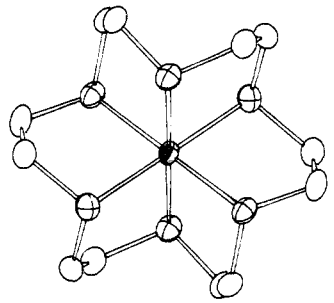

Figure 1. ORTEP drawing of the $Ni^{II}(picrate)_2$ complex of 1,4,7,10,13,16-hexathiacyclooctadecane (hexathia-18-crown-6) showing thermal ellipsoids at 50% probability level (hydrogen atoms are omitted for clarity).

around the metal ion to yield the achiral meso geometric isomer in which each $-S(CH_2)_2S(CH_2)_2S-$ segment of the ligand coordinates to a trigonal face of the metal ion (facial coordination).[10,11] The NiS_6 coordination sphere is essentially octahedral: the *cis*-S–Ni–S bond angles are 90 ± 1.5° (range 88.5–91.3°), while the *trans*-S–Ni–S bond angles are required by the inversion symmetry to be 180°. The [Ni(II)·hexathia-18-crown-6]$^{2+}$ cation closely approaches D_{3d} ($\bar{3}m$) symmetry, which is the maximum symmetry possible for this complex. Approximately pseudo-tetrahedral geometry is found at all of the sulfur atoms, with bond angles decreased somewhat from the tetrahedral value. This decrease is typical of metal–thioether complexes and has been attributed to the steric effect of the remaining sulfur lone-pair electrons.[2]

The Ni–S bond lengths in [Ni(II)·hexathia-18-crown-6]$^{2+}$ at 2.376 (1), 2.389 (1), and 2.397 (1) Å are all considerably shorter than the 2.44 Å predicted from the covalent radii of Ni(II) (1.39 Å) and thioether sulfur (1.05 Å).[2,12] Furthermore, the Ni(II)–S bond lengths found here are also short in comparison with those found in earlier structures. For example, a Ni–S distance of 2.431 (1) Å was found in $Ni(thiodiglycol)_2(Br)_2$[13] while $Ni(1,5\text{-dithiacyclooctane})_2Cl_2$[14] has Ni–S distances of 2.478 (3) and 2.497 (3) Å, compared with the average value of 2.39 Å observed here. From molecular models it appears that any increase in the Ni–S bond lengths of [Ni(II)·hexathia-18-crown-6]$^{2+}$ from the observed values would cause considerable strain in the macrocycle. We suggest that the short Ni–S bond lengths of hexathia-18-crown-6 derive from the "macrocyclic constriction" effect:[15,16] hexathia-18-crown-6 compresses the Ni–S bonds in order to minimize strain in the ligand. Hence the metal–ligand fit is not perfect, despite the lack of angular distortion in the NiS_6 unit. Since the ligand itself has bond distances comparable to those of free hexathia-18-crown-6,[3,17] apparently the intraligand and not the Ni–S interactions dominate in determining the Ni–S bond lengths.

While the macrocycle strongly influences the Ni–S bond lengths, the nickel ion determines the *geometry* of the complex. In crown ether–alkali metal ion complexes electrostatic considerations and the fit of the metal ion in the cavity determine the geometry of the complex. In contrast, in [Ni(II)·hexathia-18-crown-6]$^{2+}$ the rigid sterochemical demands of the transition-metal ion dictate the geometry of the complex. Comparison of the Ni(II) complex of hexathia-18-crown-6 with the K^+ complex of 18-crown-6 underscores this point. Although both [K·18-crown-6]$^+$ and [Ni(II)·hexathia-18-crown-6]$^{2+}$ have idealized D_{3d} symmetry, the two complexes differ markedly in the extent of compression along the trigonal pseudoaxis. In the former the six oxygen atoms are nearly coplanar, with only 0.38 Å between the top and bottom trigonal faces.[18] In contrast, in [Ni(II)·hexathia-18-crown-6]$^{2+}$ the transition-metal ion enforces octahedral geometry on the sulfur atoms and thereby causes those on opposite trigonal faces to be 2.78 Å apart. In a planar arrangement hexathia-18-crown-6 would have about the same "cavity size" as 18-crown-6, since the larger size of the sulfur atoms is roughly offset by the longer C–S bond length.[19] However, the octahedral stereochemistry about Ni(II) decreases the effective cavity diameter of hexathia-18-crown-6 by approximately a factor of 2.

Several conclusions can be drawn from the present work. This structure proves that hexathia-18-crown-6 can wrap around a transition-metal ion to afford octahedral coordination. Moreover, since hexathia-18-crown-6 forces the Ni(II) ion to accept unusually short Ni–S distances, ionic radius–cavity size arguments clearly cannot be applied rigidly to predict which transition-metal ions will form complexes with hexathia-18-crown-6. In addition, the unusual Ni–S bond lengths found here strongly suggest that unusual reaction chemistry may be found as well. Further studies of the coordination chemistry of this and related ligands are presently underway.

Acknowledgment. We are grateful to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the Research Corp. for support of this research. The purchase of the diffractometer was supported in part by NSF grant CHE 8000670.

Registry No. [Ni^{II}·hexathia-18-crown-6](picrate)$_2$, 33270-88-1.

Supplementary Material Available: Listings of atomic positional and thermal parameters and of interatomic distances and angles (5 pages). Ordering information is given on any current masthead page.

(10) Very recently Royer et al. reported the structure (Royer, D. J.; Grant, G. J.; Van Derveer, D. G.; Castillo, M. J. *Inorg. Chem.* **1982**, *21*, 1902–8) of the racemic isomer of [Co(III)·1,4,7,10,13,16-hexaazacyclooctadecane]$^{2+}$ (the hexaamine analogue of hexathia-18-crown-6), in which two $-N-(CH_2)_2N(CH_2)_2N-$ segments coordinate in a meridional fashion.

(11) For other reports on the hexaamine analogue of hexathia-18-crown-6 see: Yoshikawa, Y. *Chem. Lett.* **1978**, 109–112. Searle, G. H.; Dwyer, M.; *Inorg. Chim. Acta* **1981**, *52*, 251–5. Hay, R. W.; Jeragh, B.; Lincoln, S. F.; Searle, G. H. *Inorg. Nucl. Chem. Lett.* **1978**, *14*, 435–40.

(12) Drummond, L. A.; Henrick, K.; Kanagasundaram, M. J. L.; Lindoy, L. F.; McPartlin, M.; Tasker, P. A. *Inorg. Chem.* **1982**, *21*, 3923–7.

(13) Udupa, M. R.; Krebs, B. *Inorg. Chim. Acta* **1981**, *52*, 215–8.

(14) Hill, N. L.; Hope, H.; *Inorg. Chem.* **1974**, *13*, 2079–82.

(15) Hung, Y.; Martin, L. Y.; Jackels, S. C.; Tait, A. M.; Busch, D. H. *J. Am. Chem. Soc.* **1977**, *99*, 4029–39.

(16) Martin, L. Y.; DeHayes, L. J.; Zompa, L. J.; Busch, D. H. *J. Am. Chem. Soc.* **1974**, *96*, 4046–8.

(17) The individual bond lengths of hexathia-18-crown-6 in an asymmetric unit are (Å) S(1)–C(9a) 1.809 (5), S(1)–C(2) 1.814 (5), S(4)–C(3) 1.823 (5), S(4)–C(5) 1.813 (6), S(7)–C(6) 1.814 (5), S(7)–C(8) 1.812 (5), C-(2)–C(3) 1.512 (6), C(5)–C(6) 1.516 (7), C(8)–C(9) 1.518 (7).

(18) Dunitz, J. D.; Seiler, P. *Acta Crystallogr., Sect. B* **1974**, *B30*, 2744–5.

(19) This point has been emphasized recently. See ref 12.

Sesbanimide, a Potent Antitumor Substance from *Sesbania drummondii* Seed

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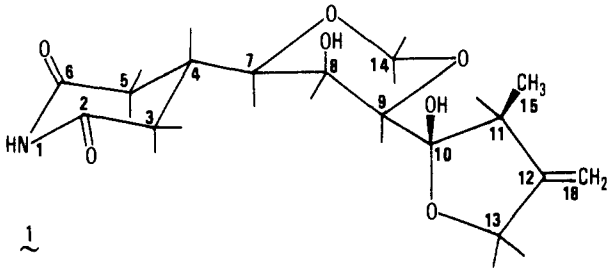
We have reported previously that extracts from seeds of *Sesbania drummondii* (Rydb.) Cory (Fabaceae) have pronounced antitumor activity in experimental systems.[1-3] We now report

† The mention of firm names or trade products does not imply that they are endorsed or recommended by the U.S. Department of Agriculture over other firms or similar products not mentioned.

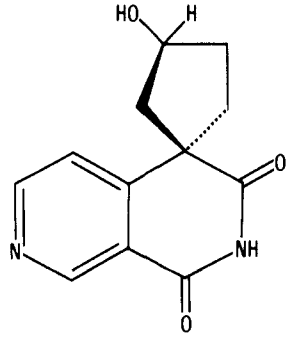
0002-7863/83/1505-3739$01.50/0

the structure elucidation of an exceptionally potent antitumor compound, sesbanimide (**1**), derived from this source. This compound has a novel tricyclic structure in which three rings are linked by single bonds.



1

Sesbanimide (**1**) was obtained from fractions 3 and 7 of a countercurrent distribution described in an earlier study;[3] compound **1** was separated from sesbanine (**2**) by a complex scheme



2

that involved successive application of open-column chromatography on silica, preparative HPLC, preparative TLC, and semi-preparative HPLC.[4] Crystallization from ethyl ether–dichloromethane afforded **1** as a white solid: mp 158–159 °C, $[\alpha]^{23}_D$ −5.6° (*c* 0.27, MeOH); approximate yield, 5 × 10^{-5}% of seed; IR 3555, 3480, 3380, 2945, 2880, 1700, 1080 cm^{-1} ($CHCl_3$); UV, end absorption <220 nm. Anal. Calcd for $C_{15}H_{21}NO_7$: C, 55.06; H, 6.42; N, 4.28. Found: C, 54.94; H, 6.42; N, 4.22; MS ($M^+ - H_2O$) *m/z* 309.1246 (calcd for $C_{15}H_{19}NO_6$ 309.1212). Two other significant ions were observed in the MS at *m/z* 179 ($C_{10}H_{11}O_3$) and 125 ($C_7H_9O_2$). Pure **1** gave ED_{50} values of 7.7 × 10^{-3} μg/mL against KB cells and T/C of 171 against PS leukemia in mice at 1 × 10^{-2} mg/kg.[5]

At 470 MHz, the ^1H NMR spectrum of **1** revealed 21 protons, of which three were readily exchanged in D_2O (δ 8.12, 4.22, 3.56). Signals for 15 carbon atoms were apparent in the ^{13}C NMR spectrum **1**. Taken together, these spectral data indicated a glutarimide ring, in the chair conformation, substituted at C-4.[6] However, since the available data did not readily distinguish among a number of possible structures for **1** and insufficient material was available for extensive chemical studies, a single-crystal X-ray crystallographic study was undertaken.

A thin plate-shaped crystal measuring approximately 0.05 × 0.3 × 0.3 mm was used in all X-ray experiments. Preliminary photographs showed monoclinic symmetry and diffractometer measured cell constants were *a* = 11.065 (2) Å, *b* = 6.841 (1) Å, *c* = 21.994 (3) Å, β = 105.29 (1)°. The systematic extinctions conformed to space group *C*2 with one molecule of $C_{15}H_{21}NO_7$ forming the asymmetric unit. All unique diffraction maxima with $2\theta \leq 114°$ were collected by using graphite monochromated Cu Kα radiation (1.541 78 Å) and variable speed, 1° ω scans. Of those 1264 reflections measured, 901 (71%) were judged observed after correction for Lorentz, polarization, and background effects. The structure was solved uneventfully by using MULTAN and block-diagonal least-squares refinements, with anisotropic heavy atoms and isotropic hydrogens having converged to a standard crystallographic residual of 0.045.[7] Additional crystallographic details can be found in the supplementary material described at the end of this paper.

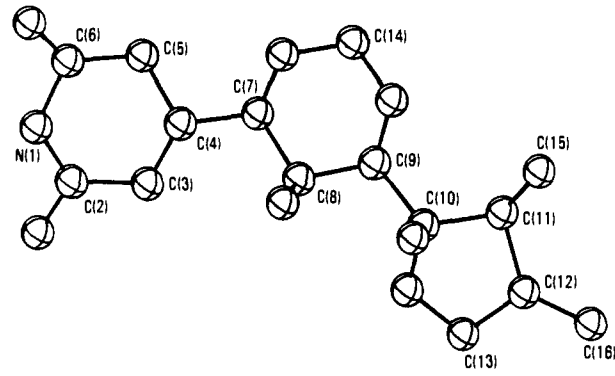


Figure 1. Computer-generated perspective drawing of the final X-ray model of sesbanimide. Hydrogens are omitted for clarity, and no absolute configuration is implied.

A computer-generated perspective drawing of the final X-ray model of sesbanimide is given in Figure 1. The X-ray experiment defined only the relative stereostructure, and the pertinent stereochemical descriptors are 7*R**, 8*S**, 9*R**, 10*R**, and 11*S**. The glutarimide and 1,3-dioxy rings are both in chair conformations.

On completion of the X-ray experiment (Figure 1), it was possible to assign most of the ^1H and ^{13}C NMR signals unambiguously; a table presenting full details is available as supplementary material.

Sesbanimide bears an obvious structural relationship to the glutarimide antibiotics (e.g., cycloheximide, streptovitacin A, or streptimidone[8]), although the tricyclic structure of **1** is unprecedented. Because of this relationship, questions will arise as to whether **1** may be a fungal metabolite rather than a higher plant product, and further study may be necessary to clarify the origin of **1**. At present, we have no evidence that supports the view that **1** is of fungal or microbial origin.

Against PS leukemia in vivo, **1** is active at substantially lower dose levels than streptovitacin A and other related glutarimide derivatives.[9] Sesbanine (**2**), isolated from *S. drummondii* seed and characterized earlier,[2,3] has been synthesized by several groups.[10] Availability of synthetic **2** facilitated adequate bioassay of this novel alkaloid, and it has demonstrated no activity in experimental tumor systems.[9]

Several isomers or structural analogues of sesbanimide have also been isolated from *S. drummondii* seed; structures and

(1) Powell, R. G.; Smith, C. R., Jr.; Madrigal, R. V. *Planta Med.* **1976**, *30*, 1–8.

(2) Powell, R. G.; Smith, C. R., Jr.; Weisleder, D.; Muthard, D. A.; Clardy, J. *J. Am. Chem. Soc.* **1979**, *101*, 2784–2785.

(3) Powell, R. G.; Smith, C. R., Jr. *J. Nat. Prod.* **1981**, *44*, 86–90.

(4) Partition of fractions between 5% aqueous sodium carbonate and ethyl acetate, used in our earlier work, was avoided after it became apparent that the active materials were inordinately base labile.

(5) Cytotoxic and antitumor activities were assayed under auspices of the National Cancer Institute by the procedures described by Geran et al.: Geran, R. I.; Greenberg, N. H.; MacDonald, M. M.; Schumacher, A. M.; Abbott, B. J. *Cancer Chemother. Rep., Part 3* **1972**, *3*, 1–103.

(6) Numbering of **1** is patterned after that of the following: Sayers, J.; Schindler, D.; Sundaralingam, M. *J. Am. Chem. Soc.* **1977**, *99*, 3848–3850.

(7) All crystallographic calculations were done on a Prime 400 computer operated by the Materials Science Center and the Department of Chemistry, Cornell University. The principal programs used were as follows: REDUCE and UNIQUE, data reduction programs, M. E. Leonowicz, Cornell University, 1978; BLS, block-diagonal least-squares refinement, K. Hirotsu, Cornell University, 1978; ORFLS (modified), full-matrix least-squares, W. R. Busing, K. O. Martin, and H. S. Levy, Oak Ridge, ORNL-TM-305; ORTEP, crystallographic illustration program, C. Johnson, Oak Ridge, ORNL-3794; BOND, structural parameters and errors, K. Hirotsu, Cornell University, 1978; MULTAN-76, direct methods and fast Fourier transform, G. Germain, P. Main, and M. Woolfson, University of York.

(8) A number of glutarimide antibiotics have been tested for effectiveness as protein synthesis inhibitors, and some, such as streptovitacin A and cycloheximide, are of interest as antitumor or antifungal agents. See: Sisler, H. D.; Siegel, M. R. *Antibiot. (Mech. Action)* **1967**, *1*, 283–307.

(9) Suffness, M., personal communication.

(10) (a) Kende, A. S.; Demuth, T. P. *Tetrahedron Lett.* **1980**, *21*, 715–718. (b) Bottaro, J. C.; Berchtold, G. A. *J. Org. Chem.* **1980**, *45*, 1176. (c) Wanner, M. J.; Koomen, G.; Pandit, U. K. *Heterocycles* **1981**, *15*, 377. (d) Tomioka, K.; Koga, K. *Tetrahedron Lett.* **1980**, *21*, 2321–2324.

chemistry of these novel compounds will be described in a full paper.

Acknowledgment. The diffractometer used in this work was purchased with a National Science Foundation equipment grant. We thank Dr. W. K. Rohwedder and Ronald Plattner for mass spectra and Tim Mueser and Barry Jones for technical assistance. The 470-MHz ^1H NMR spectra were obtained through cooperation of the Purdue University Biological Magnetic Research Laboratory supported in part by the National Institutes of Health, Division of Research Resources, Grant No. RR 01077. We express our appreciation to Drs. J. Otvos and D. M. Doddrell for assistance in obtaining the initial DEPT experimental results.

Registry No. Sesbanimide, 85719-78-4.

Supplementary Material Available: Tables of fractional coordinates, thermal parameters, bond distances, bond angles, and both ^1H NMR and ^{13}C NMR spectra for sesbanimide (4 pages). Ordering information is given on any current masthead page.

Free-Radical Cyclization of Bromoacetals. Use in the Construction of Bicyclic Acetals and Lactones†

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Received February 8, 1983

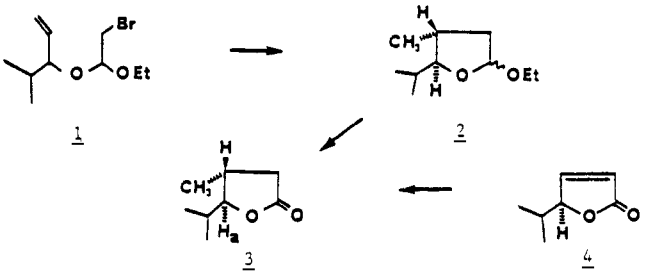
Radical cyclization is rapidly becoming an important method for the formation of bicyclic systems.[1] We recently reported[1b] a general regiospecific synthesis of vinyl radical intermediates by an intramolecular process starting with the bromoacetals of ethynyl carbinols (cf. A → B), and during the course of this work, we

A B

became interested in the cyclization of radicals derived from the bromoacetals of allylic and homoallylic alcohols. Such cyclizations will be especially valuable in the construction of cis-bicyclic systems bearing latent functionality (vide infra). We mention first the simpler synthesis of monocyclic acetals.

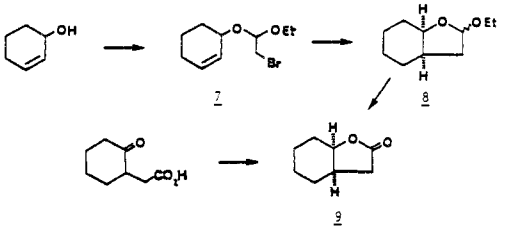
Treatment of the mixed bromoacetal **1** (Scheme I) derived from vinylisopropylcarbinol with tri-*n*-butylstannane (1.2 equiv of Bu_3SnH (0.02–0.04 M), AIBN catalyst, 4 h of reflux in benzene; potassium fluoride workup[2]) gave in 81% yield the cyclic acetal **2**, which was oxidized in quantitative yield with Jones reagent (4 equiv; room temperature) to the lactone **3**.[3] NMR as well as GLC analysis showed 97–98% of a major isomer,[4] which had a methyl resonance at δ 1.15 (d, J = 6.6 Hz) and H_a at δ 3.85 (dd, J = 5.6, 6.2 Hz).

Scheme I



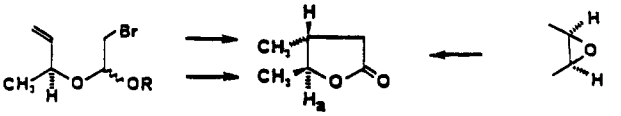
1 2 3 4

Scheme II



7 8 9

The stereochemistry of the lactone **3** was established to be trans by correlation with the product of lithium dimethylcuprate addition[5] to the butenolide **4**.[4,6] Our stereochemical conclusions are at variance with a report[7] that appeared while our work was being readied for publication[8] and that states that a very similar cyclization starting with the bromoacetal **5** led to the *cis*-4,5-



5 6

dimethyl isomer of **6**. Our expectation that the product of the cyclization of **5** should be trans-4,5-disubstituted (cf. **1** → **2** → **3** above) is clearly correct since the derived lactone 6 is identical with the necessarily *trans*-dimethyl lactone obtained by opening of the epoxide of *cis*-2-butene with malonic ester anion.[9]

Useful as these simple cyclizations may be, we believe that it is in the formation of bicyclic systems that the greater potential lies. The cis fusion of the bicyclic lactol produced by such a process (C → D, n = 0, 1) follows from the expected transition-state

C D

geometry and thus leads to the regio- and stereocontrolled formation of a carbon–carbon bond.

We illustrate the method starting with 2-cyclohexenol (Scheme II). Conversion to the mixed acetal **7** with 1,2-dibromoethyl ethyl ether,[1b,10] followed by treatment with tri-*n*-butylstannane readily gave the bicyclic lactol ether **8** as a mixture of anomers.[11] The

† This paper is dedicated to Professor Edgar Leherer on the occasion of his 75th birthday.

(1) (a) Stork, G.; Baine, N. H. *J. Am. Chem. Soc.* **1982**, *104*, 2321. (b) Stork, G.; Mook, R., Jr. *Ibid.*, in press. (c) Hart, D. J.; Tsai, Y.-M. *Ibid.* **1982**, *104*, 1430. (d) Hart, D. J.; Choi, J.-K.; Tsai, Y.-M. *Tetrahedron Lett.* **1982**, *23*, 4765.

(2) Jacobus, J.; Leibner, J. E. *J. Org. Chem.* **1979**, *44*, 449.

(3) The substances referred to in this paper were normally purified by flash chromatography with ethyl acetate–petroleum ether on silica gel.

(4) The minor isomer was the cis isomer of **3**, identical with the major product of the hydrogenation (cf. ref 5) of the 4-methyl derivative of the unsaturated lactone **4**. The methyl and H_a resonances of the cis isomer were at δ 1.09 (d, J = 6.5 Hz) and 3.94 (dd, J = 4.8, 12.5 Hz).

(5) Vigneron, J. P.; Meric, R.; Dhaenens, M. *Tetrahedron Lett.* **1980**, *21*, 2057.

(6) Made by reaction of the disodium salt of ethynylisopropylcarbinol with carbon dioxide, followed by semihydrogenation.

(7) Ueno, Y.; Chino, K.; Watanabe, M.; Moriya, O.; Okawara, M. *J. Am. Chem. Soc.* **1982**, *104*, 5564.

(8) Some of our work on bromoacetal cyclizations was presented in a plenary lecture at the Fourth International Conference on Organic Synthesis, Tokyo, Aug 1982.

(9) Bystrom, S.; Hogberg, H. E.; Norin, T. *Tetrahedron* **1981**, *37*, 2249. The NMR absorptions due to H_a in the authentic *cis*- and *trans*-dimethyl lactones are very characteristic of their stereochemistry.

(10) Rowlands, D. C.; Greenlee, K. W.; Derfer, J. M.; Boord, C. E. *J. Org. Chem.* **1952**, *17*, 807.

(11) The yield of purified cyclization product derived from the bromoacetal **7** and from the bromoacetal from **10** (50–55%) may be a lower limit, at least in the case of **8**, because of its volatility.

0002-7863/83/1505-3741$01.50/0