CULARINE N-OXIDE ALKALOIDS FROM CERATOCAPNOS HETEROCARPA

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Abstract—Two new alkaloids, (+)-cis-sarcocapnine N-oxide and (+)-cis-cularine N-oxide, were isolated from Ceratocapnos heterocarpa. 1H 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 C20H23NO5 for the optically active compounds (+)-3 and (+)-4. The non-phenolic nature of these alkaloids, with three methoxyl groups and five quaternary aromatic carbons bonded to oxygen in the 13C NMR spectra, suggest a cularine-type structure. The aromatic protons in the 1H 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 El-mass spectrum and the low-field chemical shift exhibited in the 13C 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 1H 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-αβ, inferred from the large coupling constant (J1-αβ ~ 12 Hz) suggested a dihydroxepine ring in a twist-boat conformation.

The chemical shift for H-1 varied very little (Δδ ~ 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-αβ, 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-αβ, δ = 5 and δ = 3, respectively, in the trans-series, and δ = 4.5 and δ = 3.4 in the cis-series. Thus, we

| Relevant 1H and 13C NMR data for cularine N-oxides |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| trans           | cis             |
| H-1             | C-1             | C-3             | C-α             | N-Me            |
| 4.94            | 69.6            | 59.4            | 32.3            | 55.3            |
| 4.40            | 73.8            | 66.0            | 28.8            | 49.1            |
| 4.43            | 72.8            | 63.9            | 30.0            | 51.3            |
| 4.64            | 73.1            | 64.9            | 28.8            | 49.0            |

*Ref [7].
†See Experimental.
‡Ref. [9].
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 (+)-sarcocapnidle N-oxide (5), isolated from Sarcocapnos baetica subsp. integrifolia [9], which was reported with no mention of its relative configuration. The 1H 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 1α-dehydrocularines; on the other hand, 6α,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-norsecocularines 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 GF254 for TLC. 1H and 13C NMR signals were measured at 200 and 50 MHz, respectively. Proton chemical shifts are referred to residual CHCl3 (δ 7.24) and carbon chemical shifts to the solvent (13C,δ 77). 1H and 13C NMR signals were assigned from 2D COSY and DEPT expts.

**Isolation.** For a description of plant material and extraction conditions, see ref. [5]. The CHCl3-MeOH-sol. part of the crude alkaloid extract was subjected to CC over silica gel. The ft. 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°. [α]D + 174° (MeOH; c 0.065). UV λmax nm (log ε) MeOH: 230h (4.08), 284 (4.30). 1H NMR (200 MHz, CDCl3): δ 7.03 (1H, d, J = 8.5 Hz), 6.91 (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-2), 3.91 (6H, s, 2×OMe), 3.40 (1H, t, J= 12.1 Hz, H-aft), 3.9–3.7 (2H, m, H-3a, H-3ft), 3.08 (3H, s, NMe), 3.2–2.9 (2H, m, H-4a, H-4ft). 13C NMR (50 MHz, CDCl3): δ 153.2 (C-7), 150.8, 150.7 (C-6', C-4'), 145.3 (C-5'), 141.1 (C-3'), 124.1, 123.9 (C-5'), 122.7, 122.4, 122.1 (C-4a-C-1', C-8a), 113.6 (C-6), 109.4 (C-3'), 73.1 (C-1), 64.9 (C-3), 61.5, 56.5 (3×OMe), 49.0 (NMe), 28.8 (C-3), 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), 298 [M-59] + (100), 178 (48), 60 (44). FABMS, m/z: 358 [M+H] +. HRMS m/z: 357.1580 ([M] +, calcd, for C20H23NO5: 357.1576).

(+)-(1S,2S)-Sarcocapnine N-oxide (4). Amorphous powder. Mp 110–114°. [α]D + 174° (MeOH; c 0.065). UV λmax nm (log ε) MeOH: 230h (4.08), 284 (4.30). 1H NMR (200 MHz, CDCl3): 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-αα), 3.90 (3H, s, OMe), 3.84 (3H, s, OMe), 3.81 (3H, s, OMe), 3.35 (1H, t, J = 12.0 Hz, H-aft), 3.9–3.6 (2H, m, H-3a, H-3ft), 3.11 (3H, s, NMe), 3.2–2.9 (2H, m, H-4a, H-4fl). 13C NMR (50 MHz, CDCl3): 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 C20H23NO5: 357.1576).

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