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METHOD FOR THE PREPARATION OF DIHYDROTESTOSTERONE AND ITS ESTERS

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10 Claims. (Cl. 260—397.4)

This invention relates the the production of dihydrotestosterone and its esters; it is a development of our copending application, Serial No. 404,378 filed January 15, 1954.

In the said application, a process for the preparation of testosterone and its esters is described wherein one of the intermediates is Δ-4-andronstene-17-cyan-17-ol-3-one.

This compound, according to the above mentioned invention, is treated in such a way that the carbonyl group present in it is protected in the form of derivatives of the type enol-ether or ketal; the new compound so obtained is then submitted to the combined action of an aliphatic alcohol and an alkali metal, in order to obtain an enol ether or a ketal of testosterone from which finally the testosterone and its esters may be obtained.

The applicants have now discovered that a process perfectly analogous is suitable also in the preparation of dihydrogenated (in position 4–5) testosterone, or androstan-17β-ol-3-one (VI), commonly known under the name of 4-dihydro-testosterone.

In this case the necessary intermediate is the androstan-17-cyan-17-ol-3-one (III).

The present invention relates to the manufacture of this intermediate (III) and its further transformation into dihydrotestosterone (VI) or in its esters (VIII: where R—CO=radical of organic acid) according to a series of reactions which are substantially analogous to those described in the above mentioned application.

The process according to the invention may be illustrated by the scheme represented on the last page hereof containing the formulas from I to VIII. In practicing our invention we proceed as follows:

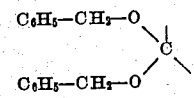
The cyanohydrin of androstan-3β-ol-17-one or androstan-17-cyan-3β,17-diol, mixture of two 17-epimers (II)—which may be easily prepared from androstan-3β-ol-17-one (I) or directly from the mixture of the neutral crude desacetylated products, separable from the oxidation of the acetyldihydro-cholesterol—is oxidised by chromic anhydride keeping the reaction product from contact with substances of alkaline nature: in this manner the 17-monocyanohydrin of the androstan-3,17-dione [or androstan-17-cyan-17-ol-3-one (III), mixture of two 17-epimers] is obtained. This intermediate by treatment with ethyl orthoformate in the presence of catalysts of acid nature is transformed into the 3-diethyl-ketal of the 17-monocyanohydrin of androstan-3,17-dione (IV); this product in its turn by treatment with sodium and propyl alcohol is transformed into a solution of 3-diethyl-ketal of 4-dihydrotestosterone (V). The propyl alcohol solution containing the new intermediate, by acidification in the hot with dilute hydrochloric acid, yields directly the 4-dihydrotestosterone (VI). The intermediate V may also be isolated by simple dilution of the propyl alcohol solution and the esters of the 4-dihydrotestosterone (VIII) may be obtained by acylation of the group OH in position 17, with intermediate formation of esters of 3-diethyl-ketal of the 4-dihydrotestosterone (VII): after

hydrolysis the esters of 4-dihydrotestosterone (VIII) are obtained.

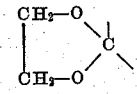
Instead of using the cyanohydrin of androstan-3β-ol-17-one, the cyanohydrin of androstan-3α-ol-17-one may be also employed which, by chromic oxidation, yields the same intermediate III.

Instead of using ethyl orthoformate, other acetalysing agents may be also employed as for instance other esters of orthoformic acid, alcohols (e. g., benzyl alcohol), glycols (e. g., ethylene glycol) always in the presence of catalysers of acid nature; intermediate products containing in position 3 the ketal groups corresponding to the acetalysing agents employed, are thus prepared:

(e. g.:



or



and similar products)

which at the end—as indicated above for the 3-diethyl-ketal compounds—are transformed either directly into the 4-dihydrotestosterone, or into its esters.

Instead of using sodium and propyl alcohol, other alkali metals and aliphatic alcohols may be employed, as for instance, ethyl-, isopropyl-, butyl-, and amyl-alcohol and its isomers.

In order that the invention may be well understood the following examples are given as illustrations only:

Example 1

From androstan-3β-ol-17-one (I) as starting material or directly from the crude oxidation products of the dihydrocholesterol, the corresponding cyanohydrin (II) is prepared by action of acetone cyanohydrin (according to the French Patent No. 1,058,454 dated November 4, 1953).

The cyanohydrin (II) (mixture of two 17-epimers: androstan-17-α-cyan-3β-17β-diol and androstan-17β-cyan-3β-17α-diol, M. P. dec. about 170° C.) is used in the crude state, simply well washed with petrol ether and dried in the vacuum.

10 g. of this cyanohydrin are suspended in a mixture of 80 cc. of ethylene chloride and 200 cc. of acetic acid. Then a solution of 3 g. of chromic anhydride in 60 cc. of acetic acid at 90% is slowly added at the temperature of 15° C. during 15 minutes. The mixture is maintained in agitation. After 24 hours, ether and water are added to the solution. The ethereal layer, which separates off, is repeatedly washed with water, dried over sodium sulfate and evaporated in the vacuum. A solid crystalline residue of about 8.85 g. is obtained which, recrystallised from ether, yields 8.35 g. of androstan-17-cyan-17-ol-3-one (III) (mixture of two possible 17-epimers, M. P. 207° C. dec.). This intermediate will be called androstandione-17-monocyanohydrin hereinafter.

8.35 g. of androstandione-17-monocyanohydrin are suspended in 110 cc. of benzene, then 55 cc. of benzene are distilled in order to eliminate moisture. The temperature is brought to 65° C. and, while maintaining it, 9.5 g. of ethyl orthoformate, 5 cc. of absolute ethyl alcohol and 0.43 cc. of a 7% hydrogen chloride solution in absolute ethyl alcohol (0.03 g. of HCl) are added. After 15 minutes all the original product goes into solution and a new crystallisation begins. After another 45 minutes at 65° C., 0.075 cc. of pyridine are added and the solution is evaporated in the vacuum to dryness; a residue

of 8.9 g. of crude 3-diethyl-ketal of androstandione-17-monocyanohydrin (IV) is obtained.

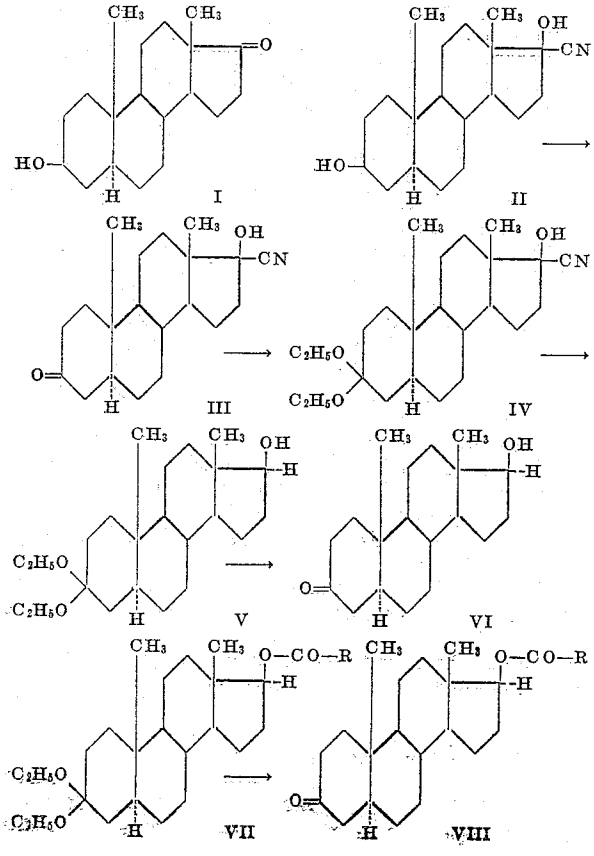
This residue is dissolved in 230 cc. of propyl alcohol and treated on the boiling water bath with 9 g. of sodium in small pieces for about 30 minutes.

When the reaction is achieved the mixture, which now contains the 3-diethyl-ketal of androstan-17β-ol-3-one (V), is acidified to red-congo with 2 N hydrochloric acid and diluted with boiling water. Most of the propyl alcohol is eliminated by distillation at reduced temperature and then, by cooling and allowing to rest, crystallisation of 6.9 g. of 4-dihydrotestosterone (VI) M. P. 176–178° C. is obtained.

Example 2

The reaction is carried out with the same procedure as in Example 1 using the same starting materials in the same quantities until the treatment with propyl alcohol and sodium of the 3-diethyl-ketal of androstandione-17-monocyanohydrin (IV). The solution in propyl alcohol so obtained is diluted with water and allowed to crystallise. The separation of about 8 g. of crude 3-diethyl-ketal of androstan-17β-ol-3-one (V) M. P. 120–138° C. is obtained. The product is dissolved in 75 cc. of pyridine and acetylated at room temperature by adding 35 cc. of acetic anhydride. After a night the excess of acetic anhydride is decomposed by dilution with water and the acetyl derivative is extracted with ether. The ether, washed with dilute sodium carbonate and water, after desiccation and evaporation, gives a residue of 3-diethyl-ketal of 17β-acetoxy-androstan-3-one (VII where: R=CH_3) in a crude state. This product is dissolved in 35 cc. of acetone and the solution is heated with reflux for 10 minutes with addition of 0.75 cc. of concentrated hydrochloric acid. The mixture is then diluted with water and allowed to cool: the product which separates off, after crystallisation from petrol ether, yields about 7 g. of dihydrotestosterone acetate (VII where: R=CH_3) M. P. 153–156° C.

Similarly the other esters of dihydrotestosterone are prepared.



We claim:

1. A process for the preparation of 4-dihydrotestosterone which comprises oxidizing with chromic acid the cyanohydrin of androstan-3-ol-17-one to form androstan-17-cyan-17-ol-3-one; treating this intermediate in the presence of an acid catalyst with an acetalysing agent, selected from the group consisting of orthoformic acid esters, aryl alcohols and aliphatic glycols, thereby obtaining as a second intermediate a 3-ketal derivative of the androstan-17-cyan-17-ol-3-one; subjecting the second intermediate compound to the concomitant action of a boiling aliphatic alcohol of the series containing 2 to 5 carbon atoms and an alkali metal to eliminate the CN group in 17-position and to form in the alkaline alcoholic solution a 3-ketal derivative of 4-dihydrotestosterone, acidifying the said boiling alkaline alcoholic solution with a mineral acid and diluting the same with boiling water to obtain 4-dihydrotestosterone.

2. A process as defined in claim 1 wherein the acetalysing agent is ethyl orthoformate.

3. A process as defined in claim 1 wherein the acetalysing agent is benzyl alcohol.

4. A process as defined in claim 1 wherein the acetalysing agent is ethylene glycol.

5. A process as defined in claim 1 wherein an acid of the group consisting of mineral and aromatic sulfonic acids is employed as catalyst in the acetalysation step.

6. A process as defined in claim 1 wherein the acetalysation step is carried out in presence of a solvent of the series of benzene and its methyl homologues, and water formed in the acetalysation is removed by distillation of the same solvent forming an azeotropic mixture therewith.

6. A process as defined in claim 1 wherein the acetalysation step is carried out in presence of a solvent of cyanohydrin of androstan-3-ol-17-one to form androstan-17-cyan-17-ol-3-one; treating this intermediate in the presence of an acid catalyst with an acetalysing agent selected from the group consisting of orthoformic acid esters, aryl alcohols and aliphatic glycols, thereby obtaining as a second intermediate a 3-glycol ketal derivative of 4-dihydrotestosterone; diluting the said alkaline alcoholic solution with water to precipitate and isolate the 3-ketal derivative of 4-dihydrotestosterone; acylating the latter in the dried state at the OH group in 17-position with an organic carboxylic acid anhydride of the series of aliphatic acid anhydrides corresponding to the acids containing from 2 to 6 carbon atoms, in the presence of pyridine, to obtain a 17-acylester of the 3-ketal derivative of 4-dihydrotestosterone; hydrolysing the 3-ketal function of the latter by gentle boiling in acetone in the presence of traces of mineral acid and water to obtain the corresponding 4-dihydrotestosterone-17-acyl ester.

8. A process as defined in claim 7 wherein the acetalysing agent is ethyl orthoformate.

9. A process as defined in claim 7 wherein the acetalysing agent is benzyl alcohol.

10. A process as defined in claim 7 wherein the acetalysing agent is ethylene glycol.

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