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3-ALKOXYESTRA-1,3,5(10)-TRIENE-17-OL-(N-SUBSTITUTED AMINOALKYL ETHERS)

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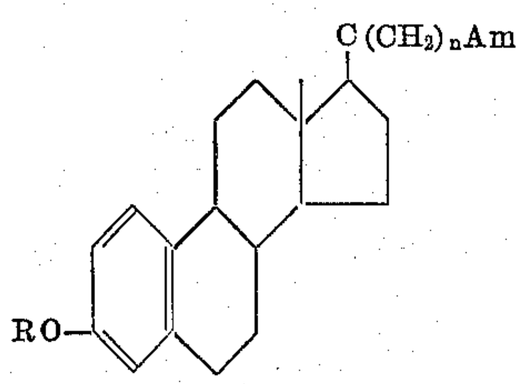
7 Claims. (Cl. 260—239.5)

The present invention relates to a new group of steroids. More particularly it relates to a new series of 17-aminoalkyl ethers of the estrane series. Still more precisely it concerns a novel class of substituted aminoalkyl ethers of 3-alkoxyestra-1,3,5(10)-trienes wherein the characteristic aminoalkyl ether group is introduced in position 17 of the steroid nucleus. The invention further provides means of manufacture and use of these novel compositions in pharmaceutical chemistry.

The primary object of our invention therefore may be said to be to disclose the concept and concrete embodiments of 17β-(ω-amino alkoxy)-3-alkoxyestra-1,3,5(10)-trienes and simple derivatives thereof which may be illustrated at least in part by the general Formula I:



(I)

Methods for the manufacture of these steroids either in base or acid addition salt form and methods for their use in shifting lipids or cholesterol in mammals are additional specific objects intended.

The symbol R in the above graphic representation of the composition aspect of our invention is intended to designate various lower alkyl groups among which we include methyl and ethyl as the preferred lower alkyl groups but also more broadly equivalently encompass other lower alkyl and carbocyclic lower alkyl groups both of straight and branched chain arrangement having up to about 8 carbon atoms therein. In this regard such groups as propyl, isopropyl, butyl, isobutyl, pentyl, cyclopentyl, cyclohexyl, and the like would be included. The symbol "Am" is intended to represent various groups which we generally designate as "amino" and more particularly disclose to include such specific radicals as primary amino, dialkylamino, piperidino, N-lower alkyl substituted piperazino, morpholino, and the like, all of which are considered functional equivalents within the concept of our invention. The symbol *n* represents either 2 or 3.

When we employ the term "dialkylamino" here it should be understood that various functions such as methyl, ethyl, propyl, and butyl for instance comprise the alkyl moiety thereof giving rise to the corresponding dimethylamino, diethylamino, dipropylamino and dibutylamino radicals. As previously indicated the term "lower alkyl" is intended to embrace cyclic alkyl functions as well as straight chain alkyl functions, i. e. cyclopentyl and cyclohexyl radicals.

The invention sought to be patented in its composition aspect therefore may be described as residing in the concept of a novel steroidal compound having a 17-aminoalkoxy sidechain thereon, a 1,3,5(10)-estratriene nucleus and in its preferred product aspects a 3-methoxy sidechain attached thereto as included above in Formula I.

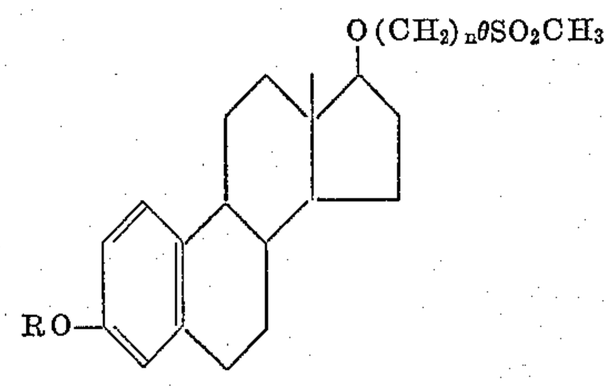
The process of making and manner of use aspects of our novel steroidal compositions will now be generally

described so as to enable any person skilled in the art of chemistry to make and use a specific embodiment thereof.

In such process of preparing the novel compounds of our invention the steroidal materials employed as starting materials are not considered part of the invention described and claimed herein save as starting materials and are adquately described in the prior art literature. A preferred mode of synthesis of our new compounds is to treat a known steroid such as estradiol 3-methyl ether with a suitable amino alkyl halide under reflux conditions in the presence of a suitable organic reaction solvent after first treating the starting material with a suspension of sodium hydride. The reaction usually continues from 12 to 24 hours until a product is obtained in the crude state. This product is then purified according to conventional techniques to obtain one of the compounds of our series.

Under normal operating conditions the alkylation goes to completion in about 14–18 hours using xylene as a solvent although other equally well known organic reaction solvents such as benzene, toluene and the like may be equivalently and alternatively employed as is known to those in the art.

Alternatively, our novel compounds may be prepared from novel starting materials disclosed and claimed in our copending application Serial Number 320,836, filed November 1, 1963. In this mode of synthesis starting reagents of the general formula:



(II)

wherein R is a lower alkyl group such as methyl, ethyl and so forth up to about 8 carbon atoms and *n* is 2 or 3, are reacted with a suitable amine such as diethylamine, piperidine, morpholine, and the like in an autoclave if desired at elevated temperature in some instances although the reaction may be conducted at room temperature under reflux conditions for a longer period of time than if the reaction is carried out with increased temperature and pressure.

When the methanesulfonic acid ester-amine reaction is employed as our method of synthesis, any suitable reaction solvent such as ethanol, methanol, etc. may be used and preferably a reaction solvent is employed which can be easily evaporated although most preferably an excess of the amine may suitably serve as the solvent. In any event the product of the invention may be recovered in good yield as a result of synthesis by either of the principal routes noted herein.

The manner of utilizing the invention sought to be patented will now be briefly described particularly as it relates to the employment in pharmacology of the physical embodiments resulting from the methods of preparation generally indicated above.

There is and has long been a desire in medicine to make available to the profession agents capable of reducing the incidence of atherosclerosis. Since a high cholesterol level in the blood of the animal has long been held to bear a casual relation to such medical condition, a continuing search for compounds of our invention have been found to demonstrate a capability to shift cholesterol from the blood of mammals. For example, the compound d-17β - (2-dimethylaminoethoxy)-3-methoxyestra-1,3,5(10)-triene has been found to be an effective agent in shifting cholesterol from the blood of laboratory

animals (rats) when administered at dosages of 20 mg./kilo or greater.

Beside having capacity to regulate blood lipids, the compounds of the invention are useful for their general hormonal effect particularly in the female and would therefore be expected to exhibit utility in those areas where natural estrogens are employed. When so utilized, the effective dosage of the compounds of this invention will depend upon the severity and the individual characteristics of each case wherein they are employed and specific dosage will, of course, be determined by the attending physician or veterinarian. Generally a dosage range of from about 1.25 to about 40.0 mg. per kg. of body weight per day would constitute the overall range.

The novel compounds of our invention in their concrete embodiment form may be administered in a number of ways, i.e. either orally, intravenously or intramuscularly. When contemplated for use in pharmaceutical products they, of course, can be administered singly or in combination with other active or inert ingredients in dosage unit form. If desired, they may be combined with a large number of compatible diluents, carriers, binders, and excipients to form a pharmaceutical preparation. Such typical liquid carriers as water, mineral oil, or a nontoxic alcohol may be admixed where preparations suitable for injection are to be the form of administration. Carboxymethylcellulose, starches, various sugars and the like may be employed where tablets or powders are to be compounded as a vehicle for oral administration.

The novel compounds as generally and specifically illustrated are basic in nature and thus exhibit a capacity for reaction with certain pharmaceutically acceptable acids to form the non-toxic pharmaceutically acceptable acid salts thereof by reactions well known to those versed in the steroid art. Any suitable inorganic acid such as hydrochloric, sulfuric, phosphoric, and the like or alternatively mild organic acids such as acetic, fumaric, maleic and the like may be employed to form such salts.

The invention in its concrete embodiment aspects as well as the general concept of the compounds and processes involved in our invention will be illustrated by the following several examples. It is, of course, to be understood that the general nature of our invention is intended to include those compositions, uses, compounds and processes which would in the scientific opinion of the inventors be considered as substantial equivalents to the embodiments described in the hereinafter typical illustrations.

EXAMPLE 1

d-17β-(2-dimethylaminoethoxy)-3-methoxyestra-1,3,5(10)-triene

A mixture of 5.0 g. of d-estradiol 3-methyl ether, 100 ml. of xylene, and 1.95 g. of a 50% sodium hydride suspension in oil was refluxed for 2 hours. After the addition of 5.52 g. of 2-dimethylaminoethyl chloride hydrochloride refluxing was continued for 14 hours. The reaction mixture was diluted with water followed by 10% sodium hydroxide solution to adjust to pH 12 and extracted with ether. The organic layer was extracted with 10% aqueous acetic acid and the acidic solution made basic with 10% sodium hydroxide and again extracted with ether. After evaporation of the ether, the resulting residue was distilled to yield d-17β-(2-diethylaminoethoxy)-3-methoxyestra-1,3,5(10)-triene, B.P. 180–190°, 3×10^{-4} mm. The product solidified on standing, M.P. 60–65°. (Found: C, 77.03; H, 9.63; N, 4.18. $C_{23}H_{35}O_2N$ requires: C, 77.26; H, 9.87; N, 3.92%.)

EXAMPLE 2

d-17β-(2-diethylaminoethoxy)-3-methoxyestra-1,3,5(10)-triene

A mixture of 3.0 g. of the methanesulfonic acid ester of d-17β - (2-hydroxyethoxy)-3-methoxyestra-1,3,5(10)-triene and 75 ml. of diethylamine was reacted in an autoclave at 100° for 6 hours. The solvent was evaporated and the resulting residue dissolved in aqueous acetic acid. After extracting the mixture with ether, the aqueous layer was made basic with a 10% sodium hydroxide solution and extracted with ether. The ethereal solution was washed with water followed by brine, dried over magnesium sulfate and filtered. Treatment of the filtrate with 10% aqueous hydrochloric acid furnished crystalline d-17β - (2-diethylaminoethoxy) - 3 - methoxyestra-1,3,5(10)-triene hydrochloride. U.V. (2,350). (Found: C, 71.02; H, 9.65; N, 3.43; Cl, 8.70. $C_{25}H_{40}NO_2$ requires: C, 71.13; H, 9.55; N, 3.32; Cl, 8.40%.)

EXAMPLE 3

d-17β-(2-piperidinoethoxy)-3-methoxyestra-1,3,5(10)-triene

A mixture of 8.0 g. of the methanesulfonic acid ester of d - 17β - (2-hydroxyethoxy)-3-methoxyestra-1,3,5(10)-triene and 110 ml. of piperidine was refluxed for 18 hours. After evaporation of the solvent, the resulting residue was treated with 10% aqueous acetic acid, extracted with ether, and the aqueous layer made basic with a 10% sodium hydroxide solution. The material was separated with ether from the aqueous layer and after evaporation of the solvent the resulting residue was crystallized from methanol yielding 3.1 g. of d-17β-(2-piperidinoethoxy)-3-methoxyestra-1,3,5,(10)-triene, M.P. 84–85°. (Found: C, 78.42; H, 9.75; N, 3.74. $C_{26}H_{39}O_2N$ requires: C, 78.54; H, 9.89; N, 3.52%.)

EXAMPLE 4

d-17β-(2-morpholinoethoxy)-3-butoxyestra-1,3,5(10)-triene

When the methanesulfonic acid ester of d-17β-(2-hydroxyethoxy)-3-butoxyestra-1,3,5(10)-triene is used in place of the methanesulfonic acid ester of d-17β-(2-hydroxyethoxy) - 3-methoxyestra-1,3,5(10)-triene, and morpholine in place of piperidine as described in Example III, d-17β-(2-morpholinoethoxy) - 3 - butoxyestra-1,3,5-(10)-triene is obtained.

EXAMPLE 5

d-17β-(2-diethylaminoethoxy)-3-cyclopentyloxyestra-1,3,5(10)-triene

Substituting the methanesulfonic acid ester of d-17β-(2-hydroxyethoxy)-3-methoxyestra-1,3,5(10) - triene by the methanesulfonic acid ester of d-17β-(2-hydroxyethoxy)-3-cyclopentyloxyestra-1,3,5(10)-triene and carrying out the reaction as described for Example III, d-17β-(2-diethylaminoethoxy) - 3-cyclopentyloxyestra-1,3,5(10)-triene is obtained.

EXAMPLE 6

d-17β-(3-dimethylaminopropoxy)-3-methoxyestra-1,3,5(10)-triene

A mixture of 5.0 g of d-estradiol-3-methyl ether, 100 ml. of xylene, and 3.9 g. of a 50% suspension sodium hydride in oil was refluxed for 2 hours. After the addition of 5.5 g. of 3-dimethylaminopropyl chloride hydrochloride, the reaction mixture was refluxed for 15 hours, cooled and the excess of sodium hydride destroyed with water. After adjusting the pH to 10 with 10% sodium hydroxide solution the reaction mixture was extracted with ether. The organic layer was then treated with a 10% aqueous acetic acid, the aqueous solution made alkaline (pH 10) with 10% sodium hydroxide solution and the material collected with ether. The residue left after evaporation of the ether was recrystallized from methanol-water to give 4.1 g. of d-17β-(3-dimethylamino-

propoxy) - 3 - methoxyestra-1,3,5(10)-triene, M.P. 63.5–64.5°; I.R. no OH. (Found: C, 77.31; H, 9.98; N. 3.76. $C_{24}H_{37}O_2N$ requires: C, 77.58; H, 10.04; N, 3.77%.)

EXAMPLE 7

d-17β-(3-piperidinopropoxy)-3-butoxyestra-1,3,5(10)-triene

When d-estradiol 3-butyl ether is reacted with 3-piperidinopropyl chloride hydrochloride as outlined in Example 6, d-17β-(3 - piperidinopropoxy)-3-butoxyestra-1,3,5(10)-triene is obtained.

EXAMPLE 8

d-17β-(3-morpholinopropoxy)-3-cyclopentyloxyestra-1,3,5(10)-triene

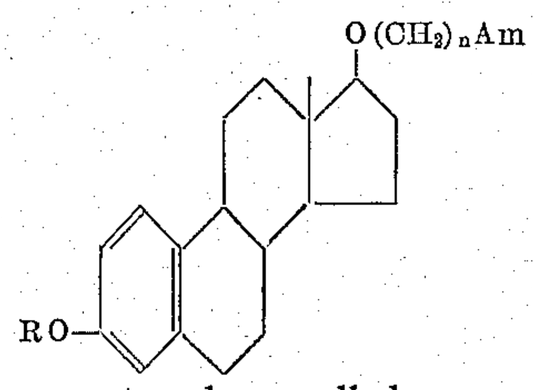
When d-estradiol 3-cyclopentyl ether is reacted with 3-morpholinopropyl chloride hydrochloride as outlined in Example 6, d-17β-(3-morpholinopropoxy) - 3 - cyclopentyloxyestra-1,3,5(10)-triene is obtained.

We claim:

1. A 17β-(2-aminoethoxy)ether of 3-loweralkoxyestra-1,3,5(10)-triene.

2. A 17β-(2 - aminoethoxy)ether of 3-methoxy-1,3,5-(10)-triene.

3. A compound selected from the group consisting of those bases having the structural formula:



wherein R represents a lower alkyl group and Am represents an amino substituent selected from the group consisting of primary amino, di-(lower)alkylamino, piperidino, and morpholino, and *n* represents from 2 to 3, and the non-toxic acid addition salts thereof.

4. d-17β - (2 - dimethylaminoethoxy)-3-methoxyestra-1,3,5(10)-triene.

5. d - 17β - (2 - diethylaminoethoxy)-3-methoxyestra-1,3,5(10)-triene.

6. d-17β-(2-piperidinoethoxy) - 3 - methoxyestra-1,3,5-(10)-triene.

7. d-17β-(3 - dimethylaminopropoxy)-3-methoxyestra-1,3,5(10)-triene.

No references cited.

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