New 5-Alkylpyrrole-2-carboxaldehyde Derivatives from the Sponge *Mycale tenuispiculata*[1]

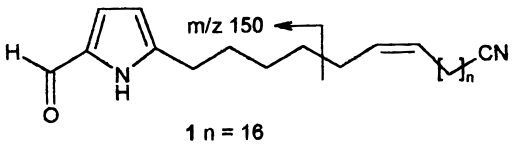
U. Venkatesham, M. Rama Rao, and Y. Venkateswarlu*

Natural Products Laboratory, Organic Chemistry Division-I, Indian Institute of Chemical Technology, Hyderabad-500 007, India

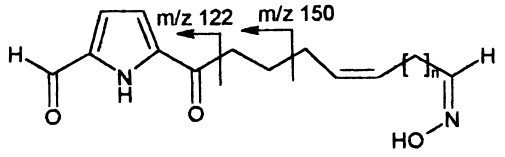
Received February 29, 2000

The sponge *Mycale tenuispiculata* afforded three new compounds—(6′*Z*)-5-(23′-cyano-6′-tricosenyl)pyrrole-2-carboxaldehyde (**1**), mycaleoxime (**2**), and (6′*E*)-5-(6′-penta decenyl)pyrrole-2-carboxaldehyde (**3**)—and three known compounds, 3-formyl indole, an admixture of 5-alkyl pyrrole-2-carboxaldehydes, and thymidine. The structures of the above compounds were elucidated by the interpretation of their spectral data.

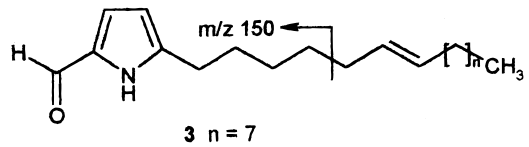
Sponges of the genus *Mycale* are a rich source of bioactive natural compounds having different structures. The mycalamides (triisooxazole-containing macrolides),[2] mycalolides,[3] diterpenoid rotalins,[4] mycalisines,[5] polybromminated C-15 acetogenins,[6] brominated isocoumarins,[7] and norterpene cyclic peroxides[8] are examples of different compounds isolated from the genus *Mycale*. Recently, 12 new 5-acyl-2-hydroxylmethylpyrroles and two new 5-alkylpyrrole-2-carbaldehydes have been isolated from the sponge *M. micracanthoxea*.[15] In continuation of our search for biologically active secondary metabolites from sponges of the genus *Mycale*,[9] we have investigated the sponge *M. tenuispiculata* Dendy (Mycalidae). The CH_2Cl_2−MeOH (1:1) extract of this sponge was subjected to gel filtration (Sephadex LH-20) using CH_2Cl_2−MeOH (1:1) as eluent, followed by Si gel chromatography using hexane through hexane−EtOAc mixtures and then MeOH as eluents. This afforded three new compounds−(6′*Z*)-5-(23′-cyano-6′-tricosenyl)pyrrole-2-carboxaldehyde (**1**), mycaleoxime (**2**), and (6′*E*)-5-(6′-penta decenyl)pyrrole-2-carboxaldehyde (**3**)—and the known compounds, 3-formyl indole,[10] an admixture of 5-alkyl pyrrole-2-carboxaldehydes,[11] and thymidine.[12] The structures of the above compounds were elucidated by the interpretation of their spectral data.



1 n = 16



2 n = 10



3 n = 7

Compound **1** was obtained as an optically inactive white solid, mp 56−58 °C, and its molecular formula, $C_{29}H_{48}N_2O$, was established from high-resolution mass measurements. The ^{1}H NMR spectrum contained an aldehyde proton signal at δ 9.35 (1H, s); two pyrrole proton signals at δ 6.82 (1H, m) and 6.01 (1H, m), both of which were coupled to a broad NH signal at δ 9.60 (1H, br s); two olefinic proton signals at δ 5.34 (2H, m), and signals at δ 2.68 (2H, t, J = 7.0 Hz), 2.32 (2H, t, J = 7.0 Hz), and 2.0 (4H, m) due to methylene groups adjacent to the pyrrole ring, the nitrile, and the olefin, respectively. Deuterium exchange of the NH proton converted the pyrrole proton signals to sharp doublets with a coupling constant of 3.8 Hz, a typical value for $J_{3,4}$ in pyrroles.[13] The infrared spectrum indicated the presence of pyrrole carboxaldehyde (3460, 2750, 1630 cm^{-1}) and nitrile (2250 cm^{-1}) functionalities. The ultraviolet spectrum [λ_{max} 297 (ϵ 15 300)] was typical of a pyrrole-2-carboxaldehyde.[11] The ^{13}C NMR spectrum confirmed the presence of the aldehyde [δ 178.07 (d)], pyrrole carbons [δ 143.0 (s), 131.74 (s), 122.75 (d), and 109.4 (d)], olefin [δ 130.2 (d), 129.37 (d)], and a nitrile carbon [δ 119.86 (s)]. The presence of signals at δ 27.81 (t) and 28.85 (t) with no signals in the range 31−35 ppm indicated that the olefinic bond has the *Z* geometry.[11] The position of the olefinic bond in the long chain was determined from the mass spectrum, which contains a fragment ion at *m*/*z* 150 that resulted from the allylic cleavage of the side chain.[11] From the above spectral data, compound **1** was characterized as (6′Z)-5-(23′-cyano-6′-tricosenyl)pyrrole-2-carboxaldehyde.

Compound **2** was isolated as an optically inactive viscous liquid. The molecular formula, $C_{22}H_{34}N_2O_3$, was obtained from elemental analysis. The ^{1}H NMR spectrum of compound **2** contained an aldehyde proton signal at δ 9.32 (1H, s) and two pyrrole proton signals at δ 6.85 (1H, m) and 6.02 (1H, m), both of which were coupled to a broad NH signal at δ 10.83 (1H, br s). Further its ^{1}H NMR spectrum showed a peak at δ 6.42 (1H, t, J = 6.5 Hz) attributed to the aldoxime CH proton signal[14] and two olefinic proton signals at δ 5.34 (2H, m). Deuterium exchange of the NH proton converted the pyrrole proton signals from multiplets to doublets with a coupling constant of 3.8 Hz, a typical value for $J_{3,4}$ in pyrroles.[13] The IR (3440 and 2775, 1630 cm^{-1}) and UV [λ_{max} 304 nm (ϵ 19 637), 232 nm (ϵ 8228)] spectra supported the presence of a pyrrole-2-carboxaldehyde.[11] The ^{13}C NMR spectrum of compound **2** showed a signal at δ 195.4 (s) due to the carbonyl group conjugated with the pyrrole nucleus,[15] an aldehyde signal at δ 178.01

* To whom correspondence should be addressed. Tel.: (040) 7170512. Fax: +91-40-7173757/7173387. E-mail: luchem@iict.ap.nic.in.

10.1021/np000101a CCC: $19.00
Published on Web 07/22/2000

(d), pyrrole signals at δ 143.85 (s), 131.85 (s), 122.91 (d), and 109.4 (d); the aldoxime carbon signal at δ 155.16 (d); and disubstituted olefinic carbon signals at δ 130.16 (d) and 129.41 (d). The presence of signals at δ 28.83 (t) and 27.8 (t) indicated that the olefinic bond and the aldoxime geometry have the *Z* configuration.[11,14] The position of the olefinic bond in the side chain was determined from the mass spectral fragmentation, which contained a fragment ion at *m*/*z* 150 (80) that resulted from the allylic cleavage of the side chain. From the above spectral data, the structure of compound **2**, mycaleoxime, was established as shown.

Compound **3** was isolated as an optically inactive, pale yellow solid, mp 42−44 °C. The molecular formula $C_{20}H_{33}NO$ was obtained from elemental analysis. From the ^{1}H and ^{13}C NMR, IR, and UV spectral data of compound **3**, it was clear that the structure of compound **3** was similar to that of compound **1**. The two were differing only in their alkenyl chain lengths and the functional groups. The ^{1}H NMR spectrum of compound **3** indicated the presence of a primary methyl group signal at δ 0.88 (3H, t, J = 6.5 Hz) and lacked a nitrile carbon signal at around δ 119.86 (s). The position of the olefinic bond in the long chain was determined from the mass spectrum, which contained a fragment ion at *m*/*z* 150 that resulted from the allylic cleavage of the side chain.[11] The geometry of the double bond was assigned as *E* by the ^{13}C NMR spectral values of allylic methylenes at δ 31.9 (t) and 31.75 (t).[11] Thus, from the above spectral data the structure of compound **3** was established as (6′*E*)-5-(6′-pentadecenyl)pyrrole-2-carboxaldehyde.

The known compounds, 3-formyl indole,[10] thymidine,[12] and the admixture of 5-alkylpyrrole-2-carboxaldehydes[11] were characterized by comparing their spectral data with those reported in the literature.

Experimental Section

General Experimental Procedures. The ^{1}H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectra were recorded on a Varian Gemini 200 MHz spectrometer using TMS as internal standard. Chemical shifts were reported in parts per million (ppm), and coupling constants (*J*) were expressed in hertz (Hz). UV and IR spectra were recorded on Shimadzu 240 and Perkin-Elmer 1310 spectrophotometers, respectively. Elemental analysis was carried out on a Perkin-Elmer 240C instrument. Mass spectra were recorded on a Finnigan-MAT 1020 instrument. Optical rotations were measured on a JASCO DIP-370 polarimeter.

Animal Material. The sponge *M. tenuispiculata* Dendy (Mycalidae) (IIC-309) was collected at a depth of 45 ft from Arabian sea near the Thiruvananthapuram coast (N 8°30′, E 76°31′) in southern India during October 1998. A voucher specimen (IIC-309) is on deposit at the National Institute of Oceanography, Goa, India.

Extraction and Isolation. The freshly collected sponge (1.5 kg dry wt) was soaked in methanol until workup. The initial aqueous methanol from the organism was decanted, and the sponge was freeze-dried. The freeze-dried material was extracted with CH_2Cl_2−MeOH (1:1, 3 × 2.5 L) at room temperature. The combined extracts were concentrated under reduced pressure, and the crude extract (25 g) was partitioned between H_2O and EtOAc. Concentration of the organic layer afforded a brownish, gummy crude extract (15 g). It was subjected to gel filtration (Sephadex LH-20) using CH_2Cl_2−MeOH (1:1) as eluent, followed by Si gel (100−200 mesh) column chromatography using hexane through hexane−EtOAc mixtures to methanol as eluents. The fraction eluted with 5% EtOAc in hexane yielded compound **3** (12 mg) and the known compound admixture of 5-alkyl pyrrole-2-carboxaldehydes (250 mg). The 10% EtOAc-in-hexane fraction afforded compound **1** (15 mg). The fraction eluted with 15% EtOAc in hexane yielded compound **2** (100 mg), and the fraction eluted with the 30% EtOAc in hexane yielded the known compound 3-formylindole (5 mg). The lyophilized water extract (10 g) was subjected to gel filtration (Sephadex LH-20) CH_2Cl_2−MeOH (1:1) as eluent, followed by Si gel column chromatography (100−200 mesh) using EtOAc through EtOAc−MeOH mixtures to MeOH as eluents. The fraction eluted with 10% MeOH in EtOAc afforded the known compound thymidine (10 mg).

(6′*Z*)-5-(23′-Cyano-6′-tricosenyl)pyrrole-2-carboxaldehyde (1): optically inactive white solid (15 mg), mp 56−58 °C; UV (CH_3CN) λ_{max} 297 nm (ϵ 15 300); IR (KBr) ν_{max} 3460, 2750, 2250, 1630, 1480, and 1035 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.60 (1H, br s), 9.35 (1H, s), 6.82 (1H, m), 6.01 (1H, m), 5.34 (2H, m), 2.68 (2H, t, J = 7.0 Hz), 2.32 (2H, t, J = 7.0 Hz), 2.0 (4H, m), 1.25 (34H, br s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 178.07 (d), 143.0 (s), 131.74 (s), 130.20 (d), 129.37 (d), 122.75 (d), 119.86 (s), 109.4 (d), 29.64 (t), 29.46 (t), 29.36 (t), 29.27 (t), 29.18 (t), 28.92 (t), 28.85 (t), 28.72 (t), 28.62 (t), 27.81 (t), 27.2 (t), 26.98 (t), 25.31 (t) and 17.08 (t); EIMS (70 eV) *m*/*z* 440 (31.8) $(M)^+$, 414 (3) $(M - CN)^+$, 150 (12.1) $(M - C_{20}H_{36}N)^+$, 136 (4.5) $(M - C_{21}H_{38}N)^+$, 122 (100) $(M - C_{22}H_{40}N)^+$, and 108 (93.9) $(M - C_{23}H_{42}N)^+$; HREIMS *m*/*z* 440.3760 calcd for $C_{29}H_{48}N_2O$, 440.3766.

Mycaleoxime (2): optically inactive viscous liquid (100 mg), UV (CH_3CN) λ_{max} 304 nm (ϵ 19 637), 232 nm (ϵ 8228); IR (neat) ν_{max} 3440, 2775, 1620, 1460, and 1045 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 10.83 (1H, br s), 9.33 (1H, s), 6.85(1H, m), 6.42 (1H, t, J = 6.5 Hz), 6.02 (1H, m), 5.34 (2H, m), 2.68 (2H, t, J = 7.0 Hz), 2.32 (2H, m), 2.0 (4H, m) and 1.25 (18H, br s); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 195.24 (s), 178.01 (d), 155.16 (d), 143.85 (s), 131.85 (s), 130.16 (d), 129.41 (d), 122.91 (d), 109.4 (d), 29.62 (t), 29.53 (t), 29.37 (t), 29.29 (t), 29.16 (t), 29.09 (t), 28.90 (t), 28.83 (t), 28.66 (t), 27.8 (t), 27.2 (t), 27.0 (t), and 24.01 (t); EIMS (70 eV) *m*/*z* 374 (6.1) $(M)^+$, 150 (10.7) $(M - C_{14}H_{26}NO)^+$, 136 (10.7) $(M - C_{15}H_{28}NO)^+$, and 122 (64.6) $(M - C_{16}H_{30}NO)^+$; *anal*. C 70.55%, H 9.15%, N 7.47%, calcd for $C_{22}H_{34}N_2O_3$, C 70.55%, H 9.15%, N 7.47%.

(6′*E*)-5-(6′-Penta decenyl)pyrrole-2-carboxaldehyde (3) optically inactive, pale yellow solid (12 mg), mp 42−44 °C; UV (CH_3CN) λ_{max} 297 nm (ϵ 15 400); IR (KBr) ν_{max} 3460, 2750, 1630, 1480, 1035, and 930 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 10.15 (1H, br s), 9.32 (1H, s), 6.82 (1H, m), 6.01 (1H, m), 5.34 (2H, m), 2.68 (2H, t, J = 7.0 Hz), 2.0 (2H, m), 1.66 (2H, m), 1.20 (18H, br s), and 0.88 (3H, t, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 178.09 (d), 143.20 (s), 131.76 (s), 130.0 (d, 2C), 122.66 (d), 109.44 (d), 31.9 (t), 31. 75 (t), 29.63 (t), 29.47 (t), 29.29 (t), 29.19 (t), 28.92 (t), 27.86 (t), 27.19 (t), 22.67 (t), and 14.1 (q); EIMS (70 eV) *m*/*z* 303 (10.6) $(M)^+$, 150 (10.5) $(M - C_{11}H_{21})^+$, 136 (7.5) $(M - C_{12}H_{23})^+$, 122 (63.6) $(M - C_{13}H_{25})^+$, and 108 (100) $(M - C_{14}H_{27})^+$; *anal*. C 79.15%, H 10.96%, N 4.61%, calcd for $C_{20}H_{33}NO$, C 79.15%, H 10.95%, N 4.61%.

Acknowledgment. We are thankful to Dr. P. A. Thomas, Central Marine Fisheries Research Institute, Thiruvananthapuram, India, for identifying the sponge; the Department of Ocean Development for financial assistance; the Director, Indian Institute of Chemical Technology, and Dr. J. S. Yadav for constant encouragement; and the Council of Scientific and Industrial Research and University Grants Commission for providing fellowships to U.V. and M.R.R.

References and Notes

(1) IICT communication no. 4506.
(2) Perry, N. B.; Blunt, W. J.; Munro, M. H. G.; Thompson, A. M. *J. Org. Chem*. **1990**, *55*, 223−227.
(3) Fusetani, N.; Yasumuro, K.; Matsunaga, S.; Hashimoto, K. *Tetrahedron Lett*. **1989**, *30*, 2809−2812.
(4) Corriero, G.; Madaio, A.; Mayol, L.; Piccialli, V.; Sica, D. *Tetrahedron* **1989**, *45*, 277−288.
(5) Kato, Y.; Fusetani, N.; Matsunaga, S.; Hashimoto, K. *Tetrahedron Lett*. **1985**, *26*, 3483−3486.
(6) Giordano, F.; Mayol, L.; Notaro, G.; Piccialli, V.; Sica, D. *J. Chem. Soc., Chem. Commun*. **1990**, *22*, 1951−1961.
(7) Fusetani, N.; Sugawara, T.; Matsunaga, S.; Hirota, H. *J. Org. Chem*. **1991**, *56*, 4971−4974.

(8) Capon, R. J.; Macleod, J. K. *J. Nat. Prod*. **1987**, *50*, 225−229.
(9) Venkateswarlu, Y.; Rama Rao, M.; Farooq Biabani, M. A. *Ind. J. Chem*. **1996**, *35B*, 876−877.
(10) Chowdhury, B. K.; Chakraborty, D. P. *Phytochemistry* **1971**, *10*, 481−483.
(11) Stierle, D. B.; Faulkner, D. J. *J. Org. Chem*. **1980**, *45*, 4980−4982.
(12) Levene, P. A.; London, E. S. *J. Biol. Chem*. **1929**, *83*, 793−802.
(13) Jones, R. A.; Bean, G. P. *The Chemistry of Pyrroles*; Academic Press: New York, 1977; p 473.
(14) Carroll, A. R.; Scheuer, P. J. *Tetrahedron* **1990**, *46*, 6637−6644.
(15) Ortega, M. J.; Zubia, E.; Carballo, J. L.; Salva, J. *Tetrahedron* **1997**, *53*, 331−340.

NP000101A