(+)-Bulbocapnine-*β*-*N*-oxide from *Glaucium fimbrilligerum*

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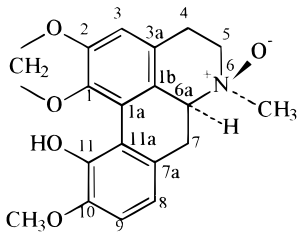
A new aporphine alkaloid, (+)-bulbocapnine-*β*-*N*-oxide (**1**), was isolated from *Glaucium fimbrilligerum*. Its structure and the stereochemistry at the *N*-oxide center were determined by spectroscopic methods and confirmed by synthesis.

Seven plant families, viz. Annonaceae, Berberidaceae, Magnoliaceae, Menispermaceae, Monimiaceae, Papaveraceae, and Ranunculaceae, are known to produce aporphine *N*-oxides.[1] Since some enthusiasm for the clinical use of *N*-oxides was engendered by their purported delayed-release properties, low toxicities, and low addictive properties compared with the corresponding tertiary alkaloids, further study of these compounds may help to answer the intriguing question as to what alkaloids are doing in plants.[2]

In the course of a study of the chemical constituents of the Iranian flora, we had occasion to investigate the alkaloids of *Glaucium fimbrilligerum* Boiss., one of the Iranian species belonging to the botanical family Papaveraceae.[3] The plant yielded the new aporphine (+)-bulbocapnine-*β*-*N*-oxide (**1**), $C_{19}H_{19}NO_5$.



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The 400 MHz ^{1}H-NMR spectrum of **1** in $CDCl_3$ exhibited the *N*-methyl signal at *δ* 3.45, while H-6a appeared as a doublet of doublets at *δ* 4.13. Difference NOE experiments was used to settle the stereochemistry at the *N*-oxide center. Irradiation of the *δ* 3.45 *N*-methyl singlet led to a 10.3% enhancement of the signal at *δ* 4.13 (H-6a). Conversely, irradiation at *δ* 4.13 produced a 5.4% enhancement of the *δ* 3.45 singlet (*N*-CH_3). It follows that the *N*-methyl group and H-6a must be syn to each other. The (+)-bulbocapnine has the *S* configuration, therefore the (+)-bulbocapnine-*β*-*N*-oxide belongs to the C-6a *S* absolute configuration as indicated in structure **1**.[4]

The new alkaloid was identical in all respects with the sample of bulbocapnine-*β*-*N*-oxide prepared by treatment of bulbocapnine with *m*-chloroperbenzoic acid.

Known alkaloids from the plant (1 kg) were bulbocapnine (4.7 g), protopine (3.9 g), isocorydine (2.4 g), *N*-methyllindcarpine (400 mg), salutaridine (100 mg), and thaliporphine (30 mg). The alkaloids were identified by comparison with data already reported (mp, IR, UV, ^{1}H-NMR, and MS).[5−7]

Experimental Section

General Experimental Procedures. Melting points were taken on a Kofler hot stage apparatus and are uncorrected. The UV spectra were recorded on a Perkin-Elmer 550 SE spectrophotometer. The IR spectra were obtained on a Perkin-Elmer 267 spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker FT-80 or a Varian FT-400 unity plus spectrometer. Chemical shifts are reported in ppm from TMS as an internal standard and are given in *δ* units. The mass spectra were run on a Finnigan TSQ-70 spectrometer at 70 eV. Column chromatography was carried out on Si gel 60 (230−400 mesh), column fractions were monitored via TLC over precoated sheets of Si gel 60 $HF_{254+366}$ (0.2 mm layer thickness) under UV (254 and 366 nm), and the alkaloids were detected by Dragendorff reagent.

Plant Material. *G. fimbrilligerum* Boiss. was collected in April 1996 from Gaduk of Abbasabad, north of Iran and identified by Dr. Gholamreza Amin, Department of Botany, Faculty of Pharmacy. A voucher specimen (no. 6507-T) is deposited in the herbarium of this Faculty.

Extraction and Isolation. The aerial parts of plant (1 kg) were extracted with methanol, and the solvent was evaporated. To the residue was added 400 mL of acetic acid solution (50%), and the mixure was filtered. The filtrate was extracted with petroleum ether (4 × 150 mL) to remove the colored material. The aqueous layer was made alkaline with ammonia (25%) and extracted with $CHCl_3$ (4 × 300 mL). The $CHCl_3$ extracts were pooled, dried (anhydrous Na_2SO_4), and filtered. The filtrate was evaporated to give a crude mixture of alkaloids (15 g). This residue was chromatographed over Si gel (500 g) in $CHCl_3$, and elution was achieved *via* $CHCl_3$ and $CHCl_3$−MeOH mixtures of increasing polarity. Combined fractions which were eluted with $CHCl_3$−MeOH (90:10) had one alkaloid which was crystallized from Me_2CO to give bulbocapnine-*β*-*N*-oxide (1) (72 mg).

Bulbocapnine-*β*-*N*-oxide (1): white needles, mp 153−155 °C; $[\alpha]^{20}_D$ +180° (*c* 0.65, MeOH); UV (MeOH) λ_{max} (log ϵ) 225 (4.19), 269 (3.86), 307 (3.57) nm; IR (KBr) ν_{max} 3380, 1050, 950 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) *δ* 6.88, 6.84 (each 1H, d, *J* = 8 Hz, H-9, H-8), 6.69 (1H, s, H-3), 6.14, 5.94 (each 1H, d, *J* = 1.2 Hz, OCH_2O), 4.13 (1H, dd, *J* = 2.8, 2.8 Hz, H-6a), 3.90 (3H, s, OCH_3), 3.45 (3H, s, NCH_3); ^{13}C-NMR ($CDCl_3$, 100.6 MHz) *δ* 148.1 (s, C-10), 147.2 (s, C-2), 142.7 (s, C-11), 141.7 (s, C-1), 126.9 (s, C-7a), 124.6 (s, C-3a), 122.1 (s, C-1b), 119.4 (d, C-8), 117.2 (s, C-11a), 114.3 (s, C-1a), 110.9 (d, C-9), 107.2 (d, C-3), 100.6 (t, OCH_2O), 71.4 (d, C-6a), 63.8 (t, C-5), 57.5 (q, NCH_3), 56.1 (q, OCH_3), 30.4 (t, C-7), 24.5 (t, C-4); EIMS *m*/*z* 341 $[M]^+$ (73), 325 (100), 310 (50), 295 (18), 282 (81), 165 (22), 152 (21).

Preparation of 1. (+)-Bulbocapnine (200 mg) was dissolved in $CHCl_3$ (5 mL), and *m*-chloroperbenzoic acid (200 mg)

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in $CHCl_3$ (5 mL) was added slowly. The ice-cold mixture was stirred for 1 h, brought to room temperature, diluted with $CHCl_3$, and washed with 10% aqueous $NaHCO_3$ to remove excess acid. The $CHCl_3$ solution was washed with a little H_2O, dried, filtered, and concentrated under vacuum to yield an amorphous solid, 199 mg (95%). Bulbocapnine-*β*-*N*-oxide was separated by TLC (solvent system: CCl_4−*n*-BuOH−MeOH−conc. NH_4OH, 40:30:30:10) to yield 160 mg (76%). It was identical with plant material (**1**) in terms of MS, ^{13}C- and ^1H-NMR spectra, TLC R_f value, mp, and specific rotation.

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