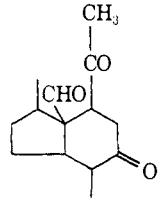
ized gyrinidone to a mixture containing large amounts of the three aldehydes. However, chromatography (gas and thin layer) of material obtained by either wiping or dissecting glands verified the presence of these aldehydes as well as gyrinidone in the original secretion. Each[16] has a base peak at *m/e* 151 suggesting loss of CHO and C_4H_8 from the original aldehyde. Although all three aldehydes still contain the CH_3CO group (*m/e* 43), loss of the conjugated system is indicated by the absence of absorption in the vinyl proton region of their pmr spectra, their ultraviolet spectra (231 nm (ε 4100) and 311 (410)), and their infrared spectra (5.85 and 5.95 μ). Although **2** exhibited slight optical activity, $[\alpha]^{25}_{400}$ −69°, $[\alpha]_{350}$ −103°, $[\alpha]_{255}$ +138° (*c* 0.058, C_2H_5OH), the mixture **4** showed $[\alpha]^{25}_{400}$ +57°, $[\alpha]_{350}$ +48°, $[\alpha]_{320}$ −38°, $[\alpha]_{300}$ +280°, $[\alpha]_{280}$ +760° (*c* 0.21, C_2H_5OH).

Air oxidation of the mixture of aldehydes gave isomeric acids (*m/e* 252) which were converted to their isomeric methyl esters (*m/e* 266) each of which still contains a base peak at *m/e* 43 and forms a dimethoxime (*m/e* 324). A Michael addition leading to epimers of **4** is postulated for the isomeric aldehydes.



4

Acylic aldehyde **1** may well be the precursor for **2** involving addition across the conjugated system.[17] A second addition to the remaining double bond would give **4**.

(16) The aldehyde mixture could not be separated by tlc and was analyzed by combined gas chromatography–mass spectrometry on an LKB-9000 combined gas chromatograph–mass spectrometer using columns containing 1% OV-17 on Supelcoport (Supelco, Inc., Bellefonte, Pa.).

(17) Examination of milkings from other species (*Dineutes assimilis* and *Gyrinus analis*) by gas chromatography–mass spectrometry indicates that some species contain isomers of both $C_{14}H_{18}O_3$ and $C_{14}H_{20}O_3$ while other gyrinids have isomers of only one molecular formula.

(18) This work was completed during the tenure of a special fellowship at the National Institutes of Health in the laboratory of H. M. Fales. We thank Dr. Fales, Dr. R. J. Highet, and Dr. G. W. A. Milne for valuable discussions and assistance and the Public Health Service for financial support (CC-00270).

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Synthesis of Disulfide Analogs of Penicillins[1]

Sir:

In the past few years we have been concerned with the synthesis of azetidinone compounds related to cephalosporins and penicillins. Our initial efforts were concentrated on the preparation of key intermediates which could be used in the synthesis of modified azetidinone derivatives. The results of these investigations were described recently.[2] In this paper we report the synthesis of 2-carboxy-3,3-dimethyl-8-oxo-7-phthalimido-4,5-dithia-1-azabicyclo[4.2.0]octane and related compounds.

The starting material, 2-chloro-1-((1′*S*)-alkyloxycarbonyl-2′-chlorothio-2′-methylpropyl)-(3*R*)-phthalimido-4-azetidinone (**1a,b**), prepared by chlorinolysis of the corresponding penicillin ester,[2] is treated with an alkanethiol at room temperature for 5 min to give disulfide **2a** or **2b** (R_1 = *p*-$MeOC_6H_4CH_2$ or *t*-Bu) in almost quantitative yield. These disulfides are isolated as colorless amorphous solids by chromatography and their ir spectra ($CHCl_3$) show peaks for **2a** (R_1 = *p*-$MeOC_6H_4CH_2$) at 1794 (azetidinone CO), 1782 and 1730 (phthalimido CO), and 1750 cm^{-1} (ester CO), and for **2b** (R_1 = *p*-$MeOC_6H_4CH_2$) at 1797 (azetidinone CO), 1785 and 1730 (phthalimido CO), and 1750 cm^{-1} (ester CO). The structures of **1** and **2** were ascertained by analysis and spectral data (see Table I).

Table I. Chemical-Shift Values ($CDCl_3$)[a,b]

Compd[c]	$-(CH_3)_2$	*R*[d]	H_2	H_6	H_7
2a	100, 102	229	278	335 (d, *J* = 2.0)	366 (d, *J* = 2.0)
2b	100 (s, 6 H)	309	277	329 (d, *J* = 1.5)	358 (d, *J* = 1.5)
3a	94, 108	230	251	313 (d, *J* = 2.0)	323 (q, *J* = 1.0, 2.0)
3b	87, 110	309	256	312 (d, *J* = 2.0)	326 (q, *J* = 1.0, 2.0)
3c	92, 105		255	314 (d, *J* = 1.5)	331 (d, *J* = 1.5)
4a	84, 120	230	270	334 (d, *J* = 4.5)	346 (d, *J* = 4.5)
4b	82, 120	320	274	332 (d, *J* = 4.5)	345 (d, *J* = 4.5)
4c	87, 118		268	333 (d, *J* = 4.5)	341 (d, *J* = 4.5)

[a] *J* values in hertz. [b] We thank L. A. Spangle and T. Elzey for determination of the nmr spectra. [c] Satisfactory elemental analyses were obtained for all compounds. [d] **a** = CH_3 and **b** = *p*-nitrobenzyl group.

The reaction of disulfide **2** (a or **b**, R_1 = *p*-$MeOC_6H_4CH_2$ or *t*-Bu) with boiling trifluoroacetic acid (TFA) for 30–60 min yields a mixture from which four compounds are isolated by chromatography over silica gel. Comparison of the nmr and ir spectra of the separated compounds indicates the presence of an azetidinone function in two compounds, **3** and **4**, and the absence of the same function in compounds **5** and **6**. Compound **3a** is isolated as a colorless amorphous solid: $[\alpha]_D$ +175.6° (MeCN); ir ($CHCl_3$) 1790 (azetidinone CO), 1785 and 1730 (phthalimido CO), and 1752 cm^{-1} (ester CO). Compound **4a** is obtained as colorless prisms: mp 185–186°; $[\alpha]_D$ + 161.1° (MeCN); ir ($CHCl_3$) 1790 (azetidinone CO), 1779 and 1739 (phthalimido CO), and 1745 cm^{-1} (ester CO).[3] The magnitudes of the coupling constants (Table I) establish that compound **3** has the trans arrangement of azetidinone protons (*J* = 2.0 Hz) while **4** is of the

(1) Azetidinone Antibiotics. VII.

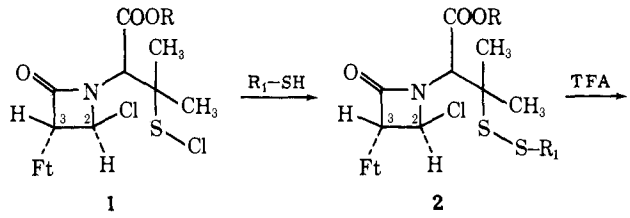
(2) S. Kukolja, *J. Amer. Chem. Soc.*, 93, 6267 (1971); S. Kukolja and S. R. Lammert, *ibid.*, 94, 7169 (1972); S. Kukolja and S. R. Lammert, *Croat. Chem. Acta*, 44, 299, 423 (1972).

(3) The ester **3b**, mp 143–144°, $[\alpha]_D$ +86° (MeCN), has an ir spectrum almost identical with that of **3a**. The ir carbonyl peaks of **4b**, $[\alpha]_D$ +128.1° (MeCN), are nearly the same as those of **4a**.

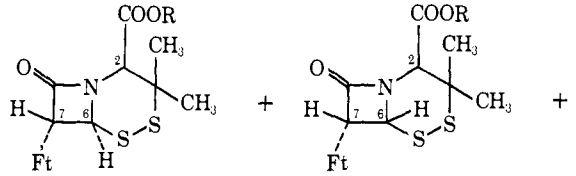
cis configuration (J = 4.5 Hz).[4] In the mass spectra compounds **3a** and **4a** give a molecular ion peak at m/e 392, corresponding to $C_{17}H_{16}N_2O_5S_2$, and major fragmentation peaks at m/e 364 (M^+, CO), 300 (M^+, CO, S_2), and 241 (M^+, CO, S_2, COOMe).[5] The above data and the elemental analyses suggest the bicyclic azetidinone disulfide structures **3** and **4**. Since the presence of chiral disulfide function in a dithiazabicyclooctane ring system creates the possibility for different spatial arrangements, these compounds exist as enantiomeric conformers. The assignment of the stereochemistry of **3** and **4** depends on the absolute configuration at C-2 and the helicity of the disulfide bond. The configuration and conformation of the compounds described here are reported in an accompanying paper.[6]

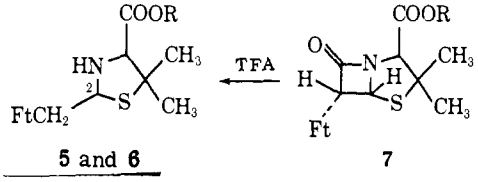
The remaining two nonazetidinone-containing products, **5a** and **6a**, are isomeric, having the empirical formula $C_{16}H_{18}N_2O_4S$ and molecular ion peaks at m/e 334. Compound **5a** is isolated as colorless prisms: mp 113–114°; ir ($CHCl_3$) 1771 and 1735 (phthalimido CO) and 1710 cm^{-1} (ester CO); nmr ($CDCl_3$) 72 (s, 3, CH_3), 101 (s, 3, CH_3), 190 (m, NH, D_2O exchangeable), 216 (d of d, 1, J = 5.5, 14.5 Hz, H-6), 226 (s, 3, CH_3), 236 (d of d, 1, J = 10, 14.5, Hz H-6), 236 (d, 1, J = 14.5 Hz, H-4), and 303 Hz (m, 1, J = 5.5 ,10 Hz). The isomer **6a** is obtained as an amorphous solid: ir ($CHCl_3$) 1773 and 1738 (phthalimido CO) and 1715 cm^{-1} (ester CO).[7] The major fragmentation peaks for **5a** and **6a** at m/e 174 and 160 indicate the presence of the thiazolidine ring and the phthalimidomethyl fragment in the molecule.[8] A similar fragmentation is noted in the mass spectrum of methyl 6-phthalimidopenicillanate (**7**). This fact suggests that **7** could be formed in the reaction of **2** with trifluoroacetic acid and subsequently degraded to thiazolidines (**5** and **6**) and carbon dioxide. This assumption is proven to be correct; *viz.* when **7a** is refluxed with trifluoroacetic acid for 60 min and subjected to an aqueous work-up, a mixture of two products (identical with **5a** and **6a**) is obtained in the ratio of *ca.* 1:1. A degradation under acidic conditions at the reflux temperature has precedent in penicillin chemistry.[9-11]

In order to prepare bicyclic azetidinones for biological testing, the carboxyl protective group (R = p-$NO_2C_6H_4CH_2$) is removed by catalytic hydrogenolysis. Isomeric esters **3b** and **4b** are hydrogenated with 5% palladium on carbon in tetrahydrofuran–methanol (1:1) at room temperature to give the corresponding 3,3-dimethyl-8-oxo-(7*R*)-phthalimido-4,5-dithia-1-azabicyclo[4.2.0]octane-2-carboxylic acids (**3c** and **4c**) which display significantly diminished antibacterial



$R_1 = CH_2C_6H_4$-p-OCH_3
$R_1 = t$-Bu





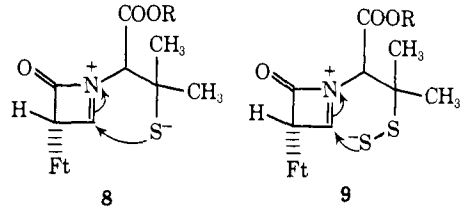
5 and 6

a, R = CH_3
b, R = $CH_2C_6H_4$-p-NO_2
c, R = H

Ft = phthalimido

activity when compared to **7c**. The structures of acids **3c** and **4c** are supported by chemical means, elemental analysis, and spectral data (Table I).

We believe that formation of **3** and **4** and the intermediacy of **7** involve stabilized carbonium ions **8** and **9**. These ions are most likely formed by initial cleav-



age of the C–S and S–S bonds and subsequent elimination of chloride ion in **2**. The fact that epimeric bicyclic systems are produced indicates that the sulfur anion can approach a carbonium ion from either side. Similar intermediacy of **8** and the stereochemical course of cyclization were described previously.[2,12]

Degradation of **7** to **5** and **6** can be rationalized by opening of the azetidinone ring with trifluoroacetic acid and formation of the corresponding mixed anhydride of penicilloic acid which is subsequently hydrolyzed and decarboxylated to give **5** and **6**.[11]

The application of azetidinone sulfenyl chlorides **1** in the synthesis of **2**, **3**, and **4** demonstrates an additional utility for these compounds. The synthesis of **3** and **4** represents the successful modification of the thiazolidine ring in the penicillins, and the method may be useful for the synthesis of similar heterocyclic systems. Further modifications of azetidinone antibiotics are under investigation.

(4) D. A. Johnson and D. Mania, *Tetrahedron Lett.*, 267 (1969), and references cited therein.

(5) Similar data are also obtained for p-nitrobenzyl esters **3b** and **4b**.

(6) S. Kukolja, P. V. Demarco, N. D. Jones, M. O. Chaney, and J. W. Paschal, *J. Amer. Chem. Soc.*, **94**, 7592 (1972).

(7) The esters **5b** and **6b** are isolated as amorphous solids and the ir and nmr data are nearly identical with those of **5a** and **6a**. The nmr data of **6a** are reported in footnote 11 of the accompanying paper.[6]

(8) The mass spectra of **5b** and **6b** also show similar peaks at m/e 295 and 160.

(9) H. T. Clarke, J. R. Johnson, and R. Robinson, Ed., "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, pp 539 and 562.

(10) J. C. Sheehan and P. A. Cruickshank, *J. Amer. Chem. Soc.*, **78**, 3677 (1956).

(11) M. R. Bell, J. A. Carlston, and R. Oesterlin, *ibid.*, **92**, 2177 (1970); *J. Org. Chem.*, **37**, 2733 (1972).

(12) S. Kukolja, *J. Amer. Chem. Soc.*, **93**, 6269 (1971).

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Configuration and Conformation of Disulfide Analogs of Penicillins[1]

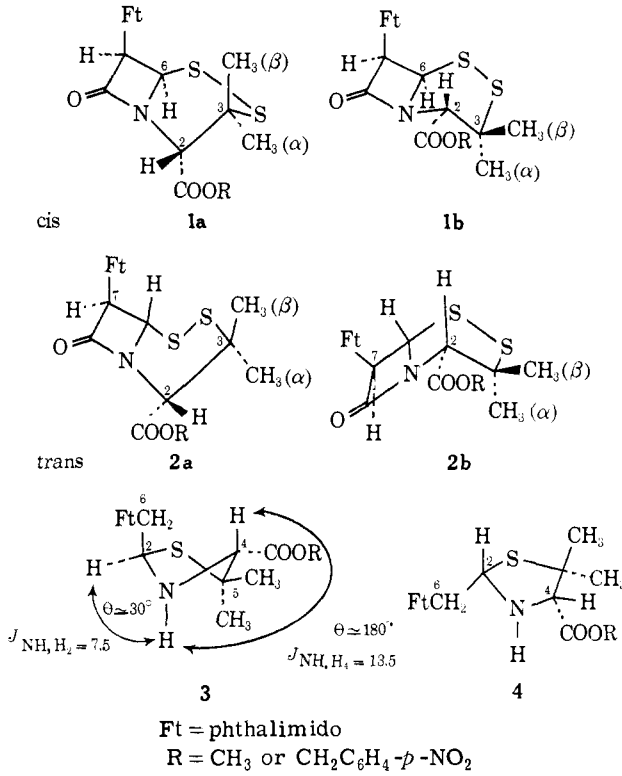
Sir.

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.



Ft = phthalimido
R = CH_3 or $CH_2C_6H_4$-*p*-NO_2

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).