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ALKALOIDS FROM THE PLANT *Haplophyllum griffithianum*

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Alkaloids from plants of the genus *Haplophyllum* (Rutaceae) exert a calming action on the central nervous system and have low toxicity [1]. Several of the alkaloids exhibit analgesic, anticonvulsive, soporific, sedative [2, 3], and estrogenic [4, 5] in addition to anticancer activity [6].

Furthermore, alkaloids of this genus are used in folk medicine to treat animals for helminths, diseases of the gastrointestinal tract, and respiratory organs of animals and humans. Rational use of pastures with incorporation of *Haplophyllum* species can facilitate the revitalization of animals and increase the production of the herd [7]. This all indicates that studies of plants of the genus *Haplophyllum* are promising.

H. griffithianum Boiss. is a perennial herbaceous plant indigenous to mountainous regions of Central Asia (southwest Pamir-Alai) and Afghanistan [8].

We studied for the first time the alkaloid composition of the previously unstudied plant *H. griffithianum* collected during flowering in Surkhandarin Oblast (Nilu village). Ground air-dried roots (370 g) and aerial part (580 g) were extracted with MeOH. The MeOH extracts were condensed. Basic, acidic, and neutral fractions were separated by the known procedure to afford $CHCl_3$ total alkaloids from the aerial part (2.32 g, 0.4% of dry aerial part mass) and roots (2.15 g, 0.58% of dry root mass).

Total alkaloids from the aerial part were worked up with acetone to isolate dubinine (**1**, 0.32 g). The dubinine mother liquor was chromatographed over a column of silica gel to isolate dubinine (**1**), dictamnine (**2**), skimmianine (**3**), dubinidine (**4**), dubamine (**5**), and *N*-methylhaplofoline (**6**).

Chromatographic separation of total alkaloids from roots of *H. griffithianum* over a column of silica gel isolated dictamnine and skimmianine.

Alkaloids **2**, **3**, and **4** were identified based on TLC and mixtures with authentic samples obtained previously from *H. perforatum* [10].

Pure compounds **1**, **5**, and **6** were identified based on UV, IR, PMR, ^{13}C NMR, and DEPT data as dubinine, dubamine, and *N*-methylhaplofoline.

Dubinine (1), mp 185–186°C (EtOH), $C_{17}H_{19}NO_5$. UV spectrum (EtOH, λ_{max}, nm): 229, 282, 302 (log ε 4.86, 4.12, 4.00). IR spectrum (mineral oil, λ_{max}, cm^{-1}): 3262 (OH), 1719 ($OCOCH_3$), 1627, 1584, 1516 (aromatic).

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz, 0 = HMDS): 1.24 (3H, s, CH_3), 2.08 (3H, s, CH_3COO), 4.10 (3H, s, 4-OCH_3), 3.83 (1H, dd, J = 15.3, 6.9, H-3a), 3.49 (1H, dd, J = 15.3, 9.3, H-3b), 4.39 and 4.44 (1H each, d, J = 11.0, CH_2–O), 4.86 (1H, dd, J = 9.3, 6.9, H-2), 5.68 (1H, br.s, OH), 7.02 (1H, td, J = 8.3, 1.3, H-7), 7.31 (1H, td, J = 8.3, 1.3, H-6), 7.43 (1H, d, J = 8.3, H-8), 7.56 (1H, dd, J = 8.3, 1.3, H-5).

^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 171.28 (CO), 168.81 (C-2), 158.91 (C-4), 146.55 (C-8a), 129.57 (C-7), 125.74 (C-6), 122.12 (C-5), 123.28 (C-8), 119.66 (C-4a), 101.42 (C-3), 83.52 (C-2a), 72.81 (C-9), 68.78 (C-10), 58.35 (4-OCH_3), 28.44 (C-3a), 21.34 ($COCH_3$), 20.88 (C-11).

Dubamine (5), mp 93–95°C (EtOH), $C_{16}H_{11}NO_2$. UV spectrum (EtOH, λ_{max}, nm): 221, 226, 337, 308 (log ε 4.35, 5.34, 3.18, 4.84). Changed upon adding acid.

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 8.10 (1H, d, J = 8.6, H-4), 8.05 (1H, d, J = 8.2, H-5), 7.72 (1H, d, J = 8.6, H-3), 7.64 (1H, td, J = 8.2, 1.5, H-6), 7.44 (1H, td, J = 8.2, 1.2, H-7), 7.74 (1H, dd, J = 8.2, 1.5, H-8), 7.67 (1H, d, J = 1.7, H-2′), 6.88 (1H, d, J = 8.2, H-5′), 7.59 (1H, dd, J = 8.2, 1.7, H-6′), 5.97 (2H, s, OCH_2O).

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^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 157.01 (C-2), 149.16 (C-8a), 148.72 (C-4′), 148.49 (C-3′), 137.04 (C-4), 134.45 (C-1′), 130.00 (C-7), 129.86 (C-8), 127.75 (C-5), 127.33 (C-4a), 126.40 (C-6), 122.09 (C-6), 118.97 (C-3), 108.81 (C-2′), 108.25 (C-5′), 101.74 (O–CH_2–O).

The spectral characteristics of **1** and **5** agreed with those of dubinine and dubamine that were isolated previously from *H. dubium* [9].

***N*-Methylhaplofoline (6)**, mp 122–123°C, $C_{15}H_{17}NO_2$, $[M]^+$ 243 (mass spectrum). UV spectrum (EtOH, λ_{max}, nm): 237.6, 259.0, 316.0, 328.0. These spectral data were characteristic of dihydropyrano-4-quinolone compounds. The absorption spectrum did not change upon adding base.

IR spectrum (mineral oil, λ_{max}, cm^{-1}): 3402, 2976, 2948, 1602, 1531, 1447, 1354, 1285, 1244, 1182, 1165, 1115, 932, 892.

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 8.37 (1H, dd, J = 8.0, 1.7, H-5), 7.54 (1H, td, J = 8.0, 7.84, 1.7, H-7), 7.34 (1H, d, J = 8.0, H-8), 7.24 (1H, td, J = 8.0, 1.0, H-6), 3.60 (3H, s, N–CH_3), 2.68 (2H, t, J = 6.8, 2H-10), 1.78 (2H, t, J = 6.8, 2H-9), 1.38 (6H, s, 2 × CH_3).

^{13}C NMR spectrum (100 MHz, $CDCl_3$, δ, ppm): 176.78 (C-4), 168.74 (C-2), 155.34 (C-3), 139.28 (C-8a), 131.47 (C-7), 126.71 (C-6), 122.60 (C-8), 115.87 (C-4a), 114.49 (C-8), 80.32 (C-11), 32.32 (C-9), 30.28 (N–CH_3), 26.92 (2 × CH_3), 16.84 (C-10).

A study of the UV and NMR spectral data of **6** showed that the alkaloid was the N–CH_3 derivative of haplofoline [10], which was found earlier in the plant *Almeidea guyanensis* (Rutaceae) [11]. All isolated alkaloids **1**–**6** were observed for the first time in *H. griffithianum*.

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