14. DEC. 1962

AMENDED SPECIFICATION

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Reprinted as amended in accordance with the Decision of the Superintending Examiner acting for the Comptroller General dated the twenty third day of July 1962, under Section 14, of the Patents Act, 1949.

PATENT SPECIFICATION

NO DRAWINGS

864,609

Date of Application and filing Complete Specification: May 20, 1957.

No. 15920/57.

Application made in Italy on May 25, 1956.

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Index at acceptance:—Classes 2(3), U2, U4(A2:B1:B2:C4:C5:X); and 81(1), B2Z.

International Classification:—C07c. A61k.

COMPLETE SPECIFICATION

Improvements in or relating to the preparation of 4-Chloro-3-Keto-Δ^4-Steroids

We, SOCIETA FARMACEUTICI ITALIA, a Company incorporated 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:—

The present invention relates to steroid compounds and has as an object the provision of an improved process for the production of 4-chloro - 3 - keto - Δ^4 - steroids.

In the Specification of our co-pending Applications Nos. 10030/57, 40915/59 and 41225/59 (Serial Nos. 864,608, 838,773 and 864,613) we have claimed certain 4 - chloro-3 - keto - Δ^4 - steroids and the preparation thereof from the corresponding 4,5 - epoxy - 3-keto - steroids by reaction with hydrogen chloride in a subsequent stage to give 4-chloro compounds.

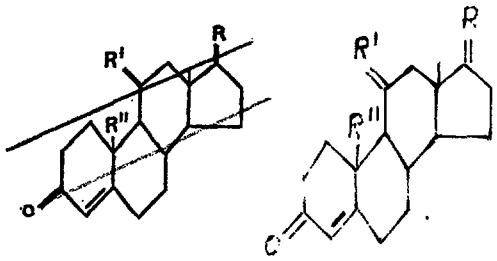
Patent Specification No. 792,727—British Drug Houses describes and claims a two-stage method for the preparation of 4 - chloro - 3-oxo - Δ^4 - steroids of the androstane and pregnane series, which method comprises chlorinating the corresponding 3 - oxo - Δ^4 - steroid and treating the resulting 4ξ:5ξ - dichloride with a base to remove hydrogen chloride therefrom. We lay no claim to such a method for we have discovered a one-stage process.

In accordance with the present invention there is provided a one-stage process for the preparation of a 4 - chloro - 3 - keto - Δ^4-steroid which comprises reacting, preferably at a temperature of from −15° C. to +60° C., a 3 - keto - Δ^4 - steroid with chlorine in solution in an organic solvent which is inert to chlorine, e.g. carbon tetrachloride and in the presence of a tertiary organic base. Advantageously the reaction is carried out in the presence of pyridine.

The reaction of bromine with a 3-keto-Δ^4-steroid, results in the production of a 2-bromo- or 6-bromo-steroid and it would therefore be expected that the reaction of chlorine would follow an analogous course. That the process provided in accordance with the present invention leads to the formation of the 4-chloro-steroid in substantial amount, is in consequence surprising.

The chlorine employed in the process may be provided in elemental form, for example it may be introduced into the reaction mixture in solution in carbon tetrachloride or other organic solvent which is inert thereto. Alternatively the chlorine may, in accordance with a feature of the invention, be provided by a substance which releases chlorine under the conditions of the reaction; for example, using acetic acid as the organic solvent the chlorine may be provided in the form of tert-butyl-hypochlorite.

The 4 - chloro - steroids produced in accordance with the present invention are of considerable pharmacological interest, especially those produced from 3 - keto - Δ^4-steroids of the general formula:



[*Price 4s. 6d.*]

in which

R represents $=(H)OR^{111}$, $=O$, $=(CH_3)OH$, $=(C_2H_5)OH$, $=(H)COCH_3$, $=(H)OCOCH_3$, $=(H)COCH_2O\,COCH_3$ or $=(OH)COCH_2OCOCH_3$

R^1 represents $=(H)H$, $=(H)OH$ or $=O$

R^{11} represents —H or $—CH_3$

and

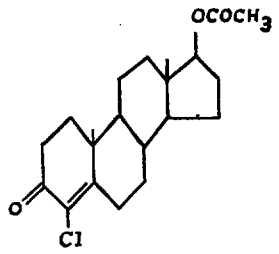
R^{111} represents an acyl group.

Especially preferred 3 - keto - Δ^4 - steroids of the foregoing general formula are testosterone acetate, 19 - nortestosterone acetate and testosterone cyclopentyl propionate which yield 4 - chloro - steroids having a high anabolic activity on the proteins without an equivalent androgenic action.

The following Examples are given in order to illustrate the invention.

EXAMPLE 1.

4-chlorotestosterone acetate.



2g testosterone acetate, dissolved in 20 cc anhydrous carbon tetrachloride and 10 cc anhydrous pyridine, are placed into a 4-necked flask provided with stirrer, thermometer, separating funnel and a calcium chloride tube. 14 cc of a 1.7 - molar solution of chlorine in carbon tetrachloride are then added while keeping the temperature at about $-5°$ C. There is, initially, a slight evolution of heat accompanied by the precipitation of a white solid. After the addition has been completed, stirring is continued for 15 minutes and the mixture is then left to stand without further cooling, so that the temperature of the reaction mixture slowly reaches room temperature. 5 hours after the starting of the reaction 200 cc chloroform are added, the solution is treated with a sodium bisulphite solution, with diluted hydrochloric acid, with diluted sodium bicarbonate solution, with water, and finally dried by distilling off the solvent.

A residue of 2.2 g is obtained which, recrystallized from 150 cc ethanol, gives 1.5 g 4 - chloro - testosterone acetate, melting point 228 to 230° C.; $(\alpha)_D = +120°$ (in chloroform); λmax 255mμ; $\epsilon = 13{,}200$.

EXAMPLE 2.

To 2 g testosterone acetate in 20 cc chloroform and 20 cc pyridine, heated to 50° C., 4.6 cc of a 1.7-molar solution of chlorine in chloroform are added. The temperature is raised to from 65 to 70° C. and the formation of a brown precipitate is observed. The whole is stirred for 30 minutes at 50° C., chloroform is added, the solution is treated with a solution of sodium bisulphite with diluted hydrochloric acid, dilute sodium bicarbonate, water, and is finally dehydrated and evaporated to dryness. After crystallisation from ethanol, 0.9 g 4 - chlorotestosterone acetate, having a melting point of 228° to 230° C., are obtained.

EXAMPLE 3.

4-chloro-testosterone acetate.

4 g testosterone are treated at room temperature with 16 cc pyridine and 4 cc acetic anhydride for 20 hours. To this solution, placed in a 3-necked flask provided with a stirrer and a reflux condenser, 20 cc chloroform and 17 cc of a 1.7-molar solution of chlorine in carbon tetrachloride are added. A strong evolution of heat and the formation of a dark precipitate are noted. After 4 hours at room temperature the reaction mixture is diluted with carbon tetrachloride treated with sodium bisulphite solution, with dilute acids, dilute alkalies and water until the solution is neutralised; it is then dehydrated and the carbon tetrachloride evaporated.

A residue of 4.4 g is obtained which, by recrystallisation from 100 cm^3 ethanol gives 2.4 g 4 - chlorotestosterone acetate, with melting point of 227 to 230° C.

EXAMPLE 4.

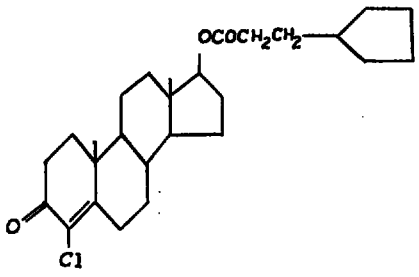
4-chloro-testosterone acetate.

3.3 g testosterone acetate are dissolved in 40 cc acetic acid and heated for 1 hour on water bath with 1.08 g *tert*-butylhypochlorite. The solution is concentrated *in vacuo*, the residue is recovered with alcohol and the crystals formed are filtered and recrystallised from ethanol.

0.9 g 4-chlorotestosterone acetate; m.p. 226° to 229° C., are obtained.

EXAMPLE 5.

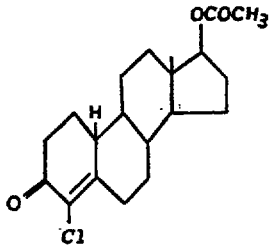
4-chlorotestosterone β-cyclopentylpropionate.



The procedure is as described in Example 1, but using 2 g testosterone cyclopentylpropionate as starting material.

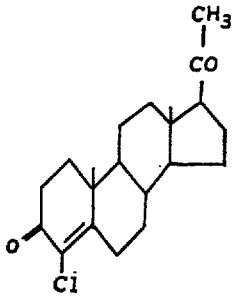
1.2 g 4 - chlorotestosterone cyclopentylpropionate, m.p. 108° to 110° C., are obtained.

EXAMPLE 6.
4-chloro-19-nortestosterone acetate.



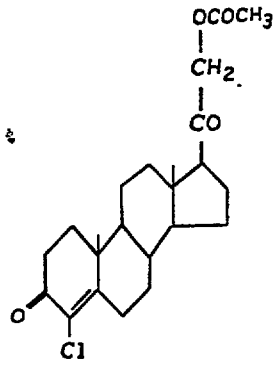
The procedure is as described in Example 1, but using 0.5 g of 19 - nortestosterone acetate as starting material. 0.3 g 4 - chloro-19 - nortestosterone acetate, m.p. 168° to 170° C. λmax. 255 mμ; ε = 13,800, are obtained.

EXAMPLE 7.
4-chloroprogesterone.



To 2 g progesterone, dissolved in 20 cc chloroform and 8 cc pyridine, 5 cc of a 1.7-molar solution of chlorine in carbon tetrachloride are added at 0° C. 5 hours later the reaction mixture is diluted with chloroform treated with sodium bisulphite solution, with dilute acids, dilute alkalies and water and reduced to dryness. The residue is recrystallised from ethanol and gives 0.9 g 4-chloroprogesterone, m.p. 216° to 219° C., λmax. 257 mμ; ε = 12,950.

EXAMPLE 8.
4-chloro-desoxicortiscosterone acetate.



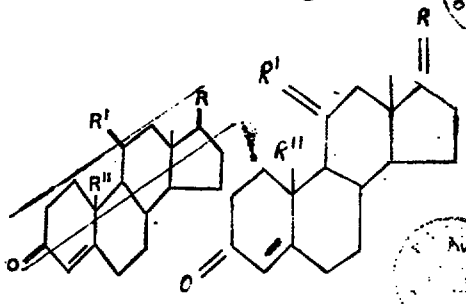
To 1 g desoxicortiscosterone acetate in 10 cc chloroform and 2.5 cc pyridine, are added 7 cc of a 1.7 molar solution of chlorine in chloroform at −10° C. 5 hours later the reaction mixture is diluted with carbon tetrachloride treated with sodium bisulphite solution, with acids, dilute alkalies water and reduced to dryness.

By crystallisation from ethanol and cooling to 0° C. crystals of m.p. 185° C. are recovered, which after a second crystallisation ~~gives~~ give 0.35 g 4 - chloro - desoxicorticosterone acetate, m.p. 190 to 192° C. λmax. 255mμ; ε = 13,500.

WHAT WE CLAIM IS:—

1. A one-stage process for the preparation of a 4 - chloro - 3 - keto - Δ^4 - steroid which comprises reacting a 3-keto - Δ^4 - steroid with chlorine in solution in an organic solvent which is inert to chlorine and in the presence of a tertiary organic base.

2. A process according to Claim 1 in which the 3 - keto - Δ^4 - steroid has the general formula:



~~R^{111} represents an acyl group.~~ in which

R represents $=(H)OR^{111}$, $=O$, $=(CH_3)OH$, $=(C_2H_5)OH$, $=(H)COCH_3$, $=(H)OCOCH_3$, $=(H)COCH_2O\,COCH_3$ or $=(OH)COCH_2OCOCH_3$

R^1 represents $=(H)H$, $=(H)OH$ or $=O$

R^{11} represents —H or —CH_3

and

R^{111} represents an acyl group.

3. A process according to either of Claims 1 or 2 in which the organic solvent is carbon tetrachloride.

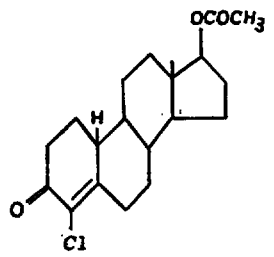
4. A process according to any one of Claims 1 to 3, in which the reaction is carried out in the presence of pyridine.

5. A process according to any one of the preceding Claims in which the chlorine for the reaction is provided by a substance which releases chlorine under the conditions of the reaction.

6. A process according to Claim 5 in which the organic solvent is acetic acid and the chlorine is provided in the form of *tert*-butyl-hypochlorite from which it is released during the reaction.

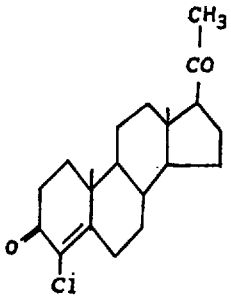
7. A process according to any one of the preceding Claims in which reaction is effected at a temperature of from −15° C. to +60° C.

EXAMPLE 6.
4-chloro-19-nortestosterone acetate.



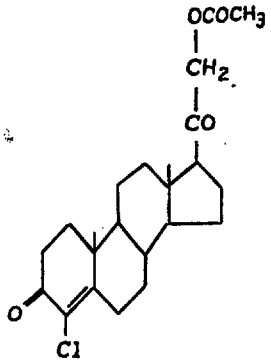
The procedure is as described in Example 1, but using 0.5 g of 19 - nortestosterone acetate as starting material. 0.3 g 4 - chloro-19 - nortestosterone acetate, m.p. 168° to 170° C. λmax. 255 mμ; ε = 13,800, are obtained.

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4-chloroprogesterone.



To 2 g progesterone, dissolved in 20 cc chloroform and 8 cc pyridine, 5 cc of a 1.7-molar solution of chlorine in carbon tetrachloride are added at 0° C. 5 hours later the reaction mixture is diluted with chloroform treated with sodium bisulphite solution, with dilute acids, dilute alkalies and water and reduced to dryness. The residue is recrystallised from ethanol and gives 0.9 g 4-chloroprogesterone, m.p. 216° to 219° C., λmax. 257 mμ; ε = 12,950.

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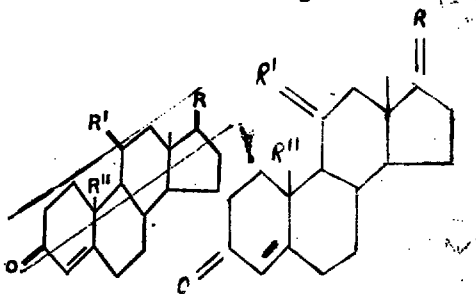
To 1 g desoxicortiscosterone acetate in 10 cc chloroform and 2.5 cc pyridine, are added 7 cc of a 1.7 molar solution of chlorine in chloroform at − 10° C. 5 hours later the reaction mixture is diluted with carbon tetrachloride treated with sodium bisulphite solution, with acids, dilute alkalies water and reduced to dryness.

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WHAT WE CLAIM IS:—

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2. A process according to Claim 1 in which the 3 - keto - Δ^4 - steroid has the general formula:



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4. A process according to any one of Claims 1 to 3, in which the reaction is carried out in the presence of pyridine.

5. A process according to any one of the preceding Claims in which the chlorine for the reaction is provided by a substance which releases chlorine under the conditions of the reaction.

6. A process according to Claim ~~5~~ 6 in which the organic solvent is acetic acid and the chlorine is provided in the form of *tert*-butyl-hypochlorite from which it is released during the reaction.

7. A process according to any one of the preceding Claims in which reaction is effected at a temperature of from − 15° C. to + 60° C.

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8. A process according to any one of the preceding claims in which the 3 - keto - Δ^4- steroid is testosterone acetate, 19 - nortestosterone acetate or testosterone cyclopentyl propionate.

9. A process for the preparation of a 4-chloro - 3 - keto - Δ^4 - steroid substantially as hereinbefore described and illustrated by the foregoing Examples.

10. A 4 - chloro - 3 - keto - Δ^4 - steroid when produced by a process in accordance with any one of the preceding claims.

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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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