PREPARATION OF TESTOSTERONE ESTERS

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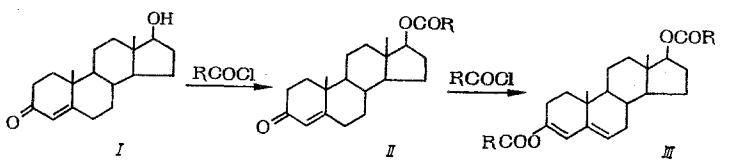
Esters of testosterone with certain higher aliphatic acids (enanthic, capric, isocapric) have found wide use in medicine as highly active male sex hormone preparations of prolonged effect (from 2 to 4 weeks). They can be obtained [1, 2] upon reaction of testosterone (I) with acid chlorides of these acids, taken in 30% excess, in the presence of pyridine at room temperature.

Esterification of (I) under these conditions occurs completely, but, as we established, formation of 3-enol esters of (I) is observed. Despite the simplicity of this method, the preparation of esters of (I) by this method was found to be very difficult. The stability of acid chlorides of higher aliphatic acids to decomposition with water, aqueous solutions of bases, and alkali metal carbonates does not make it possible to carry out their selective saponification with subsequent separation of the water-soluble salts of these acids. Saponification of esters of (I) occurs simultaneously, which decreases their yield and worsens the quality. It is not possible to carry out the separation of excess acid chloride from esters of (I) by crystallization from various solvents as a result of their high solubility.

Another method of obtaining esters of (I) with higher aliphatic and alicyclic acids, described in a patent [3], is based on the transesterification reaction of the propionate of (I) upon heating it with a large excess of the methyl or ethyl ester of the corresponding acid in the presence of catalytic amounts of sodium methoxide. The formed ester of (I) can be separated easily by this method from excess reagents, which are distilled in vacuum. Its disadvantage is the necessity of starting from esters of (I) with lower aliphatic acids (acetic, propionic), which makes this method more complex and decreases the total yield.

A third method of obtaining esters of (I) consists of reaction of (I) with the corresponding acids at a temperature of 200° in a stream of nitrogen [4] or upon lengthy boiling (36 h) in toluene solution in the presence of an acidic ion exchange resin [5].

We have found a method, convenient for manufacture, of obtaining esters of (I) (IIa, b, c) by reaction with acid chlorides of higher aliphatic acids in the presence of pyridine in inert-solvent solution,



I II III

a) R = $(CH_2)_5CH_3$; b) R = $(CH_2)_8CH_3$; c) R = $(CH_2)_7CH(CH_3)_2$

for example, benzene, with subsequent removal of excess acid chloride from the reaction mass as water-soluble diethylaminoethyl esters [6]. These esters are formed upon addition of diethylaminoethanol to the reaction solution. They are separated easily from (IIa, b, c) by washing with hydrochloric acid solution and water.

As we established, a significant factor affecting the quality of esters of (I) is their preparation at lower temperatures (from −6 to + 10°C). As a result of the high reactivity of aliphatic acid chlorides they

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react not only with the hydroxyl group at C_{17}, but also with the keto group at C_3 with formation of enol esters (IIa, b, c), which are observed upon thin-layer chromatography in a benzene–acetone (4:1) system as a less polar spot. We could avoid formation of (IIIa, b, c) by carrying out the esterification reaction at a low temperature.

EXPERIMENTAL

Specific rotation was determined in dioxane (C 1) on an ÉLPU-01 instrument. Specific absorption index was determined in alcohol (C 1) at λ 241 mμ on an SF-4 spectrophotometer. Chromatography was carried out on plates having a fixed layer of silica gel in benzene–acetone (4:1) system. The materials were detected by spraying the plates with concentrated sulfuric acid and subsequent heating at 70-80° for 10-15 min. The following R_f values were obtained: (I) 0.77, (IIa) 0.71, (IIb) 0.72, (IIc) 0.81, (IIIa) 0.85, (IIIb) 0.96, (IIIc) 0.95.

Enanthate of Testosterone (IIa). To a solution of 4 g of (I) (mp 155-156°) in 4 ml of pyridine and 14 ml of benzene, cooled to 5-10°, was added at this temperature 2.56 g of enanthyl chloride in 3.2 ml of benzene during 30 min and the mixture was stirred at this temperature for 1 h. After control using thin-layer chromatography [absence of (I)], the mixture was cooled to 0° and to it was added 1.1 ml of diethylaminoethanol; the mixture was stirred at this temperature for 4-5 h and poured into 52 ml of 5% aqueous hydrochloric acid solution. The benzene layer was separated, and the aqueous layer was extracted with 40 ml of benzene. The combined benzene extracts were washed consecutively with a 5% hydrochloric acid solution, 1% sodium hydroxide solution, and water. The obtained benzene solution of (IIa), dried by partial distillation of benzene at atmospheric pressure and brought with benzene to a volume of 108 ml, was passed through a layer (3-5 cm high) of aluminum oxide (22 g), which was washed with benzene. The benzene was distilled in vacuum (bath temperature 40-50°). We obtained 5.07-5.16 g (92.5-93.5%) of (IIa), mp 35-36°, $[\alpha]_D^{20} = +78°$, E = 406 ± 3.

Literature data [1, 5]: oil, $[\alpha]_D^{20} = +75.3°$; mp 36-37°, $[\alpha]_D^{20} = +75-+76°$.

Caprate of Testosterone (IIb). Under conditions analogous to those described for (IIa) by reaction of 20 g of (I) with capryl chloride at 0° for 30 min with subsequent maintainance at this temperature for 1 h was obtained 26-27.4 g (85-89%) of (IIb), mp 53-54°, $[\alpha]_D^{20} = +70-+74°$, E = 375 ± 3 after crystallization from a single amount of methanol.

Literature data [1, 5]: mp 54-56°, $[\alpha]_D^{20} = +70.7°$, mp 55-57°.

Isocaprate of Testosterone (IIc). Under conditions analogous to those described for (IIa) by reaction of 15 g of (I) with isocapryl chloride at −6° for 30 min with subsequent maintainance at this temperature for 1 h was obtained 17.5 g (88%) of (IIc), mp 78.5-79.5°, $[\alpha]_D^{20} = +82-+85°$, E = 430 ± 3 after crystallization from a 1.5-fold amount of n-hexane.

Literature data [1, 2]: mp 79-80°, mp 82-84.5°, $[\alpha]_D^{20} = +82.3°$.

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