ATISINE CHLORIDE AND ISOATISINE FROM Aconitum coreanum and A. rotundifolium

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The presence in the plants A. coreanum (Levl). Rapaics and A. rotundifolium Kar. et Kir. of three unidentified bases [1, 2], and also of the isolation from A. coreanum of the alkaloids acorine and of Guan-Fu base Z [3] have been reported previously [3]. The epigeal parts of these plants, collected in the flowering phase in Maritime Territory (1950) and in the Santash pass (Tien Shan) (1300 g) were moistened with a 5% solution of sodium carbonate and extracted with chloroform. The total amounts of alcohols, obtained by the method described in [3], were 0.8 and 0.7% on the weights of the dry raw material of A. coreanum and A. rotundifolium respectively.

Continuing the chromatographic separation of the mixture of alkaloids from A. coreanum [3], from chloroform–methanolic eluates we obtained substance (I) with mp 297-299°C (decomp.), which was isolated in a similar manner from A. rotundifolium. The substance dissolved readily in water and methanol, did not dissolve in the usual organic solvents, gave the reaction for alkaloids with tungosilic acid and for halogen with an aqueous solution of silver nitrate. Under the conditions of mass spectrometry, (I) split out a molecule of HCl, which is characteristic for quaternary bases [4]; the peak of the molecular ions corresponding to the tertiary base was observed at m/z 343. The IR spectrum of (I) showed absorption bands at (cm^{-1}) 3390, 3320, 3270, 2935, 2870, 1685, 1665, 1455, 1371, 1225, 1075, 1005, 900.

In the PMR spectrum of (I) (taken on a BS-567 A instrument, 100 MHz, CD_3OD, 0 – HMDS) a one-proton broadened singlet was observed at 8.65 ppm (H-20), a two-proton singlet at 5.00 ppm (2 H-17), two-proton multiplets at 4.14 and 3.90 ppm, and a three-proton signal at 3.75-3.56 ppm (2 H-19, -21, -22, and H-15), and also a three-proton singlet at 1.03 ppm (18-CH_3). Signals at 8.65 and 5.00 ppm and an absorption band at 1685 cm^{-1} were absent from the PMR and IR spectra of the tetrahydro derivative, which had M^+ 347 (mass spectrometry) and was obtained by the hydrogenation of (I) in the presence of a platinum catalyst. The facts given above are similar to those for atisine chloride [5, 6].

When the combined strongly basic fractions from A. coreanum [3] and A. rotundifolium were chromatographed, hexane–ether eluates yielded a base (II) with mp 152-153°C (from hexane–acetone), M^+ 343 (mass spectrometry); and chloroform–methanol elutates yielded (I). The spectral characteristics of (II) corresponded to those of the alkaloid isoatisine [5, 6]. A direct comparison of (I) and (II) with authentic samples of atisine chloride and of isoatisine, respectively, isolated from Aconitum zeravschanicum [7] confirmed their identities. It must be mentioned that the strongly basic fraction, mainly containing these alkaloids, amounted to 0.1% of the weight of the dry epigeal part of A. coreanum and to 0.2% of that of A. rotundifolium. The alkaloids artisine chloride and isoatisine have not been isolated from A. coreanum growing in China [8, 9].

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

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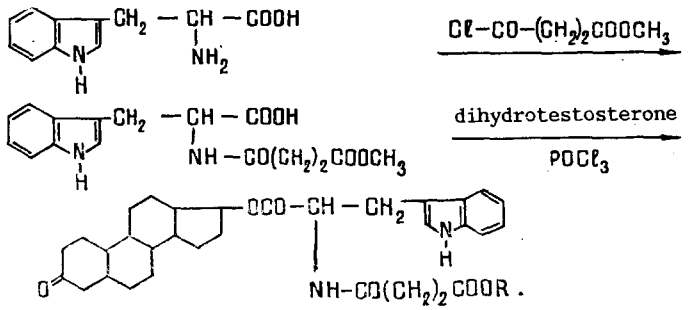
Dihydrotestosterone is widely used in the treatment of diseases of the heart and of hormone-dependent tumors and for the normalization of the lipid metabolism [1-3]. The esterification of the hydroxy group at C-17 prolongs the action of this androstane hydroxyketone and, depending on the radical of the 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

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