

PATENT SPECIFICATION

NO DRAWINGS

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Germany.

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The inventor of this invention in the sense of being the actual deviser thereof within the meaning of Section 16 of the Patents Act 1949 is ALBERTO ERCOLI an Italian Citizen of Via Circo 12, Milan, Italy.

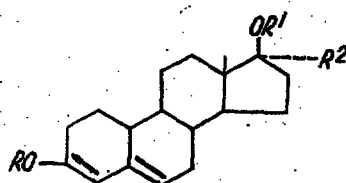
COMPLETE SPECIFICATION

Steroids

We, FRANCESCO VISMARA S.p.A., an Italian Body Corporate of Casatenovo, Como, Italy, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention is concerned with improvements in or relating to steroid derivatives, more particularly with enol ethers of 17-substituted 19-nortestosterones.

The enolethers of the present invention have the formula:—



where R represents a hydrocarbon radical (particularly an alkyl or cycloalkyl radical) containing from 1 to 12 carbon atoms inclusive, R¹ represents hydrogen or the residue of an alkanolic acid containing up to 3 carbon atoms and R² represents an alkyl or alkynyl radical containing up to 4 carbon atoms. More particularly R₂ represents an alkyl radical, such as methyl, ethyl, propyl, iso-propyl or butyl or an unsaturated hydrocarbon radical of the structure —C≡CR³ in which R³ represents a hydrogen atom or a methyl or ethyl group.

The new enolethers of the present invention possess improved biological activity over the corresponding free Δ⁴-3-ketones.

Particularly the enolethers of 17α-ethynyl 19-nortestosterone and of the compounds of Formula I above having the grouping C≡CR³, possess especially by the oral route, improved

[Price 4s. 6d.]

progestational activity. They can be usefully employed in gynaecological field, for the treatment of dysmenorrhea, amenorrhea, endometriosis, abortion and similar troubles. The compounds can be conveniently administered by the oral route in an oily solution contained in a capsule, e.g. of gelatine or other material, preferably in dosage unit form comprising the active compound in an amount of from 1 mg. to about 100 mg., preferably from about 5 mg. to about 50 mg. per dosage unit form.

The 3-enolethers of 17α-alkyl and alkynyl derivatives of 19-nortestosterone can be prepared by any convenient method. Thus, the aliphatic enolethers, in which the aliphatic group contains up to 5 carbon atoms can readily be obtained by the action of a corresponding aliphatic orthoformate on the corresponding Δ⁴-3-ketone, preferably carrying out the reaction at room temperature in the presence of a small amount of an acid catalyst.

The aliphatic enolethers in which the aliphatic group is other than an ethyl group as well as cyclo- and arylaliphatic enolethers, can be obtained by reacting the preformed 3-enol ethyl ether with an excess of the appropriate aliphatic, cyclo- or arylaliphatic alcohol, in solution in an organic solvent and in the presence of a catalytic amount of an acid catalyst. Suitable catalysts are the aromatic sulphonic acids such as toluene, benzene and naphthalene sulphonic acids as well as Lewis acids. Salts of organic bases with mineral acids, such as, for example, pyridine hydrochloride can also be employed as catalyst.

The organic solvent is preferably substantially non-polar. Benzene and its homologues, cyclohexane, isooctane, tetrahydrofuran or dioxan can be advantageously employed. Halogenated organic solvents, such as ethylene

bromide, chloroform or tetrachlorethane, may be also employed, alone or in addition to one of the above solvents.

5 The reaction mixture constituted by the pre-formed enol ethyl ether of 17 α -alkyl or alkynyl 19-nortestosterone—suspended or dissolved in one of the above solvents—, the desired alcohol and the acid catalyst, is heated to boiling with an ascending or descending condenser. In
10 the latter case some liquid is distilled off at ordinary pressure so that the ethanol which forms during the exchange reaction can be removed. The distillation period depends, of course, on the volume of the solvent employed and the amount of the enol ethyl ether to be
15 reacted.

The remaining solution is then made slightly alkaline by the addition of a weak organic base, such as pyridine, and is evaporated to
20 small bulk or dryness *in vacuo*. Crystallization of the resulting 3-enol higher ether, contained in the residue, can be suitably facilitated by adding ether, methyl or ethyl alcohol, or hexane or another solvent of this type.

25 In order that the invention may be well understood the following examples are given by way of illustration only:

EXAMPLE 1.

800 mg. of 17 α -methyl 19-nortestosterone
30 dissolved in 3 cc. of tetrahydrofuran are treated with 0.8 cc. of ethyl orthoformate, 0.5 cc. of anhydrous ethanol and 8 mg. of *p*-toluenesulphonic acid. The mixture is allowed to stand at room temperature for approxi-
35 mately 1 hour, then a few drops of pyridine are added and the solvent is completely driven off *in vacuo*. The residue taken up with a little dilute methanol, filtered and dried yields 680 mg. of 3-ethyl enolether of 17 α -methyl
40 19-nortestosterone melting at 125–128° C.; [α]_D = –165° (dioxan).

In the same manner 3-ethyl enolether of 17 α -ethynyl 19-nortestosterone is obtained,
45 melting at 172–174° C.; [α]_D = –222° (dioxan).

Similarly, 17 α -ethynyl 19-nortestosterone acetate is reacted with methyl orthoformate and methyl alcohol to give 3-methyl enolether of 17 α -ethynyl 19-nortestosterone acetate at
50 melting point 183–185° C.; [α]_D = –212° (dioxan).

EXAMPLE 2.

A mixture consisting of 1 g. of 17 α -ethynyl-19-nortestosterone acetate, 1 cc. of ethyl ortho-
55 formate, 2 cc. of anhydrous ethanol and 15 mg. of sulphosalicylic acid is allowed to stand for 40 minutes at room temperature under continuous stirring until the solids are dissolved. The solution is then poured into a
60 boiling mixture consisting of 400 cc. of benzene, 3 cc. of *n*-amyl alcohol and 20 mg. of sulphosalicylic acid and the resulting mixture refluxed for 30 minutes. After cooling, a few drops of pyridine are added and the solvent eliminated under vacuum, thus yielding

0.850 g. of 3-amyl enolether of 17 α -ethynyl 19-nortestosterone acetate melting at 108–110° C.; [α]_D = –194° (dioxan).

In the same manner, 3-butyl and hexyl enolethers of 17 α -ethynyl-19-nortestosterone acetate are obtained.

EXAMPLE 3.

700 mg. of 3-ethyl enolether of 17 α -ethynyl 19-nortestosterone acetate are treated in
75 benzene solution with 1.8 cc. of cyclopentyl alcohol and 25 mg. of *p*-toluenesulphonic acid, as in Example 2 to give 3-cyclopentyl enol ether of 17 α -ethynyl 19-nortestosterone acetate melting at 180–183° C.; [α]_D = –212° ± 1° (dioxan).
80

Analogously, the cyclopentyl enolethers of 17 α -methyl and 17 α -ethyl-19-nortestosterone acetate are obtained.

EXAMPLE 4.

A solution of 300 mg. of 3-ethyl enolether of 17 α -ethynyl 19-nortestosterone acetate in 50
85 cc. of benzene is treated with 2 cc. of *n*-heptyl alcohol and 50 mg. of pyridine hydrochloride, as in Example 2, to give 230 mg. of *n*-heptyl enolether of 17 α -ethynyl 19-nortestosterone acetate melting at 38–40° C.; [α]_D = –153° ± 1° (dioxan).
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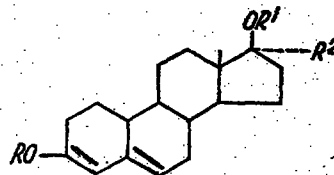
In the same manner, the corresponding heptyl enolether of 17 α -methyl 19-nortestosterone acetate is prepared.
95

EXAMPLE 5.

In a manner corresponding to that of the previous examples, the following new enol-ethers are prepared; butyl enolether of 17 α -methyl 19-nortestosterone; hexyl enolether of 17 α -methyl 19-nortestosterone acetate; cyclo-
100 hexyl enol ether of 17 α -methyl-19-nortestosterone; benzyl enolether of 17 α -methyl-19-nortestosterone acetate; (2-methyl)-pentyl enolether of 17 α -ethynyl 19-nortestosterone and
105 cyclohexyl enolether of 17 α -ethynyl 19-nortestosterone acetate.

WHAT WE CLAIM IS:—

1. Enolethers of 17-substituted 19-nortestosterone of the formula:



where R represents a hydrocarbon radical containing from 1 to 12 carbon atoms inclusive, R¹ represents hydrogen or the residue of an alkanolic acid containing up to 3 carbon atoms
115 and R² represents an alkyl or alkynyl radical containing up to 4 carbon atoms.

2. 3-Alkyl and 3-cycloalkyl enolethers of

bromide, chloroform or tetrachlorethane, may be also employed, alone or in addition to one of the above solvents.

5 The reaction mixture constituted by the pre-formed enol ethyl ether of 17 α -alkyl or alkynyl 19-nortestosterone—suspended or dissolved in one of the above solvents—, the desired alcohol and the acid catalyst, is heated to boiling with an ascending or descending condenser. In
10 the latter case some liquid is distilled off at ordinary pressure so that the ethanol which forms during the exchange reaction can be removed. The distillation period depends, of course, on the volume of the solvent employed
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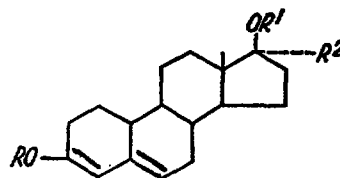
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105 cyclohexyl enolether of 17 α -ethynyl 19-nortestosterone acetate.

WHAT WE CLAIM IS:—

1. Enolethers of 17-substituted 19-nortestosterone of the formula:



where R represents a hydrocarbon radical containing from 1 to 12 carbon atoms inclusive, R¹ represents hydrogen or the residue of an alkanic acid containing up to 3 carbon atoms and R² represents an alkyl or alkynyl radical containing up to 4 carbon atoms.

2. 3-Alkyl and 3-cycloalkyl enolethers of



- 17 α -ethynyl-19-nortestosterone and esters thereof. 20
3. 3-Amyl enolether of 17 α -ethynyl 19-nortestosterone acetate.
- 5 4. 3-Cyclopentyl enolether of 17 α -ethynyl 19-nortestosterone acetate. 25
5. A pharmaceutical composition for oral administration comprising a compound as claimed in any of claims 1—4 in an oily solution. 30
- 10 6. A composition as claimed in claim 5 in dosage unit form comprising the active compound in an amount of from 1 mg. to 100 mg.
- 15 7. A composition as claimed in claim 5 in dosage unit form comprising the active compound in an amount of from 5 mg. to 50 mg.
8. A process for the preparation of 3-aliphatic enolethers as claimed in claim 1 in which the aliphatic group contains up to five carbon atoms, which comprises reacting the corresponding Δ^4 -3-ketone with a corresponding aliphatic orthoformate.
9. A process for the preparation of the 3-aliphatic, cyclo- and arylaliphatic ethers as claimed in claim 1, other than 3-ethyl enolethers, which comprises reacting preformed 3-enol ethyl ether with an excess of the appropriate alcohol in solution in an organic solvent in the presence of a catalytic amount of an acid catalyst.
10. A process as claimed in claim 8 or claim 9 substantially as herein described with reference to any of the examples.
- For the Applicants,
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