

PATENT SPECIFICATION

(11)

1403800

1403800

(21) Application No. 56790/72 (22) Filed 8 Dec. 1972

(44) Complete Specification published 20 Aug. 1975

(51) INT CL² C07J 51/00 A61K 31/56//C07J 21/00

(52) Index at acceptance

C2U 2 4A2A 4B1 4B2B 4C3 4C4A 4C9A 4DX 4N18 4N9
6A1 7B 8A1

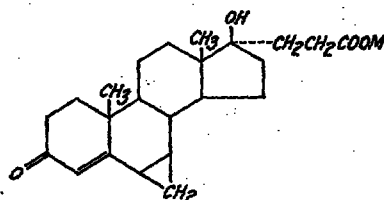
(72) Inventor GLEN EDWARD ARTH



(54) 6,7-METHYLENE STEROIDS

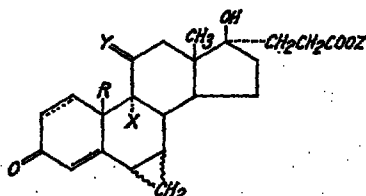
(71) We, MERCK & CO. INC., a corporation duly organised and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

In the specification of our copending application number 33403/72 (1361362) there are claimed compounds having the formula



and their 1,2-unsaturated analogues, in which M is an alkali metal and the 6,7-methylene group is in the β -configuration. The specification also discloses and claims a method of preparing such compounds by hydrolysis of 6 β ,7 β - methylene - 20 - spirox - 4 - ene - 3,21 - dione or 6 β ,7 β - methylene - 20 - spiroxa - 1,4 - diene - 3,21 - dione, using an alkali metal hydroxide and a C₁₋₃ alkanol.

The present invention provides compounds having the general formula



(apart from those claimed in the said copending application) in which R is hydrogen or methyl; X is hydrogen or fluorine; Y is two hydrogen atoms, a hydrogen atom and β -hydroxy group, or a keto group; Z is hydrogen or a pharmaceutically acceptable salt-forming cation; the wavy line to the 6,7-methylene

group indicates that it is in the α or β configuration and the dotted line between carbons 1 and 2 of the A ring indicates the optional presence of a double bond. These steroids can be conveniently referred to as 3' - (3 - oxo - 17 β - hydroxy - 6,7 - methylene - androst - (or 19 - norandrost)4 - en - 17 α - yl) propionic acid compounds. They are prepared by reacting the corresponding 6,7 - methylene 20 - spirox - (or 19 - nor - spirox)4 - ene - 3,21 - dione steroid lactone with an alkaline solution thereby hydrolysing the lactone ring of the steroid to form the propionic acid compound.

It has been found that compounds of the above formula are potent aldosterone inhibitors. The block the salt-retaining effects of aldosterone and other salt-retaining steroids and are therefore useful in the alleviation of diseases such as congestive heart failure, nephrosis and cirrhosis of the kidney in which aldosterone secretion is increased.

The compounds of the present invention are made up into pharmaceutical compositions that also contain a pharmaceutical diluent, carrier, coating or excipient. They may be in the form of a pill, tablet, capsule or injectable liquid.

The hereinabove-noted reaction of the 6,7 - methylene - 20 - spirox - (or 19 - nor - spirox -)4 - ene - 3,21 - dione steroid lactone with the alkaline hydrolysing agent is conveniently conducted by dissolving the steroid in an alcohol such as ethanol or methanol and heating the solution with the said aqueous alkaline hydrolysing agent, for example an aqueous alkali metal hydroxide such as aqueous sodium hydroxide or aqueous potassium hydroxide. The alcohol is then evaporated from the hydrolysis mixture, the residual aqueous solution is extracted with a water-immiscible organic solvent such as chloroform, and the aqueous solution is freeze-dried to give the hydrolyzed lactone, that is, the salt of the corresponding 3' - (3 - oxo - 17 β - hydroxy - 6,7 - methylene - androst - (or 19 - nor - androst -)4 - ene - 17 α - yl) propionic acid, in substantially quantitative yield.

[Price

Superoxide prepared by reacting the starting materials as described above. The starting materials are conveniently prepared by reacting dimethyl - oxo - sulfonium methylide with a 3 - oxo - 20 - spiroxa - 4,6 - diene, for example 20 - spiroxa - 4,6 - dien - 3 - one; 19 - nor - 20 - spiroxa - 4,6 - dien - 3 - one; 20 - spiroxa - 4,6 - diene - 3,21 - dione; and 19 - nor - 20 - spiroxa - 4,6 - diene - 3,21 - dione; 20 - spiroxa - 4,6 - dien - 11 β - ol - 3 - one; 9 α - fluoro - 20 - spiroxa - 4,6 - dien - 11 β - ol - 3 - one; 20 - spiroxa - 4,6 - dien - 11 β - ol - 3,21 - dione; and 9 α - fluoro - 20 - spiroxa - 4,6 - diene - 11 β - ol - 3,21 - dione, thereby forming the corresponding 6,7 - methylene derivative. The reaction is conveniently conducted by bringing together, under nitrogen, a mineral-oil dispersion of sodium hydride and trimethyl sulfoxonium iodide and slowly adding dry dimethyl sulfoxide, whereupon reaction occurs with the formation of dimethyl - oxo - sulfonium methylide. To the resulting mixture is then added the 3 - oxo - 20 - spiroxa - 4,6 - diene, preferably an amount such that the molar ratio of dimethyl - oxo - sulfonium methylide to steroid is within the range of 1:1 to 5:1. It is ordinarily preferred to use a molar ratio of about 1:1 where the 3 - oxo - 20 - spiroxa - 4,6 - diene starting steroid is a 19 - nor - 20 - spiroxa - 4,6 - diene - 3 - one (or 3,21-dione) or 20 - spiroxa - 4,6 - diene - 3,21 - dione. The reaction is allowed to proceed for approximately 15 hours at about room temperature, and the steroid product is conveniently recovered from the reaction mixture by adding the reaction mixture to ice-water, extracting the steroid product with a water-immiscible organic solvent such as ether, evaporating the organic solvent, and purifying the residual material by chromatography over alumina. There is thus obtained the corresponding 3 - oxo - 6,7 - methylene - 20 - spirox - 4 - ene product such as 6,7 - methylene - 20 - spirox - 4 - en - 3 - one; 6,7 - methylene - 19 - nor - 20 - spirox - 4 - en - 3 - one; 6,7 - methylene - 20 - spirox - 4 - ene - 3,21 - dione; 6,7 - methylene - 19 - nor - 20 - spirox - 4 - ene - 3,21 - dione; 6,7 - methylene - 20 - spirox - 4 - en - 11 β - ol - 3 - one; 6,7 - methylene - 9 α - fluoro - 20 - spirox - 4 - en - 11 β - ol - 3 - one; 6,7 - methylene - 20 - spirox - 4 - en - 11 β - ol - 3,21 - dione; or 6,7 - methylene - 9 α - fluoro - 20 - spirox - 4 - en - 11 β - ol - 3,21 - dione.

The oxo - 6,7 - methylene - 20 - spirox - 4 - ene - compound may be treated with 2,3 - dichloro - 5,6 - dicyanobenzoquinone to introduce Δ' unsaturation. This reaction may be conducted by heating the reactants together in an organic solvent such as dioxane, preferably under substantially anhydrous conditions and under a nitrogen atmosphere. When dioxane is used as the reaction solvent, the reac-

tion is ordinarily carried out by heating the reaction mixture at a reflux temperature for a period of about 3 hours. The resulting mixture is then diluted with a water-immiscible organic solvent such as ethyl acetate; the organic solution is washed with a dilute aqueous alkaline solution and then with water, dried and evaporated to dryness; the residual material is conveniently purified by chromatography using a silica gel column to produce the corresponding 3 - oxo - 6,7 - methylene - 20 - spiroxa - 1,4 - diene product such as 6,7 - methylene - 20 - spiroxa - 1,4 - dien - 3 - one; 6,7 - methylene - 19 - nor - 20 - spiroxa - 1,4 - dien - 3 - one; 6,7 - methylene - 20 - spiroxa - 1,4 - diene - 3,21 - dione; 6,7 - methylene - 19 - nor - 20 - spiroxa - 1,4 - diene - 3,21 - dione; 6,7 - methylene - 20 - spiroxa - 1,4 - dien - 11 β - ol - 3 - one; 6,7 - methylene - 9 α - fluoro - 20 - spiroxa - 1,4 - dien - 11 β - ol - 3 - one; 6,7 - methylene - 20 - spiroxa - 1,4 - dien - 11 β - ol - 3,21 - dione; or 6,7 - methylene - 9 α - fluoro - 20 - spiroxa - 1,4 - dien - 11 β - ol - 3,21 - dione.

When there is obtained, in accordance with the procedures hereinabove described, a 6,7 - methylene - 20 - spirox - 4 - en (or 1,4 - dien) - 3 - one steroid containing an 11 β - hydroxy substituent, this compound may be converted to the corresponding 11-ketone by reaction with an oxidizing agent such as chromium trioxide-pyridine complex; the reaction is ordinarily conducted by adding a pyridine solution of the 11 β -hydroxy - steroid compound to the complex formed by adding chromium trioxide to an excess of pyridine, and allowing the oxidation reaction to proceed at approximately room temperature for a period of about 15 hours. The 11-keto steroid product is conveniently recovered from the reaction mixture by pouring the latter into water and extracting the aqueous mixture with a water-immiscible organic solvent such as ether or ethyl acetate; the organic solvent layer is then washed with dilute aqueous acid and then with water, dried and evaporated to dryness; the residual material is purified by crystallization from an organic solvent such as petroleum ether to give the corresponding 6,7 - methylene - 20 - spirox - 4 - ene (or 1,4 - diene) - 3,11 - dione steroid such as 6,7 - methylene - 20 - spirox - 4 - ene - 3,11 - dione; 6,7 - methylene - 20 - spirox - 4 - ene - 3,11, 21 - trione; 6,7 - methylene - 9 α - fluoro - 20 - spirox - 4 - ene - 3,11 - dione; 6,7 - methylene - 9 α - fluoro - 20 - spirox - 4 - ene - 3,11,21 - trione; 6,7 - methylene - 20 - spiroxa - 1,4 - diene - 3,11 - dione; 6,7 - methylene - 20 - spiroxa - 1,4 - diene - 3,11,21 - trione; 6,7 - methylene - 9 α - fluoro - 20 - spiroxa - 1,4 - diene - 3,11 - dione or 6,7 - methylene - 9 α -

fluoro - 20 - spiroxa - 1,4 - diene - 3,11,21 - trione.

When there is obtained, in accordance with the procedures hereinabove described, a
 5 6,7 - methylene - 20 - spirox - 4 - en (or 1,4 - dien) - 3 - one steroid which contains only hydrogen at C-21, such as 6,7 - methylene - 20 - spirox - 4 - en - 3 - one or 6,7 -
 10 methylene - 20 - spirox - 4 - ene - 3,11 - dione, this may be converted to the corresponding 21-ketone by reaction with an oxidizing agent such as *t*-butyl chromate. The *t*-butyl chromate is conveniently prepared by reacting chromium trioxide with butanol at
 15 about room temperature. The oxidation reaction is ordinarily conducted by adding an anhydrous carbon tetrachloride solution of *t*-butyl chromate, containing acetic anhydride and acetic acid, to a chloroform solution of the 6,7 - methylene - 20 - spirox - 4 - en
 20 (or 1,4 - dien) - 3 - one, and heating the resulting mixture, preferably under reflux, under which conditions the oxidation reaction to form the C-21 ketone is substantially complete in about five hours. The 21-keto steroid product is conveniently recovered from the reaction mixture by adding a reducing agent such as an aqueous oxalic acid to reduce excess
 25 of *t*-butyl chromate, then extracting with carbon tetrachloride; the organic layer is then washed, dried and evaporated, and the residual material is conveniently purified by chromatography to give the corresponding 6,7 - methylene - 20 - spirox - 4 - ene - (or 1,4 - diene) -
 30 3,21 - dione steroid such as 6,7 - methylene - 20 - spirox - 4 - ene - 3,21 - dione; 6,7 - methylene - 20 - spirox - 4 - ene - 3,11,21 - trione; 6,7 - methylene - 9 α - fluoro - 20 - spirox - 4 - ene - 3,21 - dione; 6,7 - methylene - 9 α - fluoro - 20 - spirox - 4 - ene - 3,11,21 - trione; 6,7 - methylene - 20 - spiroxa - 1,4 - diene - 3,11,21 - trione; 6,7 - methylene - 9 α - fluoro - 20 - spiroxa - 1,4 - diene - 3,21 - dione; or
 40 6,7 - methylene - 9 α - fluoro - 20 - spiroxa - 1,4 - diene - 3,11,21 - trione.

Experimental details for the synthesis of these starting materials are set forth hereinbelow in the Preparations; part of Preparation 1 also appears in the said copending application. Proportions of solvents are on a volume basis.

Preparation 1

55 To a thoroughly dry mixture of 1.8 g. of a 56.37% dispersion of sodium hydride in mineral oil (0.04246 mole) and 9.81 g. (0.04246 mole + 5% excess) of trimethyl sulfoxium iodide, maintained under a nitrogen atmosphere and cooled to a temperature of about 10° C., is slowly added 50 ml. of dry dimethyl sulfoxide at such a rate that foaming is not excessive. The resulting mixture

is stirred at a temperature of about 20° C. for
 65 a period of about 2.5 hrs., or until all sodium hydride has reacted. To the thus formed dimethyl-oxo-sulfonium methylide reaction mixture, maintained substantially anhydrous and under a nitrogen atmosphere, is added rapidly,
 70 with stirring at room temperature, a solution of 3.0 g. 0.0947 mole) of 20 - spiroxa - 4,6 - dien - 3 - one in 5 ml. of dimethylsulfoxide. The reaction is allowed to proceed overnight at room temperature, and the reaction mixture is then added to about 100 ml. of an ice-water mixture. The resulting aqueous mixture is extracted with two 100-ml. portions of
 75 ether, and the combined extracts are washed with three 25-ml. portions of water. The washed ethereal extract is dried over anhydrous sodium sulfate and evaporated to dryness *in vacuo*. The resulting yellow foam, which weighs approximately 3.9 g., is suspended in petroleum ether, and solution is effected by addition of benzene. The resulting solution is chromatographed on an alumina column (ratio 30 parts by weight of alumina to 1 part by weight of crude reaction product) wet-packed with petroleum ether. The
 80 column is eluted with 10:90 mixture of ether and petroleum ether until mineral oil is eluted. The proportion of ether in the eluting solvent is then raised by 10% increments until a 60:40 mixture of ether and petroleum ether is reached; evaporation of the 60:40 eluate gives 6 α ,7 α - methylene - 20 - spirox - 4 - en - 3 - one which is obtained as an oil. Increasing concentrations of ether up to 100% ether are then used to elute the column. 100
 Evaporation of the 100% ether eluate gives substantially pure 6 β ,7 β - methylene - 20 - spirox - 4 - en - 3 - one as crystalline material; each fraction from the chromatogram is seeded with this material; the fractions which partially or completely crystallize are combined to give approximately 900 mg. of 6 β ,7 β - methylene - 20 - spirox - 4 - en - 3 - one. Upon recrystallization once from ether, twice from hexane, and then from methanol, there is obtained analytically pure 6 β ,7 β - methyl - 20 - spirox - 4 - en - 3 - one; m.p. 153—155° C.

In accordance with the foregoing procedure, but using 20 - spiroxa - 4,6 - diene - 3,21 - dione, 9 α - fluoro - 20 - spiroxa - 4,6 - dien - 11 β - ol - 3 - one, 9 α - fluoro - 20 - spiroxa - 4,6 - dien - 11 β - ol - 3,21 - dione, 20 - spiroxa - 4,6 - dien - 11 β - ol - 3 - one, 20 - spiroxa - 4,6 - dien - 11 β - ol - 3,21 - dione, 19 - nor - 20 - spiroxa - 4,6 - dien - 3 - one or 19 - nor - 20 - spiroxa - 4,6 - diene - 3,21 - dione as steroid starting material together with an approximately equimolecular proportion of dimethyl-oxo-sulfonium methylide, there are obtained, respectively, the following pairs of compounds, viz.
 115 6 β ,7 β - methylene - 20 - spirox - 4 - ene - 3,21 - dione and 6 α ,7 α - methylene - 20 - spirox - 4 - ene - 3,21 - dione, 6 β ,7 β -

5 methylene - 9 α - fluoro - 20 - spirox - 4 - en - 11 β - ol - 3 - one and 6 α ,7 α - methylene - 9 α - fluoro - 20 - spirox - 4 - en - 11 β - ol - 3 - one, 6 β ,7 β - methylene - 9 α - fluoro - 20 - spirox - 4 - en - 11 β - ol - 3,21 - dione and 6 α ,7 α - methylene - 9 α - fluoro - 20 - spirox - 4 - en - 11 β - ol - 3,21 - dione, 6 β ,7 β - methylene - 20 - spirox - 4 - en - 11 β - ol - 3 - one and 6 α ,7 α - methylene - 20 - spirox - 4 - en - 11 β - ol - 3 - one, 6 β ,7 β - methylene - 20 - spirox - 4 - en - 11 β - ol - 3,21 - dione and 6 α ,7 α - methylene - 20 - spirox - 4 - en - 11 β - ol - 3,21 - dione, 6 α ,7 α - methylene - 19 - nor - 20 - spirox - 4 - en - 3 - one (from the middle fractions) and 6 β ,7 β - methylene - 19 - nor - 20 - spirox - 4 - en - 3 - one (from the mother liquors) or 6 β ,7 β - methylene - 19 - nor - 20 - spirox - 4 - ene - 3,21 - dione and 6 α ,7 α - methylene - 19 - nor - 20 - spirox - 4 - ene - 3,21 - dione.

Preparation 2

25 A mixture of 309 mg. (0.00131 mole) of 2,3 - dichloro - 5,6 - dicyanobenzoquinone, 14.4 ml. of dry dioxane and 309 mg. (0.0010 mole) of 6 α ,7 α - methylene - 20 - spirox - 4 - en - 3 - one is heated at reflux temperature under a nitrogen atmosphere for a period of about 3 hours. The reaction mixture is cooled and diluted with about 15 ml. of ethyl acetate, and the ethyl-acetate layer is separated and washed alternately with 1.0N aqueous sodium hydroxide solution and with water until the sodium hydroxide wash solution remains clear. The washed ethyl-acetate solution is dried over anhydrous sodium sulfate, and evaporated to give approximately 335 mg. of a red oil, which is chromatographed using a 30:1 silica gel column wet-packed with petroleum ether. The column is eluted with mixtures of ether and petroleum ether, first 10:90; then 20:80; and finally 30:70. Evaporation of the 30:70 eluate gives crystalline material which, upon recrystallization first from mixtures of ether and petroleum ether, then from ether, and then from ethyl acetate containing a small amount of petroleum ether, gives approximately 71 mg. of substantially pure 6 α ,7 α - methylene - 20 - spiroxa - 1,4 - dien - 3 - one.

50 In accordance with the foregoing procedure, but using 6 β ,7 β - methylene - 20 - spirox - 4 - en - 3 - one, 6 α ,7 α - methylene - 20 - spirox - 4 - ene - 3,21 - dione, 6 β ,7 β - methylene - 20 - spirox - 4 - ene - 3,21 - dione, 6 β ,7 β - methylene - 9 α - fluoro - 20 - spirox - 4 - en - 11 β - ol - 3 - one, 6 α ,7 α - methylene - 9 α - fluoro - 20 - spirox - 4 - en - 11 β - ol - 3 - one, 6 α ,7 α - methylene - 9 α - fluoro - 20 - spirox - 4 - en - 11 β - ol - 3,21 - dione, 6 β ,7 β - methylene - 9 α - fluoro - 20 - spirox - 4 - en - 11 β - ol - 3,21 - dione, 6 β ,7 β - methylene - 20 - spirox - 4 - en - 11 β - ol - 3 - one, 6 α ,7 α -

65 methylene - 20 - spirox - 4 - en - 11 β - ol - 3 - one, 6 α ,7 α - methylene - 20 - spirox - 4 - en - 11 β - ol - 3,21 - dione or 6 β ,7 β - methylene - 20 - spirox - 4 - en - 11 β - ol - 3,21 - dione, as steroid starting material, there is obtained, respectively, 6 β ,7 β - methylene - 20 - spiroxa - 1,4 - dien - 3 - one, 6 α ,7 α - methylene - 20 - spiroxa - 1,4 - diene - 3,21 - dione, 6 β ,7 β - methylene - 20 - spiroxa - 1,4 - diene - 3,21 - dione, 6 β ,7 β - methylene - 9 α - fluoro - 20 - spiroxa - 1,4 - dien - 11 β - ol - 3 - one, 6 α ,7 α - methylene - 9 α - fluoro - 20 - spiroxa - 1,4 - diene - 11 β - ol - 3,21 - dione, 6 β ,7 β - methylene - 9 α - fluoro - 20 - spiroxa - 1,4 - dien - 11 β - ol - 3,21 - dione, 6 β ,7 β - methylene - 20 - spiroxa - 1,4 - dien - 11 β - ol - 3 - one, 6 α ,7 α - methylene - 20 - spiroxa - 1,4 - dien - 11 β - ol - 3 - one, 6 α ,7 α - methylene - 20 - spiroxa - 1,4 - dien - 11 β - ol - 3,21 - dione or 6 β ,7 β - methylene - 20 - spiroxa - 1,4 - dien - 11 β - ol - 3,21 - dione.

Preparation 3

A solution of 400 mg. of 6 α ,7 α - methylene - 20 - spirox - 4 - en - 11 β - ol - 3 - one in 4 ml. of pyridine is added to the complex formed by the addition of 400 mg. of chromium trioxide to 4 ml. of pyridine. The mixture is swirled until thoroughly mixed and then allowed to stand at room temperature overnight. The reaction mixture is poured into water, and the aqueous mixture is extracted with ether and then twice with ethyl acetate. The combined ethereal and ethyl-acetate extracts are washed with dilute aqueous sulfuric acid at about 0°C., and then with water until neutral. The organic solvent layer is then dried, the solvent is evaporated therefrom *in vacuo*, and the residual material is purified by crystallization from petroleum ether to give 6 α ,7 α - methylene - 20 - spirox - 4 - ene - 3,11 - dione.

In accordance with the foregoing procedure, but using 6 β ,7 β - methylene - 20 - spirox - 4 - en - 11 β - ol - 3 - one, 6 α ,7 α - methylene - 20 - spirox - 4 - en - 11 β - ol - 3,21 - dione, 6 β ,7 β - methylene - 20 - spirox - 4 - en - 11 β - ol - 3,21 - dione 6 α ,7 α - methylene - 9 α - fluoro - 20 - spirox - 4 - en - 11 β - ol - 3 - one, 6 β ,7 β - methylene - 9 α - fluoro - 20 - spirox - 4 - en - 11 β - ol - 3 - one, 6 α ,7 α - methylene - 9 α - fluoro - 20 - spirox - 4 - en - 11 β - ol - 3,21 - dione, 6 β ,7 β - methylene - 9 α - fluoro - 20 - spirox - 4 - en - 11 β - ol - 3,21 - dione, 6 α ,7 α - methylene - 20 - spiroxa - 1,4 - dien - 11 β - ol - 3 - one, 6 β ,7 β - methylene - 20 - spiroxa - 1,4 - dien - 11 β - ol - 3 - one, 6 α ,7 α - methylene - 20 - spiroxa - 1,4 - dien - 11 β - ol - 3,21 - dione, 6 β ,7 β - methylene - 20 - spiroxa - 1,4 - dien - 11 β - ol - 3,21 - dione, 6 α ,7 α - methylene - 9 α - fluoro - 20 - spiroxa - 1,4 - diene - 11 β - ol - 3 - one, 6 β ,7 β - methylene - 9 α - fluoro - 20 -

spiroxa - 1,4 - dien - 11 β - ol - 3 - one, 6 α ,7 α - methylene - 9 α - fluoro - 20 - spiroxa - 1,4 - dien - 11 β - ol - 3,21 - dione or 6 β ,7 β - methylene - 9 α - fluoro - 20 - spiroxa - 1,4 - diene - 11 β - ol - 3,21 - dione as the steroid starting material, there is obtained, respectively, 6 β ,7 β -methylene - 20 - spirox - 4 - ene - 3,11 - dione, 6 α ,7 α - methylene - 20 - spirox - 4 - ene - 3,11,21 - trione, 6 β ,7 β - methylene - 20 - spirox - 4 - ene - 3,11,21 - trione, 6 α ,7 α - methylene - 9 α - fluoro - 20 - spirox - 4 - ene - 3,11 - dione, 6 β ,7 β - methylene 9 α - fluoro - 20 - spirox - 4 - ene 3,11 - dione, 6 α ,7 α - methylene - 9 α - fluoro - 20 - spirox - 4 - ene - 3,11,21 - trione, 6 β ,7 β - methylene - 9 α - fluoro - 20 - spirox - 4 - ene - 3,11,21 - trione, 6 α ,7 α - methylene - 20 - spiroxa - 1,4 - diene - 3,11 - dione, 6 β ,7 β - methylene - 20 - spiroxa - 1,4 - diene - 3,11,21 - trione, 6 α ,7 α - methylene - 20 - spiroxa - 1,4 - diene - 3,11,21 - trione, 6 α ,7 α - methylene - 9 α - fluoro - 20 - spiroxa - 1,4 - diene - 3,11 - dione, 6 β ,7 β - methylene - 9 α - fluoro - 20 - spiroxa - 1,4 - diene - 3,11 - dione, 6 α ,7 α - methylene - 9 α - fluoro - 20 - spiroxa - 1,4 - diene - 3,11,21 - trione or 6 β ,7 β - methylene - 9 α - fluoro - 20 - spiroxa - 1,4 - diene - 3,11,21 - trione.

Preparation 4

7.8 grams of chromium trioxide is added portionwise with stirring to 18.7 ml. of *t*-butanol, while maintaining the temperature at about 25° C. The resulting solution is poured into 50 ml. of carbon tetrachloride, the two layers are separated, and the organic layer is dried, and then evaporated to a volume of about 40 ml. to give a solution of *t*-butyl chromate.

35 ml. of this *t*-butyl chromate in carbon tetrachloride, 8 ml. of acetic acid, and 4 ml. of acetic anhydride are added to a solution of two grams of 6 β ,7 β - methylene - 20 - spirox - 4 - en - 3 - one (prepared as described in Preparation 1 hereinabove) and the resulting mixture is heated under reflux for a period of about five hours.

To the reaction mixture is added a saturated aqueous solution of oxalic acid until the reddish color is diminished, and the mixture is then extracted with carbon tetrachloride. The organic layer is washed well with water and dried, and the solvent is evaporated. The residual material is purified by chromatography, followed by recrystallization from aqueous methanol, to give about 500 mg. of substantially pure 6 β ,7 β - methylene - 20 - spirox - 4 - ene - 3,21 - dione, m.p. 173—176°C.

In accordance with the foregoing procedure, but utilizing, as starting material, about 450 mg. of 6 β ,7 β - methylene - 20 - spiroxa - 1,4 - dien - 3 - one, there is obtained

approximately 150 mg. of 6 β ,7 β - methylene - 20 - spiroxa - 1,4 - diene - 3,21 - dione; m.p. 204—206° C.

The following Examples illustrate the process of the present invention.

EXAMPLE 1

To 177 mg. of 6 β ,7 β - methylene - 20 - spirox - 4 - ene - 3,21 - dione dissolved in 4 ml. of ethanol is added 4.5 ml. of a 0.1 *M* aqueous solution of sodium hydroxide. The mixture is warmed to reflux temperature, and heated under reflux for 4 hours. The ethanol is evaporated from the reaction mixture under vacuum, and the residual aqueous mixture is diluted with additional water. The resulting mixture is extracted with chloroform, and then with ether, and the residual aqueous solution (which contains the sodium salt of the hydrolysed lactone) is freeze-dried to give sodium 3' - (3 - oxo - 17 β - hydroxy - 6 β ,7 β - methylene - androst - 4 - en - 17 α - yl) propionate in substantially quantitative yield; m.p. 241—244°C., with decomposition.

In accordance with the foregoing procedure, but utilizing a 0.1 *M* aqueous solution of potassium hydroxide in place of the aqueous sodium hydroxide solution there is obtained, in substantially quantitative yield, potassium 3' - (3 - oxo - 17 β - hydroxy - 6 β ,7 β - methylene - androst - 4 - en - 17 α - yl) propionate.

Similarly, using as steroid starting material 6 β ,7 β - methylene - 20 - spiroxa - 1,4 - diene - 3,21 - dione, there are obtained sodium 3' - (3 - oxo - 17 β - hydroxy - 6 β ,7 β - methylene - androsta - 1,4 - dien - 17 α - yl) propionate; m.p. 185—193° C., with decomposition; and potassium 3' - (3 - oxo - 17 β - hydroxy - 6 β ,7 β - methylene - androsta - 1,4 - dien - 17 α - yl) propionate.

In similar manner, using as starting material 6 β ,7 β - methylene - 20 - spirox - 4 - ene - 3,11,21 - trione, there are obtained the sodium and potassium salts of 3' - (3,11 - dioxo - 17 β - hydroxy - 6 β ,7 β - methylene - androst - 4 - en - 17 α - yl) propionic acid; and using as starting material 6 β ,7 β - methylene - 20 - spirox - 4 - ene - 11 β - ol - 3,21 - dione, there are obtained the sodium and potassium salts of 3' - (3 - oxo - 11 β ,17 β - dihydroxy - 6 β ,7 β - methylene - androst - 4 - en - 17 α - yl) propionic acid.

EXAMPLE 2

To 177 mg. of 6 β ,7 β - methylene - 20 - spiroxa - 1,4 - diene - 3,11,21 - trione dissolved in 4 ml. of ethanol is added 4.5 ml. of a 0.1 *M* aqueous solution of sodium hydroxide. The alkaline mixture is warmed to reflux temperature, and heated under reflux for a period of about 4 hours. The ethanol is evaporated from the reaction mixture under vacuum, and the resulting mixture is diluted with additional water. The resulting mixture

is extracted with chloroform, and then with ether, and the residual aqueous solution (which contains the sodium salt of the hydrolysed lactone) is freeze-dried to give sodium 3' - (3,11 - dioxo - 17 β - hydroxy - 6 β ,7 β - methylene - androsta - 1,4 - dien - 17 α - yl) propionate in substantially quantitative yield.

In accordance with the foregoing procedure, but utilizing a 0.1M aqueous solution of potassium hydroxide in place of the aqueous sodium hydroxide solution there is obtained, in substantially quantitative yield, potassium 3' - (3,11 - dioxo - 17 β - hydroxy - 6 β ,7 β - methylene - androsta - 1,4 - dien - 17 α - yl) propionate.

Similarly, using as steroid starting material 6 β ,7 β - methylene - 20 - spiroxa - 1,4 - dien - 11 β - ol - 3,21 - dione, there are obtained sodium 3' - (3 - oxo - 11 β ,17 β - dihydroxy - 6 β ,7 β - methylene - androsta - 1,4 - dien - 17 α - yl) propionate and potassium 3' - (3 - oxo - 11 β ,17 β - dihydroxy - 6 β ,7 β - methylene - androsta - 1,4 - dien - 17 α - yl) propionate.

In similar manner, using as starting material 6 β ,7 β - methylene - 9 α - fluoro - 20 - spiroxa - 1,4 - diene - 3,11,21 - trione, there are obtained the sodium and potassium salts of 3' - (3,11 - dioxo - 9 α - fluoro - 17 β - hydroxy - 6 β ,7 β - methylene - androsta - 1,4 - dien - 17 α - yl) propionic acid; and using as starting material 6 β ,7 β - methylene - 9 α - fluoro - 20 - spiroxa - 1,4 - dien - 11 β - ol - 3,21 - dione, there are obtained the sodium and potassium salts of 3' - (3 - oxo - 9 α - fluoro - 11 β , 17 β - dihydroxy - 6 β ,7 β - methylene - androsta - 1,4 - dien - 17 α - yl) propionic acid.

EXAMPLE 3

In accordance with the procedures of Examples 1 and 2, but using the following steroid starting materials:

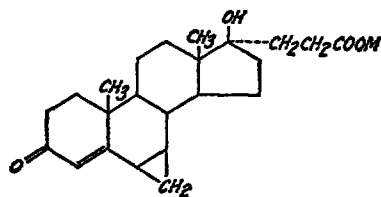
- 1) 6 α ,7 α - methylene - 20 - spirox - 4 - ene - 3,21 - dione;
- 2) 6 α ,7 α - methylene - 20 - spiroxa - 1,4 - diene - 3,21 - dione;
- 3) 6 α ,7 α - methylene - 20 - spirox - 4 - ene - 3,11,21 - trione;
- 4) 6 α ,7 α - methylene - 20 - spirox - 4 - en - 11 β - ol - 3,21 - dione;
- 5) 6 α ,7 α - methylene - 20 - spiroxa - 1,4 - diene - 3,11,21 - trione;
- 6) 6 α ,7 α - methylene - 20 - spiroxa - 1,4 - dien - 11 β - ol - 3,21 - dione;
- 7) 6 α ,7 α - methylene - 9 α - fluoro - 20 - spirox - 4 - ene - 3,21 - dione;
- 8) 6 α ,7 α - methylene - 9 α - fluoro - 20 - spiroxa - 1,4 - diene - 3,21 - dione;
- 9) 6 α ,7 α - methylene - 9 α - fluoro - 20 - spirox - 4 - ene - 3,11,21 - trione;

- 10) 6 α ,7 α - methylene - 9 α - fluoro - 20 - spirox - 4 - en - 11 β - ol - 3,21 - dione;
- 11) 6 α ,7 α - methylene - 9 α - fluoro - 20 - spiroxa - 1,4 - diene - 3,11,21 - trione;
- 12) 6 α ,7 α - methylene - 9 α - fluoro - 20 - spiroxa - 1,4 - dien - 11 β - ol - 3,21 - dione;

there are obtained the sodium and potassium salts of the following propionic acid derivatives, respectively, which have been numbered to correspond with that of the steroid starting material:

- 1) 3' - (3 - oxo - 17 β - hydroxy - 6 α ,7 α - methylene - androst - 4 - en - 17 α - yl) propionic acid;
- 2) 3' - (3 - oxo - 17 β - hydroxy - 6 α ,7 α - methylene - androsta - 1,4 - dien - 17 α - yl) propionic acid;
- 3) 3' - (3,11 - dioxo - 17 β - hydroxy - 6 β ,7 α - methylene - androst - 4 - en - 17 α - yl) propionic acid;
- 4) 3' - (3 - oxo - 11 β ,17 β - dihydroxy - 6 α ,7 α - methylene androst - 4 - en - 17 α - yl) propionic acid;
- 5) 3' - (3,11 - dioxo - 17 β - hydroxy - 6 α ,7 α - methylene - androsta - 1,4 - dien - 17 α - yl) propionic acid;
- 6) 3' - (3 - oxo - 11 β ,17 β - dihydroxy - 6 α ,7 α - methylene - androsta - 1,4 - dien - 17 α - yl) propionic acid;
- 7) 3' - (3 - oxo - 17 β - hydroxy - 6 α ,7 α - methylene - 9 α - fluoro - androst - 4 - en - 17 α - yl) propionic acid;
- 8) 3' - (3 - oxo - 17 β - hydroxy - 6 α ,7 α - methylene - 9 α - fluoro - androsta - 1,4 - dien - 17 α - yl) propionic acid;
- 9) 3' - (3,11 - dioxo - 17 β - hydroxy - 6 α ,7 α - methylene - 9 α - fluoro - androst - 4 - en - 17 α - yl) propionic acid;
- 10) 3' - (3 - oxo - 11 β ,17 β - dihydroxy - 6 α ,7 α - methylene - 9 α - fluoro - androst - 4 - en - 17 α - yl) propionic acid;
- 11) 3' - (3,11 - dioxo - 17 β - hydroxy - 6 α ,7 α - methylene - 9 α - fluoro - androsta - 1,4 - dien - 17 α - yl) propionic acid;
- 12) 3' - (3 - oxo - 11 β ,17 β - dihydroxy - 6 α ,7 α - methylene - 9 α - fluoro - androsta - 1,4 - dien - 17 α - yl) propionic acid.

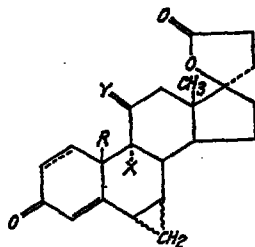
In the specification of our copending application number 33403/72 (1361362) there is described and claimed a process that comprises hydrolysing 6 β ,7 β - methylene - 20 - spirox - 4 - ene - 3,21 - dione or 6 β ,7 β - methylene - 20 - spiroxa - 1,4 - diene - 3,21 - dione, using an alkali metal hydroxide and a C₁₋₅ alkanol to produce a compound having the formula



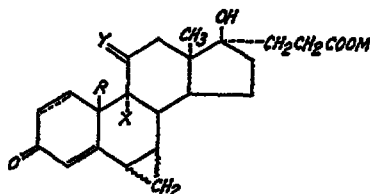
or its 1,2-unsaturated analogue, and we make no claim to that process or to those of its products not the subject of individual claims herein. Subject to the foregoing disclaimer,

WHAT WE CLAIM IS:—

1. The process which comprises reacting a 6,7 - methylene - 20 - spirox - 4 - ene - 3,21 - dione steroid lactone having the formula:



wherein R is hydrogen or methyl; X is hydrogen or fluorine; Y is two hydrogen atoms, a hydrogen atom and a β -hydroxy group, or a keto group; the wavy line to the 6,7 - methylene group indicates that it is in the α or β configuration and the dotted line between carbons 1 and 2 indicates that a double bond may be present in this position; with an alkaline hydrolysing agent thereby hydrolyzing the lactone ring of said steroid lactone and forming a 3' - (3 - oxo - 17 β - hydroxy - 6,7 - methylene - androst - 4 - en - 17 α - yl) propionate compound having the formula



wherein R, X, Y and the dotted and wavy lines have the meanings given above; and M is the cation component of the alkaline hydrolysing agent; and optionally acidifying this alkaline hydrolysis product to form the corresponding free propionic acid compound.

2. A process as claimed in claim 1 in which the steroid lactone starting material is a 6,7 - methylene - 20 - spirox - 4 - ene - 3,21 - dione and the acidification step is carried out to produce a 3' - (3 - oxo - 17 β -

hydroxy - 6,7 - methylene - androst - 4 - en - 17 α - yl) propionic acid.

3. A process as claimed in claim 2, in which the hydrolysing agent is an alkali metal hydroxide, the alkaline hydrolysis product is the corresponding alkali metal 3' - (3 - oxo - 17 β - hydroxy - 6,7 - methylene - androst - 4 - en - 17 α - yl) propionate, and the latter is acidified to produce a 3' - (3 - oxo - 17 β - hydroxy - 6,7 - methylene - androst - 4 - en - 17 α - yl) propionic acid.

4. A process as claimed in claim 3 in which the hydrolysing agent is sodium hydroxide in aqueous ethanol.

5. A process as claimed in claim 1, in which the steroid lactone starting material is a 6,7 - methylene - 20 - spiroxa - 1,4 - diene - 3,21 - dione and the acidification step is carried out to produce a 3' - (3 - oxo - 17 β - hydroxy - 6,7 - methylene - androsta - 1,4 - dien - 17 α - yl) propionic acid.

6. A process as claimed in claim 5, in which the hydrolysing agent is an alkali metal hydroxide, the alkaline hydrolysis product is the corresponding alkali metal 3' - (3 - oxo - 17 β - hydroxy - 6,7 - methylene - androsta - 1,4 - dien - 17 α - yl) propionate, and the latter is acidified to produce a 3' - (3 - oxo - 17 β - hydroxy - 6,7 - methylene - androst - 1,4 - dien - 17 α - yl) propionic acid.

7. A process as claimed in claim 6, in which the hydrolysing agent is sodium hydroxide in aqueous ethanol.

8. A process as claimed in claim 6, in which the hydrolysing agent is potassium hydroxide in aqueous ethanol.

9. A process as claimed in claim 1, in which the steroid lactone starting material is a 6,7 - methylene - 20 - spiroxa - 1,4 - diene - 3,11,21 - trione and the alkaline hydrolysis product is a salt of a 3' - (3,11 - dioxo - 17 β - hydroxy - 6,7 - methylene - androsta - 1,4 - dien - 17 α - yl) propionic acid.

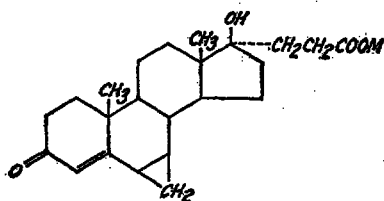
10. A process as claimed in claim 9, including the further step of acidifying the product to produce the corresponding free acid.

11. A process as claimed in claim 9 or 10, in which the hydrolysing agent is sodium hydroxide in aqueous ethanol.

12. A process as claimed in any preceding claim in which the 6,7-methylene group is in the 6 β ,7 β -configuration.

13. A process as claimed in claim 1, substantially as hereinbefore described in any one of the foregoing examples.

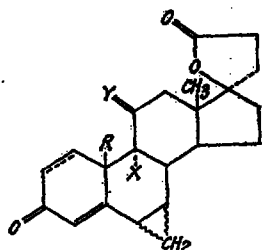
14. A process as claimed in claim 1, including the step of preparing the starting material by reaction of dimethyl - oxo - sulfonium methylide with a 3 - oxo - 20 - spiroxa - 4,6 - diene or 3,21 - dioxo - 20 - spiroxa - 4,6 - diene and, when the former diene is used, introducing a 21 - oxo group by reaction with *t*-butyl chromate, together with one or both of the optional steps of treating the



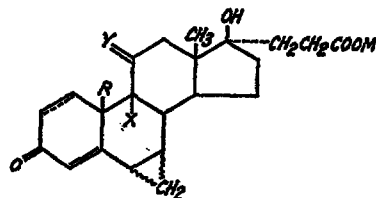
or its 1,2-unsaturated analogue, and we make no claim to that process or to those of its products not the subject of individual claims herein. Subject to the foregoing disclaimer,

WHAT WE CLAIM IS:—

1. The process which comprises reacting a 6,7 - methylene - 20 - spirox - 4 - ene - 3,21 - dione steroid lactone having the formula:



wherein R is hydrogen or methyl; X is hydrogen or fluorine; Y is two hydrogen atoms, a hydrogen atom and a β -hydroxy group, or a keto group; the wavy line to the 6,7 - methylene group indicates that it is in the α or β configuration and the dotted line between carbons 1 and 2 indicates that a double bond may be present in this position; with an alkaline hydrolysing agent thereby hydrolyzing the lactone ring of said steroid lactone and forming a 3' - (3 - oxo - 17 β - hydroxy - 6,7 - methylene - androst - 4 - en - 17 α - yl) propionate compound having the formula



wherein R, X, Y and the dotted and wavy lines have the meanings given above; and M is the cation component of the alkaline hydrolysing agent; and optionally acidifying this alkaline hydrolysis product to form the corresponding free propionic acid compound.

2. A process as claimed in claim 1 in which the steroid lactone starting material is a 6,7 - methylene - 20 - spirox - 4 - ene - 3,21 - dione and the acidification step is carried out to produce a 3' - (3 - oxo - 17 β -

hydroxy - 6,7 - methylene - androst - 4 - en - 17 α - yl) propionic acid.

3. A process as claimed in claim 2, in which the hydrolysing agent is an alkali metal hydroxide, the alkaline hydrolysis product is the corresponding alkali metal 3' - (3 - oxo - 17 β - hydroxy - 6,7 - methylene - androst - 4 - en - 17 α - yl) propionate, and the latter is acidified to produce a 3' - (3 - oxo - 17 β - hydroxy - 6,7 - methylene - androst - 4 - en - 17 α - yl) propionic acid.

4. A process as claimed in claim 3 in which the hydrolysing agent is sodium hydroxide in aqueous ethanol.

5. A process as claimed in claim 1, in which the steroid lactone starting material is a 6,7 - methylene - 20 - spirox - 1,4 - diene - 3,21 - dione and the acidification step is carried out to produce a 3' - (3 - oxo - 17 β - hydroxy - 6,7 - methylene - androsta - 1,4 - dien - 17 α - yl) propionic acid.

6. A process as claimed in claim 5, in which the hydrolysing agent is an alkali metal hydroxide, the alkaline hydrolysis product is the corresponding alkali metal 3' - (3 - oxo - 17 β - hydroxy - 6,7 - methylene - androsta - 1,4 - dien - 17 α - yl) propionate, and the latter is acidified to produce a 3' - (3 - oxo - 17 β - hydroxy - 6,7 - methylene - androst - 1,4 - dien - 17 α - yl) propionic acid.

7. A process as claimed in claim 6, in which the hydrolysing agent is sodium hydroxide in aqueous ethanol.

8. A process as claimed in claim 6, in which the hydrolysing agent is potassium hydroxide in aqueous ethanol.

9. A process as claimed in claim 1, in which the steroid lactone starting material is a 6,7 - methylene - 20 - spirox - 1,4 - diene - 3,11,21 - trione and the alkaline hydrolysis product is a salt of a 3' - (3,11 - dioxo - 17 β - hydroxy - 6,7 - methylene - androsta - 1,4 - dien - 17 α - yl) propionic acid.

10. A process as claimed in claim 9, including the further step of acidifying the product to produce the corresponding free acid.

11. A process as claimed in claim 9 or 10, in which the hydrolysing agent is sodium hydroxide in aqueous ethanol.

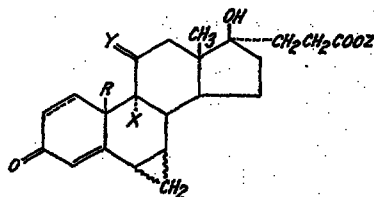
12. A process as claimed in any preceding claim in which the 6,7-methylene group is in the 6 β ,7 β -configuration.

13. A process as claimed in claim 1, substantially as hereinbefore described in any one of the foregoing examples.

14. A process as claimed in claim 1, including the step of preparing the starting material by reaction of dimethyl - oxo - sulfonium methyllide with a 3 - oxo - 20 - spirox - 4,6 - diene or 3,21 - dioxo - 20 - spirox - 4,6 - diene and, when the former diene is used, introducing a 21 - oxo group by reaction with *t*-butyl chromate, together with one or both of the optional steps of treating the

- resulting 6,7 - methylene - 20 - spirox - 4 - ene with 2,3 - dichloro - 5,6 - dicyanobenzoquinone to introduce a Δ^1 unsaturation and/or with CrO_3 /pyridine complex to convert any 11 β -hydroxy group to an 11-oxo group.

15. A 3' - (3 - oxo - 17 β - hydroxy - 6,7 - methylene - androst - 4 - en - 17 α - yl) propionic acid compound having the formula



- 10 in which R, X, Y, the wavy line to the 6,7-methylene group and the dotted line between carbons 1 and 2 have the same significance as in claim 1 and Z is hydrogen or a pharmaceutically acceptable salt-forming cation, provided that when R is methyl, Y is two hydrogen atoms, X is hydrogen and Z is an alkali metal, the 6,7-methylene group is in the α configuration.
- 15 16. 3' - (3 - oxo - 17 β - hydroxy - 6,7 - methylene - androst - 4 - en - 17 α - yl) propionic acid and pharmaceutically acceptable salts thereof, the 6,7-methylene group being in α or β configuration.
- 20 17. Sodium 3' - (3 - oxo - 17 β - hydroxy - 6 β ,7 β - methylene - androst - 4 - en - 17 α - yl) propionate.
- 25 18. 3' - (3 - oxo - 17 β - hydroxy - 6,7 - methylene - androsta - 1,4 - dien - 17 α - yl) propionic acid and pharmaceutically acceptable salts thereof, the 6,7-methylene group being in α or β configuration.
- 30 19. Sodium 3' - (3 - oxo - 17 β - hydroxy - 6 β ,7 β - methylene - androsta - 1,4 - dien - 17 α - yl) propionate.
- 35 20. Potassium 3' - (3 - oxo - 17 β - hydroxy - 6 β ,7 β - methylene - androsta - 1,4 - dien - 17 α - yl) propionate.
- 40 21. 3' - (3,11 - Dioxo - 17 β - hydroxy - 6,7 - methylene - androsta - 1,4 - dien - 17 α - yl) propionic acid and pharmaceutically acceptable salts thereof, the 6,7 - methylene group being in α or β configuration.
- 45 22. Sodium 3' - (3,11 - dioxo - 17 β - hydroxy - 6 β ,7 β - methylene - androst 4 - en - 17 α - yl) propionate.
- 50 23. A compound as claimed in Claim 15 when prepared by a process as claimed in any one of Claims 1—14 or an obvious chemical equivalent of such a process.
- 55 24. An aldosterone-inhibiting composition for pharmaceutical use, containing as active ingredient a compound as claimed in any one of Claims 15—23, together with a pharmaceutical diluent, carrier, coating or excipient.
25. A composition as claimed in Claim 24 in the form of a pill, tablet, capsule or injectable liquid.

For the Applicants,
D. YOUNG & CO.,
Chartered Patent Agents,
9 & 10 Staple Inn,
London WC1V 7RD.