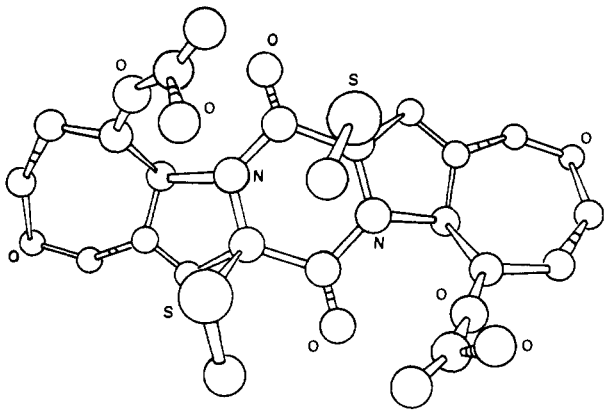

Figure 2. The BDA molecule as it appears in the crystal.

crystal. While every other pair of atoms which could be so related is indeed closely related in the crystal by the twofold molecular axis, the methyl groups bonded to the sulfur atoms are not. This is indicated in Figure 2.

A study of the possibility of the more extensive use of the small effects of anomalous scattering by sulfur atoms to facilitate structure determination is continuing.

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Aranotin and Related Metabolites. III. Configuration and Conformation of Acetylaranotin[1]

Sir:

The metabolites from *Arachniotus aureus* are of interest due to their antiviral activity.[2] We present evidence to show that the configuration at the asymmetric centers in our key metabolite acetylaranotin, **1**, and gliotoxin[3] are identical. This evidence of configurational identity in acetylaranotin, gliotoxin,[3] and apoaranotin,[4] we hope, will stimulate work on the biogenetic correlation[4,6] between the cyclohexadiene and dihydrooxepin moieties in these metabolites.

The CD curve of acetylaranotin, **1**, consists of a high amplitude negative maximum at 229, a positive maximum at 268, and a low amplitude negative maximum

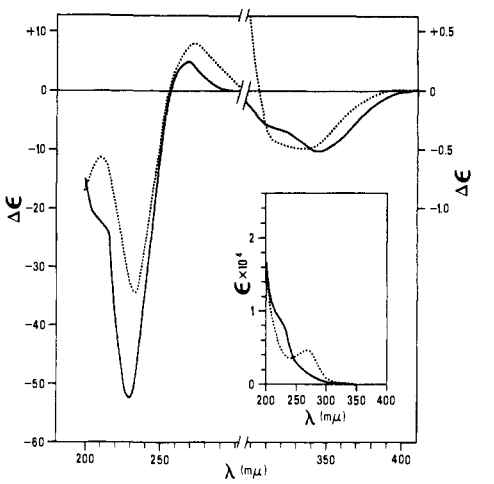

Figure 1. Circular dichroism and ultraviolet spectra of acetylaranotin (——) and gliotoxin (· · · · ·) determined in methanol solution.

at 345 with a negative inflection at ~310 mμ. This is qualitatively in good agreement with the CD curve of gliotoxin[7] (Figure 1) and shows that the absolute stereochemistry of the asymmetric carbon atom on the diketopiperazine moiety in gliotoxin[3] and acetylaranotin are identical.[8] Acetylaranotin lacks the diene chromophore of gliotoxin, and consequently the three Cotton effects at 268, 310, and 345 mμ should have their origins in the disulfide chromophore.[7,9]

Desulfurization of acetylaranotin with Raney nickel followed by reduction and deacetylation gave the diol[1] **2**. The CD spectrum of the diol **2** has a negative maximum at 222, a positive maximum at 210, and a negative maximum below 200 mμ. In the wavelength region under discussion, the diol **2** contains only the diketopiperazine chromophore, and therefore, all the three Cotton effects should have their origins in the diketopiperazine moiety. Since L-prolyl-L-proline and D-prolyl-D-proline diketopiperazines[10] are good model compounds for comparison with the diol **2** their CD spectra were determined[11] (Figure 2). A comparison of these CD spectra firmly established the L configuration at the asymmetric carbon in the diketopiperazine moiety in diol **2**. Obviously, Raney nickel desulfurization occurred with retention of configuration.[12] In

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(2) Biological properties will be described by D. C. DeLong, *et al.*
(3) J. Fridrichsons and A. M. Mathieson, *Acta Cryst.*, **23**, 439 (1967).
(4) N. Neuss, R. Nagarajan, B. B. Molloy, and L. L. Huckstep, *Tetrahedron Lett.*, 4467 (1968). The configuration at the asymmetric centers of apoaranotin is identical[5] with gliotoxin.[3]
(5) R. Nagarajan, N. Neuss, and S. M. Nash, unpublished work.
(6) J. E. Baldwin, H. H. Basson, and H. Krauss, Jr., *Chem. Commun.*, 984 (1968).
(7) H. Herrmann, R. Hodges, and A. Taylor, *J. Chem. Soc.*, 4315 (1964).
(8) Professor J. W. Moncrief of the Department of Chemistry, Emory University, Atlanta, Ga., has established by X-ray analysis that the configuration at the three asymmetric centers in bisdethiodi(methylthio)-acetylaranotin[1] and gliotoxin are identical. Independently, Dr. J. H. van den Hende of American Cyanamid Company, Pearl River, N. Y., has found by X-ray analysis that acetylaranotin and gliotoxin have the same configuration at the three asymmetric centers. We wish to thank Professor J. W. Moncrief and Dr. J. H. van den Hende for permission to quote their results.
(9) (a) H. Ziffer, U. Weiss, and E. Charney, *Tetrahedron*, **23**, 3881 (1967); (b) M. Carmack and L. A. Neubert, *J. Amer. Chem. Soc.*, **89**, 7134 (1967); (c) A. F. Beecham, J. W. Loder, and G. B. Russell, *Tetrahedron Lett.*, 1785 (1968); (d) J. A. Barltrop, P. M. Hayes, and M. Calvin, *J. Amer. Chem. Soc.*, **76**, 4348 (1954); (e) D. L. Coleman and E. R. Blout in "Conformation of Biopolymers," Vol. 1, G. N. Ramachandran, Ed., Academic Press, New York, N. Y., 1967, p 123.
(10) Obtained from Cyclo Chemical Corporation, Los Angeles, Calif.
(11) The uv spectra are not recorded in Figure 2 because the diketopiperazines gave end absorption: diol **2**, 200 (ε 11,140); prolylproline diketopiperazines, 200 mμ (ε 14,000).
(12) The X-ray result of Professor J. W. Moncrief on BDA,[1] and of Dr. J. H. van den Hende on acetylaranotin, **1**, in conjunction with our CD data proves conclusively that Raney nickel desulfurization of acetylaranotin and BDA occurred with retention of configuration. Our re-

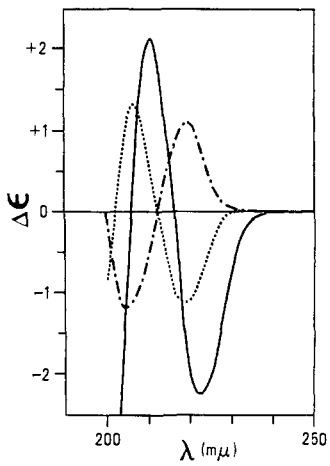

Figure 2. Circular dichroism spectra of the diol, **2** (——), L-prolyl-L-proline diketopiperazine (·····), and D-prolyl-D-proline diketopiperazine (-·-) determined in water solution.

these three diketopiperazines, the 220-mμ Cotton effect is due to the n–π* transition, and the Cotton effects at 210 and the one below 200 mμ originate from the exciton split π–π* transition of the peptide chromophore.[18]

A correlation of the configuration of the two other asymmetric carbon atoms in acetylaranotin with the asymmetric carbon in the diketopiperazine residue will completely define its configuration. Desulfurization of acetylaranotin, **1**, gave bisdethioacetylaranotin,[1] **3**, and the removal of sulfur resulted in upfield shifts of 115 Hz by proton H_{F1} and 27 Hz by H_C, whereas H_D underwent a small 11-Hz low-field shift in the nmr spectra. The removal of sulfur had a negligible effect on both the chemical shifts and coupling constants of all other protons and ruled out a conformational change. Evidently the sulfur deshielded protons H_{F1} and H_C, but not H_D in acetylaranotin (Figure 3); and this is possible only if protons H_D and H_{F1} on the five-membered ring are in *trans* and *cis* relationship, respectively, to the carbon–sulfur bond.[19] We can now write the complete configurational structure **4** for acetylaranotin; and interestingly, the configuration at the three asymmetric centers in **4** is the same as in gliotoxin.[3]

sults are not inconsistent[13] with the currently held views that the mechanism of Raney nickel desulfurization is of the free-radical type.[14] An alternate mechanism would be the SNi type suggested by van Tamelen and Grant[15] to explain the formation of camphane by desulfurization of phenyl 4-camphyl sulfide. It should be pointed out, however, that Raney nickel desulfurization of gliotoxin affords two dextrorotatory tetrahydrodethiogliotoxins.[16] Preliminary investigations[17] show that the first long-wavelength Cotton effects at ~215 mμ in both tetrahydrodethiogliotoxins show positive maximum. After our work on the stereochemistry of Raney nickel desulfurization is completed, we will submit a full report. Further, Bonner has shown that Raney nickel desulfurization of optically active 2-phenyl-2-phenylmercaptopropionamide yielded racemic product.[14]

(13) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 383; see also p 394.

(14) W. A. Bonner and R. A. Grimm in "The Chemistry of Organic Sulfur Compounds," Vol. 2, N. Kharasch and C. Y. Meyers, Ed., Pergamon Press, New York, N. Y., 1966, Chapter 2 and Appendix.

(15) E. E. van Tamelen and E. A. Grant, *J. Amer. Chem. Soc.*, **81**, 2160 (1959); see also L. F. Fieser, H. Heymann, and S. Rajagopalan, *ibid.*, **72**, 2307 (1950).

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(17) R. Nagarajan and S. M. Nash, unpublished work.

(18) (a) J. A. Schellman and E. B. Nielsen in ref 9e, p 109; (b) D. Balasubramaniam and D. B. Wetlaufer in ref 9e, p 147; (c) F. A. Bovey and F. P. Hood, *J. Amer. Chem. Soc.*, **88**, 2326 (1966); (d) B. J. Litman and J. A. Schellman, *J. Phys. Chem.*, **69**, 978 (1965).

(19) The distance between the sulfur and H_{F1} was 2.76 and H_C was 3.28 Å measured in a Dreiding model of acetylaranotin.

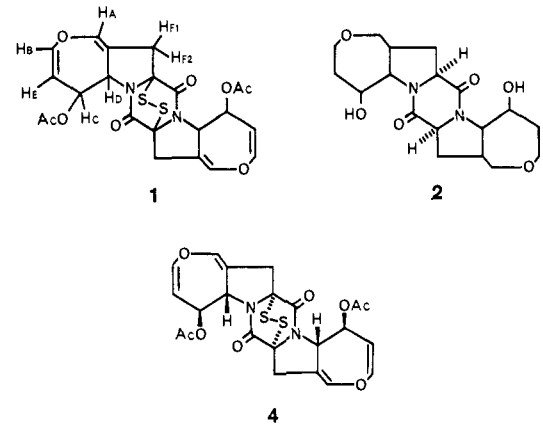

Figure 3.

An examination of the Dreiding model of acetylaranotin showed that the dihydrooxepin ring could exist in two conformations: (1) proton H_C defines a dihedral angle of ~180° with H_D and ~90° with H_E and H_B and (2) proton H_C subtends a dihedral angle of ~160° with H_D and ~130° with H_E and H_B. The observed vicinal, vinyl, and allylic coupling constants were J_{CD} = 8.7, J_{CE} = 1.5, and J_{CB} = 2.1 Hz in the nmr spectrum of acetylaranotin.[1] The vicinal coupling constant is consistent with both conformations, but clearly the vinylic and allylic couplings[20] are consistent only with the first conformation.

Acknowledgments. We gratefully acknowledge the technical assistance of F. W. Beasley.

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Crystal and Molecular Structure of LL-S88α an Antiviral Epidithiapiperazinedione Derivative from *Aspergillus terreus*

Sir:

Single crystal X-ray analysis[1] has permitted the full characterization of LL-S88α, a fermentation metabolite elaborated by *Aspergillus terreus* exhibiting antiviral activity both *in vitro* and *in vivo*, the isolation of which is to be reported.[2] The material (mol wt, 504), $C_{22}H_{20}N_2O_8S_2$, crystallizes from acetone as pale yellow monoclinic prisms with the unit cell dimensions a = 11.720, b = 14.164, c = 13.245 Å (±0.003 Å), β = 93.55° (±0.05°), in the space group $P2_1$. Since there are two independent molecules in the asymmetric unit, the analysis required the location of a structural unit consisting of 44 carbons, 16 oxygens, 4 nitrogens, and 4 sulfur atoms (ρ_{obsd} = 1.520 g/cc, ρ_{calcd} = 1.521 g/cc). Approximately 3000 reflections were monitored (d_{min} = 0.95 Å) on a General Electric XRD-6 equipped with an Eulerian cradle (Cu Kα radiation, λ 1.5418 Å, Ni–Co balanced filters, peak heights with wide open

(1) This work was reported at the Fifth International Symposium on the Chemistry of Natural Products, London, July 8–13, 1968.

(2) P. A. Miller, P. W. Trown, W. Fulmor, J. Karliner, and G. Morton, *Biochem. Biophys. Res. Commun.*, in press.