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NEW ALKALOIDS FROM *HAPLOPHYLLUM GLABRIUM*

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Key Word Index—*Haplophyllum glabrinum*; Rutaceae; furoquinoline alkaloids; NMR.

Abstract—Four furoquinoline alkaloids have been characterized from the roots of *Haplophyllum glabrinum* of which three are new compounds. Their structures were determined by spectroscopic methods, including ^{1}H NMR NOE difference spectroscopy.

INTRODUCTION

The occurrence of dihydro- and tetrahydrofuroquinoline alkaloids seem to be a characteristic of *Haplophyllum* species [1] belonging to the Rutaceae. In our former communication, two of these alkaloids were reported from *H. glabrinum* [2]. Continuing the isolation work three other compounds (**1a**, **1b**, **2**) were obtained besides a furoquinoline derivative (**3**). This is the subject of the present work.

RESULTS AND DISCUSSION

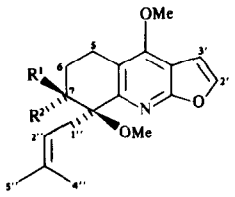
The compounds **1a**, **1b** and **2** have characteristic UV spectra for tetrahydro-, as well as, dihydrofuroquinoline derivatives [3]. Their substituents, one hydroxyl, two methoxyls and one prenyl group, seem to be identical on the basis of ^{1}H NMR and mass spectral data (Tables 1 and 2). The protons of the $-CH_2-CH_2-CH(R)-$ moiety in **1a** and **1b** appear at various δvalues. The coupling constants for the –CH(R)– proton are also different in the two compounds. Clear NOEs were observed between 8-OMe and H-7 in **1a**, as well as H-7 and H-2″ in **1b**, proving the *cis* relative configuration of these protons, respectively (Table 3). Spectral data of haplophyllidine, reported by Seitanidi *et al.* without assignment of relative configuration [4], are identical with those of **1a**, consequently their stereochemistry must be the same.

Compound **2** can be regarded as dehydroderivative of **1** according to its spectral data (Tables 1 and 2). In the ^{1}H NMR spectrum the resonances of one proton intensity each (appearing at δ6.98 and 6.72 ppm, respectively), and their couplings are in agreement with a 5,6-unsaturated structure. The 4-position of the methoxy group (δ4.27 ppm) could easily be proved by NOEDS experiments [5] (Table 3). The very small amount of material available, as well as, its relative instability prevented us determining directly the relative configuration of C(7) and C(8), but according to the very closely similar chemical shift of 8-OMe to that of haplophyllidine [4] (and **1a** as well) one may assume the isolated dehydroderivative to be the same diastereoisomer.

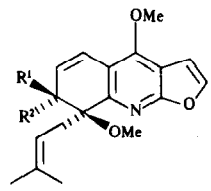
The ^{1}H NMR data of the fourth compound (**3**) show it, in agreement with mass spectral data, to be a 4,7,8-trisubstituted furoquinoline alkaloid (Table 1) [6–8]. The 2″ and two 3″ protons produce an AXX′-like spin system, while the 4″ and 5″ methyl protons of the 1,1-dimethylallyl side chain resonate at δ1.6 ppm [9, 10]. On the basis of NOE measurements (Table 3) the methoxyl group (δ4.46 ppm) can be placed at C(4), the 1,1-dimethylallyl substituent at C(8) and the OH group (δ_{OH} = 8.27 ppm) at C(7).

1,1-Dimethylallyl side-chains occur in many of the coumarin derivatives found in plants of the Rutaceae [11], but to the best of our knowledge only one compound, buhapine, among the quinoline alkaloids has earlier been reported having this substituent [12].

For the new alkaloids **1b**, **2** and **3**, the trivial names dihydroperfaminole, perfaminole and 8(1″,1″-dimethylallyl)-confusameline are proposed, respectively.



	R¹	R²
1a	H	OH
1b	OH	H



	R¹	R²
2	H	OH

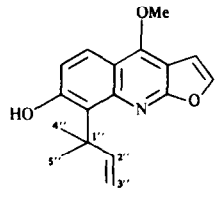


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Table 1. ^{1}H NMR spectral data of compounds **1a**, **1b**, **2** and **3** (250.13 MHz, $CDCl_3$, TMS as int. standard)

H	Haplophyllidine [4]	1a	1b	2	3
5	1.6 2.9 *m*	2.8 *m*	2.95 *dt* (17.1; 4.6; 4.6)	6.72 *dd* (10.1; 2.5)	7.66 *d* (9.0)
		2.75 *m*	~ 2.0 *m*		
6	1.6–2.9 *m*	2.3 *m*	2.47 *ddd* (18.0; 9.6; 8.3)	5.94 *dd* (10.1; 2.3)	7.42 *d* (9.0)
		2.0 *m*	~ 2.0 *m*		
7	4.26 *dd* (6.1; 3.0)	4.21 *dd* (6.0; 2.7)	3.84 *m*	4.61 *dd* (2.5; 2.3)	—
2′	7.58 *d* (2.8)	7.56 *d* (2.6)	7.57 *d* (2.6)	7.60 *d* (2.6)	7.62 *d* (2.6)
3′	6.97 *d* (2.8)	6.95 *d* (2.6)	6.95 *d* (2.6)	6.98 *d* (2.6)	7.10 *d* (2.6)
1″		3.28 *br dd* (16.1; 6.3)	3.33 *bdd* (13.5; 4.7)	3.28 *dd* (13.5; 6.6)	—
		2.67 *dd* (16.1; 7.8)	2.77 *dd* (13.5; 9.4)	2.75 *dd* (13.5; 9.6)	
2″	5.35	5.35 *m*	4.68 *m*	5.05 *br dd* (9.6; 6.6)	6.36†
3″	—	—	—	—	5.05†
4″, 5″	1.75 *s*	1.73 *br s*	1.69 *br s*	1.72 *br s*	1.63 *s*
	1.70 *s*	1.67 *br s*	1.55 *br s*	1.61 *br s*	1.63 *s*
4-OMe	4.28 *s*	4.27 *s*	4.27 *s*	4.27 *s*	4.46 *s*
8-OMe	3.18 *s*	3.17 *s*	3.36 *s*	3.13 *s*	—

*Coupling constants of first order approximation (Hz, ±0.3 Hz) are in parentheses)

†AXX′ spin system

EXPERIMENTAL

Roots of *H. glabrinum* were collected in Iran. A voucher specimen is deposited in the herbarium of the Department of Pharmacy, Tehran University, Iran.

Extn and isolation procedures were as reported in ref. [2]. After chromatography 8 mg **1a**, 115 mg **1b**, 2 mg **2** and 18 mg **3** were obtained, respectively. TLC R_f values of alkaloids were determined on Kieselgel 60 F_{254} in toluene–EtOAc–HCO_2H (5:4:1) (A) and C_6H_6–EtOAc (4:1) (B).

^{1}H NMR measurements were run at 250 MHz. Samples were dissolved in $CHCl_3$ at room temp., the int. standard was TMS. In addition to routine 1D spectra, NOEDS [5] and H,H–COSY 2D expts [13] were carried out, the latter for unambigous identification of the coupling network.

Haplophyllidine (**1a**). TLC: R_f 0.38 (A), 0.51 (B); UV λ_{max}^{MeOH} nm: 261, 277 sh, 287 sh. ^{1}H NMR and MS data (Tables 1 and 2).

Dihydroperfaminole (**1b**). TLC: R_f 0.43 (A), 0.67 (B); UV λ_{max}^{MeOH} nm: 262, 278 sh, 288 sh. ^{1}H NMR and MS data (Tables 1 and 2).

Perfaminole (**2**). TLC: R_f 0.55 (A), 0.58 (B); UV λ_{max}^{MeOH} nm: 252, 318–336. ^{1}H NMR and MS data (Tables 1 and 2).

8(1″,1″-*Dimethylallyl*)-*confusameline* (**3**). Colourless needles from Me_2CO, mp: 118–119°; UV λ_{max}^{MeOH} nm: 253, 322, 338. ^{1}H NMR data (Table 1). MS *m/z* (% rel int.): 283 $[M]^+$ (82), 268

Table 2. Some characteristic mass spectral *m/z* fragments (% rel. int.) from alkaloids **1a**, **1b** and **2**

Fragment	1a	1b	2
$[M]^+$	317 (3)	317 (3)	315 (2)
$[M-15]^+$	302 (1)	302 (1)	300 (0.5)
$[M-31]^+$	286 (4)	286 (13)	284 (5)
$[M-47]^+$	270 (49)	270 (80)	268 (22)
$[M-69]^+$	248 (49)	248 (100)	246 (60)

Table 3. NOEDS experiments (250 MHz, $CDCl_3$) on alkaloids **1a**, **1b**, **2** and **3**

Compound	Irradiate	Observe	Relative % of enhancement
1a	8-OMe	H-7	+2.3
1b	H-7	H-2″	+3.4
2	4-OMe	H-3′	+10.0
3	4-OMe	H-3′	+9.2
	4-OMe	H-5	+2.2
	H-2″	H-6	+1.7
	H-2″	H-5	no effect
	H-2″	H-3′	−1.5

$[M-15]^+$ (100), 266 $[M-17]^+$ (13), 254 $[M-29]^+$ (31.5), 240 $[M-43]^+$ (21), 228 $[M-55]^+$ (54).

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