

PATENT SPECIFICATION

(11) 1361362

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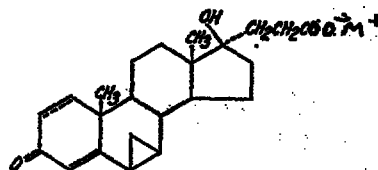
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 C2U 4A2 4C3 4C4 4C9 8A1
 (72) Inventor GLEN EDWARD ARTH



(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:—

This invention provides compounds of the formula

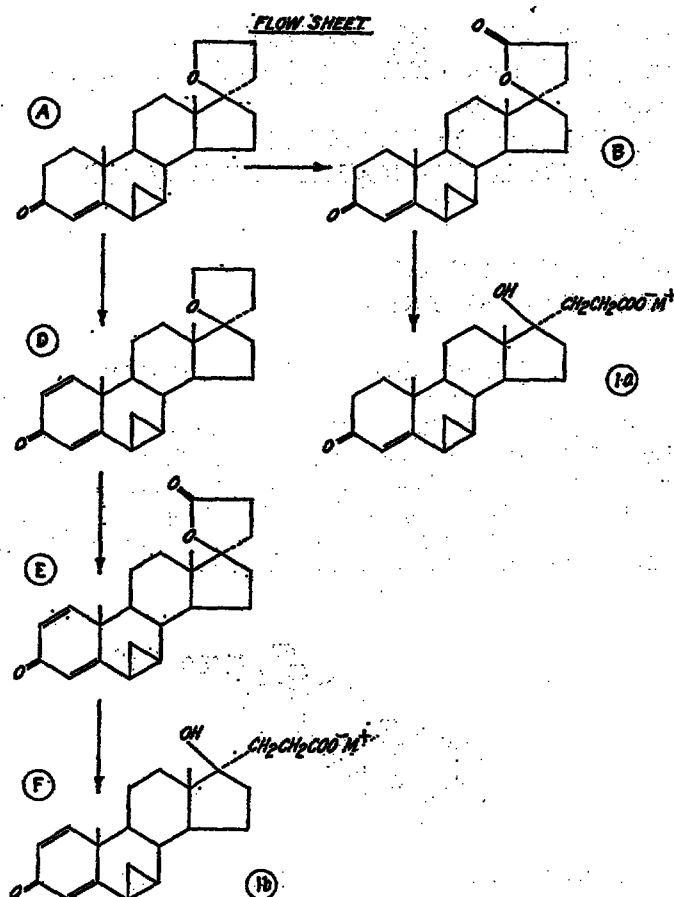


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where M is an alkali metal, preferably sodium or potassium, and the dotted line at position 1 of the A ring indicates the optional presence of a double bond. These compounds can be conveniently referred to as the alkali metal salts of 3 - [3 - oxo - 17 β - hydroxy - 6,7 β - methylene - androst - 4 - en or androsta - 1,4 - dien) - 17 α - yl]propionic acid.

These new compounds are potent aldosterone inhibitors. They 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 or the kidney in which aldosterone secretion is increased.

The compounds of this invention can be conveniently prepared. In the following discussion, reference is made to the accompanying Flow Sheet.



The starting material for both compounds is 6,7 β - methylene - 20 - spirox - 4 - ene - 3 - one, Compound A. This is oxidized to the 6,7 β - methylene - 20 - spirox - 4 - ene - 3,21 - dione, Compound B, using *t*-butyl chromate. This process is described in *Tetrahedron Letters* No. 58, pp. 5057—5059, 1970.

Following oxidation, the lactone ring is opened by hydrolysis in a C₁₋₅ alkanol containing an alkali metal hydroxide. The reaction is conveniently carried out at reflux temperature for 2—10 hours. The alkanol is preferably ethanol or methanol. When sodium hydroxide or potassium hydroxide is used as the source of the alkali metal, the desired sodium or potassium salt is isolated directly from the reaction medium to give the 4-ene final product, Compound 1a.

The other route on the Flow Sheet leads to the 1,4-diene, Compound 1b. This process is essentially identical with the addition of one step, the introduction of the double bond in the 1-position. This reaction takes place using 2,3 - dichloro - 5,6 - dicyanobenzoquinone, in an inert solvent at reflux temperatures to yield the 6,7 β - methylene - 20 - spiroxa - 1,4 - dien - 3 - one, Compound D. This latter compound is then oxidized at position 21 using *t*-butyl chromate, and the ring opened as described above. The compound 1b, the 1,4-diene, is recovered as an alkali metal salt, usually the potassium or the sodium salt, depending on the identity of the alkali metal hydroxide used in the ring-opening step.

The salt form of the steroids prepared as described is particularly useful in therapy of the salt-reducing disorders, since it is soluble and can be easily administered in a sterile intravenous or subcutaneous injection vehicle. The compounds can also be administered orally in conjunction with a pharmaceutically acceptable carrier, in which the compounds may be dissolved.

In addition to the ease of administration, assays have shown that certain of the salts described herein are rapidly absorbed and show appreciable aldosterone antagonism in a standard rat assay within one hour after oral administration. These compounds also maintain significant activity as long as twelve hours after administration.

The dosage level for human use of the compounds described herein can range from 100 to 600 mg. per day. The administration is preferably intravenous, but can also be administered intramuscularly if desired.

5 The starting material for this synthesis is, as stated, 6,7 β - methylene - 20 - spirox - 4 - en - 3 - one. This starting material is described in the literature, e.g. 5 in Belgian Patent 730,163. Briefly, this material is prepared by the reaction of dimethyl - oxo - sulfonium methylide with 20 - spiroxa - 4,6 - dien - 3 - one. This reaction is conveniently conducted by mixing a mineral oil dispersion of sodium hydride and trimethyl sulfoxonium iodide with dimethyl sulfoxide, forming 10 the dimethyl - oxo - sulfonium methylide *in situ*. The 20 - spiroxa - 4,6 - dien - 3 - one is then added to the mixture in approximately an equimolar amount, and the reaction allowed to proceed at room temperature for 5—15 hours. 10

This invention is further illustrated by the following example.

EXAMPLE

15 Step A 15
6,7 β - Methylene - 20 - Spirox - 4 - En - 3 - One

To a thoroughly dry mixture of 1.8 g of a 56.37% dispersion of sodium hydride in mineral oil and 9.81 g. of trimethyl sulfoxonium iodide, maintained under a nitrogen atmosphere and cooled to a temperature of about 10°C., is slowly added 20 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 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, with stirring at room temperature, a 25 solution of 3.0 g of 20 - spiroxa - 4,6 - dien - 3 - one in 5 ml. of dimethyl sulfoxide. 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 proportions of ether, and the combined extracts are washed with three 25-ml proportions of water. The washed ethereal extract is 30 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 column is eluted with 10:90 mixture of ether:petroleum-ether until mineral oil is eluted. The proportion of ether in the eluting solvent is then raised by 10% 35 increments until a 60:40 mixture of ether: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 40 used to elute the column. 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 45 from ether, twice from hexane, and then from methanol, there is obtained analytically pure 6,7 β - methylene - 20 - spirox - 4 - en - 3 - one; m.p. 153—155°C. 45

Step B

6,7 β Methylene - 20 - Spiroxa - 1,4 - Dien - 3 - One

One g. of 6,7 β - methylene - 20 - spirox - 4 - en - 3 - one is added to 1 g. of 50 2,3 - dichloro - 5,6 - dicyanobenzoquinone in 10 ml. of benzene. The mixture is refluxed for 3 hrs. under nitrogen. The precipitate is filtered off and discarded. The filtrate is passed through a column chromatograph packed with 100:1 basic alumina. The product is eluted with 10—20% ether in benzene. 450 mg. of 6,7 β - methylene - 20 - spiroxa - 1,4 - dien 3 - one is obtained, m.p. 122—124°C. 50

55 Step C 55
6,7 β - Methylene - 20 - Spirox - 4 - Ene - 3,21 - Dione

6,7 β - Methylene - 20 - Spiroxa - 1,4 - Diene - 3,21 - Dione

7.8 g of chromium trioxide is added portion-wise (25°C) to 18.7 ml of *t*-BuOH with stirring. The solution is poured into 50 ml. of carbon tetrachloride. The 60 two layers are separated, the organic layer dried, and concentrated to about 40 ml. to yield a solution of *t*-butyl chromate. 60

Two g. of 6,7 β - methylene - 20 - spirox - 4 - en - 3 - one is dissolved in

30 ml. of carbon tetrachloride. To this solution is added 35 ml. of the *t*-butyl chromate solution, 8 ml. of acetic acid, and 4 ml. of acetic anhydride. The mixture is refluxed for 5 hours.

The reaction product is then worked up by adding a saturated solution of oxalic acid until the reddish color diminishes. This is then extracted with carbon tetrachloride. The organic layer is washed well with water and dried, and the solvent is evaporated. After purification, 600 mg. of pure product is obtained. An analytical sample is recrystallized from methanol/water. The product is identified as 6,7 β - methylene - 20 - spirox - 4 - ene - 3,21 - dione, m.p. 173—176°C.

In the same manner, 150 mg. of 6,7 β - methylene - 20 - spiroxa - 1,4 - diene - 3,21 - dione is prepared, m.p. 204—206°C., from 450 mg. of the starting material, 6,7 β - methylene - 20 - spiroxa - 1,4 - dien - 3 - one, as prepared in Step B.

Step D

Sodium 3 - (3 - Oxo - 17 β - Hydroxy - 6,7 β - Methylene - Androst - 4 - En - 17 α - Yl) Propionic Acid

Potassium 3 - (3 - Oxo - 17 β - Hydroxy - 6,7 β - Methylene - Androst - 4 - En - 17 α - Yl) Propionic Acid

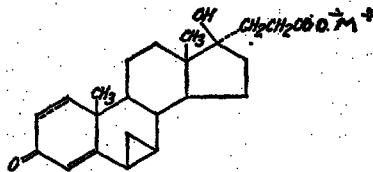
To 177 mg. of 6,7 - methylene - 20 - spirox - 4 - ene - 3,21 - dione dissolved in 4 ml. of ethanol is added 4.5ml. of a 0.1 M solution of sodium hydroxide. The mixture is heated to reflux, and kept at reflux for 4 hours. The ethanol is evaporated under vacuum. The residue is diluted with more water. This is extracted with chloroform and then with ether. The aqueous solution containing the sodium salt is freeze-dried. The product, sodium 3 - (3 - oxo - 17 β - hydroxy - 6,7 β - methylene - androst - 4 - en - 17 α - yl) propionic acid is recovered in quantitative yield, m.p. 241—244°C., with decomposition.

The potassium salt is prepared in a similar fashion using potassium hydroxide, a quantitative yield is recovered.

In analogous manner, sodium 3 - (3 - oxo - 17 β - hydroxy - 6,7 β - methylene - androsta - 1,4 - dien - 17 α - yl) propionic acid and potassium 3 - (3 - oxo - 17 β - hydroxy - 6,7 β - methylene - androsta 1,4 - dien - 17 α - yl) propionic acid are prepared in quantitative yields.

WHAT WE CLAIM IS:—

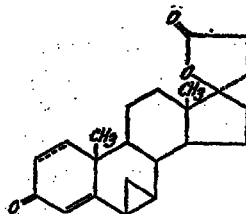
1. A compound of the formula



in which M is an alkali metal and the dotted line at position 1 indicates the optional presence of a double bond.

2. A compound as claimed in claim 1, in which M is sodium or potassium.

3. The process that comprises hydrolysing a compound of the formula



in which the dotted line at position 1 indicates the optional presence of a double bond, with a C₁₋₅ alkanol and an alkali metal hydroxide until a compound as claimed in claim 1 is produced.



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30 ml. of carbon tetrachloride. To this solution is added 35 ml. of the *t*-butyl chromate solution, 8 ml. of acetic acid, and 4 ml. of acetic anhydride. The mixture is refluxed for 5 hours.

5 The reaction product is then worked up by adding a saturated solution of oxalic acid until the reddish color diminishes. This is then extracted with carbon tetrachloride. The organic layer is washed well with water and dried, and the solvent is evaporated. After purification, 600 mg. of pure product is obtained. An analytical sample is recrystallized from methanol/water. The product is identified as 6,7 β - methylene - 20 - spirox - 4 - ene - 3,21 - dione, m.p. 173—176°C.

10 In the same manner, 150 mg. of 6,7 β - methylene - 20 - spiroxa - 1,4 - diene - 3,21 - dione is prepared, m.p. 204—206°C., from 450 mg. of the starting material, 6,7 β - methylene - 20 - spiroxa - 1,4 - dien - 3 - one, as prepared in Step B.

Step D

15 Sodium 3 - (3 - Oxo - 17 β - Hydroxy - 6,7 β - Methylene - Androst - 4 - En - 17 α - Yl) Propionic Acid

Potassium 3 - (3 - Oxo - 17 β - Hydroxy - 6,7 β - Methylene - Androst - 4 - En - 17 α - Yl) Propionic Acid

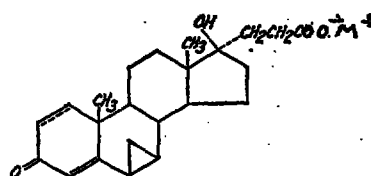
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The potassium salt is prepared in a similar fashion using potassium hydroxide, a quantitative yield is recovered.

30 In analogous manner, sodium 3 - (3 - oxo - 17 β - hydroxy - 6,7 β - methylene - androsta - 1,4 - dien - 17 α - yl) propionic acid and potassium 3 - (3 - oxo - 17 β - hydroxy - 6,7 β - methylene - androsta 1,4 - dien - 17 α - yl) propionic acid are prepared in quantitative yields.

WHAT WE CLAIM IS:—

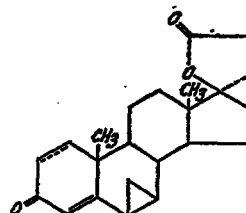
1. A compound of the formula



35 in which M is an alkali metal and the dotted line at position 1 indicates the optional presence of a double bond.

2. A compound as claimed in claim 1, in which M is sodium or potassium.

3. The process that comprises hydrolysing a compound of the formula



40 in which the dotted line at position 1 indicates the optional presence of a double bond, with a C₁₋₅ alkanol and an alkali metal hydroxide until a compound as claimed in claim 1 is produced.

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4. A process as claimed in claim 3, in which the alkali metal hydroxide is sodium hydroxide or potassium hydroxide.
5. A process as claimed in claim 3 or 4, carried out under reflux for from 2 to 10 hours.
6. A process as claimed in Claim 3, 4 or 5 including the step of preparing the starting material by oxidizing 6,7 β - methylene - 20 - spirox - 4 - en - 3 - one or 6,7 β - methylene - 20 - spiroxa - 1,4 - dien - 3 - one with *t*-butyl chromate.
7. A process as claimed in Claim 3, substantially as hereinbefore described in the foregoing Example.
8. A compound as claimed in Claim 1, when prepared by a process as claimed in any one of Claims 3—7.
9. A pharmaceutical composition comprising a solution of a compound as claimed in Claim 1, 2 or 8 in a sterile injectable carrier.
10. A pharmaceutical composition comprising a compound as claimed in Claim 1, 2 or 8 and an orally administrable pharmaceutical carrier.
11. A composition as claimed in Claim 10, in which the said compound is dissolved in the carrier.

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

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