Bull. Chem. Soc. Jpn., ***70***, *2515—2518 (1997)* 2515

Synthesis of Macrocyclic Bis(dithiocarbonic ester)s and Bis(thiocarbamate)s from Diethylene, Triethylene, and Tetraethylene Glycols

Naoaki Fukada,* Takashi Tanaka, Tetsuo Fukuya, and Yasuyuki Takeda

Department of Chemistry, Faculty of Science, Chiba University, Yayoi-cho, Inage-ku, Chiba 263

(Received March 31, 1997)

The reaction of dipotassium bis(dithiocarbonate)s from diethylene, triethylene, and tetraethylene glycols with dibromoalkanes or ethereal oxygen-containing diiodides under high-dilution conditions gave 1 : 1 reaction products, 14—25-membered macrocyclic bis(dithiocarbonic ester)s. From dimethyl esters of the bis(dithiocarbonic acid)s and diaminoalkanes or ethereal oxygen-containing diamines, macrocyclic bis(thiocarbamate)s were obtained.

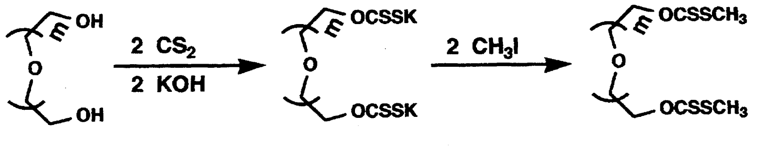
Many dithiocarbonic acid derivatives are known as cellulose dithiocarbonates, analytical reagents, and intermediates in organic synthesis. Recently, Kamata et al. prepared some α,ω-alkanediyl bis(*O*-butyl or *O*-3-thiapentyl dithiocarbonate)s as a new reagent for the solvent extraction of precious-metal ions[1] or active ionophores for rare-earth ions in membrane electrodes.[2] Although many macrocyclic compounds have been synthesized since crown ethers appeared in 1967,[3] there have been few macrocycles of dithiocarboxylic acid derivatives discussed in the literature.[4] In our continuing study of the synthesis and reactions of dithiocarboxylic acid derivatives, we have reported on the preparation of macrocyclic compounds using dithiocarbamic acid esters.[5—7] In this paper, we wish to report on the synthesis of new macrocyclic bis(dithiocarbonic ester)s and bis(thiocarbamate)s from diethylene, triethylene, and tetraethylene glycols (**1a**—**c**) for the purpose of seeking novel macrocyclic ligands.

Bis(potassium dithiocarbonate)s **2a**, **b**[8], and **2c** were obtained in quantitative yields as pale-yellow solids by the reaction of diols **1a**—**c** with carbon disulfide in dioxane at room temperature in the presence of potassium hydroxide. Salts **2a**—**c** reacted with methyl iodide in water at room temperature to give the corresponding dimethyl esters **3a**—**c** in good yields (Scheme 1).

The synthesis of 14—20-membered macrocyclic bis(*O*-dithiocarbonic ester)s **4** was conducted using equimolar amounts of salts **2** and α, ω-dibromoalkanes (1,3-dibromopropane and 1,4-dibromobutane) under high-dilution conditions. The reaction in ethanol under reflux conditions afforded yellow solid products in low yields (Table 1) (Scheme 2). Better yields would probably be obtained using diiodoalkanes instead of dibromides. It was difficult to prepare macrocyclic dithiocarbonic esters from salts **2** and dibromomethane or 1,2-dibromoethane.

Salts **2** reacted with ethereal oxygen-containing diiodides [bis(2-iodoethyl) ether and 1,2-bis(2-iodoethoxy)ethane] in acetone at room temperature. The reaction mixtures were chromatographed, except for **5d**, on a silica-gel column to give the expected 16—25-membered thiocarbonyl-containing thiacrown ethers **5**. However, attempts to isolate macrocycles using bis[2-(2-iodoethoxy)ethyl] ether were unsuccessful. Macrocyclic compounds **4** and **5** may be formed by the template effect of one or two potassium ions in the starting material salts **2**. All FAB mass spectra (matrix: 3-nitrobenzyl alcohol) of **4** and **5** showed $(M+H)^+$ peaks for the 1 : 1 reaction product with no further peaks above them.

Bogatsky et al. previously reported on the synthesis of 1 : 1 and 2 : 2 reaction macrocyclic thioureas from carbon disulfide and ethereal oxygen-containing diamines.[9] Many displacement reactions of a methylthio group of dithiocarboxylates with an amino group to give various heterocyclic compounds



1a: m=1
1b: m=2
1c: m=3

2a: m=1
2b: m=2
2c: m=3

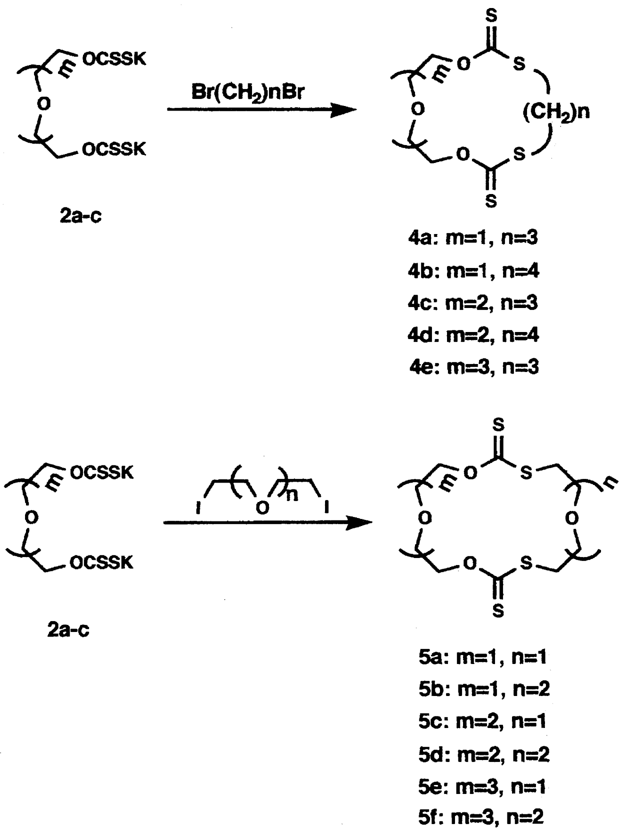
3a: m=1
3b: m=2
3c: m=3

Scheme 1.

Table 1. Yields, Melting Points, and Mass Spectral Data of Macrocyclic Bis(dithiocarbonic *O*-ester)s **4** and **5**

Compd	Ring member	Yield %	Mp °C (Solvent)	MS[a)] $(M+H)^+$ m/z (M_w)
4a	14	35	145—146 (EtOH)	299 (298.46)
4b	15	18	119—121 (EtOH)	313 (312.49)
4c	17	19	100—103 (EtOH)	343 (342.52)
4d	18	23	71—74 (Me_2CO)	357 (356.54)
4e	20	15	67—70 (Me_2CO)	387 (386.57)
5a	16	35[b)]	90—92 (EtOH)	329 (328.49)
5b	19	23[b)]	Oil	373 (372.54)
5c	19	58[b)]	Oil	373 (372.54)
5d	22	44	90—92 (Me_2CO)	417 (416.60)
5e	22	7[b)]	Oil	417 (416.60)
5f	25	21[b)]	Oil	461 (460.65)

a) FAB mass spectrometry. b) Silica-gel column chromatography.



Scheme 2.

Table 2. Yields, Melting Points, and Mass Spectral Data of Macrocyclic Bis(*O*-thiocarbamate)s **6**—**9**

Compd	Ring member	Yield %	Mp °C (Solvent)	MS[a)] $(M+H)^+$ m/z (M_w)
6a	14	29	219—221 (DMF)	264[b)] (264.37)
6b	15	25	188—190 ($CHCl_3$)	278[b)] (278.39)
6c	17	33	173—175 ($CHCl_3$)	306[b)] (306.45)
6d	18	11	140—143 (Me_2CO)	323 (322.45)
6e	20	13	152—154 (Me_2CO)	351 (350.50)
7	21	58[c)]	105—107 (EtOAc)	367 (366.50)
8	42	6[c)]	103—105 (EtOAc)	733 (733.00)
9	24	38[c)]	79—81 (EtOAc)	411 (410.55)

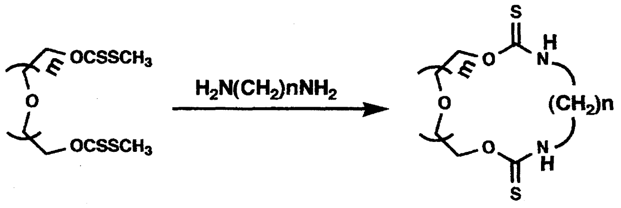
a) FAB mass spectrometry. b) EI mass spectra. c) Silica-gel column chromatography.

and intermediates in organic synthesis are known.[10,11)] We previously obtained azacrown ethers by the reaction of dimethyl *N*-benzoylcarbonimidodithioates,[5)] dimethyl *N*-phenylsulfonylcarbonimidodithioates,[6)] or dimethyl 2-oxo-1,3-imidazolidinebis(carbodithioate)[7)] with diamines.

From bifunctional esters **3** and *α*, *ω*-diaminoalkanes (1, 3-diaminopropane, 1,4-diaminobutane, and 1,6-diaminohexane), 1 : 1 reaction products, 15—20-membered macrocyclic bis(thiocarbamate)s **6** could be synthesized as white crystals (Table 2) (Scheme 3). The reaction mixtures were refluxed for 24 h in ethanol, while the same reactions at room temperature required 4—7 d stirring. Although these reactions were carried out under high-dilution conditions, tarry polymers frequently precipitated in the flasks, which were removed. The isolation of macrocycles by a reaction using 1, 2-diaminoethane was difficult. The progress and termination of every reaction of dimethyl esters with diamines could be judged by detecting the odor of methanethiol.

The reaction of **3a** with 1,2-bis(3-aminopropoxy)ethane was conducted in ethanol with stirring for 5 d at room temperature. The resulting oily substance was chromatographed on a silica-gel column to give two major products at a ratio of ca. 10 : 1—21-membered macrocyclic 1 : 1 reaction product **7** and 42-membered macrocyclic 2 : 2 reaction product **8** (Fig. 1). However, from the reaction mixture of **3a** and bis-[2-(3-aminopropoxy)ethyl] ether, only 1 : 1 cyclization compound **9** was obtained. The formation of macrocycles **6**—**9** resulted in the absence of any template. Also, attempts to isolate 1 : 1 or 2 : 2 reaction products[6,9,12)] by the reaction of **3b, c** with ethereal oxygen-containing diamines were unsuccessful.

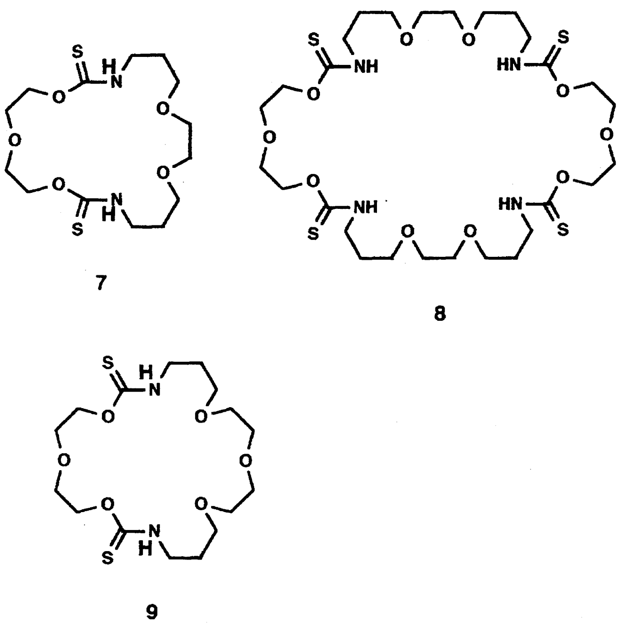
All of the new compounds **3**—**9** were characterized by microanalysis as well as by spectral data. Most of molecular weights of the macrocycles obtained here were determined by the FAB mass spectra due to the hardly measurable EI mass



3a,b

6a: m=1, n=3
6b: m=1, n=4
6c: m=1, n=6
6d: m=2, n=4
6e: m=2, n=6

Scheme 3.



7

8

9

Fig. 1.

spectra. The EI mass spectra of compounds **6a**—**c**, having high melting points, showed their molecular ion peaks. Also, in general, the smaller ring system of these macrocycles tends to have higher melting points. All organic compounds including the starting materials treated in this work have a plane of symmetry in their structures.

Experimental

Dipotassium 3-Oxapentane-1,5-diyl Bis(dithiocarbonate) (2a), Dipotassium 3,6-Dioxaoctane-1,8-diyl Bis(dithiocarbonate) (2b), and Dipotassium 3,6,9-Trioxaundecane-1,11-diyl Bis(dithiocarbonate) (2c). To a suspension of finely powdered potassium hydroxide (11.3 g, 0.2 mol) in dioxane (200 ml) was added a solution of diol (diethylene, triethylene, or tetraethylene glycol) **1** (0.1 mol) and carbon disulfide (18 g, 0.24 mol) in dioxane (100 ml). The mixture was stirred overnight at room temperature. Ether (70 ml) was added and the whole mixture was stirred for an additional 1 h. The pale-yellow solid which precipitated was collected, washed several times with ether, and thoroughly dried under reduced pressure in a desiccator. The practically pure salts **2a**—**c** obtained in quantitative yields were used as starting materials without further purification.

Dimethyl 3-Oxapentane-1,5-diyl Bis(dithiocarbonate) (3a). A mixture of salt **2a** (16.7 g, 0.05 mol), water (100 ml), and methyl iodide (16 g, 0.11 mol) was stirred for 3 h at room temperature. The aqueous mixture was extracted with benzene. After the solvent was evaporated, the residual yellow oil was transferred to a refrigerator. The white solid was recrystallized from ethanol: Yield 70%; mp 66—67 °C; IR (KBr) 1060vs $\mathrm{cm^{-1}}$ (C=S); FAB MS *m/z* 287 $[(\mathrm{M+H})^+]$. Found: C, 33.59; H, 4.77%. Calcd for $\mathrm{C_8H_{14}O_3S_4}$: C, 33.54; H, 4.93%.

Dimethyl 3,6-Dioxaoctane-1,8-diyl Bis(dithiocarbonate) (3b) was prepared from salt **2b** (19 g, 0.05 mol) and methyl iodide (16 g, 0.11 mol) by the method described for **3a**. The yellow oil was chromatographed on a silica-gel column with ethyl acetate–hexane (1 : 3) as an eluent. The pale-yellow oil solidifies in a refrigerator: Yield 65%; mp 25—29 °C; IR (neat) 1050vs $\mathrm{cm^{-1}}$ (C=S); FAB MS *m/z* 331 $[(\mathrm{M+H})^+]$. Found: C, 36.40; H, 5.50%. Calcd for $\mathrm{C_{10}H_{18}O_4S_4}$: C, 36.34; H, 5.49%.

Dimethyl 3,6,9-Trioxaundecane-1,11-diyl Bis(dithiocarbonate) (3c) was prepared from salt **2c** (21.2 g, 0.05 mol) and methyl iodide (16 g, 0.11 mol) by the method described for **3a**. The yellow oil was chromatographed on a silica-gel column with ethyl acetate–hexane (1 : 3) as an eluent: Yellow oil; yield 60%; IR (neat) 1065vs $\mathrm{cm^{-1}}$ (C=S); FAB MS *m/z* 375 $[(\mathrm{M+H})^+]$. Found: C, 38.50; H, 6.02%. Calcd for $\mathrm{C_{12}H_{22}O_5S_4}$: C, 38.48; H, 5.92%.

Macrocyclic Bis(dithiocarbonic O-ester)s 4. General Procedure. To a refluxing suspension of salt **2** (0.01 mol) in ethanol (200 ml) was added dropwise over 3 h a solution of 1,3-dibromopropane or 1,4-dibromobutane (0.01 mol) in ethanol (20 ml). The reaction mixture was refluxed for 24 h and concentrated. Water was added and the mixture was extracted with benzene. After the solvent was evaporated, the residual yellow oil was transferred to a refrigerator and kept for several days. The yellow solid was recrystallized.

8,14-Dithioxo-1,4,7-trioxa-9,13-dithiacyclotetradecane (4a): IR (KBr) 1055vs $\mathrm{cm^{-1}}$ (C=S). Found: C, 36.45; H, 4.68%. Calcd for $\mathrm{C_9H_{14}O_3S_4}$: C, 36.22; H, 4.73%.

8,15-Dithioxo-1,4,7-trioxa-9,14-dithiacyclopentadecane (4b): IR (KBr) 1055vs $\mathrm{cm^{-1}}$ (C=S). Found: C, 38.44; H, 5.16%. Calcd for $\mathrm{C_{10}H_{16}O_3S_4}$: C, 38.44; H, 5.16%.

11,17-Dithioxo-1,4,7,10-tetraoxa-12,16-dithiacycloheptadecane (4c); IR (KBr) 1040vs $\mathrm{cm^{-1}}$ (C=S). Found: C, 38.74; H, 5.30%. Calcd for $\mathrm{C_{11}H_{18}O_4S_4}$: C, 38.57; H, 5.30%.

11,18-Dithioxo-1,4,7,10-tetraoxa-12,17-dithiacyclooctadecane (4d): IR (KBr) 1060vs $\mathrm{cm^{-1}}$ (C=S). Found: C, 40.10; H, 5.64%. Calcd for $\mathrm{C_{12}H_{20}O_4S_4}$: C, 40.42; H, 5.65%.

14,20-Dithioxo-1,4,7,10,13-pentaoxa-15,19-dithiacycloicosane (4e): IR (KBr) 1070vs $\mathrm{cm^{-1}}$ (C=S). Found: C, 40.15; H, 5.48%. Calcd for $\mathrm{C_{13}H_{22}O_5S_4}$: C, 40.39; H, 5.74%.

Macrocyclic Bis(dithiocarbonic O-ester)s 5. General Procedure. To a suspension of salt **2** (0.005 mol) in acetone (200 ml) was added dropwise over 5 h a solution of bis(2-iodoethyl) ether or 1,2-bis(2-iodoethoxy)ethane (0.005 mol) in acetone (50 ml) at room temperature. The reaction mixture was stirred for 3 d at room temperature. The precipitated potassium iodide was removed by filtration and the filtrate was concentrated. Water was added and the mixture was extracted with benzene. After the solvent was evaporated, the residual yellow oil was chromatographed, except for **5d**, on a silica-gel column to give yellow crystals or oil.

8,16-Dithioxo-1,4,7,12-tetraoxa-9,15-dithiacyclohexadecane (5a): Chromatographed with ethyl acetate–hexane (1 : 2); yellow crystals; IR (KBr) 1055vs $\mathrm{cm^{-1}}$ (C=S). Found: C, 36.53; H, 4.93%. Calcd for $\mathrm{C_{10}H_{16}O_4S_4}$: C, 36.56; H, 4.91%.

8,19-Dithioxo-1,4,7,12,15-pentaoxa-9,18-dithiacyclononadecane (5b): Chromatographed with ethyl acetate–hexane (1 : 2);

yellow oil; IR (neat) 1060vs cm^{-1} (C=S). Found: C, 38.91; H, 5.39%. Calcd for $C_{12}H_{20}O_5S_4$: C, 38.69; H, 5.41%.

11,19-Dithioxo-1,4,7,10,15-pentaoxa-12,18-dithiacyclononadecane (5c): Chromatographed with ethyl acetate–hexane (1 : 4); yellow oil; IR (neat) 1060vs cm^{-1} (C=S). Found: C, 38.43; H, 5.35%. Calcd for $C_{12}H_{20}O_5S_4$: C, 38.69; H, 5.41%.

11,22-Dithioxo-1,4,7,10,15,18-hexaoxa-12,21-dithiacyclodocosane (5d): Yellow crystals; IR (KBr) 1065vs cm^{-1} (C=S). Found: C, 40.39; H, 5.84%. Calcd for $C_{14}H_{24}O_6S_4$: C, 40.36; H, 5.81%.

14,22-Dithioxo-1,4,7,10,13,18-hexaoxa-15,21-dithiacyclodocosane (5e): Chromatographed with ethyl acetate–hexane (1 : 1); yellow oil; IR (neat) 1060vs cm^{-1} (C=S). Found: C, 40.29; H, 5.80%. Calcd for $C_{14}H_{24}O_6S_4$: C, 40.36; H, 5.81%.

14,25-Dithioxo-1,4,7,10,13,18,21-heptaoxa-15,24-dithiacyclopentacosane (5f): Chromatographed with ethyl acetate; yellow oil; IR (neat) 1060vs cm^{-1} (C=S). Found: C, 42.04; H, 6.17%. Calcd for $C_{16}H_{28}O_7S_4$: C, 41.72; H, 6.13%.

Macrocyclic Bis(O-thiocarbamate)s 6. General Procedure. To a solution of ester **3** (0.01 mol) in ethanol (200 ml) in a 500-ml flask with a cotton wool-topped reflux condenser under a fume hood was added diaminoalkane (1,3-diaminopropane, 1,4-diaminobutane, or 1,6-diaminohexane) (0.01 mol). The reaction mixture was refluxed until the methanethiol odor could no longer be detected (ca. 24 h). Tarry polymers which precipitated or stuck to the flask wall were removed. After the solvent was evaporated, the residual solid was recrystallized to give white crystals.

8,14-Dithioxo-1,4,7-trioxa-9,13-diazacyclotetradecane (6a): IR (KBr) 3160vs (NH) and 1120vs cm^{-1} (C=S). Found: C, 40.88; H, 5.99; N, 10.49%. Calcd for $C_9H_{16}N_2O_3S_2$: C, 40.89; H, 6.10; N, 10.60%.

8,15-Dithioxo-1,4,7-trioxa-9,14-diazacyclopentadecane (6b): IR (KBr) 3150vs (NH) and 1170vs cm^{-1} (C=S). Found: C, 43.08; H, 6.50; N, 10.24%. Calcd for $C_{10}H_{18}N_2O_3S_2$: C, 43.14; H, 6.52; N, 10.06%.

8,17-Dithioxo-1,4,7-trioxa-9,16-diazacycloheptadecane (6c): IR (KBr) 3160vs (NH) and 1165vs cm^{-1} (C=S). Found: C, 47.05; H, 7.20; N, 9.10%. Calcd for $C_{12}H_{22}N_2O_3S_2$: C, 47.03; H, 7.24; N, 9.14%.

11,18-Dithioxo-1,4,7,10-tetraoxa-12,17-diazacyclooctadecane (6d): IR (KBr) 3200vs (NH) and 1165vs cm^{-1} (C=S). Found: C, 44.50; H, 6.85; N, 8.45%. Calcd for $C_{12}H_{22}N_2O_4S_2$: C, 44.70; H, 6.88; N, 8.69%.

11,20-Dithioxo-1,4,7,10-tetraoxa-12,19-diazacycloicosane (6e): IR (KBr) 3165vs (NH) and 1120vs cm^{-1} (C=S). Found: C, 48.23; H, 7.49; N, 7.81%. Calcd for $C_{14}H_{26}N_2O_4S_2$: C, 47.98; H, 7.48; N, 7.99%.

Macrocyclic Bis(O-thiocarbamate) 7 and Its Dimer 8. To a solution of ester **3a** (1.43 g, 0.005 mol) in ethanol (200 ml) was added 1,2-bis(3-aminopropoxy)ethane (0.88 g, 0.005 mol) in ethanol (50 ml). The reaction mixture was stirred until the methanethiol odor could no longer be detected (ca. 5 d). After the solvent was evaporated, an orange oil was chromatographed on a silica-gel column with ethyl acetate–hexane (2 : 1) as an eluent. Compounds **7** and **8** were in order eluted and recrystallized.

8,21-Dithioxo-1,4,7,13,16-pentaoxa-9,20-diazacycloheneicosane (7): White crystals; IR (KBr) 3300vs, 3225vs (NH), and 1110vs cm^{-1} (C=S). Found: C, 45.96; H, 7.17; N, 7.64%. Calcd for $C_{14}H_{26}N_2O_5S_2$: C, 45.88; H, 7.15; N, 7.64%.

8,21,29,42-Tetrathioxo-1,4,7,13,16,22,25,28,34,37-decaoxa-9,20,30,41-tetraazacyclodotetracontane (8): Pale-yellow crystals; IR (KBr) 3270vs (NH) and 1110vs cm^{-1} (C=S). Found: C, 46.08; H, 7.11; N, 7.66%. Calcd for $C_{28}H_{52}N_4O_{10}S_4$: C, 45.88; H, 7.15; N, 7.64%.

8,24-Dithioxo-1,4,7,13,16,19-hexaoxa-9,23-diazacyclotetracosane (9) was prepared from ester **3a** (1.43 g, 0.005 mol) and bis[2-(3-aminopropoxy)ethyl] ether (1.1 g, 0.005 mol) by the method described for **7** and **8**. An orange oil was chromatographed on a silica-gel column with ethyl acetate–hexane (1 : 1) as an eluent. The white solid was recrystallized: White crystals; IR (KBr) 3300vs (NH) and 1110vs cm^{-1} (C=S). Found: C, 46.93; H, 7.39; N, 6.85%. Calcd for $C_{16}H_{30}N_2O_6S_2$: C, 46.81; H, 7.37; N, 6.82%.

References

1) D. A. Chowdhury and S. Kamata, *Chem. Lett.*, **1994**, 589.

2) T. Ogata, D. A. Chowdhury, S. Kamata, Y. Usui, and K. Ohashi, *Chem. Lett.*, **1995**, 1041.

3) C. J. Pedersen, *J. Am. Chem. Soc.*, **89**, 2495 and 7019 (1967).

4) For example, see: a) M. Hiraoka, "Kuraun Kagobutsu (Japanese)," Kodansha, Tokyo (1978); b) "Synthetic Multidentate Macrocyclic Compounds," ed by R. M. Izatt and J. J. Christensen, Academic Press, New York (1978); c) L. F. Lindoy, "The Chemistry of Macrocyclic Ligand Complexes," Cambridge University Press, Cambridge (1989); d) "Crown Ethers and Analogous Compounds," ed by M. Hiraoka, Elsevier, Amsterdam (1992).

5) N. Fukada, M. Saigo, M. Mashino, K. Yanagisawa, and Y. Takeda, *J. Chem. Res., Synop.*, **1990**, 254.

6) N. Fukada, M. Takano, K. Nakai, S. Kuboike, and Y. Takeda, *Bull. Chem. Soc. Jpn.*, **66**, 148 (1993).

7) N. Fukada, Y. Hasegawa, Y. Kamiya, H. Yabuta, and T. Takeshima, *Bull. Chem. Soc. Jpn.*, **67**, 1399 (1994).

8) G. Winter and J. T. Woodcock, Australian Patent 464505 (1974); *Chem. Abstr.*, **84**, 20692q (1976).

9) A. V. Bogatsky, N. G. Lukyanenko, and T. I. Kirichenko, *Tetrahedron Lett.*, **21**, 313 (1980).

10) R. K. Dieter, *Tetrahedron*, **42**, 3029 (1986).

11) M. Kolb, *Synthesis*, **1990**, 171.

12) N. Fukada, T. Ohtsu, M. Miwa, M. Mashino, and Y. Takeda, *Bull. Chem. Soc. Jpn.*, **69**, 1397 (1996).