Heteroatom Chemistry
Volume 18, Number 5, 2007

Oxidation of Cyclic Polysulfides Fused to Aromatics

Ryu Sato

Department of Chemical Engineering, Faculty of Engineering, Iwate University, Morioka, 020-8551, Japan

Received 30 October 2006; revised 28 November 2006

ABSTRACT: *Considerable interest has been focused on the reactivity and oxidation of cyclic polysulfides such as benzopentathiepins and benzotrithioles. In this review, some oxidations of cyclic polysulfides fused to aromatics such as bezopentathiepins and related compounds with a few oxidizing reagents are described.* © 2007 Wiley Periodicals, Inc. Heteroatom Chem 18:482–488, 2007; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20347

INTRODUCTION

Organic polysulfides have generated significant interest among organic chemists for their physical and biological properties and synthetic utilities [1–7]. Especially, benzopentathiepins were recently found to display DNA-cleaving properties [8–14]. On the other hand, use of pentathiepins is also expanding on various dimensions to fulfill the growing demand of materials science. Accordingly, it is very important to clarify the oxidation of pentathiepins in the chemistry of cyclic polysulfides [15–19]. However, the oxidation of the pentathiepin ring such as benzopentathiepin has never been reported to date. In this review, oxidations of cyclic polysulfides fused to aromatics such as benzopentathiepins and related compounds with a few of oxidizing reagents are described.

Correspondence to: Ryu sato; e-mail: rsato@iwate-u.ac.jp.

OXIDATION OF BENZOTRITHIOLE ANALOGS

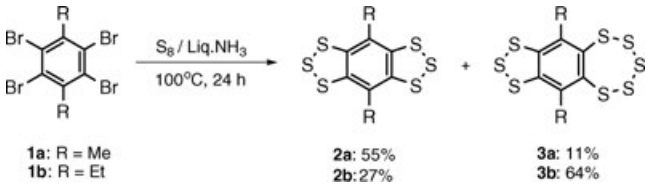
Photochemical Rearrangement of Benzotrithiole 2-Oxides to Benzotrithiole 1-Oxides Involving Intramolecular Oxygen Migration

Benzopentathiepin and benzotrithiole derivatives, *varacin* and *lisoclinotoxin A*, *B*, and *C*, which exhibit potent antifungal activity and cytotoxicity, have been isolated from the methanolic extracts of marine organisms. Therefore, considerable interest has been focused on the reactivity and oxidation of cyclic polysulfides such as benzopentathiepins and benzotrithioles. Here, oxidations of cyclic polysulfides as types of trithiolobenzopentathiepin and benzobistrithiole with several oxidizing agents are described, in addition to a novel intramolecular photochemical oxygen migration from benzotrithiole 2-oxides to benzotrithiole 1-oxides and related sulfoxides.

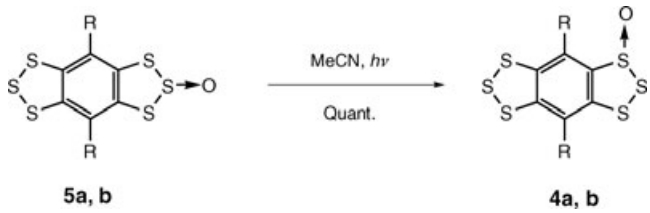
We succeeded in the synthesis of benzotrithiole analogs, 4,8-dialkylbenzobistrithioles (**2a** and **2b**) and 6,10-dialkyl[1,2,3]trithiolo[4,5-*h*]benzopentathiepin (**3a** and **3b**), from 1,4-dialkyl 2,3,5,6-tetrabromobenzene (**1a** and **1b**) by the treatment with elemental sulfur in liquid ammonia (Scheme 1) [20,21].

The oxidation of 4,8-dimethylbenzobistrithiole **2a** with *mcpba* of 1 equiv at 0°C for 3 h in the dark gave two oxidized products, 4,8-dimethylbenzobistrithiol 1-oxide (**4a**) (55%) and 4,8-dimethylbenzobistrithiole 2-oxide (**5a**) (19%). Here, we found that the oxidized product, 2-oxide **5a**, was slowly converted into their isomers, 1-oxide **4a**.

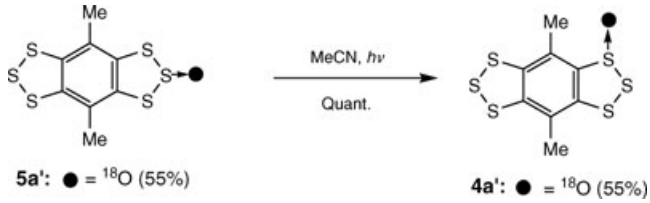
The oxidation of 4,8-diethylbenzobistrithiole **2b** with 1 equiv of *mcpba* under the same



SCHEME 1 Synthesis of 4,8-dimethylbenzobistrithiole (**2a** and **2b**) and 6,10-dialkyl[1,2,3]trithiolo[4,5-*h*]benzopentathiepin (**3a** and **3b**).



SCHEME 3 Oxygen migration from 4,8-dimethylbenzobistrithiole 2-oxide (**5a** and **5b**) to 4,8-dimethylbenzobistrithiole 1-oxide (**4a** and **4b**).



SCHEME 4 ^{18}O-labelled isotope experiment from oxide **5a′** to **4a′**.

conditions also gave two oxidized products, 4,8-diethylbenzobistrithiole 1-oxide (**4b**) (68%) and 4,8-diethylbenzobistrithiole 2-oxide (**5b**) (18%). The oxidation of benzobistrithioles **2** with 2 equiv of *mcpba* or further oxidation of 1-oxides **4** and 2-oxides **5** with 1 equiv of *mcpba* gave a complex mixture. In summary, the oxidation of benzobistrithioles **2** with *mcpba* gave the 1-oxides **4** preferentially, regardless of the substituents bound to the benzene ring of substrate **2** (Scheme 2). These results suggest that the terminal sulfur atom in the trithiole ring of **2** is more electron-rich compared with the middle sulfur atoms since *mcpba* acts as an electrophilic oxidizing agent.

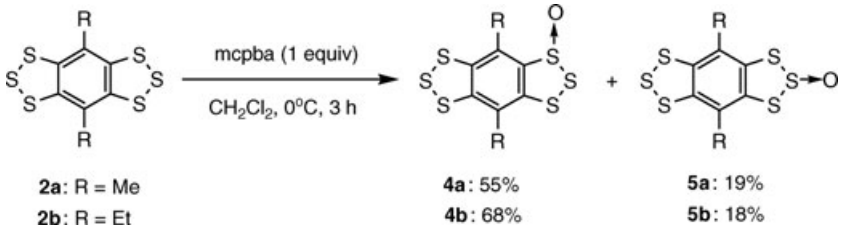
We found a novel oxygen migration from benzobistrithiole 2-oxides **5** to benzobistrithiole 1-oxides **4**. Thus, the irradiation of the 2-oxides **5** in acetonitrile with a 100 W high-pressure mercury lamp using a Pyrex filter for 1 h gave the 1-oxides **4** quantitatively (Scheme 3). These migrations did not occur thermally and were not initiated by addition of an acid such as trifluoroacetic acid in the dark. Moreover, photolysis of 1-oxides **4** under the same conditions left substrates 1-oxides **4** unchanged quantitatively [22,23].

To see whether the oxygen migration proceeds intra- or intermolecularly, we carried out ^{18}O-labeled and crossover experiments. Photolysis of the ^{18}O-labeled 2-oxide **5a′** (^{18}O content 55%) in acetonitrile containing dissolving oxygen gave ^{18}O-containing 1-oxide **4a′** (^{18}O content 55%). Hence, the possibility for a trioxide intermediate that was reported on the O_2-catalyzed isomerization of norbornanetrithiolane 2-oxide is ruled out (Scheme 4).

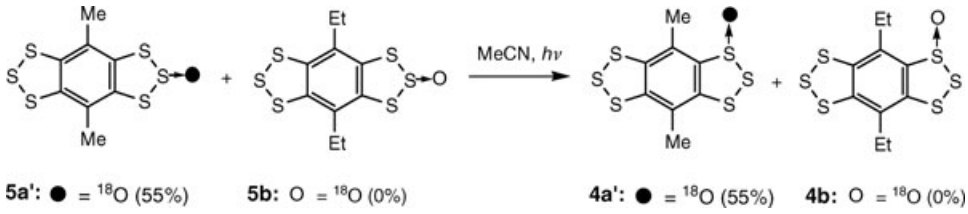
The crossover photolysis experiment using a 1:1 mixture of ^{18}O-labeled 2-oxide **5a′** and nonlabeled 2-oxide **5b** in acetonitrile under argon gave ^{18}O-containing 1-oxide **4a′** (^{18}O content 55%) and non–^{18}O-incorporating 1-oxide **4b**. These results apparently indicate that the photochemical oxygen migration proceeded intramolecularly (Scheme 5) [24,25].

To study the generality of these photochemical oxygen migrations, 1,2,3-benzotrithiole 2-oxides **6** and naphtho[2,3-*d*]-1,2,3-trithiole 2-oxide (**8**) were examined. These compounds, 2-oxides **6** and **8**, were found to convert to 1-oxides **7** and **9** respectively (Scheme 6) [26].

On the other hand, another 2-oxide such as dihydroacenaphtho[1,2-*d*][1,2,3]trithiolane 8-oxide (**10**), 1,2,3-trithiolane 2-oxide (**11**), and 3*H*-1,2-benzodithiole 2-oxide (**12**) were not converted into the corresponding 1-oxides by irradiation (Fig. 1). Accordingly, it seems that the aromatic ring fused to the trithiole 2-oxide ring plays an important role in these oxygen migrations.



SCHEME 2 Oxidation of 4,8-dimethylbenzotrithiole (**2a** and **2b**) with *mcpba*.



SCHEME 5 Crossover experiment using ^{18}O of oxides **5a′** and **5b**.

REACTION OF CYCLIC POLYSULFIDES

Oxidation of 6b,9a-Dihydroacenaphtho[1,2-d][1,2,3]trithiole

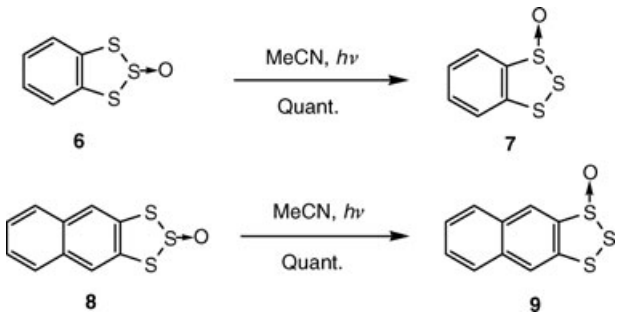
We have found the formation of a new cyclic polysulfide, 6*b*,9*a*-dihydroacenaphtho[1,2-*d*][1,2,3]trithiole (**1**), which is regarded as a good model for studying the chemical behavior of trithiolanes, upon treating 5-*H*-benzo[*e*][1,2,3,4]tetrathiepin or 6*H*-benzo[*f*][1,2,3,4,5]pentathiocin with acenaphthylene. Since only a few examples of oxidation of trithiolanes have been reported, many problems still remain to be resolved, for example, the regio- and chemoselectivity in the oxidation of cyclic polysulfides involving trithiolanes with a variety of oxidizing agents. We succeeded in the oxidation of dihydroacenaphthotrithiole **1** with several oxidizing agents such as *mcpba*, *N*-halosuccinimide (*NXS*), and chloramine T [27].

The treatment of trithiole **1** with 1 equiv of *mcpba* at room temperature for 3 h gave an oxidized product, 6*b*,9*a*-dihydroacenaphtho[1,2-*d*][1,2,3]trithiole 7-oxide (**2**), regio- and chemospecifically in 88% yield (Scheme 7). ^1H NMR spectra for two methine protons showed two sets of doublet peaks at $\delta = 6.10$ and 5.72, and ^{13}C NMR spectra also appeared as twelve peaks based on twelve unequivalent carbons. The IR spectrum of **2** showed a characteristic absorption for the —S-SO— group at 1075 cm^{-1}. The oxidation of **1** using 2 equiv of *mcpba* followed by hydrolysis resulted in the formation of 1,2-acenaphthene disulfinic acid and generation of hydrogen sulfide (Scheme 7). The second oxidation of **2** occurred at the 3-position in **2** to give intermediate **A**, since the sulfur atom of 9-position in **2** is electron-rich compared to the central sulfur and *mcpba* is an electrophilic oxidizing agent [15,28].

The oxidation of **1** with 1 equiv of *N*-bromosuccinimide (*NBS*) at room temperature for 3 h followed by hydrolysis gave 6*b*,9*a*-dihydroacenaphtho[1,2-*d*][1,2,3]trithiole 7,7-dioxide (**3**) in 41% yield. Furthermore, the treatment of **2**, which was formed from **1** by oxidation using *mcpba*, with 1 equiv of *NBS* resulted in the production of **3** in 33% yield and **2** was recovered in 20% yield. Similarly, the reaction of **1** with *N*-chlorosuccinimide (*NCS*) gave two oxidized products **2** (14%) and **3** (16%). This result suggests that the first oxidation of **1** with *NXS* proceeds electrophilically to give **2**, and further oxidation of **2** occurs at the electron-poor sulfinyl sulfur atom. It is very interesting that further oxidation of **2** with *NXS* gave the 7,7-dioxide **3** only. As is well known, the oxidation of sulfide to sulfoxide with *NXS* proceeds by nucleophilic attack of the sulfur atom toward the halogen atom to form a halosulfonium ion, which is hydrolyzed to give the corresponding sulfoxide (Scheme 8) [29,30].

PREPARATION AND CONFORMATION ANALYSIS OF 6,10-DISUBSTITUTED [1,2,3]TRITHIOLO[h]BENZOPENTATHIEPIN MONOOXIDES

6,10-Diethyl[1,2,3]trithiolo[*h*]benzopentathiepin (**1**) was oxidized with *mcpba* (1 equiv) to produce



SCHEME 6 Oxygen migrations of compounds **6** and **8**.

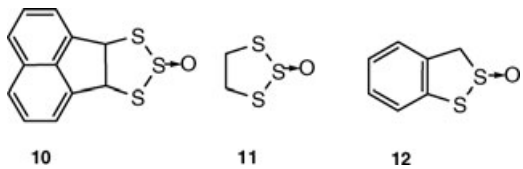
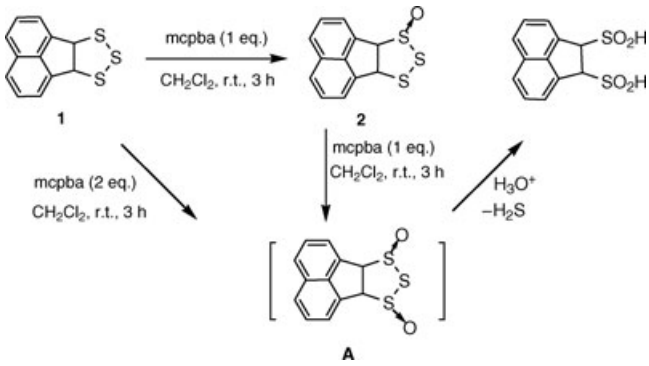
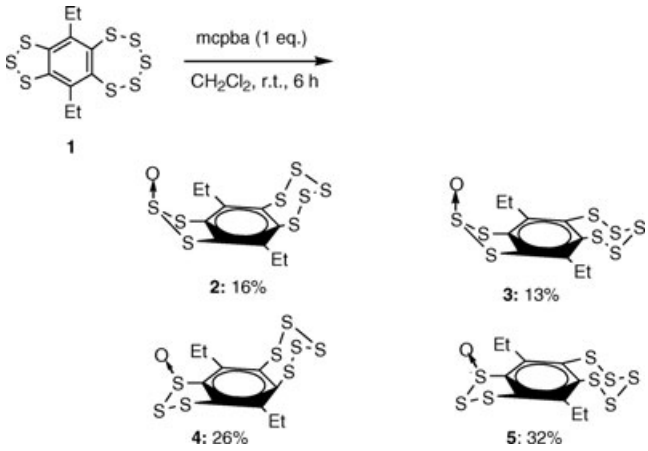


FIGURE 1 Trithiole and dithiole 2-oxides (**10**, **11**, and **12**).



SCHEME 7 Oxidation of 6*b*,9*a*-dihydroacenaphto[1,2-*d*][1,2,3]trithiole (**1**) with *mcpba*.

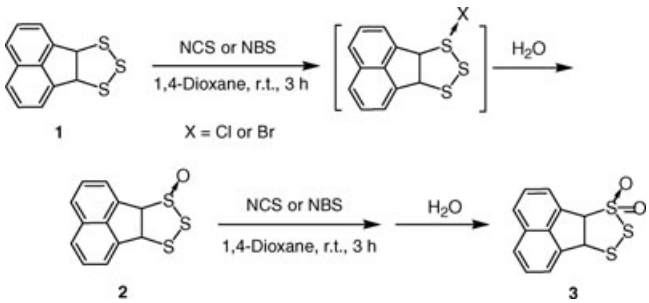


SCHEME 9 Oxidation of 6,10-diethyl[1,2,3]trithiolo[*h*]-benzopentathiepin (**1**) with *mcpba*.

four monooxides: 6,10-diethyl[1,2,3]trithiolo[*h*]benzopentathiepin 8-oxides (**2** and **3**) and 6,10-diethyl[1,2,3]trithiolo[*h*]benzopentathiepin 7-oxides (**4** and **5**) [20,21]. The yields were calculated on the basis of the integral ratios determined by ^{1}H NMR: 8-oxides **2** (16%) and **3** (13%) and 7-oxides **4** (26%) and **5** (32%) (Scheme 9) [31].

The structures of the four monooxides obtained were determined by X-ray crystallography, which revealed that they have the oxygen atom on the trithiole ring, not on the pentathiepin ring.

As shown in Fig. 2, while the trithiole 8-oxides **2** and **3** are the conformational isomers with respect to the pentathiepin ring, the trithiole 7-oxides **4** and **5** are the diastereomers with respect to the conformation of the pentathiepin ring and the configuration of the sulfinyl sulfur atom. Interestingly, we found that the trithiole 8-oxides **2** and **3** and the trithiole 7-oxides **4** and **5** are stable in the crystalline forms and isomerize to each other slowly in a $CHCl_3$ solution at room temperature. Both of the purified **2** and **3** isomerized to an about 1:1 mixture, and similar isomerization was observed in the case of **4** and **5**. The equilibrium ratios of these compounds were determined by the homo-spin-decoupled ^{1}H NMR spectroscopy in $CDCl_3$; the equilibrium ratio of **2** and **3** was found to be 55:45. The pyramidal inversion of the sulfinyl group has been known not to proceed at room temperature [32,33]. Therefore, the isomerization reactions of **2**, **3**, **4**, and **5** should proceed via the inversion of their pentathiepin rings. The activation parameters $\Delta G^{\neq}$, $\Delta H^{\neq}$, and $\Delta S^{\neq}$ of these compounds with respect to the inversion of their pentathiepin rings were determined by the results of ^{1}H NMR spectroscopy, as shown in the Table 1.



SCHEME 8 Oxidation of **1** with NCS and NBS.

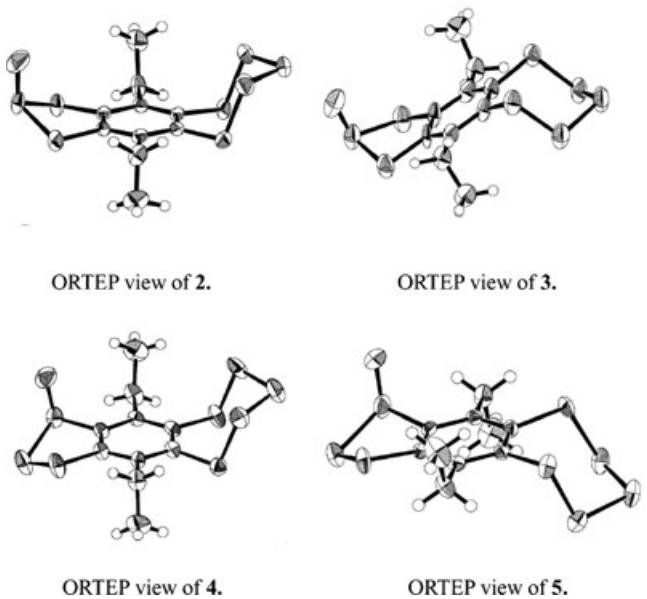


FIGURE 2 ORTEP view of 6,10-diethyl[1,2,3]trithiolo[*h*]benzopentathiepin 1-oxides (**2** and **3**) and 2-oxides (**4** and **5**).

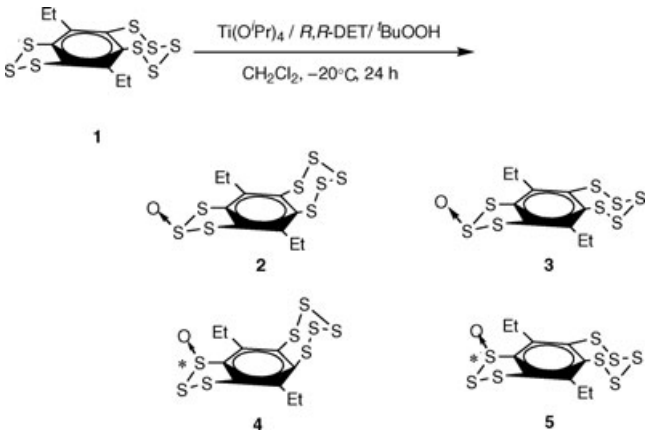
TABLE 1 Kinetic and Thermodynamic Parameters for the Isomerization of **2, 3, 4**, and **5**

	2	**3**	**4**	**5**
$^{298}\Delta G^{\ddagger}$ (kcal/mol)	23.8 ± 0.1	23.9 ± 0.1	24.0 ± 0.1	24.1 ± 0.0
$\Delta H^{\ddagger}$ (kcal/mol)	25.1 ± 1.0	27.0 ± 1.8	25.4 ± 0.7	27.1 ± 0.1
$\Delta S^{\ddagger}$ (eu)	4.4 ± 3.1	10.3 ± 5.9	4.7 ± 2.2	9.9 ± 0.0

PREPARATION AND STRUCTURAL DETERMINATION OF OPTICALLY PURE CYCLIC POLYSULFIDES, 6,10-DIETHYLTRITHIOLO[h]-BENZOPENTATHIEPIN MONOOXIDES

Experimental determination of the inversion energy of the pentathiepin and pentathiepin rings of 6,10-diethyltrithiolo[*h*]benzopentathiepin showed that the ring inversion of these polysulfide rings proceeds very slowly at room temperature [31,34,35]. Although two diastereomers were prepared by treatment of varacin with a chiral auxiliary, only one isomer was isolated and detected by ^{1}H NMR. To study a chiral molecule from benzopentathiepin derivatives, asymmetric oxidation of 6,10-diethyltrithiolo[*h*]benzopentathiepin (**1**) was carried out by a Sharpless reagent to produce the optically active trithiole monooxides; thus, the diastereomers, 6,10-diethyltrithiolo[*h*]benzopentathiepin 7-oxides (**4** and **5**), were isolated as optically pure crystals [36–38].

When we used a Sharpless reagent, Ti(O^{i}Pr)$_4$/R,R-DET/^{t}BuOOH, as the oxidizing reagent, four monooxides, 6,10-diethyltrithiolo[*h*]benzopentathiepin 8-oxides (**2** and **3**) and 7-oxides (**4** and **5**) were obtained similarly to that in the oxidation of **1** with *mcpba* (Scheme 10). The compounds **4** and **5** could be separated easily by column chromatography in 18% and 23% yields, respectively. Meanwhile, the compounds **2** and **3** were obtained as a mixture in 29% yield. Here, we could not observe the formation of the corresponding bissulfoxide or sulfone in the reaction. After column chromatography, the specific rotation $[\alpha]_D$ of **4** and **5** were measured by irradiation with a Na lamp in $CHCl_3$: $[\alpha]_D^{19} = -613^\circ$ ($c = 0.130$) for **4** and $[\alpha]_D^{20} = -971^\circ$ ($c = 0.282$) for **5**. The specific rotation $[\alpha]_D$ of these pure compounds **4** and **5**, after purification by recrystallization from *n*-hexane/CH_2Cl_2 (1:1) at -20°C, was measured in $CHCl_3$ and established as $[\alpha]_D^{20} = -775^\circ$ ($c = 0.204$) for **4** and $[\alpha]_D^{19} = -1364^\circ$ ($c = 0.161$) for **5**. The diastereomeric excess of these compounds was determined by measurement of 400 MHz ^{1}H NMR using Eu(hfc)$_3$ as *de*'s = of 100% for **4** and of 98% for **5**. The X-ray crystallographic analysis of the optically pure **4** and **5** showed that these compounds have the oxygen atom on the trithiole ring, not on the pentathiepin ring (Fig. 2). The oxygen atoms coordinated to the sulfur atoms of **4** and **5** are located on the axial position of the trithiole ring. Furthermore, the oxygen atom of **4** is on the *syn* side to the pentathiepin ring, and that of **5** exists on the *anti* side to the pentathiepin ring, suggesting that $[\alpha]_D$ of **4** and **5** was affected by the orientation of the pentathiepin ring. On the other hand, the configuration of **4** and **5** is *R* configuration on the sulfinyl sulfur atoms, respectively [39].



SCHEME 10 Asymmetric oxidations of 6,10-diethyl[1,2,3]trithiolo[*h*]benzopentathiepin (**1**) with Sharpless reagent.

OXIDATION OF PENTATHIEPINS FUSED TO AROMATICS

The oxidation of cyclic benzopolysulfides such as benzopentathiepin (BPT) is very important research work since the isolation of benzopentathiepin monooxide is related to the bioactivity of the marine product varacin [40]. The bioactivity of varacin, however, is not yet clarified fully. On the other hand, varacin C is also a natural sea product and a bioactive compound. Varacin is a benzopentathiepin derivative and varacin C is a benzotrithiole 1-oxide (Fig. 3). The formation of varacin C from varacin seems to need a varacin oxide as an intermediate [8–14]. Here, we studied the oxidation of benzopentathiepin (BPT) with some oxidizing agents such as *mcpba* and dimethyldioxirane [41,42].

To our knowledge, the synthesis and isolation of benzopentathiepin oxides (BPT-O) have never been reported. On the other hand, benzotrithiole (BTT) cannot be synthesized without kinetic or

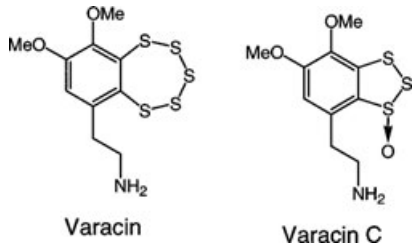
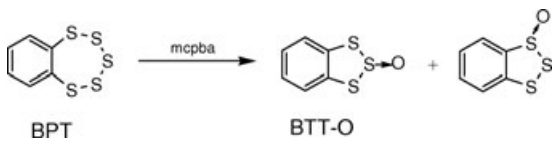


FIGURE 3 Varacin and Varacin C.

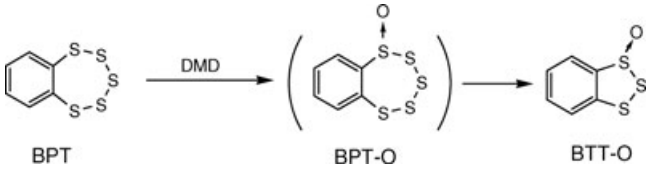
thermodynamic substituent effect, but benzotithiole oxides (BTT-O), in contrast, are very stable. Exactly, we obtained benzotrithiole 1-oxide and 2-oxide (BTT-O) in the oxidation of BPT with *mcpba* (1 equiv) as an oxidizing reagent at room temperature as shown in Scheme 11. This result suggests that the oxidation of BPT with *mcpba* is accompanied by ring contraction of the polysulfide ring from pentathiepin to trithiole. In spite of our many efforts, we could not obtain any benzopentathiepin oxide (BPT-O) at this stage.

Next, we performed the oxidation of BPT at room temperature with dimethyldioxirane (1 equiv), which is known to be a mild nucleophilic oxidizing reagent. When we separated the products using silica gel chromatography, we obtained only benzotrithiole 1-oxide (BTT-O) similar to the reaction using *mcpba*, suggesting that the product is very sensitive to silica gel (Scheme 12).

Further studies of the chemical and physical properties of pentathiepin monooxides are now in progress in our laboratory.



SCHEME 11 Oxidation of benzopentathiepin (BPT) with *mcpba*.



SCHEME 12 Oxidation of benzopentathiepin (BPT) with dimethyldioxirane.

REFERENCES

[1] Sato, R. Heteroatom Chem 2000, 22, 121.
[2] Rees, C. W. Chem Rev 2004, 104, 2617.
[3] Kimura, T.; Ogawa, S.; Sato, R. Mini-Rev Org Chem (in press).
[4] Fehèr, F.; Langer, M. Tetrahedron Lett 1971, 2125.
[5] Fehèr, F.; Engelen, B. Z Anorg Allg Chem 1979, 37, 452.
[6] Chenard, B. L.; Hallow, R. L.; Johnson, A. L.; Vladuchick, S. A. J Am Chem Soc 1985, 107, 3871.
[7] Chenard, B. L.; Dixon, D. A.; Harlow, R. L.; Roe, D. C.; Fukunaga, T. J Org Chem 1987, 52, 2411.
[8] Davidson, B. S.; Molinski, T. F.; Barrow, L. R.; Ireland, C. M. J Am Chem Soc 1991, 113, 4709.
[9] Ford, P. W.; Davidson, B. S. J Org Chem 1993, 58, 4522.
[10] Searle, P. W.; Davidson, B. S. J Org Chem 1994, 59, 6600.
[11] Greer, A. J Am Chem Soc 2001, 123, 10379.
[12] Lee, A. H. F.; Chan, A. S. C.; Li, T. Chem Commun 2002, 2112.
[13] Lee, A. H. F.; Chen, J.; Liu, D.; Leung, Y.; Chan, A. S. C.; Li, T. J Am Chem Soc 2002, 124, 13972.
[14] Brzostowska, E. M.; Greer, A. J Am Chem Soc 2003, 125, 396.
[15] Milligan, B.; Swan, J. M. J Chem Soc 1965, 2905.
[16] Steudel, R.; Latte, J. Angew Chem 1974, 86, 657.
[17] Kato, A.; Hashimoto, Y.; Otsuka, I. Nakatsu, K. Chem Lett 1978, 1219.
[18] Ghosh, T.; Bartlett, P. D. J Am Chem Soc 1988, 110, 7499.
[19] Ishii, A.; Oshida, H.; Nakayama, J. Bull Chem Soc Jpn 2002, 75, 319.
[20] Sato, R.; Kimura, T.; Goto, T.; Saito, M. Tetrahedron Lett 1988, 29, 6291.
[21] Sato, R.; Kimura, T.; Goto, T.; Saito, M.; Kabuto, C. Tetrahedron Lett 1989, 30, 3453.
[22] Yomoji, N.; Satoh, S.; Ogawa, S.; Sato, R. Tetrahedron Lett 1993, 34, 673.
[23] Yomoji, N.; Takahashi, S.; Chida, S.; Ogawa, S.; Sato, R. J Chem Soc Perkin Trans I, 1993, 1995.
[24] Tanikaga, R.; Higashino, Y.; Kaji, A. Tetrahedron Lett 1970, 3273.
[25] Tanikaga, R.; Kaji, A. Bull Chem Soc Jpn 1973, 46, 3814.
[26] Tezuka, T.; Suzuki, H.; Miyazaki, H. Tetrahedron Lett 1978, 4885.
[27] Satoh, S.; Sato, R. Bull Chem Soc Jpn 1992, 65, 1188.
[28] Nakayama, J.; Ito, Y. Sulfur Lett 1989, 9, 135.
[29] Takagi, W.; Kikukawa, K.; Ando, W.; Oae, S. Chem Ind (London) 1964, 1624.
[30] Harville, R.; Read, S. F. J Org Chem 1968, 33, 3976.
[31] Kimura, T.; Hanzawa, M.; Horn, E.; Kawai, Y.; Ogawa, S.; Sato, R. Tetrahedron Lett 1997, 38, 1607.
[32] Furukawa, N.; Harada, K.; Oae, S. Tetrahedron Lett 1972, 1377.
[33] Rayner, D. R.; Gordon, A. J.; Mislow, K. J Am Chem Soc 1968, 90, 4854.
[34] Sugihara, Y.; Takeda, H.; Nakayama, J. Tetrahedron Lett 1998, 39, 2605.

[35] Sugihara, Y.; Takeda, H.; Nakayama, J. Eur J Org Chem 1999, 597.
[36] Davidson, B. S.; Ford, P. W.; Wahlman, M. Tetrahedron Lett 1994, 35, 7175.
[37] Pitchen, P.; Dunach, E.; Deshmukh, M. N.; Kagan, H. B. J Am Chem Soc 1984, 106, 8188.
[38] Furia, D. F.; Modena, G.; Serglia, R. Synthesis 1984, 325.
[39] Kimura, T.; Kawai, Y.; Ogawa, S.; Sato, R. Chem Lett 1999, 1305.
[40] Steudel, R.; Sandow, T.; Steidel, J. Chem Commun 1980, 180.
[41] Ishii, A.; Nakabayashi, M.; Nakayama, J. J Am Chem Soc 1999, 121, 7959.
[42] Ishii, A.; Oshida, H.; Nakayama, J. Bull Chem Soc Jpn 2002, 75, 319.