SYNTHESIS OF 5α-DIHYDROTESTOSTERONE FROM AN INTERMEDIATE IN TIGOGENIN DEGRADATION

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5α-Dihydrotestosterone, which is one of the major metabolic products of testosterone [1-3], is widely used as an androgenic preparation under the trade names androlone, stanolone, neodrol, etc. Dihydrotestosterone can also be used as the starting compound for the synthesis of highly active pharmaceuticals of the 5α-androstane series, such as the antitumor preparation prolotestone (2α-methyl-5α-androstan-17β-ol-3-one propionate), the androgenic preparation gombreol (5α-androstane-3α,17β-diol), and the anabolic preparation primobolan (1-methyl-5α-androst-1-en-17β-ol-3-one acetate), etc.

Reduction of the double bond in steroidal Δ^4-3-ketones or catalytic hydrogenation of Δ^5-3-alcohols is the usual method for the preparation of compounds of the 5α series. The widely used reduction of the Δ^4 double bond (in testosterone, for example) with alkali metals in liquid ammonia is sterically controlled, forming the desired 5α-H compound [4]. However, this is accompanied by reduction of the 3-keto group to the saturated alcohol. Reduction of the double bond in an α,β-unsaturated ketone with lithium-ammonia complex, prepared by the reaction of lithium metal with gaseous ammonia, is also complicated by intense side reactions. Thus, the reduction of testosterone forms a considerable quantity of the saturated diol [5]. Analysis of the reaction mixture by GLC shows that the yield of the major product does not exceed 73%.

Though catalytic hydrogenation of the Δ^5 double bond can be used in the synthesis of dihydrotestosterone, it is not stereospecific [6,7]. Thus, when androst-5-ene-3β,17β-diol 17-benzoate is hydrogenated in isopropyl alcohol over palladium on carbon in an autoclave under 20-40 atm at 70-80°C reduction of the double bond is accompanied by hydrogenolysis of the 3-hydroxy group. This forms 3-unsubstituted steroids of the 5α series (up to 6.5%) and of the 5β series (up to 3.9%). Dehydrogenation of the 3-hydroxy group to give the 3-ketone also occurs. Purificationof 5α-androstane-3β,17β-diol 17-benzoate is difficult.

We have developed a method for the synthesis of 5α-dihydrotestosterone (IIIb) from 5α-androstan-3β-ol-17-one acetate (I), an intermediate in the degradation of tigogenin. Use of tigogenin, which has a trans-A/B ring junction, for the synthesis of dihydrotestosterone is convenient, since it obviates the difficulties of conversion from Δ^4- and Δ^5-steroids (intermediates in the degradation of diosgenin and solasodine) to compounds of the 5α series.

Reduction of the 17-keto group of compound I with sodium borohydride in methanol gives 5α-androstane-3β,17β-diol 3-acetate (IIa) in quantitative yield. Subsequent acylation of the 17β-hydroxy group with benzoyl chloride in pyridine at 60°C gives [1] 5α-androstane-3β,17β-diol 3-acetate 17-benzoate (IIb). The 3-acetoxy group is then selectively hydrolyzed by alkali in methanol—dichloroethane. Control of alkaline hydrolysis by TLC on a fixed layer of silica gel shows that the optimum conditions for hydrolysis are 0.7 mole of alkali per mole of steroid at 20°C over 24 h. The proportion of the contaminating by-product, 5α-androstanediol (IId), can be reduced to 0.5%, while less than 0.5% of the starting diester remains. Oxidation of the free hydroxyl group with Jones reagent in acetone—methylene chloride gives 5α-androstan-17β-ol-3-one benzoate (IIIa). Hydrolysis of the benzoate by reflux with excess alkali gives [1] 5α-androstan-17β-ol-3-one (IIIb) (5α-dihydrotestosterone). The yield of IIIb is 73.2% based on I.

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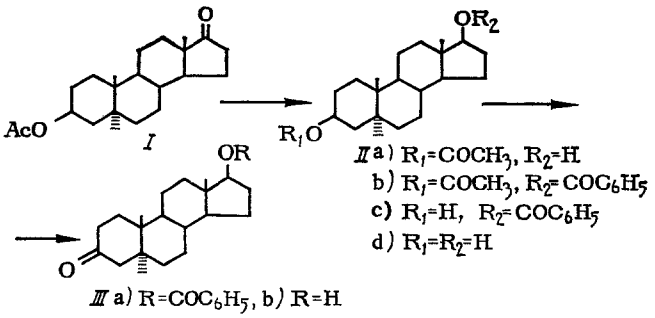

EXPERIMENTAL

Chromatography of compounds I-III was carried out on Silufol plates in benzene–methanol (19:1); detection by 1% vanillin solution in 10% aqueous perchloric acid. Values of $[\alpha]_D^{20}$ were determined with an Al-EPL polarimeter.

5α-Androstane-3β,17β-diol Acetate (IIa). To a solution of I (0.97 g) in methanol (4 ml) at 0°C was added sodium borohydride (0.09 g). The reaction mixture was stirred for 30 min, acidified with dilute hydrochloric acid until weakly alkaline, and extracted with ether. The ether was then removed under vacuum. The precipitate was washed with water. We obtained IIa (0.97 g), mp 113-115°C (literature mp 114-116°C [8]). The yield was 99.4%.

5α-Androstane-3β,17β-diol 3-Acetate 17-Benzoate (IIb). To a solution of IIa (0.7 g) in dry pyridine (8 ml) was added freshly distilled benzoyl chloride (0.5 ml). The mixture was heated to 60°C and left for 1 h, whereupon water (16 ml) was added to the reaction mixture. We obtained IIb (0.87 g), mp 126-131°C. The yield was 94.8%. An analytically pure sample had mp 138-139°C, $[\alpha]_D^{20}$ +43° (1%, in chloroform). Found, %: C 76.67, H 8.49; $C_{28}H_{38}O_4$. Calculated, %: C 76.67; H 8.73.

5α-Androstane-3β,17β-diol 17-Benzoate (IIc). To a solution of IIb (0.5 g) in a mixture of dichloroethane (2.5 ml) and methanol (20 ml) was added a titrated solution (0.90 ml) of potassium hydroxide (0.045 g) in methanol. The reaction mixture was left at room temperature for 24 h and then acidified to pH 5.5-6 and concentrated under vacuum. Twice the volume of water was added. The resulting precipitate was filtered off and washed with water. We obtained IIc (0.42 g), mp 198-200°C, $[\alpha]_D^{20}$ +58° (1%, in chloroform) (literature mp 198-200°C [6]). The yield was 92.9%.

5α-Androstan-17β-ol-3-one 17-Benzoate (IIIa). To a solution of IIc (0.35 g) in a mixture of acetone (14 ml) and methylene chloride (3 ml) was added Jones reagent (0.55 ml). The reaction mixture was stirred in a stream of nitrogen for 45 min. The organic layer was separated, washed with water until neutral, and evaporated under vacuum. Recrystallization from ethyl acetate gave IIIa (0.32 g), mp 198-200°C, $[\alpha]_D^{20}$ +80.5° (1%, in chloroform) (literature mp 200-204°C [7]). The yield was 91.9%.

5α-Androstan-17β-ol-3-one (IIIb). A mixture of IIIa (0.6 g) and potassium hydroxide (1.2 g) in methanol (50 ml) was refluxed for 2 h. The reaction mixture was then acidified to pH 5.5-6.0 and concentrated under vacuum. Water was added. The resulting precipitate was filtered off. Recrystallization from alcohol gave IIIb (0.4 g), mp 179.5-181°C, $[\alpha]_D^{20}$ +31-33° (1%, in alcohol [6]). The yield was 90.9%. The overall yield of IIIb, based on I, was 73.2%.

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EUTECTIC POINTS OF SOME SOLUTIONS OF THERMALLY LABILE PREPARATIONS

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Solutions of preparations of a biological nature (antibiotics, enzymes, etc.) are dried by sublimation to preserve their activity [1-4].

The first stage in the commercial dewatering of solutions by lyophilization is cooling to a temperature below the eutectic point, which must not be overlooked in drying [5-7].

If the preparation is dried at a temperature above that permissible for the particular solution, partial thawing of the solution can occur, causing destruction of the biologically active substances.

An attempt to improve the process for drying preparations of streptomycin calcium chloride complex, ristomycin sulfate, and terrilytin required knowledge of the eutectic points of solutions of these substances.

We determined the eutectic points from the temperature dependence of the resistivity (ρ) of the solutions from −50°C to +20°C.

We found experimentally that the conductance of a completely frozen solution, the so-called eutectic, is zero. On thawing, i.e., the appearance of the first signs of a liquid solution, the conductance is already measureable, corresponding to transition from infinite to finite resistivity.

On a graph of $\rho = f(t)$ the eutectic point can be found by extrapolating the linear part of the plot, corresponding to infinitely high ρ, onto the temperature axis.

EXPERIMENTAL

The equipment for the determination of the resistivity of the solutions at various temperatures consisted of an E 10-2 admittance meter and a fluoroplast [Teflon] cell with platinum electrodes.

Temperatures were measured with a chromel–copel thermocouple connected to a PSRL-03 recording potentiometer to within 0.5°C. Solutions of the preparations were cooled in a thermostated cell with freezing mixture.

We were able to reach −70°C in the cell and 20°C by gradual warming at room temperature. The conductance was measured at 1°C intervals near the eutectic point and at 3-5°C intervals elsewhere.

Measurements used solutions of streptomycin calcium chloride complex (activity 80,000 IU/ml), ristomycin sulfate (31,000 IU/ml), and terrilytin (88 PE/ml).

The control was 10% sodium chloride solution, whose eutectic point is known [1, 5].

The experimental temperature dependence of the resistivity of these solutions is shown in a logarithmic plot in Fig. 1.

Figure 1 shows that the eutectic point of the sodium chloride solution is −21.6°C, which is consistent with published results [1, 5]. The eutectic points of the other solutions are

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