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CULARINE *N*-OXIDE ALKALOIDS FROM *CERATOCAPNOS HETEROCARPA*

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Key Word Index—*Ceratocapnos heterocarpa*; Fumariaceae; (+)-*cis*-sarcocapnine *N*-oxide; (+)-*cis*-cularine *N*-oxide; sarcocapnidine *N*-oxide.

Abstract—Two new alkaloids, (+)-*cis*-sarcocapnine *N*-oxide and (+)-*cis*-cularine-*N*-oxide, were isolated from *Ceratocapnos heterocarpa*. ^{1}H NMR spectroscopy clearly distinguishes the *cis*- and *trans*-series of cularine *N*-oxides. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

The genus *Ceratocapnos* has attracted phytochemical interest because it contains alkaloids related to the metabolism of the 1-benzylisoquinoline, crassifoline [1]. *Ceratocapnos claviculata* (syn. *Corydalis claviculata*) [2, 3] and *C. palaestinus* [4] have been found to contain mainly cularine alkaloids, while the third species, *C. heterocarpa*, is interesting from a biosynthetic point of view on account of the presence of cularine [5] and 1,2-berbine [6] alkaloids. From our studies on *C. heterocarpa*, we have reported the isolation and structural elucidation of both *trans*- and *cis*-cularidine *N*-oxides (**1** and **2**) that exhibit a different conformation at the dihydroxepine ring and a distinct chemical behavior [7]. In the present paper, we report the isolation of two new alkaloids, (+)-*cis*-cularine *N*-oxide (**3**) and (+)-*cis*-sarcocapnine N-oxide (**4**).

RESULTS AND DISCUSSION

High-resolution mass spectrometry provided the molecular formula $C_{20}H_{23}NO_5$ for the optically active compounds (+)-**3** and (+)-**4**. The non-phenolic nature of these alkaloids, with three methoxyl groups and five quarternary aromatic carbons bonded to oxygen in the ^{13}C NMR spectra, suggest a cularine-type structure. The aromatic protons in the ^{1}H NMR spectra revealed a 3′, 4′-oxygenation pattern at ring D for compound **3**, while positions 4′,5′- were substituted in compound **4**; consequently, the compounds must be derivatives of cularine and sarcocapnine, respectively. The *N*-oxide function was inferred from the presence of a peak at *m/z* 341 $[M-16]^+$ in the EI-mass spectrum and the low-field chemical shift exhibited in the ^{13}C NMR spectra by carbon atoms bonded to nitrogen (Table 1). Moreover, the large β-substituent effect [8] induced by the N–O oxygen over C-1 and C-3 suggested a *cis*-relationship between H-1 and the *N*-oxide function, while the high-field for the *N*-Me group indicated an axial position. The ^{1}H NMR of **3** and **4** exhibited the characteristic ABX-system for the protons at C-1 and C-α of cularines. The *trans*-diaxial relationship between H-1 and H-$\alpha\beta$, inferred from the large coupling constant ($J_{1-\alpha\beta} \simeq 12$ Hz) suggested a dihydroxepine ring in a twist-boat conformation.

The chemical shift for H-1 varied very little ($\Delta\delta \approx +0.1$ p.p.m.) from the free base (cularine and sarcocapnine) to the *cis*-*N*-oxides **3** and **4**; this can be ascribed to a conformational change at the dihydroxepine ring. The heterocyclic oxygen departs from H-1 and approaches H-$\alpha\beta$, which is shifted to low-field. Thus, the nitrogen configuration in cularine *N*-oxides can easily be established from the chemical shift for H-1 and H-$\alpha\beta$, $\delta \approx 5$ and $\delta \approx 3$, respectively, in the *trans*-series, and $\delta \approx 4.5$ and $\delta \approx 3.4$ in the *cis*-series. Thus, we

Table 1. Relevant ^{1}H and ^{13}C NMR data for cularine *N*-oxides

	trans	*cis*			
	1*	**2***	**3**†	**4**†	**5**‡
C-1	69.6	73.8	72.8	73.1	
C-3	59.4	66.0	63.9	64.9	
C-α	32.3	28.8	30.0	28.8	
N-Me	55.3	49.1	51.3	49.0	
H-1	4.94	4.46	4.57	4.43	4.64
H-$\alpha\alpha$	4.40	4.20	4.02	4.10	3.93
H-$\alpha\beta$	2.99	3.36	3.35	3.40	3.52
N-Me	3.34	3.08	3.11	3.08	3.13

*Ref [7].
†See Experimental.
‡Ref. [9].

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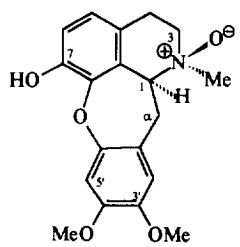
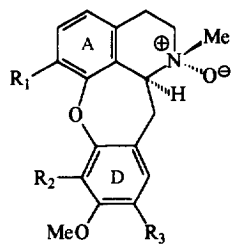


1



2 R_1= OH, R_2=H, R_3=OMe
3 R_1= OMe, R_2=H, R_3=OMe
4 R_1= OMe, R_2=OMe, R_3=H
5 R_1= OMe, R_2=OH, R_3=H

concluded that both **3** and **4** are the *cis-N*-oxides derived from (+)-cularine and (+)-sarcocapnine, respectively. In fact, (+)-**3** and (+)-**4** were obtained by oxidation of the corresponding free bases with *m*-CPBA. These results can be applied to (+)-sarcocapnidine *N*-oxide (**5**), isolated from *Sarcocapnos baetica* subsp. *integrifolia* [9], which was reported with no mention of its relative configuration. The ^{1}H NMR data obtained (Table 1) reveal that it belongs to the *cis*-series.

The parallelism between the aporphine and the cularine group of alkaloids has already been noted [3]. The greatest differences lie in the absence of naturally occurring 1,α-dehydrocularines; on the other hand, 6a,7-dehydroaporphines are of frequent occurrence [10]. Based on available knowledge, cularines can undergo quaternization at the nitrogen atom (either as *N*-oxide or as *N*-methyl cularinium salts), followed by β-elimination to the B-secocularine, as the preferential metabolic pathway. The chemical transformation of cularine *N*-oxides to the corresponding *N*-hydroxy-*nor*-secocularines has been reported [11] and proved to be particularly easy for the *trans-N*-oxides [7].

EXPERIMENTAL

General. Mps: uncorr. EIMS: direct inlet, 70 eV. FABMS: 2-hydroxyethyl disulphide as matrix. Silica gel 60 (70–230 mesh) was used for CC and silica GF_{254} for TLC. ^{1}H and ^{13}C NMR signals were measured at 200 and 50 MHz, respectively. Proton chemical shifts are referred to residual $CHCl_3$ (δ 7.24) and carbon chemical shifts to the solvent ($^{13}CDCl_3$, δ 77). ^{1}H and ^{13}C NMR signals were assigned from 2D COSY and DEPT expts.

Isolation. For a description of plant material and extraction conditions, see ref. [5]. The $CHCl_3$–MeOH-sol. part of the crude alkaloid extract was subjected to CC over silica gel. The fr. eluted with EtOAc–MeOH (1:4) was subsequently purified by CC and TLC to obtain the new compounds **3** (10 mg) and **4** (30 mg).

(+)-(1S,2S)-*Cularine* N-*oxide* (**3**). Amorphous powder. Mp 122–124°. $[\alpha]_D$ + 202° (MeOH; *c* 0.081). UV λ_{max} nm (log ε) MeOH: 230h (4.09), 284 (3.74). ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.87 (2H, *s*, H-5, H-6), 6.80 (1H, *s*, H-2′), 6.79 (1H, *s*, H-5′), 4.57 (1H, *dd*, J = 3.2 and 12.0 Hz, H-1), 4.02 (1H, *dd*, J = 3.2 and 12.0 Hz, H-$\alpha\alpha$), 3.90 (3H, *s*, OMe), 3.84 (3H, *s*, OMe), 3.81 (3H, *s*, OMe), 3.35 (1H, *t*, J = 12.0 Hz, H-$\alpha\beta$), 3.9–3.6 (2H, *m*, H-3α, H-3β), 3.11 (3H, *s*, NMe), 3.2–2.9 (2H, *m*, H-4α, H-4β). ^{13}C NMR (50 MHz, $CDCl_3$): δ 150.4, 150.3 (C-7, C-6′), 148.7, 146.7, 140.9 (C-8, C-3′, C-4′), 124.0 (C-5), 123.9, 123.0 (C-8a, C-4a), 118.3 (C-1′), 112.9, 112.7 (C-2′, C-6), 105.3 (C-5′), 72.8 (C-1), 63.9 (C-3), 56.4 (2 × OMe), 56.2 (OMe), 51.3 (NMe), 30.0 (C-α), 25.7 (C-4). EIMS *m/z* (rel. int.): 357 $[M]^+$ (2), 341 $[M-16]^+$ (40), 326 $[M-16-15]^+$ (100), 298 $[M-59]^+$ (23). FABMS, *m/z*: 358 $[M+H]^+$. HRMS *m/z*: 357.1581 ($[M]^+$, calcd. for $C_{20}H_{23}NO_5$: 357.1576).

(−)-(1S,2S)-*Sarcocapnine* N-*oxide* (**4**). Amorphous powder. Mp 110–114°. $[\alpha]_D$ + 174° (MeOH; *c* 0.065). UV λ_{max} nm (log ε) MeOH: 230h (4.08), 284 (3.40). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.03 (1H, *d*, J = 8.5 Hz), 6.91 (1H, *d*, J = 8.5 Hz), 6.85 (1H, *d*, J = 8.5 Hz), 6.67 (1H, *d*, J = 8.5 Hz) 4.43 (1H, *dd*, J = 2.7 and 12.1 Hz, H-1), 4.10 (1H, *dd*, J = 2.7 and 12.1 Hz, H-$\alpha\alpha$), 3.91 (6H, *s*, 2 × OMe), 3.81 (3H, *s*, OMe), 3.40 (1H, *t*, J = 12.1 Hz, H-$\alpha\beta$), 3.9–3.7 (2H, *m*, H-3α, H-3β), 3.08 (3H, *s*, NMe), 3.2–2.9 (2H, *m*, H-4α, H-4β). ^{13}C NMR (50 MHz, $CDCl_3$): δ 153.2 (C-7), 150.8, 150.7 (C-6′, C-4′), 145.3, 141.1 (C-8, C-5′), 124.1, 123.9 (C-5, C-2′), 122.7, 122.4, 122.1 (C-4a, C-8a, C-1′), 113.6 (C-6), 109.4 (C-3′), 73.1 (C-1), 64.9 (C-3), 61.5, 56.5, 56.3 (3 × OMe), 49.0 (NMe), 28.8 (C-α), 25.9 (C-4). EIMS *m/z* (rel. int.): 357 $[M]^+$ (6), 341 $[M-16]^+$ (74), 326 $[M-16-15]^+$ (53), 308 (45), 298 $[M-59]^+$ (100), 178 (48), 60 (44). FABMS, *m/z*: 358 $[M+H]^+$. HRMS *m/z*: 357.1580 ($[M]^+$, calcd. for $C_{20}H_{23}NO_5$: 357.1576).

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