PATENT SPECIFICATION

NO DRAWINGS

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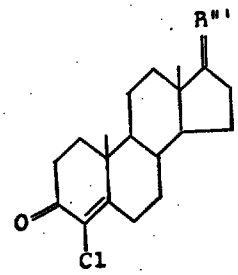
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COMPLETE SPECIFICATION

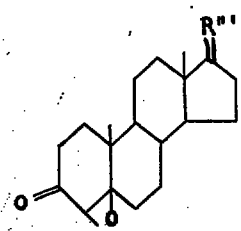
4-Chloro-Testosterone-17β-Acetate

We, SOCIETA FARMACEUTICI ITALIA, a Body Corporate organised and existing under the laws of Italy, of 18 Via Filippo Turati, Milan, Italy, 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:—

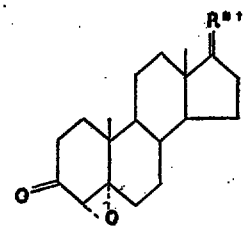
In the Specification of our copending Application 41225/59 (Serial No. 864,613) we have described and claimed 4-substituted steroid compounds having the general formula:



wherein R^{111} represents α-alkyl, β-OH where alkyl is methyl or ethyl, and a process for the production of these 4-substituted steroid compounds and compounds wherein R^{111} represents α-H, β-OH which comprises reacting a 4,5 - epoxy - 3 - keto steroid of the general formula:



or of the general formula:



wherein R^{111} is as above or a mixture of both α- and β-forms with hydrogen chloride in solution in chloroform or methylene chloride.

The invention provides a process for the production of 4 - chloro - testosterone - 17β - acetate which comprises reacting 4α,5 - epoxy-androstan - 17β - ol - 3 - one - acetate or 4β,5 - epoxy - etiocholan - 17β - ol - 3 - one - acetate or a mixture of a pair of these compounds with hydrogen chloride in solution in chloroform or methylene chloride.

Hydrogen chloride may be employed in the form of a gaseous stream. Suitably the reaction period lies between the time required to saturate the solution and twice this time. Best results are obtained at reaction temperatures of from −10° C. to 25° C. The preferred solvent is chloroform containing about 10% of ethanol, the hydrogen chloride may be added to the reaction mixture in the form of a salt with an organic base such as pyridinium chloride followed by boiling the reaction mixture for from 1 to 10 hours. A starting material comprising a mixture of 4α,5- and 4β,5-epoxides may be obtained by treating the corresponding 3-keto-Δ^4-steroid with alkaline hydrogen peroxide. The product of that reaction may then be treated directly according to the process of the invention thereby increasing the overall yield and simplifying the procedure.

The invention includes a process for the

production of 4 - chloro - testosterone - 17β - acetate which comprises acetylating, preferably with acetic anhydride and preferably in the presence of a basic reagent such as pyridine, the corresponding 17β-hydroxy compound.

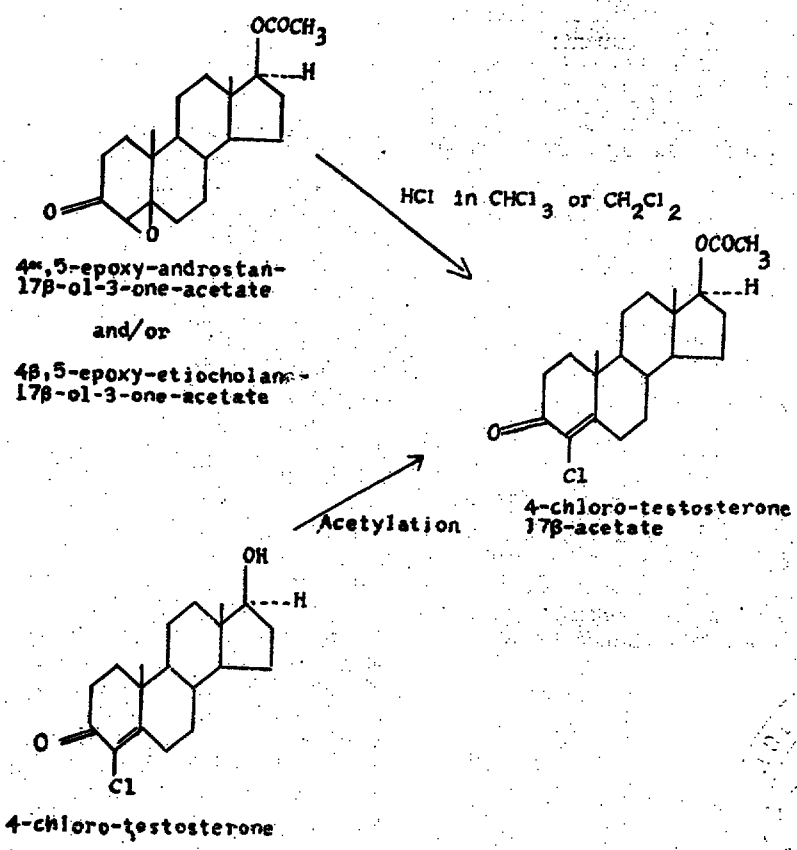
4 - Chloro - testosterone - acetate shows strong anabolic activity on proteins while being devoid of equivalent androgen activity. These activities have hitherto been present to the same degree in the steroids used in therapy. The invention therefore renders it possible to take advantage of anabolic activity without stimulating sexual activity and this property is particularly useful for the treatment of decay, osteoporosis, meagerness, convalescence, premature infants, undergrowth or senility. Besides being useful for these purposes the product shows the other properties of anabolic substances used hitherto and is useful for the treatment of such conditions as mammary cancer and certain ovarian conditions.

It is to be understood that the invention includes within its scope therapeutic compositions which comprise the steroid compound and a therapeutically acceptable carrier therefor. The carrier may take the form of a liquid in which the active material is dissolved or suspended to provide a composition suitable for administration orally or by injection, of an ointment base to provide a composition suitable for topical administration or of a solid or capsule to provide a composition in solid encapsulated form.

The 4α,5- and 4β,5-epoxide reactants and the preparation thereof are described and claimed in the Specification of the copending Application 10029/57 (Serial No. 864,607).

The following diagram illustrates schematically the processes of the invention:

Schematic diagram



The invention is illustrated by the following Examples:

EXAMPLE 1

4-chloro-testosterone-17β-acetate

5 g. 4β,5 - epoxy - etiocholan - 17β - ol - 3 - one - acetate, m.p. 156° C., are dissolved in 125 ml anhydrous chloroform and treated with a stream of gaseous HCl at room temperature.

The solution becomes yellow-green and later dark and turbid—2 hours later the organic solution is washed first with a sodium

bicarbonate solution and thereafter with water; finally it is dried and the drying is completed under vacuum.

The residue is taken up with 400 ml of hot methanol the solution is cooled and filtered. 3.3 g. 4 - chloro - testosterone - 17β - acetate are obtained, m.p. 228—230° C., λ max 255 mμ, $\epsilon = 13{,}300$, $[\alpha]_D = +118° \pm 4°$ (in chloroform).

From the filtrate 0.5 g. of a product having m.p. 215—220° C. are recovered by concentration.

EXAMPLE 2

4-chloro-testosterone-17β-acetate

4 g. 4β,5 - epoxy - etiocholan - 17β - ol - 3 - one - acetate, m.p. 156° C., are refluxed with 50 ml of a 1.2/N solution of pyridinium chloride in chloroform for 5 hours. The organic solution is washed with diluted hydrochloric acid, sodium bicarbonate and water and finally dried.

The crystalline residue, m.p. 220—228° C., consists of an already pure 4 - chloro - testosterone - 17β - acetate. After a recrystallisation the product melts at 228—230° C.

EXAMPLE 3

4-chloro-testosterone-17β-acetate

2 g. 4α,5 - epoxy - androstan - 17β - ol - 3 - one - acetate m.p. 170—172° C., dissolved in 50 ml anhydrous chloroform, are treated with anhydrous HCl for 2 hours at room temperature. The solution becomes pale-yellow without a further darkening. The solution is neutralised by washing and concentrated. The residue is recrystallised from methanol and 1.5 g. 4 - chloro - testosterone - 17β - acetate, m.p. 226—228° C., is obtained.

EXAMPLE 4

4-chloro-testosterone-17β-acetate

1 g. 4α,5 - epoxy - androstan - 17β - ol - 3 one - acetate are boiled with 15 ml of a chloroform 1.2/N solution of pyridinium chloride for 8 hours.

The resulting solution is washed with dilute hydrochloric acid, diluted with alkali and water and finally dried. An almost quantitative yield of 4 - chloro - testosterone - 17β - acetate is obtained.

EXAMPLE 5

4-chloro-testosterone-17β-acetate

1 g. 4 - chloro - tesosterone which may be obtained as described and claimed in our co-pending Application 41225/59 are acetylated with 1 ml. acetic anhydride and 5 ml pyridine at room temperature for 16 hours. The solution is diluted with ice, the precipitate is filtered off and recrystallised from chloroform-ethanol; 1 g. 4 - chloro - testosterone - 17β - acetate, m.p. 228—230° C., is obtained.

Pharmacological activity of 4-chloro-testosterone-17β-acetate

The 4 - chloro - testosterone - 17β - acetate, injected into impuberal rats castrated according to the Hershberger et al. method (Proc. Soc. Exp. Biol. and Med. *83*, 175 (1953)), shows a remarkable anabolic activity and a poor androgen activity.

In fact a daily dose of 500 γ of said compound increases the weight of the "levator ani" muscle from 5 to 42 mg while 500 γ testosterone propionate increases the weight of the muscle to 28.5 mg. In the same condition the 4 - chloro - testosterone - 17β - acetate increases the prostate weight from 6.7 to 48 mg while the testosterone proprionate increases this weight to 90 mg. The seminal bladders increase from 4.1 mg to 36.5 mg for the action of the 4-chloro-testosterone - 17β - acetate and to 96 mg for the action of the testosterone propionate.

Consequently, the ratio between the anabolic and the androgen activity, calculated according to Hershberger et al., is 0.88 for the 4 - chloro - testosterone - 17β - acetate and 0.28 for testosterone - propionate.

The 4 - chloro - testosterone - 17β - acetate is still active in doses of 250 γ and 100 γ per day.

The toxicity of the 4 - chloro - testosterone-17β - acetate is poor; a dose of 1.5 g/kg administered by one subcutaneous injection of the aqueous solution is easily tolerated in rats.

Doses of 50 mg/kg a day for 10 days are also well tolerated in rats while a dose 10 times as great may be considered the minimum dose tolerable in chronic administration.

WHAT WE CLAIM IS:—

1. A process for the production of 4 - chloro - testosterone - 17β - acetate which comprises reacting 4α,5 - epoxy - androstan - 17β - ol - 3 - one - acetate or 4β,5 - epoxy - etiocholan - 17β - ol - 3 - one - acetate or a mixture of these compound with hydrogen chloride in solution in chloroform or methylene chloride.

2. A process according to Claim 1, in which the hydrogen chloride is in the form of a gaseous stream.

3. A process according to Claim 1 or Claim 2 in which the reaction is effected at a temperature of from −10° C. to 25° C.

4. A process according to any one of Claims 1 to 3 in which the reaction is effected in solution in chloroform containing about 10% of ethanol.

5. A process according to any one of Claims 1 to 4 in which the hydrogen chloride is added in the form of a salt with an organic base.

6. A process according to Claim 5 in which the salt with an organic base is pyridinium chloride and the reaction mixture is boiled for from 1 to 10 hours.

7. A process for the production of 4 - chloro - testosterone - 17β - acetate which comprises acetylating the corresponding 17β - hydroxy compound.

8. A process according to Claim 7 in which the acetylation is effected with acetic anhydride.

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bicarbonate solution and thereafter with water; finally it is dried and the drying is completed under vacuum.

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7. A process for the production of 4 - chloro - testosterone - 17β - acetate which comprises acetylating the corresponding 17β - hydroxy compound.

8. A process according to Claim 7 in which the acetylation is effected with acetic anhydride.

9. A process according to Claim 8 in which the reaction is carried out in the presence of a basic reagent.

10. A process according to Claim 9 in which the basic reagent is pyridine.

11. A process for the production of 4 - chloro - testosterone - 17β - acetate as described in any one of the Examples.

12. 4 - chloro - testosterone - 17β - acetate when prepared by a process according to any one of Claims 1 to 11.

13. A therapeutic composition comprising 4 - chloro - testosterone 17β - acetate and a therapeutically acceptable carrier compatible therewith.

ERIC POTTER & CLARKSON,
Chartered Patent Agents,
317, High Holborn, London, W.C.1.

Reference has been directed in pursuance of Section 9, subsection (1) of the Patents Act, 1949, to patent No. 792,727.

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