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# 1,2-Bis(1*H*-indol-3-yl)ethane-1,2-dione, an Indole Alkaloid from the Marine Sponge *Smenospongia* sp.

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1,2-Bis(1*H*-indol-3-yl)ethane-1,2-dione (**1**), a bisindole alkaloid, was isolated from the marine sponge *Smenospongia* sp. The known compounds indole-3-carbaldehyde (**2**), 6-bromoindole-3-carbaldehyde (**3**), and tryptamine (**4**) and mixtures of the (*Z/E*) isomers of 6-bromo-2'-demethylaplysinopsin (**5a/5b**) and 6-bromo-3'-deimino-2',4'-bis(demethyl)-3'-oxoaplysinopsin (**6a/6b**) were also isolated.

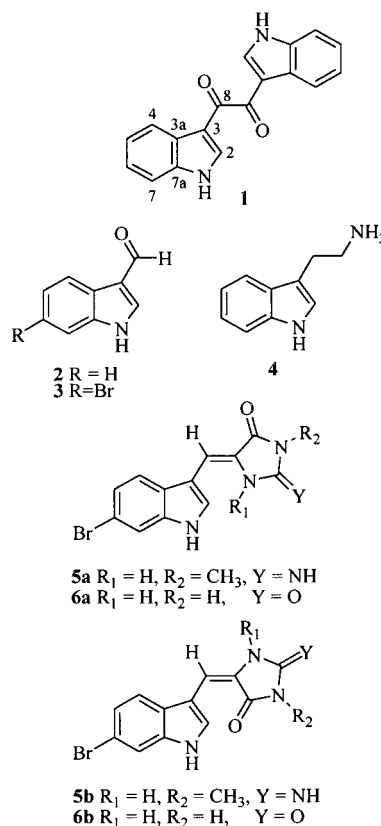
An extensive variety of indole alkaloids have been isolated from marine organisms.<sup>1–6</sup> In our investigations into the chemistry of marine organisms, we have isolated a variety of simple indole alkaloids from a marine sponge, including a symmetrical bisindole alkaloid. We report here the isolation and structural elucidation of the symmetrical bisindole dimer 1,2-bis(1*H*-indol-3-yl)ethane-1,2-dione (**1**) from the marine sponge *Smenospongia* sp (Thorectidae). Although **1** has been synthesized previously,<sup>7–11</sup> this is the first report on the isolation of this compound from a natural source. The known alkaloids indole-3-carbaldehyde (**2**), 6-bromoindole-3-carbaldehyde (**3**), and tryptamine (**4**) and mixtures of the (*Z/E*) isomers of 6-bromo-2'-demethylaplysinopsin (**5a/5b**) and 6-bromo-3'-deimino-2',4'-bis(demethyl)-3'-oxoaplysinopsin (**6a/6b**) were also isolated.

Aplysinopsin-type alkaloids have previously been isolated from several marine sponges,<sup>12,13</sup> particularly of the family Thorectidae,<sup>14–18</sup> and some dendrophylliid corals.<sup>19–22</sup> The isolation of **1–6** provided an insight into the taxonomy of the sponge under investigation.

The freeze-dried marine sponge *Smenospongia* sp. was exhaustively extracted with MeOH. The extract was chromatographed on a DIOL bonded silica column using stepwise elution with *i*-PrOH/hexane mixtures. The fraction eluting with 25% *i*-PrOH/hexane was purified by semipreparative HPLC using DIOL bonded silica. Gradient elution afforded 6-bromoindole-3-carbaldehyde **3**,<sup>23–28</sup> indole-3-carbaldehyde **2**,<sup>21,23–25,28–30</sup> 1,2-bis(1*H*-indol-3-yl)ethane-1,2-dione **1**, a 9:1 mixture of (*Z/E*) isomers of 6-bromo-2'-demethylaplysinopsin **5a/5b**,<sup>12,20</sup> a 9:1 mixture of (*Z/E*) isomers of 6-bromo-3'-deimino-2',4'-bis(demethyl)-3'-oxoaplysinopsin **6a/6b**,<sup>14,19</sup> and tryptamine **4**,<sup>18,31</sup> respectively.

The high-resolution negative electrospray mass spectrum [(–)-HRESMS] of **1** gave a  $M - H^+$  ion at  $m/z$  287.0818, appropriate for a molecular formula  $C_{18}H_{12}N_2O_2$ . The IR spectrum contained characteristic bands at 3300 (broad, N–H) and 1605  $cm^{-1}$  (strong, C=O).

The <sup>13</sup>C NMR spectrum of **1** shows only nine signals (see Table 1). Analysis of the <sup>13</sup>C NMR spectrum in conjunction with DEPT and HMQC spectra indicated that four quaternary (189.3, 137.8, 127.0, and 114.1 ppm) and five methine carbons (137.3, 124.2, 123.1, 122.6, and 112.8 ppm) were present. The <sup>1</sup>H NMR spectrum of **1** (see Table 1) shows only six downfield signals, including resonances at



$\delta$  8.42 (d,  $J = 7.2$  Hz), 7.31 (dd,  $J = 7.2, 6.1$  Hz), 7.29 (dd,  $J = 7.2$  and 6.1 Hz), and 7.58 (m) indicative of an *ortho*-disubstituted benzene ring. The remaining two signals in the <sup>1</sup>H NMR spectrum are for an aromatic methine proton at  $\delta$  8.33 (d,  $J = 3.1$  Hz) and an exchangeable NH proton at  $\delta$  11.26 (br s). Consideration of the molecular formula in conjunction with the <sup>1</sup>H and <sup>13</sup>C NMR data suggested that **1** is a symmetrical dimer. A comparison of the NMR data for **1** with that of the known metabolite **2** indicated that **1** is similarly composed of a 3-substituted indole nucleus.

HMBC and COSY correlations for the four aromatic methine proton signals were used to identify the connectivity of the *ortho*-disubstituted benzene ring of the indole nucleus. Specifically, <sup>3</sup> $J_{C-H}$  HMBC correlations were observed from the aromatic methine protons at  $\delta$  8.42 and 7.29 to a quaternary carbon at 137.8 ppm and from the aromatic methine protons at  $\delta$  7.58 and 7.31 to a quaternary carbon at 127.0 ppm. <sup>3</sup> $J_{C-H}$  HMBC correlations from

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**Table 1.** NMR Data for 1,2-Bis(1*H*-indol-3-yl)ethane-1,2-dione (**1**)<sup>a</sup>

| position    | <sup>13</sup> C ppm (mult) <sup>b</sup> | $\delta$ <sup>1</sup> H (mult, <i>J</i> in Hz) | COSY       | HMBC (H to C)       |
|-------------|---|--|------------|---------------------|
| 1-NH, 1-NH' |   | 11.26 (br s)                                   | 8.33       | 114.1, 127.0        |
| 2, 2'       | 137.3 (d)                               | 8.33 (d, 3.1)                                  | 11.26      | 114.1, 127.0, 137.8 |
| 3, 3'       | 114.1 (s)                               |  |            |                     |
| 3a, 3a'     | 127.0 (s)                               |  |            |                     |
| 4, 4'       | 124.2 (d)                               | 8.42 (d, 7.2)                                  | 7.31       | 123.1, 137.8        |
| 5, 5'       | 122.6 (d)                               | 7.31 (dd, 7.2, 6.1)                            | 8.42, 7.29 | 127.0, 112.8        |
| 6, 6'       | 123.1 (d)                               | 7.29 (dd, 7.2, 6.1)                            | 7.31, 7.58 | 124.2, 137.8        |
| 7, 7'       | 112.8 (d)                               | 7.58 (m)                                       | 7.29       | 127.0, 122.6, 123.1 |
| 7a, 7a'     | 137.8 (s)                               |  |            |                     |
| 8, 8'       | 189.3 (s)                               |  |            |                     |

<sup>a</sup> Data recorded in acetone-*d*<sub>6</sub> at 30 °C. <sup>b</sup> Multiplicity assignments based on DEPT and HMQC spectra.

an aromatic methine proton at  $\delta$  8.33 to the quaternary carbons at 127.0 and 137.8 ppm confirmed that a 3-substituted indole nucleus is present. This was supported by the observation of <sup>2</sup>*J*<sub>C-H</sub> and <sup>3</sup>*J*<sub>C-H</sub> HMBC correlations from the NH proton at  $\delta$  11.26 to the quaternary carbons at 127.0 and 114.1 ppm. Only a downfield carbonyl resonance at 189.3 ppm in the <sup>13</sup>C NMR spectrum remained to be assigned. A comparison of the chemical shifts for C2, C3, and C3a of the indole nucleus of **1** (in DMSO-*d*<sub>6</sub>) with those for **2** and **3** indicated that the indole nucleus is substituted at position 3 with a carbonyl group. The <sup>13</sup>C NMR chemical shift at 189.3 ppm and a strong band at 1605 cm<sup>-1</sup> in the IR spectrum indicated that this carbonyl group is a conjugated diketo group.<sup>7-9</sup> Hence, the structure **1** was assigned to the symmetrical dimer 1,2-bis(1*H*-indol-3-yl)-ethane-1,2-dione. No HMBC correlation was observed from the aromatic methine proton(s) H2/H2' to the conjugated diketo carbonyl(s) C8/C8'. However, this observation is consistent with other 3-diketo-indoles isolated from marine organisms.<sup>32,33</sup> A comparison of the <sup>1</sup>H and <sup>13</sup>C NMR chemical shifts for **1** (in DMSO-*d*<sub>6</sub>) with those reported for synthetic **1** supported the structural assignment.<sup>9</sup>

The structures of compounds **2**,<sup>28,34</sup> **3**,<sup>25,26</sup> **4**,<sup>34</sup> **5a/5b**,<sup>12,20</sup> and **6a/6b**<sup>14,19</sup> were determined by interpretation of 1D and 2D NMR spectral data (<sup>1</sup>H, <sup>13</sup>C, DEPT, COSY, HMQC, and HMBC) and confirmed by comparison of the spectral data with reported values. Each of the geometric isomers **5a/5b** and **6a/6b** could be obtained in the pure form by HPLC; however, their structures were determined from mixtures of the geometric pairs due to the rapid interconversion and equilibration of the pure isomers. The rapid isomerization of other aplysinopsin-type alkaloids has previously been reported.<sup>19,20</sup>

This is the first report on the isolation of 1,2-bis(1*H*-indol-3-yl)ethane-1,2-dione **1** from a marine organism. However, **1** has previously been prepared synthetically.<sup>7-11</sup>

Identification of the sponge proved difficult since it displayed morphological characteristics common to both *Aplysina* and *Smenospongia* species. Previous reports have also indicated that some *Aplysina* and *Smenospongia* species display similar morphological characteristics.<sup>14,17,18</sup> Sponges of the genus *Aplysina* have been studied frequently and are known to characteristically contain bromotyrosine derivatives,<sup>18</sup> while aplysinopsin-type alkaloids and some tryptamine derivatives have previously been reported from sponges of the genus *Smenospongia*.<sup>14,17,18</sup> Therefore, the presence of the symmetrical dimer **1** and the alkaloids **4**–**6** indicate that the sponge was more likely

to be a *Smenospongia* sp. (Thorectidae) rather than an *Aplysina* sp.

Hyrotisin B, the 5/5'-dihydroxy analogue of **1**, has previously been isolated from the Thorectidae sponge *Hyrtios erecta*.<sup>33</sup>

## Experimental Section

**General Experimental Procedures.** NMR spectra for all compounds were recorded in DMSO-*d*<sub>6</sub> (<sup>1</sup>H  $\delta$  2.49, <sup>13</sup>C 39.5 ppm) at 25 °C on a Varian UNITY 400 MHz spectrometer operating at 400.009 MHz for <sup>1</sup>H and 100.582 MHz for <sup>13</sup>C. NMR spectra for **1** in acetone-*d*<sub>6</sub> (<sup>1</sup>H  $\delta$  2.05, <sup>13</sup>C 206.0 and 30.5 ppm) were recorded at 30 °C on a Varian UNITY INOVA 600 MHz spectrometer operating at 599.926 MHz for <sup>1</sup>H and 149.980 MHz for <sup>13</sup>C and on a Varian UNITY 400 MHz spectrometer at 25 °C. LRESMS were recorded on a VG platform II electrospray mass spectrometer. HRESMS were recorded on a Bruker BioAPEX 47e mass spectrometer equipped with Bradford CT 06405 electrospray ion source. FTIR spectra were recorded on a Perkin-Elmer 1725X spectrophotometer. UV spectra were recorded in methanol on a GBC UV/vis 916 spectrophotometer. Alltech Davisil 30–40  $\mu$ m 60 Å DIOL was used for flash column chromatography (30 mm D  $\times$  60 mm L). HPLC separations were performed with a Waters 600 pump, Waters 600 controller, and Waters 996 PDA detector equipped with a Waters fraction collector. A YMC 5  $\mu$ m 120 Å DIOL column (10 mm D  $\times$  250 mm L) was used for HPLC separations.

**Animal Material.** A specimen of the sponge *Smenospongia* sp. was collected in January 1996 by scuba at a depth of 30 m on the south side of Porpoise Cay, Queensland, Australia. A voucher specimen, QMG 306511, has been deposited at the Queensland Museum, South Brisbane, Queensland, Australia.

**Extraction and Isolation.** A sample of the olive-yellow sponge (16 g) was freeze-dried, then exhaustively extracted with methanol (5  $\times$  100 mL). The combined extracts were filtered, and the solvent was evaporated under vacuum. The extract (990 mg) was fractionated on a DIOL-bonded silica flash column eluted in a stepwise manner with hexane, 25% *i*-PrOH/hexane, 50% *i*-PrOH/hexane, 75% *i*-PrOH/hexane, and 100% *i*-PrOH. The fraction eluting with 25% *i*-PrOH/hexane was subjected to semipreparative HPLC using DIOL-bonded silica. Gradient elution from 15% *i*-PrOH/hexane to 30% *i*-PrOH/hexane using a flowrate of 3 mL/min afforded 6-bromoindole-3-carbaldehyde (**3**, 5.3 mg, 0.033% dry wt), indole-3-carbaldehyde (**2**, 7.4 mg, 0.046% dry wt), 1,2-bis(1*H*-indol-3-yl)ethane-1,2-dione (**1**, 3.2 mg, 0.020% dry wt), a 9:1 mixtures of (Z/E) stereoisomers of 6-bromo-2'-demethylaplysinopsin (**5a/5b**, 6.2 mg, 0.039% dry wt), a 9:1 mixture of (Z/E) stereoisomers of 6-bromo-3'-deimino-2',4'-bis(demethyl)-3'-oxoaplysinopsin (**6a/6b**, 4.2 mg, 0.026% dry wt), and tryptamine (**4**, 15.2 mg, 0.095% dry wt), respectively.

**1,2-Bis(1*H*-indol-3-yl)ethane-1,2-dione (**1**):** colorless solid; UV (MeOH)  $\lambda_{\text{max}}$  247 (13 200), 267 (13 600), 324 (12 400), 354 (5600); IR (film)  $\nu_{\text{max}}$  3300, 1605, 1433, 1240, 1118, 780, 732 cm<sup>-1</sup>; <sup>1</sup>H and <sup>13</sup>C NMR data in acetone-*d*<sub>6</sub>, see Table 1; (–)-HRESMS *m/z* 287.0818 (calcd for C<sub>18</sub>H<sub>11</sub>N<sub>2</sub>O<sub>2</sub> [M – H]<sup>–</sup>, 287.0826).

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