Acknowledgments. We wish to acknowledge our many helpful discussions with M. Gorman and S. R. Lammert of the Lilly Research Laboratories.

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Received July 1, 1972

Configuration and Conformation of Disulfide Analogs of Penicillins[1]

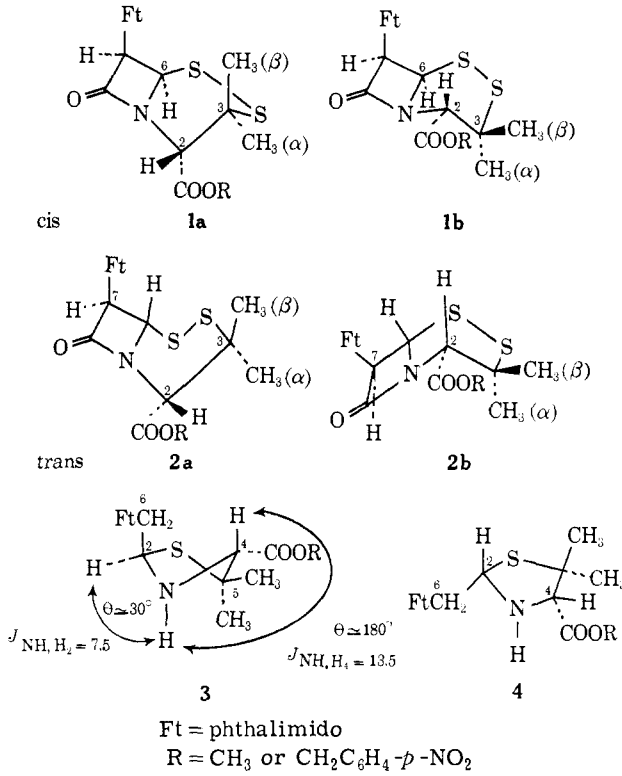
Sir.

In the preceding communication[2] both the synthesis and gross structure of the title compounds were reported. In this article, we present physical data which allow both a conformational and configurational definition of 2-alkyloxycarbonyl-3,3-dimethyl-8-oxo-7-phthalimido-4,5-dithia-1-azabicyclo[4.2.0]octane and related compounds.

The dithiazabicyclooctanes were distinguished as cis (**1**) and trans (**2**) isomers on the grounds that couplings of 4 and 2 Hz between H-6 and H-7 dictate the cis and trans orientation, respectively, between these protons. Molecular Dreiding models of both the *cis*- and *trans*-dithiazabicyclooctanes (**1** and **2**) show that four conformations are possible for each of these isomers,[3] since the disulfide bond in dithiazabicyclooctanes **1** and **2** can be arranged with either P-helical or M-helical chirality.[4] The CD spectra of the cis isomers **1** (R = CH_3 and $CH_2C_6H_4$-*p*-NO_2) show that the first transition at 293 mμ has a negative Cotton effect. This indicates a left-handed (M) screw sense.[5] Trans esters **2** (R = CH_3 and $CH_2C_6H_4$-*p*-NO_2) have a positive Cotton effect at 292 mμ which relates to a right-handed (*P*) helical arrangement of the disulfide group (see Figure 1).

Gross conformational elucidation of these conformers is obtained from a study of internal nuclear Overhauser effects (NOE).[6] Irradiation at the high- and low-field methyl singlets in the spectrum of **1** results in integrated intensity increases of approximately 8 ± 3 and 16 ± 3%, respectively, for H-2 only, with no detectable increases in the intensity of H-6. These results require that both geminal dimethyl groups be in spatial proximity to H-2 and distant from H-6, a spatial requirement inherent in conformation **1a**, but not in **1b**. Accordingly, on the basis of circular dichroism and nmr data, the cis isomer **1** exists in conformation **1a**.

An independent analysis of cis isomer **1** by X-ray diffraction was undertaken to determine the nucleus conformation and the dihedral angle of the disulfide bond. Compound **1** (R = CH_3) crystallizes from a mixture of methyl ethyl ketone–cyclohexane as colorless needles and melts at 185–186°. The crystals belong to the space group $P2_12_12_1$, with four molecules in a unit cell having the dimensions a = 10.247 ± 0.001, b = 10.322 ± 0.001, and c = 17.011 ± 0.001 Å. The density measured by flotation is 1.43 g/cm^{-3}, as compared to the value 1.45 g/cm^{-3} calculated for $C_{17}H_{16}N_2O_5S_2$ (mol wt 392.5). Diffraction intensities were measured on an automated diffractometer. The structure was solved by direct phasing methods using the computer program MULTAN[7] and refined by least squares.



The conformation of the entire molecule, without hydrogen atoms, is shown in Figure 2. Dithiazabicyclooctane nucleus **1** clearly has conformation **1a**, rather than **1b**. The helical sense of the disulfide group is M, with a dihedral angle of 60.5°. The six-membered ring assumes a chair conformation, distorted slightly by the disulfide group. The methyl groups are β axial and α equatorial, and the carbomethoxy group is β axial. It is interesting to note that the nitrogen atom of the β-lactam is nearly planar. This same planarity was found by Sweet and Dahl[8] in a biologically inactive Δ^2-cephalosporin.

Conformational distinction can also be made for trans isomer **2** on the basis of NOE and long-range coupling data. Conformation **2a** dictates that the 3α- and 3β-methyl groups lie close to H-2, whereas in conformation **2b** only the 3β-methyl protons are situated proximal to H-2. Thus the β-methyl protons in either conformation should contribute to the intramolecular relaxations of H-2, while to a lesser degree the α-methyl protons should relax H-2 in **2a** only. The

(1) Azetidinone Antibiotics. VIII.
(2) S. Kukolja, *J. Amer. Chem. Soc.*, **94**, 7590 (1972).
(3) Two chair and two boat conformers can exist for the six-membered ring. In stereoformulas **1** and **2**, only two (**a** and **b**) conformers for cis and trans compounds are shown. Enantiomeric forms resulting from the rotation about the S–S bond are not shown because of the limited space.
(4) R. S. Cahn, C. Ingold, and V. Prelog, *Angew. Chem., Int. Ed. Engl.*, **5**, 385 (1966); see especially pp 391 and 406.
(5) R. Nagarajan, N. Neuss, and M. M. Marsh, *J. Amer. Chem. Soc.*, **90**, 6518 (1968), and references cited therein.
(6) R. D. G. Cooper, P. V. Demarco, J. C. Cheng, and N. D. Jones, *ibid.*, **91**, 1408 (1969); R. D. G. Cooper, P. V. Demarco, and D. O. Spry, *ibid.*, **91**, 1528 (1969); G. V. Kaiser, C. W. Ashbrook, and J. E. Baldwin, *ibid.*, **93**, 2342 (1971); D. O. Spry, *ibid.*, **92**, 5006 (1970).
(7) P. Main, M. M. Woolfson, and G. Germain, "MULTAN, A Computer Programme for the Automatic Solution of Crystal Structures," University of York Printing Unit, York, England, 1971.
(8) R. M. Sweet and L. F. Dahl, *J. Amer. Chem. Soc.*, **92**, 5489 (1970).

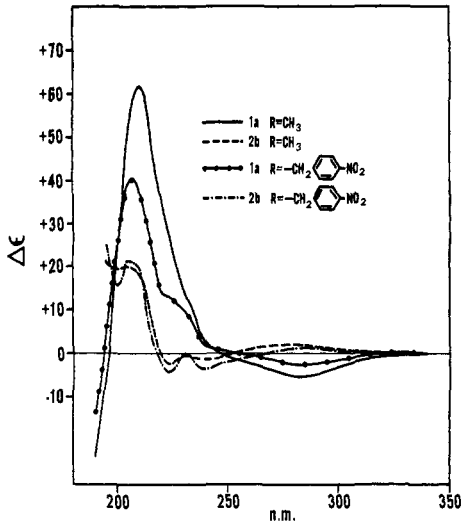


Figure 1. Circular dichroism curves in acetonitrile.

observation that an NOE exists between H-2 and the high-field methyl (16–20%) and not between H-2 and the low-field methyl in the spectra of **2** strongly supports conformation **2b** over **2a**. This conformational assignment is supported further by the observed long-range, five-bond coupling between H-2 and H-7 in **2** ($^5J_{4,7} \simeq 1.0$ Hz). Similar long-range coupling between H-2 and H-7 has been observed in cepham where the C-4 proton occupies an α-axial configuration.[9] Accordingly, trans isomer **2** must adopt a conformation where H-2 is axially oriented and is in the same geometrical relationship to H-7 as in cepham systems where coupling of this nature has been previously observed. Such a geometrical relationship is satisfied by stereoformula **2b**.

Clear conformational and configurational assignments for thiazolidine derivative **3**, obtained as a by-product in the synthesis of **1a** and **2b**, can be made from an analysis of the 100-MHz DMSO-d_6 spectrum of this compound. The following nmr data are offered as evidence for the assignment of this product to structure **3**: δ 1.13 (s, 3, CH_3), 1.61 (s, 3, CH_3), 3.51 (d of d, 1, J = 5.5; 14.5 Hz, H-6), 3.84 (d of d, 1, J = 10, 14.5 Hz, H-6), 3.84 (d, 1, J = 13.5 Hz, H-4), 4.25 (d of d, 1, J = 7.5, 13.5 Hz, NH, D_2O exchangeable), 4.95 (m, 1, J = 5.5, 10, 7.5 Hz, H-2). The observed couplings of 13.5 Hz between NH and H-4 and 7.5 Hz between NH and H-2 require dihedral angles of approximately 180 and 30°, respectively, between these protons[10] and establish the C-2 configurations and thiazolidine conformation shown in structure **3**. Other thiazolidine conformational and C-2 configurational possibilities are eliminated readily on the basis of incompatibility with recorded NH coupling information.

Unfortunately, the nmr spectrum of **4** in DMSO-d_6 does not reveal a discernible NH signal. As a result vicinal NH couplings cannot be measured and a complete stereochemical assignment for **4** could not be determined unequivocally. However, on the basis of nmr data[11] and mechanistic considerations, we believe that **4** has the structure shown above.

(9) (a) D. O. Spry, Eli Lilly & Co., private communication; (b) P. V. Demarco and R. Nagarajan in "Cephalosporins and Penicillins—Chemistry and Biology," E. H. Flynn, Ed., Academic Press, New York, N. Y., 1972, Chapter 8.

(10) V. F. Bystrov, S. L. Portnova, T. A. Balashova, V. I. Tsetlin, V. T. Ivanov, P. V. Kostetzky, and Yu. A. Ovchinnikov, *Tetrahedron Lett.*, 5225 (1969); K. G. R. Pachler, *Spectrochim. Acta*, **19**, 2085 (1963); **20**, 581 (1964).

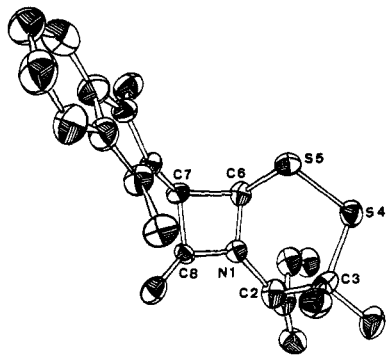


Figure 2. Skeletal conformation of the cis isomer in the crystalline state. Thermal ellipsoids are drawn to include 50% probability.

Acknowledgments. We thank Mr. R. D. Miller for circular dichroism measurements and Mr. D. W. Smith for computer assistance.

(11) Compound **4** shows the following nmr data in $CDCl_3$: δ 1.20 (s, 3, CH_3), 1.60 (s, 3, CH_3), 3.95 (d of d, 1, J = 4.5, 14.5 Hz, H-6), 4.05 (d of d, 1, J = 7.5, 14.5 Hz, H-6), 3.59 (s, 1, H-4), 3.20 (m, NH), and 4.95 (d of d, 1, J = 4.5, 7.5 Hz, H-2).

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2,3-Dimethylenebicyclo[2.2.0]hexane and Its Cycloreversion to 2,3-Dimethylenecyclohexa-1,3-diene

Sir:

Vapor phase thermolysis at 250–300° of 1,2-dimethylenecyclobutane (**1**) appears to generate tetramethyleneethane (**2**) as a transient intermediate.[1,2] The chemistry of this latter species is of considerable current interest.[1–8] The bicyclic diene **3** of the title seemed to offer an ideal means for producing a simple tetramethyleneethane derivative **4** in solution at moderate temperatures, thus providing an unprecedented opportunity to study the bimolecular reactions, particularly the cycloadditions, of a member of this novel class of compounds. Such a study might also be expected to yield valuable insights into the electronic configurations of tetramethyleneethanes. The activation enthalpy for the cycloreversion **1** → **2** is 45.7 kcal/mol.[2] In view of the additional cyclobutane ring strain energy present

(1) J. J. Gajewski and C. N. Shih, *J. Amer. Chem. Soc.*, **89**, 4532 (1967).
(2) W. von E. Doering and W. R. Dolbier, *ibid.*, **89**, 4534 (1967).
(3) J. J. Gajewski and C. N. Shin, *ibid.*, **91**, 5900 (1969).
(4) W. R. Moore, R. D. Bach, and T. M. Ozretich, *ibid.*, **91**, 5918 (1969).
(5) P. Dowd, *ibid.*, **92**, 1066 (1970).
(6) J. J. Gajewski and C. N. Shih, *ibid.*, **92**, 4457 (1970).
(7) B. G. Odell, R. Hoffman, and A. Imamura, *J. Chem. Soc. B*, 1675 (1970).
(8) O. J. Muscio, Jr., and T. L. Jacobs, *Tetrahedron Lett.*, 2867 (1969).