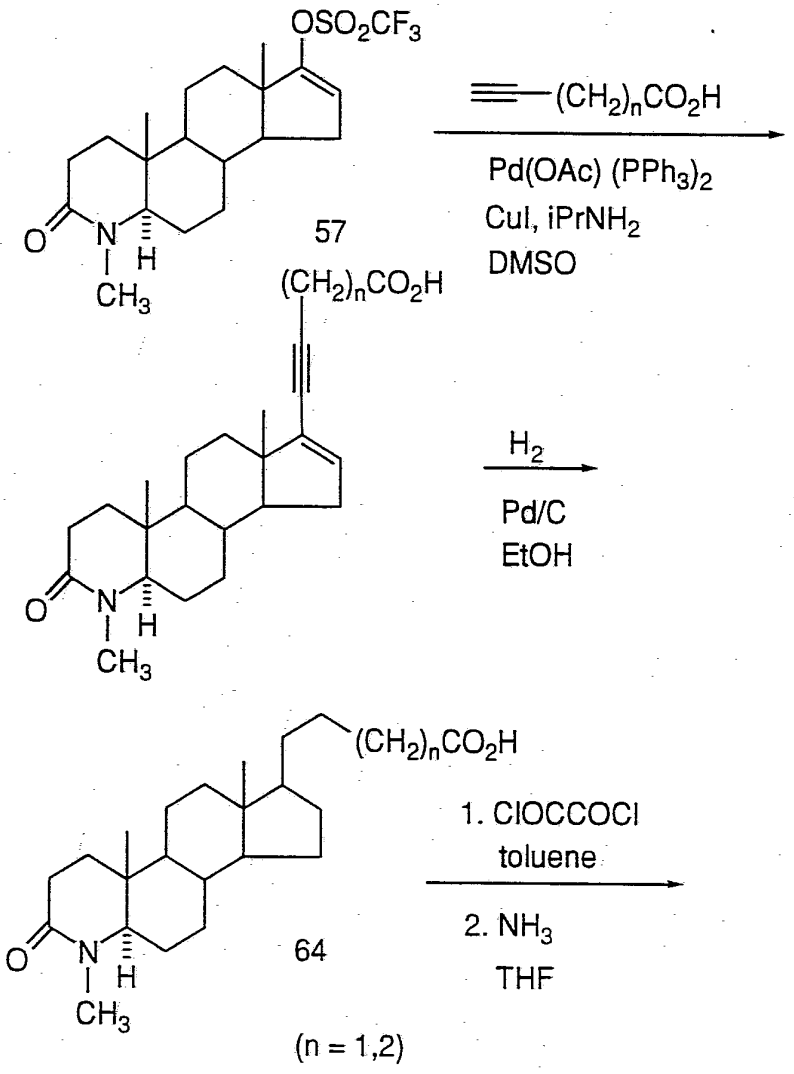

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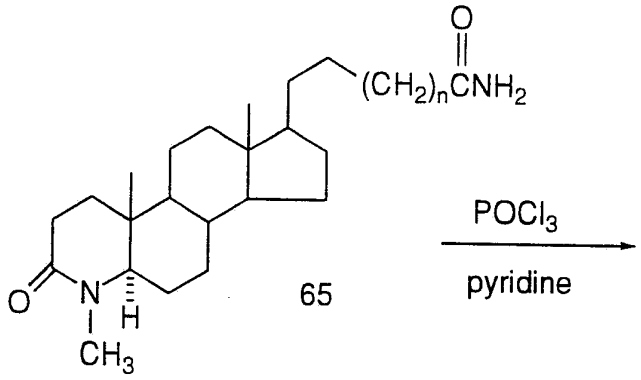
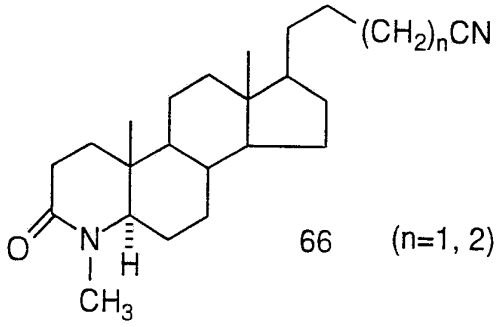


65



66 (n=1, 2)

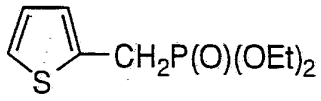
As described in Example 10, the nitriles 54 (R=CH_3, H) were prepared from a "second order" Beckmann rearrangement on the homologous carboxylic acids (55, R=CH_3, H) with sodium nitrite in trifluoroacetic acid and trifluoroacetic anhydride. (J. of Lipid Research 29 1387 (1988)).

The synthesis of other nitriles is outlined in Flowsheet D. The pregnane-21-carbonitriles 59 and 60 can be prepared from the ketones F and G by phosphonate olefination with diethyl cyanomethylphosphonate (Steroids 27, 431 (1976)) followed by reduction with magnesium in methanol (J. Org. Chem. 40, 127 (1975)). By the same reaction sequence the ketone E can be converted into the Δ1-4-H-24-norcholane-23-nitrile 61 and its reduction product 62. The 24-cholane-24-carbonitrile 63 can be prepared from the cholanic acid 55 by conversion

to the primary amide with oxalyl chloride and ammonia followed by dehydration with $POCl_3$ in pyridine (J. Med. Chem. 29, 2298 (1986)). Similarly the 17-butyric (64, n=1) and valeric (n=2) acids, prepared by palladium-catalyzed coupling of 57 with 3-butynoic and 4-pentynoic acids followed by hydrogenation, can converted into the nitriles 66 (n=1,2).

The method of preparing the novel delta-20-olefinic 4-aza-5α-androstan-3-one compounds of the present invention, already described above in general terms, may be further illustrated by the following examples.

PREPARATION OF STARTING MATERIALS



1

A. Preparation of diethyl 2-thienylmethylphosphonate, (1)

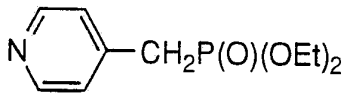
Following the general procedure for carrying out the Arbuzov reaction (reference cite: Chem. Rev. 81, 415, 1981) 0.1 mole (17.5 ml) of triethyl phosphite and 0.1 mole (13.2 g) of 2-chloro-methylthiophene were combined and heated under N_2 at 150°C for 5 hours. The reaction mixture was cooled and partitioned between 100 ml methylene chloride and 50 ml. water. The organic phase was separated, washed with saturated $NaHCO_3$ solution, dried over magnesium sulfate and concentrated under vacuum to yield 17.5 g. crude liquid product.

The liquid was distilled at 113-115°C at 0.5-0.6 mm Hg to yield 5.78 g of the titled product. The proton NMR confirmed the structure of the distilled product.

The following phosphonate reagents were also prepared by the above-described method: diethyl 3-thienylmethylphosphonate,

diethyl 2-furanylmethylphosphonate, diethyl 2-fluorobenzyl-phosphonate , and diethyl 3,4,5-trimethoxybenzylphos-phonate.

B. Preparation of Diethyl 4-Pyridylmethylphosphonate, (2)



2

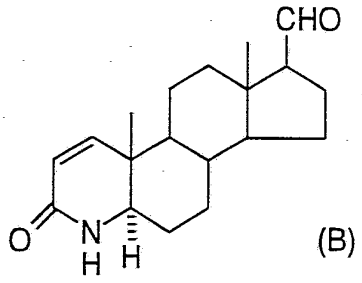
4-Picolyl chloride HCl salt (20 mmol, 3.38g) was partitioned between 40 milliters 50% K_2CO_3 and 40 milliliters ethyl acetate. The black aqueous phase was extracted (2x) with ethyl acetate and the combined organic phases were dried over magnesium sulfate, and concentrated under reduced pressure. The residue was dissolved in 20 milliliters of toluene.

Sodium hydride (800 mg., 20 mmol) was washed with (3x) hexane and suspended in 8 milliliters of toluene. Diethyl phosphite (5.15 ml, 40 mmol) was added dropwise with stirring and the mixture heated at 80°C for 30 minutes to yield a clear solution. The toluene solution of the picolyl chloride was added dropwise and the reaction mixture heated at 80°C for 30 minutes. After cooling, the mixture was poured into water, saturated with sodium chloride, and extracted (3x) with ethyl acetate. The combined organic phases were dried over magnesium sulfate and concentrated under reduced pressure. The liquid residue was distilled under vacuum to yield 2.45 g. (53.5% of theory), b.pt. 123-125/@ 0.3 mm Hg. The proton nmr spectrum confirmed the compound structure.

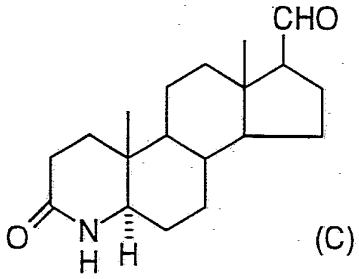
The following phosphonate reagents were also prepared by the above-described method: diethyl 3-chlorobenzylphosphonate, diethyl 2-chlorobenzylphosphonate, diethyl 2-pyridylmethyl-phosphonate, diethyl 3-pyridylmethylphosphonate, diethyl 4-pyridyl-methylphosphonate, diethyl 4-carbethoxybenzylphosphonate, diethyl 4-(N-phenylcarbamoyl)benzylphosphonate, diethyl pyridazyl-

methylphosphonate, diethyl 5-thiazolyl-methylphosphonate, diethyl 4-methylsulfonylbenzylphosphonate, and diethyl 2-methoxybenzyl-phosphonate.

C. Preparation of 4-aza-5α-androst-1-en-3-one-17β-aldehyde (B) and 4-aza-5α-androstan-3-one-17β-aldehyde (C)



(B)



(C)

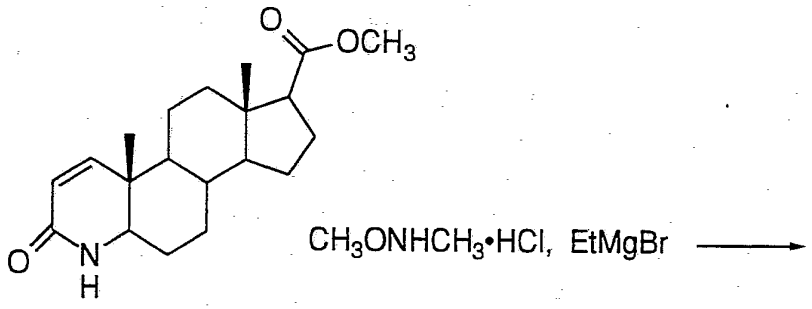
17β-(N-methyl-N-methoxy) carboxamide-5α-4-aza-androst-1-en-3-one (prepared as in following Example D), 3.6g. (10 mmol) was suspended in 100 ml dry THF at 0°C under dry nitrogen, lithium aluminum hydride (10 ml of 1M lithium aluminum hydride in dry THF) was added slowly dropwise with stirring maintaining temp at <5°C. After addition was complete the reaction was allowed to stir for 20 minutes. 2N HCl was added to the reaction mixture to pH 3, additional water added and the reaction mixture extracted with (3x) chloroform. The organic phases were combined, dried over magnesium sulfate and concentrated to yield 3.2 g. residue. The crude product was flash chromatographed on a 50mm. x 7" silica gel column with 4:1 methylene chloride/acetone.

The first fractions eluted (12-22) yielded 1.75 g. (58% of the unsaturated aldehyde (B). m.p. 260-263°.

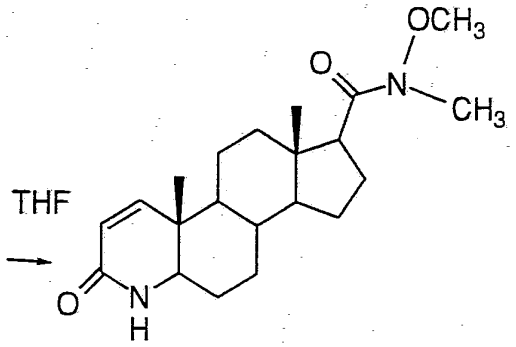
Fractions (25-36) yielded 0.70 g. (23%) of the saturated aldehyde (C). m.p. 246-249°.

Proton NMR confirmed the assigned structures for both compounds.

D. Preparation of (5α, 17β)-N-Methoxy-N-methyl-3-oxo-4-aza-androst-1-ene-17β-carboxamide (4)



3



4

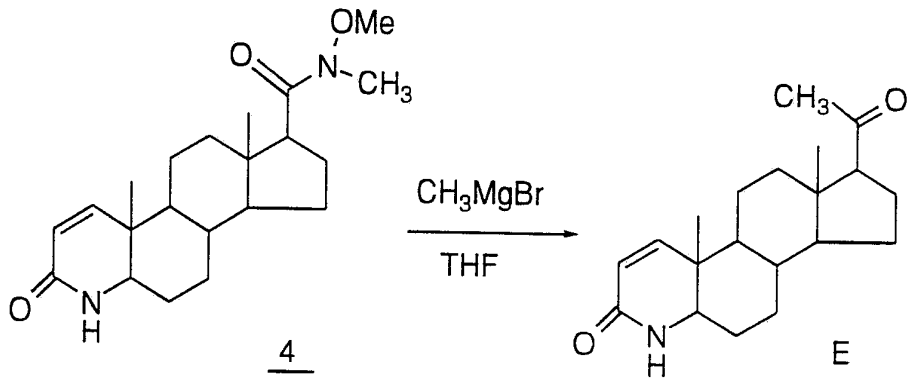
A 2 L three-neck flask equipped with an overhead stirrer, nitrogen inlet, internal thermometer, and/dropping funnel was charged with 800 mL of sieve-dried tetrahydrofuran, 19.72 g (59.6 mmol)of Δ^1-aza ester (Compound 3) (for synthesis, see Rasmusson, Johnston and Arth. U.S. Patent 4,377,584, March 22, 1983.) and 25.6 g (262.4 mmole) of N,O-dimethyl-hydroxylamine hydrochloride. The resulting slurry was cooled to 0 to 5°C.

A warm solution (30-40°C) of ethylmagnesium bromide in dry tetrahydrofuran (252 mL, 2.0 Molar, 504 mmole) was added over fifteen minutes. The pot temperature was maintained at 0-5°C during the addition. The reaction mixture was warmed to 25°C over thirty minutes and aged at 22-25°C for one hour. The reaction was cooled to 0-5°C and quenched into 650 mL of 25 wt% aqueous ammonium chloride. The mixture was warmed to 40-45°C and the layers were

separated. The organic solution was cooled to 25°C and treated with activated carbon.

The THF solution after filtration was concentrated by atmospheric distillation to 200 mL. The resulting slurry was cooled to 35°C and 1 L of water was added over one hour. The slurry was cooled to 25°C and aged for 2 hours. The amide was collected by filtration and washed with 200 mL of water then dried at 80°C/house vacuum to yield 19.6 g (91.4%) of amide 4 (98.8 area % pure by LC).

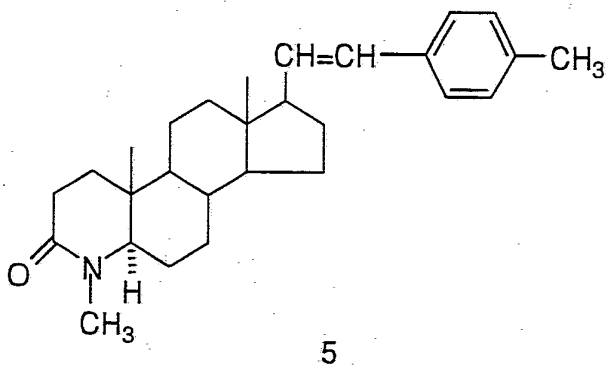
E. Preparation of 4-aza-5α-pregn-1-ene-3,20-dione (E)



To a slurry of 4 (12 g, 33 mmoles) in 480 ml of dry tetrahydrofuran was added dropwise 83.3 ml (250 mmoles) of 3.0 M methylmagnesium bromide in diethyl ether while maintaining the temperature of the reaction <5° with cooling with an ice bath. The mixture was stirred at room temperature for 8 hours. After cooling in an ice bath, 500 ml of aqueous ammonium chloride (1 g/3 ml H_2O) was added. Most of the tetrahydrofuran was removed in vacuo. The slurry was filtered, and the solid washed with H_2O, dried, triturated with Et_2O, filtered and dried to give 10.5 g of 4-aza-5α-pregn-1-ene-3,20-dione, mp. 310-312°. The NMR spectrum confirmed the assigned structure.

EXAMPLE 1

REACTION OF 17-CARBOXALDEHYDE WITH PHOSPHONATE REAGENT



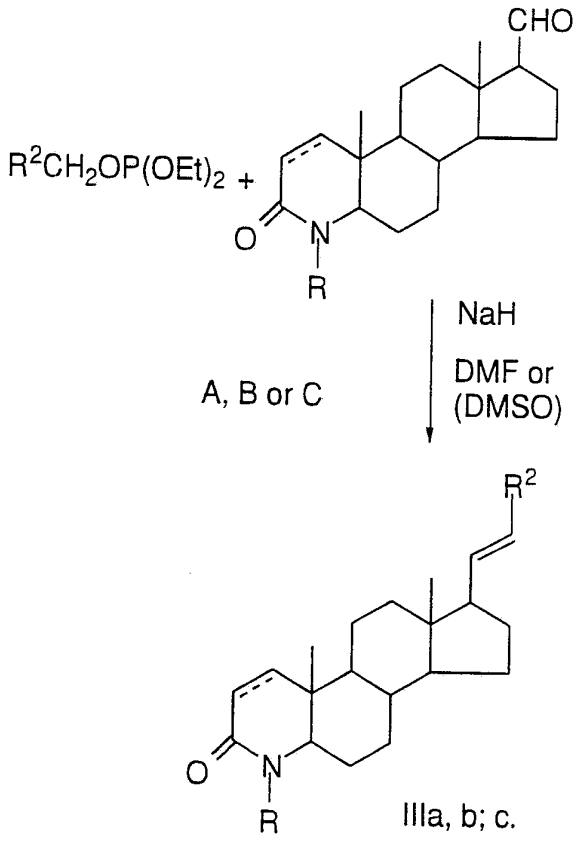
5

1. Preparation of 17β-(1-(2-(4-tolyl))ethenyl)-4-methyl-4-aza-5α-androstan-3-one, (5).

Following the general procedure of Wadsworth, et al., (see Chem. Rev. 74, 87 (1974) and JACS, Vol. 83, p. 1733 (1961), 5-alpha-4-aza-4-methyl-androstan-3-one-17-aldehyde, Carboxaldehyde A, (245 mg, 0.77 mol), sodium hydride (31 mg, 0.78 mol), diethyl 4-methylbenzylphosphonate (189 mg., 0.78 mol) in 2 ml. anhydrous dimethylformamide was stirred at 80°C in a nitrogen atmosphere for 1.5 hours. The reaction was cooled and partitioned with 20 ml. each of 0.1 N HCl/methylene chloride. The organic phase was washed with water, dried over magnesium sulfate and concentrated under reduced pressure to yield 391 mg. crude solid. Recrystallization from ethyl acetate yielded a white solid, mp 225-227°C. The proton NMR and mass spectrum confirmed the assigned structure for 5.

EXAMPLE 2

Following the general procedure described above in Example 1, the following tabulated compounds were prepared.



IIIa, b; c.

Structure	Compound No.	R	R^2	Mass Spec. method:m/e		TLC solvent system	Rf
IIIa	6	Me	4-methoxyphenyl	EI	421	A	0.4
"	7	Me	phenyl	EI	391	B	0.5
	8	Me	4-tolyl	EI	405	B	0.4
"	9	Me	4-chlorophenyl	EI	425	B	0.5
"	10	Me	4-pyridyl	EI	392	C	0.25
"	11	Me	3-chlorophenyl	EI	425	B	0.5
"	12	Me	2-chlorophenyl	EI	425	B	0.5
"	13	Me	2-pyridyl	EI	392	C	0.3
"	14	Me	2-thienyl	EI	397	B	0.5
IIIc	15	H	4-methoxyphenyl	EI	407	C	0.5
IIIa	16	Me	3-thienyl	EI	397	B	0.4
"	17	Me	2-furanyl	EI	381	B	0.4
"	18	Me	2-fluorophenyl	EI	409	B	0.4
IIIb	19	H*	4-pyridyl	EI	376	C	0.3
IIIc	20	H	4-pyridyl	EI	378	D	0.3
IIIb	21	H*	4-methoxyphenyl	EI	405	C	0.5
"	22	H*	2-furanyl	EI	365	C	0.5
"	23	H*	2-pyridyl	EI	376	C	0.3
"	24	H*	3-pyridyl	FB'	377	C	0.3
"	25	H*	4-ethoxycarbonyl phenyl	FB'	447	C	0.4
"	26	H*	4(N-phenylcarbamoyl)phenyl	FB'	495	E	0.7
"							
IIIc	27	H	2-pyridyl	FB"	380	C	0.2
"	28	H	3-pyridyl	EI	378	F	0.3
"	29	H	2-thienyl	FB'	384	C	0.2

	IIIa	29a	Me	3,4,5-trimethoxy-phenyl	EI	481	C	0.5
	"	29b	Me	pyrazinyl	EI	393	C	0.3
	"	29c	Me	3-pyridyl	EI	392	C	0.4
	IIIb	29d	H*	pyrazinyl	EI	377	C	0.4
	"	29e	H*	5-thiazolyl	EI	382	C	0.4
	"	29f	H*	4-methylsulfonyl-phenyl	FB'	454	C	0.5
	"	29g	H*	2-methoxyphenyl	FB'	406	C	0.6
	"	29h	H*	4-(N-(4-pyridyl) carbamoylphenyl	EI	495	G	0.4
	"	29i	H*	4-(N-methyl-N-(4-pyridyl)carbamoyl)-phenyl	EI	509	G	0.5

Note: in the above table the TLC symbols used are indicated as:

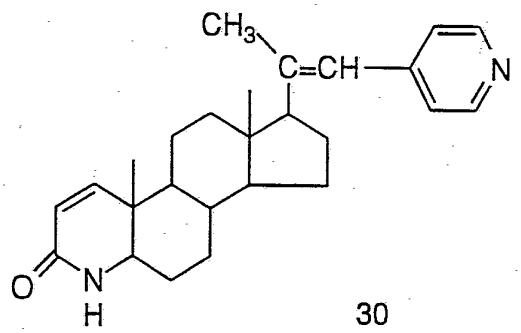
A - ethyl acetate
B - 4:1 ethyl acetate/hexane
C - 4:1 methylene chloride/acetone
D - 3% methanol/methylene chloride
E - 1:1 methylene chloride/acetone
F - 7:3 methylene chloride/acetone
G - 5% methanol/methylene chloride

The mass spectral data were obtained by either electron impact (EI) or fast atom bombardment (FB) techniques.

The FB recorded results with one prime, FB1, indicates m+1; with two primes, FB11, indicates m+2. Also, the asterisk denotes the presence of the 1,2-double bond (Δ'). The starting materials used were the aldehyde, A, for the 4-N-methyl derivatives; C, for 4-NH derivatives; and B, for the 1-ene-4-NH derivatives.

EXAMPLE 3

REACTION OF 17-METHYL KETONES WITH PHOSPHONATE REAGENT



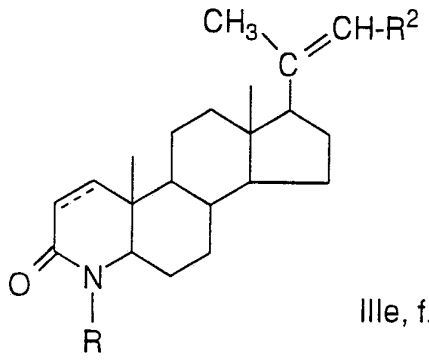
30

Preparation of: (20E)-20-methyl-21-(4-pyridyl)-4-aza-5α-pregn-1,20-dien-3-one, (30)

Following the general procedure of Wadsworth et al.; cited above, to a solution of 4-aza-5α-pregn-1-ene-3,20-dione (E) (158 mg., 0.5 mmol) and 229 mg (1.0mol) diethyl 4-pyridylmethylphosphonate in 2 ml.anhydrous DMSO, was added all at once under N_2 atmosphere, 50 mg. (1.25 mmol) of sodium hydride (60%). The reaction mixture was stirred and heated at 85°C under a N_2 atmosphere for 3 hours. Hydrogen evolution stopped after 15 minutes. The dark reaction mixture was cooled, poured into 30 ml H_2O and extracted (3x) with methylene chloride. The combined organic phase was washed with water, dried over magnesium sulfate and concentrated under reduced pressure to yield a brown gum. The crude material was chromatographed on silica gel plates with 1:1 methylene chloride/acetone and the strong UV active band was eluted 2:1 methylene chloride/methanol. The eluate was concentrated to yield pure product after trituration with ether, mp 268-270°C (dec.). The proton NMR comfirmed the assigned structure for 30.

EXAMPLE 4

Following the general procedure of Example 3, the following tabulated compounds were prepared.



IIIe, f.

TABLE 2

Structure	Compound No.	R	R^2	Physical Properties
IIIe	31	Me	Phenyl	NMR*
"	32	Me	4-chlorophenyl	mp. 208-211°C
"	33	Me	2-thienyl	mp. 220-222°C
"	34	Me	2-pyridyl	mp. 200-203°C
IIIf	35	H*	4-pyridyl	mp. 268-278°C (dec.)
IIIe	36	Me	4-pyridyl	NMR**
IIIf	37	H*	2-furyl	mp. 290-294°C (dec.)
"	38	H*	2-pyridyl	mp. 255-258°C (dec.)

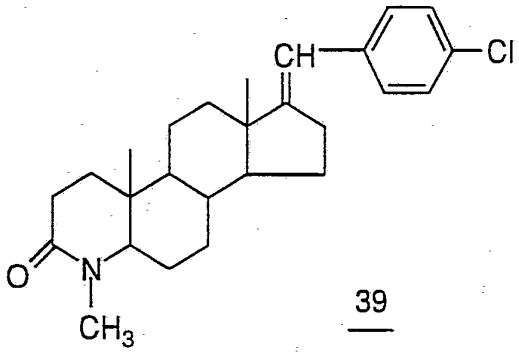
*NMR($CDCl_3$) δ 0.65 (S,3H, 18-Me), 0.90 (S, 3H, 19-Me), 1.88 (S, 3H, 21-Me), 2.94 (S, 3H, N-Me), 6.35 (bs, 1H C=C<u>H</u>-), 7.1-7.4 (m, 5H, ArH).

**NMR($CDCl_3$) δ 0.65 (S, 3H, 18-Me), 0.91 (S, 3H, 19-Me), 1.92

(S, 3H, 21-Me), 2.94 (S, 3H, N-Me), 6.25 (bs, 1H, C=CH-), 7.19 (vbs, 2H, pyridyl H), 8.6 (vbs, 2H, pyridyl H).

EXAMPLE 5

REACTION OF PHOSPHONATE REAGENTS WITH 17-KETO ANDROSTANES



39

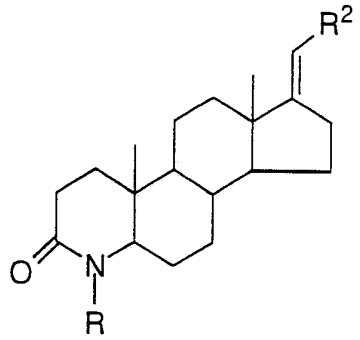
Preparation of 17-[(2-chlorophenyl)methylene]-4-methyl-5α-androstan-3-one, (39)

Sodium hydride (60%, 26 mg, 0.66 mmole) was added to a solution of 101 mg. (0.33 mol) of 17-keto-4-methyl-5α-androstan-3-one (F) and 173 mg (0.66 mol) of diethyl 2-chlorobenzylphosphonate in 1.0 ml of dry DMF at room temperature. The mixture was heated at 70°C in a nitrogen atmosphere with stirring for 110 minutes, cooled, poured into 0.5 N HCl (20 ml) and extracted with methylene chloride (3x). The organic phases were combined, washed with water (3x), saturated NaCl solution and dried over magnesium sulfate. The organic phase was concentrated under reduced pressure to yield a tan, gummy solid. Flash chromatography of the crude solid was conducted on a silica gel 60x20 mm column, and eluted with 4:1 methylene chloride/acetone in 6 ml. fractions. Fractions 18-24 contained the product which were combined and evaporated to yield a white solid, mp 205-208°C, yielding one spot on silica gel TLC using 4:1 methylene chloride/acetone. The

proton NMR confirmed the assigned structure for 39.

EXAMPLE 6

Following the general procedure of Example 5 but using different phosphonate reactants, the following compounds were prepared as listed in the following Table 3.



II

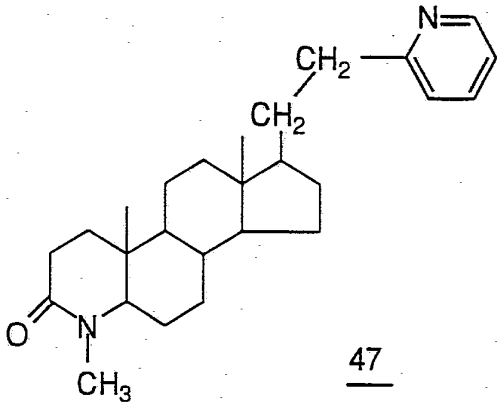
TABLE 3

No.	R	R^2	Physical Properties
40	Me	phenyl	mp. 193-197°C
41	Me	4-chlorophenyl	mp. 138-141°C
42	Me	3-chlorophenyl	mp. 236-240°C
43	Me	2-chlorophenyl	mp. 205-208°C
44	Me	4-ethoxycarbonylphenyl	mp. 178-182°C
45	Me	4-carboxyphenyl	mp. >330°C
46	Me	4-(t-butyl)amino-carbonylphenyl	NMR*

*NMR($CDCl_3$) δ 0.86 (S, 3H, 18-Me), 0.90 (S, 3H, 19-Me),

1.45 (S, 9H, CMe3), 2.92 (S, 3H, N-Me), 5.92 (bs, 1H, NH), 6.05 (t, 1H, C=CH-), 7.32 (d, J=8 Hz, 2H, ArH), 7.65 (d, J=8 Hz, 2H, ArH).

EXAMPLE 7



47

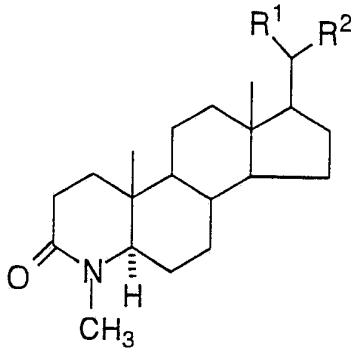
CATALYTIC REDUCTION OF DELTA-17 and -20 OLEFINS

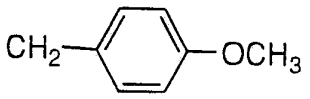
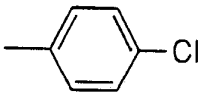
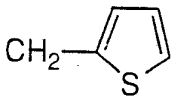
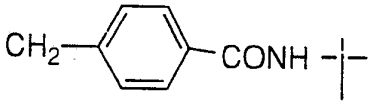
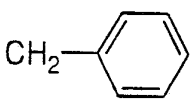
Preparation of 21-(2-pyridyl)-4-dimethyl-4-aza-5α-pregnan-3-one, (47)

A mixture of 0.075 g. (0.191 mmol) of (20E)-4,20-dimethyl-21-(2-pyridyl)-4-aza-5α-pregn-20-en-3-one, 0.075 mg 10% Pd/C catalyst in 3 ml ethanol were hydrogenated at room temperature under a 45 psig hydrogen atmosphere with shaking for 45 minutes. The reaction mixture was filtered through Celite and concentrated to yield 74 mg of product. The crude solid was chromatographed on a 2000 micron silica gel plate in 4:1 methylene chloride/acetone. The product was eluted using 5% MeOH/methylene chloride and concentrated to yield product 21-(2-pyridyl)-4-methyl-4-aza-5α-pregnan-3-one. The assigned structure for 41 was confirmed by proton NMR. Fast atom bombardment mass spectrum also con- firmed a molecular ion peak of M+2 = 396, and the Rf value on silica gel in 4:1 methylene chloride eluant was 0.2.

EXAMPLE 8

Following the general procedure of Example 7, the following saturated compounds were prepared from the corresponding Δ17 or Δ20 olefin, or Δ 16,20 diene (See Example 11):

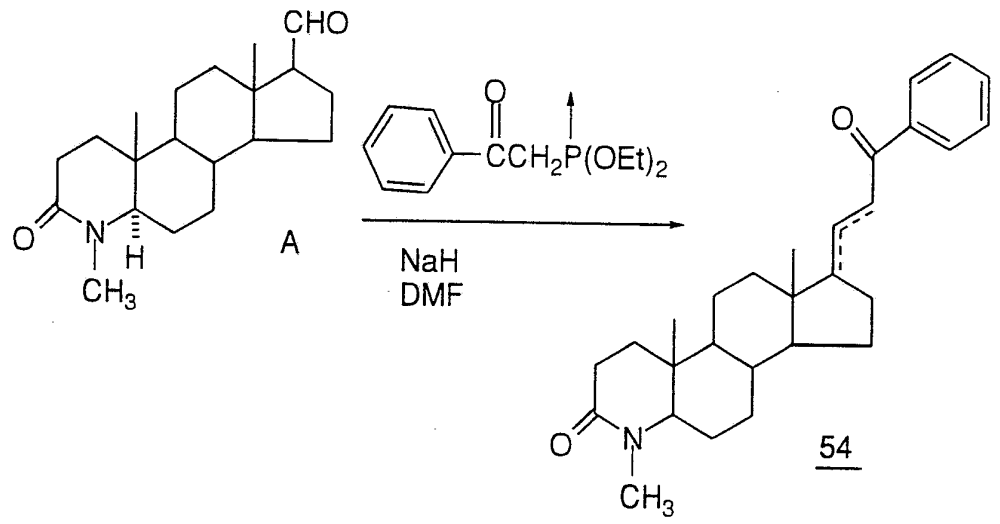


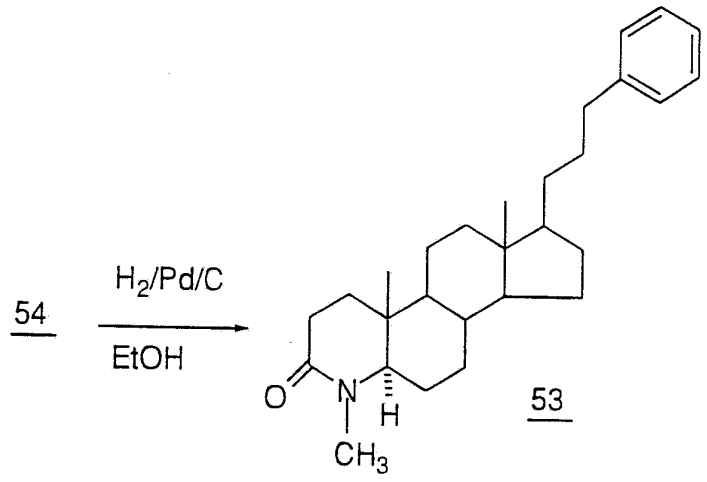
Structure	No.	R^1	R^2	Physical Properties
IVa R^2=H	48	H		M^+ 423 m/e (EI); R_f 0.4 EtOAc
IVc R=H	49	H		*
IVa R^2=H	50	H		M+1 400 m/e (FAB); R_f 0.6 CH_2Cl_2-acetone (4:1)
IVa R^2=H	51	H		**
IVe R=Me	52	CH_3		***

*NMR ($CDCl_3$) δ	0.69 (s, 3H, 18-Me), 0.89 (s, 3H, 19-Me), 2.92 (s, 3H, N-Me), 7.08 (d, 2H, ArH), 7.22 (d, 2H, ArH).
**NMR ($CDCl_3$) δ	0.59 (s, 3H, 18-Me), 0.75 (s, 3H, 19-Me), 1.44 (s, 9H, CMe_3), 2.91 (s, 3H, N-Me), 5.90 (bs, 1H, NH), 7.19 (d, 2H, ArH), 7.61 (d, 2H, ArH).
***NMR ($CDCl_3$) δ	0.68, 0.70, 0.78, 0.80, 0.84, 0.86, 0.91, 0.92 (s, 9H, 2 sets of 18- and 19-Me and 2(two) 21-Me doublets), 2.93 (s, 3H, N-Me), 7.1-7.3 (m, 5H, ArH).

EXAMPLE 9

Preparation of 4-Methyl-17ß-[3-(phenyl)propyl]-4-aza-5α-androstan-3-one (53)





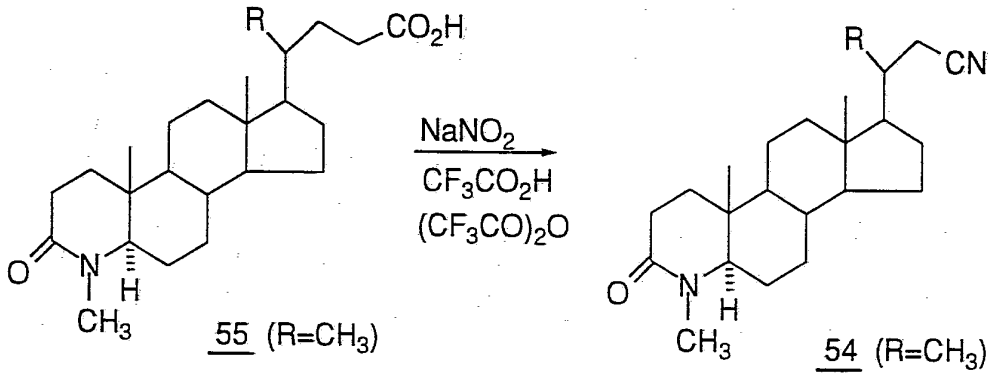
To a solution of 225 mg (0.71 mmoles) of aldehyde A and 185 mg (0.72 mmoles) of diethyl benzoylmethylphosphonate in 2 ml of DMF was added 29 mg (0.72 mmoles) of sodium hydride (60%) and the mixture heated at 80° in a N_2 atmosphere for 1 hour. The cooled reaction was poured into H_2O (50 ml) and extracted with CH_2Cl_2 (3x). The combined extracts were washed with water and brine and dried

with magnesium sulfate. Evaporation in vacuo gave an oily solid, which was flash chromatographed on a 20 m x 7" silica gel column with 7:3 ethyl acetate-hexane taking 18 ml fractions. Evaporation of fractions 25-42 gave 160 mg of a solid. NMR and TLC indicated it was a 1:1 mixture of Δ^{17} and Δ^{20} olefin isomers (54).

A 60 mg sample of 54 was hydrogenated with 50 mg of 10% palladium on carbon in 3 ml of ethanol at 40 psi for 5 hours. The reaction was filtered through a bed of Celite, and the solid washed with ethanol (3x). The filtrated was evaporated in vacuo to give pure 53. Mass spectrum: m/e 408 (M+1) (FAB) Rf 0.35 EtOAc-hexane (4:1).

EXAMPLE 10

Preparation of 4-Methyl-24-nor-4-aza-5α-cholane-23-nitrile (54) (R=CH_3)



55 (R=CH_3) 54 (R=CH_3)

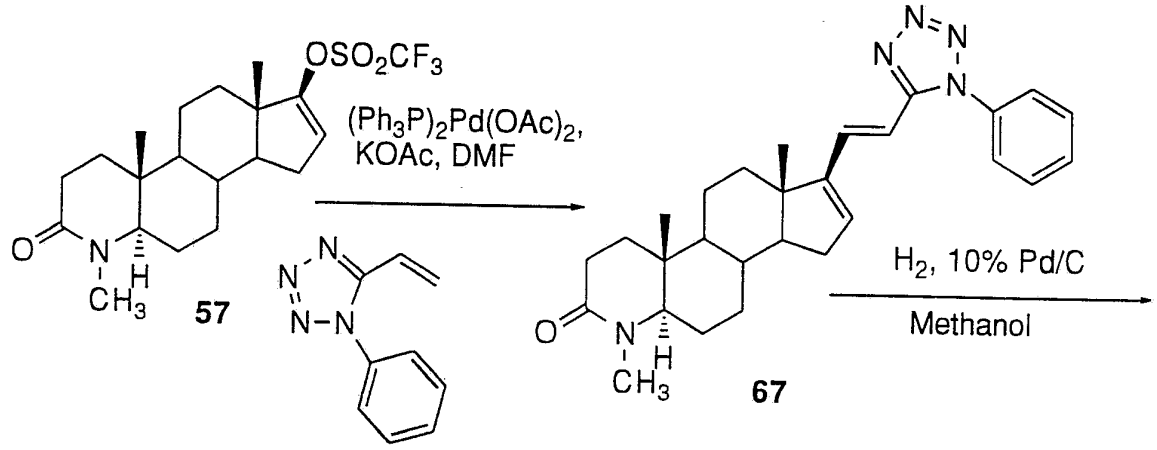
To a solution of 470 mg (1.18 mmoles) of 4-methyl-3-oxo-4-aza-5α-cholan-24-oic acid [G.H. Rasmusson, et al, J. Med. Chem. 1986, 29, 2298 (1986)] in 2.0 ml of trifluoroacetic acid and 0.52 ml of trifluoroacetic anhydride, cooled to 0°C, was added all at once 92 mg (1.33 mmoles) of sodium nitrite. After stirring at 0° for 45 min, the reaction was placed in a 40° oil bath. There was copious evolution of nitrogen, and the reaction darkened. After 20 minutes, the reaction was poured into 2 ml of 2N NaOH and 16 g of ice, extracted with CH_2Cl_2 (4x). The extracts were washed with H_2O and dried with magnesium

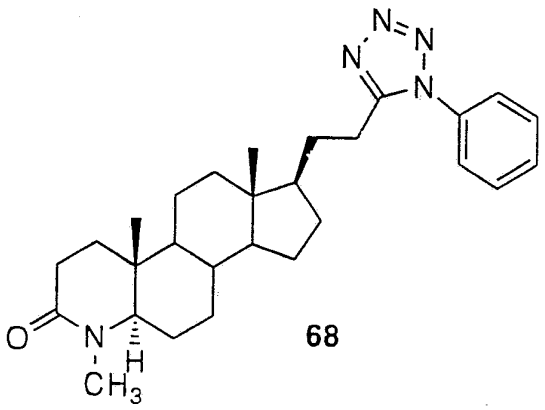
sulfate. Evaporation in vacuo gave 195 mg of a tan solid. Flash chromatography on a 20 mm x 7" column of silica gel with 6:1 CH_2Cl_2-acetone taking 10 ml fractions. Evaporation in vacuo of fractions 13-30 gave pure 54, m.p. 211-214°. The NMR spectrum confirmed the assigned structure.

Using the same procedure, 4-methyl-3-oxo- 21-nor-4-aza-5α-cholan-24-oic acid (55, R=H) gave 4-methyl-3-oxo-4-aza-5α-pregnane-21-carbonitrile (54, R=H) Mass spectrum: M+ 342 m/e; Rf 0.5 CH2Cl2-acetone (4:1).

EXAMPLE 11

21-(1-Phenyltetrazol-5-yl)-4-aza-4-methyl-5a-pregnan-3-one (52c)





To a solution of the triflate (57) (131 mg, 0.3 mmole) in 3 ml of dry DMF under N2 was added 5-vinyl-1-phenyltetrazole (207 mg, 1.2 mmole), bis(triphenylphosphine)palladium(II) acetate (22 mg, 0.03 mmole), and potassium acetate (118 mg, 1.2 mmole) and the reaction mix stirred at 80oC for 2 hours. The mixture was cooled to room temperature and partitioned with methylene chloride - water. The organic phase was washed with water, brine, dried over magnesium sulfate, filtered and concentrated in vacuo to give 305 mg of crude product. Purification by flash chromatography on silica gel in 7:1 methylene chloride:acetone gave 64 mg of the bis olefin (67).

To a solution of the bis olefin (67) in 2 ml of methanol was added 30 mg of 10% Palladium on activated carbon and the mixture stirred under a balloon of hydrogen for 6 hours at room temperature. The mixture was filtered through Celite washing with methanol and the filtrate was concentrated in vacuo to give 63 mg of crude product. Purification by preparative thin layer chromatography on silica gel in 4:1 ethyl acetate:hexane (running the solvent mix up the plate 2 times) gave 30 mg of the reduced phenyl tetrazole (52c).

Compounds 52b, 52d, and 52e were prepared by the same procedure.

Also included with the scope of this invention are 4-N-X analogs where X is OH, NH_2 or SCH_3. The 4-N-OH and 4-N-NH_2 derivatives can be made by incorporating hydroxylamine or hydrazine, respectively, in place of methylamine in the seco acid ring A closure for the starting androstanes herein as described in J. Med. Chem. 29, 2998-2315 (1986) by Rasmusson, et al. Further, reaction of the anion of the saturated 4-N-H androstanes, wherein the anion is generated from the 4-NH precursor by sodium hydride, and methylsulfenyl chloride can product the corresponding 4-N-S-CH_3 derivative. Thus, Substituent R

on the 4N-position also includes CH, NH_2 and 5-CH_3.

The present invention has the objective of providing suitable topical, oral and parenteral pharmaceutical formulations for use in the novel methods of treatment of the present invention.

The compositions containing the compounds of the present invention as the active ingredient for use in the treatment of e.g., benign prostatic hypertrophy, prostatitis, and treatment and prevention of prostatic carcinoma, hyperandrogenic conditions, can be administered in a wide variety of therapeutic dosage forms in conventional vehicles for systemic administration, as, for example, by oral administration in the form of tablets, capsules, solutions, or suspensions, or by injection. The daily dosage of the products may be varied over a wide range varying from 0.5 to 1,000 mg per adult human/per day. The compositions are preferably provided in the form of scored tablets containing 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, and 50.0 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. An effective amount of the drug is ordinarily supplied at a dosage level of from about 0.002 mg. to about 50 mg./kg. of body weight per day. Preferably the range is from about 0.01 mg. to 7 mg./kgs. of body weight per day. These dosages are well below the toxic dose of the product. For the treatment of androgenic alopecia, acne vulgaris, seborrhea, female hirsutism, the compounds of the present invention are administered in a pharmaceutical composition comprising the active compound in combination with a pharmacologically acceptable carrier adapted for topical, oral or parenteral administration.

These topical pharmaceutical compositions may be in the form of a cream, ointment, gel or aerosol formulation adapted for application to the skin. These topical pharmaceutical compositions containing the compounds of the present invention ordinarily include about 0.1% to 15%, preferably about 5%, of the active compound, in admixture with about 95% of vehicle.

The compounds of the present invention can be

administered in such oral dosage forms as tablets, capsules (each including timed release and sustained release formulations), pills, powders, granules, elixers, tinctures, suspensions, syrups and emulsions. Likewise, they may also be administered in intravenous (both bolus and infusion), intraperitoneal, subcutaneous or intramuscular form, all using forms well known to those of ordinary skill in the pharmaceutical arts. An effective but non-toxic amount of the compound desired can be employed as a 5 α–reductase agent.

The dosage regimen utilizing the compounds of the present invention is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition. Optimal precision in achieving concentration of drug within the range that yields efficacy without toxicity requires a regimen based on the kinetics of the drug's availability to target sites. This involves a consideration of the distribution, equilibrium, and elimination of a drug.

Oral dosages of the present invention, when used for the indicated effects, will range between about Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, preferred compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittant throughout the dosage regimen.

In the methods of the present invention, the compounds herein described in detail can form the active ingredient, and are

typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as "carrier" materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, zanthan gum and the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropyl- methacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic

acid, polepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

BIOLOGICAL ASSAYS

Preparation of Human prostatic and scalp 5a-reductases.

Samples of human tissue were pulverized using a freezer mill and homogenized in 40 mM potassium phosphate, pH 6.5, 5 mM magnesium sulfate, 25 mM potassium chloride, 1 mM phenylmethyl-sulfonyl fluoride, 1 mM dithiothreitol (DTT) containing 0.25 M sucrose using a Potter-Elvehjem homogenizer. A crude nuclear pellet was prepared by centrifugation of the homogenate at 1,500xg for 15 min. The crude nuclear pellet was washed two times and resuspended in two volumes of buffer. Glycerol was added to the resuspended pellet to a final concentration of 20%. The enzyme suspension was frozen in aliquots at -80°C. The prostatic and scalp reductases were stable for at least 4 months when stored under these conditions.

5α-reductase assay.

The reaction mixture contained in a final volume of 100 µl is: 40 mM buffer (human scalp, potassium phosphate, pH 6.5; human prostatic 5α-reductase, sodium citrate, pH 5.5), 0.3-10 µM ^{14}C-T (or ^{3}H-T), 1 mM DTT, and 500 µM NADPH. Typically, the assay was initiated by the addition of 50-100 µg prostatic homogenate or 75-200 µg scalp homogenate and incubated at 37°C. After 10-50 min the reaction was quenched by extraction with 250 µl of a mixture of 70% cyclohexane: 30% ethyl acetate containing 10 µg each DHT and T. The aqueous and organic layers were separated by centrifugation at 14,000 rpm in an Eppendorf microfuge. The organic layer was subjected to normal phase HPLC (10 cm Whatman partisil 5 silica column equilibrated in 1 ml/min 70 % cyclohexane: 30 % ethyl acetate; retention times DHT, 6.8-7.2 min; androstanediol, 7.6-8.0; T, 9.1-9.7 min). The HPLC system consisted of a Waters Model 680 Gradient System equipped with a Hitachi Model 655A autosampler, Applied Biosystems

Model 757 variable UV detector, and a Radiomatic Model A120 radioactivity analyzer. The conversion of T to DHT was monitored using the radioactivity flow detector by mixing the HPLC effluent with one volume of Flo Scint 1 (Radiomatic). Under the conditions described, the production of DHT was linear for at least 25 min. The only steroids observed with the human prostate and scalp preparations were T, DHT and androstanediol.

Stumptail macaque protocol

The following protocol is utilized with the stumptail macaque monkey to demonstrate the effect of compounds of the present invention for promoting hair growth.

Twenty-one male stumptail macaque monkeys of species *Macaca speciosa* are assigned to vehicle control and drug treatment groups on the basis of baseline hair weight data. This assignment procedure is necessary to insure that the average baseline hair growth for each control and experimental group is comparable. The control and drug treatment groups are as follows:

1. Topical 50:30:20 vehicle (N = 6)
2. Oral 5α-reductase and topical 50:30:20 vehicle (N = 5)
3. Oral placebo (N = 5)
4. 5α-reductase in vehicle (N = 5)

The vehicle consists of 50% propylene glycol, 30% ethanol and 20% water. A 100 mM concentration of topical 5α-reductase is formulated in this vehicle. The same 5α-reductase is administered as an oral dose of 0.5mg per monkey. Immediately prior to the dosing phase of the study, hair is removed from a 1 inch square area (identified by four tattoos) in the center of the balding scalp. This hair collection is the baseline hair growth determination prior to the beginning of treatment. Approximatly 250μL of vehicle and 5α-reductase in vehicle is prepared and topically administered to the tatooed area of the scelp. The selected 5α-reductase and placebo is ingested by the monekys at the same time as

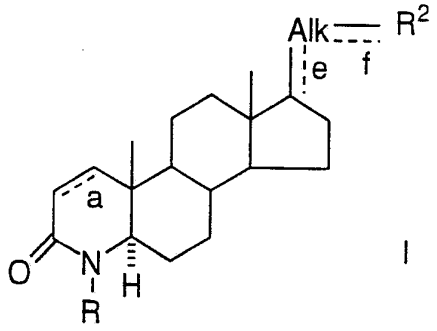
the topical doses are administered. The monkeys are dosed once per day, seven days per week for twenty weeks.

At four week intervals throughout the dosing phase of the study, each monkey is shaved and the hair is collected and weighed. The body weight data (at baseline and during assay) is analyzed by the nonparametric Wilcoxon rank-sum test. Differences are significant at $p < 0.05$. Hair weight data at each week collection for vehicle, placebo and treatment groups are expressed as the change from baseline. Statistical analysis is performed on the rank of the data to show overall differences among groups at each four week collection.

While the invention has been described and illustrated with reference to certain preferred embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the preferred dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of the indications for the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be limited only by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

WHAT IS CLAIMED IS:

1. A compound of the formula:



I

wherein:

Alk is C_1-C_4 straight or branched chain alkyl or alkenyl; dashed lines a, e and f each can independently represent a double bond when present, with the proviso that double bonds formed by e and f are not both present concurrently;

R is selected from hydrogen, methyl or ethyl;

R^2 is (a) C_6-C_{10} aryl, cyano or 5-6 membered heteroaryl radical which can contain 1-4 nitrogen atoms, one oxygen or sulfur atoms or combinations thereof with 1-2 nitrogen atoms, providing that where R^2 is cyano, double bonds e and f are not present,

(b) COR_1, where R_1 is C_6-C_{10} aryl, substituted C_6-C_{10} aryl, and heteroaryl;

(c) $CONHR_2$, where R_2 is substituted phenyl, heteroaryl, substituted heteroaryl, or C_7 to C_{12} cycloalkyl;

(d) CO_2R_3, where R_3 is C_1-C_{18} linear or branched alkyl, C_6-

C_{10} aryl, substituted C_6-C_{10} aryl, or C_7-C_{12} cycloalkyl; providing that in (b), (c) or (d), Alk is alkenyl; wherein the above aryl or heteroaryl radicals can also be fused with a benzo or another heteroraryl ring and can further be substituted with one or more substitutents; and pharmaceutically acceptable salts and esters thereof.

2. The compound of Claim 1 wherein said aryl radical is selected from phenyl, benzyl and naphthyl.

3. The compound of Claim 1 wherein the heteroaryl radical is selected from:

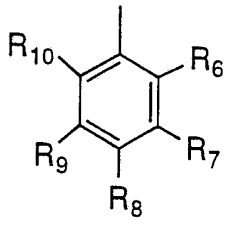
pyridyl, pyrryl, thienyl, isothiazolyl, thiazolyl, benzothienyl, isobenzofuryl, pyrazolyl, indolyl, purinyl, carbazolyl, isoxazolyl, triazolyl, furanyl, oxazolyl,oxadiazolyl or thiadiazolyl.

4. The compound of Claim 1 wherein said substituents are selected from:

hydrogen;
C_{1-8} straight or branched alkyl;
C_{2-8} straight or branched alkenyl;
C_{3-8} cycloalkyl;
C_{2-8} alkynyl;
$-CONR^4R^5$ where R^4 and R^5 independently are H, C_{1-8} alkyl, C_{3-8} cycloalkyl, C_{1-4} perhaloalkyl, phenyl, or substituted phenyl, as described below;

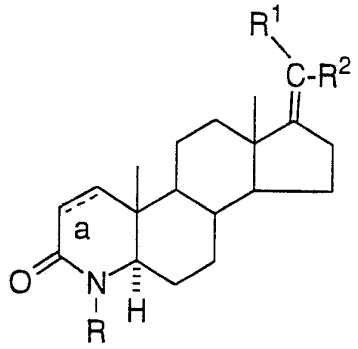
$-COR^4$;
$-S(O)_nR^4$ where n=0-2;
$-OCOR^4$;
$-SO_2NR^4R^5$;
$-NR^4(CO)R^5$;
$-NR^4(CO)NHR^5$;

-$NHSO_2R^4$;
-OR^4;
-NR^4R^5;
CN;
NO_2;
halo;
perhalo C_1-C_4alkyl;
-CO_2R^4;
phenyl or substituted phenyl of the formula:



where R6-R10 independently represent one or more of the substituents as defined above.

5. The compound of Claim 1 of the formula:



II

wherein the dashed line a represents a double bond when present,

R and R1 are selected from hydrogen, methyl and ethyl; and

R^2 is as defined in Claim 1, including both (E) and (Z) forms, and mixtures thereof.

6. The compound of Claim 5 wherein R^1 is methyl.

7. The compound of Claim 5 wherein R^1 is hydrogen.

8. The compound of Claim 5 being

(17E)-17-[phenyl)methylene]-4-methyl-4-aza-5α-androstan-3-one,

(17E)-17-[(4-chlorophenyl)methylene]-4-methyl-4-aza-5α-androstan-3-one,

(17E)-17-[(3-chlorophenyl)methylene]-4-methyl-4-aza-5α-androstan-3-one,

(17E)-17-[(2-chlorophenyl)methylene]-4-methyl-4-aza-5α-androstan-3-one,

(17E)-17-[(4-ethoxycarbonylphenyl)methyl-ene]-4-methyl-4-aza-5α-androstan-one,

(17E)-17-[(4-carboxyphenyl)methylene]-4-methyl-4-aza-5α-androstan-3-one,

(17E)-17-[4-[(1,1-dimethylethyl)amino)carbonyl]-phenyl]methylene]-4-methyl-4-aza-5α-androstan-3-one,

(17E)-17-[(3,4,5-trimethoxyphenyl)methylene]-4-aza-5α-androstan-3-one,

(17E)-17-[(2-methoxyphenyl)methylene]-4-methyl-4-aza-5α-androstan-3-one,

(17E)-17-[(4-methylsulfonylphenyl)methylene]-4-methyl-4-aza-5α-androstan-3-one,

(17E)-17-[(4-biphenyl)methylene]-4-aza-5α-androstan-3-one,

(17E)-17-[(4-nitrophenyl)methylene]-4-methyl-4-aza-5α-androstan-3-one,

(17E)-17-[(4-aminophenyl)methylene]-4-aza-5α-androstan-3-one,

(17E)-17-[(4-acetylaminophenyl)methylene]-4-methyl-4-aza-5α-androstan-3-one,

(17E)-17-[(4-pivaloylamino)phenyl)methylene]-4-methyl-4-aza-5α-androstan-3-one,

(17E)-17-[(4-phenoxyphenyl)methylene]-4-aza-5α- androstan-3-one,

(17E)-17-[(2-imidazolyl)methylene]-4-methyl-4-aza-5α-androstan-3-one,

(17E)-17-[(2-thiazolyl)methylene]-4-aza-5α-androst-1-en-3-one,

(17E)-17-[(2-pyrazinyl)methylene]-4-methyl-4-aza-5α-androstan-3-one,

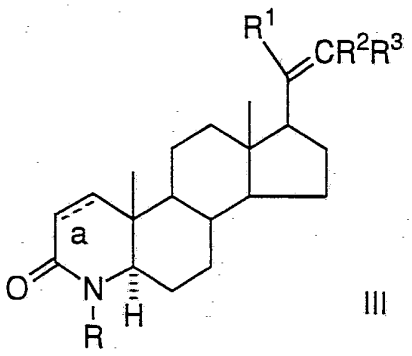
(17E)-20-phenyl-4-methyl-4-aza-5α-pregn-17-en-3-one,

(17E)-20-[(4-chloro)phenyl]-4-aza-5α-pregn-17-en-3-one,

(17E)-20-(3-pyridyl)-4-aza-5α-pregna-1,17-dien-3-one,

(17E)-4-methyl-20-(2-pyrazinyl)-4-aza-5α-pregna-1,17-diene-3-one.

9. A compound of Claim 1 of the formula:



III

wherein:

the dashed line a can represent a double bond when present,

R, R^1 and R^3 are

independently selected from hydrogen, methyl and ethyl, with the proviso that at least one of R^1 and R^3 is hydrogen,

R^2 is C_6-C_{10} aryl or heteroaryl as defined in claim 1, and R^2 and R^3 can be in a E or Z bond configuration, and mixtures thereof.

10. The compound of Claim 9 wherein R^1 and R^3 are both hydrogen.

11. The compound of Claim 9 wherein R^1 is methyl or ethyl and R^3 is hydrogen.

12. The compound of Claim 9 wherein R^1 is hydrogen and R^3 is methyl or ethyl.

13. The compound of Claim 9 being

(20E)-4-methyl-21-[(4-methoxy)phenyl]-4-aza-5α-pregn-20-en-3-one.

(20E)-4-methyl-21-phenyl-4-aza-5α-pregn-20-en-3-one,

(20E)-4-methyl-21-[(4-methyl)phenyl]-4-aza-5α-pregn-20-en-3-one,

(20E)-4-methyl-21-[(4-chloro)phenyl]-4-aza-5α-pregn-20-en-3-one,

(20E)-4-methyl-21-(4-pyridyl)-4-aza-5α-pregn-20-en-3-one,

(20E)-4-methyl-21-[(3-chloro)phenyl]-4-aza-5α-pregn-20-en-3-one,

(20E)-4-methyl-21-[(2-chloro)phenyl]-4-aza-5α-pregn-20-en-3-one,

(20E)-4-methyl-21-(2-pyridyl)-4-aza-5α-pregn-20-en-3-one,

(20E)-4-methyl-21-(2-thienyl)-4-aza-5α-pregn-20-en-3-one,

(20E)-21-[(4-methoxy)phenyl]-4-aza-5α-pregn-20-en-3-one,

(20E)-4-methyl-21-(3-thienyl)-4-aza-5α-pregn-20-en-3-one,

(20E)-4-methyl-21-(2-furanyl)-4-aza-5α-pregn-20-en-3-one,

(20E)-4-methyl-21-[(2-fluoro)phenyl]-4-aza-5α-pregn-20-en-3-one,

(20E)-21-(4-pyridyl)-4-aza-5α-pregn-1,20-dien-3-one,

20E)-21-(4-pyridyl)-4-aza-5α-pregn-20-en-3-one,

(20E)-21-[(4-methoxy)phenyl]-4-aza-5α-pregn-1,20-dien-3-one,

(20E)-21-(2-furanyl)-4-aza-5α-pregn-1,20-dien-3-one,

(20E)-21-(2-pyridyl)-4-aza-5α-pregn-1,20-dien-3-one,

(20E)-21-(3-pyridyl)-4-aza-5α-pregn-1,20-dien-3-one

(20E)-21-[(4-ethoxycarbonyl)-phenyl]-4-aza-5α-pregn-1,20-dien-3-one,

(20E)-21-(4-N-phenylbenzamido)-4-aza-5α-pregn-1,20-dien-3-one,

(20E)-21-(2-pyridyl)-4-aza-5α-pregn-1,20-en-3-one,

(20E)-21-(3-pyridyl)-4-aza-5α-pregn-20-en-3-one,

(20E)-21-(2-thienyl)-4-aza-5α-pregn-20-en-3-one,

(20E)-4,20-dimethyl-21-phenyl-4-aza-5α-pregn-20-en-3-one,

(20E)-4,20-dimethyl-21-(4-chlorophenyl)-4-aza-5α-pregn-20-en-3-one,

(20E)-4,20-dimethyl-21-(2-thienyl)-4-aza-5α-pregn-20-ene-3-one,

(20E)-4,20-dimethyl-21-(2-pyridyl)-4-aza-5α-pregn-20-ene-3-one,

(20E)-20-methyl-21-(4-pyridyl)-4-aza-5α-pregna-1,20-dien-3-one,

(20E)-4,20-dimethyl-21-(4-pyridyl)-4-aza-5α-pregna-20-ene-3-one,

(20E)-20-methyl-21-(2-furanyl)-4-aza-5α-pregna-1,20-dien-3-one,

(20E)-20-methyl-21-(2-pyridyl)-4-aza-5α-pregna-1,20-diene-3-one,

(20E)-20-ethyl-21-phenyl-4-aza-5α-pregna-1,20-diene-3-one,

(20E)-20-ethyl-21-(2-pyridyl)-4-aza-5α-pregna-1,20-diene-3-one,

20(E,Z)-4,21-dimethyl-21-phenyl-4-aza-5α-pregn-20-en-3-one,

20(E,Z)-21-methyl-21-(4-chlorophenyl)-4-aza-5α-pregn-20-en-3-one

20(E,Z)-4,21-dimethyl-21-(2-pyridyl)-4-aza-5α-pregna-1,20-dien-3-one.

4-methyl-21-(4-carboxyphenyl)-4-aza-5α-pregn-1,20-dien-3-one,

4-ethyl-21-(4-carbamoylphenyl)-4-aza-5α-pregn-1,20-dien-3-one,

20-ethyl-4-methyl-21-phenyl-4-aza-5α-pregn-20-en-3-one,

4,20-dimethyl-21-(2,6-dimethoxyphenyl)-4-aza-5α-pregna-1,20-dien-3-one,

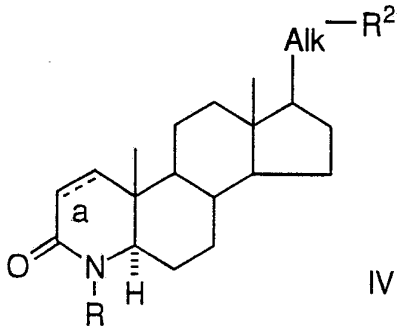
20-ethyl-4-methyl-21-(s-triazinyl)-4-aza-5α-pregna-1,20-dien-3-one,

4,21-dimethyl-21-(4-pyridyl)-4-aza-5α-pregna-1,20-dien-3-one,

4-methyl-21-(3-pyridyl)-4-aza-5α-pregn-20-en-3-one,

4-Methyl-21-(2-pyrazinyl)-4-aza-5α-pregn-20-en-3-one,

14. The compound of Claim 1 of the following formula.



IV

wherein:

Alk is C_1-C_4 straight or branched chain alkyl; dashed line a can represent a double bond when present;

R is selected from hydrogen, methyl or ethyl;

R^2 is (a) C_6-C_{10} aryl, cyano, or 5-6 membered heteroaryl radical which can contain 1-4 nitrogen atoms; one oxygen or sulfur atoms or combinations thereof with 1-2 nitrogen atoms;

(b) COR_1, where R_1 is C_6-C_{10} aryl, substituted C_6-C_{10} aryl, and heteroaryl;

(c) $CONHR_2$, where R_2 is substituted phenyl, heteroaryl, substituted heteroaryl, or C_7 to C_{12} cycloalkyl;

(d) CO_2R_3, where R_3 is C_1-C_{18} linear or branched alkyl, C_6-C_{10} aryl, substituted C_6-C_{10} aryl, or C_7-C_{12} cycloalkyl; providing that in (b), (c) or (d), Alk is alkenyl; wherein the above aryl or heteroaryl radicals can also be fused with a benzo or another heteroraryl ring and can further be substituted with one or more substitutents; and pharmaceutically acceptable salts and esters thereof.

15. The compound of Claim 14 wherein said Alk and R^2 are of the combined structure:
$-CH_2R^2$, $-CH(CH_3)R^2$, $-CH_2CH_2R^2$, $-CH(CH_3)CH_2R^2$, $-CH(CH_3CH_2)CH_2R^2$, $CH_2CH(CH_3)R^2$, $CH_2CH_2CH_2R^2$, or $-CH_2CH_2CH_2CH_2R^2$.

16. The compound of Claim 14 being:

17β-[(4-chlorophenyl)methyl]-4-methyl-4-aza-5α-androstan-3-one,

17β-[(phenyl)methyl]-4-aza-5α-androstan-3-one,

17β-[(2-pyridyl)methyl]-4-methyl-4-aza-5α-androst-1-en-3-one,

17β-[(2-thienyl)methyl]-4-aza-5α-androst- 1-en-3-one,

20-phenyl-4-methyl-4-aza-5α-pregnan-3-one,

20-(4-chloro)phenyl-4-aza-5α-pregnan-3-one,

20-(2-pyridyl)-4-methyl-4-aza-5α-pregn-1-en-3-one,

20-(2-thienyl)-4-aza-5α-pregn-1-en-3-one,

21-phenyl-4-aza-5α-pregnan-3-one,

21-(2-pyridyl)-4-methyl-4-aza-5α-pregnan-3-one,

21-[(4-methoxy)phenyl]-4-methyl-4-aza-5α-pregnan-3-one,

21-(2-thienyl)-4-methyl-4-aza-5α-pregnan-3-one,

21-[(4-chloro)phenyl]-4-aza-5α-pregn-1-en-3-one,

4-methyl-17β-[3-(phenyl)propyl]-4-aza-5α-androstan-3-one.

17β-[3-(2-pyridyl)propyl]-4-aza-5α-androst-1-en-3-one,

17β-[3-(4-chlorophenyl)propyl]-4-aza-5α-androstan-3-one,

4-methyl-17β-[2-(thienyl)propyl]-4-aza-5α-androst-1-en-3-one,

4-methyl-17β-[4-(phenyl)butyl]-4-aza-5α-androstan-3-one,

17β-[3-(2-pyridyl)butyl]-4-aza-5α- androst-1-en-3-one,

17β-[3-(4-chlorophenyl)butyl]-4-aza-5α-androstan-3-one,

4-methyl-17β-[(2-thienyl)butyl]-4-aza-5α-androst-1-en-3-one,

20-ethyl-21-(2-pyridyl)-4-aza-5α-pregnan-3-one,

20-ethyl-21-phenyl-4-aza-5α-pregnan-3-one,

20-ethyl-21-(2-methoxyphenyl)-4-aza-5α-pregnan-3-one,

4,21-dimethyl-21-(2-pyridyl)-4-aza-5α- pregnan-3-one,

4,21-dimethyl-21-[(4-benzoylamino)phenyl]-4-aza-5α-pregnan-3-one,

4,21-dimethyl-21-(2-thiazolyl)-4-aza-5α-pregnan-3-one,

21-phenyl-4-aza-5α-pregnan-3-one,

21-(2-pyridyl)-4-aza-5α-pregnan-3-one,

21-(2-thienyl)-4-aza-5α-pregnan-3-one,

21-(2-methoxyphenyl)-4-aza-5α-pregn-1-en-3-one,

21-(3-pyridyl)-4-aza-5α-pregn-1-en-3-one,

21-(2-thiazolyl)-4-aza-5α-pregn-1-en-3-one,

4-methyl-21-(4-methylsulfinylphenyl)-4-aza-5α-pregn-1-en-3-one,

4-ethyl-21-(4-fluorophenyl)-4-aza-5α-pregnan-3-one,

4-methyl-20-(phenylmethyl)-4-aza-5α-pregn-1-en-3-one,

20-ethyl-4-methyl-21-(2-pyridyl)-4-aza-5α-pregnan-3-one,

20-(2-thiazolyl)-4-aza-5α-pregnan-3-one,

20-ethyl-21-(3-pyridyl)-4-aza-5α-pregnan-3-one,

20-(4-methylsulfonylphenyl)-4-aza-5α-pregn-1-en-3-one,

20-ethyl-21-(4-methoxyphenyl)-4-aza-5α-pregn-1-en-3-one,

4-methyl-20-(3,4-dimethoxyphenyl)-4-aza-5α-pregn-1-en-3-one,

20-ethyl-4-methyl-21-(2-pyrimidinyl)-4-aza-5α-pregn-1-en-3-one,

21-methyl-21-(2-thienyl)-4-aza-5α-pregn-1-en-3-one,

21-methyl-21-(1-imidazolyl)-4-aza-5α-pregnan-3-one,

4,21-dimethyl-21-(4-carbamoylphenyl)-4-aza-5α-pregn-1-en-3-one,

4-methyl-17β-[(4-chlorophenyl)methyl]-4-aza-5α-androstan-3-one,

N-(1,1-dimethylethyl)-4-(4-methyl-3-oxo-4-aza-5α-pregn-21-yl)benzamide,

4-methyl-21-(2-pyrazinyl)-4-aza-5α-pregnan-3-one,

4-methyl-24-nor-4-aza-5α-cholane-23- nitrile,

(20R)-4-methyl-3-oxo-24-nor-4-aza-5a-cholane-23-nitrile,

4-methyl-3-oxo-4-aza-5α-pregnane-21-carbonitrile,

24-nor-4-aza-5α-chol-1-ene-23-nitrile,

24-nor-4-aza-5α-cholane-23-nitrile,

4-methyl-24-nor-4-aza-5α-chol-1-ene-23-nitrile,

3-oxo-4-aza-5α-pregn-1-en-21-carbonitrile,

3-oxo-4-aza-5α-pregnane-21-carbonitrile,

4-methyl-3-oxo-4-aza-5α-pregnane-21-nitrile,

4-methyl-3-oxo-4-aza-5α-cholane-24-nitrile,

3-oxo-4-aza-5α-chol-1-ene-24-nitrile,

4-methyl-3-oxo-21-nor-4-aza-5α-cholane-24-nitrile,

3-oxo-21-nor-4-aza-5α-cholane-24-nitrile,

20.20-dimethyl-3-oxo-4-aza-5a-preg-1-ene-21-nitrile,

3-oxo-4,20,20-trimethyl-4-aza-5a-pregnane-21-nitrile.

17. A method for treating the hyperandrogenic conditions of acne, androgenic alopecia, male pattern baldness, female hirsutism, benign prostatic hyperplasia, prostatitis, treatment and prevention of prostatic cancer, comprising administering to a patient in need of such treatment a therapeutically effective amount of the compound of Claim 1.

18. The method of Claim 17 wherein said compound is a 5α-reductase 1 inhibitor.

19. The method of Claim 17 wherein said compound is a 5α-reductase 2 inhibitor.

20. The method of Claim 17 wherein said compound is a dual inhibitor for both 5α-reductase 1 and 2.

21. A pharmaceutical composition comprising a therapeutically effective amount of the compound of Claim 1 in a pharmaceutically acceptable vehicle therefor.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/04630

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 31/495; C07D 241/02
US CL :544/336; 514/253

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : A61K 31/435, 470; 546/77; 514/284; 544/336; 514/253

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS Online Structure Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Jour. Clinical Endoc. and Metab., Vol. 74 1992, Diani et al. "HAIR GROWTH EFFECTS OF ORAL ADMINISTRATION OF FINASTERIDE A STEROID 5α Reductase Inhibitor, Alone and In combination with topical Minoxidil in the Balding Stumptail Macaque, pages 345-350. See page 345, para. bridging cols. 1-2, last 3 lines.	17-20
A	J. Org. Chem., Vol. 46, 1981, Back "OXIDATION OF AZASTEROID LACTAMS AND ALCOHOLS WITH BENZENESELENIC ANHYDRIDE" pages 1442-6. See entire document.	1

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 28 JULY 1993	Date of mailing of the international search report 20 AUG 1993
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. NOT APPLICABLE	Authorized officer [signature] C.S. DAUS Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/04630

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	Jour. Med. Chem., Vol. 27, 1984, Rasmusson et al. "AZASTEROIDS AS INHIBITORS OF RAT PROSTATIC 5α REDUCTASE" pages 1690-1701. See p. 1699 compound 23a, page 1700 compound 25, page 1691, Table 21.	1-6, 14-15, 17-21 1-21
X Y	Jour. Med. Chem., Vol. 29, 1986 Rasmusson et al. "AZASTEROIDS, STRUCTURE ACTIVITY RELATIONSHIPS FOR INHIBITION OF 5α REDUCTASE AND OF ANDROGEN RECEPTOR BINDING" pages 2298-2315. See page 2300 compounds "10an", "10ac", p. 2304, "5ae", See also "10be", "13ay", "140y".	1-6, 14-15, 17-21 1-21
X	EP, B, 0,200,859 (CAINELLI et al.) 12 November 1986. See Genus, page 2.	1, 4, 14-15, 17-21
A	US, A, 4,377,584 (RASMUSSON et al.) 22 March 1983. See entire document.	1-21
A	US, A, 4,760,071 (RASMUSSON et al.) 26 July 1988. See entire document.	1-21
A	US, A, 4,882,319 (HOLT et al.) 21 November 1989. See entire document.	1-21
A	US, A, 5,049,562 (RASMUSSON et al.) 17 September 1991. See entire document.	1-21
A,P	US, A, 5,116,983 (BHAHACHARYA et al.) 26 May 1992. See entire document.	1-21
A	US, A, 5,110,939 (HOLT) 05 May 1992. See entire document.	1-21
A	Jour. Organic Chem. Vol. 54, 1989 Back et al. "N CHLORO AZASTEROIDS A NOVEL CLASS OF REACTIVE STEROID ANALOGUES. PREPARATION, REACTION WITH THIOLS AND PHOTOCHEMICAL CONVERSION TO ELECTROPHILIC N ACYL IMINES" pages 1904-10. See entire document.	1-21
Y	US, A, 4,859,681 (RASMUSSON et al.) 22 August 1989. See Abstract, claims.	1-21

International application No.
PCT/US93/04630

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

I. Claims 1, 3-21 (part of each), drawn to pyrazines, classified in Class 544, subclass 336 and 514/253.

II. Claims 1, 3-21 (part of each) and 2, drawn to compounds with no heteroaryls, classified in Classes 546/77 and 514/284; and drawn to 5-member heteroaryls or pyridyl not in I or III-IV, classified in Class 546, subclass 77 and 514/284.

III. Claims 1, 3-7, 9-12, 14-21 (part of each), drawn to pyrimidines, classified in Class 544, subclass 242 plus and 514/269 plus.

IV. Claims 1, 3-7, 9-12, 14-15, 17-21 (part of each), drawn to purines, classified in Class 544, subclasses 265 plus and 514/261 plus.

V. Claims 1, 4-7, 9-15, 17-21, drawn to triazines, classified in Class 544, subclasses 180 plus and (part of each) 514/241 and 43.

VI. Claims 1, 3-7, 9-12, 14-15, 17-21 (part of each), drawn to 6 or 7 membered multi N heterocyclics, or N plus another hetero 6 or 7 membered heterocyclic not provided above, classified in Class 544, various subclasses and 514/various.