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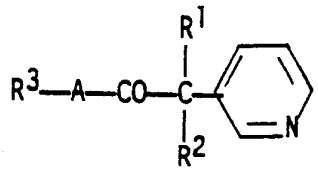

(3)

(57) Abstract

Compounds having the general formula (3), wherein each of R^1 and R^2 independently represents hydrogen or C_{1-4} alkyl or together represent the residue of a cycloalkyl group of 3 to 6 carbon atoms; A represents O, NR^4 wherein R^4 is defined as for R^1 or R^2 or CR^5R^6 wherein R^5 and R^6 are as defined for R^1 or R^2 as separate substituents; and R^3 represents a bridged alicyclic group; as free bases or their pharmaceutically acceptable salts are useful in treating androgen-dependent, especially prostatic, cancer.

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HETEROCYCLIC COMPOUNDS, THEIR PREPARATION AND PHARMACEUTICAL USE

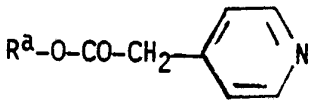
Background of the invention

1. Field of the invention

This invention relates to derivatives containing the 3-pyridylacetyl function, namely esters and amides of 3-pyridylacetic acid as well as 3-pyridylmethyl ketones, together with certain derivatives thereof, their preparation and use in treating prostatic cancer.

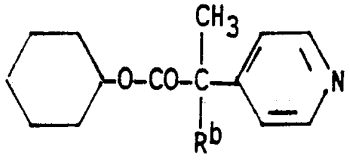
2. Description of related art

R. McCague, M. G. Rowlands, S. E. Barrie and J. Houghton, J. Med. Chem. 33, 3050-3055 (1990), have reported that certain esters of 4-pyridylacetic acid, of general formula:



(1)

wherein R^a represents a specified alicyclic group (e.g. cyclohexyl or a terpene residue) or



(2)

wherein R^b represents a hydrogen atom or a methyl group, inhibit the 17α-hydroxylase/C_{17-20} lyase enzyme complex which is essential for biosynthesis of androgens. The inhibition of androgen biosynthesis by virtue of the hydroxylase/lyase inhibition indicates that the compounds of McCague et al., supra, could be useful for the treatment of prostate cancer since many such tumours depend on androgens for growth.

The compounds of McCague et al. are also inhibitors of aromatase. Aromatase is an enzyme required in the biosynthesis of estrogens. The ability to inhibit aromatase is considered a desirable property in compounds which are to be used to treat breast cancer. It is undesirable, however, for the treatment of prostatic cancer that a compound should be a strong inhibitor of both aromatase and hydroylase/lyase since the inhibition of aromatase would prevent the removal, by further conversion into oestrogens, of any products of the hydroxylase/lyase enzyme complex which escaped the blockade of hydroxylase/lyase. As a result, a patient could lose some of the benefits of hydroxylase/lyase inhibition.

Accordingly, for the present application of treating prostatic cancer it is desirable to keep the ratio:

$$\frac{IC_{50} \text{ versus lyase}}{IC_{50} \text{ versus aromatase}}$$

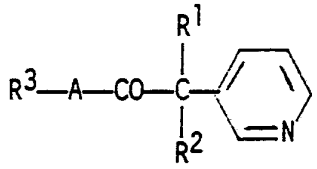
as low as possible. (A small numerator indicates that the compound is a powerful inhibitor of lyase. A large denominator indicates that it is a poor inhibitor of aromatase). Their best compound from that viewpoint is cyclohexyl 2-methyl-2-(4-pyridyl) propanoate of formula (2) above wherein R^b is methyl and formula (26) in the paper, although it must be borne in mind that their data are based on human aromatase and rat lyase. The same compound was also degraded more slowly by hog liver esterases than the monomethylated compound [formula (2), R^b = H] or the unmethylated counterpart [formula (1), R^a = cyclohexyl]. The paper envisages similar dimethyl substitution of compound of formula (1) wherein R^a is an alicyclic group of the terpene residue type, notwithstanding that in such compounds the IC_{50} lyase/aromatase ratio in unmethylated compounds is bigger than for the cyclohexyl compounds (1).

An immediately following companion paper by C. A. Laughton and S. Neidle, J. Med. Chem. 33, 3055-3060 (1990) attempts to explain the data of the McCague et al paper in terms of mimicry of the natural steroid substrates for aromatase and hydroxylase/

lyase by the 4-pyridylacetates and propanoates with reference to cyclohexyl 4-pyridylacetate [formula (1); R^a = cyclohexyl] and its α-methyl derivative, cyclohexyl 2-(4-pyridyl)propanoate [formula (2); R^b = H], since the α-methyl substitution lowers the IC_{50} lyase/aromatase ratio from 67 to 1.0. The conclusions of the paper are rather hard to discern. As regards aromatase inhibition, the paper suggests that the carbon atom adjacent to the ester carbonyl function occupies a spatial position mimicing that of the C(2)-atom of the natural steroid substrate (testosterone), and that the conformation of the overall molecular "fit" is favourable, but that the α-methyl substituent would then mimic a substituent on C(2) of the steroid. Since other evidence has suggested that steric bulk in the C(2) region is unfavourable for aromatase inhibition, the poorer inhibition of the α-methyl substituted ester could be rationalised in this manner. However, as regards hydroxylase/lyase inhibition, there are no such literature precedents, and the authors make many assumptions in suggesting that the α-methyl group of the cyclohexyl 2-(4-pyridyl)propanoate lies in a spatial position mimicing the C(16) or C(20)-atom of the natural steroid substrate pregnenolone, and conclude that the inhibitory activity stems from hydrophobic interactions of the methyl group with the active site of the enzyme. This view does not, however, explain why the hydroxylase/lyase activity of compounds lacking the α-methyl group, e.g. 4-ethylcyclohexyl 4-pyridylacetate, is just as good as the α-methyl compound used for modelling and thereby suggests that the structural requirements for hydroxylase/lyase activity are unpredictable.

Summary of the invention

It has now surprisingly been found that 3-pyridylacetyl compounds of formula (3) below have useful hydroxylase/lyase inhibitory activity with low IC_{50} lyase/aromatase ratios, and are therefore of potential value in treating androgen-induced cancers such as prostatic cancer. These compounds have the general formula:



(3)

wherein each of R^1 and R^2 independently represents hydrogen or lower alkyl or together represent the residue of a cycloalkyl group of 3 to 6 carbon atoms;

A represents O, NR^4 where R^4 is defined as for R^1 and R^2, or CR^5R^6 where R^5 and R^6 are defined as for R^1 or R^2 as separate substituents; and

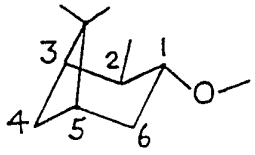
R^3 represents a bridged alicyclic group;

as free bases or their pharmaceutically acceptable salts, especially acid addition salts. The term "lower" herein signifies that the group has 1 to 4 carbon atoms. The invention includes each of the optical isomers and mixtures thereof, especially racemic mixtures.

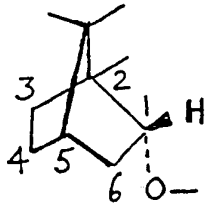
Description of the preferred embodiments

The R^3 group in the preferred compounds of the invention can be defined in various ways, all reflecting the fact that R^3 is hydrocarbyl, cyclic and non-aromatic and has at least one bridge across a ring. Because R^3 is defined as bridged, it contains at least two alicyclic rings. It can contain more than two alicyclic rings, either by having more than one bridge or by having one or more other fused rings (not resulting from a bridge). In this invention, a bridge is regarded as joining two non-adjacent carbon atoms of the ring by means of at least one intermediate carbon atom. A fused ring is produced when two non-adjacent carbon atoms are joined directly by a bond.

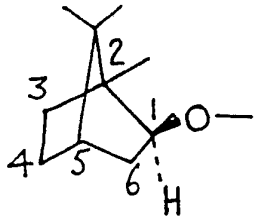
In the preferred compounds it is possible to regard the R^3 group as a substituted cyclohexyl group in which the substituents comprise bridging members. Examples of preferred R^3 groups fitting this definition are shown below, along with the adjacent oxygen atom:-



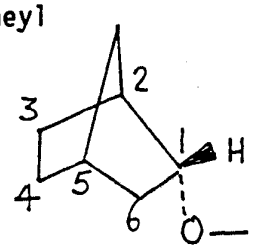
isopinocampheyl (cyclohexyl substituted by a 3,5-isopropylidene bridge and additionally having a 2-methyl substituent)



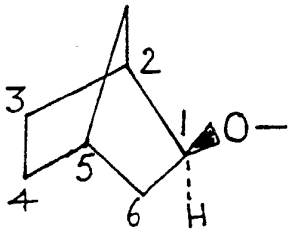
borneyl (cyclohexyl substituted by a 2,5-isopropylidene bridge and additionally having a 2-methyl substituent)



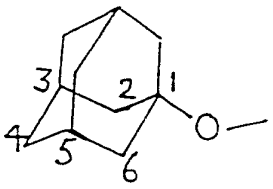
isoborneyl



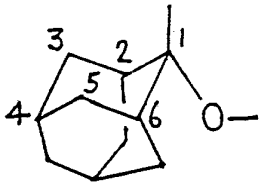
endo-norborneyl (cyclohexyl substituted by a 2,5-methylene bridge)



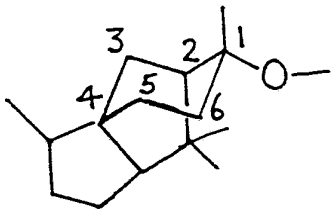
exo-norborneyl



adamantyl (cyclohexyl substituted by a first 1,3-(1,3-propylene), bridge and further substituted by a second bridge between its 5-carbon atom and the middle carbon atom of the first bridge)



methyladamantyl (cyclohexyl substituted by a first 2,4-(1,3-propylene) bridge, further substituted by a second bridge between its 6-carbon atom and the middle carbon of the first bridge, and additionally having a 1-methyl substituent on the cyclohexane ring)



cedryl (cyclohexyl substituted by a 2,4-isobutylene bridge, having a methyl-substituted cyclopentane ring fused to the 4 carbon atom of the cyclohexane ring and the 1-carbon atom of the bridge and additionally having a 1-methyl substituent on the cyclohexane ring).

Alternatively, the preferred R^3 groups can be defined by reference to the largest carbocyclic ring which is bridged, which in cedryl is a cycloheptane ring and in adamantyl is a cyclooctane ring. According to this definition, R^3 represents a bridged alicyclic group having from 6 to 8 ring atoms (excluding any bridge atoms) and optionally having one or more alicyclic groups fused to the bridged ring, e.g. a substituted

cyclopentane or cyclohexane ring. In this definition the bridges are normally of 1 or 2 carbon atoms in linear length (counting only those carbon atoms lying within the bridge, between the ring atoms, not counting as within the bridge the ring atoms with which the bridge starts or finishes and not counting as within the linear length any carbon atoms pendant from a bridge atom, e.g. in the two methyls of an isopropylidene bridging group).

The alicyclic groups of R^3 which are bridged are cycloalkane rings, which can contain unsaturation, but are not aromatic, and can be substituted by one or more simple hydrocarbyl substituents such as alkyl of 1-4 carbon atoms, especially methyl. The bridges need not be wholly linear and thus may have pendant C_{1-4} alkyl, especially methyl groups, for example. Likewise the said cycloalkane rings or bridges or both can have cycloalkane, especially cyclopentane or cyclohexane, rings fused thereto. The fused rings may themselves be simply substituted, as mentioned above for the bridged rings, especially by alkyl of 1 to 4 carbon atoms.

The invention includes optically active forms of the compounds of formula (3), particularly with reference to borneyl, isoborneyl, cedryl and isopinocampheyl.

The A group in formula (3) is preferably -O-, but when it is $-CH_2-$ potentially hydrolysable ester and amide bonds are not present, which is also advantageous.

All "lower alkyl" groups herein are preferably methyl or ethyl.

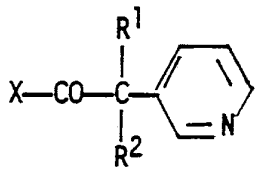
R^1 and R^2 are preferably both methyl except when R^3 is an extremely bulky group, such as cedryl, in which substituents pendant from a bridge extend into the vicinity of the ester oxygen atom. In such an event preferably no more than one of R^1 and R^2 is a lower alkyl group and most preferably they are both hydrogen. Alternatively R^1 and R^2 together with the carbon atom to which they are attached can complete a ring of 3, 4, 5 or 6 carbon atoms, cyclopentane being preferred.

In the divalent amino group NR^4, R^4 is preferably hydrogen, but can have any of the other meanings for the individual R^1

and R^2 substituents, of which lower alkyl, especially methyl, is preferred.

In the ketones, R^5 and R^6 are preferably hydrogen, one is methyl and the other hydrogen or both are methyl. R^5 and R^6 do not together represent a cycloalkyl or alkylene group.

The compounds of the invention can be prepared in various ways, conveniently starting from 3-pyridylacetic acid or an ester thereof. Preferably, the starting ester is the methyl or ethyl ester. The starting compounds (A = -O-) have the general formula (4):



(4)

wherein X represents -OH or a reactive substitutent and R^1 and R^2 are as defined for formula (3). Simple esterification or trans-esterification with an alcohol of formula R^3-OH where R^3 is as defined for formula (3) leads to the esters of formula (3).

The reactive substituent X is any reactive for the purpose of forming an ester or amide of formula (3). For preparation of amides (A = -NH-) the compounds of formula (4) can be reacted with primary amines in the usual way.

To prepare the ketones of formula (3) in which A = $-CH_2-$, a suitable procedure would involve the reaction between an alkali metal salt of 3-picoline, e.g. 3-picolyllithium (C. G. Screttas, T. F. Estham, C. W. Kamienski, Chimia, 24, 109-111, 1970) and an appropriate methyl ester R^3ACO_2Me where A is another CR^5R^6 group, according to the method used by J. L. Bond, D. L. Krottinger, R. M. Schumacher, E. H. Sund and T. J. Weaver, Journal of Chemical and Engineering Data, 18, 349-350, (1973) to make alkyl 4-pyridylmethylketones from 4-picolylsodium and RCO_2Me.

Where the compounds of formula (3) being prepared are those in which R^1 or R^2 is other than hydrogen, it may be convenient

to use as the starting compound of formula (4) an unsubstituted pyridylacetic acid compound wherein R^1 and R^2 are hydrogen, prepare the corresponding compound of formula (3) and subsequently introduce the desired R^1 or R^2 substituent by the action of an alkali metal hydride followed by a lower alkyl or cycloalkyl bromide or iodide. Methylene (CH_2=) or ethylidene (CH_3CH_2=) derivatives may be prepared from corresponding methyl and ethyl derivatives by thermal decomposition of phenylsulphoxide B. M. Trost et al., J. Amer. Chem. Soc., 98, 4887-4902 (1976).

The compounds may be prepared as salts, e.g. the hydrochloride and converted to the free base form and thereafter to such other conventional pharmaceutically acceptable salts as acetates, citrates and lactates, as may seem appropriate.

The present invention also provides a pharmaceutical composition which comprises a therapeutically effective amount of a compound of the invention, in association with a therapeutically acceptable carrier or diluent. The composition of the invention can, for example, be in a form suitable for parenteral (e.g. intravenous, intramuscular or intracavital), oral, topical or rectal administration. Particular forms of the composition may be, for example, solutions, suspensions, emulsions, creams, tablets, capsules, lipsomes or micro-reservoirs, especially compositions in orally ingestible or sterile injectable form. The preferred form of composition contemplated is the dry solid form, which includes capsules, granules, tablets, pills, boluses and powders. The solid carrier may comprise one or more excipients, e.g. lactose, fillers, disintegrating agents, binders, e.g. cellulose, carboxymethylcellulose or starch or anti-stick agents, e.g. magnesium stearate, to prevent tablets from adhering to tabletting equipment. Tablets, pills and boluses may be formed so as to disintegrate rapidly or to provide slow release of the active ingredient.

Where national patent law permits, the present invention also includes a method of treating androgen-dependent tumours in the mammalian body, which comprises administering a compound of the invention to a mammalian patient in a therapeutically effective dose, e.g. in the range 0.001-0.04 mmole/kg body weight, preferably 0.001-0.01 mmole/kg, administered daily or twice daily during the course of treatment. This works out (for humans) at 20-800 mg/patient per day. Alternatively the invention includes the compounds of the invention for use in said treatment and their use in the manufacture of medicaments for that purpose.

The following Examples illustrate the invention. Temperatures are in °C.

Example 1

(1S,2S,3S,5R)-Isopinocampheyl 3-pyridylacetate.

A stirred solution of (+)-isopinocampheol (3.086 g, 20 mmol) in dry tetrahydrofuran (20 ml) under N_2 was cooled with an ice-salt bath. A solution of n-butyllithium (1.6 M, 12.5 ml, 20 mmol) in hexane was added followed, after 5 min, by a solution of ethyl 3-pyridylacetate (2.746 g, 16.7 mmol) in tetrahydrofuran (5 ml) and the clear yellow solution allowed to attain room temperature. After 4 h, the mixture was partitioned between diethyl ether and water and the ether layers were concentrated. Chromatography of the residue gave on elution with 50:50:1 light petroleum (bp 60-80°)-diethyl ether-triethylamine the title compound (3.79 g, 76%) as an oil. By passing hydrogen chloride gas through a solution of the product in diethyl ether, the hydrochloride was obtained. This was recrystallised from dioxan-ether 1:1, mp 158-160°C. Anal. Calcd: C, 65.90: H, 7.81; N, 4.52. Found: C, 65.36; H, 7.62; N, 4.65%.

Example 2

(1S,2S,3S,5R)-Isopinocampheyl 2-(3-pyridyl)propanoate.

A solution of the free base product of Example 1 (912 mg, 3.34 mmol) in dry tetrahydrofuran (3 ml) was added to a stirred suspension of potassium hydride (35% by weight dispersion in

oil, 383 mg, 3.34 mmol) in tetrahydrofuran (10 ml) under nitrogen at 0°C. After 10 min, methyl iodide (0.17 ml, 380 mg, 2.68 mmol) was added, and after 1 h at 20°, worked up as above and column chromatographed with 5:4 diethyl ether-light petroleum to give the title compound (345 mg, 36%) as an oil. ^{1}H-NMR ($CDCl_3$) inter alia δ 0.97, 1.20 (2s, 6H, Me_2C), 1.53 (d, 3H, J = 6.8 Hz, $COCHCH_3$), 3.75 (q, 1H, $COCHCH_3$), 5.10 (m, 1H, OCH), 7.30 (dd, 1H, J_{ortho} = 4.8, 7.95 Hz, H-5), 7.80 (m, 1H, H-4), 8.60 (m, 2 H, H-2 and H-6). Anal. Calcd: C, 75.23; H, 8.77; N, 4.87. Found: C, 75.31; H, 8.86; N, 4.69%.

Example 3

(1S,2S,3S,5R)-Isopinocampheyl 2-methyl-2-(3-pyridyl)propanoate.

A solution of (1S,2S,3S,5R)-isopinocampheyl 3-pyridylacetate (706 mg, 2.58 mmol) in dry tetrahydrofuran (8 ml) was added to a stirred suspension of potassium hydride (35% by weight dispersion in oil, 650 mg, 5.68 mmol) in tetrahydrofuran (6 ml) under argon at 0°C. After 10 min, methyl iodide (733 mg, 5.16 mmol) was added in two equal portions, each in tetrahydrofuran (2 ml). On addition of 1 equivalent, the mixture became cloudy and hydrogen evolved. On adding the second equivalent the yellow solution turned colourless. After 20 min, the reaction was quenched by addition of isopropanol (0.5 ml). Work-up as in Example 1 with chromatography in the same solvent mixture gave the title compound (539 mg, 69%) as a colourless oil which similarly gave a crystalline hydrochloride, mp 144-146°C. Anal. Calcd: C, 67.57; H, 8.35; N, 4.15; Cl 10.49. Found: C, 67.56; H, 8.30; N, 4.11; Cl 10.61%.

Example 4

(1S,2R)-Borneyl 3-pyridylacetate.

By essentially the procedure of Example 1, using (-)-borneol (2.232 g, 14.47 mmol) in dry tetrahydrofuran (15 ml), n-butyllithium (5.79 ml, 14.47 mmol) and ethyl 3-pyridylacetate (1.91 g, 11.57 mol) in tetrahydrofuran (5 ml) afforded the title compound, isolated after elution with 1:1 diethyl ether-light petroleum as a colourless oil (2.87 g, 73%). ^{1}H-NMR inter alia

δ 0.77 (s, 3H, $C\underline{CH_3}$), 0.84, 0.87 (2S, 6H, $C(\underline{CH_3})_2$), 3.64 (S, 2H, $CO\underline{CH_2}$), 4.90 (m, 1H, C<u>H</u>OCO), 7.26 (m, 1H, <u>H</u>-5), 7.64 (m, 1H, <u>H</u>-4), 8.50 (m, 2H, <u>H</u>-2 and <u>H</u>-6). The <u>hydrochloride</u> had mp 151-153°. Anal. Calcd: C, 65.90; H, 7.81; N, 4.52; Cl, 11.44. Found: C, 65.61; H, 7.69; N, 4.46; Cl, 11.49%.

<u>Example 5</u>

(1<u>R</u>,2<u>S</u>)-Borneyl 3-pyridylacetate

The procedure followed that of Example 4 but using (+)-borneol and afforded the title compound as a colourless oil (2.95g, 75%). ^{1}H-NMR data was the same as given in Example 4. Anal. Calcd (free base): C, 74.69; H, 8.48; N, 5.13. Found: C, 74.71; H, 8.62; N, 4.87%.

<u>Example 6</u>

1-Adamantyl 3-pyridylacetate.

The method essentially followed that described in Example 1, using 1-adamantanol (3.35g, 22mmol) in dry THF (20ml), n-butyllithium (1.6M, 12.5ml, 20mmol) in hexane, and methyl 3-pyridylacetate (3.02g, 20mmol) in THF (8ml). After allowing the reaction mixture to attain room temperature it was heated under reflux for 18h. The product obtained following work-up and chromatography, as described in Example 1, contained unreacted 1-adamantanol. This was further purified by conversion to the hydrochloride, which was washed with dry ether, and the free base reliberated to afford the <u>title compound</u> (1.30g, 24%) which crystallised from hexane (mp 71-72°C). ^{1}H-NMR ($CDCl_3$) δ1.70 and 2.08 (2S, 12H, adamantyl $C\underline{H_2}$), 2.14 (s, 3H, adamantyl C<u>H</u>), 3.54 (s, 2H, $CO\underline{CH_2}$), 7.27 (m, 1H, <u>H</u>-5), 7.66 (m, 1H, <u>H</u>-4), 8.50 (m, 2H, <u>H</u>-2 and <u>H</u>-6). Anal. Calcd: C, 75.25; H, 7.80; N, 5.16. Found: C, 75.12; H, 7.89; N, 5.03%.

<u>Example 7</u>

1-Adamantyl 2-(3-pyridyl)propanoate.

The method essentially followed that described in Example 2, using 1-adamantyl 3-pyridylacetate (542mg, 2.0mmol) in dry THF (2ml), potassium hydride (35% w/w dispersion in oil, 229mg,

2.0mmol) in THF (6ml) and methyl iodide (0.10ml, 1.6mmol). Chromatography, upon elution with 50:50:1 light petroleum (bp 60-80°)-diethyl ether-triethylamine, gave the title compound (143mg, 25%), as an oil. ^{1}H-NMR ($CDCl_3$) δ1.47 (d, 3H, J = 7.2 Hz, CHMe), 1.64 and 2.04 (2s, 12H, adamantyl CH_2), 2.14 (s, 3H, adamantyl CH), 3.63 (q, 1H, J = 7.2 Hz, CHMe), 7.26 (m, 1H, H-5), 7.66 (m, 1H, H-4), 8.52 (m, 2H, H-2 and H-6). Anal. Calcd: C, 75.76; H, 8.12; N, 4.81. Found: C, 75.76; H, 8.28, N, 4.54%.

Example 8

1-Adamantyl 2-methyl-2-(3-pyridyl)propanoate.

The method essentially followed that described in Example 3, using 1-adamantyl 3-pyridylacetate (542mg, 2.0mmol) in dry THF (2ml), potassium hydride (35% w/w dispersion in oil, 504mg, 4.4mmol) in THF (6ml), and methyl iodide (0.25ml, 4.0mmol). Chromatography upon elution with 50:50:1 light petroleum (bp 60-80°C)-diethyl ether-triethylamine afforded the title compound (262mg, 39%) as an oil. ^{1}H-NMR ($CDCl_3$) δ1.56 (s, 6H, CMe_2), 1.63 and 2.03 (2s, 12H, adamantyl CH_2), 2.13 (s, 3H, adamantyl CH), 7.26 (m, 1H, H-5), 7.65 (m, 1H, H-4), 8.47 (m, 1H, H-2 or 6), 8.62 (m, 1H, H-2 or 6). Anal. Calcd: C, 67.95; H, 7.80; N, 4.17. Found: C, 68.00; H, 7.86; N, 4.17%.

Example 9

(1S,2R,5S,7R,8R)-Cedryl 3-pyridylacetate.

The method essentially followed that described in Example 1, using (+)-cedrol (2.45g, 11mmol) in dry THF (15ml), n-butyllithium (2.5M, 4.4ml, 11mmol) in hexane, and methyl 3-pyridylacetate (1.51g, 10 mmol) in THF (5ml). After allowing the reaction mixture to attain room temperature, stirring was maintained for an additional 24h. Following work-up and chromatography, eluting with 250:50:1 light petroleum (bp 60-80°C)-diethyl ether-triethylamine, the product obtained contained some unreacted cedrol. This was further purified by forming the hydrochloride, which was washed with dry diethyl ether, and the free base reliberated to afford the title compound (1.30g, 38%) as an oil. ^{1}H-NMR ($CDCl_3$) inter alia

δ 0.83 (d, 3H, J = 7.2Hz, cedryl CHMe), 0.96 and 1.08 (2s, 6H, cedryl CMe_2), 1.52 (s, 3H, cedryl OCMe), 3.53 (s, 2H, $COCH_2$), 7.26 (m, 1H, H-5), 7.63 (m, 1H, H-4), 8.51 (m, 2H, H-2 and H-6). Anal. Calcd: C, 77.37; H, 9.15; N, 4.10. Found: C, 77.56; H, 9.19; N, 3.99%.

Example 10

2-Methyl-2-adamantyl 3-pyridylacetate

The method essentially followed that described in Example 1, but using 2-methyl-2-adamantanol (3.66g, 22 mmol) in dry THF (30ml), n-butyllithium (2.5M, 8.8ml, 22mmol) in hexane, and methyl 3-pyridylacetate (3.02g, 20mmol) in THF (10ml). After allowing the reaction mixture to attain room temperature, stirring was maintained for an additional 96h. Following work-up and chromatography, eluting with 250:50:1 light petroleum-diethyl ether-triethylamine, the product obtained contained some unreacted 2-methyl-2-adamantanol. This was further purified by forming the hydrochloride, which was washed with diethyl ether, and the free base reliberated to afford the title compound (1.77g, 31%) as an oil, ^{1}H-NMR($CDCl_3$) inter alia δ 1.59 (s, 3H, adamantyl OCMe), 3.60(s, 2H, $COCH_2$), 7.26 (m, 1H, H-5), 7.65 (m, 1H, H-4), 8.52 (m, 2H, H-2 and H-6). FAB-MS m/z 286 (M+1). Anal, Calcd: C, 75.75; H, 8.12; N, 4.91. Found: C, 75.19; H, 8.16; N, 4.83%.

Example 11

N-(1-Adamantyl)-3-pyridylacetamide

To a solution of 3-pyridylacetic acid hydrochloride (2.60g, 15mmol) in dry HMPA (30ml) and dry THF (15ml) was added 1,1'-carbonyldiimidazole (2.43g, 15mmol). After stirring for 30 min 1-adamantanamine (2.50g, 16.5 mmol) was added and stirring continued for 12h. The mixture was poured into water (50ml), basified with aqueous sodium hydroxide (1M) and extracted with diethyl ether (3 x 50ml). The ether extracts were combined, dried (Na_2CO_3), and concentrated. Chromatography, on elution with 15:5:1 ethyl acetate-dichloromethane-triethylamine, afforded the title compound (2.63g, 65%) as white crystals,

mp 176-177°C, IR ν_{max} 1649 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.66 and 1.96 (2m, 12H, adamantyl C<u>H</u>$_2$), 2.05(s, 3H, adamantyl C<u>H</u>), 3.46 (s, 2H, COC<u>H</u>$_2$), 5.10 (s, 1H, N<u>H</u>), 7.29 (m, 1H, <u>H</u>-5), 7.68 (m, 1H, <u>H</u>-4), 8.51 (m, 2H, <u>H</u>-2 and <u>H</u>-6). FAB-MS <u>m</u>/<u>z</u> 271 (M+1).

<u>Example 12</u>

(1<u>S</u>,2<u>R</u>,5<u>S</u>,7<u>R</u>,8<u>R</u>)-Cedryl 1-(3-pyridyl)cyclopentanecarboxylate

A solution of (1<u>S</u>,2<u>R</u>,5<u>S</u>,7<u>R</u>,8<u>R</u>)-cedryl 3-pyridylacetate (341mg, 1.0 mmol) in dry THF (3 ml) was added to a stirred suspension of potassium hydride (35% w/w disperson in oil, 252mg, 2.2 mmol) in THF (2 ml) under argon. After 20 min, 1,4-diicodobutane (132µl, 1.0 mmol) was added, and after 30 min. the mixture was partitioned between diethyl ether and water, the ether extracts dried (Na_2CO_3) and concentrated. Chromatography, on elution with light petroleum-diethyl ether (3:1), afford the <u>title compound</u> (96mg, 24%) which crystallised from the light petroleum at -20°C, m.p. 81-82°C. ^{1}H-NMR ($CDCl_3$) <u>inter alia</u> δ 0.73 and 0.87 (2s,6H, cedryl C<u>Me</u>$_2$), 0.80 (d,3H,J=7.1Hz, cedryl CH<u>Me</u>), 1.34 (s,3H, cedryl OC<u>Me</u>), 7.22 (m,1H,5-<u>H</u>), 7.66 (m,1H,4-<u>H</u>), 8.45 (m,1H,6-<u>H</u>), 8.62 (m,1H,2-<u>H</u>). Anal. Calcd: C, 78.94; H, 9.43, N, 3.54. Found: C, 79.01; H, 9.61; N, 3.48%.

<u>Test results</u>

Assay of the rat 17α-hydroxylase/C_{17}-C_{20} lyase.

The assay was carried out as described by S. E. Barrie <u>et al</u>., J. Steroid Biochem. <u>6</u>, 1191-5, (1989) except that recently the radioactivity in the peaks of interest has been monitored on-line by mixing the HPLC effluent with Ecoscint A (National Diagnostics) scintillation fluid, 1:1, and passing the mixture through a Bertold LB506C radiochemical monitor.

Assay of the human 17α-hydroxylase/C_{17}-C_{20} lyase.

Human testes were obtained from previously untreated patients undergoing orchidectomy for prostatic cancer. The testes were decapsulated and stored in liquid nitrogen until

use. A microsomal preparation was prepared essentially as described by S. E. Barrie et al., supra. The material was then thawed, finely chopped, and homogenised in 0.25M sucrose (5ml/gm wet weight) using a Potter homogeniser. The homogenate was centrifuged at 12000g for 30 min, and then the microsomes were pelleted by spinning the supernatant at 100,000g for 1hr. The pellet was washed by being resuspended in 0.25M sucrose and repelleted. The microsomal pellet was then resuspended in 50mM sodium phosphate pH 7.4/glycerol (3/1 v/v) and stored in aliquots in liquid nitrogen.

The enzyme activities were measured separately.

For the 17α-hydroxylase: The basic assay mixture was similar to that used for the rat enzyme except that the EDTA concentration was 0.2mM, and the substrate, ^{3}H-progesterone, concentration was 3μM. The human enzyme was more sensitive to ethanol than the rat one, and so the compound under test were dissolved in 50% DMSO and the final concentrations of ethanol and DMSO were 1% each. For the compound of Example 2 and its 4-pyridyl analogue, reaction was carried out for 15min. For all other compounds, the reaction time was extended to 1 hour. It was terminated by the addition of 2 vols. of methanol/ acetonitrile (2/1 v/v) containing approx. 100μM unlabelled progesterone, 17α-hydroxyprogesterone, androstenedione, testosterone, and 16α-hydroxyprogesterone. The last steroid was added as it appeared that the human enzyme was capable of 16α-hydroxylation as well as 17α-hydroxylation.

For the compound of Example 2 and its 4-pyridyl analogue, the separation of the steroids by HPLC was by the same method as described for the rat assay in S.E. Barrie et al., supra. For all other compounds, the separation was carried out on a 10cm. "Nucleosil" 5μ C18 column with a "Nucleosil" pre-column. Elution was with 60% methanol at 1ml/min. The effluent was mixed on-line 1:1 with Ecoscint A containing 25% acetonitrile and then passed through a Berthold LB506C radiochemical detector. In all cases, the hydroxylase activity was measured

as the production of 17α-hydroxyprogesterone, androstenedione and testosterone.

For the C_{17}-C_{20} lyase: The mixture was the same as described above for the 17α-hydroxylase except that the substrate was ^{3}H-17α-hydroxyprogesterone. The reaction was carried out for 1hr. and was stopped by the addition of 2 vols. of methanol/acetonitrile (2/1 v/v) containing approx. 100μM 17α-hydroxyprogesterone, androstenedione and testosterone.

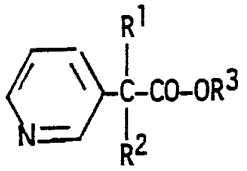
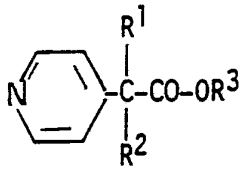
The HPLC separation used for the lyase involved a 10cm 5μ Apex C18 column with a 5cm PELL ODS C18 precolumn. The eluant was 38:12:50 methanol:acetonitrile:water flowing at 1ml/min. The effluent was mixed 1:1 with Ecoscint A containing 10% methanol and the radioactivity was measured directly by a Berthold LB506C radiochemical detector. The lyase activity was measured as the production of androstenedione and testosterone.

Calculation of IC_{50}.

The enzyme activity was measured in the presence of at least 4 concentrations of each compound, and the data were fitted by linear regression to the Dixon equation (Dixon, M., Webb, E. C. Enzymes, 2nd ed., Academic Press, New York, 1964). The IC_{50} and its 95% confidence limits were calculated from the slope and its 95% confidence limits. Where the full determination of the IC_{50} has not been carried out the values given are approximate and no confidence limits are shown.

Results are shown in Table 1 below.

Table 1 : 17α-hydroxylase/C_{17}-C_{20} lyase activities
IC_{50} (μM) with 95% confidence limits in parenthesis, measured with the rat enzymes, (R) or human enzymes (H)

	3-PYRIDYL SERIES		4-PYRIDYL SERIES	
	 (5)		 (6)	
Compound	Hydroxylase	Lyase	Hydroxylase	Lyase
Ex. 1, $R^1 = R^2 = H$, R^3 = isopino-campheyl	H 0.50 (0.44-0.58)	0.10 (0.09-0.12)	0.041 (0.038-0.045)	0.0066 (0.006-0.007)
	R 0.46 (0.42-0.50)	0.52 (0.48-0.57)	0.26 (0.24-0.27)	0.28 (0.24-0.34)
Ex. 2, $R^1 = CH_3$, $R^2 = H$, R^3 = isopino-campheyl	H 0.1-0.3	0.04	0.02	0.005
	R not tested			
Ex. 3, $R^1 = CH_3$, $R^2 = CH_3$, R^3 = isopino-campheyl	H 0.043	0.016	0.05-0.1	0.01
	R 0.047 (0.042-0.052)	0.052 (0.045-0.061)	not tested	

	3-PYRIDYL SERIES		4-PYRIDYL SERIES	
Compound	Hydroxylase	Lyase	Hydroxylase	Lyase
Ex. 4, $R^1 = R^2 = H$, R^3 = (-)borneyl	H not tested			
	R 2.0 (1.9-2.1)	2.3 (2.0-2.6)	1.5 (1.4-1.6)	2.2 (2.0-2.5)
Ex. 5 $R^1 = R^2 = H$, R^3 = (+)borneyl	H 1.5	0.4	not tested	
Ex. 6 $R^1 = R^2 = H$, R^3 = adamantyl	H 1.0	0.6	not tested	
Ex. 7 $R^1 = CH_3$, $R^2 = H$, R^3 = adamantyl	H 0.3	0.1	not tested	
Ex. 8 $R^1 = CH_3$, $R^2 = CH_3$, R^3 = adamantyl	H 0.06	0.04	not tested	
Ex. 9 $R^1 = R^2 = H$, R^3 = (+)cedryl	H 0.16	0.12	not tested	

Assay of aromatase activity

Aromatase activity was determined by the method of A. B. Foster et al., J. Med. Chem. 26, 50-54 (1983), using human placental microsomes. For the microsomes used, the Michaelis constant K_m for [1β - ^{3}H] androstenedione was 0.039μM. K_i values were obtained from Dixon plots of reciprocal velocity of

reaction versus concentration of inhibitor at two concentrations of the androstenedione substrate. K_i values are given in parenthesis after IC_{50} values. The comparative results are shown in Table 2.

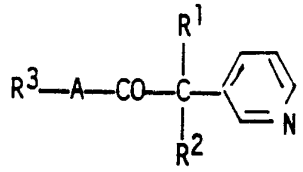
Table 2 : Aromatase activities, IC_{50} μM with K_i values in parenthesis in μM, human enzyme

Compound	3-PYRIDYL SERIES	4-PYRIDYL SERIES
Ex. 1	6 (1.01 ± 0.07)	0.12 (0.015 ± 0.005)
Ex. 2	8.9 (0.81 + 0.09)	1.32 (0.12 ± 0.03)
Ex. 3	30 (5.2 ± 1.0)	3.85 (0.35 ± 0.06)
Ex. 4	3.0 (0.207 ± 0.03)	0.097 (0.009 ± 0.0003)
Ex. 5	2.9	not tested
Ex. 6	8.9	"
Ex. 7	9.1	"
Ex. 8	35	"
Ex. 9	1.7	"

The poorer inhibition of aromatase demonstrated by the compounds of the 3-pyridyl series would benefit the IC_{50} lyase/ aromatase ratio.

CLAIMS

1. Compounds having the general formula:



(3)

wherein each of R^1 and R^2 independently represents hydrogen or C_{1-4} alkyl or together represent the residue of a cycloalkyl group of 3 to 6 carbon atoms;

A represents O, NR^4 wherein R^4 is defined as for R^1 or R^2 or CR^5R^6 wherein R^5 and R^6 are as defined for R^1 or R^2 as separate substituents; and

R^3 represents a bridged alicyclic group;

as free bases or their pharmaceutically acceptable salts.

2. Compounds according to claim 1 wherein A represents, O, NH or CH_2.

3. Compounds according to claim 1 or 2 wherein R^3 represents a bridged alicyclic group having from 6 to 8 ring atoms (excluding bridge atoms), which is unsubstituted or substituted by alkyl of 1 to 4 carbon atoms or by a fused alicyclic group.

4. Compounds according to claim 3 wherein the fused alicyclic group is a cyclopentane or cyclohexane ring which itself is unsubstituted or substituted by alkyl of 1 to 4 carbon atoms.

5. Compounds according to claim 1, 2, 3 or 4 wherein R^3 has one or two bridges, each of 1 or 2 carbon atoms in linear length, unsubstituted or substituted by alkyl of 1 to 4 carbon atoms.

6. Compounds according to claim 1, 2, 3, 4 or 5 wherein any alkyl group of 1 to 4 carbon atoms is a methyl group.

7. Compounds according to claim 1, 2, 3, 4, 5 or 6 wherein R^3 represents a borneyl, isobcrneyl, cedryl or isopinocampheyl group, in each of their optically active forms, or an adamantyl group.

8. Compounds according to claim 1, 2, 3, 4, 5 or 6 wherein R^3 represents a methyladamantyl group.

9. A pharmaceutical composition comprising a compound claimed in claim 1, 2, 3, 4, 5, 6, 7 or 8 in association with a therapeutically acceptable carrier or diluent.

10. A compound claimed in claim 1, 2, 3, 4, 5, 6, 7 or 8 for use in treating prostatic cancer.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 92/00509

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D213/55; C07D213/56; A61K31/445; C07D213/50

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D ; A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
A	EP,A,0 253 681 (FARMITALIA) 20 January 1988 cited in the application see the whole document	1-10
A	EP,A,0 194 901 (SHIONOGI) 17 September 1986 see page 36; example 21	1
A	EP,A,0 169 062 (NATIONAL RESEARCH DEVELOPMENT) 22 January 1986 see the whole document	1-10
A	JOURNAL OF MEDICINAL CHEMISTRY. vol. 33, no. 11, 1990, WASHINGTON US pages 3050 - 3055; R. MCCAGUE ET. AL.: 'INHIBITION OF ENZYMES OF ESTROGEN AND ANDROGEN BIOSYNTHESIS BY ESTERS OF 4-PYRIDYLACETIC ACID' see the whole document	1-10

-/--

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
03 JUNE 1992	15. 06. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	KISSLER B.E.

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	STEROIDS vol. 50, no. 1-3, 1988, pages 219 - 233; HENDERSON D. ET. AL.: 'Estrogens and Benign Prostatic Hyperplasma' see the whole document	1-10
A	STEROIDS vol. 50, no. 4-6, 1988, pages 449 - 457; KARR J. P. ET. AL.: 'The potential significance of aromatase in the etiology and treatment of prostatic disease.' see the whole document	1-10
A	J. STEROID BIOCHEMISTRY vol. 25, no. 5B, 1988, pages 867 - 876; HENDERSON D. ET AL.: 'Aromatase Inhibitors and benign prostatic hyperplasia.' see the whole document	1-10
A	J. STEROID BIOCHEMISTRY vol. 31, no. 4B, 1988, pages 677 - 683; ZOPPI S. ET. AL.: 'Antihormonal activities of 5-alpha-reductase and aromatase inhibitors' see the whole document	1-10
A	J. STEROID BIOCHEMISTRY vol. 37, no. 6, 20 December 1990, pages 1043 - 1048; BRODIE A. M. ET. AL.: 'Aromatase and other inhibitors in breast and prostatic cancer.' see the whole document	1-10

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9200509 SA 57737

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
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		US-A- 4668689	26-05-87