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PATENT SPECIFICATION

NO DRAWINGS

909,662

Date of Application and filing Complete Specification: April 7, 1960.

No. 12452/60.

Application made in Italy (No. 2125) on Feb. 8, 1960.

Complete Specification Published: Oct. 31, 1962.

Index at acceptance:—Class 2(3), U4(A1:C4:C5:X), U6.

International Classification:—C07c.

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.

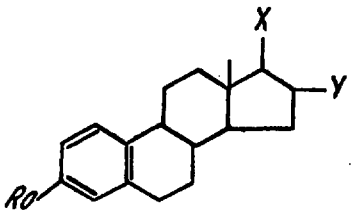
COMPLETE SPECIFICATION

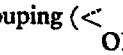
New Estrogen Derivatives and Therapeutic Compositions

We, FRANCESCO VISMARA S.p.A., an Italian Body Corporate of Casatenovo, Como, Italy and ALBERTO ERCOLI, an Italian citizen of Via Circo 12, Milan, 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 relates to new derivatives of estrogen hormones and is more particularly concerned with the novel mono-pentyl ethers of 3 - hydroxy - oestra - 1,3,5 - trien - 17-oxygenated, for example the amyl and cyclopentyl ethers of 3-hydroxy-17-keto-oestratriene (estrone), the amyl and cyclopentyl ethers of 3,16α,17β - trihydroxy - oestratriene (estriol), the amyl and cyclopentyl ethers of 3,17β-dihydroxy - oestratriene (estradiol), of the corresponding 17α-ethynyl derivative and 17β-acyl esters thereof.

The new compounds of this invention can be represented by the following structural formula:—



where X represents a ketonic oxygen (=O), a β-hydroxy group, or a β-hydroxy α-ethynyl grouping (), Y represents hydrogen or, when X represents a hydroxy group, a hydroxy group, and R represents an aliphatic hydrocarbon radical having an open, branched or cyclic chain, containing five carbon atoms. In particular R represents an amyl or a cyclopentyl radical.

The hydroxy group present at the 17β-position can be free or esterified with an alkanoic acid containing from one to four carbon atoms, inclusive.

The compounds of this invention are physiologically active agents possessing orally an exceptional estrogenic activity by far superior to that of the corresponding free 3-hydroxy steroids.

While the esterification of the phenolic hydroxyl of the estrogens, for instance under the form of propionate, benzoate or palmitate, apparently increases the efficaciousness of the substances by parenteral administration, although causing only a delay of the absorption from the site of injection, the etherification of said hydroxyl group with a pentyl alcohol, and especially with *n*-amyl or cyclopentyl alcohol, really enhances the oral activity of such hormones.

Certain mono ether derivatives of estrogens are already known, but none of the prior art compounds show an adequate potency by oral route. We have found that new mono-pentyl ethers of natural and synthetic estrogens, containing an open, branched or cyclic chain hydrocarbon, exhibit a higher degree of oral activity and a superior therapeutic ratio when compared with the corresponding free 3-hydroxy steroids.

In particular, the new mono-pentyl ethers of estrone and estradiol are orally effective with an activity about ten times higher, than the corresponding natural hormones which, as known, lose much of their effectiveness when given orally.

Also the amyl and cyclopentyl ethers of estriol show orally an activity two to three times superior to estrone which, among the natural estrogens, is the unique possessing by oral route an effect nearly equal to that shown in the parenteral administration.

[*Price 4s. 6d.*]

Furthermore the cyclopentyl ether of 17α-ethynyl estradiol exhibit in the uterotrophic activity test an efficaciousness several times superior to 17α-ethynyl estradiol itself which has been considered till now the most potent estrogen on oral administration.

The new mono-pentyl ethers derivatives of this invention, which possess a marked intrinsic estrogenic activity, are of practical value as oral estrogens because they allow oral treatment with low dosages.

Such compounds can be given orally in association with a suitable pharmaceutical carrier which is not incompatible with the active substance. The carrier can be solid or liquid and can be chosen among those usually employed in pharmaceutical technique for manufacturing preparations suitable for oral ingestion. According to the nature of the carrier the compositions may be in solid or liquid form; in the first case they may take the form of pills, tablets, sweets or capsules, in the second case they may be administered under the form of syrup, suspensions, or also capsules or gelatin or other material soluble or disintegratable in the alimentary tract.

A suitable manner to administer the pentyl ethers of estrogen hormones is to give them orally dissolved in a fluid vehicle, e.g. an orally acceptable lipid, such as a vegetable oil, an alcohol or a glycol orally accepted in an amount necessary to dissolve and carry the active substances.

The new compounds of this invention can be obtained, according to prior art methods. The pentyl mono ethers of estrone can be easily prepared by reacting 3-hydroxy-17-keto-estratriene or its sodium salt with the chosen hydrocarbon halide, for instance, amyl, isoamyl or cyclopentyl bromide or chloride, in the presence of a suitable condensing agent and thereafter recovering the desired ether from the mixture of reaction products. As condensing agent an alkaline hydrate or carbonate or alcoholate can be employed.

The preparation of the pentyl monoethers of 3,17-dihydroxy-estratriene can be carried out either directly by submitting the diol to partial etherification, or indirectly by first preparing the desired pentyl monoether of the corresponding 3 - hydroxy - 17 - keto - estratriene and then transforming the 17-keto group into a hydroxy group by normal reduction methods to form the 3-pentyl ether of estradiol. The same procedure can be followed for the preparation of the pentyl mono-ethers of 3,17β - dihydroxy oestratriene - 17α-ethynyl-substituted. For instance, the 3-pentyl ether of 17α-ethynyl-estradiol can be prepared either by partial etherification of the 17α-ethynyl-estradiol itself, or by direct ethynylation with potassium acetylide of the corresponding pentyl ether of estrone, according to known methods. In each case the 17β-hydroxy group may be subsequently acylated.

The following examples are illustrative of the process and products of the present invention, but are not to be construed as limiting.

EXAMPLE 1.

A mixture of 1 g. of estrone and 1 g. of cyclopentyl bromide is added slowly to a solution of sodium ethylate, obtained from 0.1 g. of sodium and 8 cc of absolute ethanol. The reaction mixture is heated to reflux for 4 hours, then ethyl alcohol is eliminated by distillation and then the residue treated with a little water. A precipitate is obtained consisting of cyclopentyl ether of estrone which, after recrystallization from a mixture of methylene chloride-methanol, melts at 149—150°C.; $[\alpha]_D = +137°$ (0.5% in dioxan).

EXAMPLE 2.

0.2 g. of potassium hydrate are dissolved in 10 cc of absolute ethanol and to the solution is added slowly a mixture of 1.2 g. of estradiol and 1 g. of cyclopentyl chloride. After heating to reflux for three hours, the solvent is evaporated, and the residue treated with water, thus obtaining 1.5 g. of a product which, filtered, washed with little water and dried melts at 109°C. After recrystallization from methanol, 1.1 g. of estradiol 3-cyclopentyl ether is obtained at M.P. 110—111°C.; $[\alpha]_D = +63.5 \pm 1$ (0.5% in dioxan).

0.5 g. of this ether dissolved in 4 cc of anhydrous pyridine are treated with 2 cc. of propionic anhydride. The mixture is allowed to stand for 15 hours approximately, then poured into water, causing a solid to precipitate. The product is collected, washed and dried to give 0.45 g. of estradiol 17-propionate 3-cyclopentyl ether which, after recrystallisation from methanol, melts at 91.5—93°C.; $[\alpha]_D = +33$ (0.5% in dioxan).

EXAMPLE 3.

To a suspension of 2 g. of estrone cyclopentyl ether in 50 cc. of ethanol are added 0.2 g. of sodium borohydride in 3 cc. of water solution. This mixture is stirred for about 6 hours at room temperature, then treated with 10 cc. of acetic acid and diluted with water up to complete precipitation. The product filtered and dried, consists of 3-cyclopentyl ether of estradiol which, after recrystallization from methanol, melts at 110°C.

EXAMPLE 4.

A solution of 1.5 g. of 17α-ethynyl-estradiol in 50 cc. of absolute ethanol is added slowly to a mixture of 3 g. of cyclopentyl bromide and 2 g. of potassium carbonate. This mixture is heated at reflux and stirred for three hours, then filtered. Most of the alcohol is eliminated by distillation and the resulting solution diluted with water, and cooled in an ice bath. The product which precipitates is collected by filtration, washed and dried. After recrystallisation from methanol the 3-cyclopentyl ether of 17α-ethynyl-estradiol shows melting point 80.5—82°C.

EXAMPLE 5.

A solution of potassium *t*-amylate obtained from 2 g. of potassium and 40 cc. of tertiary amyl alcohol, is saturated with acetylene. 2 g. of estrone cyclopentyl ether in 50 cc. of anhydrous toluene solution are added and addition of acetylene is continued for ten hours at a temperature of about 20°C.

The reaction mixture is then reacted with 100 cc of an aqueous solution of 10% ammonium chloride, the organic layer separated washed with water, dried over anhydrous sodium carbonate and evaporated to dryness to give 1.7 g. of a crude product, which recrystallized from methanol, melts at 80—82°C. The melting point is undepressed on admixture with a specimen of 3-cyclopentyl ether of 17α-ethynylestradiol obtained as in Example 4.

EXAMPLE 6.

A mixture of 1.5 g. of estriol and 1.5 g. of cyclopentyl bromide in 20 cc. of sodium ethylate solution, containing 0.2 g. of sodium, is refluxed for three hours, then ethyl alcohol is eliminated by distillation and the residue decomposed with a little water to give 1.7 g. of estriol 3-cyclopentyl ether. M.P. 98—100°C. The *n*-amyl ether of estriol is similarly prepared using *n*-amyl bromide.

EXAMPLE 7.

To 1.1 g. of estrone there is added 35 cc. of absolute methanol, 1.5 g. of *n*-amyl bromide and 1.5 g. of potassium carbonate. The mixture is refluxed for four hours under stirring then most of the solvent is eliminated by distillation and the resulting solution diluted with water. Thus a precipitate of *n*-amyl ether of estrone is obtained which, filtered and recrystallised from a mixture methylene chloride-methanol, melts at 86—87°C.; $[\alpha]_D = +133.8°$ (1.5 in dioxan). Yield 100% in weight.

EXAMPLE 8.

Reacting 1.8 g. of estrone with 2.5 g. of isoamyl bromide in methanol solution and the presence of 1.9 g. of potassium carbonate as in Example 7, the *iso*-amyl ether of estrone is obtained, melting at 99—101°C.; $[\alpha]_D = +140°$ (1.1% in dioxan). Yield 98% in weight.

In the same manner as above, 17α-ethynylestradiol is reacted with *iso*-amyl bromide to give 3-*iso*-amyl ether of 17α-ethynyl estradiol.

EXAMPLE 9.

To a sodium ethylate solution (obtained from 0.2 g. sodium) in 12 cc. absolute ethanol there is added a mixture of 1.5 g. of estradiol and 1.2 g. of *n*-amyl iodide. After heating at reflux for three hours, the solvent is eliminated and the residue diluted with a little water and cooled at 0°C. to give 3-*n*-amyl ether of estradiol, melting at 83—85°C. Yield 83%.

1 g. of this product dissolved in 5 cc. of anhydrous pyridine, is treated at reflux for about one hour with 2 g. acetic anhydride. After cooling, the mixture is diluted with water causing the precipitation of a product which is collected by filtration, dried and recrystallised from methanol. Yield 95%. The 3-*n*-amyl ether of estradiol 17β-acetate shows melting point 64—65°C. and $[\alpha]_D = +38 \pm 3$ (dioxan).

Similarly from 3-*n*-amyl ether of estradiol, isobutyric anhydride and pyridine, the 3-*n*-amyl ether of estradiol 17β-isobutyrate is obtained at melting point 66—67°C.; $[\alpha]_D = +36 \pm 1$ (dioxan c=1).

EXAMPLE 10.

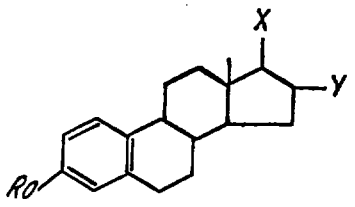
1 g. of *n*-amyl ether of estrone, obtained as described in Example 7, is dissolved in 20 c.c. of tetrahydrofuran. To the resulting solution there is added 0.1 g. of sodium borohydride in 5 cc. of water solution and the mixture is stirred for some minutes, at room temperature (about 20°C.), then heated at reflux for about one hour. After cooling some water is poured into the reaction flask up to complete precipitation of 3-*n*-amyl ether of estradiol which, recrystallised from methanol, melts at 85°C.

500 mg. of this product are dissolved in 3 cc. of 99% formic acid and to the resulting solution 25 mg. of *p*-toluenesulfonic acid are added. The mixture is stirred vigorously for a few minutes, then allowed to stand for about fifteen hours at a temperature of about 15°C.

After addition of water a precipitate is obtained of estradiol 17β-formate 3-*n*-amyl ether which, recrystallised from methanol, melts at 63—65°C.; $[\alpha]_D = +32.5 \pm 1$ (dioxan c=0.3). Yield 80% of the theoretical amount.

WHAT WE CLAIM IS:—

1. Pentyl mono ethers of 3-hydroxy-oestra-1,3,5-triene-17-oxygenated of the formula:



where X represents a ketonic oxygen or a β-hydroxy group or a β-hydroxy α-ethynyl grouping in which in each case the said β-hydroxyl group may be esterified with an alkanoic acid containing from one to four carbon atoms inclusive, Y is hydrogen or, when X represents a hydroxy group, a hydroxy group and R represents a five carbon open chain, branched chain or cyclic aliphatic group.

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3. 3-cyclopentyl ether of estrone.
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7. 3-cyclopentyl ether of estradiol.
8. 3-iso-amyl ether of 17α-ethynylestradiol.
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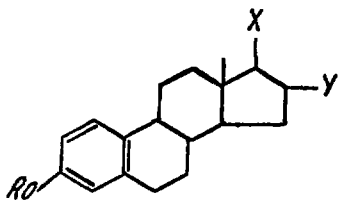
WHAT WE CLAIM IS:—

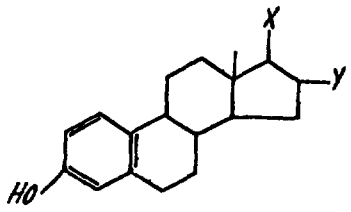
1. Pentyl mono ethers of 3-hydroxy-oestra-1,3,5-triene-17-oxygenated of the formula:



where X represents a ketonic oxygen or a β-hydroxy group or a β-hydroxy α-ethynyl grouping in which in each case the said β-hydroxyl group may be esterified with an alkanoic acid containing from one to four carbon atoms inclusive, Y is hydrogen or, when X represents a hydroxy group, a hydroxy group and R represents a five carbon open chain, branched chain or cyclic aliphatic group.

2. 3-*n*-amyl ether of estrone.
3. 3-cyclopentyl ether of estrone.
4. 3-*n*-amyl ether of estriol.
5. 3-cyclopentyl ether of estriol.
6. 3-*n*-amyl ether of estradiol.
7. 3-cyclopentyl ether of estradiol.
8. 3-iso-amyl ether of 17α-ethynylestradiol.
9. 3-cyclopentyl ether of 17α-ethynylestradiol.
10. A process for the preparation of the

compounds claimed in claim 1 in which a 3-hydroxy-oestra-1,3,5-triene-17-oxygenated of the formula



or its sodium salt, where X represents a ketonic oxygen atom or a β-hydroxy group or a β-hydroxy α-ethynyl grouping and Y is hydrogen or a hydroxy group when X represents a hydroxy group, is reacted with a five carbon chain aliphatic hydrocarbon halide in the presence of a condensing agent.

11. A process as claimed in claim 10 in which the 17β-hydroxy group is subsequently acylated with an alkanoic acid containing from 1 to 4 carbon atoms.

12. A process as claimed in claim 10 or claim 11 in which the five carbon chain hydrocarbon halide is the *n*-amyl or isoamyl bromide or chloride.

13. A process as claimed in claim 10 or claim 11 in which the five carbon chain hydrocarbon halide is the cyclopentyl bromide or chloride.

14. A process as claimed in claim 10 in which the 3 - hydroxy - oestra - 1,3,5 - triene-17-oxygenated is the 3 - hydroxy - 17 - keto-oestratriene.

15. A process as claimed in claim 14 in which the pentyl ether of 3-hydroxy-17-keto-oestratriene is either further reduced to form a 17β-hydroxy group or 17α-ethynylated and 17β-hydroxylated with potassium acetylide to form a 17β - hydroxy - 17α - ethynyl grouping, followed in each case by acylation of the 17-hydroxy group, in order to obtain the desired end product.

16. A pharmaceutical composition suitable for oral administration including one of the compounds mentioned in claim 1 to 9 mixed with a pharmaceutically acceptable carrier.

17. A pharmaceutical composition as defined in claim 16 where the carrier includes an orally acceptable lipid.

For the Applicants,
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Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press (Leamington) Ltd.—1962. Published by The Patent Office, 25 Southampton Buildings, London, W.C.2, from which copies may be obtained.

PATENTS ACT, 1949

SPECIFICATION NO. 909,662

In accordance with the Decision of the Superintending Examiner, acting for the Comptroller-General, dated the twenty-second day of August, 1963 this Specification has been amended under Section 29 in the following manner:-

Page 1, line 73, *for* "estrone" *read* "estriol"

Attention is also directed to the following printer's errors:-

Page 2, line 26, *for* "disintegratable" *read* "disintegrateable"

Page 2, line 50, *for* "monoether" *read* "mono-ether"

Page 3, line 78, *for* "C.C." *read* "CC."

THE PATENT OFFICE,
27th September, 1963

D 29472/1(13)/R.109 200 9/63 PL

* C L M S *