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EUDISTOMIN K SULFOXIDE - AN ANTIVIRAL SULFOXIDE FROM THE NEW ZEALAND ASCIDIAN *RITTERELLA SIGILLINOIDES*

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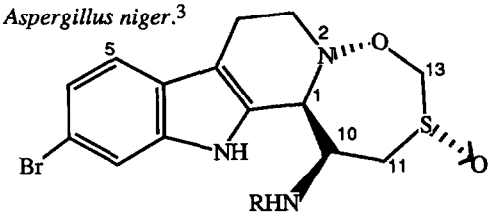
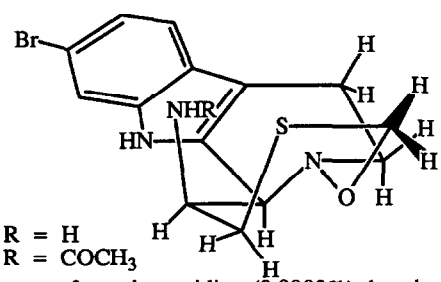
SUMMARY: A naturally occurring sulfoxide, eudistomin K sulfoxide (**1**), has been isolated from the New Zealand ascidian *Ritterella sigillinoides*. Eudistomin K sulfoxide has antiviral properties against both DNA and RNA viruses. The semisynthesis of (**1**) is presented.

The occurrence of sulfoxides in nature is limited, being confined mostly to sulfoxide compounds from onions and from other *Allium* species.[1] We now report the occurrence of eudistomin K sulfoxide (**1**), from the New Zealand ascidian *Ritterella sigillinoides* (Brewin 1958). This compound, which was detected in a programme seeking compounds with potential pharmaceutical activity from New Zealand marine invertebrates, displayed *in vitro* activity against *Herpes simplex* Type I and *Polio* vaccine Type I viruses. The occurrence of this sulfoxide and the parent sulfide, eudistomin K (**3**)[2] is reminiscent of the isolation of biotin / biotin sulfoxide from *Aspergillus niger*.[3]



1 R = H
2 R = $COCH_3$



3 R = H
4 R = $COCH_3$

Eudistomin K sulfoxide (**1**) was isolated[4] as a trifluoroacetate from the ascidian (0.0003%), but the structural work was carried out on the acetyl derivative (**2**). The close similarity between **2** and acetyl eudistomin K (**4**)[2] was predicated by the spectroscopic data.[5,6] The UV spectrum of **2** showed absorptions appropriate for an indole chromophore (280 and 229 nm)[7] and the ^1H and homonuclear correlated NMR spectra[6] displayed multiplets and connectivities consistent with a eudistomin K type skeleton. The variances noted were in the chemical shifts of the protons in the oxathiazepine ring, in particular the H_{11} and H_{13} protons. This located the structural difference at the sulfur atom, and the dissimilar effects on the chemical shifts of the H_{13} protons implied a strongly dipolar substituent. A sulfoxide was the most likely candidate and the additional oxygen required in such a structure was confirmed by high resolution mass spectroscopy on **2**.[8]

Difference nOe experiments,[9] performed on the acetyl derivative (**2**), established the same spatial relationships for the hydrogen atoms as found in the other eudistomins isolated from this ascidian. This indicated that the stereochemistry and conformation of the oxathiazepine ring was the same as that previously determined,[2] with the N-O bond α to the ring (**3** or **4**).

The stereochemistry of the sulfur - oxygen bond was assigned as α, by utilising the model compound studies of Buchanan and Durst[10] and by comparing the ^{13}C NMR shifts of C_{10}, C_{11} and C_{13} for acetyl eudistomin K (**4**)[2,6] with those for the acetyl derivative (**2**). This assignment was supported by calculation of the changes in the chemical shift for the C_{11} and C_{13} protons in **2** induced by the S-O dipole[10] and was based on the dihedral angles obtained from a Drieding model of the preferred conformation (cf. **3** or **4**).[2] Only the α orientation gives appropriate shifts.

While eudistomin K sulfoxide was present in only small quantities from *R. sigillinoides* it is not considered an artefact. The reasoning is based on the oxidising conditions usually needed for the preparation of sulfoxides from sulfides (eg. 30% H_2O_2, peroxy acids, $NaIO_4$), the constancy of the ratio of the sulfoxide (**1**) to the sulfide (**3**) in freshly prepared as well as "old" extracts, and the occurrence of only one stereoisomer of the sulfoxide.

Eudistomin K sulfoxide (**1**) was synthesised by *meta*-chloroperbenzoic acid oxidation of the butyloxycarbonyl (BOC) protected eudistomin K at 5^0C. Purification, followed by removal of the BOC group with trifluoroacetic acid, gave semisynthetic eudistomin K sulfoxide (**1**) as the trifluoroacetate salt, identical with the natural product in all respects, including biological activity.[11]

The acetyl and butyloxycarbonyl derivatives of eudistomin K and eudistomin K sulfoxide were inactive in *in vitro* assays against *Herpes simplex* Type I and *Polio* vaccine Type I viruses.[12] Both semisynthetic and natural eudistomin K sulfoxide showed inhibitory activity against these viruses at concentrations of 200ng/ml.

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4 For isolation method see Ref. 2
5 ^1H NMR and ^{13}C NMR spectra were recorded on a Varian XL300 spectrometer. Chemical ionisation spectra were recorded on a Finnigan 4500 mass spectrometer using a DCI probe and high resolution measurements were obtained in the electron impact (EI) mode on a VG7070F mass spectrometer.
6 (1) light yellow oil, $[\alpha]_D^{25}$ -3.3° (*c* 0.09, CH_3OH); UV (CH_3OH) 284 nm (ε 3470), 229 nm (ε 11920); IR (film) 3450(br), 1690, 1205, 1120, 800 and 710 cm^{-1}; ^1H NMR (CD_3OD) δ 7.53 (d, *J*=1.2, H_8), 7.37 (d, *J*=8.6, H_5), 7.16 (dd, *J*=1.2, 8.6, H_6), 5.83 (d, *J*=10.1, $H_{13}\beta$), 4.68 (bs, H_1), 4.36 (d, *J*=10.1, $H_{13}\alpha$), 4.35 (bs, H_{10}), 4.18 (d, *J*=13.6, $H_{11}\alpha$), 3.73 (m, $H_3\beta$), 3.43 (dd, *J*=5.9, 13.6, $H_{11}\beta$), 3.12 (m, $H_3\alpha$), 3.0 (m, $H_4\beta$), 2.9 (m, $H_4\alpha$); ^{13}C NMR (CD_3OD) δ 124.2 (C_6), 121.1 (C_5), 115.9 (C_8), 89.9 (C_{13}), 67.2 (C_1), 54.5 (C_3), 52.7 (C_{11}), 51.7 (C_{10}), 20.9 (C_4), (quaternary carbons were not observed due to the small sample size).
(2) ^1H NMR ($CDCl_3$) δ 8.52 (bs, H_9), 7.45 (d, *J*=1.7, H_8), 7.27 (d, *J*=8.3, H_5), 7.19 (dd, *J*=1.7, 8.3, H_6), 5.74 (bd, *J*=9.6, NH), 5.66 (d, *J*=9.8, $H_{13}\beta$), 5.17 (bs, H_{10}), 4.45 (bs, H_1), 4.31 (d, *J*=9.8, $H_{13}\alpha$), 3.94 (dd, *J*=12.7, 1.6, $H_{11}\alpha$), 3.67 (ddd, *J*=10.2, 5.0, 1.7, $H_3\beta$), 3.41 (dd, *J*=12.7, 6.3, $H_{11}\beta$), 3.13 (ddd, *J*=10.2, 11.5, 4.8, $H_3\alpha$), 2.91 (dddd, *J* =15.8, 11.5, 5.0, 2.4, $H_4\beta$), 2.84 (dddd, *J*=15.8, 4.8, 1.7, 0.9, $H_4\alpha$), 1.72 (s, CH_3); ^{13}C NMR ($CDCl_3$) δ 123.1 (C_6), 119.3 (C_5), 114.4 (C_8), 109.5 (C_{4a}), 88.8 (C_{13}), 68.2 (C_1), 54.1 (C_{11}), 54.1 (C_3), 46.3 (C_{10}), 23.0 (CH_3), 20.2 (C_4), (other carbons not observed).
(4) ^1H NMR ($CDCl_3$) δ 8.81 (bs, H_9), 7.45 (d, *J* =1.9, H_8), 7.27 (d, *J* =8.5, H_5), 7.16 (dd, *J* =1.9, 8.5, H_6) 6.63 (d, *J* =9.7, NH), 5.02 (m, *J* =9.7, 5.5, H_{10}), 4.96 (d, *J* =8.9, $H_{13}\alpha$), 4.83 (d, *J* =8.9, $H_{13}\beta$), 4.13 (bs, H_1), 3.61 (ddd, *J* =10.2, 5.0, 1.7, $H_3\beta$), 3.33 (d, *J* =14.5, $H_{11}\alpha$), 3.14 (ddd, *J* =11.5, 10.2, 4.8, $H_3\alpha$), 2.92 (m, *J* =15.8, 11.5, 5.0, 2.4, $H_4\beta$), 2.80 (m, *J* =15.8, 4.8, 1.7, 0.9, $H_4\alpha$), 2.78 (dd, *J* =14.5, 5.5, $H_{11}\beta$), 1.75 (s, CH_3); ^{13}C NMR ($CDCl_3$) δ 170.4 (C=O), 137.9 (C_{8a}), 131.2 (C_{9a}), 125.1 (C_{4b}), 122.7 (C_6), 119.1 (C_5), 115.4 (C_7), 114.5 (C_8), 109.3 (C_{4a}), 71.0 (C_{13}), 69.0 (C_1), 54.8 (C_3), 46.7 (C_{10}), 32.1 (C_{11}), 23.3 (CH_3), 20.6 (C_4).
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