

5

- 1 -

10

TITLE OF THE INVENTION

PHARMACEUTICAL COMBINATION FOR THE TREATMENT OF PROSTATIC HYPERPLASIA. CONTAINING A 5 ALPHA-REDUCTASE INHIBITOR AND AN ANTIANDROGEN

CROSS REFERENCE TO RELATED APPLICATIONS

15

This application is a continuation-in-part of U.S.S.N. 07/672,511 (Case 18354), filed March 20, 1991.

BACKGROUND OF THE INVENTION

20

1. Field of the Invention

25

This invention relates to a new method of treatment for patients, i.e. men having benign prostatic hyperplasia (BPH), involving combination therapy of administering therapeutically effective amounts of a 5 α -reductase inhibitor in combination with an α_1 -adrenergic receptor blocker.

2. Background of the Invention

30

Benign prostatic hyperplasia (BPH) affects a substantial number of males over the age of 50 and usually requires surgery in advanced stages for relief.

This Sheet Has Been Replaced



- 2 -

It is known that testosterone (T) is secreted by the testes and adrenal glands but can undergo a 5α -reductase mediated conversion to dihydrotestosterone (DHT) in peripheral sites including the liver, skin, and prostate. DHT is preferentially bound by the nucleus of prostatic cells thus indicating that DHT, rather than T, is the primary androgen required by the prostate for its growth and function. This led to the hypothesis that, by inhibiting 5α -reductase, the formation of DHT could be curtailed and hopefully prostate regression obtained.

Finasteride, 17 β -(N-t-butyl)carbamoyl-4-aza- 5α -androst-1-en-3-one, was developed as a compound which was found to inhibit 5α -reductase and exhibit positive effects against benign prostatic hyperplasia. Finasteride is a 4-azasteroid and a competitive, inhibitor of the enzyme. It shows no affinity for the androgen receptor and so would not be expected to interfere with the binding and action of T in those tissues, such as muscle, which respond to T, and thus should not result in feminizing characteristics.

Typical 4-aza steroid 5α -reductase inhibitors include those developed by Merck. (See U.S. Pat. 4,377,584 to Rasmusson, et al.; U.S. Pat. 4,220,735 to Rasmusson, et al.; U.S. Pat. 4,845,104 to Carlin, et al.; U.S. Pat. 4,760,071 to Rasmusson, et al., which discloses finasteride, being 17 β -(N-t-butyl)carbamoyl-4-aza- 5α -androst-1-en-3-one, known by its trademark as PROSCAR*; U.S. Pat. 4,732,897 to Cainelli, et al.; U.S. Pat. 4,859,681 to Rasmusson, et al.; EPO Publn. 0 155 076; EPO Publn. 0 004 949; and EPO Publn. 0 314 189.

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 3 -

In many instances, reversal of the prostate enlargement process is accompanied by symptomatic relief from nocturia, hesitancy, and difficulty in urination. However, symptomatic relief does not occur in all cases. When the 5 α -reductase inhibitor inhibits the rate of development of the enlarged prostate without attendant shrinkage, symptomatic relief as experienced by the patients may not occur.

What is desired in the art is a combination therapy both to treat the underlying cause of BPH and to treat the short-term symptoms of the disease as well.

SUMMARY OF THE INVENTION

By this invention there is provided a method of treating benign prostatic hypertrophy patients being treated with a 4-aza steroid 5 α -reductase inhibitor and are experiencing inadequate symptomatic relief who are in need of such treatment comprising the step of administering in combination to such patients therapeutically effective amounts of a 5 α -reductase inhibitor, a 17 β -substituted 4-azasteroid, a 17 β -substituted non-azasteroid, 17 β -acyl-3-carboxyandrost-3,5-diene, benzoylaminophenoxybutanoic acid derivative, fused benz(thio)amide or cinnamoyl-amide derivative, aromatic 1,2-diethers or thioethers, aromatic ortho acylaminophenoxy alkanolic acids, ortho thioalkylacylaminophenoxy alkanolic acids, pharmaceutically acceptable salts and esters thereof, and particularly an α_1 -adrenergic receptor blocking agent, also termed herein " α_1 -blocker".

This Sheet Has Been Replaced



- 4 -

Thus, the combined effect of a 5 α -reductase inhibitor in inhibiting DHT production in the prostate and the α_1 -adrenergic receptor blocker, i.e. terazosin, will result in a greater effect on suppressing the growth and symptomatic relief of enlarged prostate than either agent by itself.

BRIEF DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS

In one preferred aspect, the present invention provides an effective method of treating BPH in patients in need of symptomatic relief by administering therapeutically effective amounts of the α_1 -blocker in association with a 5 α -reductase inhibitor or pharmaceutical composition thereof. The active compounds may be administered together or in any order, as discussed hereinafter.

By the term "patients in need of such treating" is meant male patients with functioning gonads who are being treated with a 5 α -reductase inhibitor in a therapeutic program designed to combat benign prostatic hyperplasia (BPH) and are discovered to be in need of symptomatic relief.

The use of therapeutically effective amounts of the 5 α -reductase inhibitor and the α_1 -blocker in accordance with this invention effectively treats the adverse symptoms of BPH including nocturia, hesitancy, decreased urinary flow, and the like.

It has been shown that stimulation of α -adrenoreceptors contributes to the obstruction

This Sheet Has Been Replaced



- 5 -

of benign prostatic hyperplasia (See M. Caine, et al., Br. J. Urol., Vol. 48, pp. 255-263 (1976)).

Alpha₁-adrenergic receptor blockers function generally as anti-hypertensive agents by blocking
5 α-adrenergic receptor sites. They relax stromal (smooth) tissue in the bladder, which cause fibrous tissue to contract when stimulated by noradrenaline and results in decreased urinary flow rates. Thus, the effect of the α₁-blocker is to relax the fibrous
10 tissue and result in increased urinary flow rates.

α-Adrenergic blocking agents bind selectively to the α class of adrenergic receptors and thereby interfere with the capacity of sympathomimetic amines to initiate actions at these sites.

15 There are prominent differences in the relative abilities of α-adrenergic blocking agents to antagonize the effects of sympathomimetic amines at the two subtypes of α receptors. It is known that Prazosin is much more potent in blocking
20 α₁-(postsynaptic) receptors than α₂-receptors that, among other effects, modulate neural release of transmitter (presumed presynaptic receptors). Phenoxybenzamine is a moderately selective α₁-blocking agent, while phentolamine is only three
25 to five times more potent in inhibiting α₁- than α₂-adrenergic receptors. In contrast, yohimbine is a selective α₂-blocker and has been shown to prevent the antihypertensive effects of clonidine, an α₂-agonist.

30 However, preferred in this invention are α-adrenergic blockers which preferably be α₁-blockers and have little or no α₂-blocking activity.

This Sheet Has Been Replaced



- 6 -

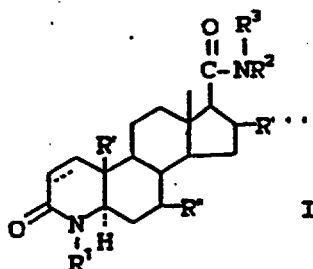
Examples of α -adrenergic receptor blockers are terazosin (Abbott-Hytrin*) whose chemical name is 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(tetrahydro-2-furanyl)carbonyl]piperazine, as described in German Patent 2,646, 186 and U.S. Patent 4,026,894; doxazosin (Pfizer-Cardura*) whose chemical name is 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]piperazine, as described in German Patent 2,847,623 and U.S. Patent 4,188,390; prazosin (Pfizer-Minipres*) whose chemical name is 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl)piperazine, as described in British Patent 1,156,973, U.S. Patent 3,511,836 and Netherlands Patent Appln. 7,206,067; bunazosin (Sandoz-Dequantol*) whose chemical name is 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)hexahydro 4-(1-oxobutyl)-1H-1,4-diazepine, as described in Belgian Pat. Appln. 806,626, U.S. Patent 3,920,636 and Japanese Kokai 75,140,474; indoramin (Baratol*-Wyeth) whose chemical name is N-[1-[2-(1H-indol-3-yl)ethyl]-4-piperidinyl]benzamide, as described in South African Patent 68 03204, U.S. Patent 3,527,761; Alfuzosin (Synthelabs) whose chemical name is N-[3-[(4-amino-6,7-dimethoxy-2-quinazolinyl)methylamino]propyl]tetrahydro-2-furancarboxamide, as described in German Patent 2,904,445 and U.S. Patent 4,315,007.

Preferred is where the 4-aza steroid has the formula:

This Sheet Has Been Replaced



- 7 -



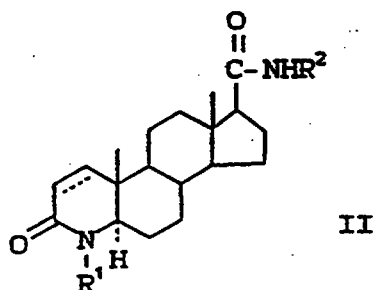
10 wherein the dotted line represents a double bond when present, R^1 and R^3 are independently hydrogen, methyl or ethyl,

15 R^2 is a hydrocarbon radical selected from straight or branched chain substituted or unsubstituted alkyl, cycloalkyl, or aralkyl of from 1-12 carbons or monocyclic aryl optionally containing 1 or more lower alkyl substituents of from 1-2 carbon atoms and/or 1 or more halogen substituents,

20 R' is hydrogen or methyl,
 R'' is hydrogen or β -methyl,

R''' is hydrogen, α -methyl or β -methyl, and pharmaceutically acceptable salts or esters thereof.

25 A preferred embodiment of the compound of formula I applicable in the process of our invention is represented by the formula:



This Sheet Has Been Replaced



- 8 -

wherein

R¹ is hydrogen, methyl or ethyl, and

R² is branched chain alkyl cycloalkyl, aralkyl of
from 4-12 carbons, phenyl, optionally substituted
by methyl, chloro or fluoro, substituted or
unsubstituted 1-, 2-adamantyl, 1-, 2-adamantyl-
methyl, 1-, 2- or 7-norbornanyl, 1-, 2- or
7-norbornanymethyl.

Representative compounds of the present
invention include the following:

- 17 β -(N-tert-amylcarbamoyl)-4-aza-5 α -androst-1-en-
3-one,
17 β -(N-tert-hexylcarbamoyl)-4-aza-5 α -androst-1-en-
3-one.
17 β -(N-tert-butylcarbamoyl)-4-aza-5 α -androst-1-en-
3-one,
17 β -(N-isobutylcarbamoyl)-4-aza-5 α -androst-1-en-
3-one,
17 β -(N-tert-octylcarbamoyl)-4-aza-5 α -androst-1-en-
3-one,
17 β -(N-octylcarbamoyl)-4-aza-5 α -androst-1-en- 3-one,
17 β -(N-1,1-diethylbutylcarbamoyl)-4-aza-5 α -androst-
1-en-3-one,
17 β -(N-neopentylcarbamoyl)-4-aza-5 α -androst-1-en-
3-one,
17 β -(N-2-adamantylcarbamoyl)-4-aza-5 α -androst-1-en-
3-one,
17 β -(N-1-adamantylcarbamoyl)-4-aza-5 α -androst-1-en-
3-one,
17 β -(N-2-norbornylcarbamoyl)-4-aza-5 α -androst-1-en-
3-one,

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 9 -

- 17B-(N-1-norbornylcarbamoyl)-4-aza-5 α -androst-1-en-3-one,
17B-(N-phenylcarbamoyl)-4-aza-4-methyl-5 α -androst-1-en-3-one,
5 17B-(N-benzylcarbamoyl)-4-aza-4-methyl-5 α -androst-1-en-3-one,
17B-(N-tert-amylcarbamoyl)-4-aza-4-methyl-5 α -androst-1-en-3-one,
17B-(N-tert-hexylcarbamoyl)-4-aza-4-methyl-5 α -
10 androst-1-en-3-one,
17B-(N-tert-butylcarbamoyl)-4-aza-4-methyl-5 α -androst-1-en-3-one,
17B-(N-isobutylcarbamoyl)-4-aza-4-methyl-5 α -androst-1-en-3-one,
15 17B-(N-tert-octylcarbamoyl)-4-aza-4-methyl-5 α -androst-1-en-3-one,
17B-(N-1,1,3,3-tetramethylbutylcarbamoyl)-4-aza-5 α -androst-1-en-3-one,
17B-(N-octylcarbamoyl)-4-aza-4-methyl-5 α -
20 androst-1-en-3-one,
17B-(N-1,1-diethylbutylcarbamoyl)-4-aza-4-methyl-5 α -androst-1-en-3-one,
17B-(N-neopentylcarbamoyl)-4-aza-4-methyl-5 α -androst-1-en-3-one,
25 17B(N-1-adamantylcarbamoyl)-4-aza-5 α -androstan-3-one;
17B(N-1-adamantylcarbamoyl)-4-methyl-4-aza-5 α -androst-1-en-3-one;
17B(N-1-adamantylcarbamoyl)-4-methyl-4-aza-5 α -androstan-3-one;
30 17B-(N-1-adamantylmethylcarbamoyl)-4-aza-5 α -androst-1-en-3-one;

This Sheet Has Been Replaced



- 10 -

- 17B-(N-2-adamantylcarbamoyl)-4-aza-5 α -androstan-3-one;
- 17B-(N-methyl-N-2-adamantylcarbamoyl)-4-methyl-4-aza-androstan-3-one;
- 5 17B-(N-2-adamantylcarbamoyl)-4-methyl-4-aza-5 α -androstane-3-one;
- 17B-(N-2-adamantylcarbamoyl)-4-methyl-4-aza-5 α -androst-1-en-3-one;
- 10 17B-(N-methyl-N-2-adamantyl)carbamoyl-4-methyl-4-aza-androst-1-en-3-one;
- 17B-(N-(3-methyl)-1-adamantyl-carbamoyl)-4-aza-4-methyl-5 α -androst-an-3-one;
- 17B-(N-exo-2-norbornanylcarbamoyl)-4-aza-4-methyl-5 α -androst-1-en-3-one;
- 15 17B-(N-exo-2-norbornanylcarbamoyl)-4-aza-5 α -androst-1-en-3-one; 17B-(N-2-adamantylcarbamoyl)-4-aza-5 α -androst-en-3-one;
- 17B-(N-methyl-N-2-adamantylcarbamoyl)-4-aza-4-methyl-androstan-3-one;
- 20 17B-(N-2-adamantylcarbamoyl)-4-methyl-4-aza-5 α -androstan-3-one; and
- 17B-(N-methyl-N-2-adamantyl)carbamoyl-4-methyl-4-aza-androst-1-en-3-one.

- 25 The corresponding compounds of those above wherein the 4-aza substituent is substituted in each of the above named compounds with a hydrogen, methyl or an ethyl radical, to form a different N-substituent, and wherein a double bond can be
- 30 optionally present as indicated by the dotted line in position 1.

This Sheet Has Been Replaced

SUBSTITUTE SHEET

- 11 -

The alkyl, cycloalkyl, aralkyl, monocyclic aryl, 1-, 2-adamantyl or 1-, 2-norbornanyl moieties can be substituted with one or more substituents of the following: C₁-C₄ linear/branched alkyl, including methyl, ethyl, isopropyl, n-butyl; nitro; oxo; C₇-C₉ aralkyl, including benzyl; (CH₂)_n COOR where n is 0-2 and R is H or C₁-C₄ linear/branched alkyl including methyl, ethyl; CH₂OH; OH; OR where R is C₁-C₄ linear/branched alkyl including methyl, ethyl; halo, including fluoro, bromo, iodo; COOH; COOR, where R is linear/branched C₁-C₄ alkyl; -CONH₂; CH₂NH₂; CH₂NHCOR where R is C₁-C₄ linear/branched alkyl including methyl, ethyl; phenyl; o, m, p-substituted phenyl including p-nitro, p-amino and p-sulfo; or cyano. The amino group of the adamantyl or norbornanyl moiety can also be substituted as R¹ with methyl and ethyl, as well as hydrogen.

Also included within the scope of this invention are pharmaceutically acceptable salts or esters, where a basic or acidic group is present on the substituted alkyl, cycloalkyl, aralkyl, adamantyl or norbornanyl moiety. When an acidic substituent is present, i.e. -COOH, there can be formed the ammonium, sodium, potassium, calcium salt, and the like, for use as the dosage form.

Where a basic group is present, i.e. amino, acidic salts, i.e. hydrochloride, hydrobromide, acetate, pamoate, and the like, can be used as the dosage form.

This Sheet Has Been Replaced



- 12 -

Also, in the case of the -COOH group being present, pharmaceutically acceptable esters can be employed, e.g. acetate, maleate, pivaloyloxymethyl, and the like, and those esters known in the art for
5 modifying solubility or hydrolysis characteristics for use as sustained release or prodrug formulations.

Representative examples include for R²

(where AD is adamantyl):

3, 5, 7-trinitro-1-AD; 4-oxo-1-AD; 1-benzyl-1-AD;
10 4,4-dimethyl-1-AD; 3,7-dimethyl-5-carboxymethyl-1-AD;
3-carboxymethyl-1-AD; 3-chloro-1-AD; 1,3-dihydroxy-
6,6-dimethyl-2-AD; 3-chloro-1-AD; 4-carbethoxy-2-AD;
4-carboxy-2-AD; 3-isopropyl-1-AD; 3-n-butyl-1-AD;
3-propyl-1-AD; 3-,5-diethyl-1-AD; 3-hydroxymethyl-
15 1-AD; 2-carboxy-1-AD; 3-methyl-1-AD; 5-hydroxy-2-AD;
2-hydroxy-1-AD; 1-aminomethyl-1-hydroxy-2-AD;
2-oxo-1-AD; 2-phenyl-2-AD; 1-amino-methyl-2-AD;
1-carboxy-2-AD; 1-aminocarbonyl-2-AD; 3-hydroxy-
5,7-dimethyl-1-AD; 4-fluoro-1-AD; 3-fluoro-1-AD;
20 4-hydroxy-2-AD; 3-phenyl-1-AD; 3-(p-aminophenyl)-
1-AD; 3-(p-nitrophenyl)-1-AD; 3-methyl-5-
hydroxymethyl-1-AD; 3,5-dimethyl-4-hydroxy-1-AD;
2-hydroxymethyl-2-AD; 3-(p-sulfophenyl)-1-AD; 3-
methyl-5-ethyl-1-AD; 2-carboxy-2-AD; 3,5-7-trimethyl-
25 1-AD; 4-iodo-2-AD; 4-bromo-2-AD; 4-chloro-2-AD;
1-acetylaminomethyl-2-AD; 1-carboxymethyl-2-AD;
1-methyl-2-AD; 1-aminocarboxymethyl-2-AD;
1-aminocarboxyl-1-AD; 2-cyano-2-AD; 3,5-dimethyl-
7-ethyl-1-AD; 4-hydroxy-1-AD; 1-hydroxy-2-AD;
30 5-carboxy-3-methyl-1-AD; 3,5-dimethyl-7-carboxy-
1-AD; 3-carboxy-1-AD; 3-hydroxy-1-AD; and the like.

This Sheet Has Been Replaced



SUBSTITUTE SHEET

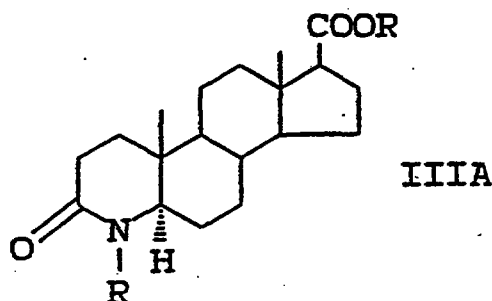
- 13 -

Representative examples include for R² as substituted norbornanyl moieties are (where NB is norbornanyl):

2-NB; 1,7,7-trimethyl-4-phenyl-2-NB; 3-carboxy-2-NB; 3-phenyl-2-carboxy-2-NB; 2-cyano-3-phenyl-2-NB; 3-hydroxy-4,7,7-trimethyl-2-NB; 6-hydroxymethyl-2-NB; 5-cyano-2-NB; 3-allyl-2-NB; 1-NB; 7,7-dimethyl-1-hydroxymethyl-2-NB; 3-methoxy-4,7,7-trimethyl-2-NB; 3-aminocarbonyl-2-NB; 3-ethoxycarbonyl-2-NB; 3,3-dimethyl-2-NB; 7-oxo-1-NB; 3-phenyl-2-NB; 1-carboxymethyl-7,7-dimethyl-2-NB; 1-ethyl-2-NB; 1-methyl-2-NB; 2,2,3,3,5,5,6,6,7,7-decafluoro-1-NB; 3-hydroxy-2-NB; 3-chloro-2-NB; 3-(p-methoxyphenyl)-2-NB; 2,2-dimethyl-3-methylene-7-NB; 3-oxo-2-NB; 1-methoxy-2-NB; 7-NB; 3-isopropyl-2-NB; 2-bromo-1-NB; 3-chloro-1-NB; and the like.

Procedures for preparing the compounds of Formula I useful in this invention, including the above, are well known in the art.

The novel compounds of formula I of the present invention can be prepared by a method starting with the known steroid ester (IIIA) of the formula:



This Sheet Has Been Replaced



- 14 -

17B-(carbomethoxy)-4-aza-5- α -androstan-3-ones which includes the stages of optionally 1) dehydrogenating said starting material to produce the corresponding compound containing a double-bond in the 1,2-position of the A-ring, 2) converting the 17-carbomethoxy substituent into an N-substituted alkyl, cycloalkyl, aralkyl, monocyclic acyl, or adamantylcarbonyl substituent and, if desired, 3) alkylating the A-ring nitrogen to introduce a N-methyl or N-ethyl substituent into the A ring 4-position. For the dehydrogenation step, it is preferable that the 4-aza nitrogen be unsubstituted. The alternate pathways can consist of one or more discrete chemical steps and if desired can take place before step (1) or following step (1) or step (3).

In accordance with the process of the present invention (see flow sheet), the products of our invention are formed by optionally: (1) heating a 17B-alkoxycarbonyl-4-aza-5 α -androstan-3-ones, compound III, (prepared in the literature as described in the reference US Patent 4,377,584) with a dehydrogenating agent such as benzeneseleninic anhydride in a refluxing inert solvent, e.g. chlorobenzene, to form a 17B-alkoxycarbonyl-4-aza-5 α -androst-1-ene-3-one IV (alternately, the dichlorodicyanobenzoquinone process of Dolling, et al., JACS 1988, Vol. 110, pp. 3318-3319, can be used); (2) the formed 5 α -androst-1-en-3-one compound from Step 1 can be reacted with, e.g. sodium hydride under anhydrous conditions in a neutral solvent such as dimethylformamide; (3) contacting the resulting reaction mixture with an alkyl (methyl or ethyl) iodide to form the corresponding

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 15 -

17- β -alkoxy-adamantyl-carbamoyl-4-alkyl-4-aza-5 α -androst-1-en-3-one V; (4) subsequently hydrolyzing said 17 β -alkoxycarbonyl-4-alkyl-4-aza-5 α -androst-1-en-3-one with a strong base, such as aqueous methanolic potassium hydroxide at the reflux temperature, followed by acidification and isolation of the resulting steroidal acid to yield 17 β -carboxy 4-alkyl-4-aza-5 α -androst-1-en-3-one VI; (5) said steroidal acid can be then converted to its corresponding 2-pyridylthio ester by refluxing with triphenyl phosphine and 2,2'-dipyridyl disulfide in an inert solvent such as toluene and the resulting product 17 β -(2-pyridylthiocarbonyl)-4-alkyl-4-aza-5 α -androst-1-en-3-one VII can be isolated by chromatography on e.g. silica gel; and (6) said pyridylthio ester can be then reacted with 1-adamantyl-, 2-adamantylamine or norbornanylamine in an inert solvent e.g. tetrahydrofuran, to form the desired product 17 β -N-adamantyl-carbamoyl-4-alkyl-4-aza-5 α -androst-1-en-3-one VIII which can be isolated by chromatography e.g. on silica gel. When the previous reaction is carried out in the absence of first forming the double bond at position 1, the corresponding 17 β -(N-adamantyl-carbamoyl)-4-alkyl-4-aza-5 α -androstan-3-one (or N-norbornanyl carbamoyl compound) is prepared.

In accordance with an alternate process of our invention the corresponding N-unsubstituted-17 β -(N-adamantyl-carbamoyl)-4-aza-5 α -androst-1-en-3-one XIV is readily prepared from the 17 β (alkoxycarbonyl)-4-aza-5 α -androstone-3-one IV by repeating the above series of reaction steps but omitting the alkylation Step 2 herein above, i.e. treatment of the 4-aza-5-

This Sheet Has Been Replaced



- 16 -

α -androst-1-en-3-one with e.g. sodium amide followed by methyl or ethyl iodide via intermediates XII and XIII.

5 In accordance with a further alternate process of preparing the compounds of our invention having only hydrogen as the sole substituent on the ring A - nitrogen, the double bond in the A ring is introduced as the last step of the process. Thus, a 17 β -alkoxycarbonyl 4-aza-5 α -androstan-3-one III is
10 hydrolyzed to the corresponding steroidal acid IX 17 β -carboxy-4-aza-5 α -androstan-3-one which in turn is converted to the corresponding pyridylthio ester, 17 β (2-pyridylthiocarbonyl)-4-aza-5 α -androstan-3-one, X followed by treatment of the ester with an amine of
15 formula R²-NH₂ wherein R² is as defined hereinabove as 1- or 2-adamantyl or 1-, 2-, or 7-norbornanyl to form a 17 β (N-adamantyl-carbamoyl)-4-aza-5 α -androstone-3-one XI which is dehydrogenated as previously described to produce compound XIV,
20 17 β -(N-adamantyl-carbamoyl)-4-aza-androst-1-en-3-one or corresponding norbornanyl derivative.

In another alternate method of introducing the 17 β -(N-adamantyl-carbamoyl)substituent into a 17 β -carboxy androstane compound of formula VI, XII
25 or IX, each is treated in a manner similar to the procedure described in Steroids, Vol. 35 #3, March 1980, p. 1-7 with dicyclohexylcarbodiimide and 1-hydroxybenzo-triazole to form the 17 β -(1-benzo-triazoloxycarbonyl)-4-aza-5 α -androst-1-en-3-one,
30 VII, XIII or compound X, wherein the substituent X is benzotriazoloxo group.

This Sheet Has Been Replaced

SUBSTITUTE SHEET

- 17 -

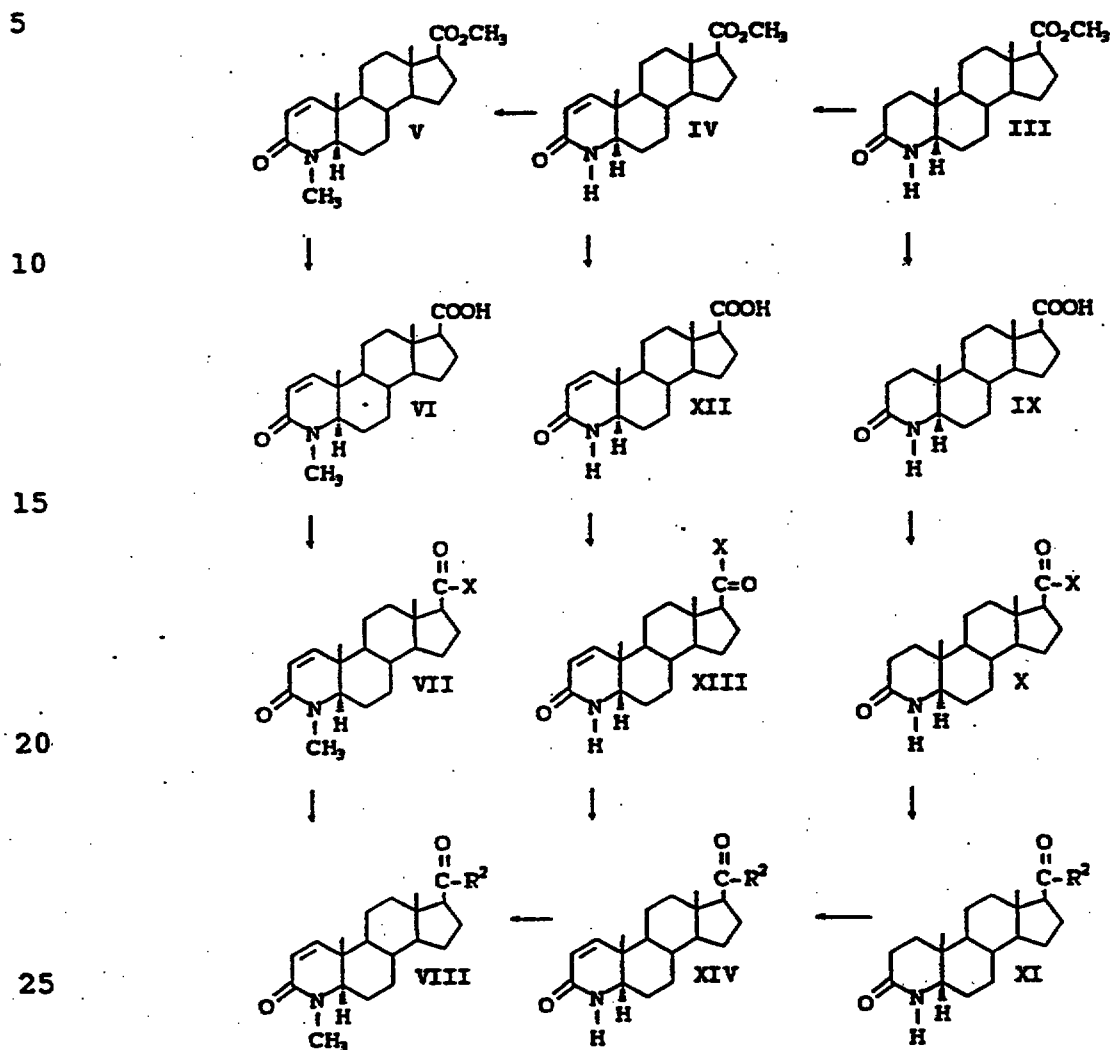
The 16-methyl derivative wherein R''' is methyl are prepared from known 16-methyl-17-acyl-4-methyl-4-aza-5 α -androstan-3-ones, e.g. 4,16 β -dimethyl-17 β -acetyl-4-aza-5 α -androstan-3-one by known dehydrogenation procedures for 4-methyl-4-aza compounds to produce the corresponding 4,16 β -dimethyl-17 β -acetyl-4-aza-5 α -androst-1-en-3-one.

The above reactions are schematically represented in the following flowsheet.

This Sheet Has Been Replaced



- 18 -

Flowsheet

X is 2-pyridylthio or 1-benzotriazoloxy.
 R^2 is 1- or 2-adamantyl or norbornanyl.

This Sheet Has Been Replaced



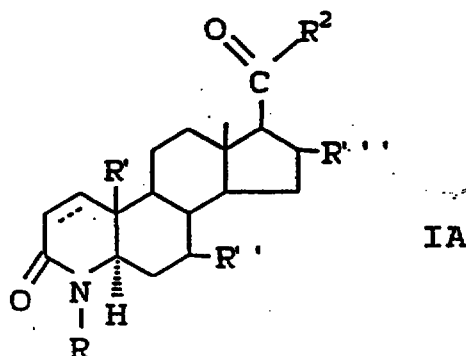
SUBSTITUTE SHEET

- 19 -

Also preferred is where the 4-aza steroid has the formula:
 17 β -acyl-4-aza-5 α -androst-1-ene-3-one compound
 of the formula:

5

10



15

wherein the dotted line represents a double bond when present;

- R is selected from hydrogen, methyl and ethyl;
- 20 R² is (a) a monovalent radical selected from straight or branched chain alkyl, or cycloalkyl, of from 1-12 carbons, which can be substituted by one or more of C₁-C₂ alkyl or halo;
- 25 (b) an aralkyl radical selected from benzyl or phenethyl;
- (c) a polycyclic aromatic radical which can be substituted with one or more of: -OH, protected -OH, -OC₁-C₄ alkyl, C₁-C₄ alkyl, halo or nitro;
- 30 (d) a monocyclic aromatic radical which can be substituted with one or more of:

This Sheet Has Been Replaced



- 20 -

- 5 (1) $-\text{OH}$, $-\text{OC}_1-\text{C}_4$ alkyl, C_1-C_4 alkyl, $-(\text{CH}_2)_m\text{OH}$, $-(\text{CH}_2)_n\text{COOH}$, including protected hydroxy, where m is 1-4, n is 1-3, providing C_1-C_4 alkyl is only present when one of the above oxygen-containing radicals is present;
- 10 (2) $-\text{SH}$, $-\text{SC}_1-\text{C}_4$ alkyl, $-\text{SOC}_1-\text{C}_4$ alkyl, $-\text{SO}_2\text{C}_1-\text{C}_4$ alkyl, $-\text{SO}_2\text{N}(\text{C}_1-\text{C}_4\text{-alkyl})_2$, C_1-C_4 alkyl $-(\text{CH}_2)_m\text{SH}$, $-\text{S}-(\text{CH}_2)_n-\text{O}-\text{COCH}_3$, where m is 1-4 n is 1-3, providing C_1-C_4 alkyl is only present when one of the above sulfur containing radicals is present;
- 15 (3) $\text{N}(\text{R}^3)_2$, which can be protected, where R^3 is independently H or C_1-C_4 alkyl, where the monoaryl ring can also be further substituted with C_1-C_4 alkyl; and
- 20 (4) heterocyclic radical selected from 2- or 4-pyridyl, 2-pyrrolyl, 2-furyl or thiophenyl;
- 25 and R' , R'' and R''' are each selected from hydrogen and methyl, and pharmaceutically acceptable salts thereof.

30 A preferred embodiment of the compounds of our invention process is:

the compound of above Structure IA

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 21 -

wherein the dotted line is a double bond,
R is hydrogen or methyl, and
R² is branched chain alkyl, or cycloalkyl of from
4-10 carbons, and R' and R'' are hydrogen.

5 Another embodiment of the invention is the
compounds of above Structure I where R² is phenyl, or
phenyl substituted by substituents described above,
including where

R² is phenyl, 2-, 3-, or 4-tolyl, xylyl,
10 2-bromophenyl, 2-chlorophenyl,
2,6-dichlorophenyl, 2,6-dibromophenyl,
aminophenyl, N-alkylaminophenyl, N-N-dialkyl-
aminophenyl, 4-biphenyl, 3-biphenyl,
15 naphthyl, anthracyl, phenanthryl,
thiophenyl, methylthiophenyl,
methylsulfinyl, phenyl, methylsulfophenyl,
aminosulfophenyl, thioethylphenyl,
acetoxymethylthiophenyl,
17 β -(4-hydroxyphenyl), 17 β -(3-hydroxyphenyl),
20 17 β -(3,4-dihydroxyphenyl), or 17 β -(3,5-
dimethyl-4-hydroxyphenyl).

Representative compounds of the invention are:

17 β -(phenylcarbonyl)-4-aza-4-methyl-5 α -androst-
1-ene-3-one;

25 17 β -(2-tolylcarbonyl)-4-aza-4-methyl-5 α -androst-
1-ene-3-one;

17 β -(3-tolylcarbonyl)-4-aza-4-methyl-5 α -androst-
1-ene-3-one;

17 β -(4-tolylcarbonyl)-4-aza-4-methyl-5 α -androst-
30 1-ene-3-one;

17 β -(2-bromophenylcarbonyl)-4-aza-4-methyl-5 α -
androst-1-ene-3-one;

This Sheet Has Been Replaced



- 22 -

- 17 β -(2-chlorophenylcarbonyl)-4-aza-4-methyl-5 α -
androst-1-ene-3-one;
- 17 β -(2,6-dichlorophenylcarbonyl)-4-aza-4-methyl-5 α -
androst-1-ene-3-one;
- 5 17 β -(2,6-dibromophenylcarbonyl)-4-aza-4-methyl-5 α -
androst-1-ene-3-one;
- 17 β -(xylylcarbonyl)-4-aza-4-methyl-5 α -androst-
1-ene-3-one;
- 17 β -(t-butylcarbonyl)-4-aza-5 α -androst-1-ene-3-one;
- 10 17 β -(isobutylcarbonyl)-4-aza-5 α -androst-1-ene-3-one;
- 17 β -(isooctylcarbonyl)-4-aza-5 α -androst-1-ene-3-one;
- 17 β -(n-octylcarbonyl)-4-aza-5 α -androst-1-ene-3-one;
- 17 β -(1,1-diethylbutylcarbonyl)-4-aza-5 α -androst-1-
ene-3-one;
- 15 17 β -(neopentylcarbonyl)-4-aza-5 α -androst-1-ene-3-one;
- 17 β -(tert-amylcarbonyl)-4-aza-4-5 α -androst-1-ene-3-
one;
- 17 β -(tert-hexylcarbonyl)-4-aza-4-5 α -androst-1-ene-3-
one;
- 20 17 β -(cyclohexylcarbonyl)-4-aza-5 α -androst-1-ene-3-
one;
- 17 β -(cyclopentylcarbonyl)-4-aza-5 α -androst-1-ene-3-
one;
- 17 β -(benzylcarbonyl)-4-aza-5 α -androst-1-ene-3-one;
- 25 17 β -(2-pyridylcarbonyl)-4-aza-5 α -androst-1-ene-3-one;
- 17 β -(4-pyridylcarbonyl)-4-aza-5 α -androst-1-ene-3-one;
- 17 β -(2-pyrrolylcarbonyl)-4-aza-5 α -androst-1-ene-3-
one;
- 17 β -(2-furylcarbonyl)-4-aza-5 α -androst-1-ene-3-one;
- 30 17 β -(2-thiophenylcarbonyl)-4-aza-5 α -androst-1-ene-3-
one;
- 17 β -(2-adamantylcarbonyl)-4-aza-5 α -androst-1-ene-3-
one;

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 23 -

- 17B-(phenylcarbonyl)-4-aza-5 α -androst-1-ene-3-one;
17B-(2-tolylcarbonyl)-4-aza-5 α -androst-1-ene-3-one;
17B-(3-tolylcarbonyl)-4-aza-5 α -androst-1-ene-3-one;
17B-(4-tolylcarbonyl)-4-aza-5 α -androst-1-ene-3-one;
5 17B-(2-bromophenylcarbonyl)-4-aza-5 α -androst-1-ene-3-one;
17B-(2-chlorophenylcarbonyl)-4-aza-5 α -androst-1-ene-3-one;
17B-(2,6-dichlorophenylcarbonyl)-4-aza-5 α -androst-1-ene-3-one;
10 17B-(2,6-dibromophenylcarbonyl)-4-aza-5 α -androst-1-ene-3-one;
17B-(xylylcarbonyl)-4-aza-5 α -androst-1-ene-3-one;
17B-(phenylethyl)carbonyl-4-aza-5 α -androst-1-ene-3-one;
15 17B-(4-dimethylaminophenylcarbonyl)-4-aza-5 α -androst-1-en-3-one;
17B-(3-dimethylaminophenylcarbonyl)-4-aza-5 α -androst-1-en-3-one.
20 17B-(3,4-diethylaminophenylcarbonyl)-4-aza-androst-1-en-3-one.
17B-(3,5-dimethyl-4-diethylaminophenylcarbonyl)-4-aza-5 α -androst-1-en-3-one;
17B-(4-N-methylaminomethylphenylcarbonyl)-4-aza-5 α -androst-1-en-3-one; or
25 17B-(2-N-ethylamino-4-ethylphenylcarbonyl)-4-aza-5 α -androst-1-en-3-one.
17B-(4-phenylbenzoyl)-4-aza-5 α -androst-1-en-3-one;
17B-(3-phenylbenzoyl)-4-aza-5 α -androst-1-en-3-one;
30 17B-(4-biphenyl)-4-aza-5 α -androst-1-en-3-one;
17B-(3-biphenyl)-4-aza-5 α -androst-1-en-3-one;
17B-(1-naphthyl)-4-aza-5 α -androst-1-en-3-one;

This Sheet Has Been Replaced



- 24 -

- 17 β -(2-naphthyl)-4-aza-5 α -androst-1-en-3-one;
17 β -(1-phenanthryl)-4-aza-5 α -androst-1-en-3-one;
17 β -(2-phenanthryl)-4-aza-5 α -androst-1-en-3-one;
17 β -(1-biphenyl)-4-aza-5 α -androst-1-en-3-one;
5 17 β -(9-anthracyl)-4-aza-5 α -androst-1-en-3-one;
17 β -(4-thiophenylcarbonyl)-4-aza-5 α -androst-1-en-3-one;
17 β -(3-thiophenylcarbonyl)-4-aza-5 α -androst-1-en-3-one;
10 17 β -(4-methylthiophenylcarbonyl)-4-aza-5 α -androst-1-en-3-one;
17 β -(4-methylsulfinylphenylcarbonyl)-4-aza-5 α -androst-1-en-3-one;
17 β -(4-methylsulfophenylcarbonyl)-4-aza-5 α -androst-1-en-3-one;
15 17 β -(3-methylsulfinylphenylcarbonyl)-4-aza-5 α -androst-1-en-3-one;
17 β -(4-N,N-dimethylaminosulfophenylcarbonyl)-4-aza-5 α -androst-1-en-3-one;
20 17 β -(2-ethyl-4-methylthiophenylcarbonyl)-4-aza-5 α -androst-1-en-3-one;
17 β -(4-thioethylphenylcarbonyl)-4-aza-4-methyl-5 α -androst-1-en-3-one;
17 β -(4-acetoxymethylthiophenylcarbonyl)-4-aza-4-methyl-5 α -androst-1-en-3-one;
25 17 β -(2-methyl-4-methylthiophenylcarbonyl)-4-aza-4-methyl-5 α -androst-1-en-3-one;
17 β -(2-methyl-4-methylsulfinylphenylcarbonyl)-4-aza-4-methyl-5 α -androst-1-en-3-one;
30 17 β -(2-isopropyl-4-methylsulfophenylcarbonyl)-4-aza-4-methyl-5 α -androst-1-en-3-one;

This Sheet Has Been Replaced

**SUBSTITUTE SHEET**

- 25 -

- 17B-(4-methylthiophenylcarbonyl)-4-aza-4-methyl-5 α -androstan-3-one;
- 17B-(4-methylsulfinylphenylcarbonyl)-4-aza-4-methyl-5 α -androstan-3-one;
- 5 17B-(4-methylsulfonylphenylcarbonyl)-4-aza-4-methyl-5 α -androstan-3-one;
- 17B-(4-hydroxyphenyl)-4-aza-5 α -androst-1-en-3-one;
- 17B-(3-hydroxyphenyl)-4-aza-5 α -androst-1-en-3-one;
- 17B-(3,4-dihydroxyphenyl)-4-aza-5 α -androst-1-en-3-one;
- 10 one;
- 17B-(3,5-dimethyl-4-hydroxyphenyl)-4-aza-5 α -androst-1-en-3-one;
- 17B-(4-hydroxymethylphenyl)-4-aza-5 α -androst-1-en-3-one;
- 15 17B-(2-hydroxyethylphenylcarbonyl)-4-aza-5 α -androst-1-en-3-one;
- 17B-(4-methoxyphenyl)-4-aza-5 α -androst-1-en-3-one;
- 17B-(4-carboxymethylphenyl)-4-aza-5 α -androst-1-en-3-one;
- 20 17B-(4-hydroxyphenyl)-4-aza-4-methyl-5 α -androst-1-en-3-one;
- 17B-(3-hydroxyphenyl)-4-aza-4-methyl-5 α -androst-1-en-3-one;
- 17B-(3,4-dihydroxyphenyl)-4-aza-4-methyl-5 α -androst-1-en-3-one;
- 25 17B-(3,5-dimethyl-4-hydroxyphenyl)-4-aza-4-methyl-5 α -androst-1-en-3-one;
- 17B-(4-hydroxymethylphenyl)-4-aza-4-methyl-5 α -androst-1-en-3-one;
- 30 17B-(2-hydroxyethylphenylcarbonyl)-4-aza-4-methyl-5 α -androst-1-en-3-one;
- 17B-(4-methoxyphenyl)-4-aza-4-methyl-5 α -androst-1-en-3-one;

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 26 -

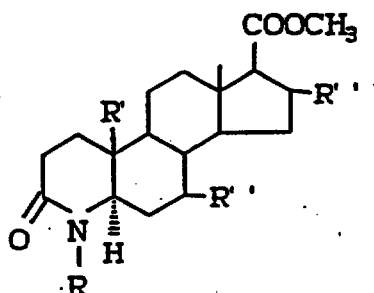
17 β -(4-carboxymethylphenyl)-4-aza-4-methyl-5 α -
androst-1-en-3-one; and

17 β -(4-carboxyphenyl)-4-aza-5 α -androst-1-en-3-one,

and the corresponding compounds wherein the

5 4-hydrogen substituent is replaced in each of the
above named compounds by a methyl or an ethyl radical.

The compounds of formula IA of the present
invention are prepared by a method starting with the
10 known steroid ester of the formula:



20

named 17 β -(carbomethoxy)-4-aza-5 α -androstan-3-one,
which includes the stages of (1) dehydrogenating said
starting material to produce the corresponding com-
25 pound containing a double bond in the 1,2-position of
the A-ring, (2) converting the 17-carbomethoxy substi-
tuent into a 17 β -acyl substituent and, if desired (3)
alkylating the A-ring nitrogen to introduce 4-methyl
or 4-ethyl substituents into the A-ring. For the
30 dehydrogenation step, it is preferable that the 4-aza
nitrogen be unsubstituted. The dehydrogenation step
can be carried out, e.g. according to the procedure
of Dolling, et al. involving dichlorodicyanobenzo-
quinone, JACS (1988) Vol. 110, pp. 3318-3319. Stage

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 27 -

(2) may consist of one or more chemical steps and if desired may take place before stage (1) or following stage (1) or stage (3).

In accordance with the process of the present invention, the products of our invention are formed by (1) heating a 17 β -alkoxycarbonyl-4-aza-5 α -androstan-3-one compound III with a dehydrogenating agent such as benzeneseleninic anhydride in refluxing chlorobenzene to form a 17 β -alkoxycarbonyl-4-aza-5 α -androst-1-en-3-one (IV), (2) the formed 5 α -androst-1-en-3-one compound from step (1) is reacted with sodium hydride and under anhydrous conditions in a neutral solvent such as dimethylformamide, (2) contacting the resulting reaction mixture with an alkyl (methyl or ethyl) iodide to form the corresponding 17 β -alkoxycarbonyl-4-alkyl-4-aza-5 α -androst-1-en-3-one (V), (3) subsequently hydrolyzing said 17 β -alkoxycarbonyl-4-alkyl-4-aza-5 α -androst-1-en-3-one with a strong base such as aqueous methanolic potassium hydroxide at the reflux temperature, followed by acidification and isolation of the resulting steroidal acid, 17 β -carboxy-4-alkyl-4-aza-5 α -androst-1-en-3-one (VI), (4) said steroidal acid is then converted to its corresponding 2-thiopyridyl ester by refluxing with triphenyl phosphine and 2,2'-dipyridyl disulfide in an inert solvent and the product 17 β -(2-pyridylthiocarbonyl)-4-alkyl-4-aza-5 α -androst-1-en-3-one (VII) is isolated by chromatography on silica, (5) said pyridylthio ester is then reacted with an R²-Li or an R²MgX (X=Cl, Br) compound, such as sec-butylmagnesium chloride in tetrahydrofuran, to form

This Sheet Has Been Replaced

- 28 -

the desired product, e.g., 17 β -(sec-butylcarbonyl)-4-alkyl-4-aza-5 α -androst-1-en-3-one (VIII) which is isolated by chromatography on silica gel. When the previous reaction is carried out using an R²MgX or, an R²-Li compound in place of sec-butyilmagnesium chloride, the corresponding 17 β -(acyl)-4-alkyl-4-aza-5 α -androst-1-en-3-one is prepared wherein acyl is R² carbonyl.

In accordance with the process of our invention, the corresponding 17 β -acyl-4-aza-5 α -androst-1-en-3-one XV is readily prepared from the 17 β -(alkoxycarbonyl)-4-aza-5 α -androsten-3-one (IV) by repeating the above series of reaction steps but omitting step 2 hereinabove, i.e., treatment of the 4-aza-5 α -androst-1-en-3-one with sodium amide followed by methyl or ethyl iodide.

In accordance with a further alternate process of preparing the compounds of our invention, having only hydrogen as the sole substituent on the ring A-nitrogen, the 1,2-double bond in the A-ring is introduced as the last step of the process. Thus, a 17 β -alkoxycarbonyl-4-aza-5 α -androstan-3-one (III) is hydrolyzed to the corresponding steroidal acid, 17 β -carboxy-4-aza-5 α -androstan-3-one, (IX) which, in turn, is converted to the corresponding thiopyridyl ester, 17 β -(2-pyridylthiocarbonyl)-4-aza-5 α -androstan-1-one (X) followed by treatment of the ester with an R²MgX or R²Li compound wherein R² is as defined hereinabove to form a 17 β -(acyl)-4-aza-5 α -androstan-3-one (XI) which is dehydrogenated as previously described to produce compound XIV, 17 β -(acyl)-4-aza-5 α -androst-1-en-3-one.

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 29 -

In an additional alternative process for making the compounds of formula I when the starting material is an ester, particularly methyl ester as shown in formula III-V in the schematic, reaction with a Grignard reagent R^2MgX , gives the ketone, 17 β - R^2CO -, corresponding to the R^2 moiety associated with the Grignard reagent.

The 16-methyl derivative wherein R^{111} is methyl are prepared from known 16-methyl-17-acyl-4-methyl-4-aza-5 α -androstan-3-ones, e.g. 4,16 β -dimethyl-17 β -acetyl-4-aza-5 α -androstan-3-one by known dehydrogenation procedures for 4-methyl-4-aza compounds to produce the corresponding 4,16 β -dimethyl-17 β -acetyl-4-aza-5 α -androst-1-en-3-one.

The above reactions are schematically represented in the following structural outline:

This Sheet Has Been Replaced



- 30 -

5

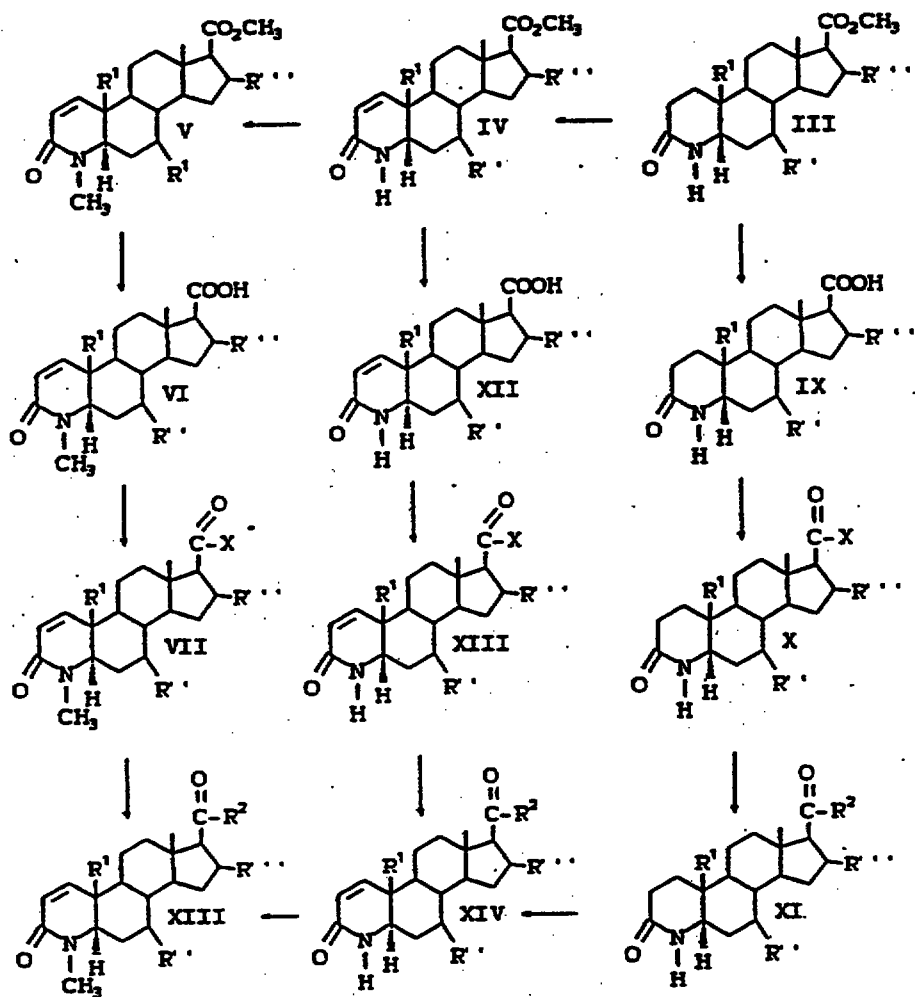
10

15

20

25

30



X is 2-pyridylthio

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 31 -

wherein X is a 2-pyridylthio substituent and R^2 is defined as hereinabove.

5 In the above described reaction Scheme, where R^2 is p-hydroxybiphenyl, this can be derived by starting with an appropriate bromobiphenylphenol, e.g. p-bromobiphenylphenol, protecting the phenolic -OH with a conventional blocking group, e.g. triorganosilyl, i.e. t-butyldimethylsilyl, carrying out the Grignard reaction and then deblocking
10 the silyl group by the use of, e.g. refluxing aqueous tetrabutylammonium fluoride.

Other halo substituted benzenes to form the appropriate Grignard reagent useful in the instant invention will be obvious to one skilled in the art
15 from this disclosure.

By the term "protected hydroxy" as used herein, is meant the alcoholic or carboxylic -OH groups which can be protected by conventional blocking groups in the art as described in
20 "Protective Groups In Organic Synthesis" by Theodora W. Greene, Wiley-Interscience, 1981, New York. Preferred are the triorganosilyl groups, e.g. t-butyl-dimethylsilyl, phenyldimethylsilyl, diphenylmethyl-silyl, and the like.

25 By the term " C_1 - C_4 alkyl" is used herein, is meant linear or branched alkyl, including methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, sec-butyl and t-butyl.

30 When this reaction scheme is carried out using an R^2MgX or R^2-Li compound containing an thiophenyl substituted R^2 , e.g. p-methylthiophenyl

This Sheet Has Been Replaced



- 32 -

magnesium chloride, the corresponding 17 β -(substituted thio-benzoyl)-4-alkyl-4-aza-5 α -androst-1-en-3-one is prepared wherein phenyl is R².

5 The Grignard reagent, R²MgX, for all the species included within the scope of this invention, are available or can readily be made by one skilled in the art. For example, where R² is C₁-C₄ alkyl thiophenyl, can be formed from the appropriate C₁-C₄ alkyl thiobromobenzene, e.g. p-methylthiobromobenzene.

10 The formed C₁-C₄ alkyl thiobenzene can be used to further prepare C₁-C₄ alkyl sulfoxides by oxidation with e.g. m-chloroperbenzoic acid. The resulting sulfoxide can be further oxidized by the use of the m-chloroperbenzoic acid reaction to
15 proceed for a longer period of time to form the C₁-C₄ alkyl sulfone.

Further, the sulfoxide can be used in the Pummerer rearrangement to form the corresponding thiol.

20 The -SO₂N(C₁-C₄ alkyl)₂ substituted phenyl (R²) is formed from the appropriate bromobenzene, e.g. p-N,N-dimethylaminosulfobromobenzene which is used directly in the Grignard reaction to form the final product.

25 The thioalkyl groups on the phenyl ring, i.e. -(CH₂)_mSH, where m is 1-4, are readily formed via a four step procedure from an alkoxy alkyl phenyl bromide, Br-C₆H₄-(CH₂)_mOCH₃. Direct addition of the Grignard reagent prepared from above-bromoalkyl
30 phenyl derivative to the thiopyridyl ester results in the keto derivative, i.e. 17 β (4-methoxyalkyl-benzoyl)-4-aza-5 α -androst-1-ene-3-one. This can be

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 33 -

readily converted into thio analogue via BBr_3 at -70°C to form the hydroxyalkyl derivative, followed by displacement by halogen, e.g. bromo and then converting the halogenated compound through NaSH displacement to give the final mercapto compound. Where in the Reaction Scheme said pyridylthio ester is reacted with an aminophenyl containing $\text{R}^2\text{-Li}$ or an R^2MgX ($\text{X}=\text{Cl}, \text{Br}$) compound, such as p-dimethylaminophenyl magnesium chloride, this is carried out in tetrahydrofuran to form the desired product 17B-(p-dimethylaminophenyl-carbonyl)-4-alkyl-4-aza-5 α -androst-1-en-3-one (VIII) which is isolated by chromatography on silica gel.

The Grignard reagent, R^2MgX , for all of the aminophenyl species included within the scope of this invention, are available and can be made readily by one skilled in the art.

Where in the process said Grignard reagent contains a phenolic type R^2 moiety, then said pyridylthio ester is then reacted with an $\text{R}^2\text{-Li}$ or an R^2MgX ($\text{X}=\text{Cl}, \text{Br}$) Grignard reagent, such as p-methoxyphenyl-magnesium chloride in tetrahydrofuran to form the desired product, e.g. 17B-(p-methoxyphenylcarbonyl)-4-alkyl-4-aza-5 α -androst-1-en-3-one (VIII) which is isolated by chromatography on silica gel. When this reaction is carried out using another R^2MgX or, an $\text{R}^2\text{-Li}$ compound in place of p-methoxyphenylmagnesium chloride, the corresponding 17B-(substituted benzoyl)-4-alkyl-4-aza-5 α -androst-1-en-3-one is prepared wherein phenyl is R^2 .

The Grignard reagent, R^2MgX , for all of the species included within the scope of this invention,

This Sheet Has Been Replaced



- 34 -

are available and can be made readily by one skilled in the art.

For example, where R^2 is hydroxyphenyl, this can be derived by starting with an appropriate bromophenol, e.g. p-bromophenol, protecting the phenolic -OH with a conventional blocking group, e.g. trioganosilyl, i.e. t-butyldimethylsilyl, carrying out the Grignard reaction and then deblocking the silyl group by the use of, e.g. refluxing aqueous tetrabutylammonium fluoride.

For R^2 being hydroxyethylphenyl, the same blocking procedure can be analogously conducted, starting with the appropriate hydroxyalkyl bromophenol, e.g. p-hydroxymethylbromobenzene, or p-hydroxyethylbromobenzene.

Where R^2 is carboxyphenyl, this can be obtained by the chromic acid oxidation of the appropriate hydroxymethylbenzene, e.g. p-bromo-hydroxymethylbenzene, formed as described above.

Where R^2 is $-O-C_1-C_4$ alkyl, the appropriate bromo- $-O-C_1-C_4$ alkyl benzene, e.g. p-methoxybromobenzene, is utilized for the Grignard reaction.

Other halo substituted benzenes to form the appropriate Grignard reagent useful in the instant invention will be obvious to one skilled in the art from this disclosure.

By the term "protected hydroxy" as used herein, is meant the alcoholic or carboxylic -OH groups which can be protected by conventional blocking groups in the art as described in "Protective Groups In Organic Synthesis" by Theodora

This Sheet Has Been Replaced



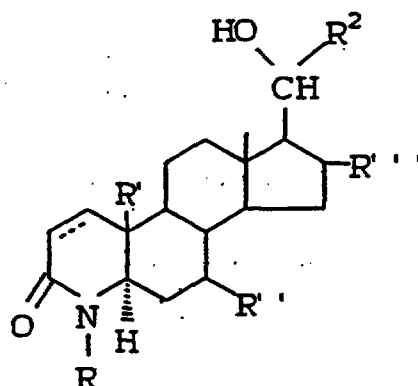
SUBSTITUTE SHEET

- 35 -

W. Greene, Wiley-Interscience, 1981, New York.

Preferred are the triorganosilyl groups, e.g. t-butyl-dimethylsilyl, phenyldimethylsilyl, diphenylmethylsilyl, and the like.

Also within the scope of the present invention is the use of ketone reduction products of IA, in combination with minoxidil for treatment of patterned alopecia, being secondary alcohols of the formula:



This Sheet Has Been Replaced



wherein R is selected from hydrogen, methyl and ethyl;

R^2 is (a) a monovalent radical selected from straight or branched chain alkyl, or cycloalkyl, of from 1-12 carbons, which can be substituted by one or more of C_1 - C_2 alkyl or halo;

(b) an aralkyl radical selected from benzyl or phenethyl;

(c) a polycyclic aromatic radical which can be substituted with one or more of: -OH, protected -OH, $-OC_1$ - C_4 alkyl, C_1 - C_4 alkyl, halo or nitro;

- 36 -

(d) a monocyclic aromatic radical which can be substituted with one or more of:

(1) -OH, -OC₁-C₄ alkyl, C₁-C₄ alkyl, -(CH₂)_mOH, -(CH₂)_nCOOH, including protecting hydroxy, where m is 1-4, n is 1-3, providing C₁-C₄ alkyl is only present when one of the above oxygen-containing radicals is present;

(2) -SH, -SC₁-C₄ alkyl, -SOC₁-C₄ alkyl, -SO₂C₁-C₄ alkyl, -SO₂N(C₁-C₄-alkyl)₂, C₁-C₄ alkyl -(CH₂)_mSH, -S-(CH₂)_n-O-COCH₃, where m is 1-4 n is 1-3, providing C₁-C₄ alkyl is only present when one of the above sulfur containing radicals is present;

(3) N(R³)₂, which can be protected, where R³ is independently H or C₁-C₄ alkyl, where the monoaryl ring can also be further substituted with C₁-C₄ alkyl; and

(4) heterocyclic radical selected from 2- or 4-pyridyl, 2-pyrrolyl, 2-furyl or thiophenyl;

R', R'' and R''' are hydrogen or methyl, wherein the dotted line represents a double bond which can be present, and pharmaceutically acceptable salts and esters thereof.

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 37 -

These compounds can be made by conventional sodium borohydride reduction of the carbonyl attached to R² without reducing the amide carbonyl in Ring A or the 1,2-double bond, if present. If the R² phenyl contains a carbonyl function, it can be selectively blocked and then regenerated after the borohydride reduction by conventional methods.

The borohydride reduction can be carried out in, e.g. water or aqueous methanol, at a temperature of room temperature to 50°C and the product then isolated and purified by conventional means. The compounds are also active as 5-alpha reductase inhibitors in the treatment of patterned alopecia.

The compounds of the present invention, prepared in accordance with the method described above, are, as already described, potent agents in combination with an alpha-one adrenergic receptor blocker for the treatment of BPH.

17β-substituted steroidal 5α-reductase inhibitors which are non-4-aza steroids are known in the art and include those developed by SmithKline Beckmann as disclosed in U.S. Pat. 4,882,319 to Holt, et al.; U.S. Pat. 4,910,226 to Holt, et al; EPO Publn. 0 289 327 now USP 4,910,226; EPO Publn. 0 277 002 now USP 4,888,336; EPO Publn. 0 343 954; EPO Publn. 0 375 344 now USP 4,937,237; EPO Publn. 0 375 347; now USP 4,970,205; EPO Publn. 0 375 349; now USP 5,026,882.

In the method the 17β-substituted non-aza steroids are of the formula:

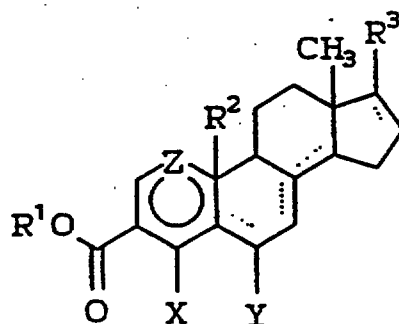
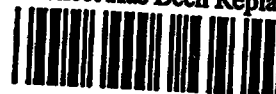
This Sheet Has Been Replaced



REPLACEMENT SHEET

- 38 -

This Sheet Has Been Replaced



in which:

- the A ring has up to 2 double bonds;
 the B, C, and D rings have optimal double bonds
 where indicated by the broken lines,
 provided that the A, B, and C rings do not
 have adjacent double bonds and the D ring
 does not have a C₁₆-C₁₇ double bond when R₃
 represents two substituents or a divalent
 substituent;

Z is (CH₂)_n and n is 0 or 2, provided that Z is
 (CH)_n when adjacent to a double bond;

X is H, Cl, F, Br, I, CF₃, or C₁₋₆alkyl;

Y is H, CF₃, F, Cl, or CH₃, provided that Y is H
 when there is no C₅-C₆ double bond;

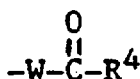
R¹ is H or C₁₋₈alkyl;

R² is absent or present as H or CH₃, provided R²
 is absent when the carbon to which it is
 attached is unsaturated; and

R³ is

(1) α-hydrogen, or α-hydroxyl, or α-acetoxy
 and/or

(a)



SUBSTITUTE SHEET

- 39 -

where W is a bond or C₁₋₁₂ alkylidene, and

R⁴ is

- 5 (i) hydrogen,
(ii) hydroxyl,
(iii) C₁₋₈alkyl,
(iv) hydroxylic C₁₋₈alkyl,
(v) C₁₋₈alkoxy,
(vi) NR⁵R⁶, where R⁵ and R⁶ are each
10 independently selected from
hydrogen, C₁₋₈alkyl,
C₃₋₆cycloalkyl, phenyl; or R⁵ and
R⁶ taken together with the
nitrogen to which they are
15 attached represent a 5-6 membered
saturated ring,
(vii) OR⁷, where R⁷ is hydrogen, alkali
metal, C₁₋₈alkyl, benzyl, or
(b) -Alk-OR⁸, where Alk is C₁₋₁₂
20 alkylidene, and R⁸ is
(i) phenyl C₁₋₆alkylcarbonyl,
(ii) C₅₋₁₀ cycloalkylcarbonyl,
(iii) benzoyl,
(iv) C₁₋₈ alkoxy carbonyl,
(v) aminocarbonyl, or C₁₋₈alkyl
25 substituted aminocarbonyl,
(vi) hydrogen, or
(vii) C₁₋₈ alkyl,
(2) =CH-W-CO-R⁴ or =CH-W-OR⁸, where W is a bond
of C₁₋₁₂ alkylidene and R⁴ and R⁸ have the same
30 meaning as above and R⁸ also is hydrogen or C₁₋₂₀
alkylcarbonyl,

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 40 -

(3)



5

10

where the dashed bond replaces the 17- α -hydrogen,

(4) α -hydrogen and NHCOR^9 where R^9 is C_{1-12} alkyl or NR^5R^6 where R^5 and R^6 have the same meaning as above,

15

(5) α -hydrogen and cyano,

(6) α -hydrogen and tetrazolyl, or

(7) keto;

or a pharmaceutically acceptable salt thereof; except compounds in which:

20

(i) the B ring has a $\text{C}_5\text{-C}_6$ double bond, R^1 is CH_3 , and R^3 is keto, methoxycarbonyl, or acetyl; or

(ii) the A-nor ring has a $\text{C}_3\text{-C}_4$ double bond and R^3 is acetoxy or acetyl;

25

(iii) R^1 is CH_3 and R^3 is acetoxy or acetyl; or

(iv) the A-nor ring has a $\text{C}_3\text{-C}_4$ double bond and R^1 is methyl; or

(v) the B ring has a $\text{C}_3\text{-C}_4$ double bond and R^3 is β -hydroxy.

30

Representative compounds whose synthesis and properties are disclosed in the above issued US patents include the following and pharmaceutically acceptable salts thereof:

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 41 -

- 4-methyl-4-aza-5a-8(14)-pregnen-3-one-(20R)-20-carboxylic acid;
(20R)-hydroxymethyl-4-methyl-4-aza-5a-8(14)-
5 pregnen-3-one;
4-methyl-4-aza-5a-8(14)-androsten-3-one-17B-N,N-diisopropylcarboxamide;
17B-(N,N-diisopropylcarboxamide)-estr-1,3,5(10)-triene-3-phosphonic acid;
10 17B-(N-tert-butylcarboxamide)-estr-1,3,5(10)-triene-3-phosphonic acid;
17B-(N,N-diisopropylcarboxamide)-estr-1,3,5(10),16-tetraene-3-phosphonic acid;
17B-(N-tert-butylcarboxamide)-estr-1,3,5(10),16-
15 tetraene-3-phosphonic acid;
17B-(N,N-diisopropylcarboxamide)-estr-1,3,5(10),6,8-pentaene-3-phosphonic acid;
17B-(N,N-diisopropylcarboxamide)-2-methyl-estr-1,3,5(10)triene-3-phosphonic acid;
20 17B-(N,N-diisopropylcarboxamide)-4-methyl-estr-1,3,5(10)-triene-3-phosphonic acid;
17B-(N,N-diisopropylcarboxamide)-estr-1,3,5(10),6-tetraene-3-phosphonic acid;
17B-(N,N-diisopropylcarboxamide)-2-chloro-estr-1,3,5
25 (10)-triene-3-phosphonic acid;
17B-(N,N-diisopropylcarboxamide)-4-chloro-estr-1,3,5(10)-triene-3-phosphonic acid;
17B-(N-butylcarboxamide)-estr-1,3,5(10)-triene-3-carboxylic acid;
30 17B-(N-butylcarboxamide)-estr-1,3,5(10)16-tetraene-3-carboxylic acid;

This Sheet Has Been Replaced

- 42 -

- 17B-(N,N-diisopropylcarboxamide)-estr-1,3,5(10)-
triene-3-phosphinic acid;
- 17B-(N-tert-butylcarboxamide)-estr-1,3,5(10)-triene-
3-phosphinic acid;
- 5 17B-(N,N-diisopropylcarboxamide)-2-methyl-estr-1,3,5
(10)-triene-3-phosphinic acid;
- 17B-(N,N-diisopropylcarboxamide)-4-methyl-estr-1,3,5
(10)-triene-3-phosphinic acid;
- 10 17B-(N,N-diisopropylcarboxamide)-2-chloro-estr-1,3,5
(10)-triene-3-phosphinic acid;
- 17B-(N,N-diisopropylcarboxamide)-4-chloro-estr-1,3,5
(10)-triene-3-phosphinic acid;
- 17B-(N,N-diisopropylcarboxamide)-1,3,5(10),16-
tetraene-3-phosphinic acid;
- 15 17B-(N-tert-butylcarboxamide)-estr-1,3,5(10),16-
tetraene-3-phosphinic acid;
- 17B-(N,N-diisopropylcarboxamide)-estr-1,3,5(10),6,8-
pentaene-3-phosphinic acid;
- 17B-(N,N-diisopropylcarboxamide)-estr-1,3,5(10),6-
20 tetraene-3-phosphinic acid;
- 17B-(N,N-diisopropylcarboxamide)-estr-1,3,5(10)-
triene-3-phosphonic acid;
- 17B-(N-tert-butylcarboxamide)-estr-1,3,5(10)-triene-3-
phosphonic acid;
- 25 17B-(N,N-diisopropylcarboxamide)-estr-1,3,5(10),16-
tetraene-3-phosphonic acid;
- 17B-(N-tert-butylcarboxamide)-estr-1,3,5(10),16-
tetraene-3-phosphonic acid;
- 17B-(N,N-diisopropylcarboxamide)-estr-1,3,5(10),6,8-
30 pentaene-3-phosphonic acid;
- 17B-(N,N-diisopropylcarboxamide)-2-methyl-estr-1,3,5
(10)-triene-3-phosphonic acid;

This Sheet Has Been Replaced

SUBSTITUTE SHEET

- 43 -

- 17B-(N,N-diisopropylcarboxamide)-4-methyl-estr-1,3,5
(10)-triene-3-phosphonic acid;
- 17B-(N,N-diisopropylcarboxamide)-estr-1,3,5(10),6-
tetraene-3-phosphonic acid;
- 5 17B-(N,N-diisopropylcarboxamide)-2-chloro-estr-1,3,5
(10)-triene-3-phosphonic acid;
- 17B-(N,N-diisopropylcarboxamide)-4-chloro-estr-1,3,5
(10)-triene-3-phosphonic acid;
- 10 17B-(N,N-diisopropylcarboxamide)-estr-1,3,5(10)-
triene-3-sulfonic acid;
- 17B-(N-tert-butylcarboxamide)-estr-1,3,5(10)-triene-3-
sulfonic acid;
- 17B-(N,N-diisopropylcarboxamide)-estr-1,3,5(10),16-
tetraene-3-sulfonic acid;
- 15 17B-(N-tert-butylcarboxamide)-estr-1,3,5(10),16-
tetraene-3-sulfonic acid;
- 17B-(N,N-diisopropylcarboxamide)-estr-1,3,5(10),6,8-
pentaene-3-sulfonic acid;
- 17B-(N,N-diisopropylcarboxamide)-2-methyl-estr-1,3,5
(10)-triene-3-sulfonic acid;
- 20 17B-(N,N-diisopropylcarboxamide)-4-methyl-estr-1,3,5
(10)-triene-3-sulfonic acid;
- 17B-(N,N-diisopropylcarboxamide)-2-chloro-estr-1,3,5
(10)-triene-3-sulfonic acid;
- 25 17B-(N,N-diisopropylcarboxamide)-4-chloro-estr-1,3,5
(10)-triene-3-sulfonic acid;
- 17B-(N,N-diisopropylcarboxamide)-androst-3,5-diene-
3-phosphinic acid;
- 17B-(N-t-butylcarboxamide)-androst-3,5-diene-3-
phosphinic acid;
- 30 17B-(N,N-diisopropylcarboxamide)-5 α -androst-3-
ene-3-phosphinic acid;

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 44 -

- 17 β -(N,N-diisopropylcarboxamide)-5 α -androst-2-ene-3-phosphinic acid;
- 17 β -(N,N-diisopropylcarboxamide)-androst-2,4-diene-3-phosphinic acid;
- 5 methyl(17 β -N,N-diisopropylcarboxamide)-androst-3,5-diene-3-phosphinic acid;
- 20 α -(hydroxymethyl)-5 α -pregn-3-ene-3-phosphinic acid;
- 17 β -(N,N-diisopropylcarboxamide)-4-fluoro-5 α -androst-3-ene-3-phosphinic acid;
- 10 20 α -(hydroxymethyl)-4-fluoro-5 α -pregn-3-ene-3-phosphinic acid;
- 20 α -(hydroxymethyl)-A-nor-5 α -pregn-1-ene-2-phosphinic acid;
- 15 17 β -(N,N-diisopropylcarboxamide)-5 α -androst-1,3-diene-3-phosphinic acid;
- 17 β -(N,N-diisopropylcarboxamide)-5 α -androstande-3 β -phosphinic acid;
- 17 β -(N,N-diisopropylcarboxamide)-estr-3,5(10)-diene-3-phosphinic acid;
- 20 17 β -(N,N-Diisopropylcarboxamide)-estr-3,5-diene-3-phosphinic acid;
- 17 β -(N,N-Diisopropylcarboxamide)-androst-3,5-11-triene-3-phosphinic acid.
- 25 20 α -(hydroxymethyl)-5 α -pregn-3-ene-3-carboxylic acid;
- N,N-diisopropyl-5 α -androst-3-ene-17 β -carboxamide-3 carboxylic acid;
- N,N-diisopropyl-androst-3,5-diene 17 β -carboxamide-3-carboxylic acid;
- 30 17 β -(N,N-diisopropylcarboxamide)-4-fluoro-5 α -androst-3-ene-3-carboxylic acid;

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 45 -

- 20 α -(hydroxymethyl)-4-fluoro-5 α -pregn-3-ene-3-carboxylic acid;
- 20 α -(hydroxymethyl)-A-nor-5 α -pregn-1-ene-2-carboxylic acid;
- 5 17 β -N,N-diisopropylcarboxamide-5 α -androst-1,3-diene-3-carboxylic acid;
- N-t-Butyl Androst-3,5-diene-17 β -carboxamide-3-carboxylic acid;
- 10 N,N-Diisopropyl-5 α -Androst-2-ene-17- β -carboxamide-3-carboxylic acid;
- N,N-Diisopropyl Androst-2,4,-diene-17 β -carboxamide-3-carboxylic acid;
- N,N-Diisopropyl 5 α -Androstane-17 β -carboxamide carboxylic acid;
- 15 N,N-Diisopropyl Estr-3,5(10)-diene-17 β -carboxamide-3-carboxylic acid;
- N,N,-Diisopropyl Estr-3,5-diene-17 β -carboxamide-3-carboxylic acid;
- 20 20 α (hydroxymethyl)-5 α -pregn-3-ene-carboxylic acid
- N,N-diisopropyl-5 α -androst-3-ene-17 β -carboxamide-3-carboxylic acid;
- N,N-diisopropyl-androst-3,5-diene-17 β -carboxamide-3-carboxylic acid;
- 25 17 β -(N,N-diisopropylcarboxamide)-4-fluoro-5 α -androst-3-ene-3-carboxylic acid;
- 17 β -(N,N-Diisopropylcarboxamide)-androst-3,5,11-triene-3-carboxylic acid;
- 17 β -(N,N-Diisopropylcarboxamide)-androst-3,5-diene-3-thiocarboxylic acid;
- 30 17 β -(N-t-Butylcarboxamide)-androst-3,5,11-triene-3-carboxylic acid;

This Sheet Has Been Replaced



- 46 -

- 17 β -(N-t-Butylcarboxamide)-androst-3,5-diene-3-thiocarboxylic acid,
N-t-butyl-androst-3,5-diene-17 β -carboxamide-3-carboxylic acid,
5 N,N-diisopropyl-androst-3,5-diene-17 β -carboxamide-3-carboxylic acid,
20- α -(hydroxymethyl)-3- α -pregn-3-ene-3-carboxylic acid,
20- α -(hydroxymethyl)-4-fluoro-5- α -pregn-3-ene-3-carboxylic acid,
10 3-carbomethoxy-N,N-diisopropyl-androst-3, 5-diene-17 β -carboxamide,
17 β -N,N-diisopropylcarboxamide-5- α -androst-1,3-diene-3-carboxylic acid,
15 N,N-Diisopropyl 5- α -androst-2-ene-17 β -carboxamide-3-carboxylic acid,
N,N-diisopropyl androst-2-4-diene-17 β -carboxamide-3-carboxylic acid,
N,N-diisopropyl 5- α -androstane-17 β -carboxamide-3 β -carboxylic acid,
20 N,N-diisopropyl estr-3,5(10)-diene-17 β -carboxamide-3-carboxylic acid,
N,N-diisopropyl estr-3,5-diene-17 β -carboxamide-3-carboxylic acid,
25 N-t-butyl-androst-3,5-diene-17 β -carboxamide-3-carboxylic acid,
N,N-diisopropyl-androst-3,5-diene-17 β -carboxamide-3-carboxylic acid,
20- α -(hydroxymethyl)4-fluoro-5- α -pregn-3-ene-3-carboxylic acid,
30 N,N-diisopropyl-5- α -androst-3-ene-17 β -carboxamide-3-carboxylic acid,

This Sheet Has Been Replaced

SUBSTITUTE SHEET

- 47 -

- 17 β -(N,N-diisopropylcarboxamide)-4-fluoro-5- α -androst-3-ene-3-carboxylic acid,
17 β -(N,N-diisopropylcarboxamide)-4-flouro-androst-3,5-diene-3-carboxylic acid,
5 3-carbomethoxy-N,N-diisopropyl-androst-3,5-diene-17 β -carboxamide,
17 β -N,N-diisopropylcarboxamide-5- α -androst-1,3-diene-3-carboxylic acid,
N,N-Diisopropyl-5- α -androst-2-ene-17 β -carboxamide-3-carboxylic acid.
10 N,N-diisopropyl androst-2,4-diene-17 β -carboxamide-3-carboxylic acid,
N,N-diisopropyl 5- α -androstane-17 β -carboxamide-3 β -carboxylic acid,
15 N,N-diisopropyl estr-3,5(10)-diene-17 β -carboxamide-3-carboxylic acid,
N,N-diisopropyl estr-3,5-diene-17 β -carboxamide-3-carboxylic acid,
17 β -(N-t-butylcarboxamide)-androst-3,5-11-triene-3-carboxylic acid,
20 17 β -(N-t-butylcarboxamide)-androst-3,5-diene-3-thiocarboxylic acid,
N-t-Butyl-5- α -androst-3-ene-17 β -carboxamide-3-carboxylic acid,
25 17 β -(N-t-Butylcarboxamide)-6-fluoro-5- α -androst-3-ene-3-carboxylic acid,
17 β -(N-t-Butylcarboxamide)-6-fluoro-androst-3,5-diene-3-carboxylic acid,

30

This Sheet Has Been Replaced

- 48 -

- 3-Carbomethoxy-N-t-butyl-androst-3,5-diene-17B-carboxamide,
17B-N-t-Butylcarboxamide-5- α -androst-1,3-diene-3-carboxylic acid
5 N-t-Butyl-5- α -androst-2-ene-17B-carboxamide-3-carboxylic acid
N-t-Butyl-androst-2,4-diene-17B-carboxamide-3-carboxylic acid,
N-t-Butyl-5- α -androstane-17B-carboxamide-3-carboxylic acid, and
10 20- α -(hydroxymethyl)-A-nor-5- α -pregn-1-ene-2-carboxylic acid,
17B-(N-t-butylcarboxamide)-androst-3,5,11-triene-3-carboxylic acid,
15 17B-(N-t-butylcarboxamide)-androst-3,5-diene-3-thiocarboxylic acid,
N-t-Butyl-5- α -androst-3-ene-17B-carboxamide-3-carboxylic acid,
17B-(N-t-Butylcarboxamide)-6-fluoro-5- α -androst-3-ene-3-carboxylic acid
20 17B-(N-t-Butylcarboxamide)-6-fluoro-androst-3,5-diene-3-carboxylic acid,
3-Carbomethoxy-N-t-butyl-androst-3,5-diene-17B-carboxamide,
25 17B-N-t-Butylcarboxamide-5- α -androst-1,3-diene-3-carboxylic acid,
N-t-Butyl-5- α -androst-2-ene-17B-carboxamide-3-carboxylic acid,

30

This Sheet Has Been Replaced



- 49 -

- N-t-Butyl-androst-2,4-diene-17 β -carboxamide-3-carboxylic acid,
N-t-Butyl-5- α -androstane-17 β -carboxamide-3-carboxylic acid,
5 N-t-Butyl-estr-3,5(10)-diene-17 β -carboxamide-3-carboxylic acid,
N-t-Butyl-estr-3,5-diene-17 β -carboxamide-3-carboxylic acid,
N-t-Butyl-estr-3,5(10)-diene-17 β -carboxamide
10 acid-3-carboxylic acid,
N-t-Butyl-estr-3,5-diene-17 β -carboxamide-3-carboxylic acid,
20- α -(t-butyldimethylsilyloxymethyl)-3-(trifluoromethylsulfonate)-5- α -pregn-3-ene,
15 17 β -(t-butyldimethylsilyloxymethyl)-3-(trifluoromethylsulfonate)-5- α -androst-3-ene,
17 β -(N,N-diisopropylcarboxamide)-3-(trifluoromethylsulfonate)-androst-3,5-diene,
17 β -(N,N-diisopropylcarboxamide)-3-(trifluoromethylsulfonate)-4-fluoro-5- α -androst-1,3-diene,
20 20- α -(t-butyldimethylsilyloxymethyl)-4-fluoro-3-(trifluoromethylsulfonate)-5- α -pregn-1,3-diene,
17 β -(N,N-diisopropylcarboxamide)-3-(trifluoromethylsulfonate)-5- α -androst-1,3 diene,
25 17 β -(N-t-butylcarboxamide)-3-(trifluoromethylsulfonate)-androst-3,5-diene,
17 β -(N,N-diisopropylcarboxamide)-3-(trifluoromethylsulfonate)-5- α -androst-2-ene,
17 β -(N,N-diisopropylcarboxamide)-3-(trifluoromethylsulfonate)-androst-2,4-diene,
30 N-t-butyl-androst-3,5-diene-3-bromo-17 β -carboxamide, and

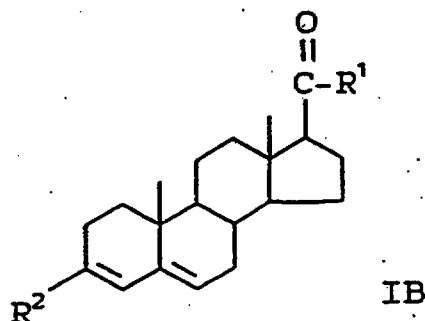
This Sheet Has Been Replaced



- 50 -

N,N-diisopropyl-androst-3,5-diene-3-bromo-
17 β -carboxamide.

Also provided are 17 β -acyl 3-carboxy-androst-3,5-
diene of the formula:



- wherein R¹ is (a) C₁-C₆ linear or branched alkyl;
C₃-C₁₂ cycloalkyl, which can be
substituted with C₁-C₄ alkoxy
or C₁-C₄ linear/branched alkyl;
C₆-C₁₂ aryl, or C₇-C₁₃ aralkyl
which can be substituted with one
or more of: -OH, -OC₁-C₄ alkyl,
C₁-C₄ alkyl, -(CH₂)_mOH, -(CH₂)_n
COOH, including protected -OH,
where m is 1-4, n is 1-3;
- (b) C₁-C₆ linear or branched alkyl;
C₃-C₁₂ cycloalkyl, which can be
substituted with C₁-C₄ alkoxy
or C₁-C₄ linear/branched alkyl;
C₆-C₁₂ aryl, or C₇-C₁₃ aralkyl

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 51 -

5

which can be substituted with one or more of: -OH, -OC₁-C₄ alkyl, C₁-C₄ alkyl, -(CH₂)_mOH, -(CH₂)_nCOOH, including protected -OH, where m is 1-4, n is 1-3, and R² is selected from COOH, SO₃H, PO(OH)₂, PH(O)OH.

10

Specifically provided is wherein R¹ is t-butyl, cycloalkyl, phenyl, p-hydroxyphenyl, 1-adamantyl, 2-adamantyl, NH-t-butyl, NH-isobutyl, NH-cyclohexyl, NH-phenyl, NH-p-hydroxy-phenyl, NH-1-adaxmantyl, NH-2-adamantyl, and R² is COOH,

15

Representative compounds include:

- 17B(4-hydroxyphenylcarbonyl)-androsta-3,5-diene-3-carboxylic acid;
17B-benzoyl-androsta-3,5-diene-3-carboxylic acid;
20 17B-cyclohexylcarbonyl-androsta-3,5-diene-3-carboxylic acid;
17B-isobutylcarbonyl-androsta-3,5-diene-3-carboxylic acid;
17B-(4-hydroxymethylphenylcarbonyl)-androsta-3,5-
25 diene-3-carboxylic acid;
17B-(2-hydroxyethylphenylcarbonyl)-androsta-3,5-diene-3-carboxylic acid;
17B-(4-methoxyphenylcarbonyl)-androsta-3,5-diene-3-carboxylic acid;
30 17B-(4-carboxymethylphenylcarbonyl)-androsta-3,5-diene-3-carboxylic acid;

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 52 -

N-t-butyl-androst-3,5-diene-17 β -carboxamide-3-carboxylic acid;

N-phenyl androst-3,5-diene-17 β -carboxamide-3-carboxylic acid;

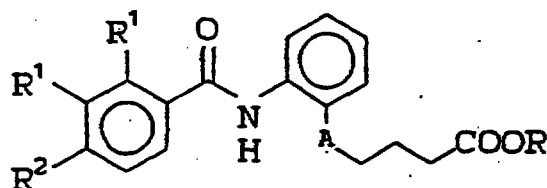
5 N-1-adamantyl androst-3,5-diene-17 β -carboxamide 3-carboxylic acid;

N-2-adamantyl androst-3,5-diene-17 β -carboxamide 3-carboxylic acid;

10 Also included and known in the art are non-steroidal 5 α -reductase inhibitors as developed by ONO Pharmaceutical Co., LTD., Osaka, Japan and as described in US patents 4,780,469; 4,847,275; 4,939,141 and EPO Publication Nos. 0 173 516 and EPO
15 0 291 245, and USP 4,980,372; and EPO Publn. 291,247 and USP 5,037,852 disclosing certain novel fused benz(thio)amides and benzylaminophenylbutanoic derivatives, respectively.

20 The benzoylaminophenoxy butanoic acid derivatives are of the formula:

25



30

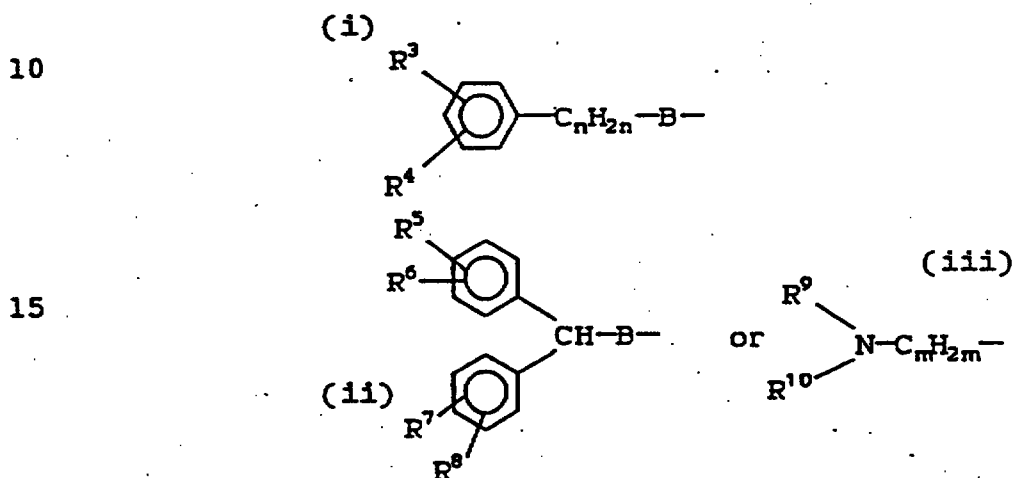
This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 53 -

wherein R' is hydrogen or alkyl of from 1 to 4 carbon atom(s); A is oxygen atom, sulfur atom or sulfinyl (SO) group; both R¹'s are methyl or chlorine, or the two R¹'s and the carbon atoms of the benzene ring to which the two R¹'s are linked together are cyclopentane, cyclohexane or a benzene ring; and R² represents a group of formula:



wherein B is oxygen, sulfur or a group of formula: NR¹¹ wherein R¹¹ is hydrogen or alkyl of from 1 to 4 carbon atom(s),

R³, R⁴, R⁵, R⁶, R⁷, and R⁸ are, independently, hydrogen, alkyl of from 1 to 4 carbon atom(s), halogen, trifluoromethyl or cyclobutylmethyl,

m is 0 or 1,

n is an integer of from 1 to 5, and

R⁹ is a hydrogen, alkyl of from 1 to 5 carbon atom(s) or a group of formula:

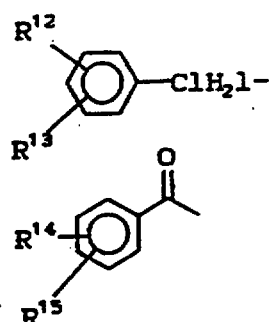
This Sheet Has Been Replaced



SUBSTITUTE SHEET

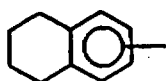
- 54 -

5



10

or



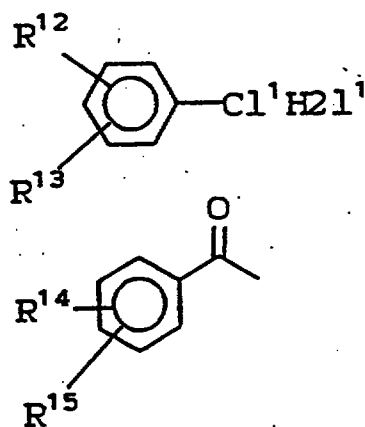
15

wherein R^{12} , R^{13} , R^{14} , and R^{15} are,
independently, hydrogen, alkyl of from 1 to
4 carbon atom(s), halogen, trifluoromethyl
or cyclobutylmethyl, and l is an integer of
from 1 to 4, and

20

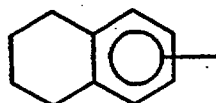
R^{10} is a group of formula:

25



30

or



This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 55 -

wherein R¹², R¹³, R¹⁴, and R¹⁵ are,
independently, hydrogen, alkyl of from 1 to
4 carbon atom(s), halogen, trifluoromethyl
or cyclobutylmethyl, and 1' is an integer of
from 1 to 4; or non-toxic salts thereof.

Representative examples of each of these two
classes of compounds whose synthesis and properties
are disclosed in the above cited US issued patents
include the following:

- 4-[2-(4-benzyloxy-2,3-dimethylbenzoylamino)phenoxy]
butanoic acid;
- 4-[2-[4-(2-methylbenzyloxy)-2,3-dimethylbenzoylamino]
butanoic acid;
- 4-[2-[4-(3-methylbenzyloxy)-2,3-dimethylbenzoylamino]
phenoxy]butanoic acid;
- 4-[2-[(4-methylbenzyloxy)-2,3-dimethylbenzoylamino]
phenoxy]butanoic acid;
- 4-[2-[4-(2,6-dimethylbenzyloxy)-2,3-dimethylbenzoyl-
amino]phenoxy]butanoic acid;
- 4-[2-[4-(4-ethylbenzyloxy)-2,3-dimethylbenzoylamino]
phenoxy]butanoic acid;
- 4-[2-[4-(4-propylbenzyloxy)-2,3-dimethylbenzoylamino]
phenoxy]butanoic acid;
- 4-[2-[4-(4-isopropylbenzyloxy)-2,3-dimethylbenzoyl-
amino]phenoxy]butanoic acid;
- 4-[2-[4-(4-isobutylbenzyloxy)-2,3-dimethylbenzoyl-
amino]phenoxy]butanoic acid;
- 4-[2-[4-(4-chlorobenzyloxy)-2,3-dimethylbenzoylamino]
phenoxy]butanoic acid;
- 4-[2-[4-(4-cyclobutylmethylbenzyloxy)-2,3-dimethyl-
benzoylamino]phenoxy]butanoic acid;

This Sheet Has Been Replaced



- 56 -

- 4-[2-[4-(2-phenylethoxy)-2,3-dimethylbenzoylamino]
phenoxy]butanoic acid;
- 4-[2-[4-(3-phenylpropoxy)-2,3-dimethylbenzoylamino]
phenoxy]butanoic acid;
- 5 4-[2-[4-(4-phenylbutoxy)-2,3-dimethylbenzoylamino]
phenoxy]butanoic acid;
- 4-[2-[4-(5-phenylpentyloxy)-2,3-dimethylbenzoylamino]
phenoxy]butanoic acid;
- 10 4-[2-[4-(1-(4-isobutylphenyl)ethoxy)-2,3-dimethyl-
benzoylamino]phenoxy]butanoic acid;
- 4-[2-[4-(4-propylbenzyloxy)-2,3-dimethylbenzoylamino]
phenylthio]butanoic acid;
- 4-[2-[1-(4-isobutylphenyl)ethoxy)-2,3-dimethylbenzoyl
amino]phenylthio]butanoic acid;
- 15 4-[2-[4-(4-propylbenzyloxy)-2,3-dimethylbenzoylamino]
phenylsulfinyl]butanoic acid;
- 4-[2-[4-[N-(4-trifluoromethylphenylmethyl)amino)-
2,3-dimethylbenzoylamino]phenoxy]butanoic acid;
- 4-[2-[4-(4-isobutylbenzyloxy)-5,6,7,8-tetrahydro
20 naphthalene-1-carbonylamino]phenoxy]butanoic acid;
- 4-[2-[4-(4-isobutylbenzyloxy)naphthalene-1-carbonyl-
amino]phenoxy]butanoic acid;
- 4-[2-[8-(4-isobutylbenzyloxy)-5,6,7,8-tetrahydro-
naphthalene-1-carbonylamino]phenylthio]butanoic
25 acid;
- 4-[2-[4-[bis(4-propylphenyl)methoxy]2,3-dimethyl-
benzoylamino]phenoxy]butanoic acid;
- 4-[2-(4-diphenylmethoxy)-2,3-dimethylbenzoylamino]
phenoxy]butanoic acid;
- 30 4-[2-[4-[bis(4-propylphenyl)methylamino]-2,3-
dimethylbenzoylamino]phenoxy]butanoic acid;
- 4-[2-[4-[bis-(4-propylphenyl)methylthio]-2,3-
dimethylbenzoylamino]phenoxy]butanoic acid;

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 57 -

- 4-[2-[4-[N,N-bis(4-propylphenylmethyl)amino]-2,3-dimethylbenzoylamino]phenoxy]butanoic acid;
4-[2-[4-[N,N-bis(4-trifluoromethylphenylmethyl)amino]-2,3-dimethylbenzoylamino]phenoxy]butanoic acid;
5 4-[2-[4-N-methyl-N-(5,6,7,8-tetrahydronaphth-1-yl)aminomethyl]-2,3-dimethylbenzoylamino]phenoxy]-butanoic acid;
8-(p-pentylbenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
10 8-(p-pentylbenzoyl)amino-2-(5-tetrazolyl)-6 chloro-1,4-benzodioxane;
8-(m-octylbenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
8-(o-pentylbenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
15 8-(p-butylbenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
8-(p-hexylbenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
20 8-(p-heptylbenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
8-(p-octylbenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
8-(p-nonylbenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
25 8-(p-decylbenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
8-(p-undecylbenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
30 8-(p-dodecylbenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
8-(p-pentyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 58 -

- 8-(m-pentyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
8-(o-pentyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
5 8-(p-butyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
8-(p-nonyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
8-(p-propoxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
10 8-(p-hexyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
8-(p-heptyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
15 8-(p-octyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
8-(o-decyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
8-(p-isopentyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
20 8-(p-isoheptyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
8-[p-(1-methylbutoxy)benzoyl]amino-2-(5-tetrazolyl)-1,4-benzodioxane;
25 8-(N-methyl-N-(p-octynyloxy)benzoyl)]amino-2-(5-tetrazolyl)-1,4-benzodioxane;
8-(p-oxtyloxybenzoyl)amino-1,4-benzodioxane-2-carboxylic acid and methyl ester thereof;
8-(p-isoheptyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
30 8-(p-isooctyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;

This Sheet Has Been Replaced**SUBSTITUTE SHEET**

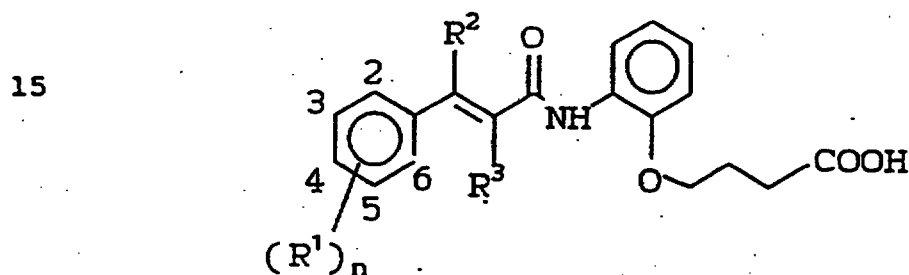
- 59 -

8-[p-(3,7-dimethyloctyloxy)benzoyl]amino-2-(5-tetrazolyl)-1,4-benzodioxane;

8-(p-octyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;

5 8-(p-heptyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane-7-carboxylic acid and methyl ester thereof, and the like.

Also included as a 5 α -reductase inhibitor
10 in this invention is a cinnamoylamide of the following formula:



wherein R² and R³ each independently represents a
25 hydrogen or methyl group with the proviso that
(i) when R² represents a methyl group, R³ represents hydrogen and (R¹)_n represents a member selected from the group consisting of 3-group, 4-pentyl group, 4-neopentyl group, 4-(2-ethylbutyl) group and
30 4-(2-methylpentyl) group, or

(ii) when R² represents hydrogen, R³ represents a methyl group and (R¹)_n represents a 3-pentyl group, or non-toxic salts thereof.

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 60 -

Representative compounds include:

- 4-[2-(4-butylthio- β -methylcinnamoylamino)phenoxy]
butanoic acid
- 5 4-[2-(4-cyclobutylmethyl)- β -methylcinnamoylamino)
phenoxy]butanoic acid
- 4-[2-(4-cyclohexylmethyl)- β -methylcinnamoylamino)
phenoxy]butanoic acid
- 10 4-[2-(4-{4-phenylbutyl}- β -methylcinnamoylamino)
phenoxy]butanoic acid
- 4-[2-(4-phenoxy- β -methylcinnamoylamino)phenoxy]
butanoic acid
- 4-[2-(3-pentyl- α -methylcinnamoylamino)phenoxy]
butanoic acid
- 15 4-[2-(4-phenethyl- α -methylcinnamoylamino)phenoxy]
butanoic acid
- 4-[2-(3-pentyl- β -methylcinnamoylamino)phenoxy]
butanoic acid
- 20 4-[2-(4-neopentyl)- β -methylcinnamoylamino)phenoxy]
butanoic acid
- 4-[2-{4-(2-ethylbutyl)- β -methylcinnamoylamino)phenoxy]
butanoic acid,
- 4-[2-{4-(2-methylpentyl)- β -methylcinnamoylamino)
phenoxy]butanoic acid, and
- 25 4-[2-(2-fluoro-4-pentyloxy- β -methylcinnamoylamino)
phenoxy]butanoic acid.

30

This Sheet Has Been Replaced

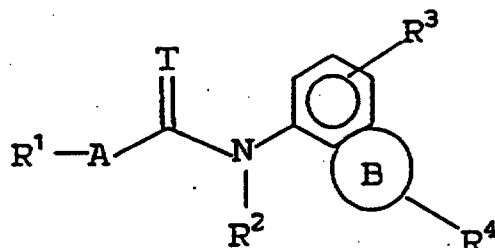
SUBSTITUTE SHEET

This Sheet Has Been Replaced



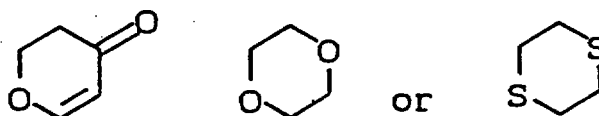
- 61 -

Also included in this invention are fused benz(thio) amides of the formula:



wherein A represents a single bond or a group of methylene, ethylene, trimethylene, tetramethylene, vinylene, propenylene, butenylene, butadienylene or ethynylene group optionally being substituted by one, two or three of straight or branched alkyl group(s) of from 1 to 10 carbon atom(s) and/or phenyl group(s);

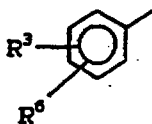
B represents a heterocyclic ring of from 4 to 8 members containing one, two or three hetero atom(s) selected from the group consisting of oxygen, nitrogen and sulphur atom(s), wherein the said ring may optionally be substituted by group(s) selected from oxo, thioxo and/or hydroxy group(s) including a ring of formula:



- 62 -

T represents an oxygen atom or a sulphur atom;
 R^1 represents a group of general formula:

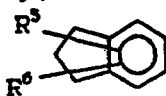
(i)



This Sheet Has Been Replaced



(iii)



or

(ii)



(iv) a straight or branched alkyl, alkenyl or alkynyl group of from 1 to 20 carbon atom(s), wherein R^5 and R^6 independently represent a hydrogen atom or a halogen atom or a straight or branched alkyl, alkenyl or alkynyl group of from 1 to 20 carbon atom(s) being unreplaced or replaced by one, two, three, four or five optional carbon atom(s), by oxygen atom(s), sulphur atom(s), halogen atom(s), nitrogen atom(s), benzene ring(s), thiophene ring(s), naphthalene ring(s), carbocyclic ring(s) of from 4 to 7 carbon atom(s), carbonyl group(s), carbonyloxy group(s), hydroxy group(s), carboxy group(s), azido group(s) and/or nitro group(s);

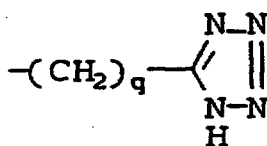
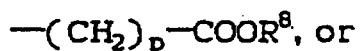
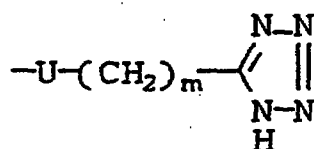
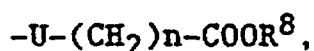
SUBSTITUTE SHEET

- 63 -

R^2 represents a hydrogen atom or a straight or branched alkyl group of from 1 to 6 carbon atom(s);

R^3 represents a hydrogen atom, a halogen atom, a hydroxy group, a nitro group, a group of general formula: $--COOR^7$, wherein R^7 represents a hydrogen atom or a straight or branched alkyl group of from 1 to 6 carbon atom(s), or a straight or branched alkyl, alkoxy or alkylthio group of from 1 to 6 carbon atom(s);

R^4 represents a group of general formula:



This Sheet Has Been Replaced



wherein U represents an oxygen atom or a sulphur atom, R^8 represents a hydrogen atom or a straight or branched alkyl group of from 1 to 6 carbon atom(s), n and m represent an integer of from 1 to 10, respectively, p and q represent zero or an integer of from 1 to 10, respectively, or non-toxic salts thereof.

SUBSTITUTE SHEET

- 64 -

Representative compounds include:

- 7-(p-hexyloxybenzoyl)amino-2-(5-tetrazolyl)benzofuran,
7-(p-octyloxybenzoyl)amino-2-(5-tetrazolyl)benzofuran,
5 7-(p-heptyloxybenzoyl)amino-2-(5-tetrazolyl)benzofuran,
7-(p-nonyloxybenzoyl)amino-2-(5-tetrazolyl)benzofuran,
7-[p-(4-phenylbutoxy)benzoyl]amino-2-(5-tetrazolyl)-
benzofuran,
10 7-[p-(2E,7-octadienyl)benzoyl]amino-2-(5-tetrazolyl)-
benzofuran,
7-[p-(6-chlorohexyloxy)benzoyl]amino-2-(5-tetrazolyl)-
benzofuran and
7-(p-pentylcinnamoyl)amino-2-(5-tetrazolyl)benzofuran,
15 7-(p-hexyloxybenzoyl)amino-2-(5-tetrazolyl)-2,3-dihydro-1-benzofuran,
7-(p-heptyloxybenzoyl)amino-2-(5-tetrazolyl)-2,3-dihydro-1-benzofuran,
7-(p-octyloxybenzoyl)amino-2-(5-tetrazolyl)-2,3-dihydro-1-benzofuran,
20 7-(p-nonyloxybenzoyl)amino-2-(5-tetrazolyl)-2,3-dihydro-1-benzofuran,
7-(p-pentylcinnamoyl)amino-2-(5-tetrazolyl)-2,3-dihydro-1-benzofuran,
25 8[p-2E,7-octadienyloxy)benzoyl]amino-2-(5-tetrazolyl)quinoline,
8-[p-(4-phenylbutoxy)benzoyl]amino-2-(5-tetrazolyl)-quinoline,
8-[p-(6-chlorohexyloxy)benzoyl]amino-2-(5-tetrazolyl)-quinoline,
30 8-[p-(2E,7-octadienyloxy)benzoyl]amino-4-hydroxyquinoline-2-carboxylic acid,

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 65 -

- 8-[p-(4-phenylbutoxy)benzoyl]amino-4-hydroxyquinoline-2-carboxylic acid,
8-[p-[4-(2-thienyl)butoxy]benzoyl]amino-4-hydroxyquinoline-2-carboxylic acid,
5 8-[p-(2E,7-octadienyloxy)benzoyl]amino-4-hydroxy-2-(tetrazolyl)quinoline,
8-[p-[4-(2-phenylbutoxy)benzoyl]amino-4-hydroxy-2-(5-tetrazolyl)quinoline and,
8-(p-pentylcinnamoyl)amino-4-hydroxy-2-(5-tetrazolyl)quinoline and,
10 4-(p-heptyloxybenzoyl)amino-2-(5-tetrazolyl)-1,3-benzodioxole,
4-(p-hexyloxybenzoyl)amino-2-(5-tetrazolyl)-1,3-benzodioxole,
15 4-[p-[4-(phenylbutoxy)benzoyl]amino-2-(5-tetrazolyl)-1,3-benzodioxole,
4-(p-pentylcinnamoyl)amino-2-(5-tetrazolyl)-1,3-benzodioxole,
9-[p-(4-phenylbutoxy)benzoyl]amino-2-(5-tetrazolyl)-3,4-dihydro-2H-1,5-benzodioxepin,
20 9-[p-(2E,7-octadienyloxy)benzoyl]amino-2-(5-tetrazolyl)-3,4-dihydro-2H-1,5-benzodioxepin,
9-[p-(7-octenyloxy)benzoyl]amino-2-(5-tetrazolyl)-3,4-dihydro-2H-1,5-benzodioxepin,
25 8-(p-heptyloxybenzoyl)amino-2-(5-tetrazolyl)-2,3-dihydro-1,4-benzoxazine,
8-[p-(4-phenylbutoxy)benzoyl]amino-2-(5-tetrazolyl)-2,3-dihydro-1,4-benzoxazine and
8-(p-pentylcinnamoyl)amino-2-(5-tetrazolyl)-2,3-dihydro-1,4-benzoxazine,
30 8-[p-(4-phenylbutoxy)benzoyl]amino-2-(5-tetrazolyl)-4-oxo-4H-1-benzothiopyran,

This Sheet Has Been Replaced



- 66 -

- 8-[p-(4-phenylbutoxy)benzoyl]amino-2-(5-tetrazolyl)-
3,4-dihydro-2H-1-benzopyran,
8-[p-(7-octenyloxy)benzoyl]amino-2-(5-tetrazolyl)-
3,4-dihydro-2H-1-benzopyran,
5 8-(p-pentylbenzoyl)amino-2-(5-tetrazolyl)-4-oxo-4H-
1-benzopyran,
8-(p-pentylbenzoyl)amino-4-oxo-4H-1-benzopyran-2-
carboxylic acid and ethyl ester thereof,
8-(p-hexylbenzoyl)amino-2-(5-tetrazolyl)-4-oxo-
10 4H-1-benzopyran,
8-(p-heptylbenzoyl)amino-2-(5-tetrazolyl)-4-oxo-
4H-1-benzopyran,
8-(p-octylbenzoyl)amino-2-(5-tetrazolyl)-4-oxo-
4H-1-benzopyran and
15 8-(p-nonylbenzoyl)amino-2-(5-tetrazolyl)-4-oxo-
4H-1-benzopyran
8-(p-butoxybenzoyl)amino-2-(5-tetrazolyl)-4-oxo-
4H-1-benzopyran,
8-(p-pentyloxybenzoyl)amino-2-(5-tetrazolyl)-4-oxo-
20 4H-1-benzopyran,
8-(p-hexyloxybenzoyl)amino-2-(5-tetrazolyl)-4-oxo-
4H-1-benzopyran,
8-(p-heptyloxybenzoyl)amino-2-(5-tetrazolyl)-4-oxo-
4H-1-benzopyran,
25 8-(p-nonyloxybenzoyl)amino-2-(5-tetrazolyl)-4-oxo-
4H-1-benzopyran,
8-(p-octyloxybenzoyl)amino-2-(5-tetrazolyl)-4-oxo-
4H-1-benzopyran,
8-(p-heptyloxybenzoyl)amino-2-(5-tetrazolyl)-6-fluoro-
30 4-oxo-4H-1-benzopyran,
8-(p-octyloxybenzoyl)amino-2-(5-tetrazolyl)-6-methyl-
4-oxo-4H-1-benzopyran and

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 67 -

- 8-(p-heptyloxybenzoyl)amino-2-(5-tetrazolyl)-6-methyl-4-oxo-4H-1-benzopyran and
8[p-(2E,7-octadienyloxy)benzoyl]amino-2-(5-tetrazolyl)-4-oxo-4H-1-benzopyran,
5 8-(p-geranyloxybenzoyl)amino-2-(5-tetrazolyl)-4-oxo-4H-1-benzopyran,
8[p-(2E-nonyloxy)benzoyl]amino-2-(5-tetrazolyl)-4-oxo-4H-1-benzopyran,
8[p-(2E-octenyloxy)benzoyl]amino-2-(5-tetrazolyl)-4-oxo-4H-1-benzopyran,
10 8[p-(7-octenyloxy)benzoyl]amino-2-(5-tetrazolyl)-4-oxo-4H-1-benzopyran,
8[p-(2E-heptenyloxy)benzoyl]amino-2-(5-tetrazolyl)-4-oxo-4H-1-benzopyran,
15 8[p-(2E-hexenyloxy)benzoyl]amino-2-(5-tetrazolyl)-4-oxo-4H-1-benzopyran,
8[p-(2E,7-octadienyloxy)benzoyl]amino-2-(5-tetrazolyl)-6-fluoro-4-oxo-4H-1-benzopyran,
8[p-(2E-octenyloxy)benzoyl]amino-2-(5-tetrazolyl)-6-methyl-4-oxo-4H-1-benzopyran,
20 8[p-(2E,7-octadienyloxy)benzoyl]amino-2-(5-tetrazolyl)-6-chloro-4-oxo-4H-1-benzopyran,
8[p-(2-octynyloxy)benzoyl]amino-2-(5-tetrazolyl)-4-oxo-4H-1-benzopyran, thereof
25 8[p-(4-chlorobutoxy)benzoyl]amino-2-(5-tetrazolyl)-4-oxo-4H-1-benzopyran,
8[p-(5-chloropentyloxy)benzoyl]amino-2-(5-tetrazolyl)-4-oxo-4H-1-benzopyran,
8[p-(6-chlorohexyloxy)benzoyl]amino-2-(5-tetrazolyl)-4-oxo-4H-1-benzopyran,
30 8[p-(6-chlorohexyloxy)benzoyl]amino-2-(5-tetrazolyl)-4-oxo-4H-1-benzopyran,

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 68 -

- 8[p-(7-chloroheptyloxy)benzoyl]amino-2-(5-tetrazolyl)-
4-oxo-4H-1-benzopyran,
- 8[p-(8-chlorooctyloxy)benzoyl]amino-2-(5-tetrazolyl)-
6-methyl-4-oxo-4H-1-benzopyran,
- 5 8[p-(7-chloroheptyloxy)benzoyl]amino-2-(5-tetrazolyl)-
6-methyl-4-oxo-4H-1-benzopyran and
- 8[p-(8-chlorooctyloxy)benzoyl]amino-2-(5-tetrazolyl)-
4-oxo-4H-1-benzopyran,
- 10 8[p-(3-phenylpropoxy)benzoyl]amino-2-(5-tetrazolyl)-
4-oxo-4H-1-benzopyran,
- 8[p-(3-phenyl-2E-propenyloxy)benzoyl]amino-2-(5-
tetrazolyl)-4-oxo-4H-1-benzopyran,
- 8[p-(4-phenylbutoxy)benzoyl]amino-2-(5-tetrazolyl)-
4-oxo-4H-1-benzopyran,
- 15 8[p-(4-phenylbutoxy)benzoyl]amino-2-(5-tetrazolyl)-
6-methyl-4-oxo-4H-1-benzopyran,
- 8[p-[2-(2-naphthyl)ethoxy]]benzoyl]amino-2-(5-
tetrazolyl)-4-oxo-4H-1-benzopyran,
- 8[p-[2-(2-naphthyl)ethoxy]]benzoyl]amino-2-(5-
20 tetrazolyl)-6-methyl-4-oxo-4H-1-benzopyran,
- 8[p-[3-(3,4-dichlorophenyl)propoxy]benzoyl]amino-2-(5-
tetrazolyl)-4-oxo-4H-1-benzopyran,
- 8[p-[3-(3,4-dichlorophenyl)propoxy]benzoyl]amino-2-(5-
tetrazolyl)-4-oxo-4H-1-benzopyran,
- 25 8[p-[3-(p-chlorophenyl)butoxy]benzoyl]amino-2-(5-
tetrazolyl)-4-oxo-4H-1-benzopyran,
- 8[p-[3-(p-chlorophenyl)butoxy]benzoyl]amino-6-
methyl-2-(5-tetrazolyl)-4-oxo-4H-1-benzopyran,
- 8[p-[3-(p-chlorophenyl)propoxy]benzoyl]amino-6-
30 methyl-2-(5-tetrazolyl)-4-oxo-4H-1-benzopyran,
- 8[p-[4-(2-thienyl)butoxy]benzoyl]amino-2-(5-
tetrazolyl)-4-oxo-4H-1-benzopyran,

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 69 -

- 8[p-[4-(2-thienyl)butoxy]benzoyl]amino-2-(5-tetrazolyl)-6-methyl-4-oxo-4H-1-benzopyran,
8-(p-pentylcinnamoyl)amino-4-oxo-4H-1-benzopyran-2-carboxylic acid and methyl ester thereof,
5 8-(p-pentylcinnamoyl)amino-2-(5-tetrazolyl)-4-oxo-4H-1-benzopyran,
8-(p-pentylcinnamoyl)amino-2-(5-tetrazolyl)-6-methyl-4-oxo-4H-1-benzopyran,
8-(p-pentylcinnamoyl)amino-2-(5-tetrazolyl)-6-fluoro-4-oxo-4H-1-benzopyran,
10 8-(p-pentylcinnamoyl)amino-6-methyl-4-oxo-4H-1-benzopyran-2-carboxylic acid and ethyl ester thereof,
8-(p-butylcinnamoyl)amino-2-(5-tetrazolyl)-4-oxo-4H-1-benzopyran,
15 8-(p-hexylcinnamoyl)amino-2-(5-tetrazolyl)-4-oxo-4H-1-benzopyran,
8-(p-heptylcinnamoyl)amino-2-(5-tetrazolyl)-4-oxo-4H-1-benzopyran,
20 8-cinnamoylamino-2-(5-tetrazolyl)-4-oxo-4H-1-benzopyran,
8-(p-hexyloxy-cinnamoyl)amino-2-(5-tetrazolyl)-4-oxo-4H-1-benzopyran,
8-(p-heptyloxy-cinnamoyl)amino-2-(5-tetrazolyl)-4-oxo-4H-1-benzopyran,
25 8-(p-isohexyloxy-cinnamoyl)amino-2-(5-tetrazolyl)-4-oxo-4H-1-benzopyran,
8[p-(2-octynyloxy)cinnamoyl]amino-4-oxo-4H-1-benzopyran-2-carboxylic acid,
30 8[p-(5-chloropentyloxy)cinnamoyl]amino-2-(5-tetrazolyl)-4-oxo-4H-1-benzopyran,
8[p-(6-chlorohexyloxy)cinnamoyl]amino-2-(5-tetrazolyl)-4-oxo-4H-1-benzopyran,

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 70 -

- 8-(p-pentylbenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
8-(p-pentylbenzoyl)amino-2-(5-tetrazolyl)-6 chloro-1,4-benzodioxane;
5 8-(m-octylbenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
8-(o-pentylbenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
8-(p-butylbenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
10 8-(p-hexylbenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
8-(p-heptylbenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
15 8-(p-octylbenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
8-(p-nonylbenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
8-(p-decylbenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
20 8-(p-undecylbenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
8-(p-dodecylbenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
25 8-(p-pentyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
8-(m-pentyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
8-(o-pentyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
30 8-(p-butyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 71 -

- 8-(p-nonyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 8-(p-propoxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 5 8-(p-hexyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 8-(p-heptyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 8-(p-octyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 10 8-(o-decyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 8-(p-isopentyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 15 8-(p-isohexyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 8-[p-(1-methylbutoxy)benzoyl]amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 8-(N-methyl-N-(p-octynyloxy)benzoyl)]amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 20 8-(p-octyloxybenzoyl)amino-1,4-benzodioxane-2-carboxylic acid and methyl ester thereof;
- 8-(p-isoheptyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 25 8-(p-isooctyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 8-[p-(3,7-dimethyloctyloxy)benzoyl]amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 8-(p-octyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane-7-carboxylic acid,
- 30 8-[p-(2E-octyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 72 -

- 8-[p-(3-butenyloxy)benzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,
8-[p-(3Z-hexenyloxy)benzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,
5 8-[p-(2Z-octenyloxy)benzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,
8-[p-(2E-nonyloxy)benzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,
8-[N-methyl-N-[p-(2E-octenyloxy)benzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,
10 8-[p-(2E-hexenyloxy)benzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,
8-[p-(3E-heptenyloxy)benzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,
15 8-[p-(2E-octenyloxy)benzoyl)amino-1,4-benzodioxane-2-carboxylic acid and methyl ester thereof,
8-[p-(2E-heptenyloxy)benzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,
8-[p-(4-pentenyloxy)benzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,
20 8-[p-(2E-decenyloxy)benzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,
8-(p-geranyloxy)benzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane-
25 8-[p-(2E,7-octadienyloxy)benzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,
8-[p-(2E-pentenyloxy)benzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,
8-[p-(2E-butenyloxy)benzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,
30 8-[p-(3E-octenyloxy)benzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,

This Sheet Has Been Replaced

SUBSTITUTE SHEET

- 73 -

- 8-[p-(7-octenyloxy)benzoyl]amino-2-(5-tetrazo-
lyl)-1,4-benzodioxane,
8-[p-(2E,4E-octadienyloxy)benzoyl]amino-2-(5-tetrazo-
lyl)-1,4-benzodioxane and
5 8-[p-(2E-octadienyloxy)benzoyl]amino-2-(5-tetrazo-
lyl)-1,4-benzodioxane,
8-[p-(2-octynyloxy)benzoyl]amino-2-(5-tetrazolyl)-
1,4-benzodioxane,
8-[p-(2-octynyloxy)benzoyl]amino-1,4-benzodioxane-2-
10 carboxylic acid and methyl ester thereof and
8-[p-(2-isooctynyloxy)benzoyl]amino-2-(5-tetrazolyl)-
1,4-benzodioxane
8-(p-pentylthiobenzoyl)amino-2-(5-tetrazolyl)-1,4-ben-
zodioxane,
15 8-(m-pentylthiobenzoyl)amino-2-(5-tetrazolyl)-1,4-ben-
zodioxane
8-(o-pentylthiobenzoyl)amino-2-(5-tetrazolyl)-1,4-ben-
zodioxane and
8-(p-heptylthiobenzoyl)amino-2-(5-tetrazolyl)-1,4-ben-
20 zodioxane
8-[p-(6-chlorohexyloxy)benzoyl]amino-2-(5-tetrazolyl)-
1,4-benzodioxane,
8-[p-(5-chloropentyloxy)benzoyl]amino-2-(5-tet-
razolyl)-1,4-benzodioxane,
25 8-[p-(4-chlorobutoxy)benzoyl]amino-2-(5-tetrazolyl)-
1,4-benzodioxane,
8-[p-(7-chloroheptyloxy)benzoyl]amino-2-(5-tetra-
zolyl)-1,4-benzodioxane,
8-[p-(8-chlorooctyloxy)benzoyl]amino-2-(5-tetra-
30 zolyl)-1,4-benzodioxane,
8-[p-(9-chlorononyloxy)benzoyl]amino-2-(5-tetra-
zolyl)-1,4-benzodioxane and

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 74 -

- 8-[p-(t-bromopentyloxy)benzoyl]amino-2-(5-tetra-
zoly1)-1,4,-benzodioxane-2-carboxylic acid and
methyl ester thereof
- 5 8-[p-hexyloxymethyl)benzoyl]amino-2-(5-tetra-
zoly1)-1,4-benzodioxane
- 8-[p-(cyclohexylmethoxy)benzoyl]amino-2-(5-tetra-
zoly1)-1,4-benzodioxane,
- 8-[p-(4-cyclohexylbutoxy)benzoyl]amino-2-(5-tetra-
zoly1)-1,4-benzodioxane, and
- 10 8-[p-(2-cyclohexylethoxy)benzoyl')amino-2-(5-tetra-
zoly1)-1,4-benzodioxane, and
- 8-[p-(p-butylphenyl)methoxybenoyl]amino-2-(5-tetra-
zoly1)-1,4-benzodioxane,
- 8-[p-(5-phenylpentyloxy)benzoyl]amino-2-(5-tetra-
15 zoly1)-1,4-benzodioxane,
- 8-[p-(3-phenylpropoxy)benzoyl')amino-2-(5-tetra-
zoly1)-1,4-benzodioxane,
- 8-[p-(p-propylphenyl)methoxybenzoyl]amino-2-(5-tetra-
zoly1)-1,4-benzodioxane,
- 20 8-[p-(3-phenyl-2-propenyloxy)benzoyl]amino-2-(5-tetra-
zoly1)-1,4-benzodioxane,
- 8-[p-(4-phenylbutoxy)benzoyl]amino-2-(5-tetrazoly1)-
1,4-benzodioxane,
- 8-[p-(o-pentylphenyl)methoxybenzoylamino-2-(5-tetra-
25 zoly1)-1,4-benzodioxane,
- 8-[p-(m-butylphenylmethoxybenzoyl]amino-2-(5-tetra-
zoly1)-1,4-benzodioxane,-
- 8-(p-phenylmethoxybenzoyl)amino-2-(5-tetrazoly1)-1,4-
benzodioxane,
- 30 8-[p-(2-phenylethoxy)benzoyl')amino-2-(5-tetrazoly1)
1,4-benzodioxane,
- 8-[p-4-phenylbutoxy)benzoyl]amino-2-(5-tetrazoly1)-
1,4-benzodioxane,

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 75 -

- 8-[p[-2-(2-naphthyl)ethoxy]benzoyl']amino-2-(5-tetra-
zoly1)-1,4-benzodioxane,
8-[p-[3-(p-chlorophenyl)propoxy]benzoyl]amino-2-(5-
tetrazoly1)-1,4-benzodioxane and
5 8-[p-[4-(p-chlorophenyl)butoxy]benzoyl]amino-2-(5-
tetrazoly1)-1,4-benzodioxane,
8-[p-(5-methoxycarbonylpentyloxy)benzoyl]amino-2-
(5-tetrazoly1)-1,4-benzodioxane,
8-[p-(6-acetyloxyhexyloxy)benzoyl]amino-2-(5-tetrazx-
10 oly1)-1,4-benzodioxane,
8-[p-(6-hydroxyhexyloxy)benzoyl]amino-2-(5-tetra-
zoly1)-1,4-benzodioxane,
8-[p-(2E-octenoyloxy)benzoyl]amino-2-(5-tetrazoly1)-
1,4-benzodioxane and
15 8-(p-octanoylbenzoyl)amino-2-(5-tetrazoly1)-1,4-ben-
zodioxane
8-[p-(3-phenylthiopropoxy)benzoyl]amino-2-(5-tetra-
zoly1)-1,4-benzodioxane,
8-[p-(3-phenoxypropoxy)benzoyl]amino-2-(5-tetrazoly1)-
20 1,4-benzodioxane,
8-[p-(2-phenylthioethoxy)benzoyl']amino-2-(5-tetra-
zoly1)-1,4-benzodioxane and
8-[p-(2-phenoxyethoxy)benzoyl']amino-2-(5-tetrazoly1)-
1,4-benzodioxane
25 8-[p-[2-(3-thienyl)ethoxy]benzoyl]amino-2-(5-tetra-
zoly1)-1,4-benzodioxane and
8-[p-[4-(2-thienyl)butoxy]benzoyl']amino-2-(5-tetra-
zoly1)-1,4-benzodioxane
8-[p-(5-azidopenyloxy)benozyl]amino-2-(5-tetrazoly1)-
30 1,4-benzodioxane,
8-[p-(5-dimethylaminopentyloxy)benzoyl]amino-2-(5-
tetrazoly1)-1,4-benzodioxane,

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 76 -

- 8-[p-(4-nitrobutoxy)benzoylamino-2-(5-tetrazolyl)-
1,4-benzodioxane,
8-[p-(2-azidoethoxy)benzoyl]amino-2-(5-tetrazolyl)-
1,4-benzodioxane,
5 8-[p-(4-azidobutoxy)benzoyl]amino-2-(5-tetrazolyl)-
1,4-benzodioxane,
8-[p-(2-octenoylamino)benzoyl']amino-2-(5-tetrazolyl)-
1,4-benzodioxane,
8-(p-pentyloxy-m-methoxybenzoyl)amino-2-(5-tetra-
10 zolyl)-1,4-benzodioxane,
8-[p-(2E-octenyloxy)-m-chlorobenzoyl]amino-2-(5-tetra-
zolyl)-1,4-benzodioxane
8-(2'-naphthylcarbonyl)amino-2-(5-tetrazolyl)-1,4-
benzodioxane,
15 8-(p-pentylcinnamoyl)amino-2-(5-tetrazolyl)-1,4-
benzodioxane,
8-(p-pentylcinnamoyl)amino-1,4-benzodioxane-2-
carboxylic acid and methyl ester thereof,
8-(p-heptylcinnamoyl)amino-2-(5-tetrazolyl)-1,4-
20 benzodioxane,
8-[N-methyl-[N-(pentylcinnamoyl)]amino]-2-(5-tetra-
zolyl)-1,4-benzodioxane,
5-(p-pentylcinnamoyl)amino-2-(5-tetrazolyl)-7-chloro-
1,4-benzodioxane,
25 8-(p-pentylcinnamoyl)amino-2-(5-tetrazolyl)-6-chloro-
1,4-benzodioxane,
8-(p-ethylcinnamoyl)amino-2-(5-tetrazolyl)-1,4-ben-
zodioxane,
8-(p-propylcinnamoyl)amino-2-(5-tetrazolyl)-1,4-ben-
30 zodioxane,
8-(p-butylcinnamoyl)amino-2-(5-tetrazolyl)-1,4-ben-
zodioxane,

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 77 -

- 8-(p-pentylcinnamoyl)amino-2-(5-tetrazolyl)-6-methyl-
1,4-benzodioxane,
8-(o-pentylcinnamoyl)amino-2-(5-tetrazolyl)-1,4-ben-
zodioxane,
5 8-(m-octylcinnamoyl)amino-2-(5-tetrazolyl)-1,4-ben-
zodioxane,
8-(p-pentylcinnamoyl)amino-2-(5-tetrazolyl)-1,4-ben-
zodioxane-5-carboxylic acid and methyl ester
thereof,
10 5-(p-pentylcinnamoyl)amino-2-(5-tetrazolyl)-1,4-ben-
zodioxane-8-carboxylic acid and methyl ester
thereof,
8-(p-hexylcinnamoyl)amino-2-(5-tetrazolyl)-1,4-ben-
zodioxane,
15 8-(p-nonylcinnamoyl)amino-2-(5-tetrazolyl)-1,4-ben-
zodioxane,
8-(p-pentylcinnamoyl)amino-2-(5-tetrazolyl)-1,4-ben-
zodioxane-6-carboxylic acid and methyl ester
thereof,
20 5-(p-pentylcinnamoyl)amino-2-(5-tetrazolyl)-1,4-ben-
zodioxane-7-carboxylic acid and methyl ester
thereof,
8-(p-octylcinnamoyl)amino-2-(5-tetrazolyl)-1,4-ben-
zodioxane,
25 8-(p-decylcinnamoyl)amino-2-(5-tetrazolyl)-1,4-ben-
zodioxane,
8-P-isopropylcinnamoyl)amino-2-(5-tetrazolyl)-1,4-
benzodioxane,
8-(p-isobutylcinnamoyl)amino-2-(5-tetrazolyl)-1,4-
benzodioxane,
30 8-(p-isopentylcinnamoyl)amino-2-(5-tetrazolyl)-1,4-
benzodioxane,

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 78 -

- 8-(p-pentyl-2-methylcinnamoyl)amino-2-(5-tetrazolyl)-
1,4-benzodioxane,
8-(p-pentyl-3-methylcinnamoyl)amino-2-(5-tetrazolyl)-
1,4-benzodioxane and
5 8-(p-pentylcinnamoyl)amino-2-(5-tetrazolyl)methyl-
1,4-benzodioxane
8-(p-pentyloxy-cinnamoyl)amino-2-(5-tetrazolyl)-1,4-
benzodioxane,
8-(m-pentyloxy-cinnamoyl)amino-2-(5-tetrazolyl)-1,4-
10 benzodioxane,
8-(o-pentyloxy-cinnamoyl)amino-2-(5-tetrazolyl)-1,4-
benzodioxane,
8-(p-propoxy-cinnamoyl)amino-2-(5-tetrazolyl)-1,4-
benzodioxane,
15 8-(p-butoxy-cinnamoyl)amino-2-(5-tetrazolyl)-1,4-
benzodioxane,
8-(p-octyloxy-cinnamoyl)amino-2-(5-tetrazolyl)-1,4-
benzodioxane,
8-(p-hexyloxy-cinnamoyl)amino-2-(5-tetrazolyl)-1,4-
20 benzodioxane,
8-(p-heptyloxy-cinnamoyl)amino-2-(5-tetrazolyl)-1,4-
benzodioxane,
8-(p-isopentyloxy-cinnamoyl)amino-2-(5-tetrazolyl)-1,4-
benzodioxane,
25 8-(p-isohexyloxy-cinnamoyl)amino-2-(5-tetrazolyl)-1,4-
benzodioxane,
8-[p-(1-methylbutoxy)cinnamoyl]amino-2-(5-tetrazolyl)-
1,4-benzodioxane,
8-(p-isoheptyloxy-cinnamoyl)amino-2-(5-tetrazolyl)-1,4-
30 benzodioxane,
8-(p-isooctyloxy-cinnamoyl)amino-2-(5-tetrazolyl)-1,4-
benzodioxane,

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 79 -

- 8-(p-isohexyloxy-2-methylcinnamoyl)amino-2-(5-tetra-
zoly1)-1,4-benzodioxane and
8-(p-isohexyloxy-2-phenylcinnamoyl)amino-2-(5-
tetrazoly1)-1,4-benzodioxane,
5 8-[p-(2E-octenyloxy)cinnamoyl]amino-2-(5-tetrazoly1)-
1,4-benzodioxane,
8-[p-(2-propenyloxy)cinnamoyl]amino-2-(5-tetrazoly1)-
1,4-benzodioxane,
8-[p-(3-butenyloxy)cinnamoyl]amino-2-(5-tetrazoly1)-
10 1,4-benzodioxane,
8-[p-(3Z-hexenyloxy)cinnamoyl]amino-2-(5-tetrazoly1)
1,4-benzodioxane,
8-[p-2Z-pentyloxy)cinnamoyl]amino-2-(5-tetrazoly1)-
1,4-benzodioxane,
15 8-[p-(2E-nonyloxy)cinnamoyl]amino-2-(5-tetrazoly1)-
1,4-benzodioxane,
8-[p-(3E-heptenyloxy)cinnamoyl]amino-2-(5-tetrazoly1)-
1,4-benzodioxane,
8-[p-(2E-heptenyloxy)cinnamoyl]amino-2-(5-tetrazoly1)-
20 1,4-benzodioxane,
8-[p-(2E-hexenyloxy)cinnamoyl]amino-2-(5-tetrazoly1)-
1,4-benzodioxane,
8-[p-(2E-pentyloxy)cinnamoyl]amino-2-(5-tetrazoly1)
1,4-benzodioxane,
25 8-[p-(4-pentyloxy)cinnamoyl]amino-2-(5-tetrazoly1)
1,4-benzodioxane,
8-[p-(2E-butenyloxy)cinnamoyl]amino-2-(5-tetrazoly1)-
1,4-benzodioxane and
8-[p-(2E-decenyloxy)cinnamoyl]amino-2-(5-tetrazoly1)-
30 1,4-benzodioxane
8-[p-(2-octynyloxy)cinnamoyl]amino-2-(5-tetrazoly1)-
1,4-benzodioxane and

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 80 -

- 8-[p-(2-pentynyloxy)cinnamoyl]amino-2-(5-tetrazolyl)-
1,4-benzodioxane,
8-(p-pentylthiocinnamoyl)amino-2-(5-tetrazolyl)-1,4-
benzodioxane,
5 8-(m-pentylthiocinnamoyl)amino-2-(5-tetrazolyl)-1,4-
benzodioxane and
8-(o-pentylthiocinnamoyl)amino-2-(5-tetrazolyl)-1,4-
benzodioxane,
8-[p-(6-chlorohexyloxy)cinnamoyl]amino-2-(5-tetra-
10 zolyl)1,4-benzodioxane,
8-[p-(4-chlorobutoxy)cinnamoyl]amino-2-(5-tetrazolyl)-
1,4-benzodioxane,
8-[p-(5-chloropentyloxy)cinnamoyl]amino-2-(5-tetra-
zolyl)-1,4-benzodioxane and
15 8-[p-(7-chloroheptyloxy)cinnamoyl']amino-2-(5-tetra-
zolyl)-1,4-benzodioxane
8-(p-isopentyloxymethyl-cinnamoyl)amino-2-(5-tetra-
zolyl)-1,4-benzodioxane,
8-(p-cyclohexylcinnamoyl)amino-2-(5-tetrazolyl)-1,4-
20 benzodioxane,
8-(p-cyclohexylmethoxycinnamoyl)amino-2-(5-tetra-
zolyl)-1,4-benzodioxane,
8-[p-(4-cyclohexylbutoxy)cinnamoyl']amino-2-(5-tetra-
zolyl)-1,4-benzodioxane and
25 8-[p-(2-cyclohexylethoxy)cinnamoyl]amino-2-(5-tetra-
zolyl)-1,4-benzodioxane,
8-(p-phenylmethylecinnamoyl)amino-2-(5-tetrazolyl)-
1,4-benzodioxane,
8-(p-phenylmethoxycinnamoyl)amino-2-(5-tetrazolyl)-
30 1,4-benzodioxane,
8-[p-(2-phenylethoxy)cinnamoyl]amino-2-(5-tetrazolyl)-
1,4-benzodioxane,

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 81 -

- 8-[p-(4-phenylbutoxy)cinnamoyl]amino-2-(5-tetrazolyl)-
1,4-benzodioxane,
8-[p-(5-phenylpentyloxy)cinnamoyl]amino-2-(5-tetra-
zolyl)-1,4-benzodioxane and
5 8-[p-(3-phenylpropoxy)cinnamoyl]amino-2-(5-tetra-
zolyl)-1,4-benzodioxane,
8-[p-(6-acetyloxyhexyloxy)cinnamoyl]amino-2-(5-tetra-
zolyl)-1,4-benzodioxane,
8-[p-[2-(2-thienyl)ethoxy]-cinnamoyl]-amino-2-(5-
10 tetrazolyl)-1,4-benzodioxane,
8-(m,p-dimethoxycinnamoyl)amino-2-(5-tetrazolyl)-1,4-
benzodioxane,
8-(m-methoxy-p-pentyloxycinnamoyl)amino-2-(5-tetra-
zolyl)-1,4-benzodioxane and
15 8-(p-pentyloxy-m-chlorocinnamoyl)amino-2-(5-tetra-
zolyl)-1,4-benzodioxane
8-[3-(5-indanyl)acryloyl]amino-2-(5-tetrazolyl)-1,4-
benzodioxane,
N-(2-hexadecenoyl)amino-2-(5-tetrazolyl)-1,4-
20 benzodioxane,
8-(p-pentylphenylacetyl)amino-2-(5-tetrazolyl)-1,4-
benzodioxane and
8-[3-(p-pentylphenyl)propionyl]amino-2-(5-tetrazolyl)-
1,4-benzodioxane
25 8-(p-hexylphenylpropioloyl)amino-2-(5-tetrazolyl)-1,4-
benzodioxane,
8-[5-(p-propoxyphenyl)penta-2E,4E-dienoyl]amino-2-
(5-tetrazolyl)-1,4-benzodioxane and
8-[5-(p-butylphenyl)penta-2E,4E-dienoyl]amino-2-(5-
30 tetrazolyl)-1,4-benzodioxane,
8-(p-pentylcinnamoyl)amino-2-(5-tetrazolyl)-2,3-di-
hydro-14-dithianaphthalene and

This Sheet Has Been Replaced

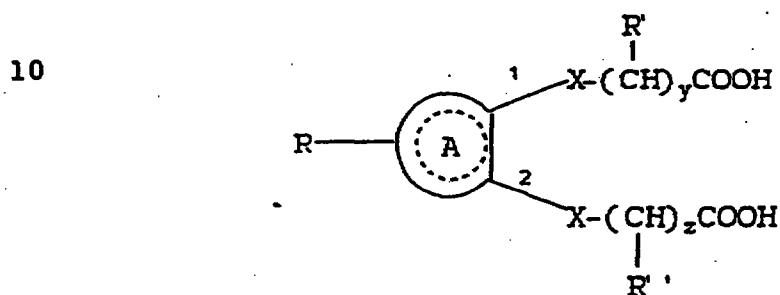


SUBSTITUTE SHEET

- 82 -

5-(p-pentylcinnamoyl)amino-2-(5-tetrazolyl)-2,3-dihydro-1,4-dithianaphthalene and sodium salts thereof.

Also included are aromatic 1,2-di(thio)ethers of the formula:



wherein

20 A is an 1,2-disubstituted aromatic ring; preferably a benzene ring;

wherein

X is independently O, S, SO, or SO₂;

25 R is H,

C₁-C₄ alkyl,

phenyl or substituted phenyl,

halo,

haloalkyl,

30 hydroxy,

carboxy,

cyano,

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 83 -

C₁-C₄ alkoxy,
C₁-C₄ alkylthio,
C₁-C₄ alkylsulfinyl,
C₁-C₄ alkylsulfonyl,
5 nitro,
amino,
C₁-C₄ mono or di-alkylamino;

R' and R'' are independently

10 H,
halo,
C₁-C₄ alkyl or C₁-C₄ alkoxy,
amino, or oxo, where CH-R' or CH-R''
in the formula become -C=O;

15 y is 1-6;

z is 6-20; and
wherein

20 R'
|
(CH)_y and
R''

(CH)_z can independently represent substituted
or unsubstituted alkyl radicals or alkenyl
25 radicals containing at least one alkene bond;
and pharmaceutically acceptable salts and esters
thereof.

The compounds of the instant invention are
inhibitors of the human testosterone-5 α -reductase
30 enzyme.

The scope of the compounds of the instant
invention are described by the above-described
formula.

This Sheet Has Been Replaced



- 84 -

In the description of the formula the following terms are used which are hereby defined:

5 X in the general formula above is O or S, preferably where one X is O, and particularly where both Xs are O, e.g., resulting in the catechol structure.

"C₁-C₄ alkyl" includes linear or branched species, e.g. methyl, ethyl, n-propyl, isopropyl, 10 cyclopropyl, n-butyl, isobutyl, sec-butyl, t-butyl.

"C₁-C₄ alkoxy" includes linear or branched species, e.g., methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, t-butoxy.

15 "Halo" includes fluoro, chloro, bromo or iodo.

"Substituted phenyl" includes phenyl substituted by one or more of C₁-C₄ alkyl, C₁-C₄ alkoxy, or halo, and the like, as defined above. representative examples include o, m-, p-methoxy 20 phenyl; 2,4-dimethoxyphenyl; 2-chloro-4-ethoxyphenyl; 3,5-dimethoxyphenyl; 2,4-dichlorophenyl; 2-bromo-4-methylphenyl, o-fluorophenyl, and the like.

25 "Haloalkyl" includes C₁-C₄ alkyl, defined above, substituted with one or more "halo" as defined above and includes: trifluoromethyl, 2,2-dichloroethyl and the like.

"C₁-C₄ alkylthio" includes C₁-C₄ alkyl, defined above, substituted with at least one 30 divalent thio (-S-) grouping including; methylthio, ethylthio, isopropylthio, n-butylthio, and the like.

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 85 -

"C₁-C₄ alkylsulfinyl" includes C₁-C₄ alkyl, defined above, substituted with at least one -SO- grouping including; methylsulfinyl, ethylsulfinyl; isopropylsulfinyl, and the like.

5 "C₁-C₄ alkylsulfonyl" includes C₁-C₄ alkyl, defined above, substituted with at least one sulfonyl group, -SO₂-, including; methylsulfonyl, ethylsulfonyl, isopropylsulfonyl, n-butylsulfonyl, and the like.

10 "C₁-C₄ mono or dialkyl amino" includes amino, substituted with one or more C₁-C₄ alkyl groups as defined hereinabove, including: methylamino, ethylamino, n-butylamino, t-butylamino, N,N-dimethylamino, N,N-diethylamino, methyl-t-butylamino, and the like.

15 The R group or groups on the benzene ring can be present initially in the process, such as in starting material I in Flow Chart A, e.g. phenyl, methyl, methoxy, cyano, trifluoromethyl, carbomethoxy, or added later by a conventional reaction, e.g. chloro, as by chlorination, nitro by nitration, or created from a starting or added functional group present, e.g. converting a nitro to an amino group by catalytic reduction, then alkylating to a mono or dialkylamine. An amino group can be subjected to diazotization to a hydroxy group, which can be followed by methylation to a methoxy group. Similarly, a hydroxy group can be converted to a thiol by the analogous procedures described in J. Org. Chem. 31, pp 3980-3984 (1966) by Newman and Karnes, and J. Org. Chem. 31, pp 410 (1966) by Kwart, H. and Evans, E.S. The resulting thiol can be alkylated to alkylthio, which can be oxidized to the

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 86 -

corresponding sulfoxide or sulfone. Preferred substituents are H, C₁-C₄ alkyl, C₁-C₄ alkoxy and phenyl. These reactions and sequences are conventional in the art and it will be obvious to one skilled in the art to modify the benzene ring to arrive at an R radical disclosed herein.

By the term "pharmaceutically acceptable salts and esters thereof" is meant, salts and esters of the acid groups in the final molecule which can be used as part of the human drug delivery system and include the salts: sodium, potassium, calcium, ammonium, substituted ammonium, quaternary ammonium, and esters: ethyl ester, acetate, besylate, edetate, phenpropionate, acetate, pamoate, and esters which serve as "prodrug" formulations which will hydrolyze in the body at physiological pH's to regenerate the acid, including pivaloylates, e.g. pivoxetil and pivoxil, and Kanebo esters, and the like.

20
$$\begin{array}{c} \text{R}' \\ | \\ (\text{CH})_y, \text{ where } y \text{ is } 1-6, \text{ preferably } 3, \text{ can} \\ \text{contain at least one R' substituent as defined above,} \\ \text{and can be, e.g., } -\text{CH}_2-; -\text{CH}_2-\text{CH}_2-; -\text{CH}_2-\text{CH}_2-\text{CH}_2-, \\ -\text{CH}-; -\text{CH}-\text{CH}_2-; -\text{CH}_2-\text{CH}-; -\text{CH}_2-\text{CH}-\text{CH}_2-; -\text{CH}_2-\text{CH}-\text{CH}_2-; \\ 25 \quad \text{CH}_3 \quad \text{CH}_3 \quad \text{Cl} \quad \text{OCH}_3 \quad \text{OCH}_2\text{CH}_3 \\ \text{and the like.} \end{array}$$

An alkene bond can also be present in R' $(\text{CH})_y-$, e.g., $\text{CH}_2-\text{CH}=\text{CH}-$; $\text{CH}_2-\text{CH}=\text{CH}-\text{CH}_2-$; $-\text{CH}_2-\text{CH}=\text{CH}-(\text{CH}_2)_2-$; and the like.

30
$$\begin{array}{c} \text{R}'' \\ | \\ (\text{CH})_z, \text{ where } z \text{ is } 6-20, \text{ preferably } 10-16, \text{ can} \\ \text{contain at least one R'' substituent as defined above,} \end{array}$$

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 87 -

and can be; e.g., $-(CH_2)_6-$, $-(CH_2)_{20}-$, $-(CH_2)_9-CH-$;
 CH_3
 $-CH_2-\underset{\substack{| \\ F}}{CH}-(CH_2)_9-$; $-(CH_2)_5-\underset{\substack{| \\ OCH_3}}{CH}-(CH_2)_4-$;

5 and the like.

An alkene bond can also be present in

$\overset{R''}{\underset{|}{(CH)}}_z$, e.g., $CH_2-CH=CH-(CH_2)_8-$; $-(CH_2)_8-CH=CH(CH_2)_2-$;
 10 $-(CH_2)_9-CH=CH-(CH_2)_9-$; $(CH_2)_4-CH=CH-(CH_2)_4-$; and the like.

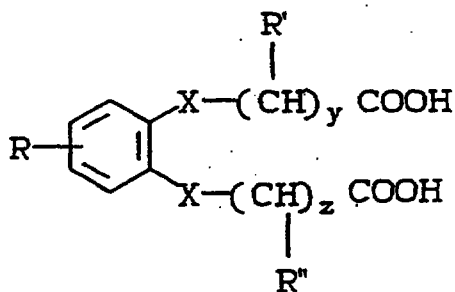
R' and R'' can also be $-NHC(O)CH_3$, which can be hydrolyzed to amino by conventional acid or base hydrolysis in the final molecule; R' and R'' can also
 15 be oxo, obtained by, for example, HBr addition to an alkene followed by conversion to an alcohol and subsequent oxidation to the ketone.

Preferred is where one R' or R'' is H and
 20 particularly preferred is where both $\overset{R'}{\underset{|}{(CH)}}_y$ and $\overset{R''}{\underset{|}{(CH)}}_z$ are alkyl.

Preferred compounds of the instant invention are given by the following formulas;

25

30



This Sheet Has Been Replaced



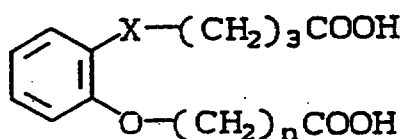
- 88 -

wherein

one X is O and R, R', R'', y and z are defined above;
and particularly preferred are the compounds,

5

10



15

wherein

20 X is O or S and n is 10-16.

The compounds of the instant invention can
be made by the procedure outlined in the following
Flowchart A-1.

25

30

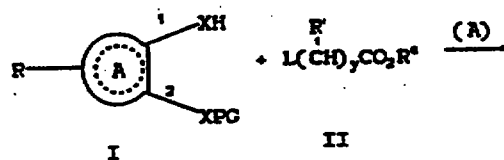
This Sheet Has Been Replaced



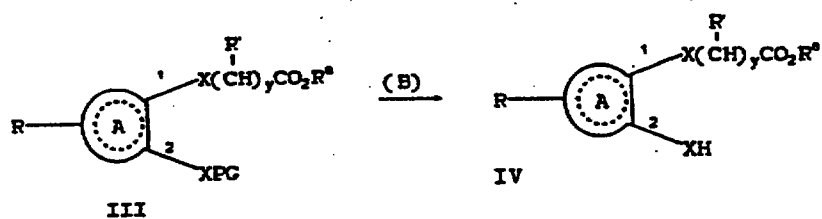
- 89 -

FLOW CHART A-1

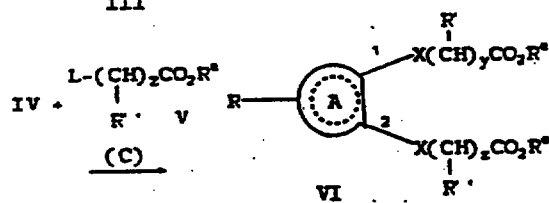
5



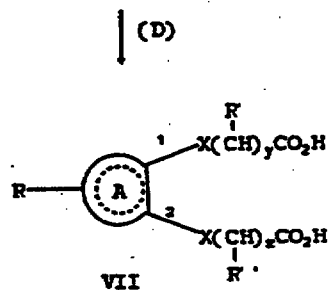
10



15



20



25

30

This Sheet Has Been Replaced



- 90 -

As seen in Flow Chart A-1, Compound I is the starting substrate in the invention process and is a 1,2-substituted benzene ring. X can be independently O or S and "PG" represents a hydroxy or thio protecting group which is inactive during Step (A) but can be subsequently removed by, e.g. palladium on carbon catalyst in ethanol under a pressurized H₂ atmosphere.

Examples of "PG" protecting groups which are conventional and known in the art (See "Protective Groups in Organic Synthesis" by Theodora W. Greene - 1981 - John Wiley - Chapter 2, "Protection for the Hydroxyl Group, Including 1,2- and 1,3-Diols" pp. 16-87 and Chapter 6 "Protection for the Thiol Group" pp. 193-218).

Representative examples of "PG" include: benzyl, p-methoxybenzyl, p-halobenzyl; including p-chlorobenzyl, p-fluorobenzyl, and the like. Other protective groups which are known will be obvious to one skilled in the art to carry out the function of Step (A).

Representative examples of compounds useful as I in the instant invention, include, but are not limited to the following:

2-(benzyloxy)-phenol,
2-benzyloxy-thiophenol,
2-(benzylthio)-phenol,
2-(benzylthio)thiophenol,
3-methoxy-2-benzyloxyphenol,
2-benzyloxy-4-methoxyphenol,
3-methyl-2-benzyloxyphenol,
2-benzyloxy-5-methylphenol,

This Sheet Has Been Replaced



- 91 -

- 2-benzyloxy-4-methylphenol,
2-benzyloxy-5-methylphenol,
2-benzyloxy-3,5-diisopropylphenol,
2-benzyloxy-3,5-di-t-butylphenol,
5 2-benzyloxy-4-t-butylphenol,
2-benzyloxy-3-ethylphenol,
2-benzyloxy-5-phenylphenol,
2-benzyloxy-4-methyl-1-thiophenol,
2-benzyloxy-5-trifluoromethyl-1-thiophenol,
10 2-benzyloxy-6-methoxy-1-thiophenol,
2-benzylthio-4-methyl-thiophenol,
2-benzylthio-5-methylsulfonyl-phenol, and the like.

- Representative examples of II useful in
15 the invention process where L is a leaving group,
e.g., halogen, including bromo, chloro, or sulfonate,
and the like, and R^a is a C₁-C₄ linear or branched
alkyl portion of the ester, including methyl, ethyl,
isopropyl, t-butyl, sec-butyl, and the like, and
20 where R¹ and Y are or defined above, include, but
are not limited to:

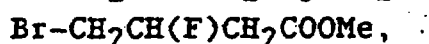
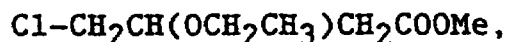
- Br-CH₂-COOMe,
Cl-CH₂CH₂CH₂COOCH₂CH₃,
25 Br-CH₂CH₂CH₂CH₂COOMe,
Br-CH₂CH₂CH₂CH₂CH₂COOEt,
Br-CH₂CH₂CH₂CH₂CH₂CH₂COOCH₂CH₂CH₂CH₃,
Br-(CH₂)₂CH(CH₃)COOMe,
Br-CH₂CH(CH₃)CH₂COOEt,
30 Br-CH₂CH₂CH₂COOMe,
Br-CH₂CH(OCH₃)CH₂COOCH(CH₃)₂.

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 92 -



and the like.

5

In Step (A) the condensation of I and II to produce III takes place in a non-hydroxylated polar organic solvent, e.g., acetone, ethyl acetate, methylethylketone, dioxan, THF, diethylketone, and
10 the like. A proton acceptor is also present, e.g. potassium carbonate, sodium bicarbonate, pyridine, triethylamine, and the like. Generally, the reaction is carried out under an inert atmosphere, e.g. dry nitrogen, and heated at reflux or allowed to sit
15 for an extended period of time at room temperature. Workup is conventional.

In Step (B) the protecting group, "PG", is catalytically removed at ambient temperature under a pressurized, hydrogen atmosphere in an
20 organic solvent to produce IV, being a phenol or thiophenol. Operable catalysts include 5% Pd/C, and the like. The organic solvent should be inert under the reaction conditions and includes ethyl acetate, ethanol, methanol, dioxane, and the like.

25 Step (C) involves reacting IV with V to produce VI, the diester. The reaction conditions are similar to those described in Step (A) utilizing an inert organic solvent for the reactants and a proton acceptor.

30 Representative examples of V useful in the invention are:

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 93 -

- $\text{Br}(\text{CH}_2)_6\text{COOMe},$
 $\text{Br}(\text{CH}_2)_7\text{COOMe},$
 $\text{Br}(\text{CH}_2)_8\text{COOMe},$
 $\text{Br}(\text{CH}_2)_9\text{COOMe},$
5 $\text{Br}(\text{CH}_2)_{10}\text{COOMe},$
 $\text{Br}(\text{CH}_2)_{11}\text{COOMe},$
 $\text{Cl}(\text{CH}_2)_{12}\text{COOEt},$
 $\text{Cl}(\text{CH}_2)_{13}\text{COOCH}(\text{CH}_3)_2,$
 $\text{Cl}(\text{CH}_2)_{14}\text{COOCH}_2\text{CH}_2\text{CH}_3,$
10 $\text{Br}-(\text{CH}_2)_{15}\text{COOMe}$
 $\text{Br}-(\text{CH}_2)_{16}\text{COOMe}$
 $\text{Br}(\text{CH}_2)_{16}\text{COOCH}_2\text{CH}_3,$
 $\text{Br}(\text{CH}_2)_{17}\text{COOC}(\text{CH}_3)_3,$
 $\text{Br}(\text{CH}_2)_{18}\text{COOMe},$
15 $\text{Br}(\text{CH}_2)_{19}\text{COOEt},$
 $\text{Br}(\text{CH}_2)_{20}\text{COOMe},$
 $\text{Br}(\text{CH}_2)_2\text{CH}(\text{CH}_3)-(\text{CH}_2)_{10}\text{COOMe},$
 $\text{Br}-\text{CH}_2\text{CH}(\text{CH}_3)(\text{CH}_2)_{10}\text{COOMe},$
 $\text{Br}-\text{CH}_2\text{CH}_3\text{CH}(\text{CH}_3)\text{CH}_2\text{COOEt},$
20 $\text{Br}-\text{CH}_2\text{CH}(\text{OCH}_3)(\text{CH}_2)_7\text{COOCH}(\text{CH}_3)_2,$
 $\text{Cl}-\text{CH}_2\text{CH}(\text{OCH}_2\text{CH}_3)\text{CH}_2\text{CH}_2\text{COOMe},$
 $\text{Br}-\text{CH}_2\text{CH}(\text{NHCOCCH}_3)-(\text{CH}_2)_{10}-\text{CH}_2-\text{COOMe},$
 $\text{Cl}-\text{CH}_2\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-(\text{CH}_2)_{11}-\text{COOEt},$
25 $\text{Br}-\text{CH}_2-\text{CH}=\text{CH}(\text{CH}_2)_8-\text{COOEt},$
 $\text{Br}-\text{CH}_2-\overset{\text{CH}_2}{\underset{\text{CH}_2}{\text{C}}}-(\text{CH}_2)_{10}\text{CH}_2\text{COOMe},$
 $\text{Br}-\text{CH}_2-(\text{CH}_2)_9-\text{CH}=\text{CH}-\text{COOMe},$
and the like.

- 30 In Step (D), the diester can be deesterified
by aqueous basic hydrolysis, e.g. NaOH in MeOH/H₂O
to yield the diacid VII upon acidification.

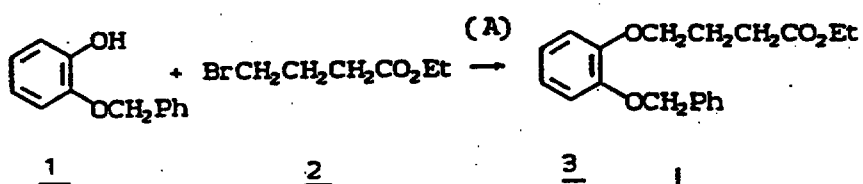
This Sheet Has Been Replaced



- 94 -

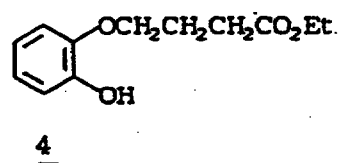
FLOW CHART B-1

5

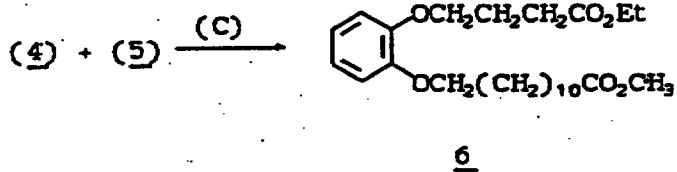


10

(B)

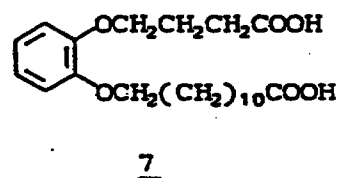


15



20

(D)



25

30

This Sheet Has Been Replaced

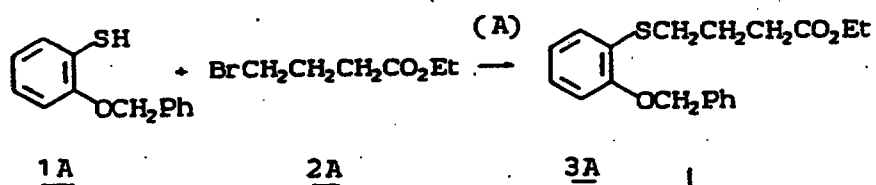


SUBSTITUTE SHEET

- 95 -

FLOW CHART C-1

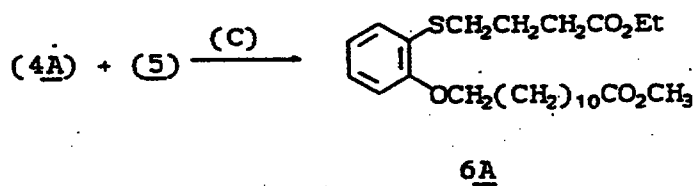
5



10



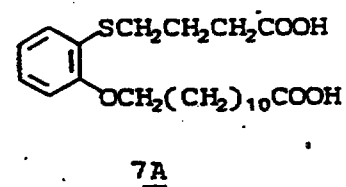
15



20



25



30

This Sheet Has Been Replaced



- 96 -

Flow Sheet B-1 illustrates the specific synthesis of 7.

As seen, 2-benzyloxyphenol 1, ethyl 4-bromo-butyrates 2 and anhydrous K_2CO_3 in e.g., dry acetone
5 are heated at reflux or stirred for an extended period of time at room temperature, under a nitrogen atmosphere to give product ethyl 4-(2-benzyloxy-phenoxy) butyrate 3, in Step (A).

A solution of 3 in e.g., ethyl acetate
10 is catalytically hydrogenated at room temperature under e.g. 40 psig of H_2 in the presence of a 5% Pd/C catalyst to yield ethyl 4-(2-hydroxyphenoxy) butyrate 4 in Step (B).

Step (C) comprises reacting 4 and methyl
15 12-bromododecanoate 5 with potassium carbonate in acetone as in Step (A) to obtain the monomethyl ester 6.

In Step (D), the diester 6 is de-esterified
by e.g., 2.5 N NaOH in MeOH/ H_2O to yield the final
20 product, diacid 7, upon acidification.

Flow Sheet C-1 illustrates the synthesis of the sulfur analog of 7 as 7A. This analogous procedure uses substantially the same steps as involved in Flow Sheet B.

It is also obvious from the above Flow
25 Sheets that suitable replacement compounds for II and 2 with other substituted and unsubstituted halo alkyl esters, known in the art and described herein, and that suitable replacement of V and 5 with other
30 bromoesters, available in the art and also described above will yield all of the compounds within the scope of the instant claims.

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 97 -

Representative examples of compounds produced by this process include:

- 4-(2-(20-Carboxyeicosyloxy)phenoxy)butyric acid;
5 4-(2-(19-Carboxynonadecyloxy)phenoxy)butyric acid;
4-(2-(18-Carboxyoctadecyloxy)phenoxy)butyric acid;
4-(2-(17-Carboxyheptadecyloxy)phenoxy)butyric acid;
4-(2-(16-Carboxyhexadecyloxy)phenoxy)butyric acid;
4-(2-(15-Carboxypentadecyloxy)phenoxy)butyric acid;
10 4-(2-(14-Carboxytetradecyloxy)phenoxy)butyric acid;
4-(2-(13-Carboxytridecyloxy)phenoxy)butyric acid;
4-(2-(12-Carboxydodecyloxy)phenoxy)butyric acid;
4-(2-(11-Carboxyundecyloxy)phenoxy)butyric acid;
4-(2-(10-Carboxydecyloxy)phenoxy)butyric acid;
15 4-(2-(9-Carboxynonyloxy)phenoxy)butyric acid;
4-(2-(8-Carboxyoctyloxy)phenoxy)butyric acid;
4-(2-(7-Carboxyheptyloxy)phenoxy)butyric acid;
4-(2-(6-Carboxyhexyloxy)phenoxy)butyric acid;
4-(2-(20-Carboxyeicosyloxy)phenylthio)butyric
20 acid;
4-(2-(19-Carboxynonadecyloxy)phenylthio)butyric
acid;
4-(2-(18-Carboxyoctadecyloxy)phenylthio)butyric
acid;
25 4-(2-(17-Carboxyheptadecyloxy)phenylthio)butyric
acid;
4-(2-(16-Carboxyhexadecyloxy)phenylthio)butyric
acid;
4-(2-(15-Carboxypentadecyloxy)phenylthio)butyric
30 acid;
4-(2-(14-Carboxytetradecyloxy)phenylthio)butyric
acid;
4-(2-(13-Carboxytridecyloxy)phenylthio)butyric
acid;

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 98 -

- 4-(2-(12-Carboxydodecyloxy)phenylthio)butyric acid;
4-(2-(11-Carboxyundecyloxy)phenylthio)butyric acid;
5 4-(2-(10-Carboxydecyloxy)phenylthio)butyric acid;
4-(2-(9-Carboxynonyloxy)phenylthio)butyric acid;
4-(2-(8-Carboxyoctyloxy)phenylthio)butyric acid;
4-(2-(7-Carboxyheptyloxy)phenylthio)butyric acid;
4-(2-(6-Carboxyhexyloxy)phenylthio)butyric acid;
10 4-(2-(20-Carboxyeicosylthio)phenoxy)butyric acid;
4-(2-(19-Carboxynonadecylthio)phenoxy)butyric acid;
4-(2-(18-Carboxyoctadecylthio)phenoxy)butyric acid;
4-(2-(17-Carboxyheptadecylthio)phenoxy)butyric acid;
4-(2-(16-Carboxyhexadecylthio)phenoxy)butyric acid;
15 4-(2-(15-Carboxypentadecylthio)phenoxy)butyric acid;
4-(2-(14-Carboxytetradecylthio)phenoxy)butyric acid;
4-(2-(13-Carboxytridecylthio)phenoxy)butyric acid;
4-(2-(12-Carboxydodecylthio)phenoxy)butyric acid;
4-(2-(11-Carboxyundecylthio)phenoxy)butyric acid;
20 4-(2-(10-Carboxydecylthio)phenoxy)butyric acid;
4-(2-(9-Carboxynonylthio)phenoxy)butyric acid;
4-(2-(8-Carboxyoctylthio)phenoxy)butyric acid;
4-(2-(7-Carboxyheptylthio)phenoxy)butyric acid;
4-(2-(6-Carboxyhexylthio)phenoxy)butyric acid;
25 4-(2-(20-Carboxyeicosylthio)phenylthio)butyric acid;
acid;
4-(2-(19-Carboxynonadecylthio)phenylthio)butyric acid;
acid;
4-(2-(18-Carboxyoctadecylthio)phenylthio)butyric acid;
30 acid;
4-(2-(17-Carboxyheptadecylthio)phenylthio)butyric acid;
acid;
4-(2-(16-Carboxyhexadecylthio)phenylthio)butyric acid;
acid;

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 99 -

- 4-(2-(15-Carboxypentadecylthio)phenylthio)butyric
acid;
4-(2-(14-Carboxytetradecylthio)phenylthio)butyric
acid;
5 4-(2-(13-Carboxytridecylthio)phenylthio)butyric
acid;
4-(2-(12-Carboxydodecylthio)phenylthio)butyric
acid;
4-(2-(11-Carboxyundecylthio)phenylthio)butyric
10 acid;
4-(2-(10-Carboxydecylthio)phenylthio)butyric acid;
4-(2-(9-Carboxynonylthio)phenylthio)butyric acid;
4-(2-(8-Carboxyoctylthio)phenylthio)butyric acid;
4-(2-(7-Carboxyheptylthio)phenylthio)butyric acid;
15 4-(2-(6-Carboxyhexylthio)phenylthio)butyric acid;
3-(2-(16-Carboxyhexadecyloxy)phenoxy)propionic acid;
3-(2-(15-Carboxyisohexadecyloxy)phenoxy)butyric acid;
3-(2-(14-Carboxytetradecyloxy)phenoxy)butyric acid;
5-(2-(13-Carboxytridecyloxy)phenoxy)valeric acid;
20 5-(2-(12-Carboxydodecyloxy)phenoxy)valeric acid;
5-(2-(11-Carboxyisododecyloxy)phenoxy)valeric acid;
4-(2-(11-Carboxyundecyloxy)phenoxy)valeric acid;
4-(2-(10-Carboxydecyloxy)phenoxy)valeric acid;
4-(2-(9-Carboxynonyloxy)phenoxy)valeric acid;
25 6-(2-(9-Carboxynonyloxy)phenoxy)caproic acid;
6-(2-(8-Carboxyoctyloxy)phenoxy)caproic acid;
6-(2-(7-Carboxyisooctyloxy)phenoxy)caproic acid;
7-(2-(7-Carboxyheptyloxy)phenoxy)enanthic acid;
7-(2-(6-Carboxyhexyloxy)phenoxy)enanthic acid;
30 7-(2-(5-Carboxyisohexyloxy)phenoxy)enanthic acid;
2-(2-(12-Carboxydodecylthio)phenoxy)acetic acid;

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 100 -

- 2-(2-(11-Carboxydecylthio)phenoxy)acetic acid;
2-(2-(10-Carboxydecylthio)phenoxy)acetic acid;
3-(2-(9-Carboxynonyloxy)phenylthio)propionic acid;
3-(2-(12-Carboxydodecyloxy)phenylthio)propionic
5 acid;
3-(2-(11-Carboxyundecyloxy)phenylthio)propionic
acid;
3-(2-(11-Carboxyundecyloxy)phenylthio)butyric acid;
3-(2-(11-Carboxyundecylthio)-4-methyl-phenylthio)
10 butyric acid;
3-(2-(12-Carboxydodecylthio)phenylthio)butyric
acid;
5-(2-(11-Carboxyundecylthio)phenylthio)valeric
acid;
15 5-(2-(10-Carboxydecyloxy)phenylthio)valeric acid;
5-(2-(9-Carboxynonyloxy)phenylthio)valeric acid;
3-(2-(12-Carboxydodecyloxy)phenylthio)valeric
acid;
3-(2-(11-Carboxydecyloxy)phenylthio)valeric acid;
20 3-(2-(10-Carboxydecyloxy)phenylthio)valeric
acid;
6-(2-(9-Carboxynonylthio)phenylthio)caproic acid;
6-(2-(12-Carboxydodecyloxy)phenylthio)caproic
acid;
25 6-(2-(11-Carboxyundecyloxy)phenylthio)caproic
acid;
6-(2-(11-Carboxyundecyloxy)-3-methylphenylthio)-
enanthic acid;
7-(2-(11-Carboxyundecyloxy)-4-methylphenylthio)-
30 enanthic acid;
7-(2-(12-Carboxydodecylthio)phenoxy)enanthic acid;

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 101 -

- 4-(2-(11-Carboxyundecyloxy)4-methyl-phenoxy)butyric
acid;
- 4-(2-(10-Carboxydecyloxy)3-methylphenoxy)butyric acid;
- 4-(2-(9-Carboxynonyloxy)5-methylphenoxy)butyric acid;
- 5 4-(2-(12-Carboxydodecyloxy)6-methylphenoxy)butyric
acid;
- 4-(2-(12-Carboxydodecyloxy)6-methylphenoxy)butyric
acid;
- 10 4-(2-(11-Carboxyundecylthio)-3-(methylthio)phenoxy)-
valeric acid;
- 4-(2-(11-Carboxyundecylthio)-3-(methylsulfonyl)
phenoxy)butyric acid;
- 4-(2-(11-Carboxyundecyloxy)-4-(methylsulfonyl)
phenoxy)butyric acid;
- 15 4-(2-(12-Carboxydodecyloxy)5-ethyl-phenoxy)butyric
acid;
- 4-(2-(11-Carboxyundecyloxy)4-phenylphenoxy)butyric
acid;
- 4-(2-(10-Carboxydecyloxy)-3,5-dimethylphenoxy)butyric
20 acid;
- 4-(2-(9-Carboxynonyloxy)-4-fluoro-phenoxy)butyric
acid;
- 4-(2-(12-Carboxydodecyloxy)-5-(trifluoromethyl)-
phenoxy)butyric acid;
- 25 4-(2-(12-Carboxydodecylthio)-5-nitrophenoxy)butyric
acid;
- 4-(2-(11-Carboxyundecylthio)-4-methylphenoxy)valeric
acid;
- 4-(2-(11-Carboxyundecylthio)-3,5-di-methylphenoxy)-
30 butyric acid;
- 4-(2-(12-Carboxydodecyloxy)-4-(dimethylamino)phenoxy)-
butyric acid;

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 102 -

- 4-(2-(11-Carboxyundecyloxy)-5-(ethylamino)phenoxy)-
butyric acid;
2-(2-(9-Carboxynonyloxy)phenoxy)propionic acid;
3-(2-(12-Carboxydodecyloxy)phenoxy)-3-methylpropionic
5 acid;
4-(2-(10-Carboxydecyloxy)phenylthio)-3-methoxy-
butyric acid;
4-(2-(9-Carboxynonyloxy)phenylthio)-3-ethoxy-
butyric acid;
10 4-(2-(11-Carboxyundecyloxy)phenoxy)but-2-enoic acid;
4-(2-(9-Carboxynonyloxy)phenoxy)-2-butenic acid;
4-(2-(11-Carboxy-2-methylundecyloxy)phenoxy)butyric
acid;
4-(2-(11-Carboxyundecyl-7-ene-oxy)phenoxy)butyric
15 acid;
4-(2-(13-Carboxy-2-methylene-tri-decyloxy)phenoxy)-
butyric acid;
4-(2-(11-Carboxyundecyloxy)phenylsulfonyl)butyric
acid;
20 4-(2-(11-Carboxyundecyloxy)phenylsulfinyl)butyric
acid;
4-(2-(11-Carboxyundecylsulfinyl)phenoxy)butyric acid;
4-(2-(11-Carboxyundecylsulfonyl)phenoxy)butyric acid;
4-(2-(11-Carboxyundecylsulfinyl)phenylsulfinyl)butyric
25 acid;
4-(2-(11-Carboxyundecylsulfonyl)phenylsulfonyl)butyric
acid;
and the like.

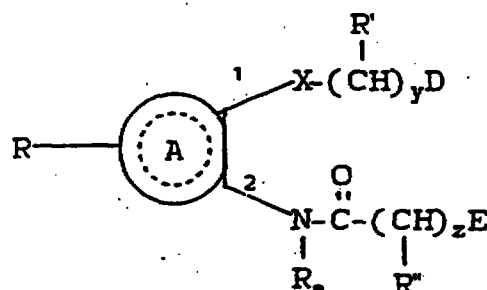
- 30 Also included as a 5 α -reductase inhibitor
in this invention is an agent for the treatment of
patterned baldness in combination with minoxidil is
of the following formula:

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 103 -



10 wherein

A is an 1,2-disubstituted aromatic ring selected from

- (a) benzene, 1,2-disubstituted naphthalene;
- (b) 5-6 membered heteroaromatic ring, containing 1-2 N atoms, 1 S or 0 atom, or combination thereof;

15 D and E are independently $-\text{COOH}$, $-\text{CONH}_2$, CONHR_b , COOR_b , SO_2OH , $\text{SO}_3(\text{OH})$, SO_2NH_2 , $-\text{SSO}_2\text{ONa}$, $\text{PH}(\text{O})(\text{OH})$, $\text{P}(\text{O})(\text{OH})_2$;

20 X is O, S, SO or SO_2 ;

R is H,

$\text{C}_1\text{-C}_4$ alkyl,
phenyl or substituted phenyl,
halo,
haloalkyl,
25 hydroxy,
carboxy,
cyano,
 $\text{C}_1\text{-C}_4$ alkoxy,
 $\text{C}_1\text{-C}_4$ alkylthio,
30 $\text{C}_1\text{-C}_4$ alkylsulfinyl,

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 104 -

C₁-C₄ alkylsulfonyl,

nitro,

amino,

C₁-C₄ mono or di-alkylamino;

5 R' and R'' are independently

H,

halo,

C₁-C₄ alkyl or C₁-C₄ alkoxy,

amino, or oxo, where CH-R' or CH-R''

10 in the formula become -C=O;

R_a is H, C₁-C₄ alkyl;

R_b is C₁-C₁₂ alkyl, phenyl or phenyl C₁-C₄ alkyl;

y is 1-6;

15 z is 6-20; and

wherein

R'

(CH)_y and

20

R''

(CH)_z can independently represent substituted

or unsubstituted alkyl radicals or alkenyl

radicals containing at least one alkene bond;

and pharmaceutically acceptable salts and esters

25 thereof.

The compounds of the instant invention are inhibitors of the human testosterone-5 α -reductase .

The scope of the compounds of the instant invention are described by the above-described
30 formula.

In the description of the formula the following terms are used which are hereby defined:

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 105 -

X is preferably O or S, and particularly preferred is O.

"C₁-C₄ alkyl" includes linear or branched species, e.g. methyl, ethyl, n-propyl, isopropyl, cyclopropyl, n-butyl, isobutyl, sec-butyl, t-butyl and "C₁-C₁₂ alkyl" includes, alkyl up to 12 carbons including n-octyl, t-decyl, n-dodecyl.

"Phenyl C₁-C₄ alkyl" includes benzyl, 2-phenethyl and the like.

"C₁-C₄ alkoxy" includes linear or branched species, e.g., methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, t-butoxy.

"Halo" includes fluoro, chloro, bromo or iodo.

By the term "heteroaromatic ring" as used herein is meant a 5-6 membered ring, containing 1-2 N-atoms, 1 S or O atom, or combination thereof, and includes: pyridine, thiophene, furan, imidazole, 1,3-thiazole, 1,3-oxazole, 1,2,3-thiadiazole, and the like. The limitation here being that the 1,2-disubstitution occurs on only ring carbons of the heteroaromatic ring. Preferred heteroaromatic rings are pyridine, furan and thiophene.

"Substituted phenyl" includes phenyl substituted by one or more of C₁-C₄ alkyl, C₁-C₄ alkoxy, or halo, and the like, as defined above; representative examples include o, m-, p-methoxy phenyl; 2,4-dimethoxyphenyl; 2-chloro-4-ethoxyphenyl; 3,5-dimethoxyphenyl; 2,4-dichlorophenyl; 2-bromo-4-methylphenyl, o-fluorophenyl, and the like.

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 106 -

"Haloalkyl" includes C₁-C₄ alkyl, defined above, substituted with one or more "halo" as defined above and includes: trifluoromethyl, 2,2-dichloroethyl and the like.

5 "C₁-C₄ alkylthio" includes C₁-C₄ alkyl, defined above, substituted with at least one divalent thio (-S-) grouping including; methylthio, ethylthio, isopropylthio, n-butylthio, and the like.

10 "C₁-C₄ alkylsulfinyl" includes C₁-C₄ alkyl, defined above, substituted with at least one -SO- grouping including; methylsulfinyl, ethylsulfinyl; isopropylsulfinyl, and the like.

15 "C₁-C₄ alkylsulfonyl" includes C₁-C₄ alkyl, defined above, substituted with at least one sulfonyl group, -SO₂-, including; methylsulfonyl, ethylsulfonyl, isopropylsulfonyl, n-butylsulfonyl, and the like.

20 "C₁-C₄ mono or dialkyl amino" includes amino, substituted with one or more C₁-C₄ alkyl groups as defined hereinabove, including: methylamino, ethylamino, n-butylamino, t-butylamino, dimethylamino, diethylamino, methyl-t-butylamino, and the like.

25 The R group or groups on the benzene or heteroaromatic ring can be present initially in the process, e.g. phenyl, methyl, methoxy, cyano carbomethoxy, trifluoromethyl, (as in the starting o-nitrophenol 1 in Flow Chart A) or added later by a conventional reaction, e.g. chloro, as by chlorination, nitro by nitration, or created from
30 a starting or added functional group present, e.g.

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 107 -

converting a later added nitro group to an amino group by catalytic reduction, then alkylating to a mono or dialkylamine. An amino group can be subjected to diazotization to a hydroxy group, which can be followed by methylation to a methoxy group. Similarly, a hydroxy group can be converted to a thiol by the analogous procedures described in J. Org. Chem. 31, pp 3980-3984 (1966) by Newman and Karnes, and J. Org. Chem. 31, pp 410 (1966) by Kwart, H. and Evans, E.S. The resulting thiol can be alkylated to alkylthio, which can be oxidized to the corresponding sulfoxide or sulfone. Preferred substituents are H, C₁-C₄ alkyl, C₁-C₄ alkoxy and phenyl. These reactions and sequences are conventional in the art and it will be obvious to one skilled in the art to modify the benzene ring to arrive at an R radical disclosed herein.

By the term "pharmaceutically acceptable salts and esters thereof" is meant, salts and esters of the acid groups in the final molecule which can be used as part of the human drug delivery system and include the salts: sodium, potassium, calcium, ammonium, substituted ammonium, quaternary ammonium, and esters: ethyl ester, aceturate, besylate, edetate, phenpropionate, acetate, pamoate, and esters which serve as "prodrug" formulations which will hydrolyze in the body at physiological pH's to regenerate the acid, including pivaloylates, e.g. pivoxetil and pivoxil, and Kanebo esters, and the like.

This Sheet Has Been Replaced

SUBSTITUTE SHEET

- 108 -

5

10

15

20

20

25

25

30

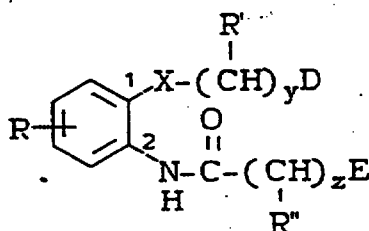
[REDACTED]

- 109 -

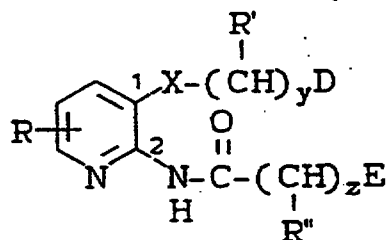
Preferred is where one R' or R'' is H and particularly preferred is where both $\overset{\text{R}'}{\underset{|}{(\text{CH})}_y}$ and $\overset{\text{R}''}{\underset{|}{(\text{CH})}_z}$ are alkyl.

5 Representative compounds of the instant invention within the above general formula are given by the following, structures;

10

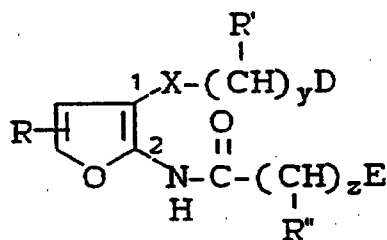


15



20

25



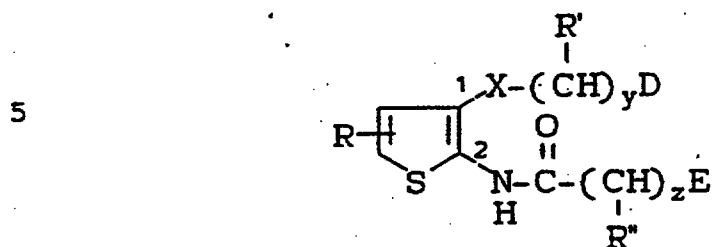
30

This Sheet Has Been Replaced

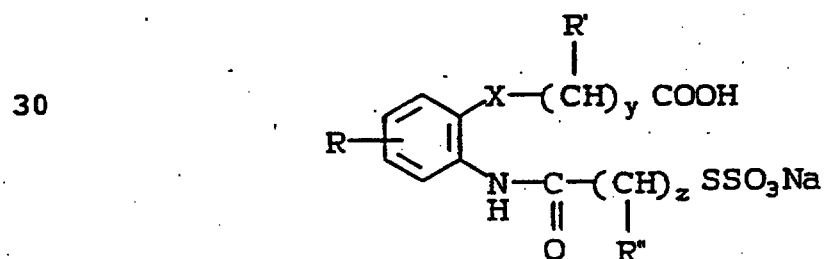
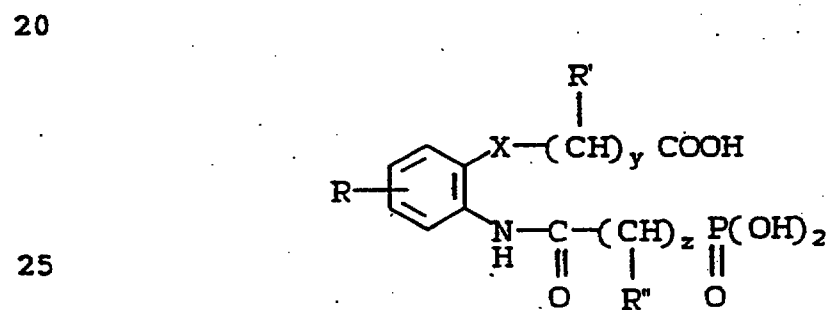
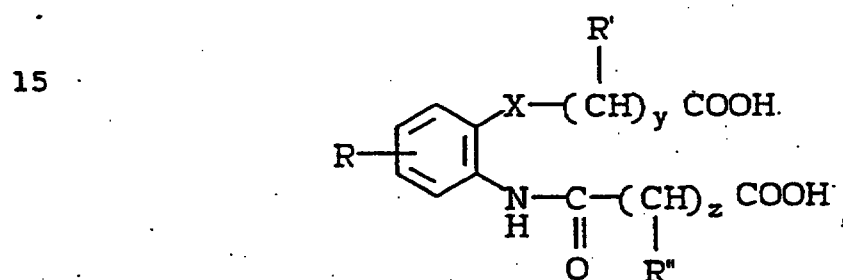


SUBSTITUTE SHEET

- 110 -



10 Particularly preferred are the following compounds:



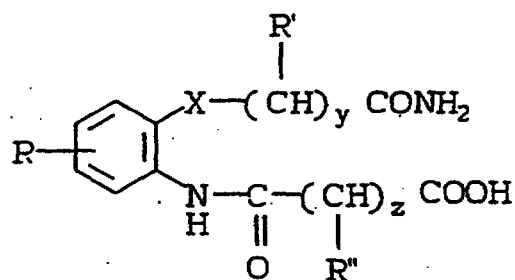
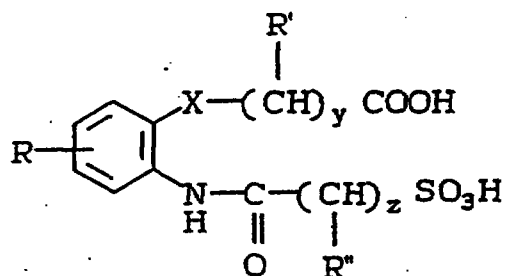
30

This Sheet Has Been Replaced



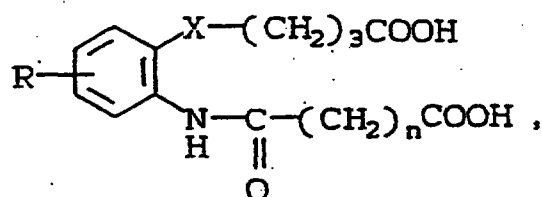
SUBSTITUTE SHEET

- 111 -



where X is O or S and R, R', R'', y and z are as defined above.

Preferred compounds within this class are:

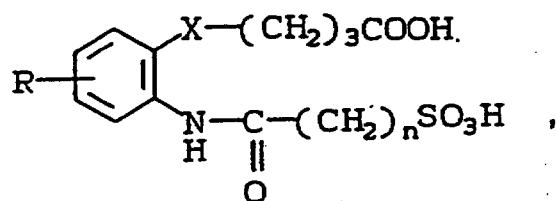


This Sheet Has Been Replaced

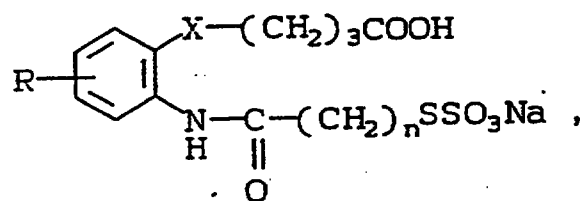


- 112 -

5

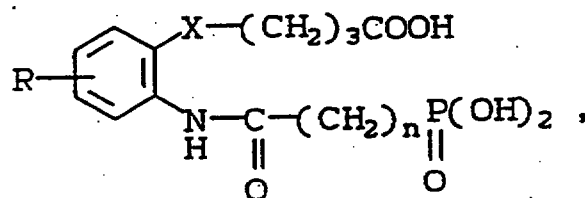


10



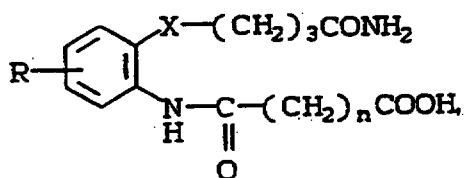
15

20



25

30



where X is O or S, and n is 8-14.

This Sheet Has Been Replaced

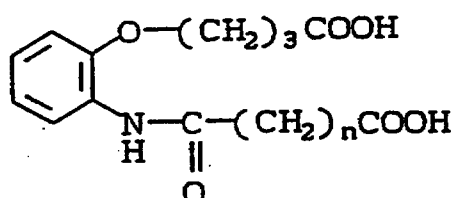


SUBSTITUTE SHEET

- 113 -

Also preferred compounds are within these classes are:

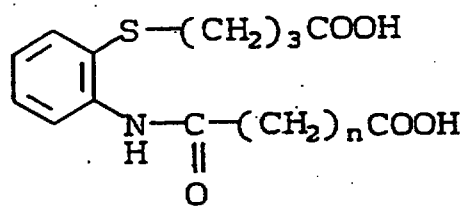
5



10

where n is 8-14.

15



20

The compounds of the instant invention can be made by the procedures outlined in the following Flowcharts.

25

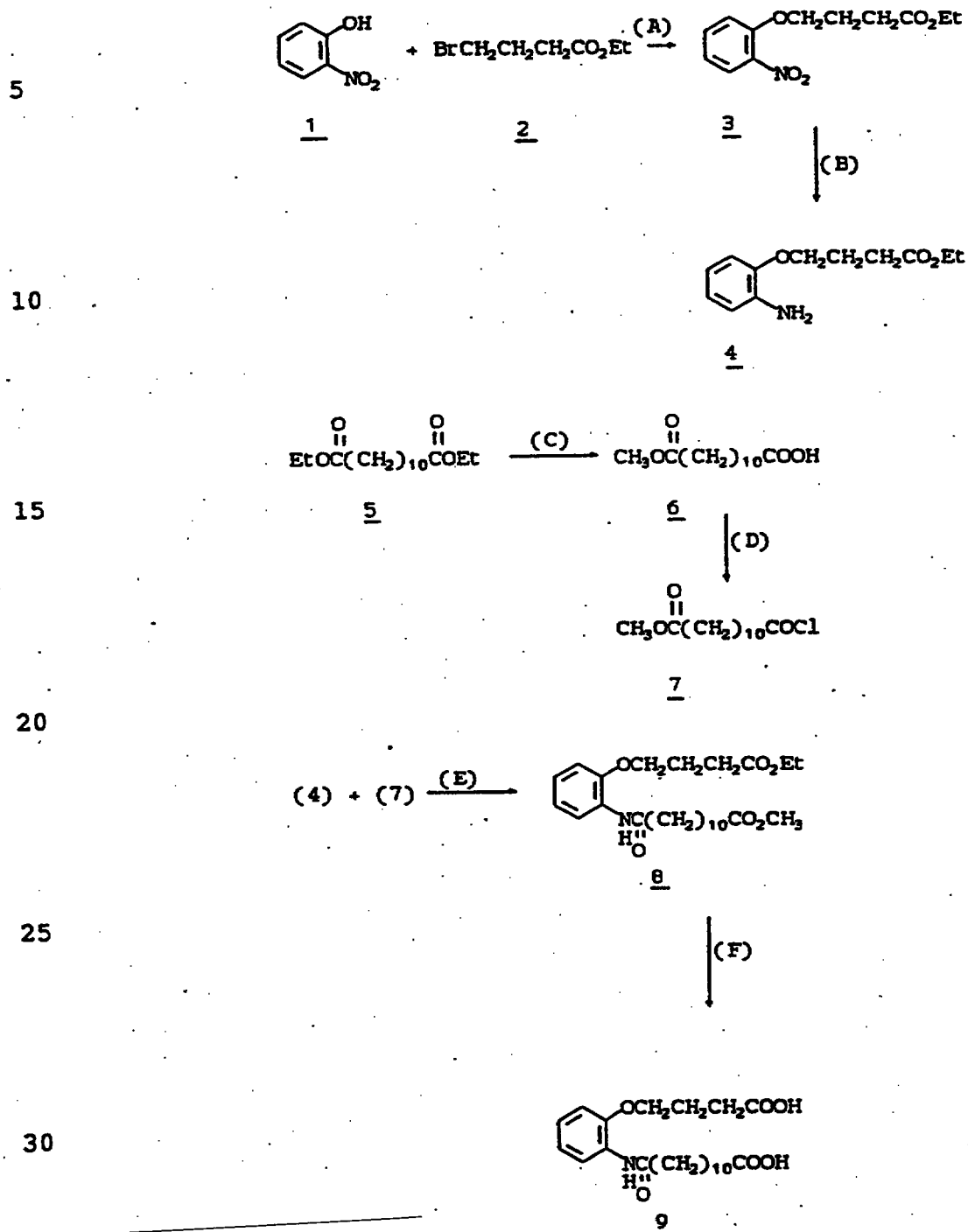
30

This Sheet Has Been Replaced



- 114 -

FLOW CHART A-2



This Sheet Has Been Replaced

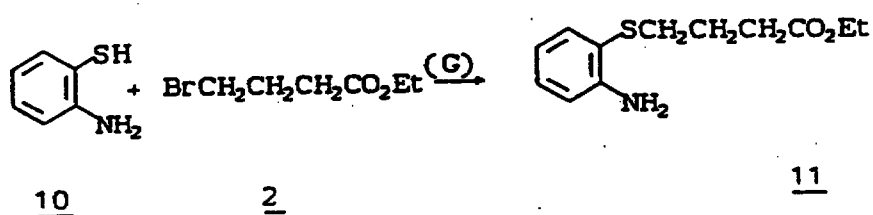


SUBSTITUTE SHEET

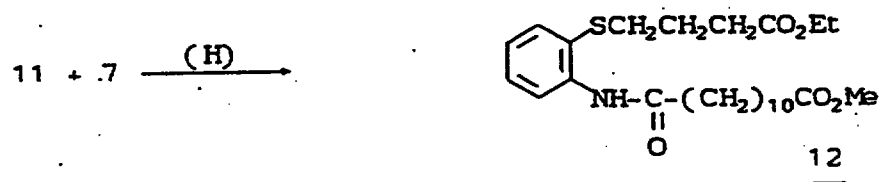
- 115 -

FLOW CHART B-2

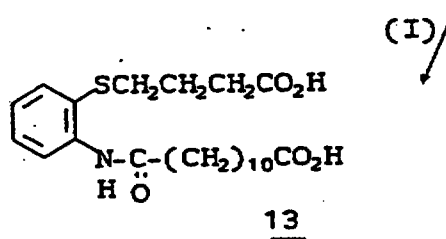
5



10



15



20

25

This Sheet Has Been Replaced

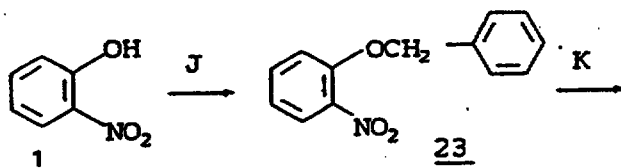


30

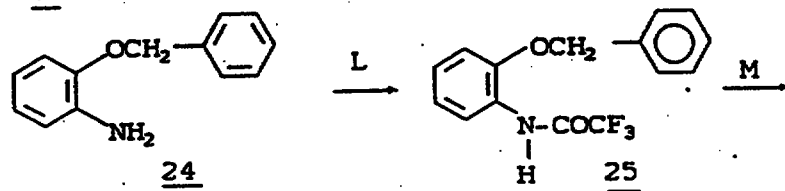
- 116 -

FLOW CHART C-2

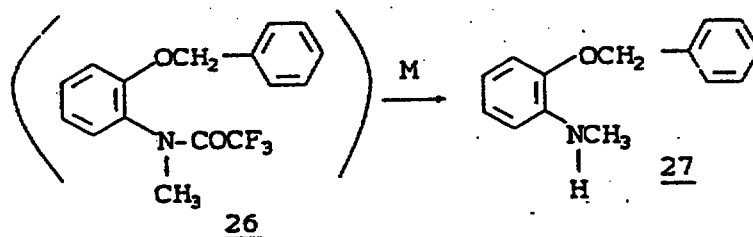
5



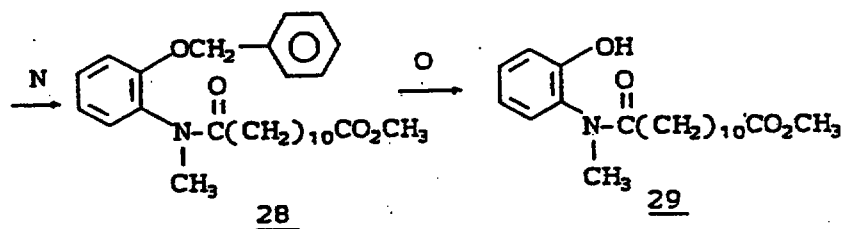
10



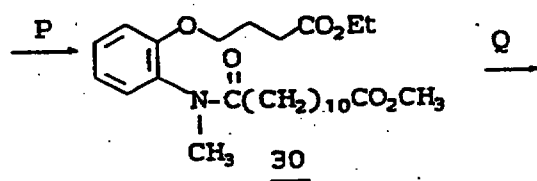
15



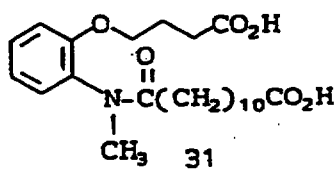
20



25



30



This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 117 -

FLOW CHART D-2

5

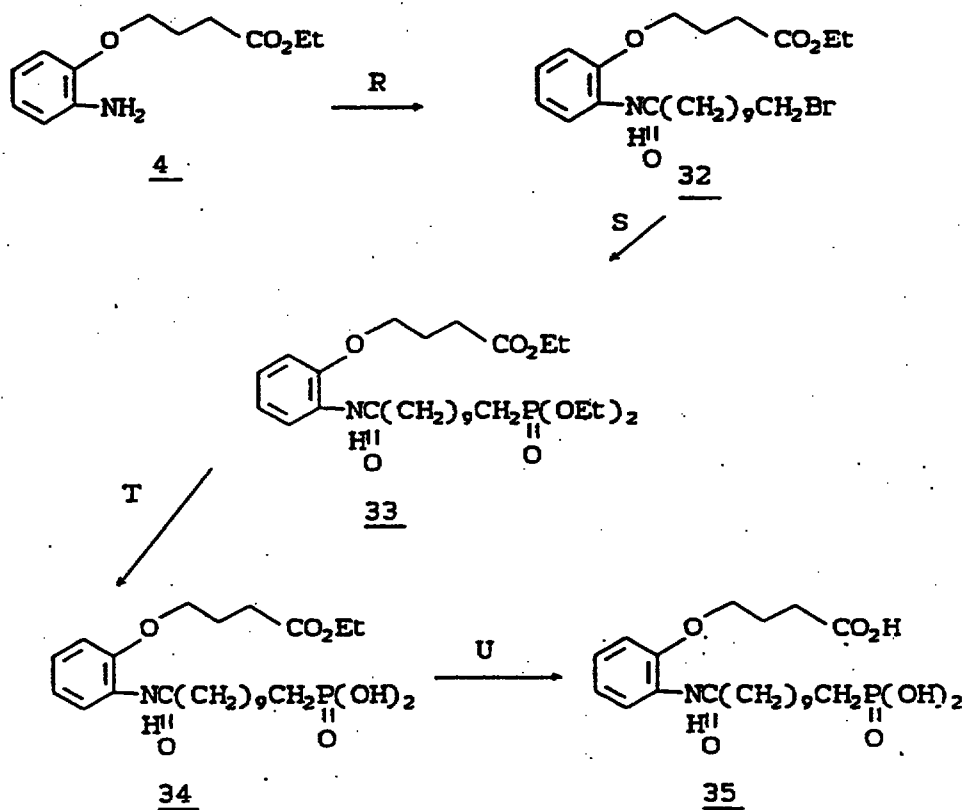
10

15

20

25

30



This Sheet Has Been Replaced

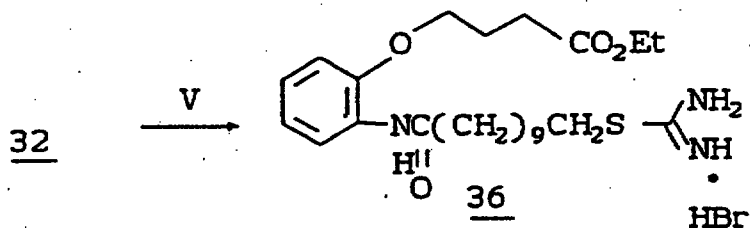


SUBSTITUTE SHEET

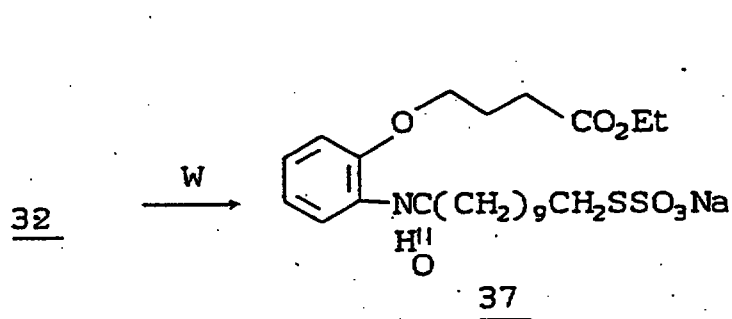
- 118 -

FLOW CHART E-2

5

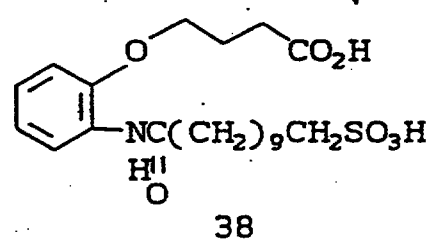


10



15

20



25

30

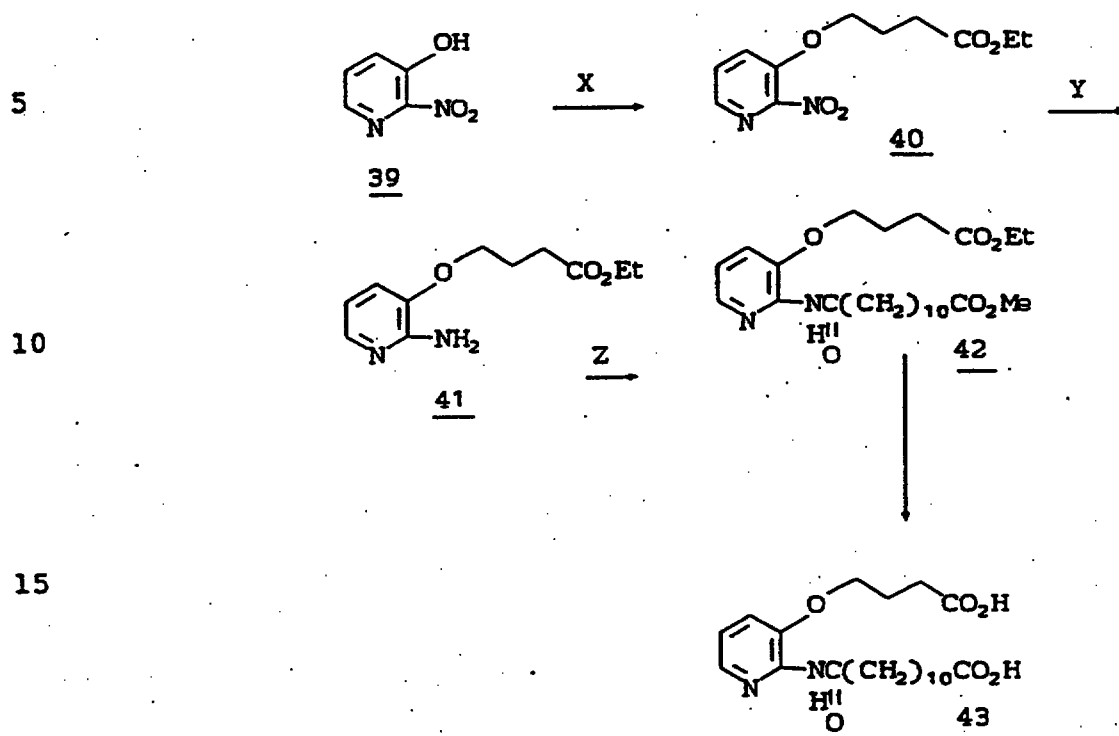
This Sheet Has Been Replaced



SUBSTITUTE SHEET.

- 119 -

FLOW CHART F-2

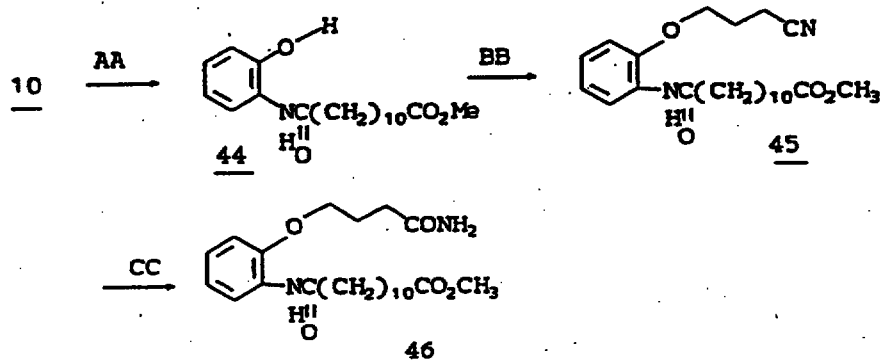


This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 120 -

FLOW CHART G-2

This Sheet Has Been Replaced



- 121 -

FLOW CHART H-2

5 44 BrCH₂CH₂CH₂CO₂Et > (9) (alternate route to 9)

As seen in Flow Chart A-2, o-nitrophenol 1, ethyl 4-bromobutyrate 2 and anhydrous K₂CO₃ in e.g., dry acetone are heated at reflux or stirred for an extended period of time at room temperature, under a nitrogen atmosphere to product ethyl 4-(2-nitrophenoxy) butyrate 3, in Step (A).

A solution of 3 in e.g., ethyl acetate is catalytically hydrogenated at room temperature under e.g. 40 psig of H₂ in the presence of a 5% Pd/C catalyst to yield ethyl 4-(2-aminophenoxy)butyrate 4 in Step (B).

Step (C) comprises reacting diethyl dodecanoate 5 with barium hydroxide octahydrate in methanol at ambient temperature to obtain the monomethyl ester 6.

In Step (D) the mono ester mono acid 6 is refluxed with thionyl chloride for about 5 hours to produce the mono acid chloride, mono methyl ester 7.

Step (E) comprises the reaction of the mono acid chloride 7 with the amine 4 at e.g., 0-10°C in e.g., dry ether in the presence of a hydrogen acceptor e.g., triethylamine, to produce the amide 8.

In Step (F), the ether-amide diester 8 is de-esterified by e.g., 2.5 N NaOH in MeOH/H₂O to yield after acidification the final product, diacid 9.

Flow Chart B-2 illustrates the synthesis of the corresponding thio compounds.

This Sheet Has Been Replaced



- 122 -

Step (G) illustrates the reaction of o-aminobenzenethiol with ethyl 4-bromobutyrate which can be carried out in e.g., dry dimethoxyethane, under dry N₂, in the presence of a proton acceptor, e.g., dry powdered K₂CO₃, to produce 11.

Step (H) illustrates the acylation of the amino group of 11 with ethyl 11-bromoundecanoate in a dry solvent, e.g., dry ether, at 0°C in the presence of an acid acceptor, e.g., pyridine.

Step (I) illustrates the hydrolysis of the diester to the final diacid 13, which can be accomplished with, e.g., NaOH/MeOH.

As seen in Flow Chart C-2, o-nitrophenol is benzylated under the same conditions as in Step (A).

Step (K) shows the reduction of the nitro group using e.g., Raney Ni in ethanol/NH₃ under 40 psig H₂.

Step (L) shows the trifluoroacetylation of 24 using e.g., trifluoroacetic anhydride in dry ether and powdered dry sodium carbonate.

Step (M) shows the N-methylation which can be accomplished using, e.g., methyl iodide in dry acetone and dry powdered KOH followed by removal of the N-trifluoroacetyl group with MeOH/H₂O.

Step (N) shows the N-acylation of 27, using an acid chloride, e.g., 7, in e.g., dry methylene chloride and pyridine at 0°C.

Step (O) shows the debenzylation of 28, which can be accomplished by e.g., 10% Pd/C in MeOH under a H₂ atmosphere.

Step (P) shows the O-alkylation of 29 using e.g., ethyl 4-bromobutyrate and K₂CO₃ in anhydrous acetone.

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 123 -

Step (Q) shows hydrolysis of the diester 30 to the diacid 31 by hydrolysis as e.g., described for Step (F).

5 Flow Chart D-2 shows the production of phosphonate type esters and acids.

Step (R) shows the condensation of 4 with 11-bromoundecanoic acid in anhydrous methylene chloride using N,N'-dicyclohexylcarbodiimide and 4-dimethylaminopyridine to produce the important
10 bromo intermediate 32.

Step (S) shows the reaction of 32 with triethylphosphite at e.g., 180°C under N₂ to produce the phosphonate ester 33.

15 Step (T) converts 33 via bromotrimethylsilane to the monoacid 34.

Step (U) uses the similar hydrolysis conditions of Step (F) to produce the phosphonic-carboxylic diacid 35.

20 The corresponding phosphinic acids can be analogously made from 32 by known procedures in the art.

Flow Chart E-2 illustrates the synthesis of the sulfonic acid types of the invention compounds.

25 Step (V) shows reaction of the intermediate 32 with thiourea in EtOH/H₂O under N₂ at 90°C to yield the isothiuronium salt 36.

Step (W) shows the reaction of 32 with sodium thiosulfate under the conditions of Step (V) to yield the thiosulfate ester 37.

30 Further oxidation of esters 36 or 37 via the Showell or Ziegler procedures described in Step W in the examples yields the corresponding sulfonic acid 38.

This Sheet Has Been Replaced



- 124 -

The corresponding sulfinic acid can be prepared from 36 by the procedure of J. M. Sprague and T. B. Johnson, JACS 59, 2440 (1937).

5 The corresponding sulfonamide can be produced from the sulfonic acid 38, by protecting, e.g., the carboxylic acid via an ester, converting the sulfonic acid to a sulfonyl chloride, treating the sulfonyl chloride with ammonia and then hydro-
10 lyzing the protected carboxylic ester to the corresponding acid.

Flow Chart F-2 shows the corresponding synthesis of the pyridine analogs of 8 and 9.

In Step (X), the nitrohydroxy pyridine is O-alkylated first using conditions analogous
15 to Step (A) to produce 40.

Step (Y) shows reducing the nitro group in the same manner as described for Step (B).

Step (Z) shows acylating the amino group in the same manner as described for 8 in Step (E)
20 to produce the diester 42. Hydrolysis produces the diacid 43.

Flow Chart G-2 shows the production of some amides 46 of the invention.

In Step (AA), o-aminophenol is reacted
25 directly with 7 under the conditions of Step (E) to produce the N-acylated phenol 44.

In Step (BB), O-alkylation of 44 as carried out using 4-bromobutyronitrile under conditions similar to Step (A), produces 45.

30 Step (CC) shows the hydrolysis of the nitrile to the amide 46 using MnO_2 in methylene chloride.

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 125 -

Flow Chart H-2 illustrates an alternate route to 2 by starting with o-aminophenol, acylating to produce 44, then reacting 44 under the conditions of Step (A) to produce 8, then hydrolysis using Step (F) to yield 2.

Thus, by using the above described methods in the Flow Charts and the reaction starting materials and reagents described herein, all of the compounds described and encompassed by the claim can be synthesized by one skilled in the art.

It is obvious that other nitrophenols can be substituted for 1 in Flow Charts A-2 and C-2 to provide the scope of the compounds covered by this invention and include the following:

2-nitrophenol
2-nitro-6-methylphenol
2-nitro-5-methylphenol
2-nitro-4-methylphenol
2-nitro-3-methylphenol
2-nitro-4-phenylphenol
2-nitro-5-phenylphenol
2-nitro-4-chlorophenol
2-nitro-4-fluorophenol
2-nitro-4-trifluoromethylphenol
2-nitro-4-hydroxyphenol
2-nitro-4-methoxyphenol
2-nitro-6-ethoxyphenol
2-nitro-4-methylthio-phenol
2-nitro-4-methylsulfinylphenol
2-nitro-4-methylsulfonylphenol
4-nitro-3-hydroxypyridine
3-nitro-4-hydroxy-5-methylpyridine

This Sheet Has Been Replaced



- 126 -

3-nitro-4-hydroxy-6-methylpyridine
2-methyl-3-nitro-4-hydroxypyridine
2-hydroxy-3-nitro-5-phenylpyridine
2-nitro-3-hydroxy-5-phenylpyridine
5 2-hydroxy-3-nitro-5-chloropyridine
2-nitro-3-hydroxy-5-trifluoromethylpyridine
2-methoxy-4-nitro-5-hydroxypyridine
3-nitro-4-hydroxy-5-ethoxypyridine
2-methylthio-4-nitro-5-hydroxypyridine
10 2-nitro-3-hydroxy-thiophene
3-nitro-4-hydroxy-thiophene
3-hydroxy-2-nitro-5-methyl-thiophene
3-hydroxy-2-nitro-4-methyl-thiophene
2-hydroxy-3-nitro-5-phenyl-thiophene
15 2-nitro-3-hydroxy-4-phenyl-thiophene
2-hydroxy-3-nitro-4-chlorothiophene
2-hydroxy-3-nitro-4-fluorothiophene
and the like.

20 It is obvious that suitable replacement
compounds for 2 with other halo alkyl esters, known
in the art, and that suitable replacement of 6 with
other diesters, available in the art, will yield all
of the ether-amide derivatives within the scope of
25 the claims.

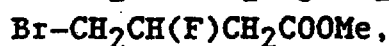
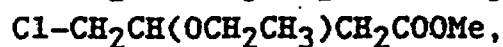
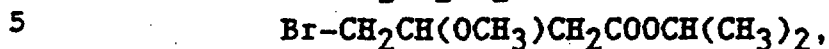
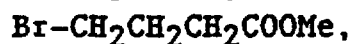
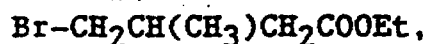
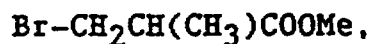
Representative examples of 2 useful in
the invention process include, but are not limited to:

30 Br-CH₂-COOMe,
Cl-CH₂CH₂CH₂COOCH(CH₃)₃,
Br-CH₂CH₂CH₂CH₂COOMe,
Br-CH₂CH₂CH₂CH₂COOEt,

This Sheet Has Been Replaced

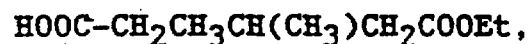
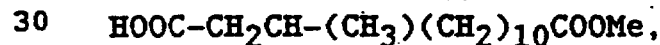
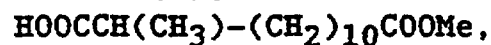
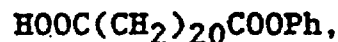
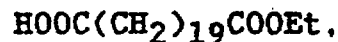
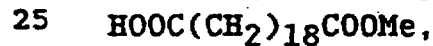
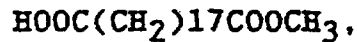
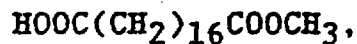
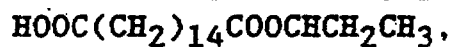
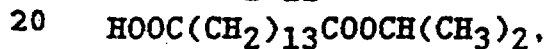
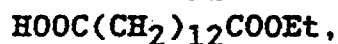
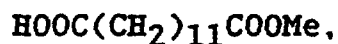
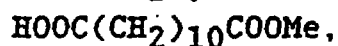
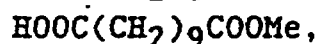
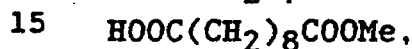
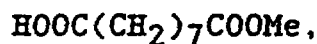
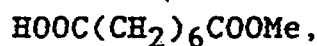


- 127 -



and the like.

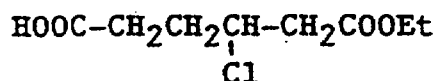
10 Representative examples of other compounds
substitutable for 6 and useful in the invention are:



This Sheet Has Been Replaced



- 128 -



where Ph is phenyl,

5 and the like.

Representative examples of compounds produced by this process include those in the following list.

10 The nomenclature used herein for the acid radicals is:

- P(O)(OH)₂, phosphono;
- COOH, carboxy;
- CONH₂, aminocarbonyl;
- SO₃H, sulfo;
- 15 -SO₂H, sulfino;
- SSO₃H, thiosulfato, as the sodium salt.

- 4-(2-(20-Carboxyeicosanoylamino)phenoxy)butyric acid;
- 4-(2-(19-Carboxynonadecanoylamino)phenoxy)butyric
- 20 acid;
- 4-(2-(18-Carboxyoctadecanoylamino)phenoxy)butyric acid;
- 4-(2-(17-Carboxyheptadecanoylamino)phenoxy)butyric acid;
- 25 4-(2-(16-Carboxyhexadecanoyl-N-methylamino)phenoxy)-butyric acid;
- 4-(2-(15-Carboxypentadecanoylamino)phenoxy)butyramide;
- 4-(2-(14-Carboxytetradecanoylamino)phenoxy)butyric acid;
- 30 4-(2-(13-Carboxyl-tridecanoylamino)phenoxy)butyric acid;
- 4-(2-(12-Carboxy-dodecanoylamino)phenoxy)butyric acid;

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 129 -

- 4-(2-(11-Carboxy-undecanoylamino)phenoxy)butyric acid;
- 4-(2-(10-Carboxy-decanoylamino)phenoxy)butyric acid;
- 5 4-(2-(9-Carboxy-nonanoylamino)phenoxy)butyric acid;
- 4-(2-(8-Carboxy-octanoylamino)phenoxy)butyric acid;
- 4-(2-(7-Carboxy-heptanoylamino)phenoxy)butyric acid;
- 4-(2-(6-Carboxy-hexanoylamino)butyric acid;
- 4-(2-(20-Carboxy-eicosanoylamino)phenylthio)butyric
- 10 acid;
- 4-(2-(19-Carboxy-nonadecanoylamino)phenylthio)butyric acid;
- 4-(2-(18-Carboxy-octadecanoylamino)phenylthio)butyric acid;
- 15 4-(2-(17-Carboxy-heptadecanoyl-N-ethylamino)phenylthio)butyric acid;
- 4-(2-(16-Carboxy-hexadecanoylamino)phenylthio)butyric acid;
- 4-(2-(15-Carboxy-pentadecanoylamino)phenylthio)butyric
- 20 acid;
- 4-(2-(14-Carboxy-tetradecanoylamino)phenylthio)butyramide;
- 4-(2-(13-Carboxy-tridecanoylamino)phenylthio) acid;
- 4-(2-(12-Carboxy-dodecanoylamino)phenylthio)butyric
- 25 acid;
- 4-(2-(11-Carboxy-undecanoylamino)phenylthio)butyric acid;
- 4-(2-(10-Carboxy-decanoylamino)phenylthio)butyric acid;
- 30 4-(2-(9-Carboxy-nonanoylamino)phenylthio)butyric acid;
- 4-(2-(8-Carboxy-octanoylamino)phenylthio)butyric acid;
- 4-(2-(7-Carboxy-heptanoylamino)phenylthio)butyric acid;

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 130 -

- 4-(2-(6-Carboxyhexanoylamino)phenylthio)butyric acid;
3-(2-(16-Carboxyhexadecanoylamino)phenoxy)propionic
acid;
4-(2-(15-Carboxyisohexadecanoylamino)phenoxy)butyric
5 acid;
4-(2-(14-Carboxytetradecanoylamino)phenoxy)butyric
acid;
5-(2-(13-Carboxytridecanoylamino)phenoxy)valeric
acid;
10 5-(2-(12-Carboxydodecanoylamino)phenoxy)valeric acid;
5-(2-(11-Carboxyisododecanoylamino)valeric acid;
4-(2-(11-Carboxyundecanoylamino)isovaleric acid;
4-(2-(10-Carboxydecanoylamino)isovaleric acid;
5-(2-(9-Carboxynonanoylamino)phenoxy)valeric acid;
15 6-(2-(9-Carboxynonanoylamino)phenoxy)caproic acid;
6-(2-(8-Carboxyoctanoylamino)phenoxy)caproic acid;
6-(2-(7-Carboxyisooctanoylamino)phenoxy)caproic acid;
7-(2-(7-Carboxyheptanoylamino)phenoxy)enanthic acid;
7-(2-(6-Carboxyhexanoylamino)phenoxy)enanthic acid;
20 7-(2-(5-Carboxyisohexanoylamino)phenoxy)enanthic
acid;
2-(2-(12-Carboxydodecanoylamino)phenoxy)acetic acid;
2-(2-(11-Carboxyundecanoylamino)phenoxy)acetic
acid;
25 2-(2-(10-Carboxydecanoylamino)phenoxy)acetic acid;
3-(2-(9-Carboxynonanoylamino)phenoxy)propionic acid;
3-(2-(12-Carboxydodecanoylamino)phenylthio)propionic
acid;
3-(2-(11-Carboxyundecanoylamino)phenylthio)propionic
30 acid;
3-(2-(11-Carboxyundecanoylamino)phenylthio)isobutyric
acid;

This Sheet Has Been Replaced

SUBSTITUTE SHEET

- 131 -

- 5-(2-(11-Carboxyundecanoylamino)phenylthio)valeric acid;
5-(2-(10-Carboxydecanoylamino)phenylthio)valeric acid;
5 5-(2-(9-Carboxynonanoylamino)phenylthio)valeric acid;
4-(2-(12-Carboxydodecanoylamino)phenylthio)isovaleric acid;
4-(2-(11-Carboxydecanoylamino)phenylthio)isovaleric acid;
10 4-(2-(10-Carboxydecanoylamino)phenylthio)isovaleric acid;
6-(2-(9-Carboxynonanoylamino)phenoxy)caproic acid;
6-(2-(12-Carboxydodecanoylamino)phenylthio)caproic acid;
15 6-(2-(11-Carboxyundecanoylamino)phenylthio)caproic acid;
7-(2-(11-Carboxyundecanoylamino)-3-methylphenylthio)-
enanthic acid;
7-(2-(11-Carboxyundecanoylamino)-4-methylphenylthio)-
20 enanthic acid;
7-(2-(12-Carboxydodecanoylamino)phenoxy)enanthic acid;
4-(2-(11-Carboxyundecanoylamino)4-methyl-phenoxy)
butyric acid;
4-(2-(10-Carboxydecanoylamino)3-methylphenoxy)butyric
25 acid;
4-(2-(9-Carboxynonanoylamino)5-methylphenoxy)butyric
acid;
4-(2-(12-Carboxydodecanoylamino)6-methylphenoxy)
butyric acid;
30 4-(2-(11-Carboxydecanoylamino)3-chloro)phenylthio)-
butyric acid;
4-(2-(10-Carboxydecanoylamino)4-methylphenoxy)butyric
acid;

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 132 -

- 4-(2-(9-Carboxynonanoylamino)5-fluoromethyl)phenylthio)butyric acid;
- 4-(2-(12-Carboxydodecanoylamino)6-methylphenoxy)-butyric acid;
- 5 5-(2-(11-Carboxyundecanoylamino)-3-methylthio)-phenoxy)valeric acid;
- 4-(2-(11-Carboxyundecanoylamino)-3-methylsulfonylphenoxy)butyric acid;
- 4-(2-(11-Carboxyundecanoylamino)-4-methylsulfonyl)-phenylthio)butyric acid;
- 10 4-(2-(12-Carboxydodecanoylamino)5-ethyl-phenoxy)-butyric acid;
- 4-(2-(11-Carboxyundecanoylamino)4-phenylphenoxy)-butyric acid;
- 15 4-(2-(10-Carboxydecanoylamino)-3,5-dimethylphenoxy)-butyric acid;
- 4-(2-(9-Carboxynonanoylamino)-4-fluoro-phenoxy)butyric acid;
- 4-(2-(12-Carboxydodecanoylamino)-5-trifluoromethylphenoxy)butyric acid;
- 20 4-(2-(11-Carboxyundecanoylamino)5-hydroxy)phenylthio)butyric acid;
- 4-(2-(10-Carboxydecanoylamino)-4-hydroxy)phenylthio)-butyric acid;
- 25 4-(2-(9-Carboxynonanoylamino)-3,5-dimethoxy-phenylthio)butyric acid;
- 4-(2-(12-Carboxydodecanoylamino)-5-nitrophenoxy)-butyric acid;
- 5-(2-(11-Carboxyundecanoylamino)-4-nitrophenoxy)-valeric acid;
- 30 4-(2-(11-Carboxyundecanoylamino)-5-amino-3-methylphenoxy)butyric acid;

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 133 -

- 4-(2-(11-Carboxyundecanoylamino)-5-amino-4-methyl-phenylthio)butyric acid;
- 4-(2-(12-Carboxydodecanoylamino)-4-dimethylamino-phenoxy)butyric acid;
- 5 4-(2-(11-Carboxyundecanoylamino)-5-ethylamino-phenoxy)butyric acid;
- 3-(2-(12-Carboxydodecanoylamino)phenoxy)-3-methylpropionic acid;
- 10 3-(2-(11-Carboxydecanoylamino)phenylthio)-2-chloro-propionic acid;
- 4-(2-(10-Carboxydecanoylamino)phenylthio)-3-methoxy-butyrlic acid;
- 4-(2-(9-Carboxynonanoylamino)phenylthio)-3-ethoxy-butyrlic acid;
- 15 4-(2-(12-Carboxydodecanoylamino)-4-methyl-3-pyridyl-oxy)butyrlic acid;
- 4-(2-(11-Carboxyundecanoylamino)-4-methyl-3-pyridyl-oxy)butyrlic acid;
- 4-(2-(10-Carboxydecanoylamino)-5-methyl-3-pyridyloxy)-butyrlic acid;
- 20 4-(2-(9-Carboxynonanoylamino)5-hydroxy-3-pyridyloxy)-butyrlic acid;
- 4-(2-(12-Carboxydodecanoylamino)-6(dimethylamino)-3-pyridyloxy)butyrlic acid;
- 25 4-(2-(11-Carboxydecanoylamino)-3-pyridylthio)-butyrlic acid;
- 4-(2-(10-Carboxydecanoylamino)-6-methylsulfonyl-3-pyridyloxy)butyrlic acid;
- 4-(2-(9-Carboxynonanoylamino)5-chloro-3-pyridylthio)-butyrlic acid;
- 30 4-(2-(12-Carboxydodecanoylamino)-5-methylpyridylthio)-butyrlic acid;

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 134 -

- 4-(2-(11-Carboxyundecanoylamino)5-methylsulfonyl-3-pyridylthio)butyric acid;
- 4-(2-(11-Carboxyundecanoylamino)-6-methyl-3-pyridylthio)butyric acid;
- 5 4-(2-(11-Carboxyundecanoylamino)-4,6-dimethyl-3-pyridyloxy)butyric acid;
- 4-(2-(12-Carboxydodecanoylamino)-5-methylthio-3-pyridyloxy)butyric acid;
- 10 4-(2-(11-Carboxyundecanoylamino)pyridyloxy)butyric acid;
- 4-(2-(10-Carboxydecanoylamino)-5-methoxy-3-pyridyloxy)butyric acid;
- 4-(2-(9-Carboxynonanoylamino)-4-fluoro-6-methyl-3-pyridyloxy)butyric acid;
- 15 4-(2-(12-Carboxydodecanoylamino)5-methylamino-3-pyridyloxy)butyric acid;
- 4-(2-(11-Carboxyundecanoylamino)4-phenyl-3-pyridylthio)butyric acid;
- 4-(2-(10-Carboxydecanoylamino)5-methyl-3-pyridylthio)-butyric acid;
- 20 4-(2-(9-Carboxylnonanoylamino)6-methoxy-3-pyridylthio)butyric acid;
- 4-(2-(12-Carboxydodecanoylamino)-6-trifluoromethyl-3-pyridyloxy)butyric acid;
- 25 5-(2-(11-Carboxyundecanoylamino)-4-methyl-3-thienyloxy)valeric acid;
- 4-(2-(11-Carboxyundecanoylamino)-4-methyl-3-thienyloxy)butyric acid;
- 4-(2-(11-Carboxyundecanoylamino)-4-methyl)-3-thienylthio)butyric acid;
- 30 4-(2-(12-Carboxydodecanoylamino)-5-methyl-3-thienylthio)butyric acid;

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 135 -

- 4-(2-(11-Carboxyundecanoylamino)-4-methyl-3-thienyl-thio)butyric acid;
- 4-(2-(10-Carboxydecanoylamino)-5-methyl-3-thienyl-thio)butyric acid;
- 5 4-(2-(9-Carboxynonanoylamino)-4-hydroxy-3-thienyloxy)-butyric acid;
- 4-(2-(12-Carboxydecanoylamino)-4-methylthio-3-thienyloxy)butyric acid;
- 10 4-(2-(11-Carboxydecanoylamino)-4-methylthio-3-thienyloxy)butyric acid;
- 4-(2-(10-Carboxydecanoylamino)-4-methylsulfonyl-3-thienyloxy)butyric acid;
- 4-(2-(9-Carboxynonanoylamino)-4-methylsulfonyl-3-thienyloxy)butyric acid;
- 15 4-(2-(12-Carboxydodecanoylamino)-5-trifluoromethyl-3-thienyloxy)butyric acid;
- 5-(2-(11-Carboxyundecanoylamino)-5-chloro-3-thienyloxy)valeric acid;
- 4-(2-(11-Carboxyundecanoylamino)-4-methyl-5-phenyl-3-thienyloxy)butyric acid;
- 20 4-(2-(11-Carboxyundecanoylamino)-5-methylamino-3-thienyloxy)butyric acid;
- 4-(2-(12-Carboxydodecanoylamino)-5-dimethylamino-3-thienyloxy)butyric acid;
- 25 4-(2-(11-Carboxyundecanoylamino)-3-thienyloxy)butyric acid;
- 4-(2-(20-Phosphonoeicosanoylamino)phenoxy)butyric acid;
- 4-(2-(19-Phosphonononadecanoylamino)phenoxy)butyric acid;
- 30 4-(2-(17-Sulfoheptadecanoylamino)phenoxy)butyric acid;

This Sheet Has Been Replaced



- 136 -

- 4-(2-(16-Sulfinohexadecanoyl-N-methylamino)phenoxy)-
butyric acid;
4-(2-(15-Thiosulfatopentadecanoylamino)phenoxy)
butyramide sodium salt;
5 4-(2-(14-Phosphonotetradecanoyl-N-methylamino)phenoxy)
butyric acid;
4-(2-(12-Sulfododecanoylamino)phenoxy)butyric acid;
4-(2-(11-Sulfoundecanoylamino)phenoxy)butyric acid;
4-(2-(10-Sulfinodecanoylamino)phenoxy)butyric acid;
10 4-(2-(9-Thiosulfatononanoylamino)phenoxy)butyric
acid, sodium salt;
4-(2-(8-Thiosulfatoctanoylamino)phenoxy)butyric acid,
sodium salt;
4-(2-(7-Sulfinohexanoylamino)phenoxy)butyric acid;
15 4-(2-(6-Phosphohexanoylamino)butyric acid;
4-(2-(19-Sulfonadecanoylamino)phenylthio)butyric
acid;
4-(2-(18-Sulfinooctadecanoylamino)phenylthio)butyric
acid;
20 4-(2-(17-Thiosulfatoheptadecanoyl N-ethylamino)phenyl-
thio)butyric acid;
4-(2-(16-Phosphohexadecanoylamino)phenylthio)
butyric acid;
4-(2-(14-Sulfotetradecanoylamino)phenylthio)butyric
25 acid;
4-(2-(13-Sulfinotridecanoylamino)butyric acid;
4-(2-(12-Thiosulfatododecanoylamino)phenylthio)-
butyric acid, salt sodium;
4-(2-(11-Phosphoundecanoylamino)phenylthio)butyric
30 acid;
4-(2-(10-Sulfinodecanoylamino)phenylthio)butyric
acid;

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 137 -

- 4-(2-(9-Carboxynonanoylamino)phenylthio)butane-sulfonic acid;
- 4-(2-(8-Carboxyoctanoylamino)phenylthio)butane-sulfinic acid;
- 5 4-(2-(7-Carboxyheptanoylamino)phenylthio)butane-thiosulfonic acid;
- 4-(2-(20-Carboxyeicosanoylamino)thio)phenoxy)butane-phosphonic acid;
- 4-(2-(19-Carboxynonadecanoylamino)phenoxy)butane-sulfonic acid;
- 10 4-(2-(18-Carboxyoctadecanoyl-N-butylamino)phenoxy)-butane-sulfinic acid;
- 4-(2-(17-Carboxyheptadecanoylamino)phenoxy)butane-thiosulfonic acid;
- 15 4-(2-(15-Carboxypentadecanoylamino)phenoxy)butane-phosphonic acid;
- 4-(2-(14-Carboxytetradecanoylamino)phenoxy)butane-sulfonic acid;
- 4-(2-(13-n-Carboxytridecanoylamino)phenoxy)butane-sulfinic acid;
- 20 4-(2-(12-Carboxydodecanoylamino)phenoxy)butane-thiosulfonic acid, sodium salt;
- 4-(2-(10-Carboxydecanoylamino)phenoxy)butane-phosphonic acid;
- 25 4-(2-(9-Carboxynonanoylamino)phenoxy)butane-sulfonic acid;
- 4-(2-(8-Carboxyoctanoylamino)phenoxy)butane-sulfinic acid;
- 4-(2-(7-Carboxyheptanoylamino)phenoxy)butane-thiosulfonic acid, sodium salt;
- 30 4-(2-(20-Carboxyeicosanoylamino)phenylthio)butane-phosphonic acid;

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 138 -

- 4-(2-(19-Carboxynonadecanoyl-N-methylamino)phenylthio)butanesulfonic acid;
- 4-(2-(18-Carboxyoctadecanoylamino)phenylthio)butanesulfonic acid;
- 5 4-(2-(17-Carboxyheptadecanoylamino)phenylthio)butanesulfinic acid;
- 4-(2-(16-Carboxyhexadecanoylamino)phenylthio)butanethiosulfonic acid, sodium salt;
- 10 4-(2-(14-Carboxytetradecanoyl N-propylamino)phenylthio)butanephosphonic acid;
- 4-(2-(13-Carboxytridecanoylamino)phenylthio)butanesulfonic acid;
- 4-(2-(12-Carboxydodecanoylamino)phenylthio)butanesulfinic acid;
- 15 4-(2-(11-Carboxyundecanoylamino)phenylthio)butanethiosulfonic acid, sodium salt;
- 4-(2-(9-Carboxynonanoylamino)phenylthio)butanephosphonic acid;
- 4-(2-(8-Carboxyoctanoylamino)phenylthio)butanesulfonic acid;
- 20 4-(2-(7-Carboxyheptanoylamino)phenylthio)butanesulfinic acid;
- 4-(2-(6-Carboxyhexanoylamino)phenylthio)butanethiosulfonic acid, sodium salt;
- 25 3-(2-(15-Carboxyisohexadecanoylamino)phenoxy)isobutanephosphonic acid;
- 3-(2-(14-Carboxytetradecanoylamino)phenoxy)isobutanoic acid;
- 5-(2-(13-Carboxytridecanoylamino)phenoxy)pentanesulfinic acid;
- 30 5-(2-(12-Phosphonododecanoylamino)phenoxy)valeramide;
- 5-(2-(11-Sulfoundecanoylamino)valeric acid;

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 139 -

- 5-(2-(10-Sulfinodecanoyl N-methylamino)phenoxy)valeric acid;
- 5-(2-(9-Thiosulfatononanoylamino)phenoxy)valeric acid, sodium salt;
- 5 6-(2-(9-Phosphonononanoylamino)phenoxy)caproic acid;
- 6-(2-(7-Sulfoisooctanoyl-N-methylamino)phenoxy) caproic acid;
- 7-(2-(7-Sulfinoheptanoyl-N-ethylamino)phenoxy) enanthic acid;
- 10 7-(2-(6-Thiosulfatohexanoylamino)phenoxy)enanthamide, sodium salt
- 7-(2-(5-Phosphonoisohexanoylamino)phenoxy)enanthic acid;
- 2-(2-(11-Sulfoundecanoylamino)phenoxy)acetic acid;
- 15 2-(2-(10-Sulfodecanoyl-N-propylamino)phenoxy)acetic acid;
- 3-(2-(9-Sulfinononanoylamino)phenoxy)propionic acid;
- 3-(2-(12-Thiosulfatododecanoylamino)phenylthio) propionamide, sodium salt;
- 20 3-(2-(11-Phosphoundecanoylamino)phenylthio) propionic acid;
- 3-(2-(11-Sulfoundecanoylamino)-4-methyl-phenylthio) isobutyric acid;
- 25 3-(2-(12-Sulfinododecanoylamino)phenylthio) isobutyramide;
- 5-(2-(11-Thiosulfoundecanoyl-N-butylamino)phenylthio) valeric acid, sodium salt;
- 5-(2-(10-Phosphonodecanoylamino)phenylthio)valeric acid;
- 30 5-(2-(12-Phosphonododecanoylamino)phenylthio) pentane-sulfonic acid;

This Sheet Has Been Replaced

SUBSTITUTE SHEET

- 140 -

- 5-(2-(11-Carboxydecanoylamino)phenylthio)
pentane sulfinic acid;
5-(2-(10-Phosphonodecanoylamino)phenylthio)pentane-
thiosulfonic acid;
5 6-(2-(12-Phosphonododecanoylamino)phenylthio)hexane-
phosphonic acid;
4-(2-(11-Sulfinoundecanoylamino)4-methyl-phenoxy)
butane-thiosulfonic acid, sodium salt;
4-(2-(12-Sulfododecanoylamino)6-methylphenoxy)butane
10 sulfonic acid;
4-(2-(11-Sulfodecanoylamino)3-chloro)phenylthio)-
butane-sulfinic acid;
4-(2-(10-Sulfodecanoylamino)4-methylphenoxy)butane-
thiosulfonic acid, sodium salt;
15 4-(2-(12-Sulfododecanoylamino)6-methylphenoxy)-
butane-phosphonic acid;
5-(2-(11-Sulfinoundecanoylamino)-3-methylphenyl-
thio)pentane-sulfonic acid;
4-(2-(11-Sulfinoundecanoylamino)-3-methylsulfonyl-
20 phenoxy)butane-sulfinic acid;
4-(2-(11-Sulfinoundecanoylamino)-4-methylsulfonyl)-
phenylthio)butanesulfonic acid;
4-(2-(12-Sulfinododecanoylamino)5-ethyl-phenoxy)-
butane-phosphonic acid;
25 4-(2-(10-Sulfinodecanoylamino)-3,5-dimethylphenoxy)-
butane-sulfonic acid;
4-(2-(9-Thiosulfatononanoylamino)-4-fluoro-phenoxy)
butane-sulfinic acid, sodium salt;
4-(2-(12-Thiosulfatododecanoylamino)-5-trifluoromethyl-
30 phenoxy)butane-thiosulfonic acid, sodium salt;
4-(2-(10-Thiosulfatodecanoylamino)-4-hydroxy-
phenylthio)butane-phosphonic acid, sodium salt;

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 141 -

- 4-(2-(9-Phosphonononanoylamino)-3,5-dimethoxyphenylthio)butyric acid;
- 5-(2-(11-Sulfoundecanoylamino)-4-nitrophenoxy)-valeric acid;
- 5 4-(2-(11-Sulfinoundecanoylamino)-5-amino-3-methylphenoxy)butyric acid;
- 4-(2-(11-Thiosulfatoundecanoylamino)-5-amino-4-methylphenylthio)butyric acid, sodium salt;
- 4-(2-(12-Phosphonododecanoylamino)-4-dimethyl-amino-10 phenoxy)butyric acid;
- 4-(2-(10-Sulfodecanoylamino)-phenoxy)butyric acid;
- 3-(2-(9-Sulfinononanoylamino)phenoxy)propionic acid;
- 3-(2-(12-Thiosulfatododecanoylamino)phenoxy)-3-methylpropionic acid, sodium salt;
- 15 3-(2-(11-Phosphonodecanoylamino)thienyloxy)-2-chloropropionic acid;
- 4-(2-(9-Sulfononoylamino)thienyloxy-3-ethoxybutyric acid;
- 4-(2-(12-Sulfinododecanoylamino)phenoxy)-2-fluorobutyric acid;
- 20 7-(2-(11-Thiosulfatoundecanoylamino)phenoxy)6-aminoenanthic acid, sodium salt;
- 5-(2-(11-Phosphonoundecanoylamino)-3-methylphenoxy)-4-oxo-valeric acid;
- 25 4-(2-12-Sulfododecanoylamino)phenoxy)but-2-enoic acid;
- 4-(2-(11-Sulfinodecanoylamino)phenoxy)but-2-enoic acid;
- 4-(2-(10-Thiosulfatodecanoylamino)phenoxy)-4-methylene valeric acid, sodium salt;
- 30 4-(2-(9-Phosphonononanoylamino)phenoxy)-4-fluoro-2-butenic acid;

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 142 -

- 4-(2-(11-Sulfo-3-methylbutanoylamino)thienyloxy)-
butyric acid;
- 4-(2-(4-Sulfin-3-chlorobutanoylamino)thienyloxy)-
butyric acid;
- 5 4-(2-(9-Thiosulfato-2-methoxynonanoylamino)thienyl-
oxy)butyric acid, sodium salt;
- 4-(2-(4-Phosphono-2-ethoxybutanoylamino)phenoxy)
butyric acid;
- 10 4-(2-(14-Sulfo-14-fluoro-2-acetamidotetradecanoyl-
amino)-3-methylphenoxy)butyric acid;
- 4-(2-13-Sulfin-2-oxotridecanoylamino)-4-methylthio)-
phenyloxy)butyric acid;
- 4-(2-(12-Thiosulfatododecanoyl-3-en-amino)phenoxy)
butyric acid;
- 15 4-(2-(11-Phosphonoundecanoyl-7-ene-amino)phenoxy)
butyric acid;
- 4-(2-(4-Sulfo-2-fluoro-2-butenoylamino)phenoxy)-
butyric acid;
- 4-(2-(12-Sulfinododecanoylamino)-4-methyl-3-pyridyl-
20 oxy)butyric acid;
- 4-(2-(11-Thiosulfatoundecanoylamino)-4-methyl-3-
pyridyloxy)butyric acid;
- 4-(2-(10-Phosphonodecanoylamino)-5-methyl-3-
pyridyloxy)butyric acid;
- 25 4-(2-(11-Sulfinodecanoylamino)-4-nitro-3-pyridylthio-
butyric acid;
- 4-(2-(10-Thiosulfatodecanoylamino)-6-methylsulfonyl-3-
pyridyloxy)butyric acid, sodium salt;
- 4-(2-(9-Phosphonononanoylamino)5-chloro-3-pyridyl-
30 thio)butyric acid;
- 4-(2-(11-Sulfoundecanoylamino)5-methylsulfonyl-3-
pyridylthio)butyric acid;

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 143 -

- 4-(2-(11-Sulfinoundecanoylamino)-6-methyl-3-pyridylthio)butyric acid;
- 4-(2-(11-Thiosulfatoundecanoylamino)-4,6-dimethyl-3-pyridyloxy)butyric acid, sodium salt;
- 5 4-(2-(12-Phosphonododecanoylamino)-5-(methylthio)-3-pyridyloxy)butyric acid;
- 4-(2-(10-Sulfodecanoylamino)-5-methoxy-3-pyridyloxy)butyric acid;
- 10 4-(2-(9-Sulfinononanoylamino)-4-fluoro-6-methyl-3-pyridyloxy)butyric acid;
- 4-(2-(12-Thiosulfatododecanoylamino)-5-(methylamino)-3-pyridyloxy)butyric acid, sodium salt;
- 4-(2-(11-Phosphonoundecanoylamino)-4-phenyl-3-pyridylthio)butyric acid;
- 15 4-(2-(9-Sulfononanoylamino)-6-methoxy-3-pyridylthio)butyric acid;
- 4-(2-(12-Sulfinododecanoylamino)-6-trifluoromethyl-3-pyridyloxy)butyric acid;
- 5-(2-(11-Thiosulfatoundecanoylamino)-4-methyl-3-thiophenyloxy)valeric acid, sodium salt;
- 20 4-(2-(11-Phosphonoundecanoylamino)-4-methyl-3-thiophenyloxy)butyric acid;
- 4-(2-(12-Sulfododecanoylamino)-5-methyl-3-thiophenylthio)butyric acid;
- 25 4-(2-(11-Sulfinoundecanoylamino)-4-methyl-3-thiophenylthio)butyric acid;
- 4-(2-(10-Thiosulfatodecanoylamino)-5-methyl-3-thienylthio)butyric acid, sodium salt;
- 4-(2-(9-Phosphonononanoylamino)-4-hydroxy-3-thienyloxy)butyric acid;
- 30 4-(2-(11-Sulfodecanoylamino)-4-methylthio-3-thienyloxy)butyric acid;

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 144 -

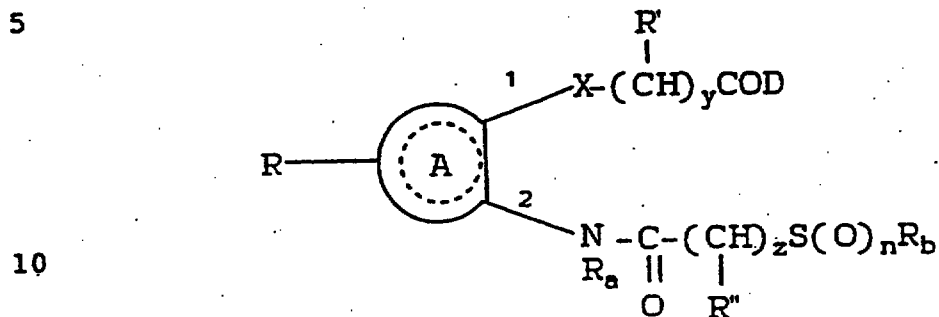
- 4-(2-(10-Sulfinodecanoylamino)-4-methylsulfonyl-3-thienyloxy)butyric acid;
4-(2-(9-Thiosulfatononanoylamino)-4-methylsulfonyl-3-thienyloxy)butyric acid, sodium salt;
5 4-(2-(12-Phosphonododecanoylamino)-5-trifluoromethyl-3-thienyloxy)butyric acid;
4-(2-(11-Sulfoundecanoylamino)-4-methyl-5-phenyl-3-thienyloxy)butyric acid;
4-(2-(11-Sulfinoundecanoylamino)-5-methylamino-3-thienyloxy)butyric acid;
10 4-(2-(12-Thiosulfatododecanoylamino)-5-dimethylamino-3-thienyloxy)butyric acid, sodium salt;
4-(2-(11-Phosphoundecanoylamino)-4-amino-3-thienyloxy)butyric acid;
15 Preferred compounds in the invention include:
4-(2-(11-Carboxyundecanoylamino)phenoxy)butyric acid,
4-(2-(11-Carboxyundecanoylamino)phenylthio)butyric acid,
4-(2-(9-Carboxynonanoylamino)phenoxy)butyric acid,
20 4-(2-(10-Carboxydecanoylamino)phenoxy)butyric acid,
4-(2-(12-Carboxydodecanoylamino)phenoxy)butyric acid,
4-(2-(13-Carboxytridecanoylamino)phenoxy)butyric acid,
4-(2-(15-Carboxypentadecanoylamino)phenoxy)butyric acid,
25 4-(2-(11-Carboxyundecanoylamino)-4-methylphenoxy)-butyric acid,
4-(2-(11-Carboxyundecanoylamino)-5-methylphenoxy)-butyric acid.

30

This Sheet Has Been Replaced

- 145 -

Also included as a 5α -reductase inhibitor in this invention is an agent of the following formula:



wherein

15 A is an 1,2-disubstituted aromatic ring, preferably a benzene ring;

D is OH, NH₂, NHR_c, OR_c;

X is O, S, SO, or SO₂;

20 R is H,

C₁-C₄ alkyl,
phenyl or substituted phenyl,
halo,

25 haloalkyl,
hydroxy,
carboxy,
cyano,

C₁-C₄ alkoxy,
C₁-C₄ alkylthio,
30 C₁-C₄ alkylsulfinyl,
C₁-C₄ alkylsulfonyl,
nitro,
amino,

C₁-C₄ mono or di-alkylamino;

This Sheet Has Been Replaced



- 146 -

R' and R'' are independently

H,

halo,

C₁-C₄ alkyl or C₁-C₄ alkoxy,

5 amino, or oxo, where CH-R' or CH-R''
in the formula become -C=O;

R_a is H, C₁-C₄ alkyl;

10 R_b, R_c are independently, C₁-C₁₂ alkyl, phenyl,
phenyl-C₁-C₄ alkyl;

n is 0-2;

15 y is 1-6;

z is 6-20; and

wherein

20 $\begin{array}{c} R' \\ | \\ (CH)_y \end{array}$ and

$\begin{array}{c} R'' \\ | \\ (CH)_z \end{array}$ can independently represent substituted or
unsubstituted alkyl radicals or alkenyl radicals
containing at least one alkene bond;

25 and pharmaceutically acceptable salts and esters
thereof.

The compounds of the instant invention are
inhibitors of the human testosterone 5 α -reductase.

30 The scope of the compounds of the instant
invention are described by the above-described
formula.

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 147 -

In the description of the formula the following terms are used which are hereby defined:

X can be O or S, preferably one X being O, and particularly preferred wherein both Xs are O, i.e., the catechol structure.

"C₁-C₄ alkyl" includes linear or branched species, e.g. methyl, ethyl, n-propyl, isopropyl, cyclopropyl, n-butyl, isobutyl, sec-butyl, t-butyl; and "C₁-C₁₂ alkyl" includes alkyl up to 12 carbons including n-octyl, t-decyl, n-dodecyl.

"Phenyl C₁-C₄ alkyl" includes benzyl, 2-phenethyl, and the like;

"C₁-C₄ alkoxy" includes linear or branched species, e.g., methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, t-butoxy;

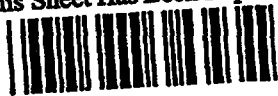
"Halo" includes fluoro, chloro, bromo or iodo;

"Substituted phenyl" includes phenyl substituted by one or more of C₁-C₄ alkyl, C₁-C₄ alkoxy, or halo, and the like, as defined above; representative examples include o, m-, p-methoxy phenyl; 2,4-dimethoxyphenyl; 2-chloro-4-ethoxyphenyl; 3,5-dimethoxyphenyl; 2,4-dichlorophenyl; 2-bromo-4-methylphenyl, o-fluorophenyl, and the like.

"Haloalkyl" includes C₁-C₄ alkyl, defined above, substituted with one or more "halo" as defined above and includes: trifluoromethyl, 2,2-dichloroethyl and the like.

"C₁-C₄ alkylthio" includes C₁-C₄ alkyl, defined above, substituted with at least one divalent thio (-S-) grouping including; methylthio, ethylthio, isopropylthio, n-butylthio, and the like.

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 148 -

"C₁-C₄ alkylsulfinyl" includes C₁-C₄ alkyl, defined above, substituted with at least one -SO- grouping including; methylsulfinyl, ethylsulfinyl; isopropylsulfinyl, and the like.

5 "C₁-C₄ alkylsulfonyl" includes C₁-C₄ alkyl, defined above, substituted with at least one sulfonyl group, -SO₂-, including; methylsulfonyl, ethylsulfonyl, isopropylsulfonyl, n-butylsulfonyl, and the like;

10 "C₁-C₄ mono or dialkyl amino" includes amino, substituted with one or more C₁-C₄ alkyl groups as defined hereinabove, including: methylamino, ethylamino, n-butylamino, t-butylamino, dimethylamino, N,N-diethylamino, methyl-t-butylamino, and the like.

15 The R group or groups on the benzene ring can be present initially in the process, e.g. phenyl, methyl, methoxy, cyano, carbomethoxy, trifluoromethyl, (present as in the starting 6-nitrophenol 1 in Flow Chart A) or added later by a
20 conventional reaction, e.g. chloro, as by chlorination, nitro by nitration, or created from a starting or added functional group present, e.g. converting a later added nitro to an amino group by catalytic reduction, then alkylating to a mono or
25 dialkylamine. An amino group can be subjected to diazotization to a hydroxy group, which can be followed by methylation to a methoxy group. Similarly, a hydroxy group can be converted to a thiol by the analogous procedures described in J.
30 Org. Chem. 31, pp 3980-3984 (1966) by Newman and Karnes, and J. Org. Chem. 31, pp 410 (1966) by Kwart, H. and Evans, E.S. The resulting thiol can be

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 149 -

alkylated to alkylthio, which can be oxidized to the corresponding sulfoxide or sulfone. Preferred substituents are H, C₁-C₄ alkyl, C₁-C₄ alkoxy and phenyl. These reactions and sequences are conventional in the art and it will be obvious to one skilled in the art to modify the benzene ring to arrive at an R radical disclosed herein.

By the term "pharmaceutically acceptable salts and esters thereof" is meant salts and esters of the acid groups in the final molecule which can be used as part of the human drug delivery system and include the salts: sodium, potassium, calcium, ammonium, substituted ammonium, quaternary ammonium, and esters: ethyl ester, acetate, besylate, edetate, phenpropionate, acetate, pamoate, and esters which serve as "prodrug" formulations which will hydrolyze in the body at physiological pH's to regenerate the acid, including pivaloylates, e.g. pivoxetil and pivoxil, and Kanebo esters, and the like.

(CH)_y, where y is 1-6, preferably 3, can contain at least one R' substituent as defined above, and can be, e.g., -CH₂-; -CH₂-CH₂-; -CH₂-CH₂-CH₂-; -CH-; -CH-CH₂-; -CH₂-CH-; -CH₂-CH-CH₂-; -CH₂-CH-CH₂-; -CH₂-CH₂-CH-; and the like.

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 150 -

An alkene bond can also be present in

$\begin{array}{c} \text{R}' \\ | \\ (\text{CH})_y \end{array}$, e.g., $\text{CH}_2\text{-CH=CH-}$; $\text{CH}_2\text{-CH=CH-CH}_2\text{-}$; $\text{-CH}_2\text{-CH=CH-}$;
 $\text{-(CH}_2)_3\text{-CH=CH-}$ and the like.

5

$\begin{array}{c} \text{R}'' \\ | \\ (\text{CH})_z \end{array}$, where z is 6-20, preferably 8-14, can contain at least one R'' substituent as defined above, and can be completely alkyl; e.g., $(\text{CH}_2)_n\text{-COOH}$, where n is 8-14 preferably and the like.

10

An alkene bond can also be present in

$\begin{array}{c} \text{R}'' \\ | \\ (\text{CH})_z \end{array}$, e.g., $\text{-(CH}_2)_4\text{-CH=CH-(CH}_2)_4\text{-}$, and the like.

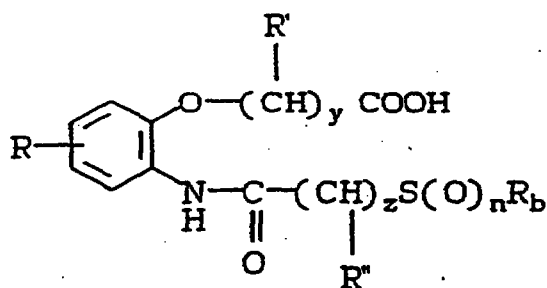
15

Preferred is where one R' or R'' is H and

particularly preferred is where both $\begin{array}{c} \text{R}' \\ | \\ (\text{CH})_y \end{array}$ and $\begin{array}{c} \text{R}'' \\ | \\ (\text{CH})_z \end{array}$ are alkyl.

Preferred compounds of the instant invention are given by the following formulas;

20



25

and,

30

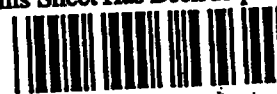
This Sheet Has Been Replaced



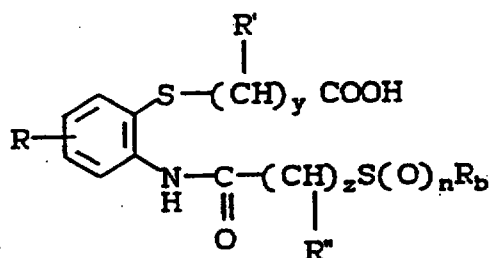
SUBSTITUTE SHEET

- 151 -

This Sheet Has Been Replaced



5

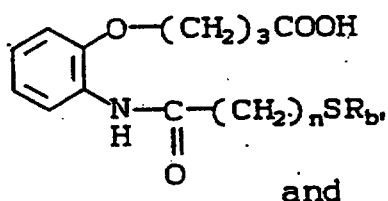


wherein R, R', R'', Y, Z, R_b are defined above;

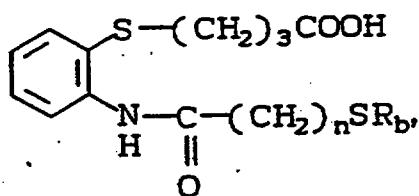
10

and particularly preferred are:

15



20



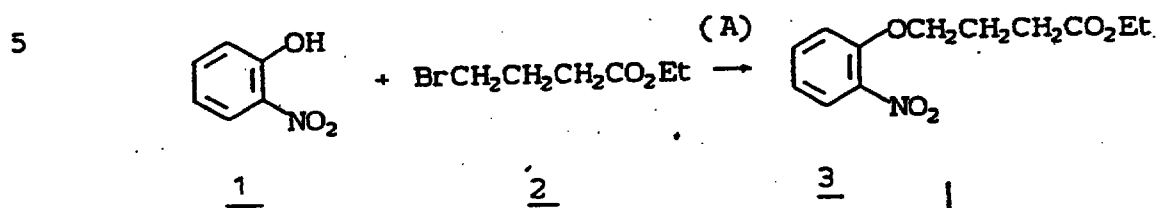
25

30

where n is 8-14, and R_b is methyl, ethyl, cyclopropyl, isopropyl, n-propyl, t-butyl, phenyl or benzyl.

The compounds of the instant invention can be made by the procedures outlined in the following Flowcharts.

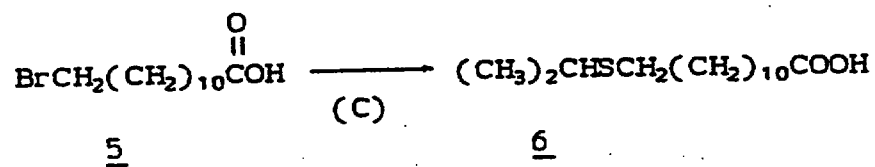
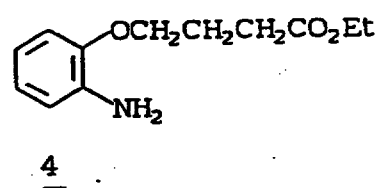
- 152 -

FLOW CHART A-3

10

(B)

15



25

30

30

This Sheet Has Been Replaced



SUBSTITUTE SHEET

- 153 -

FLOW CHART A-3 CONT'D.

5

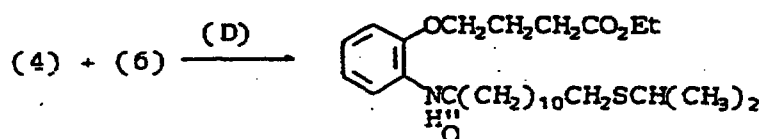
10

15

20

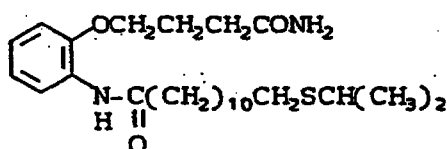
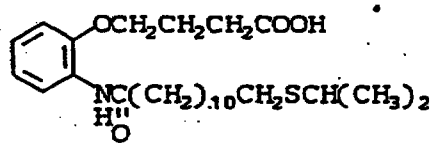
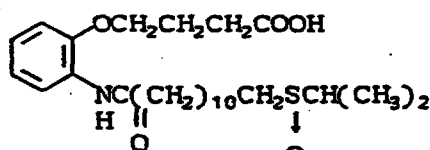
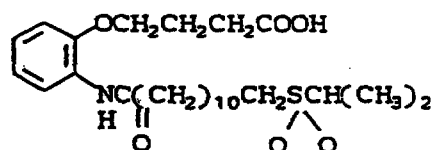
25

30

7

(F)

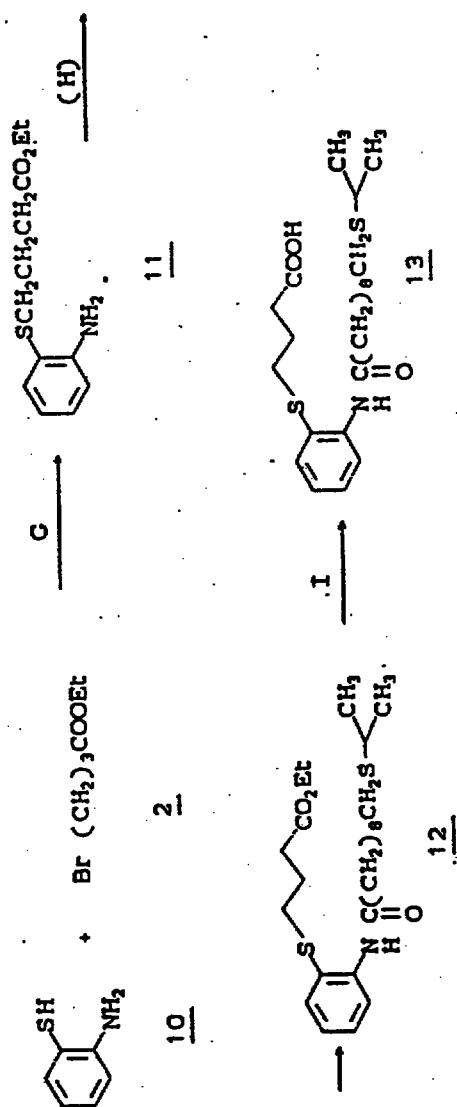
(E)

988a8b

This Sheet Has Been Replaced



FLOW CHART B-3



This Sheet Has Been Replaced



- 156 -

As seen in Flow Chart A-3, o-nitrophenol 1, ethyl 4-bromobutyrate 2 and anhydrous K_2CO_3 in e.g., dry acetone are heated at reflux e.g. for 12-100 hours, or stirred for an extended period of time at room temperature, under a nitrogen atmosphere to product ethyl 4-(2-nitrophenoxy) butyrate 3, in Step (A).

A solution of 3 in e.g., ethyl acetate is catalytically hydrogenated at room temperature under e.g. 40 psig of H_2 in the presence of a 5% Pd/C catalyst to yield ethyl 4-(2-aminophenoxy)butyrate 4 in Step (B).

Step (C) comprises reacting the 12-bromo dodecanoic acid 5 with isopropyl mercaptan in a suitable solvent, e.g., dimethoxyethane, at about 80-85°C to obtain the acid 6.

In Step (D) the mono acid 6 is reacted with the amine 4 and N'N'-dicyclohexylcarbodiimide (DCC) at e.g., room temperature in e.g., dry methylene chloride, optionally in the presence of 4-dimethylaminopyridine, to produce the amide 7.

In Step (E), the ether-amide 7 is de-esterified by e.g., 2.5 N NaOH in MeOH/ H_2O to yield the final product, monoacid 8.

The monoacid 8 can be treated with $NaIO_4$ in (acetone/water) at room temperature for (4-24 hours) to produce the corresponding sulfoxide 8a. Additionally, 8 can be treated with meta-chlorobenzoic acid in (CH_2Cl_2) at a temperature of about 0° to 25°C for (1-24 hours) to produce the corresponding sulfone 8b.

This Sheet Has Been Replaced



0-2433330

SUBSTITUTE SHEET