# PREPARATION OF THE PHENYLPROPIONATE OF 19-NORTESTOSTERONE FROM 3,3-DIMETHOXY-19-NORANDROST-5(10)-ENE-17-ONE

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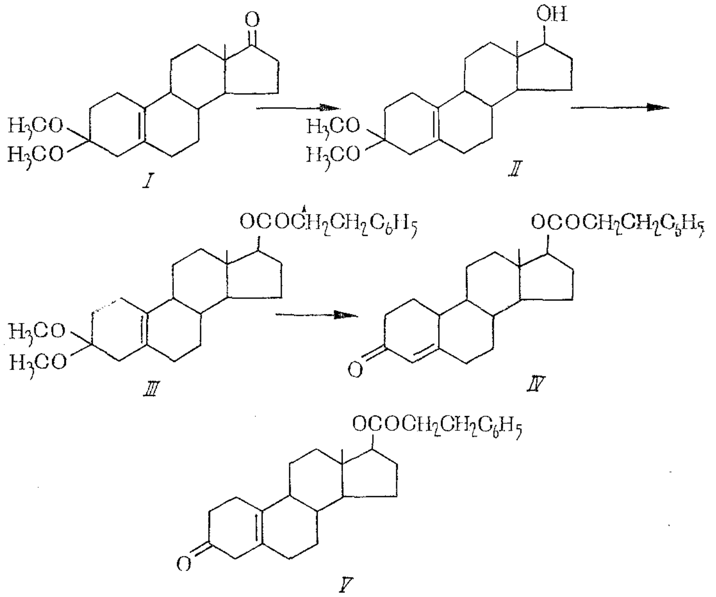
Synthesis of 19-norsteroids from the acetate of dehydroepiandrosterone can be accomplished in two ways: through an intermediate estrone using the Birch reaction [1, 2] or by oxidative cleavage of the 19-methyl group [3]. The latter method is more expedient, since it provides for a high yield of 19-norsteroids.

This communication describes the preparation of the anabolic preparation, the phenylpropionate of 19-nortestosterone (IV), from 3,3-dimethoxy-19-norandrost-5(10)-en-17-one (I) [3], the intermediate compound in the synthesis of 19-norsteroids:



3,3-Dimethoxy-19-norandrost-5(10)-ene-17β-ol (II), obtained by reduction of (I) with sodium borohydride, was treated with β-phenylpropionyl chloride to give the corresponding ester (III) in quantitative yield. Removal of the dimethyl ketal protecting group and migration of the double bond from position 6(10) to position 4 occur upon reaction of (III) with mineral acids. Upon studying this reaction using thin-layer chromatography, it was found that migration of the double bond proceeds significantly more slowly than hydrolysis of the dimethyl ketal, and several hours at room temperature are required for complete transformation of the unconjugated ketone (V)* into conjuated (IV). On the other hand, increasing the length of the reaction or

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*The phenylpropionate of 19-norandrost-5(10)-en-3-on-17-ol used in the chromatography as a reference spot was obtained by hydrolysis of ester (III) with oxalic acid [4]. This compound had mp 90-91.5°C (from methanol), $[\alpha]_D + 115°$ (c 1%, dioxane) and $R_f$ 0.61.

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increasing the temperature causes significant hydrolysis of the ester group in position 17, which is indicated by the appearance of a spot on the chromatogram at the level of 19-nortestosterone. In an optimum variation, the hydrolysis of (III) upon reaction with hydrochloric acid in acetone was carried out at a reduced temperature over 5 h. During this, (IV) (mp 95-96°) was obtained in a yield of 87%. Upon treatment with sulfuric and perchloric acids, migration of the double bond in (III) occurs more slowly than upon reaction with hydrochloric acid, while perchloric acid causes significant hydrolysis of the ester group.

## EXPERIMENTAL

Thin-layer chromatograms on silica gel were obtained in a system of ethyle acetate-cyclohexane (1:2) with concentrated sulfuric acid as the indicator.

3,3-Dimethoxy-19-norandrost-5(10)-en-17β-ol (II). To a solution of 6.24 g of (I) in 120 ml of methanol with stirring over 10 min was added 1.1 g of powdered 87% sodium borohydride. The reaction mixture was stirred for $1^{1/2}$ h at room temperature, then 63 ml of water and 63 ml of benzene were added. The benzene layer was separated and the aqueous layer was extracted with benzene. The combined benzene solutions were washed with water, dried with sodium sulfate, and evaporated in a vacuum at a bath temperature of 40-50°. We obtained 6.26 g of (II) having $R_f$ 0.46; the compound is unstable. It was used for the next step without crystallization and purification

β-Phenylpropionate of 3,3-Dimethoxy-19-norandrost-5(10)-en-17β-ol (III). To a solution of 6.26 g of (II) in 46.5 ml of anhydrous benzene and 12.5 ml of pyridine at 0° and with energetic stirring was added dropwise over 10 min a solution of 4.3 g of phenylpropionyl chloride in 6 ml of benzene. The mixture was stirred for $1^{1/2}$ h at room temperature, then cooled in an ice bath and 2.65 ml of diethylaminoethanol was added. The mixture was stirred for $1^{1/2}$ h and 30 ml of water was added. The benzene layer was separated and the aqueous layer was extracted with benzene. The combined benzene solutions were washed with a solution of diluted (1:10) hydrochloric acid, a 1.6% solution of sodium hydroxide, again with a solution of hydrochloric acid and water, dried with sodium sulfate, and evaporated to dryness in a vacuum. The residue was triturated with 8 ml of cold methanol, filtered, washed with methanol, and dried in a vacuum desiccator. We obtained 8.47 g of (III), mp 114.5-115.5°, $R_f$ 0.76. An analytically pure sample after two recrystallizations from methanol had mp 117-118° and $[\alpha]_D$+82.5° (c 1%, dioxane). Found, %: C 76.94; H 9.11. $C_{29}H_{40}O_4$. Calculated, %: C 76.95; H 8.91.

Phenylpropionate of 19-Nortestosterone (IV). A. From the β-Phenylpropionate of 3,3-Dimethoxy-19-norandrost-5(10)-en-17β-ol (III). To a solution of 13.3 g of (III) in 130 ml of acetone cooled to 0-4° with stirring was added 30 ml of a 3 N solution of hydrochloric acid. The solution was stirred for 3 h at 4-6°, then the ice bath was removed and the mixture was stirred an additional 2 h. At the end of the reaction was added 25 ml of benzene and the organic layer was separated. The aqueous layer was extracted with benzene. The combined benzene solutions were washed with water and a saturated sodium bicarbonate solution, again with water, and dried with sodium sulfate. The benzene was evaporated in a vacuum at a bath temperature of 40°. The residue was triturated with 10 ml of cold hexane, filtered, and washed on the filter with 5 ml of hexane. We obtained 11.54 g of a crystalline product having mp 93.5-95°, $R_f$ 0.46. The material was recrystallized from 14 ml of methanol and dried in a vacuum desiccator. We obtained 10.44 g of (IV), mp 95.5-96.5°, $[\alpha]_D$+49° (c 1%, dioxane); literature data [2], mp 95-96°, $[\alpha]_D$+58° (chloroform).

B. From 19-Nortestosterone. We hydrolyzed 2 g of (II) with hydrochloric acid in acetone [3] and obtained 1.43 g of 19-nortestosterone having mp 121-122° (from a mixture of ether and hexane) and $R_f$ 0.16. A solution of 0.7 g of 19-nortestosterone in 7 ml of dry benzene and 1.7 ml of pyridine was heated to 60° and with stirring 0.56 g of phenylpropionyl chloride was added. The mixture was heated for 3 h at 60°, cooled, and 3.3 ml of diethylaminoethanol was added. The mixture was stirred for 1 h and water was added. The product was extracted with benzene to give 0.86 g of a crystalline material which after recrystallization from 2 ml of methanol gave 0.64 g of (IV), mp 93.5-94.5°.

## LITERATURE CITED

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