SYNTHESIS OF 2α-METHYLDIHYDROTESTOSTERONE

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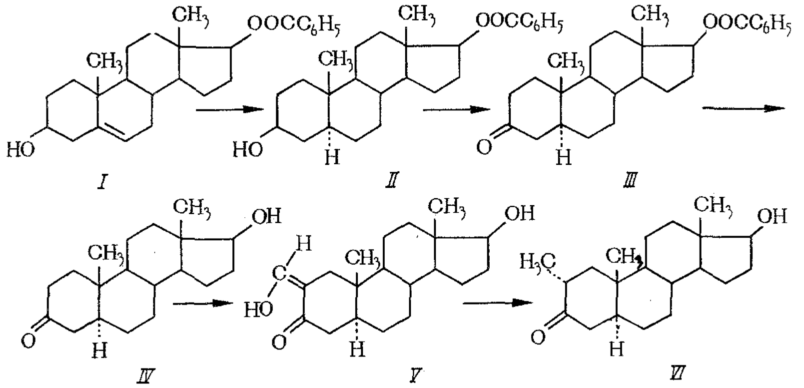
2α-Methyldihydrotestosterone (VI) and its esters are at the present time some of the most effective preparations used for the medical treatment of metastatizing cancer of the mammary gland. According to the literature, the synthesis of VI has been accomplished using dihydrotestosterone [1] or from 17-benzoatandrostendiol-3β, 17β (I)through dihydrotestosterone [2].

However, both of these methods have a number of important drawbacks.

The scheme for synthesizing 2α-methyldihydrotestosterone [2] we proposed earlier was used to eliminate them:



Compound I, which was hydrogenated into 17-benzoatandrostandiol-3β, 17β (II) at 55–70° and 20 atm of hydrogen, served as the starting material for the synthesis. The latter was oxidized with a chromate mixture in a benzene-acetone solution [3] at −2 to +2° into the dihydrotestosterone benzoate (III). This product was saponified with an alcoholic base into dihydrotestosterone (IV). When this method of oxidation is used, a product is obtained which is sufficiently pure, and after separating it from benzoic acid, IV is hydroxymethylated and the subsequent reduction of the 2-hydroxymethylene group to the methyl group follows.

The method we described permits us to carry out the entire synthesis without isolating and crystallizing the intermediate reaction products; only the final product is purified. The yield of IV was increased from the 42.5%, which was described earlier [2], to 51%.

EXPERIMENTAL

A mixture of 120 g of I, palladized carbon (obtained from 4 g of $PdCl_2$ and 8 g of activated carbon), and 3 liter of isopropyl alcohol was hydrogenated in an autoclave at 20 atm and 55–70° with constant agitation for 6 h. The solution we obtained was separated from the catalyst and the latter was washed with 1 liter of hot isopropyl alcohol. The solvent was completely distilled from the combined solutions. In order to remove the isopropyl alcohol completely, 0.5 liter of benzene was added to the residue and was then distilled off.

Unpurified II, dissolved in 1500 ml of benzene and 1200 ml of acetone, was charged into a five-liter flask equipped with a thermometer, stirrer, and dropping funnel, and the solution was cooled to −2 to −4° with an ice-salt mixture. Then, while stirring and at a temperature from −2° to +2°, a chromate mixture (65 g of CrO_3, 55 ml H_2SO_4, and 96 ml of H_2O) diluted to 240 ml with water was added through the dropping

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funnel over a 2 h period. Mixing was continued at this same temperature for another hour and the excess oxidizing mixture was reduced by adding 300 ml of methanol.

We distilled 2500 ml of solvent from the mixture and the remainder was diluted with water and extracted four times with benzene (1, 0.5, 0.5, and 0.3 liter). The benzene extracts were washed with water, a 5% solution of sodium hydroxide, again with water, and the benzene was distilled off completely. A methanolic solution of KOH (2800 ml of methanol and 62 g of KOH) was added to the technical grade III that was obtained, and the mixture was refluxed for $1^1/_2$ to 2 h. Then the solution was cooled to room temperature, neutralized with 96 ml of acetic acid, filtered free of sludge, and 2.5 liter of methanol was distilled from it. The remainder was mixed with 1 liter of benzene and diluted with 5 liter of water. The benzene extract was separated and the aqueous portion was extracted with 4 × 0.5 liter of benzene. The benzene extracts were washed with water, a 5% NaOH solution, again with water, and the benzene was distilled off completely. Technical grade IV was obtained.

A solution of IV in 4.3 liter of benzene and 225 ml of ethylformate was mixed in a five-liter flask containing sodium ethylate, which was obtained from 66.8 g of metallic sodium, and was agitated for 5 h at room temperature taking care not to admit moisture. Then, 900 ml of water was added, agitation was continued for another 10-15 min, the aqueous portion was separated, and the benzene layer was washed with 5 × 300 ml of water. The aqueous extracts were combined and acidified with hydrochloric acid to Congo red. Compound V which precipitated out was filtered off, washed with water until neutral, and dried at room temperature.

Unpurified V was dissolved in 2.5 liter of methanol, palladized carbon, which was obtained from 4 g of $PdCl_2$ and 16 g of activated carbon was added, and the mixture was hydrogenated at room temperature and atmospheric pressure. The hydrogenation practically stopped after 10 liter of hydrogen was absorbed. The methanol solution was separated from the catalyst, the latter was washed with 1 liter of hot methanol, and the solvent was distilled off completely. The remainder was dissolved in ether, chromatographed on 1200 g of Al_2O_3 and eluted with ether. After distilling the eluate off, 47.3 g (51% of theory) of 2α-methyldihydrotestosterone, mp 147-154° (in a range of 2-3°) was isolated.

LITERATURE CITED

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