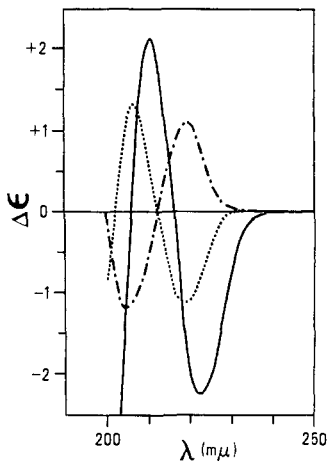

Figure 2. Circular dichroism spectra of the diol, **2** (——), L-prolyl-L-proline diketopiperazine (·····), and D-prolyl-D-proline diketopiperazine (-·-) determined in water solution.

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.

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(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).

(16) J. R. Johnson and J. B. Buchanan, *ibid.*, **75**, 2103 (1953).

(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.

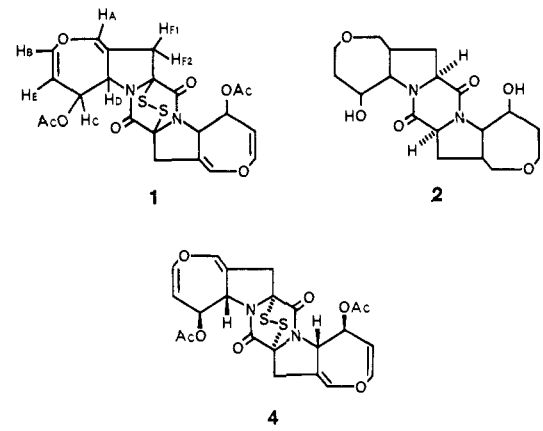

Figure 3.

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.

(20) E. W. Garbisch, Jr., *J. Amer. Chem. Soc.*, **86**, 5561 (1964).

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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.

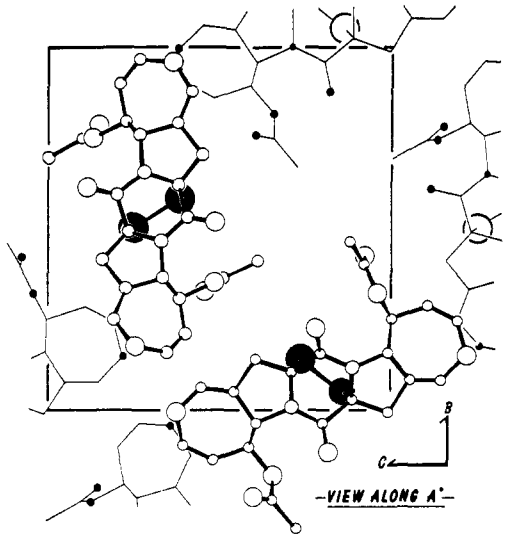

Figure 1. Projection of $^1/_2$ unit cell onto (100) plane.

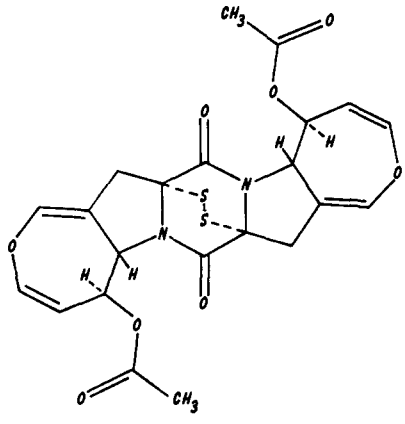

Figure 2. Absolute stereochemistry of LL-S88α.

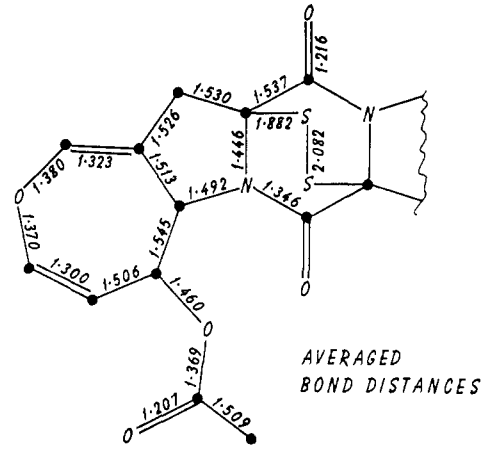

Figure 3. Averaged bond distances.

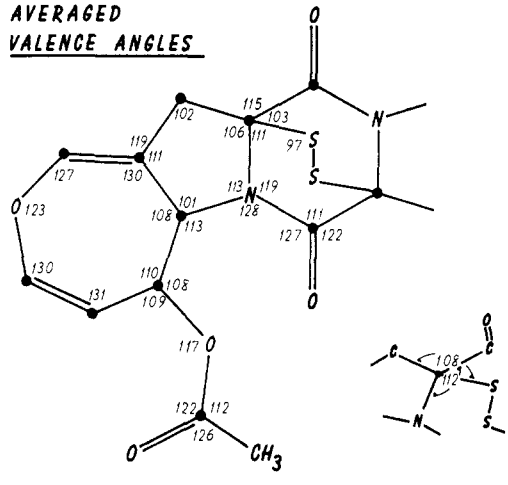

Figure 4. Averaged valence angles.

aperture), and 2600 were found to be observable. The structure was solved after the successful interpretation of the Patterson function, calculated from E^2 values, for the location of the sulfur atoms. All 56 S–S interactions were located and identified; the positions obtained were used as the start of a routine heavy-atom procedure, which yielded the entire structure after four cycles of structure factor and electron density calculations. The positions of all hydrogen atoms, except those of four methyl groups, which were found to be disordered, were determined from a difference Fourier which was calculated after conclusion of the least-squares refinement. Due to the large number of parameters not all atoms were included with anisotropic thermal parameters.

The final value of R ($\Sigma|\Delta F|/\Sigma|k.F_o|$) was 0.062. As an additional confirmation of the correctness of the structure, none of the calculated values for the unobserved reflections exceeded the accepted threshold level of the diffractometer system, indicating these reflections as truly unobserved. A view of the structure, projected onto the b–c plane, is given in Figure 1, and the chemical representation of one molecule is shown in Figure 2, which indicates the apparent internal twofold symmetry present. The two structurally independent molecules were found to be very similar both in conformation and orientation of the various functional groups. The bond distances and valence angles of the four independent half-molecules agree in general to within 0.01 Å and 2.0° and the distances and angles shown in Figures 3 and 4 are the averages of these four sets. The chemical structure of LL-S88α belongs to the class of sulfur-containing piperazinediones such as gliotoxin[3] and sporidesmin,[4] and it appears to be identical with that proposed for aranotin acetate,[5] except for the additional assignment of the conformations at the bridgehead and the adjacent acetate-bearing carbon atom, as well as their relative configuration with regard to the disulfide bridges.

The one difference observed between the two molecules in the asymmetric unit concerns the orientation of one of the acetate moieties when compared to the other three.

The conformation of the central piperazine ring is that of a skewed boat and it does not resemble the rings as they are found in gliotoxin[3] and sporidesmin.[4] This is probably due to the severe strain induced in the

(3) J. Fridrichsons and A. M. Mathieson, *Acta Cryst.*, 23, 439 (1967).
(4) J. Fridrichsons and A. M. Mathieson, *ibid.*, 18, 1043 (1965).
(5) R. Nagarajan, L. L. Huckstep, D. H. Lively, D. C. DeLong, M. M. Marsh, and N. Neuss, *J. Amer. Chem. Soc.*, 90, 2980 (1968); the X-ray powder patterns of LL-S88α and aranotin acetate, a sample of which was kindly furnished by Dr. Nagarajan, *et al.*, were found to be identical.

central part of the molecule by the attachment of two, rather than one, five-membered ring systems. The virtual identity of the two molecules of the asymmetric unit is evident from the dihedral angles of the C–S–S–C bridges, which were calculated to be 15.2 and 18.2°, respectively. The two molecules are oriented in such a way that their disulfide bridges are nearly parallel, and facing each other. The packing forces seem to consist largely of van der Waals attractions; however, the possibility of some d orbital overlap between two sulfur atoms of adjacent molecules is indicated by a short S–S nonbonded interaction of 3.27.[6]

A more detailed account of this structure determination will be published at a later date.

(6) A similar distance (3.29 Å) was observed in 4-methyl-1,2-dithia-4-cyclopentene-3-thione: W. L. Kehl and G. A. Jeffrey, *Acta Cryst.*, **11**, 813 (1958), and G. A. Jeffrey and R Shiono, *ibid.*, **12**, 447 (1959).

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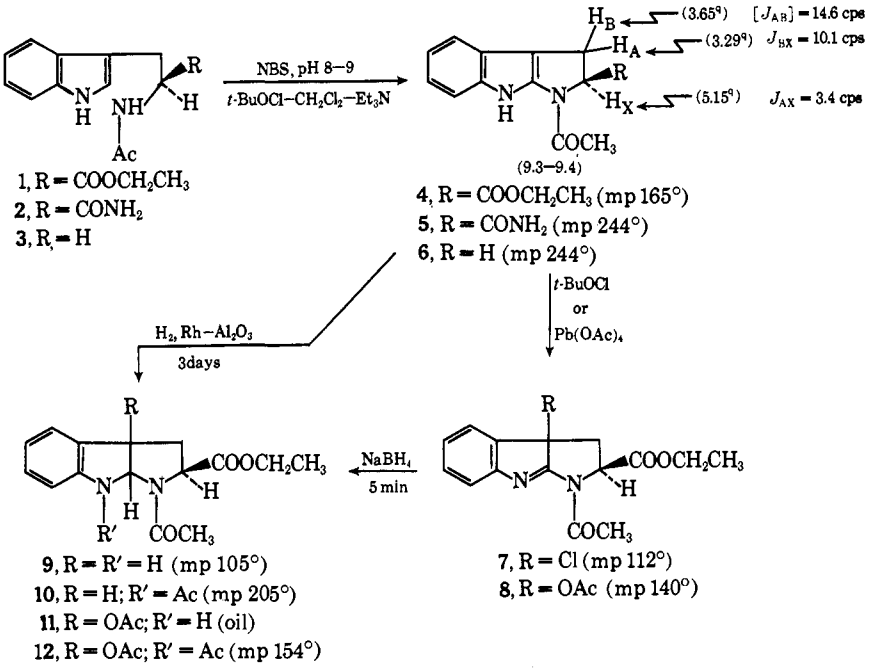
Cyclization of Tryptophan and Tryptamine Derivatives to Pyrrolo[2,3-*b*]indoles

Sir:

Although the conversion of tryptophan and tryptamine to tricyclic pyrroloindoles has been discussed in connection with oxidation mechanisms,[1] the ring-chain tautomers of tryptamine (serotonin),[2] and (bio)synthesis of alkaloids of the physostigmine type[3] and of the antibiotic sporidesmin,[4] no laboratory method for this important conversion has been available. We wish to report several useful approaches which make easily accessible cyclic tryptophan derivatives of type **4**–**13**.

While N-acyltryptophan derivatives with N-bromosuccinimide (NBS) at pH 4 yield spirooxindole-(imino)lactones, presumably *via* bromonium or β-bromoindolenine intermediates,[5] the same reaction carried out with N-acetyltryptophan ethyl ester (**1**) in 0.04 *M* phosphate, pH 9.2, with exactly 1 equiv of NBS (1.6×10^{-2} *M*) in very dilute solution (5×10^{-4} *M*) at room temperature yields an unstable product (60% yield on the basis of uv absorption) which had been recognized previously by its characteristic λ_{max}, 308 mμ[6] (ε 15,700). Since excess NBS or hydrolysis at or below pH 6 converts this product into a (bromo)-oxindole, it has to be extracted immediately into ether. The crystalline product (30% yield) has the composition $C_{15}H_{16}N_2O_3$, mol wt 272.1166 (calcd 272.1161). Structure **4**, ethyl 1-acetyl-2,3-dihydropyrrolo[2,3-*b*]-indole-2-carboxylate, is supported by the nmr data (in parentheses), by the uv absorption which resembles that of 2-acetamidoindole,[7] and by the easy hydrolysis to an oxindole. In the same way the carboxamide **5** was prepared from **2**, while the much slower oxidation of N-acetyltryptamine (**3**) led to N-acetyldehydrotryptamine (**6**) in solution only.

The pyrroloindole **4** was obtained in 80% yield by oxidation of a solution of N-acetyltryptophan ethyl ester (**1**) with *t*-BuOCl in methylene chloride containing a threefold excess of triethylamine. The same method made the cyclic tryptamine **6** easily available in 63% yield, when the reaction mixture, presumably containing the 3-chloroindolenine intermediate, was treated with 1 equiv of ethanolic NaOH.



1, R = $COOCH_2CH_3$
2, R = $CONH_2$
3, R = H

4, R = $COOCH_2CH_3$ (mp 165°)
5, R = $CONH_2$ (mp 244°)
6, R = H (mp 244°)

9, R = R′ = H (mp 105°)
10, R = H; R′ = Ac (mp 205°)
11, R = OAc; R′ = H (oil)
12, R = OAc; R′ = Ac (mp 154°)

7, R = Cl (mp 112°)
8, R = OAc (mp 140°)

The pyrroloindole **4** was slowly reduced over a $Rh–Al_2O_3$ catalyst in ethyl acetate (3 days) to 2,3,3a,8a-tetrahydropyrroloindole (**9**) (30% yield). The sharp doublet in the nmr spectrum at δ 5.70 ppm (J = 7 cps), characteristic of the 8a proton, was absent when **4**

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