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SYNTHESIS AND PROPERTIES OF DIHYDROTESTOSTERONE ESTERS OF N-(β-CARBOXYPROPIONYL)-d,ℓ-TRYPTOPHAN

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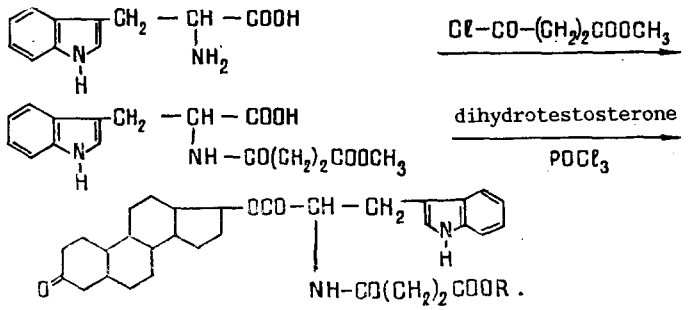
UDC 547.476.2:547.757:547.92:615.011.5:615.256.4

Dihydrotestosterone is widely used in the treatment of diseases of the heart and of hormone-dependent tumors and for the normalization of the lipid metabolism [1-3]. The esterification of the hydroxy group at C-17 prolongs the action of this androstane hydroxyketone and, depending on the radical of the acylating acid, may change its physiological action. The esterification of dihydrotestosterone is usually performed with acid chlorides, when, together with the dihydrotestosterone ester, a bis-ester is obtained with the formation of a C-3 enol acylate [5].

To obtain biologically active substances the dihydrotestosterone esters of some N-succinylamino acids are of interest. Esterification has been performed either at the carboxy group of the amino acid or at the carboxy group of the succinic acid residue [6].

A study of the products of the esterification of dihydrotestosterone by N-(β-carboxypropionyl)-d,ℓ-tryptophan showed a change in its biological activity as a function of the esterifying carboxy group in the N-(β-carboxypropionyl)-d,ℓ-tryptophan.

The synthesis of dihydrotestosterone esters of N-(β-carboxypropionyl)-d,ℓ-tryptophan derivatives was carried out by a method similar to that of [6], using the scheme:



where I – R = CH_3, II – R = H.

TABLE 1. Androgenic and Anabolic Activities of Dihydrotestosterone Esters of N-(β-Carboxypropionyl)-d,ℓ-tryptophan Derivatives

Substance	s. v. (increase)		m. l. a. (increase)	
	[1] μg	[2] μg	[1] μg	[2] μg
Dihydrotestosterone	17,0	43,7	23,8	29,1
Dihydrotestosterone ester of N-(β-methoxycarbonylmpropionyl)-d,ℓ-tryptophan	19,6	39,0	—2,5	— 1,3
Dihydrotestosterone ester of N-(β-carboxypropionyl) d,ℓ-tryptophan	25,2	45,6	—3,2	— 6,0

Khar'kov Scientific-Research Institute of Endocrinology and Hormone Chemistry. Translated from Khimiya Prirodnykh Soedinenii, No. 2, pp. 310-312, March-April, 1988. Original article submitted April 28, 1987; revision submitted October 5, 1987.

0009-3130/88/2402-0267$12.50

To synthesize N(β-carboxypropionyl)-d,ℓ-tryptophan we obtained the acid chloride of monomethyl succinate as described in [7]. The reaction of N-(β-methoxycarbonylpropionyl)-d,ℓ-tryptophan with dihydrotestosterone in the presence of phosphorus oxychloride gave the dihydrotestosterone ester of N-(β-methoxycarbonylpropionyl)-d,ℓ-tryptophan (I) from which, by partial hydrolysis with sodium hydrogen carbonate in aqueous methanol, it was possible to isolate the dihydrotestosterone ester of N-(β-carboxypropionyl)-d,ℓ-tryptophan (II).

The determination of the androgenic and anabolic activities of these compounds and the calculation of their anabolic indices were performed by the methods generally adopted [8, 9]. The experiments were carried out on male rats of the Wistar population 21 days after they had been castrated at the age of 70 days (50-60 g) (the castration and decapitation of the animals were performed under ether narcosis). The substances tested were administered every day for nine days [10]. As a prototype we used a standard solution of dihydrotestosterone in bone oil in suitable amount. Intact rats receiving the same volume of solvent were used as controls.

The results on the biological activity of the compound synthesized are given in Table 1.

While the dihydrotestosterone esters of N-succinyl derivatives of amino acids in which the dihydrotestosterone was acylated by the carboxyl of the succinic acid residue had androgenic and anabolic activities not less than those of dihydrotestosterone, and in some cases exceeding it, as we see from Table 1, on acylation by the carboxy group of the amino acid the androgenic activity basically did not change and was equal to that of dihydrotestosterone, while instead of a growth of the anal muscle it decreased in size, i.e., the anabolic activity had a negative sign.

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