[54] **17-SUBSTITUTED STEROIDS USEFUL IN CANCER TREATMENT**

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[51] **Int. Cl.**[6] **A61K 31/58**; C07J 43/00

[52] **U.S. Cl.** **514/176**; 540/95

[58] **Field of Search** 540/95; 514/176

[56] **References Cited**

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413270	2/1991	European Pat. Off. .

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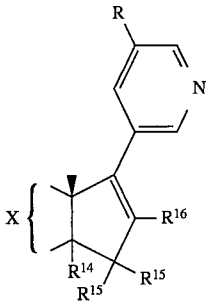
Attorney, Agent, or Firm—Nixon & Vanderhye

[57] **ABSTRACT**

Compounds of the general formula (1)



(I)

wherein X represents the residue of the A, B and C rings of a steroid, R represents a hydrogen atom or an alkyl group of 1 to 4 carbon atoms, R^{14} represents a hydrogen atom and R^{15} represents a hydrogen atom or an alkyl or alkoxy group of 1–4 carbon atoms, or a hydroxy or alkylcarbonyloxy group of 2 to 5 carbon atoms or R^{14} and R^{15} together represent a double bond, and R^{16} represents a hydrogen atom or an alkyl group of 1 to 4 carbon atoms, in the form of the free bases or phannaceutically acceptable acid addition salts, are useful for treatment of androgen-dependent disorders, especially prostatic cancer, and also oestrogen-dependent disorders such as breast cancer.

22 Claims, No Drawings

OTHER PUBLICATIONS

D. H. R. Barton et al., "Studies on the oxidation of Hydrazones with iodide . . . ", Tetrahedron 44, 147–162 (1988).

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17-SUBSTITUTED STEROIDS USEFUL IN CANCER TREATMENT

This specification is a continuation-in-part of PCT Application PCT/GB93/00531, filed Mar. 15, 1993 and which designated the United States of America.

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to 17-substituted steroids and their use in the treatment of androgen-dependent and oestrogen-dependent disorders, especially prostatic cancer and breast cancer respectively.

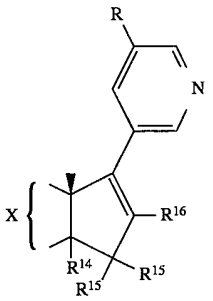
2. Description of the Related Art

The 17α-hydroxylase/C_{17-20} lyase enzyme complex (hereinafter "hydroxylase/lyase") is known to be essential for the biosynthesis of androgens and oestrogens. In the treatment of androgen-dependent disorders, especially prostatic cancer, there is a need for strong inhibitors of hydroxylase/lyase. Certain anti-androgenic steroids are well known, for example Cyproterone acetate (17α-acetoxy-6-chloro-1α, 2α-methylene-4,6-pregnadiene-3,20-dione). Many other steroids have been tested as hydroxylase/lyase inhibitors. See, for example, PCT Specification WO 92/00992 (Schering AG) which describes anti-androgenic steroids having a pyrazole or triazole ring fused to the A ring at the 2,3-position, or European Specifications EP-A 288053 and EP-A 413270 (Merrell Dow) which propose 17β-cyclopropylamino androst-5-en-3β-ol or -4-en-3-one and their derivatives.

SUMMARY OF THE INVENTION

It has now surprisingly been found that steroids lacking a C_{20} side chain and having a 17-(3-pyridyl) ring in its place, together with a 16,17-double bond, are powerful hydroxylase/lyase inhibitors, useful for the above-stated purposes.

According to the invention, there are provided compounds of the general formula



(I)

wherein X represents the residue of the A, B and C rings of asteroid, R represents a hydrogen atom or an alkyl group of 1–4 carbon atoms, R^{14} represents a hydrogen atom, a halogen atom or an alkyl group of 1 to 4 carbon atoms and each of the R^{15} substituents independently represents a hydrogen atom or an alkyl or alkoxy group of 1–4 carbon atoms, a hydroxy group or an alkylcarbonyloxy group of 2 to 5 carbon atoms or together represent an oxo or methylene group or R^{14} and one of the R^{15} groups together represent a double bond and the other R^{15} group represents a hydrogen atom or an alkyl group of 1 to 4 carbon atoms, and R^{16} represents a hydrogen atom, halogen atom, or an alkyl group of 1 to 4 carbon atoms, in the form of the free bases or pharmaceutically acceptable acid addition salts.

The term "steroid" herein includes any compound having the steroidal B and C rings, but in which all or part of the A ring is missing e.g. ring not closed (lacking the 2- or 3-position C-atom or both) or takes the form of a cyclopentane ring. It also includes azasteroids having a ring nitrogen atom in place of a ring carbon atom, especially in the A-ring such as in 4-azasteroids.

In general, the compounds of formula (1) are new and such compounds per se are included in the invention. However, certain of them have been disclosed as intermediates in the synthesis of certain steroids having a 3-pyridyl or 3-pyridonyl group in the 17β-position, see J. Wicha and M. Masnyk, Bulletin of the Polish Academy of Sciences: Chemistry 33 (1–2), 19–27 and 29–37 (1985). The first of these papers says that a 17β-side chain of the form —C=C—C=O or —C=C—C=N favours cardiotonic properties and describes the synthesis of 17β-(3-pyridyl)-14β-androst-4-ene-3β,14-diol, while the second uses this compound to prepare 17β-[3-pyrid-2(1H)onyl]-14β-androst-4-ene-3β,14-diol. Those final compounds differ from those of the present invention by having a saturated D-ting and the paper contains no test results. Insofar as certain compounds within formula (1) are known as intermediates in these syntheses, the invention extends to the compounds only for use in therapy. These are 3β-acetoxy-17-(3-pyridyl)androsta-5,14,16-triene and 3β,15α- and 3β,15β-diacetoxy-17-(3-pyridyl)androsta-5,16-diene. See also J. Wicha. et. al., Heterocycles 20, 231–234 (1983) which is a preliminary communication of the first of the above two papers.

J. Wicha et. al., Bulletin of the Polish Academy of Sciences, Chemistry 32 (1–2), 75–83 (1984) have also described the preparation of 3β-methoxy-17β-(3-pyridyl)androstane and pyridone analogues thereof via the intermediate 3β-methoxy-17-(3-pyridyl)-5α-androst-16-ene. Accordingly, the invention extends to the latter compound only for use in therapy. A preliminary communication of this paper, by J. Wicha and M. Masynk, appeared in Heterocycles 16, 521–524 (1981).

The invention also includes pharmaceutical compositions comprising a compound of formula (1) in association with a pharmaceutically acceptable diluent or carrier. The terminology "pharmaceutical compositions" implies that injectible formulations are sterile and pyrogen-free and thereby excludes any compositions comprising the compound of formula (1) and a non-sterile organic solvent, such as may be encountered in the context of the final stages of preparing these above-mentioned compounds of formula (1) which have been described in the literature but without any therapeutic use being mentioned.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

In the compounds of the invention the essential structural features comprise all of:

a 3-pyridyl ring in the 17-position

a ring double bond in the 16,17-position of the D-ring

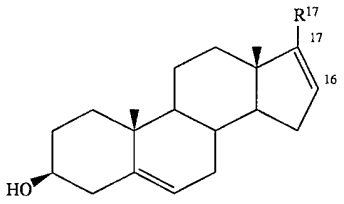
the 18-position methyl group

It is critical that the pyridine nitrogen atom be in the 3-position, not the 2- or 4-position. It is also critical that the pyridine ring be joined directly to the 17-carbon atom. This criticality is demonstrated by tests of inhibiting activity against hydroxylase and lyase (Table 1). The concentration of test compound required to achieve 50% inhibition of the

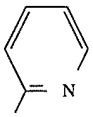
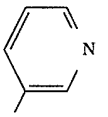
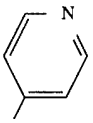
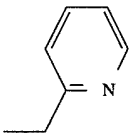
enzyme is far greater for the 2-pyridyl, 4-pyridyl and 2-pyridylmethyl compounds tested than for the 3-pyridyl. The methods of determination were as described in the Examples hereinafter.

TABLE 1

Effect of variations in the 17-substitutent on inhibition of hydroxylase and lyase, demonstrating the criticality of the 17-substituent in this invention.



(2)

R^{17}	Type	IC_{50} (μM) Lyase	IC_{50} (μM) Hydroxylase
	2-Pyridyl (for comparison)	0.13	0.32
	3-pyridyl (present invention)	0.003	0.004
	4-pyridyl (for comparison)	2.0	5.0
	2-picolyl (for comparison)	>10	>10

Note:
all the compounds of formula (2) tested were poor inhibitors of aromatase: IC_{50} >20 μM.

Our modelling of the geometry of the putative transition state of the lyase component of the hydroxylase-lyase enzyme complex, in the putative mechanism of action of the lyase component, suggests that the 16,17-double bond is essential to allow the 3-pyridine ring to adopt the orientation required for co-ordination to the haem group of the hydroxylase-lyase complex.

Elsewhere, the D-ring can have any other simple substituent. Certain simple substituents are defined in connection with the preferred general formula (1), but it will be appreciated that others could be substituted for those of formula (1). In the compounds of formula (1), R^{15} is preferably hydrogen or alkyl of 1 to 3 carbon atoms, R^{16} hydrogen, alkyl of 1 to 3 carbon atoms, fluorine, chlorine, bromine or iodine, and R hydrogen or methyl, in the 5-position of the pyridine ring.

The remainder of the molecule, designated "X" in formula (1), can be of any kind conventional in steroid chemistry or have any other feature known in steroids having anti-androgenic activity, for example the pyrazole or triazole ring, fused to the A ring at the 2- and 3- positions, disclosed in the above-cited Specification WO 92/00992, or oxazole ring fused in the same positions.

By way of example, X can represent the residue of

androstan-3α- or 3β-ol,
androst-5-en-3α- or 3β-ol,
androst-4-en-3-one,
androst-2-ene,
androst-4-ene,
androst-5-ene,
androsta-5,7-dien-3α or 3β-ol,
androsta-1,4-dien-3-one,
androsta-3,5-diene,
estra-1,3,5[10]-triene,
estra-1,3,5[10]-trien-3-ol,
5α-androstan-3-one,
androst-4-ene-3,11-dione,
6-fluoroandrost-4-ene-3-one or
androstan-4-ene-3,6-dione

each of which, where structurally permissible, can be further derivatised in one or more of the following ways:

to form 3-esters, especially 3-alkanoates and -benzoates,
to have one or more carbon to carbon ring double bonds in any of the 5,6-, 6,7-7,8-, 9,11- and 11,12-positions
as 3-oximes
as 3-methylenes
as 3-carboxylates
as 3-nitriles
as 3-nitros
as 3-desoxy derivatives
to have one or more hydroxy, halo, C_{1-4}-alkyl, trifluoromethyl, C_{1-4}-alkoxy, C_{1-4}-alkanoyloxy, benzoyloxy, oxo, methylene or alkenyl substituents in the A, B or C-ring
to be 19-nor.

Preferred C_{1-4}-alkyl and alkoxy groups are methyl and ethoxy.

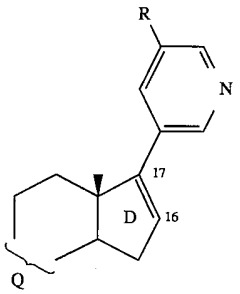
Preferred C_{1-4}-alkanoyloxy groups are acetoxy and propanoyloxy.

Preferred halo groups are fluoro, bromo and chloro and the preferred substitution position is the 6-position.

The substituents include, for instance, 2-fluoro, 4-fluoro, 6-fluoro, 9-fluoro, 3-trifluoromethyl, 6-methyl, 7-methyl, 6-oxo, 7-oxo, 11-oxo, 6-methylene, 11-methylene, 4-hydroxy, 7-hydroxy, 11-hydroxy or 12-hydroxy, each in any appropriate epimeric form, and, subject to structural compatibility (well known in general steroid chemistry), in any combination of two or more such groups.

Compounds which are likely to be unstable are considered excluded from consideration. Such compounds will be evident to steroid chemists. Compounds having esoteric substituents likely to interfere with the stereochemical alignment of the steroid molecule with the enzymes to be inhibited, by virtue of steric or electronic distribution effects, are to be avoided. For example, a 2,3,5,6-tetrafluoro-4-trifluoromethylphenoxy substituent in the 3-position is not recommended. Androst-5-en-3β-ol having such an ether substituent in place of the 3β-hydroxy group has been shown to be a very poor inhibitor for lyase and hydroxylase.

The currently preferred compounds of formula (1) include those which are saturated and unsubstituted at the 11- and 12-positions and which therefore are of the general formula (3):



(3)

wherein Q represents the residue of A, B and C rings of asteroid, and R is a hydrogen atom or an alkyl group of 1–4 carbon atoms.

However, 11- and/or 12-substituted compounds are also active. Particularly preferred are 11-oxo and 11β-hydroxy derivatives of compounds of formula (3).

Specifically preferred compounds of the invention comprise

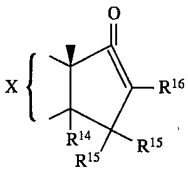
17-(3-pyridyl)androsta-5,16-dien-3β-ol,
17-(3-pyridyl)androsta-3,5,16-triene,
17-(3-pyridyl)androsta-4,16-dien-3-one,
17-(3-pyridyl)estra-1,3,5[10],16-tetraen-3-ol,
17-(3-pyridyl)-5α-androst-16-en-3α-ol
and their acid addition salts and 3-esters.

Other notable compounds of the invention comprise

17-(3-pyridyl)-5α-androst-16-en-3-one,
17-(3-pyridyl)-androsta-4,16-diene-3,11-dione,
17-(3-pyridyl)-androsta-3,5,16-trien-3-ol,
6α- and 6β-fluoro-17-(3-pyridyl)androsta-4,16-dien-3-one
17-(3-pyridyl)androsta-4,16-dien-3,6-dione,
17-[3-(5-methyl pyridyl)]androsta-5,16 dien-3β-ol
3α-trifluoromethyl-17-(3-pyridyl)androsta-16-en-3β-ol
and their acid addition salts and 3-esters.

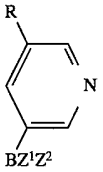
Insofar as certain compounds within formula (1) are known per se and these are compounds which are less easy to prepare than many of the others, a preferred class of compounds of formula (1) is those which do not have a 3β-alkoxy group, a 14,15-double bond or a 15-ester group.

The compounds of formula (1) can be prepared by a method which is in itself novel and inventive. Starting from a 17-oxo compound of general formula (4):



(4)

wherein X, R^{14}, R^{15} and R^{16} are as defined above and any other oxo groups and hydroxy groups in the molecule are first appropriately protected, the method comprises replacing the 17-hydroxy group of compound (4) in its enol form by a leaving group (L) which is capable of being replaced by a 3-pyridyl group in a palladium complex-catalysed cross-coupling reaction with a pyridyl ring-substituted boron compound of formula (5):

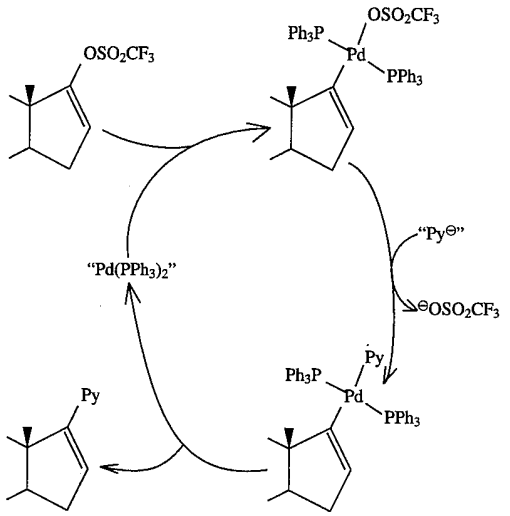


(5)

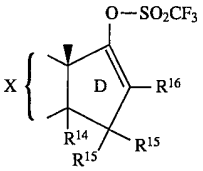
wherein Z^1 and Z^2 independently represent hydroxy or alkoxy or alkyl of 1–4 carbon atoms each, preferably 1–3 carbon atoms, most preferably ethyl or methoxy, or Z^1 and Z^2 together represent an alkylenedioxy group of 2 or 3 carbon atoms and R is as defined above and carrying out said cross-coupling reaction.

The palladium complex-catalysed cross-coupling reaction of the 17-substituted steroid with the boron compound is believed to involve the steps indicated in the following illustrative reaction scheme 1 (Py=3-pyridyl). The pyridyl anionic species is provided by the boron compound.

Scheme 1

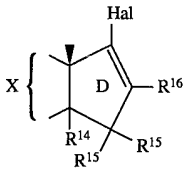


The replacement of the 17-enol group can be, for example, to form a 16,17-ene trifluoromethanesulphonate ("triflate") of formula (6):



(6)

or a 17-iodo or bromo-16,[17]-ene (a "vinyl halide") of formula (7):



(7)

(Hal=I or Br)

Compounds of formula (6) can be prepared by reacting the 17-oxo compound of formula (4) with an enol ester-forming trifluoromethanesulphonic acid derivative such as the anhydride, see S. Cacchi, E. Morera and G. Ortar, Tetrahedron Letters, 25, 4821 (1984). The 17-oxo compound can be considered notionally to exist in the enol form, the reaction being one of esterification of the enol.

For the preparation of the 17-position derivatives of formula (6) or (7) any necessary protection of other groups in the molecule may be first carried out. For example in the triflate route hydroxyl groups are conveniently protected as their acetates, whilst in the vinyl halide route the 3-oxo group of steroids can be selectively protected as their perfluorotolyl enol ethers, see M. Jarman and R. McCague, J.Chem. Soc. Perkin Trans. 1, 1129 (1987).

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