

Simple Synthesis of *Endo*-2-bromo-5-thiabicyclo[2.1.1]hexane

Eric Block* and Sriram Naganathan

Department of Chemistry, State University of New York at Albany, Albany, NY 12222

Received 16 January 1992

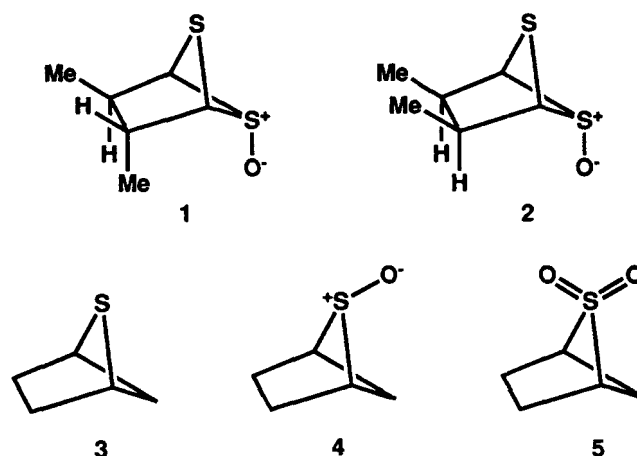
ABSTRACT

A brief synthesis of *endo*-2-bromo-5-thiabicyclo[2.1.1]hexane (**9**) has been developed involving conversion of 3-cyclopentenol (**6**) to 3-thioacetoxycyclopentene (**7**), bromination of this giving *trans*-1,2-dibromo-4-thioacetoxycyclopentane (**8**), and treatment of the latter with base. Compound **9** is oxidized to its *S*-oxide **10** and *S*, *S*-dioxide **11**. Comparative ^{13}C and ^1H NMR data are given for **9**–**11**.

INTRODUCTION

Characterization of onion-derived natural products "zwiebelane A and B" (**1** and **2**) as methyl substituted derivatives of 5, 6-dithiabicyclo[2.1.1]hexane [**1**] was based in part on detailed ^1H and ^{13}C NMR studies. In connection with these NMR studies, we sought heterobicyclo[2.1.1]hexanes as model compounds for coupling constant comparisons. When we initiated this work, the only known sulfur-containing example of this ring system was 5-thiabicyclo[2.1.1]hexane (**3**) and its *S*-oxides **4** and **5** [**2**]. Unfortunately, the high symmetry of **3**–**5** limits the number of H-H couplings seen. Furthermore, the reported nonstereospecific synthesis of **3** proved difficult to reproduce. In response to these problems, we have developed a simple stereospecific approach to the 5-thiabicyclo[2.1.1]hexane

skeleton, reported herein, which directly affords ring-substituted derivatives of **3**.



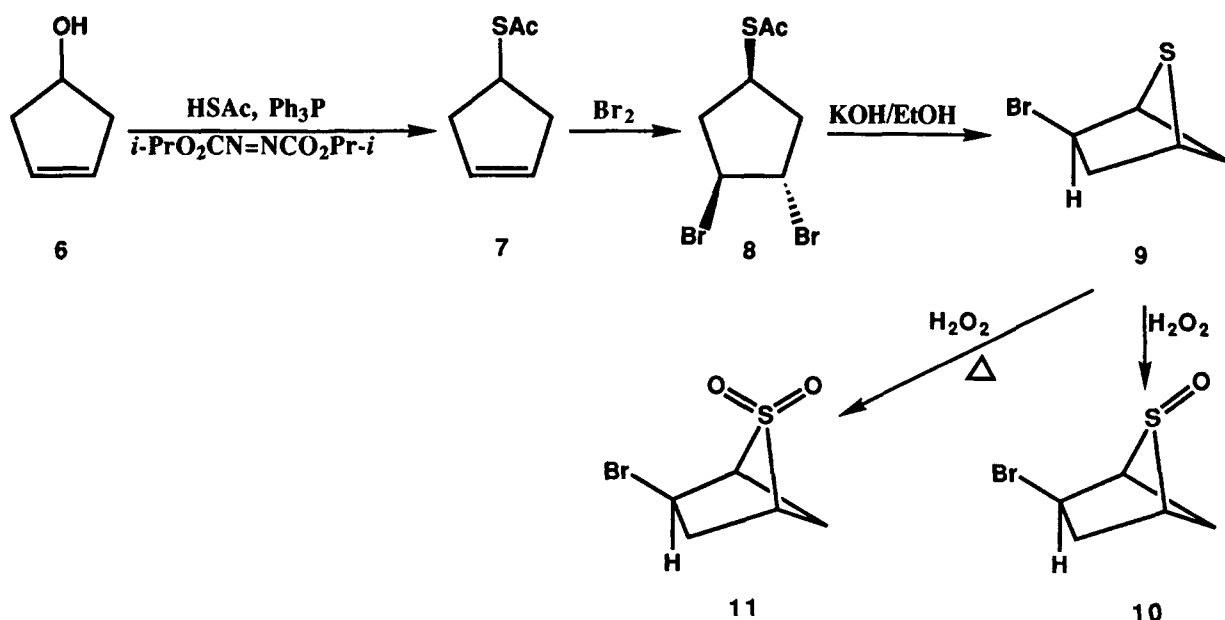
RESULTS AND DISCUSSION

Exposure of 3-cyclopentenol (**6**) [**3**] to Mitsunobu thioacetylation conditions [**4**] ($\text{Ph}_3\text{P}/i\text{-Pr-O}_2\text{CN}=\text{NCO}_2\text{Pr-}i/\text{CH}_3\text{COSH}/\text{THF}$) afforded 3-thioacetoxycyclopentene (**7**) which was directly treated with bromine in CH_2Cl_2 to give *trans*-1, 2-dibromo-4-thioacetoxycyclopentane (**8**) in 54% overall yield (Scheme 1). The structure and stereochemistry of **8** were assigned using ^1H and ^{13}C NMR spectroscopy including proton-proton decoupling and two-dimensional analysis. The stereochemistry of the dibromide must be as represented in **8**[**5**] and not as in **8a** or **8b**, because the ^{13}C NMR spectrum shows five distinct signals for the ring carbons. In **8a** and **8b**, there would only be three signals as there is a mirror plane within the molecule. The ^1H NMR spectrum also confirms this. There are proton signals corresponding to the hydrogens

*To whom correspondence should be addressed.

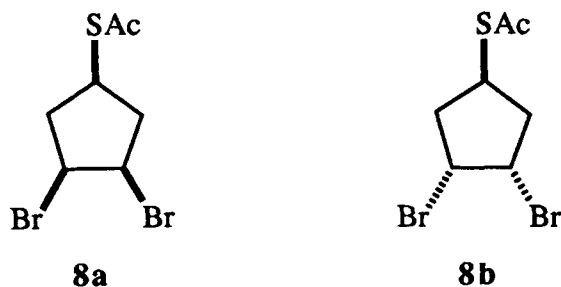
Dedicated to James Cullan Martin in honor of his forty years of outstanding research in heteroatom chemistry.

Presented at the 2nd International Conference on Heteroatom Chemistry (ICHAC-2), Albany, NY, July 1989.



SCHEME 1

geminal to the bromine at δ 4.60 and 4.55. In **8a** and **8b**, these protons would be equivalent.

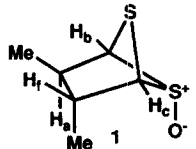
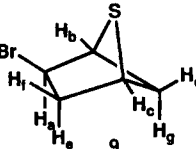
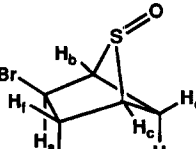
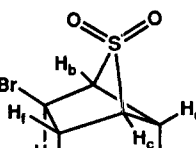


Treatment of **8** with KOH in aqueous ethanol at reflux for 90 hours gave *endo*-2-bromo-5-thiabicyclo[2.1.1]hexane (**9**) in 40% yield as a colorless oil with a pleasant camphor-like odor. The structure of **9** was assigned using ^1H and ^{13}C NMR spectroscopic methods, including proton-proton decoupling and homo- and heteronuclear two-dimensional analysis; these data are summarized in Table 1. By analogy to **3**, the doublet at δ 1.88 was assigned to the 6_{anti} proton g. This proton was found to be coupled only to the multiplet at δ 3.09. Therefore, this must be the 6_{syn} proton d. The most downfield signal was at δ 4.79 and was assigned to the proton geminal to the bromine a. The assignment is further validated by the lack of coupling between a and d. This also confirms the position of the bromine to be 2_{endo} . The bridgehead protons H_b and H_c are at δ 3.89 and 3.80, respectively, because of their similarity and their coupling to each other and the 6_{syn} proton. The distinction between H_b and

H_c could be made based on the existence (or lack thereof) of a coupling to H_a . The ^4J bridgehead coupling is 6.1 Hz. The assignment of H_e and H_f , at δ 2.87 and 2.53, respectively, is made based upon their coupling only to H_c and not to H_b . A distinction between them is made on the basis of the coupling of H_d to H_f and not to H_e . The observed coupling constants are in excellent agreement with the reported values. The ^2J for the C-6 hydrogens was found to be 7.5 Hz as compared to 6.8 Hz reported for **3** [**2a**]. The ^4J W-couplings are 2.2 Hz (2.3 Hz reported for **3** [**2a**]). The carbons were assigned based on the heteronuclear two-dimensional correlation spectrum. The carbon shifts are (for the respectively numbered carbons) 1: 62.44; 2: 51.14; 3: 43.60; 4: 54.59; 6: 48.98 ppm.

Compound **9** could be oxidized to the corresponding sulfoxide **10** and sulfone **11** with $\text{H}_2\text{O}_2/\text{HOAc}/\text{CH}_2\text{Cl}_2$ at 0°C and at reflux, respectively. The NMR spectral characteristics of **10** and **11** are similar to those of **9**. However, proton 6_d in **10** is moved upfield to δ 1.17 from 3.19 in **9**, indicating that proton 6_d in **10** is in the shielding cone of the sulfoxide oxygen. Therefore, the stereochemistry of the sulfoxide must be as shown. Spectroscopic data on **1** and **9–11** are given in Table 1. The ^{13}C shifts of **9–11** follow the "four-membered ring sulfone effect" [6]; e.g., for **10/11**, $\Delta H_b = 10$ Hz and $\Delta H_c = 9$ Hz, which is larger than the difference in α -carbon shifts in acyclic or larger ring sulfoxide/sulfone pairs. It is noteworthy that the $^4\text{J}_{\text{HH}}$ bridgehead-bridgehead coupling in **1** (6.7 Hz) is quite similar to that in **9–11** (6.1–6.2 Hz) and in bicyclo[2.1.1]hexane (6.23 Hz) [7]. Apparently, this large

TABLE 1 ^1H and ^{13}C NMR Data for Compounds 1, 9–11

Compound	Parameter	Position						
		a	b	c	d	e	f	g
 1	^{13}C	48.0	79.4	77.7			39.4	
	^1H	2.33	4.25	4.21			2.85	
	J_{HH}	J_{ab} 1.0 J_{af} 4.0	J_{bc} 6.7	J_{cd} 1.0				
 9	^{13}C	51.1	62.4	54.6	49.0	43.6		
	^1H	4.79	3.89	3.80	3.09	2.87	2.53	1.88
	J_{HH}	J_{ab} 2.2 J_{ae} 7.3 J_{af} 2.2	J_{bc} 6.2 J_{bd} 2.2	J_{cd} 2.2 J_{ce} 1.7 J_{cf} 0.7	J_{df} 2.2 J_{dg} 7.5	J_{ef} 13.0		
 10	^{13}C	41.3	68.5	63.0	33.6	22.8		
	^1H	4.49	3.88	3.66	1.17	2.97	2.79	1.49
	J_{HH}	J_{ab} 2.2 J_{ae} 7.8 J_{af} 3.2	J_{bc} 6.1 J_{bd} 2.2	J_{cd} 2.2 J_{ce} 2.2	J_{df} 2.2 J_{dg} 12.3	J_{ef} 13.4		
 11	^{13}C	38.3	78.5	72.0	33.6	31.8		
	^1H	4.49	4.14	3.98	(2.76)	(2.76)	2.65	1.76
	J_{HH}	J_{ab} 2.3 J_{ae} 10.7 J_{af} 4.6	J_{bc} 6.1	J_{cd} 2.3			J_{ef} 12.8 J_{df} 2.3	J_{dg} 12.8

“W” long range coupling is little effected by the nature of the “spacer atoms” between the C–H groups.

The now readily available compounds 9–11 offer interesting possibilities for synthesis and study of novel, strained sulfur-bridged systems, e.g., through solvolysis [8], elimination, and other reactions. We will report on the results of these studies in due course.

EXPERIMENTAL

NMR spectra were obtained in CDCl_3 on a Varian XL 300 or Varian Gemini 300 operating at 300 MHz for proton and 75.1 MHz for carbon. Mass spectra were obtained on a Hewlett-Packard 5989 MS engine. Infrared spectra were recorded on a Perkin Elmer 1600 series FTIR using NaCl plates. PCTLC refers to preparative centrifugal thin-layer chromatography and was performed on Chromatotron Model 7924T (Harrison Research, Palo Alto, CA) on silica gel (Art. No. 7749, Merck). Dichloromethane was distilled from calcium hydride; ethyl ether and THF were distilled from sodium-benzophenone ketyl; hexanes were fractionally distilled and the fraction boiling between 65–70°C was used; and

ethyl acetate was purchased from Baker and used without further purification.

3-Cyclopentenol (6)

A solution of borane-THF (1 M in THF, 300 mL, 0.3 mol) was added dropwise at 0°C to a solution of freshly distilled cyclopentadiene (66 g, 1.0 mol) in ether (500 mL). After the addition was complete, the reaction mixture was warmed to room temperature and stirred for 30 minutes and the solvent was evaporated under reduced pressure. The viscous oily residue was dissolved in ether (500 mL), cooled to 0°C, and hydrolyzed by slow addition of 3 M NaOH and 30% H_2O_2 . The organic layer was separated, and the aqueous layer was continuously extracted with ether for 18 hours. The ether layers were combined, dried, and concentrated and the fraction boiling between 60–70°C at 30 mm was collected. Chromatography on alumina using hexanes as eluent gave dicyclopentadiene. Switching to 1:4 ethyl acetate/hexanes afforded 19.6 g (23%) of 3-cyclopentenol 6 as a colorless oil.

3-Thioacetoxycyclopentene (7)

Solid triphenylphosphine (17 g, 64.8 mmol) was added to a solution of diisopropyl azodicarboxy-

late (13 g, 64.2 mmol) in dry THF (150 mL). A white precipitate resulted from a yellow solution in about 5 minutes. After stirring for an additional 30 minutes, a solution of thiolacetic acid (5.3 g, 70 mmol) and 3-cyclopentenol **6** (3 g, 35.7 mmol) in THF (75 mL) was added dropwise. A blue color appeared during the addition and then changed to a green color before resulting in a clear yellow solution as the reaction mixture was warmed to room temperature. After stirring for an additional 3 hours, the solvent was evaporated and the syrupy residue was suspended in 3:1 hexanes/CH₂Cl₂. The resulting white precipitate of triphenylphosphine oxide was filtered off, and the filtrate was concentrated. This procedure was repeated until no more precipitate was obtained. The yellow oil was then used as such in the next step. Thiolacetate **7** could be purified by distillation at room temperature and 0.01 mm vacuum into a receiver cooled to -78°C to yield 3.15 g (62%) of **7** as a pale yellow oil: ¹H NMR δ 5.71 (s, 2H), 4.02 (dd, *J* = 8, 5 Hz, 1H), 2.88 (dd, *J* = 15, 8 Hz, 2H), 2.30 (dd, *J* = 15, 5 Hz, 2H), 2.29 (s, 3H); ¹³C NMR δ 196.67, 128.97, 46.88, 39.98, 39.93, 30.40; IR (ν_{\max}) 3062 (w), 2925 (w), 2846 (w), 1689 (s), 1437 (s), 1267 (m), 1106 (m) cm⁻¹; EI-MS, *m/e* (relative intensity) 142 (M⁺, 0.6), 99 (0.5), 67 (24), 66 (100), 65 (18).

Trans-1, 2-dibromo-4-thioacetoxycyclopentane (**8**)

A solution of bromine in CH₂Cl₂ (6.4 g in 25 mL) was added dropwise to a solution of crude thiolacetate **7** in CH₂Cl₂ (100 mL) cooled to -20°C. The bromine color was discharged immediately. When the addition was complete, the reaction mixture was stirred for an additional 30 minutes and poured into water and the organic layer was washed with cold aqueous sodium bisulfite solution and extracted once with CH₂Cl₂. The organic extracts were combined, washed with cold aqueous sodium bisulfite solution, brine, dried, and concentrated. PCTLC using 1:19 ethyl acetate/hexanes yielded 5.8 g of the dibromide **8** (54% from 3-cyclopentenol) as a yellow oil: ¹H NMR δ 4.60 (m, 1H), 4.55 (m, 1H), 4.22 (m, 1H), 3.43 (m, 1H), 2.68 (m, 2H), 2.33 (s, 3H), 2.15 (m, 1H); ¹³C NMR δ 195.45, 55.37, 54.25, 41.97, 41.19, 37.64, 30.25; IR (ν_{\max}) 2954 (w), 2923 (w), 1691 (s), 1432 (m), 1353 (m), 1178 (m), 1133 (m), 631 (s) cm⁻¹; EI-MS, *m/e* (relative intensity) 304 (M⁺ + 4, 2), 302 (M⁺ + 2, 5), 300 (M⁺, 2), 262 (12), 260 (23), 258 (13), 223 (13), 221 (13), 147 (12), 145 (13), 141 (35), 99 (41), 97 (29), 66 (83), 65 (100).

2-Bromo-5-thiabicyclo[2.1.1]hexane (**9**)

KOH (7.0 g, 125 mmol) was added to a solution of the dibromide **8** (2.0 g, 6.6 mmol) in ethanol (200 mL), water (200 mL), and benzene (25 mL), and

the mixture was heated at reflux for 3 days. The dark-brown solution was saturated with salt and extracted with hexanes (3 × 250 mL). The hexane layers were combined, dried, concentrated, and purified by PCTLC using 1:19 ethyl acetate/hexanes to yield 0.47 g (40%) of **9** as a colorless oil with a camphor-like odor: ¹H NMR δ 4.79 (ddd, *J* = 7.3, 2.2, 2.2 Hz, 1H), 3.89 (ddd, *J* = 6.1, 2.2, 2.2 Hz, 1H), 3.80 (dm, *J* = 6.1, 2.2, 1.7, 0.7 Hz, 1H), 3.09 (dddd, *J* = 7.5, 2.2, 2.2, 2.2 Hz, 1H), 2.87 (ddd, *J* = 13.0, 7.3, 1.7 Hz, 1H), 2.53 (dddd, *J* = 13.0, 2.2, 2.2, 0.7 Hz, 1H), 1.88 (d, *J* = 7.5 Hz, 1H); ¹³C NMR δ 62.44, 54.59, 51.14, 48.98, 43.60; IR (ν_{\max}) 3005 (m), 2927 (s), 2896 (m), 2855 (s), 1437 (m), 1290 (m), 1262 (s), 1224 (s), 1196 (m), 1179 (m), 968 (m), 909 (m), 896 (m), 800 (m), 657 (s) cm⁻¹; UV (MeOH) λ (log ε_{max}) 251, 205; EIMS, *m/e* (relative intensity) 180 (M⁺ + 2, 20), 178 (M⁺, 21), 99 (100), 97 (22), 71 (14), 67 (18), 66 (26), 65 (98).

2-Bromo-5-thiabicyclo[2.1.1]hexane 5-oxide (**10**)

A solution of **9** (100 mg, 0.56 mmol) in CH₂Cl₂ (25 mL) at 0°C was treated with a solution of 30% aqueous H₂O₂ (2 mL, 17.6 mmol) in acetic acid (2 mL). After 12 hours at 25°C, the reaction mixture was poured into CH₂Cl₂ and solid Na₂CO₃ was added until no more CO₂ was evolved. The aqueous layer was extracted with CH₂Cl₂, washed with saturated aqueous sodium carbonate solution, dried, concentrated, and purified by PCTLC using 1:1 ethyl acetate/hexanes giving compound **10** (57 mg, 52%) as a colorless oil: ¹H NMR δ 4.49 (ddd, *J* = 7.8, 3.2, 2.2 Hz, 1H), 3.88 (ddd, *J* = 6.1, 2.2, 2.2 Hz, 1H), 3.66 (m, 1H), 2.97 (ddd, *J* = 13.4, 7.8, 2.2, 1H), 2.79 (m, 1H), 1.49 (d, *J* = 12.3 Hz, 1H), 1.17 (ddd, *J* = 12.3, 2.2, 2.2, 2.2, 1H); ¹³C NMR δ 68.50, 62.95, 41.34, 33.57, 22.83; IR (ν_{\max}) 2936, 1100 cm⁻¹; NH₃ CI-MS, *m/e* (relative intensity) 214 (M + NH₄⁺, 100), 212 (M + NH₄⁺, 80), 197 (M + H⁺, 42), 195 (M + H⁺, 39), 150 (55), 115 (9).

2-Bromo-5-thiabicyclo[2.1.1]hexane 5, 5-dioxide (**11**)

A solution of **9** (100 mg, 0.56 mmol) in CH₂Cl₂ (25 mL) was treated with a solution of 30% aqueous H₂O₂ (3 mL, 26.4 mmol) in acetic acid (3 mL) and heated at 45°C for 12 hours. The reaction mixture was poured into CH₂Cl₂, and solid Na₂CO₃ was added until no more CO₂ was evolved. The aqueous layer was extracted with CH₂Cl₂, washed with saturated aqueous sodium carbonate solution, dried, concentrated, and purified by PCTLC using 1:1 ethyl acetate/hexanes giving compound **11** (96 mg, 81%) as a colorless solid: ¹H NMR δ 4.49 (ddd, *J* = 10.7, 4.6, 2.3 Hz, 1H), 4.14 (ddd, *J* = 6.1, 2.3, 2.3 Hz, 1H), 3.98 (m, 1H), 2.76 (m, 2H), 2.65 (m, 1H), 1.76 (d, *J* = 12.8 Hz); ¹³C NMR δ 78.46, 72.02, 38.31, 33.58,

31.78; IR (ν_{\max}) 2962 (m), 1261 (s), 1103 (s), 1020 (s), 800 (s) cm^{-1} ; NH_3 CI-MS, *m/e* (relative intensity) 230 ($\text{M} + \text{NH}_4^+$, 100), 228 ($\text{M} + \text{NH}_4^+$, 95), 152 (7), 150 (5), 149 (4).

ACKNOWLEDGMENT

We gratefully acknowledge support from the donors of the Petroleum Research Fund, administered by the American Chemical Society, the Herman Frasch Foundation, the National Science Foundation, Société National Elf Aquitaine, and McCormick and Company. We thank the National Science Foundation for support for the NMR and MS facilities.

REFERENCES

- [1] (a) T. Bayer, H. Wagner, E. Block, S. Grisoni, S. H. Zhao, A. Neszmelyi, *J. Am. Chem. Soc.*, **111**, 1989, 3085. (b) E. Block, *Angew. Chem. Int. Ed. Engl.*, **31**, 1992, 1135.
- [2] (a) I. Tabushi, Y. Tamaru, Z. Yoshida, *Tetrahedron Lett.*, 1970, 2931. (b) T. Fukuyama, K. Kuchitsu, Y. Tamaru, Z. Yoshida, I. Tabushi, *J. Am. Chem. Soc.*, **93**, 1971, 2799; T. Fukuyama, K. Oyanagi, K. Kuchitsu, *Bull. Chem. Soc. Jpn.*, **49**, 1976, 638. (c) For recent examples of substituted 5,6-dithiabicyclo[2.1.1]-hexanes, see A. Ishii, J. Nakayama, M. Ding, N. Kotaka, M. Hoshino, *J. Org. Chem.*, **55**, 1990, 2421.
- [3] E. L. Allred, J. Sonnenberg, S. Winstein, *J. Org. Chem.*, **25**, 1960, 26.
- [4] R. P. Volante, *Tetrahedron Lett.*, **22**, 1981, 3119.
- [5] E. Block, A. Schwan: Electrophilic Addition of X-Y Reagents to Alkenes and Alkynes, in B. M. Trost, I. Fleming, M. Semmelhack (eds): *Comprehensive Organic Synthesis*, Pergamon Press, Oxford, pp. 329–362 (1991).
- [6] E. Block, A. A. Bazzi, J. B. Lambert, S. M. Wharry, K. K. Andersen, D. C. Dittmer, B. H. Patwardhan, D. J. H. Smith, *J. Org. Chem.* **45**, 1980, 4807.
- [7] M. Barfield, E. W. Della, P. E. Pigou, *J. Am. Chem. Soc.*, **106**, 1984, 5051.
- [8] For example, see E. Block, *Reactions of Organosulfur Compounds*, Academic Press, New York, p. 128 ff. (1978).