Tetrahedron Letters Vol. 22, pp 39 - 42 0040-4039/81/0101-0039$02.00/0

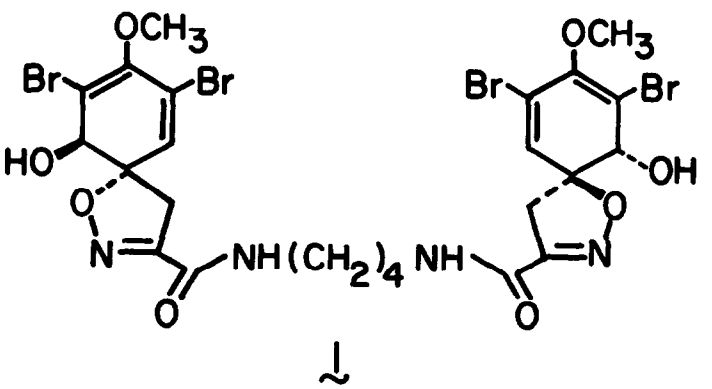
AN X-RAY STUDY OF AEROTHIONIN FROM APLYSINA FISTULARIS (PALLAS)

Joyce A. McMillan, Iain C. Paul,* Yang M. Goo, and Kenneth L. Rinehart, Jr.
School of Chemical Sciences, University of Illinois, Urbana, IL 61801, U.S.A.

William C. Krueger and Loraine M. Pschigoda
The Upjohn Company, Kalamazoo, MI 49001, U.S.A.

ABSTRACT: The structure of aerothionin, a tyrosine-derived brominated compound from the sponge Aplysina fistularis (Pallas), is confirmed by X-ray data, which with CD data assign its absolute configuration.

During our extensive studies of the bioactive constituents of Aplysina fistularis (Pallas) sensu Wiedenmayer, 1977 (formerly Verongia aurea sensu de Laubenfels, 1948)[1-6] we observed some time ago that one specimen of Aplysina fistularis (AHBE 19-III-74-1-1, collected at Bahia Concepcion, Baja California, latitude 27° N, Gulf of California at 22 m depth) gave as its major component (constituting 10% of the extract, 0.4% of the frozen sponge's wet weight) aerothionin (1), which showed a molecular ion containing four bromine atoms at m/z 814 ($C_{24}H_{26}Br_4N_4O_8$) in its field desorption mass spectrum and was identified from its uv spectrum (λ_{max} 282 nm) and ^{1}H NMR spectrum (DMSO-d_6, 8.46 ppm, t, J = 7.0 Hz, 2 H, NH; 6.55, s, 2 H, =CH; 6.34, d, J = 7.0 Hz, 2 H, OH; 3.90, d, J = 7.0 Hz, 2 H, -CHO-; 3.65, s, 6 H, OCH_3; 3.63, d, J = 17.8 Hz, H_A of H_A-C-H_B; 3.17, d, J = 17.8 Hz, H_B of H_A-C-H_B; 3.3, m, 4 H, N-CH_2; 1.44, m, 4 H, -CH_2-) compared to data for the reported compound.[7] While extensive testing[8] has revealed no significant pharmacological properties for aerothionin, its structure, assigned



earlier[7,9] from degradative experiments and spectroscopic properties, is of interest for its relation to other metabolites of dibromotyrosine.[10] We report here our X-ray assignment of the structure of aerothionin, including absolute configuration, confirmed by circular dichroism analysis.

Because the colorless crystals of 1 obtained from benzene-methanol were unstable to X-rays, data from three crystals were combined, using the intensities of three standard reflections for scaling and correcting for decay. Crystal data: $C_{24}H_{26}Br_4N_4O_8 \cdot \frac{1}{2}C_6H_6$, monoclinic, Mw = 857.3, a = 10.070(6)Å, b = 14.239(8)Å, c = 13.073(8)Å, β = 105.23(5)°, V = 1808.6Å^3, ρ_c = 1.57 gcm^{-3}, Z = 2, space group $P2_1$, [λ(CuK$_\alpha$) = 1.5418Å]. The structure was solved by Patterson and heavy atom methods and has been refined to R = 0.064 and wR = 0.072 on 2638 non-zero reflections (2σ-level). The opposite enantiomorph was refined to R and wR values of 0.066 and 0.074, respectively, suggesting, but not definitely establishing, that the correct enantiomorph is as shown in Figure 1.

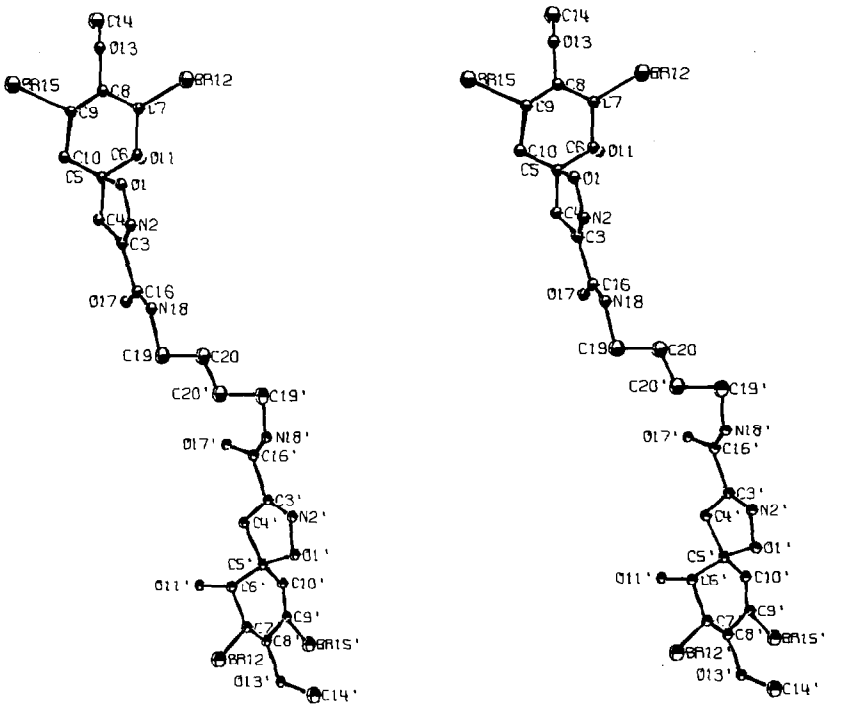
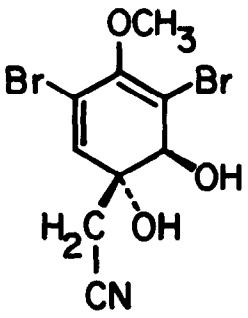
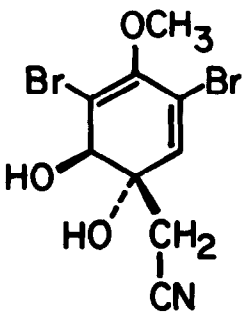


Figure 1. Stereoscopic view of a single molecule of aerothionin (1)

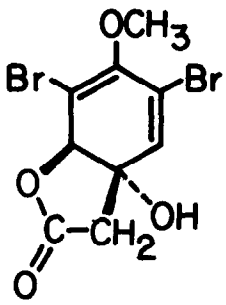
The absolute configuration suggested by the X-ray analysis was confirmed by the circular dichroism (CD) of 1. Since the adjacent ring oxygens are trans and the diene system is appropriately skewed, the absolute stereochemistry can be assigned by relation to aeroplysinin-1, whose enantiomers (2 and 3) have been assigned absolute configurations in independent X-ray studies[11,12] and one of whose enantiomers, (-)-aeroplysinin-1 (2), has reported CD behavior.[13,14]



2



3



4

Our sample of aerothionin (1) has $[\alpha]_D$ +210° (c 1.7, CH_3OH), similar to that reported for (+)-aeroplysinin-1 (3) {$[\alpha]_D$ +182° (c 0.5, acetone)}.[13] More significantly, 1, with two skew diene chromophores, gives the CD values $[\theta]^{max}_{284}$ = +70,500, $[\theta]^{max}_{245}$ = +78,200 (CH_3OH). The corresponding CD value reported for (-)-aeroplysinin-1, with only one skew diene chromophore, is $[\theta]^{max}_{282}$ = -49,500 (CH_3OH).[13] In view of the similar skew diene conformations of 1 (cf. Figure 1) and 2,[11] their absolute configurations must be opposite.

ACKNOWLEDGMENT: This work was supported in part by NIH research grants AI 04769 (to K.L.R.) and GM 19336 (to I.C.P.)

REFERENCES

1. Y. M. Goo and K. L. Rinehart, Jr., in "Drugs and Food from the Sea," P. N. Kaul and C. J. Sindermann, Eds., The University of Oklahoma Press, Norman, OK, 1978, pp. 107-115.
2. Y. M. Goo, Ph.D. Thesis, University of Illinois, Urbana, 1980.
3. G. E. Krejcarek, R. H. White, L. P. Hager, W. O. McClure, R. D. Johnson, K. L. Rinehart, Jr., J. A. McMillan, I. C. Paul, P. D. Shaw, and R. C. Brusca, Tetrahedron Lett., 507-510 (1975).
4. K. L. Rinehart, Jr., R. D. Johnson, I. C. Paul, J. A. McMillan, J. F. Siuda, and G. E. Krejcarek, in "Food-Drugs from the Sea Conference Proceedings 1974," H. H. Webber and G. D. Ruggieri, Eds., Marine Technology Society, Washington, D.C., 1976, pp. 434-442.
5. K. L. Rinehart, Jr., R. D. Johnson, J. F. Siuda, G. E. Krejcarek, P. D. Shaw, J. A. McMillan and I. C. Paul, in "The Nature of Seawater," E. D. Goldberg, Ed., Physical and Chemical Sciences Research Report 1, Abakon Verlagsgesellschaft, Berlin, 1975, pp. 651-665.
6. J. A. McMillan, and I. C. Paul, Cryst. Struct. Commun., 4, 445-450 (1975).
7. E. Fattorusso, L. Minale, G. Sodano, K. Moody, and R. H. Thomson, Chem. Commun., 752-753 (1970).
8. P. W. O'Connell, The Upjohn Company, personal communication to K.L.R.
9. Reference 62a in Minale, et al.,[10] cites X-ray confirmation of this structure as a personal communication, but the work has not, to our knowledge, been published.
10. L. Minale, G. Cimino, S. De Stefano, and G. Sodano, Fortschr. Chem. org. Naturst., 33, 1-72 (1976).
11. D. S. Cosulich and F. M. Lovell, Chem. Commun., 397-398 (1971).
12. L. Mazzarella and R. Puliti, Gazz. Chim. it., 102, 391-394 (1972).
13. W. Fulmor, G. E. Van Lear, G. O. Morton, and R. D. Mills, Tetrahedron Lett., 4551-4552 (1970).
14. The related (+)-aeroplysinin-2 has been assigned the configuration shown (4) on the basis of its ^{1}H NMR and CD properties.[15]
15. L. Minale, G. Sodano, W. R. Chan, and A. M. Chen, Chem. Commun., 674-675 (1972).

(Received in USA 16 May 1980)