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A CYTOTOXIC β-CARBOLINE FROM THE BRYOZOAN *CATENICELLA CRIBRARIA*

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ABSTRACT.—1-Vinyl-8-hydroxy-β-carboline was identified as the cytotoxic constituent of the bryozoans *Catenicella cribraria* and *Cribricellina cribraria*. Literature nmr data for this previously known compound, now reported from a new source, were corrected.

Compared to other major groups of marine invertebrates, the bryozoans remain a relatively poorly examined phylum in the realm of marine natural products chemistry (1). Extracts of two bryozoans, *Catenicella cribraria* Busk (phylum Bryozoa, class Gymnolaemata, order Cheilostomata, family Vittaticellidae) and *Cribricellina cribraria* Busk (phylum Bryozoa, class Gymnolaemata, order Cheilostomata, family Mucronellidae), showed relatively potent, but modestly differential, cytotoxicity in the NCI 60-cell human tumor assay. Bioassay-guided fractionation provided a single cytotoxic compound, 1-vinyl-8-hydroxy-β-carboline, previously isolated from the latter species (2). No previous work on the chemistry of *Cat. cribraria* has been reported.

Solvent-solvent partitioning of the crude organic extracts of each bryozoan collection yielded cytotoxic $CHCl_3$ fractions. Normal phase diol and amino bonded phase hplc provided a pure compound, which we characterized as 1-vinyl-8-hydroxy-β-carboline. Comparison of nmr spectral data with the literature values (2) for 1-vinyl-8-hydroxy-β-carboline disclosed several discrepancies which could not be explained solely by the marked pH dependence of chemical shifts in MeOH-d_4. Erroneous transcription of data into the table of Prinsep *et al.* (2) explained the remaining discrepancies (J.W. Blunt, personal communication).

The previously reported cytotoxicity of 1-vinyl-8-hydroxy-β-carboline was paralleled by the relatively potent cytotoxicity observed in the NCI human tumor 60-cell-line assay. The very modest differential cytotoxicity produced by the crude extract carried through to the purified compound; the most sensitive cell line subpanel was the melanoma subpanel, where the LC_{50} values of eight of nine cell lines were similar to or slightly less than the mean panel LC_{50}. The mean panel response parameter values for 1-vinyl-8-hydroxy-β-carboline were 1.8 μM at the GI_{50}, 5.8 μM at the TGI level, and 19 μM at the LC_{50} level.

EXPERIMENTAL

COLLECTIONS.—*Cat. cribraria*, an orange, erect, branching bushy colony, was collected at a depth of 14 m on March 15, 1989, on the underside of a rock substrate overhang, 0.6 km southwest of the light on Cape Vlamingh, Rottnest Island, Western Australia.

Cr. cribraria, an orange branching colony, was collected at a depth of 15 m on February 17, 1987, on the inside vertical rock walls of a tunnel at Poor Knights Island, The Tunnel, North Wall, New Zealand.

Voucher specimens are on deposit at the Smithsonian Institution.

EXTRACTION.—Frozen whole bryozoans were ground with dry ice in a hamburger mill, and the dry ice was allowed to sublime. The thawed tissue was stirred with distilled H_2O at 3° for 3 h and

filtered to generate an aqueous extract, and the marc was lyophilized. The dry marc was extracted with CH_2Cl_2-MeOH (1:1) overnight and rinsed with MeOH, and the solvent was removed with a rotary evaporator at 35° to yield an organic extract. *Cat. cribraria* (136 g wet wt) yielded 1.95 g of organic extract (1.4%). *Cr. cribraria* (238 g wet wt) yielded 4.29 g of organic extract (1.8%).

The crude extracts of *Cat. cribraria* (224 mg) and *Cr. cribraria* (232 mg) were subjected to a solvent-solvent partitioning scheme (3). In each case, cytotoxicity was concentrated in the $CHCl_3$ fraction; tlc indicated the same major Dragendorff-positive spot in each fraction. The $CHCl_3$ fractions of each extract were separately filtered through 3 g of diol chromatography media in MeOH and then subjected to hplc on diol media (YMC 2×25 cm, 60 Å, 5 μ), using a gradient of EtOAc to MeOH and monitoring by diode array uv detection. The major uv-absorbing peak in both $CHCl_3$ fractions was collected and found to have identical ^{1}H- and ^{13}C-nmr spectra. HMBC, HMQC, difference nOe, uv, and hr fabms characterization of this compound gave a structure identical to that of 1-vinyl-8-hydroxy-β-carboline; however, the ^{1}H-nmr spectral data were not identical to those reported in the literature (2). Communication with the senior authors of the prior work (2) revealed an error in the transcription of ^{1}H-nmr data. Our data were in close agreement with their actual ^{1}H-nmr data: δ 8.22 (d, J=5.4, H-3), 7.93 (d, 5.3, H-4), 7.62 (dd, 8, 1, H-5), 7.45 (dd, 17.4, 11, H-1′), 7.07 (dd, 8, 7.6, H-6), 6.96 (dd, 7.6, 1, H-7), 6.39 (dd, 17.4, 1.4, H_a-2′), 5.65 (dd, 11, 1.4, H_b-2′).

BIOASSAYS.—The 60-cell-line human disease-oriented tumor screening panel, its operation, and data presentation have been described previously (4). Tracking assays for the isolation procedure employed the previously described XTT tetrazolium methodology (5) and the LOX IMVI melanoma and U251 CNS tumor cell lines selected from the NCI panel.

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