Ethyl 6-Bromo-3-indolcarboxylate and 3-Hydroxyacetal-6-bromoindole, Novel Bromoindoles from the Sponge *Pleroma menoui* of the Coral Sea

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Z. Naturforsch. **44c,** 914–916 (1989); received July 14, 1989

Pleroma menoui, Demosponge, Alkaloids, Ethyl 6-Bromo-3-indolcarboxylate, 3-Hydroxyacetyl-6-bromoindole

The demosponge *Pleroma menoui* (order Lithistida, suborder Trienosina (= Desmophorina), family Pleromidae), collected in the Coral Sea south-east of Noumea at a depth of 500 m, is proven here to contain the novel alkaloids ethyl 6-bromo-3-indolcarboxylate and 3-hydroxyacetyl-6-bromoindole.

Introduction

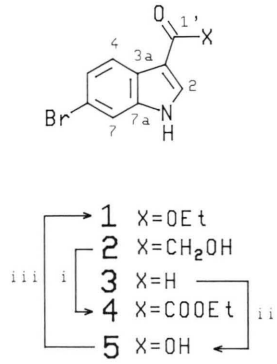
Indoles substituted by bromine at either C(3), C(5), or the non-electrophilic C(6) have been isolated from marine animals. Thus, the hemichordate *Ptychodera flava laysanica* has given 3-bromoindole [1] and 3,6-dibromoindole [2] while the sponge *Smenospongia aurea* has given 5-bromo- and 5,6-dibromo-N,N-dimethyltryptamine [3]. 6-Bromoindoles have been isolated from the bryozoan *Flustra foliacea* [4], from the sponges *Cliona celata* [5], *Iotrochota* sp. [6] and *Aplysinopsis reticulata* [7], and from scleractinian corals of the family Dendrophylliidae [8]. Moreover, 6-bromo-3-indolinones are products of prosobranch mollusks and form the basis of Tyrian purple [9].

We report here on two novel 6-bromoindoles and a previously known 6-bromoindole [8], isolated from the sponge *Pleroma menoui* (order Lithistida, suborder Trienosina (= Desmophorina), family Pleromidae) from the Coral Sea.

Results and Discussion

The first compound isolated from the sponge was the less polar **1** whose spectral data suggested a 6-bromo-3-substituted indole [8]. The ethyl ester group revealed by the spectral data must thus be located at C(3). The structure ethyl 6-bromo-3-indolcarboxylate (**1**) for this compound was confirmed by oxidation of the previously available compound **3** [8] (which was also isolated from *P. menoui* as the next more polar compound) to acid **5** which was then esterified to **1** (Scheme). Before this firm structural proof, under the hypothesis of a weak ^{13}C NMR C=O signal, we deemed structure **4** also compatible with the spectral data in the Experimental for the compound isolated from the sponge. This was ruled out by comparison with an authentic sample of **4** prepared from **2** *via* route i as described in the Experimental.

Scheme



Scheme. i) a) PCC, CH_2Cl_2; b) EtOH. ii) $KMnO_4$, 1:1 $(CH_3)_2CO-H_2O$, room temperature, 48 h. iii) DCC, DMPA, EtOH, 24 h.

The next more polar compound isolated from this sponge was **2**. The composition $C_{10}H_8BrNO_2$ was established by mass and NMR spectral analysis. Its indole nature, and the presence of an alcoholic function, were revealed by its UV and IR data. Bromine substitution at C(6) and the carbon chain at C(3) were established by comparison of its NMR data with those for aplysinopsins [8]. The structure of the side-chain was confirmed by PCC oxidation of **2** and esterification to give **4** (Experimental).

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Verlag der Zeitschrift für Naturforschung, D-7400 Tübingen
0341–0382/89/1100–0914 $ 01.30/0

Experimental

General experimental procedures

Melting points: Kofler hot-stage microscope. NMR spectra (δ values in ppm relative to internal Me_4Si (= 0 ppm) and J values in Hz): Varian XL-300 spectrometer (^1H at 300 MHz, ^{13}C at 75.4 MHz, J in Hz, multiplicities from APT [10]. MS (EI; m/z (%)) home-built spectrometer based on the ELFS-4-162-8-Extranuclear quadrupole [11]. UV spectra (λ_{max} in nm, ε in mol^{-1} l cm^{-1}): Perkin-Elmer Lambda-3 spectrophotometer. IR spectra: Perkin-Elmer 337 spectrometer (ν_{max} in cm^{-1}). Reverse-phase HPLC: 25 × 1 cm column filled with Merck LiChroprep RP-8 (7 nm); HPLC: 25 × 1 cm column filled with Merck LiChrosorb Si-60 (7 nm), UV monitoring at 254 nm, solvent flux 5 ml min^{-1}. Flash chromatography: Merck Kieselgel 60, 15–25 nm. TLC: Merck Si_{F254} plates.

Collection and isolation

The sponge was collected by dredging in September 1985 south-east of Noumea at a depth of 500 m and was identified by Professor C. Levi. The fresh sponge was lyophilized and then extracted with 80% EtOH. The extract was partly evaporated and then partitioned between water and CH_2Cl_2. The organic layer was evaporated to dryness to leave a dark sticky residue (1.18 g) which was subjected to flash chromatography on 20 g of SiO_2 with hexane/AcOEt gradient elution, collecting 20 fractions of 50 ml each. The sixth fraction was evaporated and the residue was subjected to reverse-phase HPLC with CH_3CN/H_2O 62/38 obtaining pure **1** (15 mg) at t_R = 8.2 min. Similar work-up of the ninth flash-chromatographic fraction with CH_3CN/H_2O 42/58 led to pure **3** (32 mg, t_R = 9.3 min).

Flash-chromatographic fractions 13 and 14 were evaporated and then first subjected to reverse-phase HPLC with CH_3CN/H_2O 3/7 and then the fraction containing product **2** was further subjected to HPLC with hexane/AcOEt 1/3 to give pure **2** (12 mg, t_R = 7.1 min).

*Ethyl 6-bromo-3-indolcarboxylate (**1**)*

Colorless microcrystalline powder, m.p. 147–149 °C (MeOH). ^1H NMR ($(CD_3)_2CO$) δ 11.09 (br. s, NH), 8.04 (d, J = 2.8, H-C(2)), 8.05 (dd, J = 8.5, 0.6, H-C(4)), 7.34 (dd, J = 8.5, 1.8, H-C(5)), 7.74 (dd, J = 1.8, 0.6, H-C(7)), 4.32 (q, J = 7.2, 2H-C(2′)), 1.37 (t, J = 7.2, 3H-C(3′)). ^{13}C NMR ($(CD_3)_2CO$) δ 133.28 (d, C(2)), 130.84 (s, C(3)), 126.11 (s, C(3a)), 123.42 (d, C(4)), 125.25 (d, C(5)), 116.41 (s, C(6)), 115.86 (d, C(7)), 138.47 (s, C(7a)), 164.90 (s, C(1′)), 60.00 (t, C(2′)), 14.84 (q, C(3′)). MS: 269–267 (45, $M^{+\cdot}$), 241–239 (27, $M^{+\cdot}-28$), 224–222 (100, $M^{+\cdot}-OCH_2CH_3$).

*Synthesis of ethyl 6-bromo-3-indolcarboxylate (**1**)*

6-Bromoindol-3-carboxaldehyde (**3**) [8] (9 mg, 0.04 mmol) in 2 ml of 1:1 acetone–water was added of $KMnO_4$ [12] (8 mg, 0.05 mmol). After 48 h of stirring at room temperature, TLC indicated the complete disappearance of **3** from the mixture which was filtered on silica gel. Crude **5**, obtained by evaporation of the filtrate, was dissolved in 2 ml of EtOH and added of 1,3-dicyclohexylcarbodiimide (10.3 mg, 0.05 mmol) and of 4-dimethylaminopyridine (6.1 mg, 0.05 mmol) [13]. The mixture was stirred at room temperature for 24 h and then filtered and evaporated. The residue was subjected to preparative silica-gel TLC with 2:3 hexane–AcOEt to give 3.2 mg of pure **1** with physical data identical to those of the natural product.

*Synthesis of the ethyl ester of 6-bromo-3-indolglyoxylic acid (**4**)*

3-Hydroxyacetyl-6-bromoindole (**2**) (5 mg, 0.02 mmol) was stirred with 6 molar equivalents of PCC in 1 ml of CH_2Cl_2, whereby all **2** disappeared. The mixture was added of 2 ml of EtOH and, after 1 h, it was filtered on silica gel Si-60 (15–25 μm). The filtrate was evaporated and the residue was subjected to HPLC with hexane/AcOEt 3/2 to give 1.8 mg of pure **4** (t_R = 6.1 min). M.p. 240–242 °C (lit. [14] 241–242 °C). ^1H NMR ($(CD_3)_2CO$) δ 11.48 (br. s, NH), 8.50 (br. s, H-C(2)), 8.23 (d, J = 8.5, H-C(4)), 7.45 (dd, J = 8.5, 1.9, H-C(5)), 7.70 (d, J = 1.8, H-C(7)), 4.39 (q, J = 7.2, 2H-C(3′)), 1.38 (t, J = 7.2, 3H-C(4′)).

*3-Hydroxyacetyl-6-bromoindole (**2**)*

Colorless microcrystalline powder, m.p. 194–196 °C (MeOH). UV λ_{max} 293 (9200), 265 (12200), 242 (13100), 217 (24100); IR (KBr) 3420s, 3250s, 1650s, 1635s; ^1H NMR ($(CD_3)_3CO$) δ 11.29 (br. s, NH), 8.34 (d, J = 2.9, H-C(2)), 8.20 (dd, J = 8.4, 0.6, H-C(4)), 7.37 (dd, J = 8.4, 1.8, H-C(5)),

7.74 (dd, $J = 1.8, 0.6$, H-C(7)), 4.71 (s, 2H-C(2′)). ^{13}C NMR ($(CD_3)_2CO$) δ 134.16 (d, C(2)), 114.41 (s, C(3)), 125.58 (s, C(3a)), 123.92 (d, C(4)), 125.94 (d, C(5)), 116.96 (s, C(6)), 115.83 (d, C(7)), 138.44 (s, C(7a)), 194.59 (s, C(1′)), 66.00 (t, C(2′)). MS: 255–253 (9, $M^{+\cdot}$), 224–222 (100, $M^{+\cdot}-CH_2OH$), 196–194 (20, $M^{+\cdot}-COCH_2OH$).

Acknowledgements

We thank Professor C. Levi of the Laboratoire de Biologie des Invertébrés Marins et Malacologie, Muséum National d'Histoire Naturelle, Paris, for the sponge identification. This work has been carried out within the framework of the collaborative program ORSTOM-CNRS on Marine Substances of Biological Interest. The work in Trento has been supported by MPI (Progetti di Interesse Nazionale) and CNR (Roma).

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