THE STRUCTURE OF HAPLAMIDE AND THE SYNTHESIS OF HAPLOBUCHARINE

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We have previously reported the isolation of skimmianine and haplatine from Haplophyllum latifolium [1]. Continuing the separation of the combined alkaloids by chromatography, we have obtained evoxine (0.033% on the weight of the dry plant) [2], and a base (0.001%) with mp 105-106°C which proved to be 7-isopentenyloxy-γ-fagarine [3], isolated from this plant for the first time.

We have also investigated the alkaloids of the epigeal part collected in the period of its withering (June 14, 1974) from the same growth site [1]. An evaporated aqueous methanolic extract from the plant (29 kg) was washed with ether to remove the fatty fraction (A) and was separated into basic, acidic, and neutral fractions. Treatment of the basic fraction with acetone gave a crystalline mixture, the chromatography of which on alumina and silica gel yielded skimmianine (0.14%), haplatine (0.001%), and evoxine (0.04%) [2]. From the acidic fraction we isolated haplopine (0.001%) [2], and from the neutral fraction a substance (0.07%) with mp 139-140°C, M^+ 414, identified by comparison with an authentic sample as β-sitosterol [4]. This is the first time that β-sitosterol has been found in H. latifolium. Chromatography of fraction A gave a new alkaloid (I) (0.003%), which we have called haplamide.

Haplamide is a white crystalline substance with the composition $C_{18}H_{20}N_2O_2$, mp 172-173°C (ethanol), $[\alpha]_D^{2}$ ± 0° (c 0.1; pyridine), not possessing basic properties, sparingly soluble in organic solvents, and insoluble in water and dilute acids and alkalis. The UV spectrum of (I) (ethanol) has one maximum at 224 nm (log ε 4.00). The IR spectrum shows absorption bands at 3430 and 1640 cm^{-1} ($-NH-CO-$) and 1587, 1550, 775, and 730 cm^{-1} (monosubstituted benzene ring).

The mass spectrum [m/e (%)], shows the peak of the molecular ion at 296 (3), confirming the composition and also peaks at 191 (6, M−105), 175 (11, M−121), 162 (9, M−134), 148 (6 M−148), 134 (11, M−162), 105 (100, $C_6H_5-C\equiv\overset{+}{O}$) and 77 (43, $C_6H_5^{+}$). The NMR spectrum (CF_3COOH, τ scale) shows that the compound is symmetrical. In the spectrum there are four signals with an intensity ratio of 1 : 5 : 2 : 2 at 1.75 (broadened signal, 2 NH, 2.50-2.95 (multiplet, 2 C_6H_5), 6.62 and 8.43 ppm (broadened signals, $NH-(CH_2)_4-NH$). The presence of two NH groups was confirmed by a displacement of the peak of the molecular ion by two mass units when haplamide was deuterated.

The facts given permitted us to put forward for (I) the structure of N,N'-dibenzoyltetramethylenediamine (dibenzoylputrescine) [5]. A direct comparison of haplamide with a sample of dibenzoylputrescine [6] that we synthesized showed that the substances were identical. This is the first time that alkaloid (I) has been found in nature.

The structure proposed on the basis of spectral characteristics that was put forward for haplobucharine, which we isolated from H. bucharicum [7] is now confirmed by synthesis from haplofoline [2] and 4-chloro-2-methylbut-2-ene by heating these substances in dry acetone solution in the presence of anhydrous potassium carbonate.

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EVODINE AND EVOXOIDINE FROM Haplophyllum perforatum

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We have continued a study of the alkaloid composition of the epigeal part of the plant H. perforatum growing in the Dzhungarian Ala-Tau, Kazakh SSR [1].

The ether-soluble part of the main fraction after the separation of evoxine was chromatographed on a column of alumina. From the ethereal eluate we isolated two bases with mp 152-153°C (from acetone), $[\alpha]_D -60°$ (c 0.3; ethanol) (I) and 135-136°C (from acetone) (II), having the same composition – $C_{18}H_{19}NO_5$, mol. wt. 329 (mass spectrometrically). The substances dissolve readily in acid and chloroform, more sparingly in acetone and ether, and are insoluble in water and alkalis.

The UV spectrum of (I) is similar to the spectra of the furanoquinoline alkaloids of the skimmianine type [2]. Its IR spectrum has the absorption band of a hydroxy group at 3320 cm^{-1}, the presence of which is confirmed by the preparation of acetyl derivative (III) with mp 126-127°C (from cyclohexane), mol. wt. 371 (mass spectrometrically), ν_{max} 1745 cm^{-1}. The NMR spectrum of (I) ($CDCl_3$, τ scale) shows signals at 2.10 and 2.87 ppm (doublets, 1 H each; J = 9.4 Hz; ortho protons of a benzene ring); 2.48 and 3.04 ppm (doublets, 1 H each; J = 3 Hz, α- and β-protons of a furan ring); 4.91 and 5.07 (singlets, 1 H each; protons of a terminal methylene group); 5.66 and 5.91 ppm (singlets, 3 H each; 2 OCH_3); 5.46-6.06 ppm (multiplet, 3 H), 6.53 ppm (broadened signal, 1 H; OH); and 8.21 ppm (singlet, 3 H; $CH_3-C=$).

A comparison of the facts given with literature information furnishes grounds for considering that alkaloid (I) is evodine, which has been isolated from the plant Evodia xanthoxyloides F. Muell. (family Rutaceae) [3]. This was confirmed by the mass spectrum of (I) and the NMR spectrum of (III). The mass spectrum of (I) has the peaks of ions with m/e 258 (16%), 245 (50%), 244 (25%), 227 (100%), and 216 (25%), which are characteristic of all O-isoprenoid derivatives of haplopine, and the peak of an ion with m/e 71 (7%) having the structure $CH_2=C(CH_3)-CH=\overset{+}{O}H$. In the NMR spectrum of (III), unlike that of (I), the protons of the side chain geminal to the oxygen-containing substituent appear clearly at 4.44 ppm (triplet, 1 H; J = 5.5 Hz; $HO-\underline{CH}-CH_2O$) and 5.76 (doublet, 2 H; J = 5.5 Hz; $CH-\underline{CH_2}-O$).

The mass spectrum of (II) shows strong peaks of ions with m/e 329 (M^+; 54%), 258 (47%), 245 (17%), and 244 (100%). These characteristics, and also the melting point of (II) coincide with the properties of evoxoidine, isolated from E. xanthoxyloides [5]. A mixed melting point of (II) with a sample of evoxoidine obtained from evoxine gave no depression of the melting point.

This is the first time that evodine and evoxoidine have been detected in plants of the genus Haplophyllum.

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