Aurantioemestrin from *Emericella striata* and Silvathione from *Aspergillus silvaticus*, Possible Key Intermediates from Epidithiodioxopiperazines to Trioxopiperazines

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Two biogenetically possible key intermediates, from epidithiodioxopiperazines to trioxopiperazines, aurantioemestrin (**1**) and silvathione (**2**) were isolated from *Emericella striata* and *Aspergillus silvaticus*, respectively; their structure elucidation was based on their ^1H and ^{13}C n.m.r. spectra.

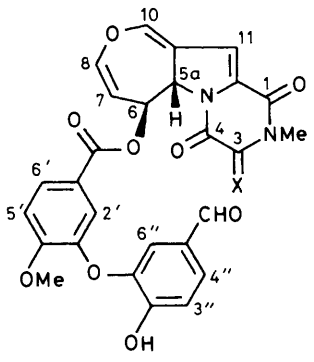
Recently we reported the isolation and structural elucidation of emestrin (**3**), a characteristic macrocyclic epidithiodioxopiperazine,[1,2] and dethiosecoemestrin (**4**), a trioxopiperazine possibly derived from (**3**),[3] from *Emericella striata* (Rai, Tewari & Mukerji) Malloch & Cain, strain 80-NE-22. In the course of successive searching for compounds related to (**3**) and (**4**), a compound designated as aurantioemestrin (**1**), m.p. 118—120 °C, $[\alpha]_D^{24}$ −556° (*c* 0.412, $CHCl_3$), was isolated from the culture filtrate of the same fungus. Field-desorption mass spectrometry and elemental analysis confirmed its empirical formula as $C_{27}H_{20}N_2O_9S$. The compound (**1**) had $\lambda_{max.}$ (EtOH) 227 sh (log ε 4.53), 263 (4.45), 287 sh (4.36), 340 (4.25), and 418 (4.01) nm; $\nu_{max.}$ (KBr) 3350, 1710, 1690, 1670, and 1595 cm^{-1}; and δ_H [$(CD_3)_2SO$] 3.665 (3H, s, NMe), 3.915 (3H, s, OMe), 5.021 (1H, br.d, *J* 8.3 Hz, 7-H), 5.445 (1H, ddd, *J* 8.3, 2.0, and 2.0 Hz, 6-H), 5.610 (1H, dd, *J* 8.3 and 2.0 Hz, 5a-H), 6.416 (1H, dd, *J* 8.3 and 2.0 Hz, 8-H), 6.870 (1H, s, 11-H), 7.052 (1H, d, *J* 8.4 Hz, 3″-H), 7.059 (1H, br.s, 10-H), 7.157 (1H, d, *J* 8.2 Hz, 5′-H), 7.425 (1H, d, *J* 1.8 Hz, 2′-H), 7.584 (1H, dd, *J* 8.2 and 1.8 Hz, 6′-H), 7.826 (1H, d, *J* 1.8 Hz, 6″-H), 7.988 (1H, dd, *J* 8.4 and 1.8 Hz, 4″-H), and 9.795 (1H, s, CHO). These ^1H n.m.r. data were closely similar to those of dethiosecoemestrin (**4**) in many respects. ^{13}C N.m.r. signals of (**1**) were also comparable to those of (**4**), except the one at δ_C 187.05, which could be assigned as the carbon of thioamide.[4] The coupling pattern of this signal suggested that the thiocarbonyl is located at the C-3 position. Similarly the compound (**2**) showed the carbon signal at δ_C 187.02 assigned to the same structural moiety (Table 1). Compound (**1**) was degraded easily to (**4**) and then to violaceic acid, which is also a metabolite of *E. striata*.[2] These results confirmed the structure of aurantioemestrin as (**1**).

Silvathione (**2**), m.p. 155—157 °C from methanol, $[\alpha]_{435}^{24}$ −20° (*c* 1.00, $CHCl_3$) was isolated from the culture filtrate of *Aspergillus silvaticus* Fennel & Raper, strain IFO 8173. Electron-impact and field-desorption mass spectrometry showed the molecular ion at *m/z* 346, and elemental analysis confirmed the empirical formula as $C_{18}H_{22}N_2O_3S$. The compound (**2**) showed $\lambda_{max.}$ (MeOH) 228 (log ε 4.43), 274 (4.30), 284 sh (3.93), and 300 sh (3.84) nm; $\nu_{max.}$ (KBr) 1690

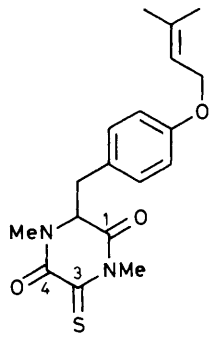
Table 1. ^{13}C N.m.r. data for diketopiperazine ring carbons of (**1**), (**2**), (**3**), and (**4**).[a]

Carbon atom	(1)	(2)[b]	(3)	(4)
1	154.07 (Sm)	166.15 (Sm)	164.28 (Sm)	155.86 (Sq)[c]
3	187.05 (Sq)	187.02 (Sq)	75.55 (Sd)	157.45 (Sq)[c]
4	148.15 (S)	153.02 (Sq)	160.55 (Sd)	149.16 (S)

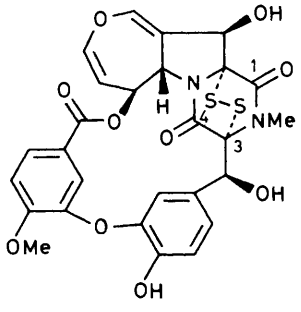
[a] Recorded on a JEOL JNM-GX 400 n.m.r. spectrometer. ^1J(C,H): d = doublet, q = quartet, m = multiplet. ^1J(C,H): S = singlet. [b] Numberings correspond to those of (**1**), (**3**), and (**4**). [c] The assignments may be reversed.



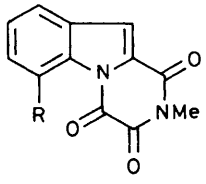
(1) X = S
(4) X = O



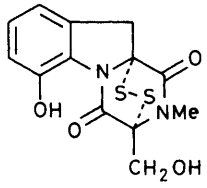
(2)



(3)



(5) R = H
(6) R = OH



(7)

and 1650 (CON) cm^{-1}; δ_H 1.731 (3H, s, olefinic Me), 1.780 (3H, s, olefinic Me), 3.188 (2H, d, *J* 3.9 Hz, $-CH_2-CH-$), 3.199 (3H, s, NMe), 3.276 (3H, s, NMe), 4.419 (2H, d, *J* 6.6 Hz, $-O-CH_2-CH=$), 4.529 (1H, t, *J* 3.9 Hz, $-CH_2-CH-$), 5.435 (1H, br.t, *J* 6.6 Hz, $-CH_2-CH=$), 6.734 (4H, br.s, aromatic protons), and δ_C (the multiplicities of the off-resonance proton decoupled signals are indicated in capital letters) 18.22 (Qm, CMe), 25.76 (Qm, CMe), 33.64 (Q, NMe), 33.70 (Q, NMe), 38.05 (Tddd), 64.41 (Dm), 65.04 (T), 115.53 (Dd × 2), 119.57 (Dm), 124.30 (Sm), 130.49 (Dddd × 2), 138.16 (Sm), 153.02 (Sq), 159.38 (Sm), 166.15 (Sm), and 187.02 (Sq). These ^1H and ^{13}C n.m.r. data established the partial structure of (**2**) as a 3-methyl-2-butenyloxyphenylalanine moiety. The ^{13}C n.m.r. signals at δ_C 153.02 and 166.15, and 187.02 (Table 1) should be assigned respectively to the two carbonyl and the thiocarbonyl carbons of the dioxopiperazinethione moiety analogous to those of aurantioemestrin (**1**). Long-range proton selective decoupling experiments at *N*-methyl groups in the ^{13}C n.m.r. spectrum of (**2**) confirmed the location of the thiocarbonyl at C-3 and structure (**2**) for silvathione.

Many epidithiodioxopiperazine derivatives have been isolated from fungi, but there are only a few examples of the concurrent isolation of the trioxopiperazines from the same fungus. Dethiosecoemestrin (**4**)[3] accompanies emestrin (**3**) in *E. striata*, and the dioxopiperazinoindoles (**5**) and (**6**) along with dehydrogliotoxin (**7**) in *Penicillium terlikowskii*.[5,6] It is noteworthy that Ali *et al.*[5] suggested the compounds (**5**) and (**6**) to have a significance in the biosynthesis of gliotoxin. Our present isolation of aurantioemestrin (**1**) is the first case of the isolation of the dioxopiperazinethione along with the epidithiodioxopiperazine, emestrin (**3**), and the trioxopiperazine, dethiosecoemestrin (**4**) from the same fungus, *E. striata*. Compound (**1**) is chemically easily degraded in the organic solvent to compound (**4**) which is further degraded slowly to violaceic acid. Silvathione (**2**) is our second example of a dioxopiperazinethione; this was isolated from *A. silvaticus* and was also accompanied by a corresponding epidithiodioxopiperazine, whose structure will be reported in another paper.

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