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Bowler et al.

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[54] STEROID DERIVATIVES

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[51] **Int. Cl.**[4] **C07J 00/00**; A61K 31/56

[52] **U.S. Cl.** **260/397.5**

[58] **Field of Search** 260/397.5; 514/182

[56] **References Cited**

U.S. PATENT DOCUMENTS

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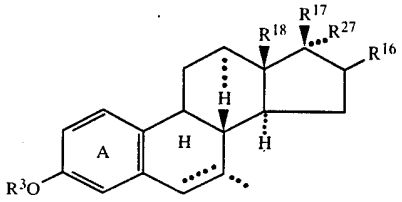
[57] **ABSTRACT**

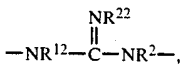
A steroid derivative of the formula:

ST—A—X—R^1

wherein ST is a 7α-linked steroid nucleus of the general formula:



wherein the double bond(s) between carbon atoms 6 and 7 and/or carbon atoms 8 and 9 are optional; wherein the aromatic ring A may optionally bear one or two halogen or alkyl substituents; wherein R^3 is hydrogen, alkyl, or acyl; wherein R^{16} is hydrogen, alkyl or hydroxy; wherein either R^{17} is hydroxy or acyloxy and R^{27} is hydrogen, alkyl, alkenyl or alkynyl, or R^{17} and R^{27} together form oxo (=O); wherein R^{18} is alkyl; wherein A is alkylene, alkenylene or alkynylene optionally fluorinated and optionally interrupted by —O—, —S—, —SO—, —SO_2—, —CO—, —NR—, —NR-CO—, —CONR—, —COO—, —OCO— or phenylene, wherein R is hydrogen or alkyl; wherein R^1 is hydrogen, alkyl, alkenyl, cycloalkyl, halogenoalkyl, carboxyalkyl, alkoxycarbonylalkyl, aryl, arylalkyl, or dialkylaminoalkyl, or R^1 is joined to R^2 as defined below; and wherein X is —$CONR^2$—, —$CSNR^2$—, —$NR^{12}CO$—, —$NR^{12}CS$—, —$NR^{12}CONR^2$—,



—SO_2NR^2— or —CO—; or, when R^1 is not hydrogen, is —O—, —NR^2—, —(NO)R^2—, —(PO)R^2—, —$NR^{12}COO$—; —$NR^{12}SO_2$—, —S—, —SO— or —SO_2—; wherein R^2 is hydrogen or alkyl or R^1 and R^2 together form alkylene or halogenoalkylene; wherein R^{12} is hydrogen or alkyl and wherein R^{22} is hydrogen, cyano or nitro; or a salt thereof when appropriate.

8 Claims, No Drawings

STEROID DERIVATIVES

This invention relates to new steroid derivatives which possess antioestrogenic activity.

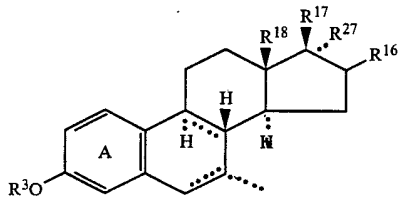
Various oestradiol derivatives are known which bear a carboxyalkyl substituent at the 7α-position. These have been used, when bound via the carboxy group to polyacrylamide resin or to agarose, for the purification of oestrogen receptors (Journal of Biological Chemistry, 1978, 253, 8221); and, when conjugated with bovine serum albumin, for the preparation of antigens (United Kingdom Specification No. 1,478,356).

We have now found that certain 7α-substituted derivatives of oestradiol and related steroids possess potent antioestrogenic activity.

According to the invention there is provided a steroid derivative of the formula:

$$ST—A—X—R^1$$

wherein ST is a 7α-linked steroid nucleus of the general formula:



wherein the dotted lines between carbon atoms 6 and 7, and carbon atoms 8 and 9, of the steroid nucleus indicate that there is an optional double bond between carbon atoms 6 and 7, or that there are two optional double bonds between carbon atoms 6 and 7 and carbon atoms 8 and 9;

wherein the aromatic ring A may optionally bear one or two halogen or alkyl substituents;

wherein R^3 is hydrogen or alkyl, alkanoyl, alkoxycarbonyl, carboxyalkanoyl or aroyl each of up to 10 carbon atoms;

wherein R^{16} is hydrogen, alkyl of up to 6 carbon atoms which is preferably in the β-configuration, or hydroxy which is preferably in the α-configuration;

wherein either R^{17} (in the β-configuration) is hydroxy or alkanoyloxy, carboxyalkanoyloxy or aroyloxy each of up to 10 carbon atoms; and R^{27} (in the α-configuration) is hydrogen or alkyl, alkenyl or alkynyl each of up to 6 carbon atoms;

or R^{17} and R^{27} together form oxo (=O);

wherein R^{18} is alkyl of up to 6 carbon atoms;

wherein A is straight- or branched-chain alkylene, alkenylene or alkynylene each of from 3 to 14 carbon atoms, which may have one or more hydrogen atoms replaced by fluorine atoms, or has the formula

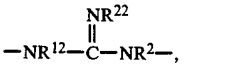
$$—A^1—Y—A^{11}—$$

wherein A^1 and A^{11} are each alkylene or alkenylene, optionally flourinated, having together a total of 2 to 13 carbon atoms and Y is —O—, —S—, —SO—, —SO_2—, —CO— or —NR— wherein R is hydrogen or alkyl of up to 3 carbon atoms;

or A^1 is alkylene or alkenylene, optionally fluorinated, and A^{11} is a direct link or alkylene or alkenylene, optionally fluorinated, such that A^1 and A^{11} together have a total of 1 to 12 carbon atoms, and Y is —NR-CO—, —CONR—, —COO—, —OCO— or phenylene wherein R has the meaning stated above;

wherein R^1 is hydrogen, or alkyl, alkenyl, cycloalkyl, halogenoalkyl, carboxyalkyl, alkoxycarbonylalkyl, aryl or arylalkyl each of up to 10 carbon atoms, or dialkylaminoalkyl wherein each alkyl is of up to 6 carbon atoms, or R^1 is joined to R^2 as defined below;

and wherein X is —$CONR^2$—, —$CSNR^2$—, —NR—CO—, —NR—CS—, —NR—$CONR^2$—,



—SO_2NR^2— or —CO—;

or, when R^1 is not hydrogen, is —O—, —NR^2—, —(NO)R^2—, —(PO)R^2—, —NR—COO—, —NR—SO_2—, —S—, —SO— or —SO_2—;

wherein R^2 is hydrogen or alkyl of up to 6 carbon atoms, or R^1 and R^2 together form alkylene or halogenoalkylene such that, with the adjacent nitrogen atom, they form a heterocyclic ring of 5 to 7 ring atoms, one of which atoms may be a second heterocyclic atom selected from oxygen, sulphur and nitrogen;

wherein R^{12} is hydrogen or alkyl of up to 6 carbon atoms;

and wherein R^{22} is hydrogen, cyano or nitro;

or a salt thereof when appropriate.

A suitable value for the halogen or alkyl substituent in ring A is, for example, fluoro, chloro, bromo, iodo, methyl or ethyl.

A suitable value for R^3 when it is alkyl, alkanoyl, alkoxycarbonyl, carboxyalkanoyl or aroyl is, for example, methyl, ethyl, acetyl, propionyl, butyryl, pivalyl, decanoyl, isopropoxycarbonyl, succinyl or benzoyl. R^3 is preferably hydrogen or alkanoyl or alkoxycarbonyl each of up to 5 carbon atoms.

A suitable value for R^{16} when it is alkyl is, for example, methyl or ethyl. R^{16} is preferably hydrogen.

A suitable value for R^{17} when it is alkanoyloxy, carboxyalkanoyloxy or aroyloxy is, for example, acetoxy, propionyloxy, succinyloxy or benzoyloxy. R^{17} is preferably hydroxy.

A suitable value for R^{27} when it is alkyl, alkenyl or alkynyl is, for example, ethyl vinyl or ethynyl. R^{27} is preferably hydrogen.

A suitable value for R^{18} is methyl or ethyl, especially methyl.

The group ST— is preferably oestra-1,3,5(10)-triene-3,17β-diol, 3-hydroxyoestra-1,3,5(10)-trien-17-one or 17α-ethynyloestra-1,3,5(10)-triene-3,17β-diol, all of which bear the —A—X—R^1 substituent in the 7α-position, or a 3-alkanoyl ester thereof.

One preferred value for the group —A— is a straight-chain alkylene group of the formula

$$—(CH_2)_n—$$

wherein n is an integer of from 3 to 14, especially from 7 to 11, which may have one of the hydrogen atoms replaced by fluorine, for example to provide the group —$(CH_2)_8CHFCH_2$—. A may also be a branched-chain alkylene group, for example the group —$(CH_2)_6CH(CH_3)$—, or a straight-chain alkenylene group, for example of the formula

$$-(CH_2)_2CH{=}CH(CH_2)_m-$$

wherein m is an integer from 0 to 10, especially from 3 to 7.

A second preferred value for the group A is a group of the formula

$$-A^1-Y-A^{11}-$$

wherein A^1 is straight-chain alkylene or alkenylene each of 2 to 9 carbon atoms, especially alkylene of 4 to 6 carbon atoms, —Y— is phenylene (ortho, meta- or, especially, para-) and A^{11} is a direct link, ethylene or vinylene, especially ethylene.

A suitable value for R^1 when it is alkyl, alkenyl or cycloalkyl is, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, t-pentyl, 2,2-dimethylpropyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, n-hexyl, 1,1-dimethylbutyl, 1,3-dimethylbutyl, n-heptyl, n-nonyl, n-decyl, n-undecyl, allyl, cyclopentyl or cyclohexyl.

A suitable value for R^1 when it is aryl or arylalkyl is, for example, phenyl, 2-ethylphenyl, p-fluorophenyl, p-chlorophenyl, m-chlorophenyl, p-cyanophenyl, p-methoxyphenyl, benzyl, α-methylbenzyl, p-chlorobenzyl, p-fluorophenethyl or p-chlorophenethyl.

A suitable value for R^1 when it is halogenoalkyl, carboxyalkyl, alkoxycarbonylalkyl or dialkylaminoalkyl is, for example, 2-chloro-2,2-difluoroethyl, 2,2,2-trifluoroethyl, 2,2,3,3,3-pentafluoropropyl, 3-chloropropyl, 2,2-difluorobutyl, 4,4,4-trifluorobutyl, 1H,1H-heptafluorobutyl, 4,4,5,5,5-pentafluoropentyl, 4,4,5,5,6,6,6-heptafluorohexyl, 1H,1H-tridecafluoroheptyl, 5-carboxypentyl, 5-methoxycarbonylpentyl or 3-dimethylaminopropyl.

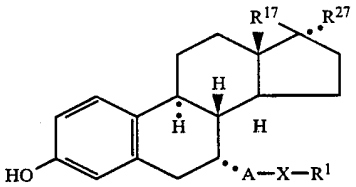
A suitable value for the heterocyclic ring $-NR^1R^2$ is, for example, pyrrolidino, piperidino, 4-methylpiperidino, 4-ethylpiperidino, 3-methylpiperidino, 3,3-dimethylpiperidino, 4-chloropiperidino, morpholino or 4-methylpiperazino.

A suitable value for R^2 or R^{12} when it is alkyl is, for example, methyl, ethyl or n-butyl.

One appropriate salt is an acid-addition salt of a steroid derivative which possesses an amino function, for example a compound wherein Y is —NR—, X is $-NR^2-$ or R^1 is dialkylaminoalkyl. A suitable acid-addition salt is, for example, a hydrochloride, hydrobromide, acetate, citrate, oxalate or tartrate.

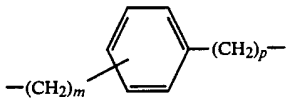
Another appropriate salt is a base-addition salt of a steroid derivative which possesses a carboxy function, for example a compound wherein R^1 is carboxyalkyl. A suitable base-addition salt is, for example, a sodium, potassium, ammonium or cyclohexylamine salt.

A preferred steroid derivative of the invention has the formula:



wherein R^{17} is hydroxy and R^{27} is hydrogen or ethynyl, or R^{17} and R^{27} together form oxo;

wherein —A— is $-(CH_2)_n-$, wherein n is an integer from 3 to 14, especially from 7 to 11, or —A— is



wherein m is an integer from 2 to 9, especially from 4 to 6, and p is 0 to 2, especially 0 or 2; wherein R^1 is alkyl, fluoroalkyl or cycloalkyl each of up to 10 carbon atoms, or phenyl, chlorophenyl or benzyl, or is linked to R^2 as stated below;

wherein X is $-CONR^2-$, $-NR^{12}CO-$, —S—, —SO— or $-SO_2-$, wherein R^2 is hydrogen or alkyl of up to 3 carbon atoms or together with R^1 forms alkylene of 5 or 6 carbon atoms, and wherein R^{12} is hydrogen or alkyl of up to 3 carbon atoms.

A particularly preferred steroid derivative of the invention has the last-mentioned formula wherein the number of carbon atoms in the two groups A and R^1 adds up to between 12 and 16, inclusive, especially 14 if neither R^1 nor A contains a phenyl or phenylene group, and 16 if there is a phenylene group in —A— or a phenyl group in R^1.

Specific steroid dervatives of the invention are hereinafter described in the Examples. Of these, particularly preferred compounds are:

N-n-butyl-N-methyl-, N-2,2,3,3,4,4,4-heptafluorobutyl-N-methyl- and N,N-(3-methylpentamethylene)-11-(3,17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)undecamide;

N-n-butyl- and N-2,2,3,3,4,4,4-heptafluorobutyl-3-p-[4-(3,17β-dihydroxyoestra-1,3,5(10)-trien-7α-yl)butyl]-phenylpropionamide;

7α-(10-p-chlorophenylthiodecyl)-, 7α-(10-p-chlorophenylsulphinyldecyl)-, 7α-[9-(4,4,5,5,5-pentafluoropentylsulphinyl)nonyl]-, 7α-[10-(4,4,4-trifluorobutylsulphinyl)-decyl]- and 7α-[10-(p-chlorobenzylsulphonyl)decyl]oestra-1,3,5(10)-triene-3,17β-diol; and

7α-(9-n-heptylsulphinylnonyl)oestra-1,3,5(10)-triene-3,17β-diol.

A preferred process for the manufacture of a steroid derivative of the invention wherein X has the formula $-CONR^2-$, $-CSNR^2-$ or $-SO_2NR^2-$ comprises the reaction of a compound of the formula ST^1-A-Z^1, wherein A has the meaning stated above, wherein ST^1 either has the same meaning as stated above for ST, or is an equivalent 7α-linked steroid nucleus which bears one or more protecting groups for functional derivatives, and wherein Z^1 is an activated group derived from a carboxylic, thiocarboxylic or sulphonic acid, with an amine of the formula HNR^1R^2, wherein R^1 and R^2 have the meanings stated above, whereafter any protecting group in ST^1 is removed by conventional means.

A suitable activated group Z^1 is, for example, a mixed anhydride, for example an anhydride formed by reaction of the acid with a chloroformate such as isobutyl chloroformate.

A suitable protecting group in ST^1 is, for example, an alkyl or aralkyl ether, for example the methyl or benzyl ether, of the 3-hydroxy function, or a tetrahydropyranyl ether of the 17β-hydroxy function.

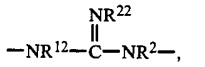
A preferred process for the manufacture of a steroid derivative of the invention wherein X has the formula

—CO— comprises the reaction of an acid of the formula ST^1—A—COOH, wherein ST^1 and A have the meanings stated above, with an organometallic compound of the formula R^1—M, wherein R^1 has the meaning stated above and M is a metal group, for example the lithium group, whereafter any protecting group in ST^1 is removed by conventional means.

A preferred process for the manufacture of a steroid derivative of the invention wherein X has the formula —S—, —O—, —NR^2— or —(PO)R^2— comprises the reaction of a compound of the formula ST^1—A—Z^2, wherein ST^1 and A have the meanings stated above and wherein Z^2 is a displaceable group, with a compound of the formula R^1SH, R^1OH, HNR^1R^2 or R^1R^2P—C_6H_5 wherein R^1 and R^2 have the meanings stated above, whereafter any protecting group in ST^1 is removed by conventional means, and whereafter a phosphonium salt is hydrolysed to the phosphinyl compound.

A suitable value for Z^2 is, for example, a halogen atom or a sulphonyloxy group, for example the methanesulphonyloxy or toluene-p-sulphonyloxy group.

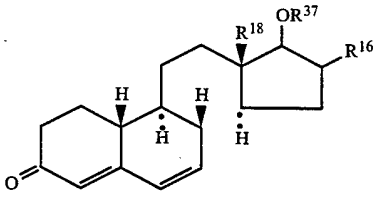
A preferred process for the manufacture of a steroid derivative of the invention wherein X has the formula —NR^{12}CO—, —NR^{12}CS—, —NR^{12}CONR^2—,



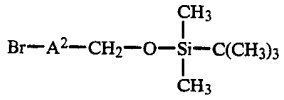
—NR^{12}COO— or —$NR^{12}SO_2$— comprises the reaction of a compound of the formula ST^1—A—NHR^{12}, wherein ST^1, A and R^{12} have the meanings stated above, with an acylating agent derived from an acid of the formula R^1COOH, R^1CSOH, R^1OCOOH or R^1SO_2OH; or, for the manufacture of a urea, with an isocyanate of the formula R^1NCO; or, for the manufacture of a guanidine, with a cyanamide of the formula R^1NR^2—CN, whereafter any protecting group in ST^1 is removed by conventional means.

A suitable acylating agent is, for example, an acyl chloride or acyl anhydride.

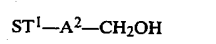
The starting materials for use in all the abovementioned processes may be obtained by reacting a steroid derivative of the formula



wherein R^{16} and R^{18} have the meanings stated above and wherein R^{37} is an acyl group, for example the acetyl group, with a compound of the formula



wherein A^2 either has the same meaning as stated above for A, or wherein —A^2—CH_2— has the same meaning as stated above for A; separating the isomers at the 7-position of the steroid nucleus to provide the 7α-isomer; hydrolysing off the dimethyl-t-butylsilyl protecting group; and converting the steroidal part of the molecular to the required structure by conventional reactions. The intermediate product obtained, which has the formula:



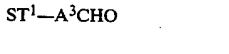
wherein ST^1 has the meaning stated above, may be oxidised to the corresponding carboxylic acid of the formula ST^1—A^2—COOH which provides the starting material for the first or second process of the invention described above;

or it may be converted into a compound of the formula ST^1—A^2—CH_2Z^2 by reaction with a halogenating agent or a sulphonylating agent to provide the starting material for the third process of the invention described above.

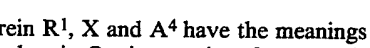
The starting material for the fourth process of the invention described above may be obtained by using the third process of the invention described above except that an amine of the formula $R^{12}NH_2$ is used in place of an amine of the formula HNR^1R^2.

The intermediate of the formula ST^1—A^2—CH_2OH may be oxidised to an aldehyde of the formula ST^1—A^2—CHO which may then be used, by reaction with an appropriately-substituted hydrocarbyltriphenylphosphonium salt or hydrocarbyltriethylphosphonate, to prepare a starting material wherein —A— is alkenylene.

An alternative process for the manufacture of a steroid derivative of the invention wherein —A— is alkenylene of the formula —A^3—CH=CH—A^4— comprises the reaction of a compound of the formula:



wherein ST^1 and A^3 have the meanings stated above, with a triphenylphosphonium salt of the formula:

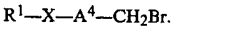


wherein R^1, X and A^4 have the meanings stated above and wherein Q^- is an anion, for example the bromide ion.

The reaction may be carried out in solution in dimethyl sulphoxide in the presence of dimsyl sodium.

The steroidal aldehyde starting material when A^3 is A^2 as defined above may be obtained by oxidation of the corresponding alcohol as described above. The steroidal aldehyde starting material wherein A^3 is a direct link may be obtained from the 3-keto-$\Delta^{4,6}$-inital steroidal starting material described above by reaction with cyanide to give the 3-keto-Δ^4-7α-cyano compound, aromatisation, suitable protection and then reduction of the cyano group to the formyl group.

The phosphonium starting material may be obtained by reaction of triphenylphosphine with a bromide of the formula



A steroid derivative of the invention wherein ST is a 17β-hydroxy-steroid derivative may be converted by conventional reactions into the corresponding 17-keto steroid derivative, and thence to the corresponding 17β-hydroxy-17α-hydrocarbyl steroid derivative (that is, a steroid derivative of the invention wherein R^{27} is alkyl, alkenyl or alkynyl). Similarly, a steroid derivative

of the invention wherein R^3 and/or R^{17} are other than hydrogen may be obtained from the corresponding compounds wherein R^3 and/or R^{17} are hydrogen by conventional etherification or esterification processes, and these may also be used in reverse to prepare the corresponding hydroxy compounds.

A steroid derivative of the invention wherein A is alkenylene may be hydrogenated to provide the corresponding compound wherein A is alkylene.

A steroid derivative of the invention wherein —X— is $—CH_2NR^2—$ or $—NR^2CH_2—$ may be obtained by the reduction, for example with borane, of the corresponding compound wherein —X— is $—CONR^2—$ or $—NR^2CO—$.

A steroid derivative of the invention wherein —X— is —CSNH— or —NHCS— may be obtained by the reaction of the corresponding compound wherein X is —CONH— or —NHCO— with 2,4-bis-(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulphide.

A steroid derivative of the invention wherein X is $—(NO)R^2$, —SO— or $—SO_2—$ may be obtained by the oxidation of the corresponding compound wherein X is $—NR^2—$ or —S—. The conditions for the oxidation will be chosen to provide the desired product; for example aqueous sodium metaperiodate will oxidise the sulphur group to sulphinyl, and m-chloroperbenzoic acid in chloroform solution will oxidise the sulphur group to sulphonyl or the amine to its oxide.

As stated above, a steroid derivative of the invention possesses antioestrogenic activity. This may be demonstrated by its effect in antagonising the increase in weight of the uterus of an immature female rat produced by administering oestradiol benzoate to said rat. Thus, when a steroid derivative of the invention and oestradiol benzoate are co-administered for 3 days to such a rat, a smaller increase in uterine weight is produced than the substantial increase which would be produced by the administration of oestradiol benzoate without the steroid derivative of the invention.

In particular, a preferred steroid derivative of the invention produces an antioestrogenic effect at a dose which produces no partial agonist effect, unlike the known antioestrogens tamoxifen and clomiphene. When a preferred steroid is coadministered with oestradiol benzoate to a rat as described above, no increase in uterine weight whatsoever is observed at a suitable dose.

A compound with the above pharmacological properties is of value in the treatment of the same conditions in which tamoxifen is beneficial, in particular, in the treatment of anovulatory infertility and in the treatment of breast tumors. It is also of value in the treatment of menstrual disorders.

When used to produce an anti-oestrogenic effect in warm-blooded animals, a typical daily dose is from 0.1 to 25 mg/kg. administered orally or by injection. In man this is equivalent to an oral dose of from 5 to 1250 mg./day. A steroid derivative of the invention is most conveniently administered to man in the form of a pharmaceutical composition.

According to a further feature of the invention, there is provided a pharmaceutical composition comprising a steroid derivative of the invention together with a pharmaceutically acceptable diluent or carrier.

The composition may be in a form suitable for oral or parenteral administration. A tablet or capsule is a particularly convenient form for oral administration and such a composition may be made by conventional methods and contain conventional excipients. Thus a tablet could contain diluents, for example mannitol or maize starch, disintegrating agents, for example alginic acid, binding agents, for example methyl-cellulose, and lubricating agents, for example magnesium stearate.

The composition may contain, in addition to the steroid derivative of the invention, one or more antiandrogenic agents or antiprogestational agents.

A composition for oral administration may conveniently contain from 5 to 500 mg. of a steroid derivative of the invention.

The invention is illustrated but not limited by the following Examples:

EXAMPLE 1

N-Methylmorpholine (0.24 ml.) and isobutyl chloroformate (0.288 ml.) were successively added to a stirred solution of 11-(17β-acetoxy-3-benzoyloxyoestra-1,3,5(10)-trien-7α-yl)undecanoic acid (1.0 g.) in methylene chloride (17 ml.) which was cooled to −10° C., and after 30 minutes n-butylamine (0.29 ml.) was added and the mixture was stirred at laboratory temperature for 15 minutes. Saturated aqueous sodium bicarbonate solution (20 ml.) was added and the mixture was extracted four times with methylene chloride (50 ml. each time). The combined extracts were washed with water (10 ml.), dried and evaporated to dryness. There was thus obtained as residue 11-(17β-acetoxy-3-benzoyloxy-N-n-butyloestra-1,3,5(10)-trien-7α-yl)undecanamide as an oil.

Aqueous N-sodium hydroxide solution (8 ml.) was added to a stirred solution of the above amide (1.06 g.) in a mixture of methanol (16 ml.) and tetrahydrofuran (8 ml.) and the mixture was stirred at laboratory temperature for 18 hours, neutralised with aqueous N-hydrochloric acid and the organic solvents were removed by evaporation. Water (40 ml.) was added and the mixture was extracted four times with methylene chloride (60 ml. each time). The combined extracts were washed with water (10 ml.), dried and evaporated to dryness and the residue was purified by chromatography on a silica gel (Merck Kieselgel 60) column using a 13:7 v/v mixture of ethyl acetate and toluene as eluant. There was thus obtained N-n-butyl-11-(3,17β-dihydroxyoestra-1,3,5(10)trien-7α-yl)undecanamide as an oil which was characterised by the following data:

Proton magnetic resonance spectrum (in $CDCl_3$)

Shift (δ)	Type of peak	No of protons	Assignment
7.16	multiplet	1	aromatic protons at positions 1, 2 and 4
6.65	"	2	
3.7		1	position 17
3.28	quartet	2	$—CH_2—$ adjacent to —CO—
0.90	triplet	3	$—CH_3$ in n-butyl
0.78	singlet	3	position 18

Mass Spectrum

$M^+ = 511.4039$ ($C_{33}H_{53}O_3N$ requires 511.4024).

$M—H_2O = 493$.

$M—(CH_2CONHC_4H_9) = 397$.

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