Structure and Absolute Configuration of Emestrin, a New Macrocyclic Epidithiodioxopiperazine from *Emericella striata*

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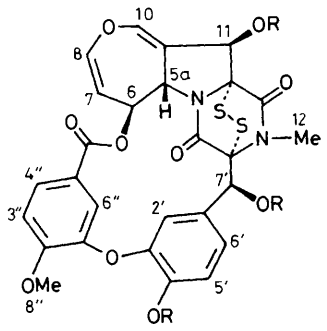
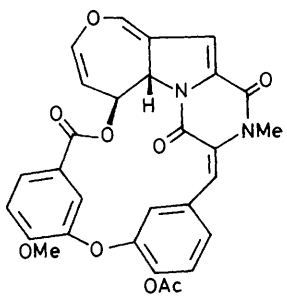
The structure elucidation of emestrin (**1**), a macrocyclic epidithiodioxopiperazine derivative isolated from the mycelial acetone extract of *Emericella striata*, is reported, based on its ^1H and ^{13}C n.m.r. spectra and an *X*-ray crystallographic study of its methanol solvate; its absolute configuration was established by its c.d. spectrum.

Emestrin (**1**), m.p. 233—236 °C (decomp.) from acetone, $[\alpha]_D^{20}$ +184° (*c* 0.23, $CHCl_3$), was isolated from the mycelium of *Emericella striata* (Rai, Tewari & Mukerji) Malloch & Cain, strain 80-NE-22,[1] a thermotolerant fungus collected in Nepal. Field-desorption mass spectrometry of (**1**) showed the molecular ion at *m/z* 598 and elemental analysis confirmed the empirical formula as $C_{27}H_{22}N_2O_{10}S_2$. The metabolite (**1**) had $\lambda_{max.}$ (MeOH) 230 (ε 27 400), 262 (15 600), and 278 (9100) nm; $\nu_{max.}$ (KBr) 3400, 1710, 1680, 1660, and 1610 cm^{-1}; and δ_H (CD_3SOCD_3) 3.255 (3H, s, 12-H), 3.944 (3H, s, 8″-H), 4.672 (1H, ddd, *J* 7.3, 2.4, and 2.0 Hz, 6-H), 4.910 (1H, dd, *J* 8.8 and 2.0 Hz, 7-H), 4.967 (1H, d, *J* 4.1 Hz, 7′-H), 5.466 (1H, d, *J* 7.1 Hz, 11-H), 5.672 (1H, dd, *J* 7.3 and 2.4 Hz, 5a-H), 5.994 (1H, d, *J* 4.1 Hz, 7′-OH), 6.254 (1H, d, *J* 7.1 Hz, 11-OH), 6.412 (1H, dd, *J* 8.8 and 2.4 Hz, 8-H), 6.883 (1H, d, *J* 8.3 Hz, 5′-H), 7.063 (1H, d, *J* 2.4 Hz, 10-H), 7.166 (1H, dd, *J* 8.3 and 2.0 Hz, 6′-H), 7.211 (1H, d, *J* 8.5 Hz, 3″-H), 7.377 (1H, d, *J* 2.0 Hz, 6″-H), 7.576 (1H, dd, *J* 8.5 and 2.0 Hz, 4″-H), 7.767 (1H, d, *J* 2.0 Hz, 2′-H), and 9.739 (1H, s, 4′-OH). Homonuclear ^1H-{^1H} decoupling experiments established the partial structure of the diphenyl ether and oxepine moiety. The triacetate (**2**), m.p. 215—217 °C (decomp.), $[\alpha]_D^{20}$ −27.4° (*c* 1.41, $CHCl_3$), was treated with Raney nickel to give compound (**3**), m.p. 282—285 °C, $[\alpha]_D^{20}$ −420° (*c* 0.87, $CHCl_3$). These ^1H and ^{13}C n.m.r. data confirm structure (**1**) for emestrin. Additional evidence was provided by *X*-ray crystallography of its methanol solvate.

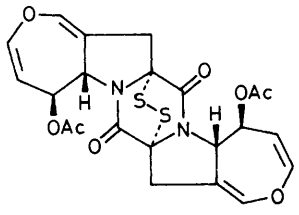
Emestrin crystallized from methanol–acetone as monoclinic crystals (m.p. 229—232 °C, $C_{27}H_{22}N_2O_{10}S_2 \cdot 2CH_4O$), space group $P2_1$ with $a = 15.256(5)$, $b = 7.788(3)$, $c = 12.203(3)$ Å, $\beta = 98.16(2)°$, $Z = 2$, $D_c = 1.53$ g cm^{-3}. Intensity measurements were made with Mo-K_α radiation (λ 0.7107 Å; graphite monochromator) on a Rigaku AFC-5 FOS diffractometer in the ω–2θ mode with $1 \leqslant \theta \leqslant 25°$. A total of 2758 unique reflections were measured, of which 1098 were regarded as unobserved with $F \leqslant 2.5\sigma(F)$. The measured reflections were corrected for Lorentz–polarization only. Accurate cell parameters were obtained by least-squares techniques from the diffractometer settings for 24 reflections. The structure was solved using MULTAN[2] and refined by block-diagonal least-squares. Convergence, with anisotropic thermal parameters for all non-hydrogen atoms except for the



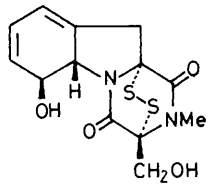
(1) R = H
(2) R = Ac



(3)



(4)



(5)

methanol atoms was reached at $R = 0.058$ ($R_w = 0.064$) using all the observed reflections. The difference electron density map based on the final atomic parameters showed no maxima greater than 0.34 e Å^{-3}.†

† The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW.

The resulting structure as well as the relative configuration was established as (**1**). The two aromatic rings are not co-planar because of the formation of the 15-membered ring. The molecules are mainly packed through hydrogen bonding interactions in the crystal.

The c.d. spectra of epidithiodioxopiperazines are known to show maxima at 235, 270, and 340 nm.[3] Comparison of the c.d. curve of (**1**) with those of the known epidithiodioxopiperazines acetylaranotin (**4**) and gliotoxin (**5**) showed that these fungal metabolites have the same absolute configuration. Emestrin must therefore have the 3*R*,11a*R* configuration and consequently the absolute structure is as depicted in (**1**).

Emestrin (**1**), which is derived biogenetically from two molecules of phenylalanine and a benzoate, has strong antifungal activity.

After the completion of this work, mycotoxin EQ-1, isolated from *Emericella quadrilineata*, *E. acristata*, and *E. parvathecia* by Professor M. Yamazaki[4] of Research Institute for Chemobiodynamics, Chiba University, was identified with emestrin.

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