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CITORELLAMINE, A NEW BROMOINDOLE DERIVATIVE FROM POLYCITORELLA MARIAE

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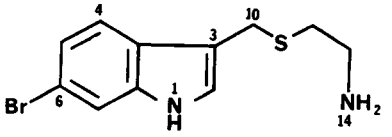
ABSTRACT: The structure of citorellamine, isolated from the tunicate Polycitorella mariae, has been deduced from spectroscopic analyses and chemical transformations.

The production of biologically active compounds from tunicates of the order Aplousobranchia has been well demonstrated.[1] In this paper we report the isolation and structure elucidation of a novel bromoindole derivative citorellamine (1), which possesses both cytotoxic and potent antimicrobial activity.[2] In addition, the methanol extract of the tunicate Polycitorella mariae Michaelsen, 1924[3] exhibits mild insecticidal activity against the tobacco budworm.

Polycitorella mariae, collected near Suva, Fiji, were kept frozen until needed. Initial extraction of the frozen tunicate with MeOH yielded a residue which was partitioned according to the Kupchan scheme.[4] The $CHCl_3$ extract showed strong inhibition toward both Gram (+) and Gram (-) bacteria. Purification of a portion of this material by HPLC (Partisil 10/25 PAC, MeOH), followed by crystallization from MeOH, gave 1 as colorless needles (0.1% dry weight).[5]



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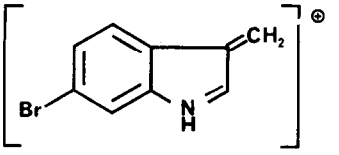
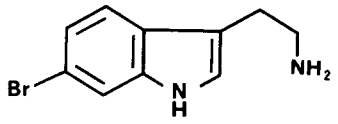


a

The presence of an indole nucleus containing bromine and alkyl substituents was suggested by UV maxima at 291 (ε 2800), 285 (3000), and 225 (18 000) nm;[6] ^{13}C NMR signals (Table I) at δ138.5 (s), 129.0 (d), 126.6 (s), 124.0 (d), 120.4 (d), 116.5 (s), 115.4 (d), and 105.8 (s); ^{1}H NMR signals for four aromatic protons at δ7.68 (1H, d, J = 8.57 Hz), 7.58 (1H, d, J = 1.97 Hz), 7.56 (1H, s), and 7.24 (1H, dd, J = 8.57, 1.97 Hz); and a fragment ion doublet at m/e 208, 210 for C_9H_7NBr which could be assigned to partial structure a. Placement of the bromine atom at C-6 and the alkyl group at C-3 was based upon comparison of the ^{13}C-^{1}H NMR chemical shift correlation data to that of 6-bromotryptamine (2),[7] and NOE enhancements of protons at C-2 and C-7 when the indole hydrogen (δ11.61, DMSO-d_6) was irradiated.



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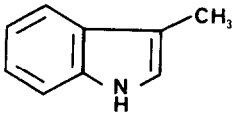
In addition to the resonances assigned to the indole protons in the ^{1}H NMR spectrum, signals were also visible at δ4.45 (2H, s), 3.39 (2H, t, J = 7.25 Hz), and 3.09 (2H, t, J = 7.25 Hz), which could be attributed to the methylene protons of the C-3 side chain in 1. A primary amine was evident from the two proton D_2O exchangeable signal that appeared at δ9.36 when the ^{1}H NMR spectrum was run in DMSO-d_6, and a broad band at 3300 cm^{-1} in the IR

TABLE I ^{13}C-^{1}H CORRELATION DATA FOR CITORELLAMINE (1)

Carbon Number	^{13}C	^{1}H
2	129.0	7.56
3	105.8	
4	120.4	7.68
5	124.0	7.24
6	116.5	
7	115.4	7.58
8	138.5	
9	126.6	
10	43.0	4.45
12	33.4	3.02
13	46.2	3.39

spectrum. EIMS produced a molecular ion doublet at 284, 286 and fragmentation ion doublets at m/e 240, 242 and 208, 210 corresponding to losses of $-CH_2CH_2NH_2$ and $-SCH_2CH_2NH_2$, respectively. The ^{13}C values at δ 43.0 (C-10), 33.4 (C-12), and 46.2 (C-13) are in good agreement with these assignments.[1a,8] Further confirmation of the relative positions of the atoms in the sidechain was provided by treatment of citorellamine with Raney nickel in EtOH (reflux, 3 hr) to yield 3-methylindole (3).[9] The data is therefore consistent with structure 1 as shown.

Citorellamine appears to be related biosynthetically to gramine in that one carbon of the tryptamine sidechain is lost.[10] Michael type addition of a decarboxylated cysteine unit to the gramine intermediate 4 would give the citorellamine skeleton.



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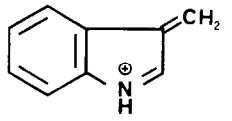

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2. IC_{50} value of 3.7 µg/ml against L1210; strong activity against Staphylococcus aureus (coagulase + and negative), Bacillus subtilis, Escherichia coli, Saccharomyces cerevisiae; mild activity against Pseudomonas aeruginosa.
3. The tunicate was identified by Dr. F. Monniot, Museum National d'Histoire Naturelle, Paris, France.
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5. 1: mp dec>210°; IR (neat) 3300 br, 2940, 2870, 1620, 1460, 900, 810 cm^{-1}; UV_{max} (MeOH) 291 (ϵ 2800), 285 (3000), 225 (18 000); ^1H NMR (DMSO-d_6) δ11.61 (1H, br s), 9.36 (2H, br s), 7.78 (1H, d, J = 8.79 Hz), 7.65 (1H, d, J = 2.20 Hz), 7.60 (1H, d, J = 1.10 Hz), 7.18 (1H, dd, J = 8.79, 1.10 Hz), 4.31 (2H, s), 3.19 (2H, d, J = 7.69 Hz), 3.08 (2H, d, J = 7.69 Hz); ^1H NMR (MeOH-d_4) δ7.68 (1H, d, J = 8.57 Hz), 7.58 (1H, d, J = 1.97 Hz), 7.56 (1H, s), 7.24 (1H, dd, J = 8.57, 1.97 Hz), 4.45 (2H, s,) 3.39 (2H, t, J = 7.25 Hz), 3.02 (2H, t, J = 7.25 Hz); ^{13}C NMR (MeOH-d_4) δ138.5 (s), 129.0 (d), 126.6 (s), 124.0 (d), 120.4 (d), 116.5 (s), 115.4 (d), 105.8 (s), 46.2 (t), 43.0 (t), 33.4 (t); HREIMS $C_{11}H_{13}BrN_2S$ (obs. 283.9974; calcd. 283.9983); HRFAB C_9H_7BrN (obs. 207.9767, calcd. 207.9761). EIMS M^+ 284 (8%), 286 (5); m/e 240 (4) M^+ $-CH_2CH_2NH_2$; 208 (62), 210 (62); 207 (96), 209 (100); 180 (12), 182 (14) m/e 207, 209-HCN; 128 (91) m/e 207-Br.

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9. ^{1}H NMR (MeOH-d_4) δ7.45 (1H, d, J = 7.26 Hz), 7.28 (1H, d, J = 7.91 Hz), 7.05 (1H, dd, J = 6.60, 7.91 Hz), 6.96 (1H, dd, J = 6.60, 7.26 Hz), 6.96 (1H, s), 2.28 (3H, s); HREIMS for C_9H_9N (obs. 131.0734; calcd. 131.0735); m/e 131 (22%, M^+) 130 (22, M^+-H), 103 (6, M^+-H[-HCN]). UV (MeOH) 290, 281, 223 nm.
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