

PATENT SPECIFICATION

NO DRAWINGS

889.310



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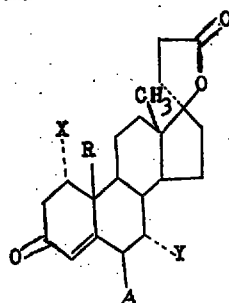
COMPLETE SPECIFICATION

Improvements in or relating to Steroid Compounds

We, G. D. SEARLE & Co., a Corporation organised and existing under the laws of the State of Delaware, United States of America, of P.O. Box 5110, Chicago, 80, Illinois, United States of America, 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:—

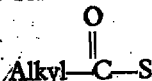
This invention relates to a new group of alkanoylthio - 17 α - carboxyethyl - 17 β - hydroxyandrostene - 3 - one lactones, the corresponding 19 - nor compounds, and processes for the manufacture thereof.

The invention provides compounds of the general formula



wherein A and R are each a hydrogen atom or methyl radical and wherein one of the radicals X and Y is an alkanoylthio radical and the other is a hydrogen atom or an alkanoylthio radical, the alkanoylthio radical containing less than 9 carbon atoms. In this, as in all subsequent steroidal formulae herein, the oxygen atom attached to the 17-carbon atom is in β -configuration.

By "alkanoylthio" herein is meant a radical of the general formula

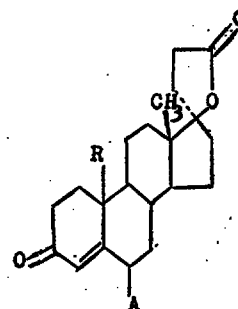


the alkyl constituent being such as methyl, ethyl, propyl, isopropyl, butyl, and hexyl radicals containing less than 9 carbon atoms. It

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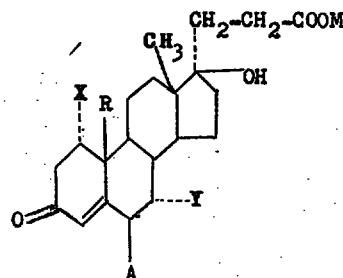
should be noted that the alkanoylthio-alkylene radicals, are limited to those which afford 1 α and/or 7 α positioning of the sulphur-containing side chain.

The compounds of this invention are preferably manufactured by mixing a thioalkanoic acid of the general formula Alkyl-CO-SH with a Δ^1 and/or Δ^6 -dehydro derivative of the corresponding steroid of the formula



wherein A and R are each a hydrogen atom or a methyl radical. A solvent medium can be employed, if desired, and ultra-violet irradiation or heating can be used to increase the reaction rate.

Equivalent to the lactones for the purposes of this invention are the corresponding hydroxyacids and their alkali metal salts, of the formula



wherein A and R are each a hydrogen atom or methyl radical, wherein M is a hydrogen

or an alkali metal atom or the ammonium radical and X and Y are as defined above.

The lactones, hydroxy acids, and salts herein described are useful because of their valuable pharmacological properties. Among other things, they are diuretic agents, and adapted to block the effect of desoxy-corticosterone acetate on urinary sodium and potassium.

Those skilled in the art of organic syntheses will readily see that the described lactones, on contact with aqueous alkali, are converted to alkali metal and ammonium salts of the corresponding hydroxy acids from which the free acids can be obtained by a brief exposure to a proton source. Prolongation of the exposure time induces lactonisation.

The following examples described in detail certain of the compounds illustrative of this invention. In these examples temperatures are given in degrees Centigrade ($^{\circ}\text{C}.$), relative amounts of materials in parts by weight (c.g.s. units) and pressures in millimetres (mm.) of mercury.

EXAMPLE 1

A mixture of 1 part of 17α - (2 - carboxy - ethyl) - 17β - hydroxyandrosta - 1, 4 - dien - 3 - one lactone and 1 part of thioacetic acid was heated at approximately $90^{\circ}\text{C}.$ for 1/2 hour. The bulk of the excess thioacetic acid was then evaporated under nitrogen and the residue crystallised from a mixture of ethyl acetate and ether. Recrystallisation from ethyl acetate afforded 1α - acetylthio - 17α - (2 - carboxyethyl) - 17β - hydroxyandrost - 4 - en - 3 - one lactone melting at approximately $199-200^{\circ}\text{C}.$ (with decomposition).

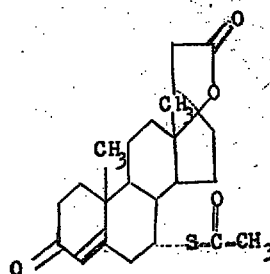
EXAMPLE 2

A mixture of 7 parts of 17α - (2 - carboxy - ethyl) - 17β - hydroxyandrosta - 1, 4 - dien - 3 - one lactone and 10 parts of thiopropionic acid was heated at approximately $90^{\circ}\text{C}.$ for 1 hour. Ethyl acetate and sufficient hexane to induce crystallisation were added, and the product which separated was further purified by recrystallisation from a mixture of benzene and hexane. The 17α - (2 - carboxy - ethyl) - 17β - hydroxy - 1α - propionylthio - androst - 4 - en - 3 - one lactone thus obtained melted at $176-178^{\circ}\text{C}.$ (with decomposition).

EXAMPLE 3

A mixture of approximately 11 parts of 17α - (2 - carboxyethyl) - 17β - hydroxy - androsta - 4, 6 - dien - 3 - one lactone and 10 parts of thioacetic acid was heated at $85-95^{\circ}\text{C}.$ for 1/2 hour. Most of the excess thioacetic acid was removed by vacuum distillation at this point, and the residue was diluted with methanol. The desired 7α - acetylthio - 17α - (2 - carboxyethyl) - 17β - hydroxy - androst - 4 - en - 3 - one lactone, melting at approximately $134-135^{\circ}\text{C}.$, crystallised out. Heated above this melting point, the product solidified and melted again at approximately

$201-202^{\circ}\text{C}.$ (with decomposition). 7α - acetylthio - 17α - (2 - carboxyethyl) - 17β - hydroxyandrost - 4 - en - 3 - one lactone has the formula



EXAMPLE 4

A mixture of 13 parts of 17α - (2 - carboxy - ethyl) - 17β - hydroxyandrosta - 4, 6 - dien - 3 - one lactone and 10 parts of thiopropionic acid was heated at $90^{\circ}\text{C}.$ for 1/2 hour. Worked-up as detailed in Example 3 afforded 17α - (2 - carboxyethyl) - 17β - hydroxy - 7α - propionylthioandrost - 4 - en - 3 - one lactone, melting at $192.5-194^{\circ}\text{C}.$

EXAMPLE 5

Octanethiolic acid was prepared by bubbling hydrogen sulphide slowly into 102 parts of octanoic anhydride for 48 hours with stirring. At the end of the 48 hour period, the solution showed a weight gain of approximately 12 parts. The octanethiolic acid was distilled from the mixture at 0.5 mm. pressure, and had a boiling point of $60-64^{\circ}\text{C}.$

A solution of 1 part of octanethiolic acid and 1 part of 17α - (2 - carboxyethyl) - 17β - hydroxyandrost - 4, 6 - dien - 3 - one lactone was heated on a steam bath for two hours. The reaction mixture was then taken up in benzene and applied to a chromatography column containing silica gel. The column was developed with benzene solutions containing increasing amounts of ethyl acetate. Upon elution, with a 5% solution of ethyl acetate in benzene and evaporation, there was obtained 7α - octanoylthio - 17α - (2 - carboxyethyl) - 17β - hydroxyandrost - 4 - en - 3 - one lactone as an oil. The compound had an absorption maximum in the ultra-violet at 237.5 millimicrons and an extinction coefficient of about 18,750. Infra-red maxima were observed at 5.65, 5.95, 6.17, 6.80 and 10.25 microns.

EXAMPLE 6

A mixture of 5 parts of 17α - (2 - carboxy - ethyl) - 17β - hydroxyandrosta - 1, 4, 6 - trien - 3 - one lactone monomethanolate and 10 parts of thioacetic acid was heated at $85-95^{\circ}\text{C}.$ for 1 hour. Excess thioacetic acid was thereupon removed by vacuum distillation; and the residue was chromatographed on silica gel, using benzene and ethyl acetate as developing solvents. From an eluate comprising 15% of ethyl acetate in



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benzene there was obtained, on evaporation of solvent, the desired 1 α , 7 α - diacetylthio - 17 α - (2 - carboxyethyl) - 17 β - hydroxyandrost - 4 - en - 3 - one lactone. The product was characterised by a maximum in the ultra-violet absorption spectrum at 236.5 m μ peaks in the infra-red absorption spectrum at 3.4, 5.65, 5.9, 6.0, 6.2, 7.4, 8.5, 8.8, and 10.5 μ .

Substitution of an equimolecular amount of thiopropionic acid for the thioacetic acid in the preceding paragraph of this example yielded 1 α , 7 α - dipropionylthio - 17 α - (2 - carboxyethyl) - 17 β - hydroxyandrost - 4 - en - 3 - one lactone.

EXAMPLE 7

To a solution of 820 parts of chloranil in 87,000 parts of xylene containing 1 part of *p*-toluene-sulphonic acid monohydrate was added, with agitation at the boiling point under reflux, 1000 parts of 17 α - (2 - carboxyethyl) - 17 β - hydroxy - 19 - norandrost - 4 - en - 3 - one lactone. The lactone dissolved. The resultant solution was maintained at the boiling point under reflux for 1 hour and then cooled and chromatographed on silica gel, using benzene and ethyl acetate as developing solvents. There was isolated by this means the desired 17 α - (2 - carboxyethyl) - 17 β - hydroxy - 19 - norandrost - 4, 6 - dien - 3 - one lactone which, recrystallised from ethyl acetate, melted in the range 235—239° C.

A mixture of 47 parts of 17 α - (2 - carboxyethyl) - 17 β - hydroxy - 19 - norandrost - 4, 6 - diene - 3 - one lactone with 100 parts of thioacetic acid was heated at 80—95° C. for several hours. The material was then taken up in benzene and chromatographed on silica gel, using benzene and ethyl acetate as developing solvents. There was isolated by this means pure 7 α - acetylthio - 17 α - (2 - carboxyethyl) - 17 β - hydroxy - 19 - norandrost - 4 - en - 3 - one lactone, which was characterised by a maximum in the ultra-violet absorption spectrum at 236.5 m μ . The product melted at 111—113° C.

Substitution of an equimolecular amount of thiopropionic acid for the thioacetic acid in the preceding paragraph of this example yielded 7 α - propionylthio - 17 α - (2 - carboxyethyl) - 17 β - hydroxy - 19 - norandrost - 4 - en - 3 - one lactone.

EXAMPLE 8

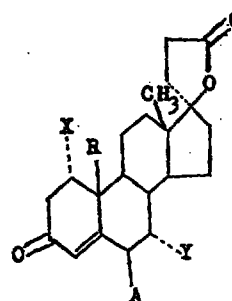
A solution of 5 parts of 17 α - (2 - carboxyethyl) - 17 β - hydroxy - 6 β - methylandrost - 4 - en - 3 - one lactone and 5 parts of chloranil in 400 parts of xylene containing a trace of *p*-toluenesulphonic acid was heated at the boiling point of the solvent under reflux overnight. The solution was then stripped of solvent by vacuum distillation, and the residue was chromatographed on silica gel, using benzene and ethyl acetate as developing solvents. By using this means there was

isolated pure 17 α - (2 - carboxyethyl) - 17 β - hydroxy - 6 - methylandrost - 4, 6 - dien - 3 - one lactone, the melting point of which was 204—205° C.

Using the technique of Example 3, but substituting 11 parts of 17 α - (2 - carboxyethyl) - 17 β - hydroxy - 6 - methylandrost - 4, 6 - dien - 3 - one lactone for the 11 parts of 17 α - (2 - carboxyethyl) - 17 β - hydroxy - androst - 1, 4, dien - 3 - one lactone called for therein, there was obtained 7 α - acetylthio - 17 α - (2 - carboxyethyl) - 17 β - hydroxy - 6 - methylandrost - 4 - en - 3 - one lactone. The product melted at 237—240° C. (with decomposition).

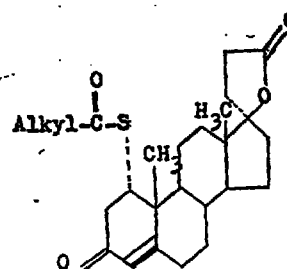
WHAT WE CLAIM IS:—

Compounds of the general formula



wherein A and R are each a hydrogen atom or methyl radical and wherein one of the radicals X and Y is an alkanoylthio radical and the other is a hydrogen atom or an alkanoylthio radical, the alkanoylthio radical containing less than 9 carbon atoms.

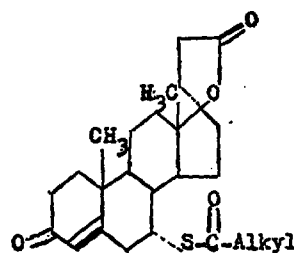
2. Compounds of the general formula



wherein the alkyl group contains less than 9 carbon atoms.

3. 1 α - acetylthio - 17 α - (2 - carboxyethyl) - 17 β - hydroxy - androst - 4 - en - 3 - one lactone.

4. Compounds of the general formula



benzene there was obtained, on evaporation of solvent, the desired 1 α , 7 α -diacetylthio - 17 α - (2 - carboxyethyl) - 17 β - hydroxyandrost - 4 - en - 3 - one lactone. The product was characterised by a maximum in the ultra-violet absorption spectrum at 236.5 m μ peaks in the infra-red absorption spectrum at 3.4, 5.65, 5.9, 6.0, 6.2, 7.4, 8.5, 8.8, and 10.5 μ .

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EXAMPLE 8

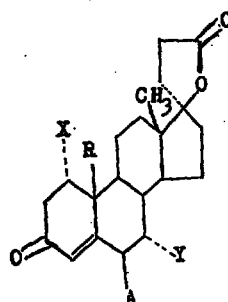
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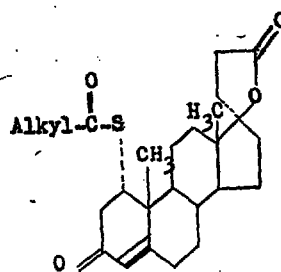
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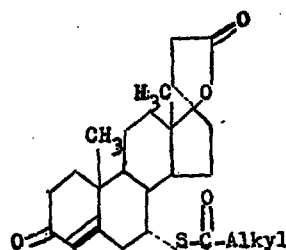
2. Compounds of the general formula



wherein the alkyl group contains less than 9 carbon atoms.

3. 1 α - acetylthio - 17 α - (2 - carboxyethyl) - 17 β - hydroxy - androst - 4 - en - 3 - one lactone.

4. Compounds of the general formula





Hydroxy-19-norandrost

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wherein the alkyl group contains less than 9 carbon atoms.

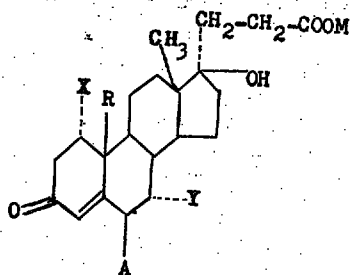
5. 7 α - acetylthio - 17 α - (2 - carboxy - ethyl) - 17 β - hydroxy - androst - 4 - en - 3 - one lactone.

6. 1 α - 7 α diacetylthio - 17 α - (2 - carboxy - ethyl) - 17 β - hydroxyandrost - 4 - en - 3 - one lactone.

7. 7 α - acetylthio - 17 α - (2 - carboxy - ethyl) - 17 β - hydroxyandrost - 4 - en - 3 - one lactone.

8. 7 α - acetylthio - 17 α - (2 - carboxy - ethyl) - 17 β - hydroxy - 6 - methylandrost - 4 - en - 3 - one lactone.

15. 9 Compounds of the general formula



wherein A and R are each a hydrogen atom or methyl radical, wherein M is a hydrogen or an alkali metal atom or the ammonium radical and wherein one of the radicals X and Y is an alkanoylthio radical and the other is a hydrogen atom or an alkanoylthio radical, the alkanoylthio radical containing less than 9 carbon atoms.

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