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# PATENT SPECIFICATION

NO DRAWINGS

835,558

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COMPLETE SPECIFICATION

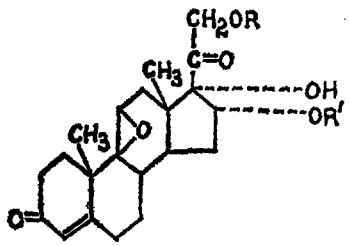
## New Steroid Compounds and the preparation thereof

We, AMERICAN CYANAMID COMPANY, a corporation organised under the laws of the State of Maine, United States of America, of 30, Rockefeller Plaza, New York, State of New York, 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 new steroid compounds and the preparation thereof. These new steroid compounds comprise 9β,11β-oxides of $\Delta^4$-pregnenes and esters thereof.

These 9β,11β-oxides of $\Delta^4$-pregnenes and esters thereof of the present invention are useful as intermediates for the preparation of 9α-halo-16α-hydroxy-hydrocortisones and esters thereof, which are described and claimed in application No. 18246/56 (Serial No. 835,557).

The 9β,11β-oxides of $\Delta^4$-pregnenes and esters thereof of the present invention have the following general formula:




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in which R and $R^1$ are both hydrogen atoms or alkanoyl radicals containing 1 to 6 carbon atoms.

These oxides of $\Delta^4$-pregnene of the present invention are relatively high melting crystalline solids. They are soluble in the common organic solvents and relatively insoluble in water.

The intermediate compounds used for the preparation of the oxides of $\Delta^4$-pregnenes of the present invention are prepared by starting with the ester (containing 1 to 6 carbon atoms in the ester group) of $\Delta^{4,9(11),16}$-pregnatriene-21-ol-3,20-dione which is treated with osmium tetroxide and the osmate ester which forms is decomposed to produce the corresponding $\Delta^{4,9(11)}$ - pregnadiene - 16α,17α,21 - triol-3,20-dione ester. The latter compound is then reacted with an alkanoic anhydride, e.g., acetic anhydride, which acylates the hydroxy group in the 16-position. The acylated compound is then reacted with a N-bromo-acid amide and perchloric acid to produce $\Delta^4$-pregnene 9α-bromo - 11β,16α,17α,21 - tetrol - 3,20 dione 16α,21-diester. The latter intermediate is then reacted in the process of this invention with an anhydrous alkali metal acetate, preferably anhydrous potassium acetate, any saponified steroid oxide formed being preferably subsequently reacylated, to produce the $\Delta^4$-pregnene - 16α,17α,21 - triol - 3,20-dione-9β,11β-oxide 16α,21-diester of the present invention, which if desired may be saponified under mildly alkaline conditions.

The following example describes in detail the preparation of the starting materials used in the method of this invention.

A solution of 0.70 g. of $\Delta^{4,9(11),16}$-pregnatriene-21-ol-3,20-dione 21-acetate and 0.50 g. of osmium tetroxide in 10 ml. of benzene and 0.5 ml. of pyridine was allowed to stand at room temperature for 18 hours. The osmate ester was decomposed by the addition of 35 ml. of water, 10 ml. of benzene, 23 ml. of methanol and 3.58 g. each of sodium sulfite and potassium bicarbonate. After stirring the mixture for 5 hours, approximately 150 ml.

[Price 3s. 6d.]

of chloroform was added and the stirring continued for ½ hour. The mixture was filtered through diatomaceous earth, the residue washed with hot chloroform and the organic layer separated. The aqueous phase was extracted several times with chloroform and the combined extracts were washed with saturated saline and with water. The dried extract was evaporated under reduced pressure and the residue crystallized from acetone-petroleum ether to give 0.62 g. of crude product, melting point 172—174° with previous softening. Three crystallizations from acetone-petroleum ether gave 0.42 g. of pure $\Delta^{4,9(11)}$-pregnadiene - 16α,17α,21 - triol - 3,20 - dione 21-acetate, melting point 195—197.5° with previous softening. One additional recrystallization did not alter the melting point; $\lambda_{max.}^{abs.\ alc.}$ 238.5 mμ (ε16,700); $[\alpha]_D^{25}$+93° (chloroform).

To a solution of 325 mg. of $\Delta^{4,9(11)}$-pregnadiene-16α,17α,21-triol-3,20-dione 21-acetate in 20 ml. of pyridine was added 2 ml. of acetic anhydride, and the mixture was allowed to stand at room temperature for 3 days. The solution was poured into water, cooled and the product was filtered and washed with water to give 0.33 g. of pure $\Delta^{4,9(11)}$-pregnadiene - 16α,17α,21 - triol-3,20-dione 16α,21-diacetate, melting point 193—195° with previous softening. Two crystallizations from acetone-petroleum ether gave 0.28 g. of pure diacetate, melting point 194—195° with previous softening: $\lambda_{max.}^{abs.\ alc.}$ 238—239 mμ (ε17,400); $[\alpha]_D^{25}$+43° (chloroform).

The diene diacetate, $\Delta^{4,9(11)}$-pregnadiene-16α,17α,21 - triol - 3,20 - dione 16α,21-diacetate (0.50 g.), in dioxane (20 ml.) and water (4 ml.) was treated with N-bromo-acetamide (0.31 g.) and 10% perchloric acid (2 ml.). After allowing to stand for 15 minutes at 20°, excess sodium sulfite and water were added. The resultant soft solid was extracted with chloroform and the extract washed with saturated saline, dried, filtered through diatomaceous earth and evaporated under reduced pressure to an oil. Crystallization from acetone-petroleum ether gave 0.45 g. of crude bromohydrin, melting point 130—133.5° dec., with previous browning. Three crystallizations from acetone-petroleum ether gave 0.31 g. of $\Delta^4$ - pregnene - 9α - bromo - 11β,16α,17α,21-tetrol-3,20-dione 16α,21-diacetate, melting point 125—126° dec. with previous browning, $\lambda_{max.}^{abs.\ alc.}$ 243 mμ (ε14,100); $[\alpha]_D^{25}$ +76° (chloroform).

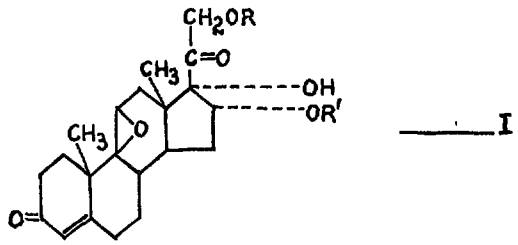
The following example illustrates the process of this invention.

A solution of 14.5 g. of $\Delta^4$-pregnene-9α-bromo - 11β,16α,17α,21 - tetrol - 3,20 - dione 16α,21-diacetate and 3.2 g. of anhydrous potassium acetate in 1 l. of absolute alcohol was refluxed for 18.5 hours. The reaction mixture was evaporated to dryness and the residue dissolved in ethyl acetate and water. The aqueous phase was extracted with ethyl acetate and the combined extracts were washed with saturated sodium bicarbonate solution and saline. The dried extract was evaporated and the residue containing $\Delta^4$-pregnene-16α,17α,21-triol-3,20-dione-9β,11β-oxide was dissolved in 35 ml. of pyridine, treated with 10 ml. of acetic anhydride and allowed to stand at room temperature overnight. Methanol and benzene were added and the solution was evaporated to dryness. Crystallization of the residue from methanol gave 6.5 g. of crude $\Delta^4$-pregnene-16α,17α,21 - triol - 3,20 - dione - 9β,11β-oxide 16α,21 diacetate, melting point 171.5—191.5° with previous softening, suitable for use in further transformations.

The above $\Delta^4$-pregnene-16α,17α,21-triol-3,20-dione 9β,11β-oxide 16α,21-diacetate is hydrolyzed under mildly alkaline conditions to produce the corresponding $\Delta^4$-pregnene-16α,17α,21 - triol - 3,20 - dione 9β,11β-oxide.

WHAT WE CLAIM IS:—

1. A method of preparing 9β,11β oxides of $\Delta^4$-pregnenes and esters thereof having the formula




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in which R and $R^1$ are both hydrogen atoms or alkanoyl radicals containing 1 to 6 carbon atoms which comprises reacting the corresponding $\Delta^4$-pregnene-9α-bromo-11β,16α,17α,21-tetrol-3,20-dione 16α,21-diester with an anhydrous alkali metal acetate to form the 9β,11β-oxide of the $\Delta^4$-pregnene diester, and if desired saponifying under mildly alkaline conditions to convert R and $R^1$ to hydrogen.

2. A method of preparing 9β,11β-oxides of $\Delta^4$-pregnenes and esters thereof of the general formula I in claim 1 substantially as hereinbefore described.

3. 9β,11β-oxides of $\Delta^4$-pregnenes and esters thereof having the formula I whenever prepared by the method according to any of the preceding claims.

of chloroform was added and the stirring continued for ½ hour. The mixture was filtered through diatomaceous earth, the residue washed with hot chloroform and the organic layer separated. The aqueous phase was extracted several times with chloroform and the combined extracts were washed with saturated saline and with water. The dried extract was evaporated under reduced pressure and the residue crystallized from acetone-petroleum ether to give 0.62 g. of crude product, melting point 172—174° with previous softening. Three crystallizations from acetone-petroleum ether gave 0.42 g. of pure $\Delta^{4,9(11)}$-pregnadiene - 16α,17α,21 - triol - 3,20 - dione 21-acetate, melting point 195—197.5° with previous softening. One additional recrystallization did not alter the melting point; $\lambda_{max.}^{abs.\ alc.}$ 238.5 mμ (ε16,700); $[\alpha]_D^{25}$ +93° (chloroform).

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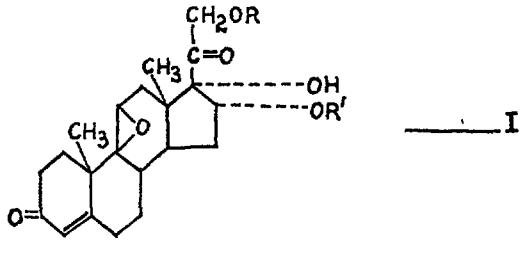
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2. A method of preparing 9β,11β-oxides of $\Delta^4$-pregnenes and esters thereof of the general formula I in claim 1 substantially as hereinbefore described.

3. 9β,11β-oxides of $\Delta^4$-pregnenes and esters thereof having the formula I whenever prepared by the method according to any of the preceding claims.

* C L M S *

4. New compounds comprising 9β,11β-oxides of $\Delta^4$-pregnenes and esters thereof having the general formula I in claim 1.

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