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Thomas Rasmussen, Jan Jensen, Uffe Anthoni, Carsten Christophersen, and Per H. Nielsen

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STRUCTURE AND SYNTHESIS OF BROMOINDOLES FROM THE MARINE SPONGE *PSEUDOSUBERITES HYALINUS*

THOMAS RASMUSSEN, JAN JENSEN, UFFE ANTHONI, CARSTEN CHRISTOPHERSEN,* and PER H. NIELSEN

Marine Chemistry Section, The H.C. Ørsted Institute, University of Copenhagen, Universitetsparken 5, DK-2100 Copenhagen, Denmark

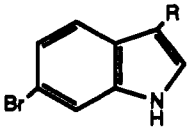
ABSTRACT.—Four new 6-bromoindoles and the known 6-bromoindole-3-carbaldehyde [**5**] have been isolated from the marine sponge *Pseudosuberites hyalinus* collected in the North Atlantic around the Faroe Islands. The structures of 6-bromoindolyl-3-acetonitrile [**1**], 6-bromoindolyl-3-acetamide [**2**], methyl 6-bromoindolyl-3-acetate [**3**], and 6-bromoindole-3-carboxylic acid [**4**], were elucidated by analysis of ir, mass, ^{1}H-nmr, and ^{13}C-nmr spectral data, and structures **1–3** were confirmed by synthesis.

Our ongoing studies of marine-derived biologically active metabolites led us to investigate the hadromerid sponge *Pseudosuberites hyalinus* (Ridley and Dendy) (family Suberitidae, class Demospongiae) made accessible by collections at the Faroe Islands during the BIOFAR program. Demosponges have long been recognized as a rich source of 6-bromoindoles (1) previously isolated from *Dercitus* sp. (Pachastrellidae) (2), *Pachymatisma johnstoni* (Geodiidae) (3), *Iotrochota* sp. (Myxillidae) (4), and *Cliona celata* (Clionidae) (5–7). However, so far all the 6-bromoindoles reported have the tryptophan carbon skeleton intact. In this study we have elucidated the structures of four novel (**1–4**) and one previously described (8–11) derivative **5** of 6-bromoindole with degraded carbon chains in the 3 position. We also report on the synthesis of **1–3**.

RESULTS AND DISCUSSION

The MeOH-CH_2Cl_2 (1:10) extract of the sponge yielded a concentrate which, after chromatography, afforded five compounds **1–5**, which exhibited characteristic bromine isotopic patterns in the mass spectra. According to the ^{1}H-nmr spectrum compounds **1–5** had substitution patterns identical to 3,5- or 3,6-substituted indoles, i.e., three protons in the benzene ring (two with ortho coupling) and a singlet from H-2. This suggested that compounds **1–5** incorporate the 5 or 6 bromoindole structure with different 3 substituents. The structures of the side chains were deduced from spectroscopic data, and the identities of **1–3** were confirmed by synthesis.

The eims pattern of **5** displayed two prominent peaks at *m/z* 225/223 $[M]^+$ and 224/222 $[M-H]^+$ which, in combination with a peak at *m/z* 196/194 $[M-CHO]^+$, indicated **5** to be 6-bromoindole-3-carbaldehyde (12). This was confirmed by comparison of the ^{1}H-nmr spectrum with published data (4,9). The mass spectrum of **4** had base



1 R=CH_2CN
2 R=CH_2CONH_2
3 R=CH_2CO_2Me
4 R=COOH
5 R=CHO

peak at *m/z* 241/239 $[M]^+$ and the most prominent fragment at *m/z* 224/222 $[M-OH]^+$, indicating formation of bromoindolyl formylium ions. The ir spectrum of **4** established the presence of a COOH group. Comparison with the spectrum of indole-3-carboxylic acid showed coinciding features including appearance of the CO stretching vibration near 1640 cm^{-1} and the presence of a broad signal extending from 2800 cm^{-1} towards lower wavelengths due to the hydrogen-bonded carboxylic acid group. Thus, the structure of **4** was formulated as 6-bromoindole-3-carboxylic acid. The ^{1}H-nmr coupling patterns are identical to those observed for **5**.

Abundant fragment ions at *m/z* 210/208 in the eims spectra strongly suggest the presence of the methylene bromoindole moiety in **1**, **2**, and **3**. This assignment finds support in the presence of a proton singlet at δ 3.80 (**1**), 3.83 (**2**), and 3.74 (**3**). The pattern of the aromatic signals closely resembles the one observed for **5** although with a less pronounced downfield shift of the signal from H-4 and H-2. This attests to the presence of methylene groups in **1**, **2**, and **3** instead of the carbonyl group of **5**. In accordance with these findings **1**, **2**, and **3** encompass the 3-methylene-5 or 6-bromoindole moiety.

Molecular ions of **1** appear at *m/z* 236/234. Loss of 26 (*m/z* 210/208) from the even $[M]^+$ is compatible with the presence of a nitrile group. The ^{13}C-nmr spectrum of **1** is comparable to that reported for indolyl-3-acetonitrile (13). This was confirmed by the presence of the highly characteristic sharp ir band with medium to strong intensity at 2254 cm^{-1}, originating from stretching of the CN triple bond. Accordingly **1** was deduced to be 5 or 6-bromoindolyl-3-acetonitrile. The molecular ions of **2** appear at *m/z* 254/252. Loss of 44 to give the base peak at *m/z* 210/208 might be due to either CO_2 or $CONH_2$. However, the carbonyl signal in the ir spectrum at 1652 cm^{-1} and a broad singlet corresponding to two protons at δ 5.52 suggest **2** to be 5 or 6-bromoindolyl-3-acetamide. The molecular ions of **3** at *m/z* 269/267 and the loss of 59 to give the base peak at *m/z* 210/208 are consistent with the structure of methyl 5- or 6-bromoindolyl-3-acetate, substantiated by the presence of a singlet at δ 3.71 (3H, OMe). In support, the ^{13}C-nmr spectrum could be readily assigned by comparison with data from methyl indolyl-3-acetate (13) and *J*-modulated spin echo experiments.

The position of the bromo substituent in **1–3** was unambiguously determined by synthesis from 6-bromogramine (14). Gramines are susceptible to nucleophilic attack at the methylene group after quaternization of the dimethyl amino function. Quarternization with dimethyl sulfate followed by reaction with cyanide furnished an excellent yield of the cyanomethylene compound **1**, which was allowed to react with H_2O_2 to give, after purification by cc, the corresponding amide **2**. This was smoothly degraded by nitrous acid to 6-bromoindolyl-3-acetic acid, which was converted to the methyl ester **3** by standard procedures. All compounds were identical with the natural products.

Most if not all sponges harbor bacteria, which reputedly often belong to the genera *Pseudomonas* or *Aeromonas* (15). In marine organisms the biogenetic origin of indoles and bromoindoles is totally unaccounted for, even though participation of bromoperoxidases has been implicated in the biogenesis of the latter (16). Indole-3-carbaldehydes occur in sponges (17), algae (18,19), and a marine pseudomonad (9), while indole-3-carboxylic acid is known from red (19,20) and brown algae (21). In the present case it cannot be excluded that **4** is formed by oxidation of **5**. In higher plants (22) and fungi (23), **4** and **5** are degradation products of indolyl-3-acetic acid. Indolyl-3-acetamide, which has been isolated from a sponge (17), and indolyl-3-acetonitrile are plant growth regulators (24,25) and intermediates in the biosynthesis of indolyl-3-acetic acid (26). Among other tryptophan derivatives with degraded carbon chains in the 3 positon (27), indolyl-3-acetamide (28) and indole-3-carbaldehyde (9,28) have been isolated from *Pseudomonas* species and at least one pseudomonad also expresses the biochemical potential for

introducing a bromo atom in the indole nucleus to elaborate 6-bromoindole-3-carbaldehyde (9). Consequently, we cannot exclude the possibility that compounds **1–5** originate with some associated microorganisms. On the other hand, the low abundance of **1–5** (10^{-5} to 10^{-3}% of wet wt) may point to a dietary origin. It has been suggested that the production of plant-growth promoters in sponges is connected with a symbiotic relation to algae (18). This is excluded in the present case, since *Pss. hyalinus* was collected at a depth of 400 m. At present it is not known what effects brominated analogues may have as plant-growth regulators.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Mass spectra were recorded at 70 eV on a VG Masslab VG20-250 Quadrupole mass spectrometer. Uv spectra were recorded on a Hewlett Packard 8452 A instrument and ir spectra in KBr pellets on a Perkin Elmer FT-IR 1760x. ^{13}C- and ^{1}H-nmr spectra were obtained from a Bruker 250 AM multinuclear spectrometer. *J*-modulated spin echo experiments served to distinguish ^{13}C signals arising from CH/Me and C/CH_2. Chemical shifts are reported in ppm downfield with TMS as internal reference.

MATERIAL.—The yellow marine sponge *Pss. hyalinus* was collected July 22, 1989 at −405 m as part of the BIOFAR program (station 483, 61°05′ W, 05°04′ N). The material was identified by Dr. Ole Tendal, Zoological Museum, University of Copenhagen, where a voucher specimen is maintained.

EXTRACTION AND ISOLATION.—The sponge (2200 g wet wt) was extracted with CH_2Cl_2-MeOH (1:10) (3×2000 ml, 3 days each time). Filtration followed by evaporation under vacuum at room temperature afforded a black aqueous suspension which was diluted with H_2O to 250 ml and sequentially extracted with heptane (250 ml×4), EtOAc (150 ml×4) and *n*-BuOH (150 ml×4). After solvent removal the three organic fractions were separately lyophilized. ^{1}H nmr indicated that both the heptane (6900 mg) and the *n*-BuOH-soluble material (800 mg) contained indole derivatives. However the major indole content appeared in the EtOAc extract (900 mg). A Beilstein test indicated this latter fraction to contain halogenated compounds. Accordingly, the heptane and the *n*-BuOH-soluble material were extracted twice with 50 ml EtOAc, combined with the 900 mg EtOAc extract, and fractionated by mplc, using the Büchi B-680 system. The column (130 ml, packed with Kieselgel Si 60, 40–63 μm) was eluted with EtOAc to give five fractions A1–A5.

6-Bromoindolyl-3-acetonitrile [**1**].—Cc [Lobar C Si 60, Merck, heptane-EtOAc-$CHCl_3$ (2:3:3)] of the most apolar fraction (A1) and further purification by hplc [Hibar 250-25 RP-18, Merck, MeCN-$CHCl_3$ (3:2)], gave pure **1** (32 mg, 1.5× 10^{-3}% wet wt): ms *m/z* (%) 236/234 (100), 210/208 (25), 155 (82), 129 (25), 101 (21), 77 (24), 64 (15), 50 (16), 28 (53). Ir 3371, 2254, 1614, 1457, 1411, 1344, 1333, 1227, 1130, 1102, 1046, 895, 838, 810, 564, 488, 424 cm^{-1}; uv λ max ($CHCl_3$) nm (log ε) 278 (4.01); ^{1}H nmr see Table 1; ^{13}C nmr see Table 2.

6-Bromoindolyl-3-acetamide [**2**].—Cc of the A4 fraction on a Lobar A Si 60, Merck [$CHCl_3$-EtOAc-EtOH (5:4:1)], gave pure **2** (ca. 1 mg, 4.5×10^{-5}% wet wt): ms *m/z* (%) 254/252 (24), 210/208 (100), 129 (47), 102 (24), 75 (13), 51 (12), 44 (19), 28 (11); ir 3438, 3371, 3181, 1652, 1455, 1412, 1336, 1277, 1089,

TABLE 1. ^{1}H-nmr Data of Compounds **1–5**.

Proton	Compound				
	1	**2**	**3**	**4**	**5**
H-1	8.28 b	8.21 b	8.19 b	8.77 b	8.67 b
H-2	7.18 t, J_{2a}=1.0	7.15 d, J_{12}=2.4	6.92 s	7.96 d, J_{12}=2.4	7.81 d, J_{12}=3.0
H-4	7.44 d, J_{45}=8.6	7.45 d, J_{45}=8.5	7.42 d, J_{45}=8.3	8.07 d, J_{45}=8.5	8.19 d, J_{45}=9.0
H-5	7.27 dd, J_{57}=1.6	7.26 dd, J_{57}=1.7	7.20 d	7.39 dd, J_{57}=1.4	7.43 dd, J_{57}=2.0
H-7	7.54 d	7.55 d	7.36 s	7.58 d	7.61 d
CH_2	3.80 d	3.71 s	3.74 s	—	—
Me	—	—	3.71 s	—	—
NH_2	—	5.52 b	—	—	—
CHO	—	—	—	—	10.05 s

TABLE 2. ^{13}C-nmr Data of Compounds **1–3** and **5**.[a]

Carbon	Compound			
	1	**2**	**3**	**5**
C-2	123.2	123.9	123.8	135.1
C-3	104.9	108.1	107.4	119.8
C-3a	124.8	125.6	125.6	126.1
C-4	119.2	121.2	119.5	123.3
C-5	123.5	119.0	125.5	126.4
C-6	116.4	114.1	115.0	118.0
C-7	114.4	113.3	114.0	114.4
C-7a	136.9	137.0	136.5	137.0
C-α	14.2	31.4	30.6	184.5
C-β	117.8	175.7	172.8	—
C-γ	—	—	51.9	—

[a]Data were recorded in $CHCl_3$-d_1. Assignments were confirmed by *J*-modulated spin echo experiments.

1065, 895, 854, 811, 692, 612, 487, 425 cm^{-1}; uv λ max (MeOH) nm (log ε) 228 (4.31); ^{1}H nmr see Table 1; ^{13}C nmr see Table 2.

Methyl 6-bromoindolyl-3-acetate [**3**].—Cc of the most apolar fraction (A1) on a Lobar C Si 60, Merck [heptane-$CHCl_3$-EtOAc (2:3:3)] followed by Lobar B CN, Merck [heptane-$CHCl_3$-EtOAc (1:1:1)] and further purification by hplc [Hibar 250-25 RP-18, Merck, MeCN-$CHCl_3$ (3:2)], gave pure **3** (19.8 mg, 9×10^{-4}% wet wt): ms *m/z* (%) 269/267 (18), 210/208 (100), 129 (75), 102 (42), 75 (18). Ir 3364, 2951, 1724, 1615, 1477, 1455, 1437, 1408, 1333, 1294, 1206, 1168, 1099, 1051, 1009, 896, 804, 585 cm^{-1}; uv λ max (MeOH) nm (log ε) 228 (4.49); ^{1}H nmr see Table 1; ^{13}C nmr see Table 2.

6-Bromoindole-3-carboxylic acid [**4**].—Cc of the most polar fraction (A5) on a Lobar B RP-8, Merck [H_2O-EtOH-MeCN (50:75:75)], followed by purification on a Lobar A Si 60, Merck [EtOAc-heptane (4:1)], gave pure **4** (ca. 1 mg, 4.5×10^{-3}% wet wt) (**4** was absorbed on the column and eluted with EtOH): ms *m/z* (%) 241/239 (100), 224/222 (38), 143 (6), 115 (18); ir 3313, 2925, 1644, 1572, 1532, 1451, 1309, 1186, 1136, 1040, 808 cm^{-1}; ^{1}H nmr see Table 1.

6-Bromoindole-3-carbaldehyde [**5**].—Repeated cc of the A2 fraction on a Lobar A Si 60, Merck [MeCN-EtOH-H_2O (3:3:2)] and further purification by hplc [Lichrosorb Si 60 250-10, Merck, $CHCl_3$-EtOAc-heptane-EtOH (80:60:60:1)] gave pure **5** (12 mg, 5.5×10^{-4}% wet wt): ms *m/z* (%) 225/223 (100), 224/222 (100), 196/194 (28), 169/167 (12), 143 (24), 115 (37); ^{1}H nmr see Table 1; ^{13}C nmr see Table 2.

SYNTHESIS.—6-Bromoindole was prepared by a variant of the Leimgruber-Batcho indole synthesis (29). 4-Bromo-2-nitrotoluene (45 mmol) was dissolved in anhydrous DMF (90 ml). Dimethylformamide dimethylacetal (135 mmol) and pyrrolidine (45 mmol) were added in one portion, and the stirred mixture was heated to 110°. Heating was maintained until tlc analysis (Si gel, toluene) showed complete consumption of the bromonitrotoluene. The deep red solution was cooled, diluted with Et_2O, and washed thoroughly with H_2O. The combined aqueous layers were re-extracted with Et_2O. After drying the combined organic phase over Na_2SO_4, the solvent was evaporated and the residual tar used in the reduction reaction without further purification.

The crude enamine, dissolved in 80% aqueous HOAc (300 ml), was heated to 75°. Zinc dust (390 matom) was added in five portions over 1 h. After the addition was complete, the temperature was raised to 85° for 2 h. After cooling and filtering, the filtrate was diluted with Et_2O, washed with H_2O, saturated with aqueous $NaHCO_3$ and dried over Na_2SO_4. The solvent was evaporated and the residue distilled in a Kugelrohr apparatus (80°, 0.2 mmHg) to give analytically pure 6-bromoindole in 62% yield, mp 93–94° [lit. (30) mp 93.5–94°]. *Anal.* calcd for C_8H_6BrN: C 49.01, H 3.08, Br 40.76, N 7.14; found C 49.17, H 3.08, Br 40.60, N 7.15.

6-Bromogramine was prepared following the directions of Schreier (14). Evaporation of the Et_2O/cyclohexane phase, redissolving in a minimum volume of Et_2O, and reprecipitating gave a second crop. Total yield 92%, mp 137–139° [lit. (30) 138–140°], pure according to tlc [RP-18, H_2O-MeCN (2:1)].

In analogy with the debromo-compound (31) a mixture of 6-bromogramine (7.5 mmol) and glacial HOAc (112.5 μl) dissolved in anhydrous THF (10 ml) was added dropwise to a solution of dimethylsulfate

(38 mmol) and glacial HOAc (112.5 µl) in anhydrous THF (10 ml) at 15°. The reaction mixture was kept for 3 h at room temperature in the dark. The precipitate was collected on a Büchner funnel and the crystals washed thoroughly with Et_2O to remove excess dimethylsulfate. The product was dried, yielding 60% of trimethyl(6-bromoskatyl)ammonium-methylsulfate used in the next step without further purification.

6-Bromoindolyl-3-acetonitrile [**1**].—Compound **1** was prepared following essentially the directions of Thesing and Schülde (32) for the corresponding debromo compound. Trimethyl(6-bromoskatyl)ammonium-methylsulfate (4.31 mmol) and NaCN (13 mmol) were dissolved in H_2O (13 ml). The mixture was heated to 70° for 1 h and a yellow oil separated. After cooling the aqueous layer was saturated with Na_2SO_4 and extracted with Et_2O. The Et_2O phase was evaporated, and the product lyophilized to give 6-bromoindolyl-3-acetonitrile [**1**] in quantitative yield, mp 114–115°. *Anal.* calcd for $C_{10}H_7BrN_2$: C 51.09, H 3.00, Br 33.99, N 11.92; found C 52.22, H 3.13, Br 33.75, N 11.73.

6-Bromoindolyl-3-acetamide [**2**].—H_2O_2 (30%, 200 µl) was added to a stirred solution of 6-bromoindolyl-3-acetonitrile (0.43 mmol) dissolved in 2 M NaOH (1 ml) and a minimum volume of EtOH. The solution initially turns green changing into orange. After 30 min the base was neutralized with 2 M HCl, the EtOH removed in vacuo, and the aqueous phase saturated with Na_2SO_4 followed by extraction twice with an equal volume of Et_2O. The Et_2O was removed and the residue lyophilized. The product was purified by cc [Si-60, heptane-EtOAc-EtOH (2:2:1)] on Lobar E. Merck, yielding 6-bromoindolyl-3-acetamide [**2**], mp 148–150°. *Anal.* calcd for $C_{10}H_9BrN_2O$: C 47.45, H 3.60, Br 31.60, N 11.07; found C 47.31, H 3.76, Br 31.50, N 10.88.

6-Bromoindolyl-3-acetic acid was prepared following the directions of Thesing *et al.* (33) for the debromo-analogue: Formaline (37%, 0.01 mol) was added to a vigorously stirred solution of 6-bromoindole (0.01 mol), and *N*-methylaniline (0.0105 mol) dissolved in MeOH (2 ml) at room temperature. Stirring was maintained for 1 h in the dark, during which a clear oil separated in contrast to the debromo-analogue (33). Leaving the reaction mixture an additional hour without stirring did not induce crystallization of (6-bromoskatyl)methyl-phenylamine. NaCN (0.1 mol), EtOH (50 ml), and H_2O (30 ml) were added, and the reaction mixture was refluxed for 2 h. EtOH was removed by distillation, NaOH (20%, 30 ml) was added, and the reaction mixture was refluxed for another 2.5 h and acidified with concentrated HCl (HCN generated!) to precipitate 6-bromoindolyl-3-acetic acid. Recrystallization from EtOH/H_2O left pure 6-bromoindolyl-3-acetic acid in 48% yield: ^{1}H nmr δ (CD_3OD) 7.67 (1H, d, J=1.4, H-7), 7.61 (1H, d, J=8.5, H-4), 7.34 (1H, s, H-2), 7.28 (1H, dd, $J_{4,5}$=8, 5, $J_{5,7}$=1.7, H-5), 3.88 (2H, d, CH_2); ^{13}C nmr δ ($CDCl_3$/DMSO) 172.85 (CO), 136.35 (C-7a), 125.37 (C-3a), 123.48 (C-2), 120.97 (C-5), 119.20 (C-4), 113.78 (C-6), 113.36 (C-7), 107.31 (C-3), 30.27 (CH_2); ir 3421, 1708, 1455, 1426, 1406, 1335, 1251, 1234, 1219, 1098, 894, 807 cm^{-1}; mp 172–177° (dec); uv λ max (MeOH) nm (log ε) 228 (4.56). *Anal.* calcd for $C_{10}H_8BrNO_2$: C 47.27, H 3.17, Br 31.45, N 5.51; found C 47.55, H 3.01, Br 31.80, N 5.66.

Methyl 6-bromoindolyl-3-acetate [**3**].—6-Bromoindolyl-3-acetic acid (1.18 mmol) was dissolved in dry MeOH (75 ml) containing a small amount of dry HCl. The mixture was refluxed for 4 h and the solvent removed in vacuo, leaving **3** in quantitative yield as a colorless oil, which could not be induced to crystallize. *Anal.* calcd for $C_{11}H_9BrN_2O$: C 49.28, H 3.76, Br 29.80, N 5.22; found C 49.39, H 3.56, Br 29.60, N 5.20.

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