Dioxopiperazine Alkaloids Produced by the Marine Mangrove Derived Endophytic Fungus *Eurotium rubrum*

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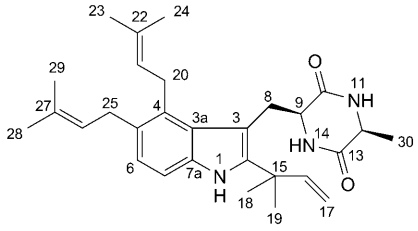
Cultivation of the fungal strain *Eurotium rubrum*, an endophytic fungus that was isolated from the inner tissue of stems of the mangrove plant *Hibiscus tiliaceus*, resulted in the isolation of two new dioxopiperazine derivatives, namely, dehydrovariecolorin L (**1**) and dehydroechinulin (**2**), together with eight known dioxopiperazine compounds including variecolorin L (**3**), echinulin (**4**), isoechinulin A (**5**), dihydroxyisoechinulin A (**6**), preechinulin (**7**), neoechinulin A (**8**), neoechinulin E (**9**), and cryptoechinuline D (**10**). The structures of the isolated compounds were determined by extensive analysis of their spectroscopic data as well as by comparison with literature. Compounds **1**, **2**, **9**, and **10** were investigated for their α,α-diphenyl-β-picrylhydrazyl (DPPH) radical-scavenging activity. In addition, the new compounds, **1** and **2**, were evaluated for their cytotoxic activity against the P-388, HL-60, and A549 cell lines.

Introduction. – A number of tryptophan-derived alkaloids, characterized by a reversed isoprenic chain in the C(2) position of the indole and a 2,5-dioxopiperazine moiety, have been isolated from the genus *Aspergillus* [1–5]. These metabolites are of interest because of their activity in various pharmacological assay systems [6]. The genus *Eurotium* is the teleomorphs of *Aspergillus*, and is also a common source of tryptophan-derived alkaloids, *i.e.*, echinulins and neoechinulins [7].

This article describes the isolation, structure elucidation, and biological activity of two new dioxopiperazine derivatives (**1** and **2**) from the endophytic fungal strain *Eurotium rubrum* which was isolated from the inner tissue of stems of the marine mangrove plant *Hibiscus tiliaceus*. In addition, eight known dioxopiperazine derivatives, including variecolorin L (**3**) [8], echinulin (**4**) [9], isoechinulin A (**5**) [10], dihydroxyisoechinulin A (**6**) [4], preechinulin (**7**) [11], neoechinulin A (**8**) [12], neoechinulin E (**9**) [12], and cryptoechinuline D (**10**) [13], were also isolated and identified. It deserves to be mentioned that just at the time when we started to prepare this manuscript, compound **3** was reported as a new metabolite of *Aspergillus variecolor* B-17, a halotolerant fungal strain isolated from a sediment collection of a salt field in inner Mongolia, China [8].



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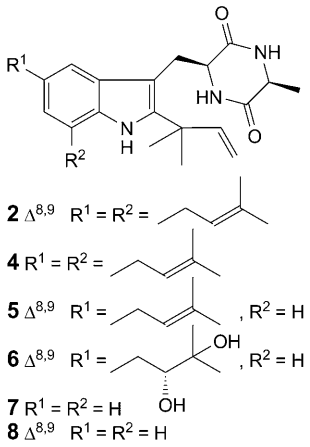
1 $\Delta^{8,9}$



2 $\Delta^{8,9}$ $R^1 = R^2 =$
4 $R^1 = R^2 =$
5 $\Delta^{8,9}$ $R^1 =$, $R^2 = H$
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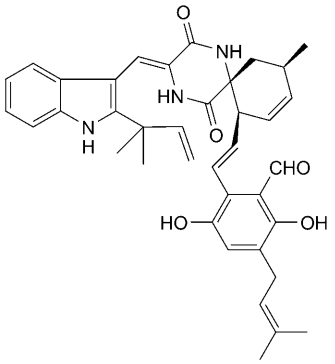
7 $R^1 = R^2 = H$
8 $\Delta^{8,9}$ $R^1 = R^2 = H$



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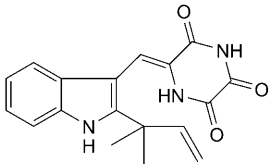

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Results and Discussion. – 1. *Isolation and Structure Elucidation*. Mycelium and culture broth of *E. rubrum* were homogenized using a *Waring* blender and exhaustively extracted with MeOH and AcOEt, respectively. Since the TLC and HPLC profiles of the two extracts were nearly identical, they were combined before further separation. The combined extracts were further purified by a combination of column chromatography on silica gel, *Sephadex LH-20*, and reversed-phase silica gel, to yield two new, **1** and **2**, and eight known dioxopiperazine derivatives, **3**–**10**.

Compound **1** was obtained as a colorless amorphous powder. The IR spectrum showed absorption bands for OH (3396 cm^{-1}), C=O (1670 cm^{-1}), and aromatic (1657 and 1562 cm^{-1}) functionalities in the molecules. Low-resolution EI-MS displayed a strong *quasi*-molecular ion peak at *m*/*z* 460 ($[M+H]^+$), and a base peak of the molecular ion at *m*/*z* 459 (M^+). The molecular formula was determined as $C_{29}H_{37}N_3O_2$ on the basis of positive HR-ESI-MS (*m*/*z* 482.2774, $[M+Na]^+$, $C_{29}H_{37}N_3NaO_2^+$; calc. 482.2783), which was in agreement with the ^{1}H- and ^{13}C-NMR spectral data (*Table*). The ^{1}H-NMR spectrum exhibited signals attributed to three NH groups at δ(H) 8.14 (H–N(1)), 7.20 (H–N(14)), and 6.67 (H–N(11)), two aromatic H-atoms at δ(H) 7.13 (H–C(7)) and 7.01 (H–C(6)), six olefinic H-atoms at δ(H) 7.20 (H–C(8)), 6.04 (H–C(16)), 5.23 (H–C(26)), 5.16 (H_a–C(17)), 5.14 (H_b–C(17)), and 4.97 (H–C(21)), one aliphatic CH group at δ(H) 4.20 (H–C(12)), two aliphatic CH_2 groups at δ(H) 3.56 (CH_2(20)) and 3.32 (CH_2(25)), and seven Me groups at δ(H) 1.70

(Me(28) and Me(29)), 1.67 (Me(24)), 1.64 (Me(23)), 1.54 (Me(30)), 1.46 (Me(18) and Me(19)) (*Table*). The ^{13}C-NMR spectrum showed the presence of 29 C-atoms including seven Me groups, three CH_2 groups, seven CH groups, and twelve quaternary C-atoms according to the DEPT experiments (*Table*). Detailed analysis of the ^{1}H- and ^{13}C-NMR spectra revealed that **1** was a dioxopiperazine alkaloid derivative containing an indole moiety. Comparison of the ^{1}H- and ^{13}C-NMR spectral data of **1** with those of variecolorin L (**3**, *Table*) [8] revealed that the structures of these two compounds are very similar. However, an additional C(8)=C(9) bond was present in **1**, which was evidenced by the fact that the aliphatic CH_2 H-atom signals observed at δ(H) 3.15 and 3.45 (H_α–C(8) and H_β–C(8), resp.) and the aliphatic CH H-atom signal at δ(H) 3.99 (H–C(9)) in **3** disappeared in the ^{1}H-NMR spectrum of **1**. Instead, a *singlet* olefinic H-atom signal at δ(H) 7.20 (H–C(8)) was present. This observation was supported by the fact that the aliphatic CH_2 and CH groups at δ(C) 30.3 and 55.6 (for C(8) and C(9), resp.) in the ^{13}C-NMR spectrum of **3** were replaced by the olefinic CH group and quaternary C-atom at δ(C) 114.9 (C(8)) and 128.1 (C(9)), respectively, in the ^{13}C-NMR spectrum of **1**. The position of the C=C bond at C(8) and C(9) was further confirmed by the observed HMBC correlations from H–C(8) at δ(H) 7.20 to C(2) at δ(C) 141.3 and C(10) at δ(C) 159.1 (*Fig.*). The chemical shift of H–C(8) (δ(H) 7.20), which is shifted to lower field by the deshielding effect of the C=O group, suggested the geometry of the C=C bond at C(8) to be (*Z*). The absolute configuration of **1** was determined to be the same as that of cristatin A [5] by comparison of their optical rotation ($[\alpha]_D^{25} = -24.6$ for **1** *vs.* -26.3 for cristatin A, both determined in $CHCl_3$). Based on the above spectral evidence, the structure of **1** was established as (6*S*)-3-{[2-(1,1-dimethylprop-2-en-1-yl)-4,5-bis(3-methylbut-2-en-1-yl)-1*H*-indol-3-yl]methylidene}-6-methylpiperazine-2,5-dione, which was named dehydrovariecolorin L.

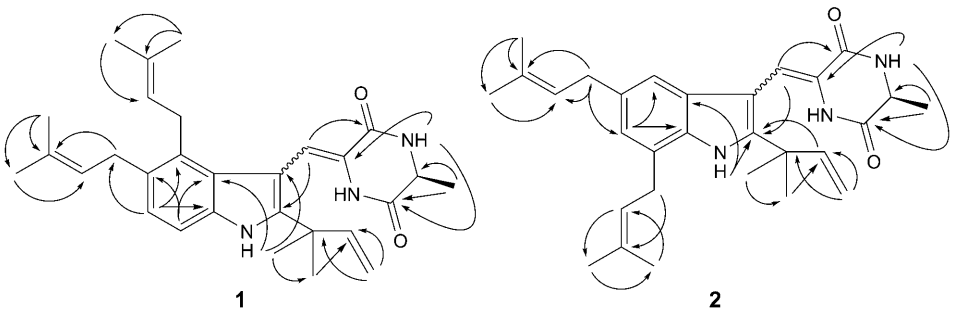

Figure. *Selected HMBC correlations for* **1** *and* **2**

Compound **2** was obtained as colorless needles. The IR spectrum showed absorption bands for OH (3400 cm^{-1}), C=O (1718 cm^{-1}), and aromatic (1655 and 1560 cm^{-1}) functionalities in the molecules. The molecular formula was determined as $C_{29}H_{37}N_3O_2$ on the basis of the signal of positive HR-ESI-MS (*m*/*z* 460.2973 ($[M+H]^+$, $C_{29}H_{38}N_3O_2^+$; calc. 460.2964)), which was in agreement with the ^{1}H- and ^{13}C-NMR spectral data (*Table*). Detailed examination of the NMR spectral data and comparison

Table. *NMR Data of* **1**–**4**. At 500 MHz for ^{1}H and 125 MHz for ^{13}C, in $CDCl_3$. Assignments were corroborated by ^{1}H,^{1}H-COSY, HMQC, and HMBC experiments.

	1		**3**[a])	**2**		**4**[b])
	δ(H)	δ(C)	δ(C)	δ(H)	δ(C)	δ(C)
H–N(1)	8.14 (br. *s*)			8.30 (br. *s*)		
C(2)		141.3 (*s*)	141.7 (*s*)		143.2 (*s*)	141.4 (*s*)
C(3)		101.8 (*s*)	104.8 (*s*)		102.9 (*s*)	104.1 (*s*)
C(3a)		126.6 (*s*)	126.2 (*s*)		126.5 (*s*)	128.9 (*s*)
C(4) or H–C(4)		131.5 (*s*)	130.4 (*s*)	6.91 (*s*)	115.9 (*d*)	115.0 (*d*)
C(5)		132.3 (*s*)	129.6 (*s*)		134.9 (*s*)	133.9 (*s*)
H–C(6)	7.01 (*d*, J = 8.3)	124.5 (*d*)	122.8 (*d*)	6.82 (*s*)	123.2 (*d*)	122.9 (*d*)
H–C(7)	7.13 (*d*, J = 8.3)	108.8 (*d*)	109.2 (*d*)		124.2 (*s*)	123.4 (*s*)
C(7a)		133.7 (*s*)	134.6 (*s*)		132.2 (*s*)	132.2 (*s*)
H–C(8)	7.20 (*s*)	114.9 (*d*)	30.3 (*t*)	7.19 (*s*)	112.2 (*d*)	29.4 (*t*)
C(9)		128.1 (*s*)	55.6 (*d*)		124.4 (*s*)	54.5 (*d*)
C(10)		159.1 (*s*)	167.8 (*s*)		160.1 (*s*)	168.3 (*s*)
H–N(11)	6.67 (br. *s*)			6.95 (br. *s*)		
H–C(12)	4.20 (br. *s*)	51.6 (*d*)	50.0 (*d*)	4.29 (*dq*, J = 7.0, 1.8)	51.7 (*d*)	50.8 (*d*)
C(13)		165.6 (*s*)	167.5 (*s*)		165.5 (*s*)	167.7 (*s*)
H–N(14)	7.20 (br. *s*)			7.44 (br. *s*)		
C(15)		39.0 (*s*)	39.3 (*s*)		39.2 (*s*)	39.0 (*s*)
H–C(16)	6.04 (*dd*, J = 17.4, 10.6)	144.8 (*d*)	146.7 (*d*)	6.05 (*dd*, J = 17.4, 10.6)	144.5 (*d*)	145.7 (*d*)
H_a–C(17)	5.16 (br. *d*, J = 10.6)	112.7 (*t*)	111.0 (*t*)	5.27 (br. *d*, J = 10.6)	113.0 (*t*)	112.3 (*t*)
H_b–C(17)	5.14 (br. *d*, J = 17.4)			5.18 (br. *d*, J = 17.4)		
Me(18)	1.46 (*s*)	27.0 (*q*)	28.6 (*q*)	1.50 (*s*)	27.3 (*q*)	27.9 (*q*)
Me(19)	1.46 (*s*)	27.0 (*q*)	28.1 (*q*)	1.50 (*s*)	27.3 (*q*)	27.8 (*q*)
CH_2(20)	3.56 (br. *s*)	28.3 (*t*)	27.3 (*t*)	3.39 (*t*, J = 7.3)	34.5 (*t*)	34.6 (*t*)
H–C(21)	4.97 (br. *s*)	124.4 (*d*)	124.5 (*d*)	5.34 (*t*, J = 7.3)	124.2 (*d*)	124.5 (*d*)
C(22)		131.1 (*s*)	130.4 (*s*)		131.9 (*s*)	131.6 (*s*)
Me(23)	1.64 (*s*)	25.5 (*q*)	25.6 (*q*)	1.73 (*s*)	25.7 (*q*)	25.7 (*q*)
Me(24)	1.67 (*s*)	18.1 (*q*)	18.1 (*q*)	1.72 (*s*)	17.8 (*q*)	17.9 (*q*)
CH_2(25)	3.32 (*d*, J = 5.7)	31.2 (*t*)	31.3 (*t*)	3.55 (*d*, J = 7.3)	31.3 (*t*)	31.4 (*t*)
H–C(26)	5.23 (*t*, J = 6.7)	124.4 (*d*)	125.0 (*d*)	5.43 (*t*, J = 7.4)	122.8 (*d*)	122.9 (*d*)
C(27)		131.2 (*s*)	129.9 (*s*)		133.1 (*s*)	132.9 (*s*)
Me(28)	1.70 (*s*)	25.7 (*q*)	25.6 (*q*)	1.81 (*s*)	25.7 (*q*)	25.8 (*q*)
Me(29)	1.70 (*s*)	17.8 (*q*)	17.7 (*q*)	1.87 (*s*)	17.9 (*q*)	17.9 (*q*)
Me(30)	1.54 (*d*, J = 6.9)	21.0 (*q*)	19.8 (*q*)	1.61 (*d*, J = 7.0)	20.9 (*q*)	19.9 (*q*)

[a]) Data cited from [8], recorded in (D_6)DMSO. [b]) Data cited from [9], recorded in $CDCl_3$.

with those reported for echinulin (**4**, *Table*) [9] showed that the structures of these two compounds are very similar. However, in the ^{1}H-NMR spectrum, the aliphatic CH_2 H-atom signals at δ(H) 3.19 (*dd*, H_α–C(8)) and 3.66 (*dd*, H_β–C(8)) and the aliphatic CH group at δ(H) 4.40 (br. *d*, H–C(9)) in **4** disappeared in **2**. Instead, an olefinic CH group at δ(H) 7.19 (*s*, H–C(8)) was observed. This observation was supported by the fact that the aliphatic CH_2 and CH groups at δ(C) 29.4 (C(8)) and 54.5 (C(9)) in **4** were replaced by the olefinic CH group and the quaternary C-atom at δ(C) 112.2 (C(8)) and 124.4 (C(9)) in **2**, respectively. The placement of the C=C bond at C(8) and C(9) was further

confirmed by the observed HMBC correlations from H–C(8) at δ(H) 7.19 to C(2) and C(10) at δ(C) 143.2 and 160.1, respectively (*Fig.*). The absolute configuration of the L-alanine residue in **2** ($[\alpha]_D^{25} = -7.7$, $CHCl_3$) was determined to be (*S*), as evidenced by the analogous optical rotation to that of **1** ($[\alpha]_D^{25} = -24.6$, $CHCl_3$). From the above deductions, the structure of **2** was assigned to be (6*S*)-3-{[2-(1,1-dimethylprop-2-en-1-yl)-5,7-bis(3-methylbut-2-en-1-yl)-1*H*-indol-3-yl]methylidene}-6-methylpiperazine-2,5-dione, which was named dehydroechinulin.

2. *Radical Scavenging Activity.* The radical scavenging activity of compounds **1**, **2**, **9**, and **10** were evaluated using the α,α-diphenyl-β-picrylhydrazyl (DPPH) radical-scavenging assay, while a similar assay for compounds **3**–**8** has already been evaluated and reported [8]. In this study, compounds **9** and **10** showed strong activities with IC_{50} values of 46.0 μM and 23.6 μM, respectively, while compounds **1** and **2** showed no activity ($IC_{50} > 160$ μM) compared to that of the positive control, butylated hydroxytoluene (BHT, with IC_{50} value of 82.6 μM).

3. *Cytotoxic Activity.* The new compounds **1** and **2** were tested for cytotoxic effects on P-388 and HL-60 cell lines by using of the MTT method and on A-549 cell line by using of the SRB method [14]. None of the two compounds was cytotoxic against any of the three cell lines.

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Experimental Part

General. Column chromatography (CC): commercial silica gel (*Qingdao Haiyang Chemical Group Co.*; 200–300 mesh), *Lobar LiChroprep RP-18* (40–63 μm; *Merck*), and/or *Sephadex LH-20* (*Sigma*). TLC: precoated silica gel plates *GF-254* (*Qingdao Haiyang*). Optical rotation: *Jasco P-1020* digital polarimeter. UV Spectra: *PuXi TU-1810* UV-visible spectrophotometer; λ_{max} (log ε) in nm. IR Spectra: *Nicolet NEXUS 470* spectrophotometer; in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: *Bruker Avance-500* spectrometer; at 500/125 MHz, resp.; δ in ppm, *J* in Hz. EI-MS and HR-ESI-MS: *VG Autospec-3000* mass spectrometer; in *m*/*z*.

Fungal Material. The endophytic fungus *Eurotium rubrum* was isolated from the inner tissue of stems of the mangrove plant *Hibiscus tiliaceus* collected from Hainan island, China, in August 2004, by a standard procedure [15]. Fungal identification was carried out by the method reported by us earlier [15]. The sequence data derived from the fungal strain has been submitted and deposited at GenBank with accession number EU001331. BLAST search result showed that the sequence was similar (99%) to the sequence of *Eurotium rubrum* (compared to gb AY373891.1). The strain is preserved with the Key Laboratory of Experimental Marine Biology, Institute of Oceanology, Chinese Academy of Sciences with accession number QEN-0407-G2.

Extraction and Isolation. For chemical investigations, the fungal strain was static cultivated in potato-dextrose (PD) liquid media containing 50% (*v*/*v*) sea water (glucose 10 g/l, mannitol 20 g/l, peptone 5 g/l, yeast extract 3 g/l, monosodium glutamate 3 g/l, pH 6.0) for 30 d at r.t. Mycelium and culture broth of *E. rubrum* (30 l) were homogenized using a *Waring* blender and exhaustively extracted with MeOH and AcOEt, resp. Since the TLC and HPLC profiles of the two extracts were nearly identical, they were combined before further separation. The combined extracts (70 g) were subjected to CC over SiO_2 (200–300 mesh) and eluted with different solvents of increasing polarity to yield 14 fractions (*Fr. 1*–*Fr. 14*) on the basis of TLC analysis. *Fr. 10* was further fractionated by CC on *Sephadex LH-20* ($CHCl_3$/MeOH, 2 : 1)

and then purified by CC on *Sephadex LH-20* (MeOH) to give compound **10** (7.0 mg). *Fr. 11* was subjected to CC over SiO_2 and then further purified by CC on *Sephadex LH-20* ($CHCl_3$/MeOH, 2:1) to yield compounds **1** (15.8 mg) and **2** (11.0 mg). *Fr. 12* was subjected to CC on *Sephadex LH-20* ($CHCl_3$/MeOH, 1:1) to afford compounds **5** (41.3 mg) and **9** (5.8 mg). *Fr. 13* was separated by CC on SiO_2 and then further purified by CC on *Sephadex LH-20* ($CHCl_3$/MeOH, 1:1) to obtain compounds **3** (45.6 mg), **4** (50.5 mg), and **8** (54.2 mg). *Fr. 14* was subjected to CC over reversed-phase silica gel C_{18} (MeOH) and further purified by CC on *Sephadex LH-20* ($CHCl_3$/MeOH, 1:1) to give compounds **6** (121.6 mg) and **7** (21.9 mg).

Dehydrovariecolorin L (=*(6S)-3-{[2-(1,1-Dimethylprop-2-en-1-yl)-4,5-bis(3-methylbut-2-en-1-yl)-1H-indol-3-yl]methylidene}-6-methylpiperazine-2,5-dione*; **1**). Colorless amorphous powder. M.p. 233–236°. $[\alpha]_D^{25} = -24.6$ ($c = 0.1$, $CHCl_3$). UV (MeOH): 225 (3.85), 337 (2.85). IR (KBr): 3396, 2958, 2923, 2852, 1670, 1657, 1562, 1545, 1439, 1220, 1097. ^{1}H- and ^{13}C-NMR: *Table*. EI-MS: 460 (33, $[M+H]^+$), 459 (100, M^+), 416 (27), 403 (13), 391 (22), 390 (87), 388 (29), 348 (16), 320 (24). HR-ESI-MS (pos.): 482.2774 ($[M+Na]^+$, $C_{29}H_{37}N_3NaO_2^+$; calc. 482.2783).

Dehydroechinulin (=*(6S)-3-{[2-(1,1-Dimethylprop-2-en-1-yl)-5,7-bis(3-methylbut-2-en-1-yl)-1H-indol-3-yl]methylidene}-6-methylpiperazine-2,5-dione*; **2**). Colorless needles. M.p. 210–214°. $[\alpha]_D^{22} = -7.7$ ($c = 0.1$, $CHCl_3$). UV (MeOH): 212 (3.38), 335 (2.85). IR (KBr): 3400, 2956, 2923, 2852, 1718, 1655, 1560, 1543, 1460, 1377, 1220, 1111. ^{1}H- and ^{13}C-NMR: *Table*. HR-ESI-MS (pos.): 460.2973 ($[M+H]^+$, $C_{29}H_{38}N_3O_2^+$; calc. 460.2964).

Determination of the DPPH Radical-Scavenging Activity. DPPH Radical-scavenging activity of compounds **1**, **2**, **9**, and **10** was evaluated by the method as our previous report [15].

Cytotoxicity Assays. Cytotoxic assay toward the P-388, HL-60, and A-549 cell lines were carried out as reported in the literature [14].

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