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Conversion of Thiols into Disulfides with Diethyl Bromomalonate

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Reactions of aliphatic, aromatic and heterocyclic thiols (**2** and **5a**—**h**) with diethyl bromomalonate (**1a**) gave the corresponding symmetrical disulfides (**3** and **6a**—**h**) in high yields. In the case of L-cysteine (**5i**), glutathione (**5j**) or thiamine (**5k**), the reaction also gave L-cystine (**6i**), oxidized glutathione (**6j**) or thiamine disulfide (**6k**) in high yields regardless of the presence of other functional groups. Dithiols (**11**) were converted into cyclic disulfides (**12**) by this method. In particular, *N*-(2-mercapto-2-methylpropionyl)-L-cysteine (**9**) was converted into (4*R*)-tetrahydro-7,7-dimethyl-6-oxo-3*H*-1,2,5-dithiazepine-4-carboxylic acid (**10**) (obtained in poor yields by general oxidation methods) in good yield. The intermediate in the reaction was considered to be sulfenyl bromide (**8**).

Keywords——diethyl bromomalonate; thiol; dithiol; disulfide; cyclic disulfide; thiol oxidation; disulfide formation; *N*-(2-mercapto-2-methylpropionyl)-L-cysteine; (4*R*)-tetrahydro-7,7-dimethyl-6-oxo-3*H*-1,2,5-dithiazepine-4-carboxylic acid

Disulfides are generally synthesized by oxidation of the corresponding thiols. There are many oxidizing agents, such as air, iodine, hydrogen peroxide, dimethyl sulfoxide and ferric chloride.[1] Recent papers have described the oxidation of thiols by nickel peroxide,[2] nitrogen oxide,[3] bis(*p*-methoxyphenyl)selenoxide,[4] ferric nitrate,[5] potassium chromate[6] and tetrabutylammonium chlorochromate.[7] On the other hand, it has been reported that halides having an electron-withdrawing group are reduced by alkoxides or thiolates.[8-11] For example, Oki *et al.*[9] discussed the dehalogenation of halides by thiolates, Baig and Owen[10] reported the undesired formation of disulfide in the reaction of benzenethiolate with diethyl bromomalonate (**1a**), and Eliel *et al.*[11] described the mechanism of the reaction of methanethiolate with diethyl chloromalonate (**1g**). However, no synthetic method for disulfides utilizing cleavage of the carbon–halogen bond of a halide such as **1a** has yet been established.

The synthesis of disulfides of 4-thiazolidinecarboxylic acid derivatives by using **1a** is described in our previous report.[12] In this paper, we describe the scope, limitations and mechanism of the reactions of thiols with organic halides for the synthesis of disulfides.

Synthesis of Acyclic Disulfides

We selected 3-mercaptopropionic acid (**2**) as a model compound in order to find optimum conditions for the synthesis of symmetrical disulfides, and studied the reaction of **2** with diethyl bromomalonate (**1a**) under various conditions as shown in Table I (Chart 1). This reaction gave only the disulfide **3** without formation of the sulfide **4a**.

In the reaction, the yield was not influenced by the amount of **1a** (entries 1, 2) or by the reaction temperature (entries 4—6), but was influenced by the amount of triethylamine (entries 1, 5; 2, 3): sufficient triethylamine to neutralize both the carboxyl group in **2** and hydrogen bromide generated during the reaction was required for the reaction. The use of pyridine or *N*,*N*-dimethylaniline instead of triethylamine resulted in a lowering of the yield,

namely the yield decreased with decrease in the basicity of these bases (entries 5, 7, 8). In ethanol, the yield became low (entries 5, 9).

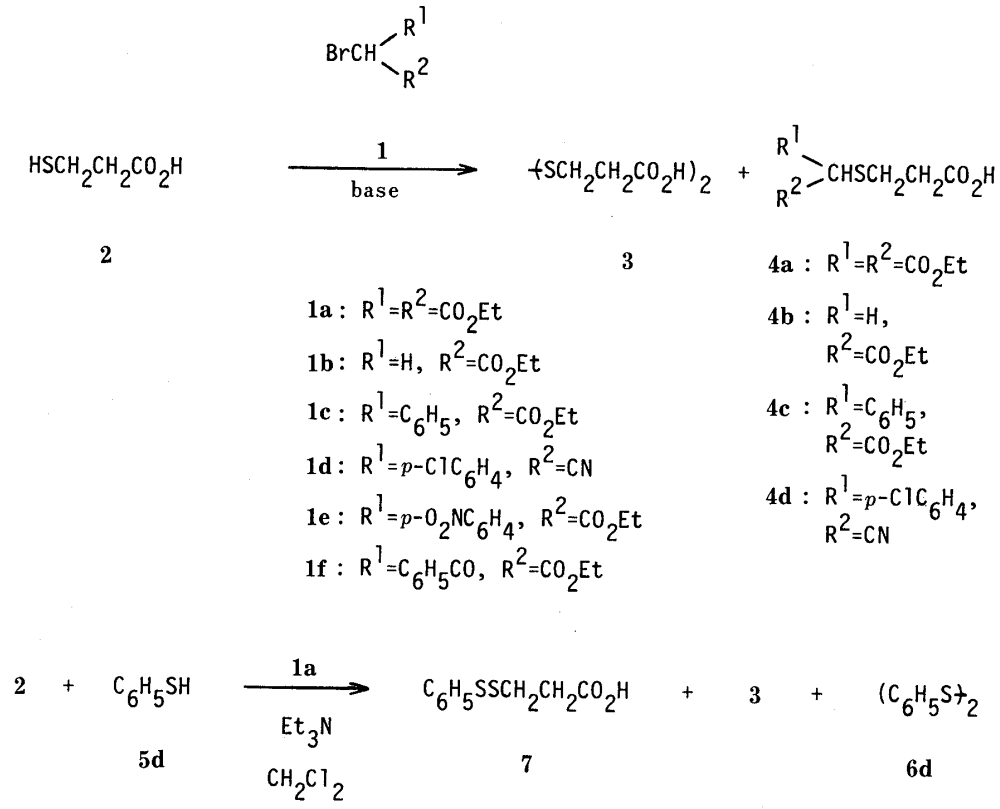


Chart 1

TABLE I. Reaction of 3-Mercaptopropionic Acid (**2**) with Diethyl Bromomalonate (**1a**)

Entry	**1a**[a]	Base[a]		Solvent	Temp. (°C)	Time (h)	Yield[b] (%)
1	0.6	Et_3N	(1.1)	CH_2Cl_2	−16	1.5	69
2	1.2	Et_3N	(1.1)	CH_2Cl_2	−16	1.5	72
3	1.2	Et_3N	(2.2)	CH_2Cl_2	−16	1.5	81
4	0.6	Et_3N	(1.6)	CH_2Cl_2	−60	1.0	76
5	0.6	Et_3N	(1.6)	CH_2Cl_2	−16	1.0	82
6	0.6	Et_3N	(1.6)	CH_2Cl_2	r.t.[c]	0.5	80
7	0.6	Pyridine	(1.6)	CH_2Cl_2	−16, r.t.	2.0[d]	65
8	0.6	$PhNMe_2$	(1.6)	CH_2Cl_2	−16, r.t.	2.0[d]	27
9	0.6	Et_3N	(1.6)	EtOH	−16	1.0	68

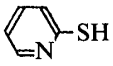
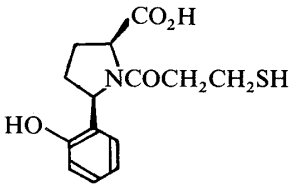
a) Molar ratio: **1a** or base/**2**. *b*) Isolation yield. *c*) r.t.: room temperature. *d*) Reaction conditions: at −16 °C for 1 h and at room temperature for 1 h.

We applied the oxidation reaction with **1a** to various thiols. Aliphatic, aromatic and heterocyclic thiols **5** were transformed into the corresponding disulfides **6** in good yield (Table II). The reaction of the thiol **5b** having a hydroxyl group gave the disulfide **6b**. In the aromatic thiols **5d**—**g**, the yield decreased with increasing electron-withdrawing character of the substituent. The reaction of 2-pyridinethiol (**5h**) gave a lower yield than those of the other thiols, presumably because of the existence of the thione tautomer.[13] L-Cysteine (**5i**), glutathione (**5j**) and thiamine (**5k**) having an amino group reacted with **1a** to give L-cystine (**6i**), oxidized glutathione (**6j**) and thiamine disulfide (**6k**) in high yields, respectively. In the

case of the proline derivative **5l**, the reaction also gave the disulfide **6l** in high yield.

TABLE II. Synthesis of the Disulfides **6** Using Diethyl Bromomalonate (**1a**)

RSH ⟶ (RS)$_2$
5 **6**

Compd. No.	Thiol	Yield[a] (%)	mp (°C) (Recrystn. solv.)	Lit. mp (°C)
6a	$CH_3(CH_2)_3SH$	97[b]	130—135[c] (34 mmHg)	110—118[c] (22 mmHg)[14]
6b	$HO(CH_2)_2SH$	91[b]	190—200[c] (1.7 mmHg)	160—162[c] (0.1 mmHg)[15]
6c	$C_6H_5CH_2SH$	74[b]	69.5—71 (CH_2Cl_2–MeOH)	70—71[16]
6d	C_6H_5SH	87[b]	57—58.5 (MeOH–H_2O)	59—60[16]
6e	*p*-$CH_3C_6H_4SH$	94[b]	45—46 (MeOH–H_2O)	45—46[17]
6f	*p*-ClC_6H_4SH	83[b]	73—74 (CH_2Cl_2–MeOH)	73—74[18]
6g	*p*-$O_2NC_6H_4SH$	62[b]	180—182 ($CHCl_3$)	182[19]
6h		59[b]	58—59 (CH_2Cl_2–hexane)	57—58[20]
6i	Cys	83[d]	256 (dec.)	260—261[21]
6j	GSH	90[e]	Amorph. (H_2O–EtOH)	
6k	Thiamine	81[d]	173—174 (dec.) (EtOH–ether)	177[22]
6l		94[b]	224.5—225.5 (dec.) (MeOH–H_2O)	

a) Isolation yield. *b*) Reaction conditions: Et_3N, CH_2Cl_2, −16 °C. *c*) Boiling point. *d*) Reaction conditions: NaOH, EtOH–H_2O, −16 °C. *e*) Reaction conditions: LiOH, EtOH–H_2O, −16 °C.

It is known that unsymmetrical disulfides can be synthesized by various methods as reported recently.[1c,23] We applied the reaction using the bromide **1a** to the synthesis of the unsymmetrical disulfide **7** (Chart 1). Treatment of a mixture of 3-mercaptopropionic acid (**2**) and thiophenol (**5d**) (1 : 1) with **1a** in the presence of triethylamine gave **7** in 47% yield, together with the symmetrical disulfides **3** (21%) and **6d** (11%).

Thus, the above results demonstrated that the method using **1a** as an oxidizing agent is useful for conversion of thiols into the corresponding symmetrical disulfides regardless of the presence of other functional groups.

Reaction of 3-Mercaptopropionic Acid (2) with Other Bromides

In order to elucidate the applicability of various bromides other than **1a** to the transformation of thiols into disulfides, the reaction of the thiol **2** with the bromides **1b**—**f** was carried out under the same conditions as for entry 3 in Table I (Chart 1). Although the reaction with **1a** gave only the disulfide **3**, the reactions with the bromo esters **1b** and **1c** having a single electron-withdrawing group converted **2** into the sulfides **4b** (97%) and **4c** (77%), respectively, without the formation of **3**. On the other hand, the reaction with the bromo ester

1e or **1f** having a nitrophenyl or benzoyl group gave only **3** (**1e**: 85%; **1f**: 80%). In the case of the bromo nitrile **1d** having a chlorophenyl group, the reaction gave both the disulfide **3** (55%) and the sulfide **4d** (22%).

These results indicated that the formation of the disulfide **3** was governed by the electron-withdrawing effect of the substituent at the α-position in the bromides.

In order to elucidate the reaction mechanism, the reaction of the thiol **2** with the chloride **1g** was carried out in the presence of triethylamine (Chart 2). The sulfide **4a** was obtained in 53% yield without the formation of **3**. On the other hand, the reaction in the presence of potassium hydroxide gave a mixture of **3** (46%) and **4a** (30%). The sulfide **4a** reacted with **2** in the presence of potassium hydroxide to give **3** (67%) and diethyl malonate (50%). From these results it is concluded that the sulfide **4** is an intermediate in the reaction with **1g**.

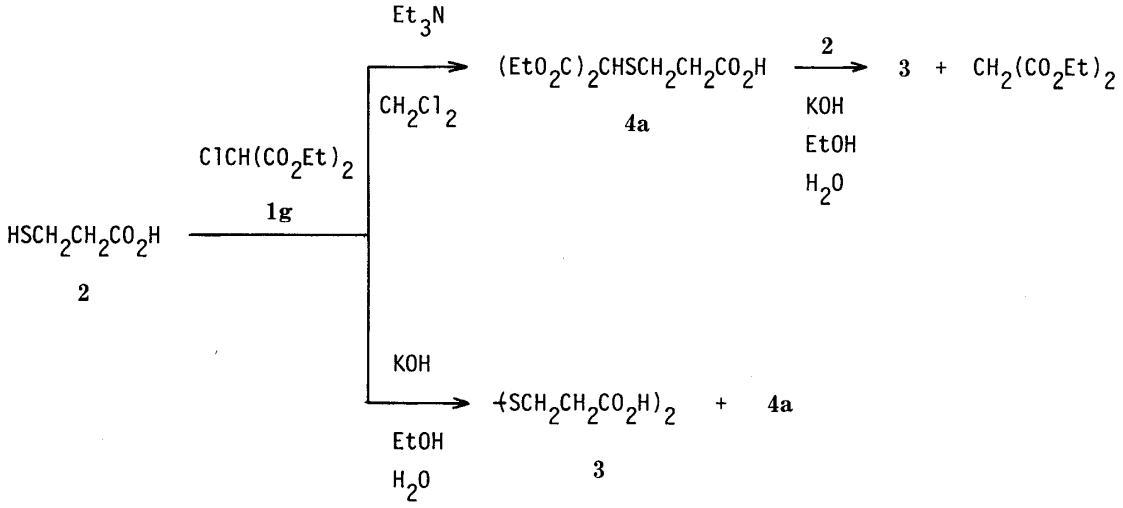


Chart 2

In the case of the bromide **1a**, however, the intermediate is considered to be sulfenyl bromide (**8**), since the reaction under any conditions gave only the disulfide **3** (Table I) (Chart 3).[24] Next, we will consider the formation mechanism of **8**. The results in the preceding section suggest the existence of both paths a and b in the reaction of **2** with **1**: (a) a nucleophilic attack of **2** at bromine in **1** forms **8** which reacts with another molecule of **2** to give **3**; (b) nucleophilic substitution of **2** at the α-carbon in **1** gives the sulfide **4**. It is considered

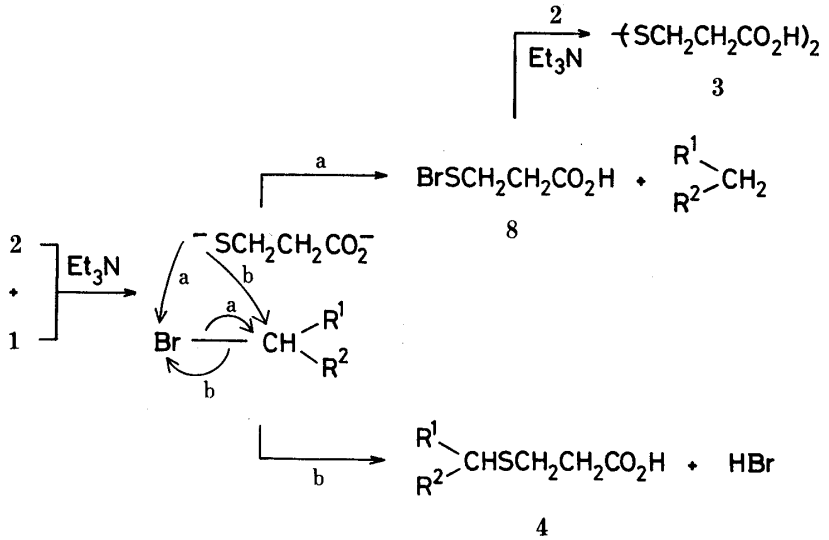


Chart 3

that these pathways are controlled by the distribution of positive charge between bromine and the α-carbon and that this is decided by the electron-withdrawing strength of the substituents (R^1 and R^2) in **1**.

Synthesis of Cyclic Disulfides

Preparation of cyclic disulfides is often achieved by oxidation of the corresponding dithiols with ferric chloride, iodine and 1,2-diiodoethane.[26-29] We applied the foregoing reaction with bromide **1a** to the formation of the seven-membered cyclic disulfide **10**, a metabolite of *N*-(2-mercapto-2-methylpropionyl)-L-cysteine (SA 96) (**9**) which is being developed as an antirheumatic.[30] In order to obtain **10**, we used the conventional methods[26-29] as well as newer methods (oxidation of the lead salt of **9** with sulfur; oxidation of the thioacetal of **9** and anisaldehyde with *m*-chloroperbenzoic acid),[31] but the reactions failed, presumably because of the predominant intermolecular reaction. On the other hand, the conversion of **9** into **10** with **1a** gave good results, as shown in Table III (Chart 4).

In this reaction, dilution of the reaction solution improved the yield (entries 1, 2, 4). The yield decreased with increasing reaction temperature or with increasing polarity of the solvent used because of the intermolecular reaction (entries 2, 3, 7, 8). The disulfide **10** was not obtained in the presence of a weaker base than triethylamine (entries 2, 5, 6).

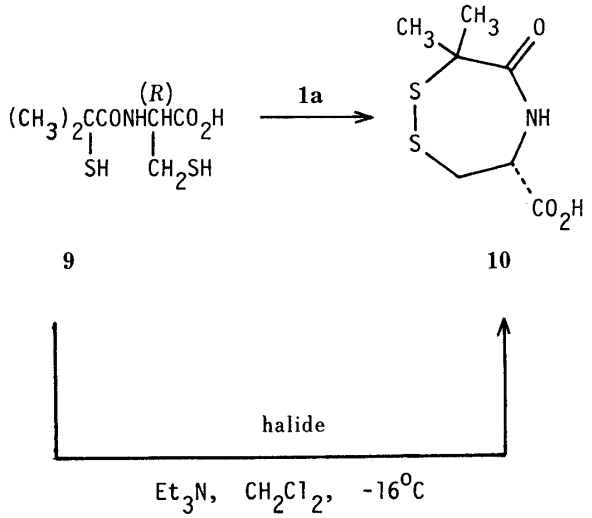


Chart 4

Table III. Reaction of the Dimercapto Carboxylic Acid (**9**) with Diethyl Bromomalonate (**1a**)

Entry	Solv.	Concn.[a] (M)	Base	Temp.[b] (°C)	Yield[c] (%)
1	CH_2Cl_2	0.23	Et_3N	−16	24
2	CH_2Cl_2	0.09	Et_3N	−16	46
3	CH_2Cl_2	0.09	Et_3N	5	32
4	CH_2Cl_2	0.04	Et_3N	−16	55
5	CH_2Cl_2	0.09	Pyridine	−16[d]	—
6	CH_2Cl_2	0.09	$PhNMe_2$	−16[d]	—
7	Acetone	0.09	Et_3N	−16	5
8	CH_3CN	0.09	Et_3N	−16	20

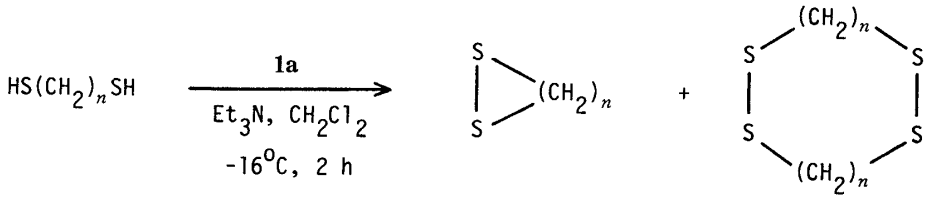
a) Concentration of **9**. *b*) Reaction time: 2 h. *c*) Isolation yield. *d*) Reacted at −16 °C for 2 h and at room temperature for 2 d.

This method was further studied by using other halides under the same conditions as for entry 2 in Table III. The reaction of **9** with the bromide **1f**, ethyl α-bromoacetoacetate and ethyl bromocyanoacetate (analogues of **1a**) gave **10** in 41%, 28% and 32% yields, respectively. In the case of *N*-chlorosuccinimide (NCS), *N*-bromosuccinimide (NBS) or *N*-bromoacetamide (NBA), the reaction resulted in a poor yield.

The reaction using the bromide **1a** was applied to the dithiols **11a—e** without any other functional group (Chart 5). In the case of 1,2-ethanedithiol (**11a**) and 1,3-propanedithiol (**11b**), 1,2-dithietane (**12a**) and 1,2-dithiolane (**12b**) were not obtained because of polymerization during isolation.[32] In the case of 1,4-butanedithiol (**11c**), 1,2-dithiane (**12c**) was isolated in 82% yield. On the other hand, the reaction of 1,5-pentanedithiol (**11d**) gave not only 1,2-dithiepane (**12d**) in 34% yield but also the dimeric cyclic disulfide (**13d**) in 19% yield. In the case of 1,6-hexanedithiol (**11e**), 1,2-dithiocane (**12e**) and the dimer (**13e**) were obtained in 10% and 26% yields, respectively.

The difference in yields between the seven-membered cyclic disulfides **10** and **12d** may be ascribable to fixation of the molecule of **9** by weak interaction between polar functional

groups of **9** and the bromide **1a**. In the synthesis of a simple cyclic disulfide, the method failed to achieve a better yield than the conventional methods which require a considerable reaction time.[26,27]



11 **12** **13**

a: $n=2$, **b**: $n=3$, **c**: $n=4$, **d**: $n=5$, **e**: $n=6$

Chart 5

Experimental

Distillation was carried out in a glass tube oven, model GTO-250R (Shibata), and boiling points were determined by measuring the bath temperature. Melting points were determined on a Yamato MP-21 melting point apparatus and are uncorrected. Specific rotations were measured with a JASCO DIP-140 polarimeter. Infrared (IR) spectra were recorded on a JASCO IRA-302 spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were measured on a JEOL PMX-60 spectrometer using tetramethylsilane or sodium 3-(trimethylsilyl)propanesulfonate as an internal standard. Mass spectra (MS) were measured with a Shimadzu GCMS-QP1000 spectrometer equipped with a direct insertion system. Commercial organic and inorganic materials were used without further purification. Reactions were performed under a nitrogen atmosphere.

General Procedure for Reaction of 3-Mercaptopropionic Acid (2) with Ethyl Bromomalonate (1a): Entries 1—8——A solution of **1a** (0.011 or 0.024 mol) in dichloromethane (5 ml) was added dropwise to a stirred solution of **2** (2.1 g, 0.02 mol) and a base (0.022, 0.032 or 0.044 mol) in dichloromethane (20 ml) at −60, −16 °C or room temperature over a period of 10 min. The mixture was stirred for 0.5—2 h at the same temperature, then 2 M HCl (10, 13 or 16 ml) was added and the crystals were filtered off to give 3,3′-dithiodipropionic acid (**3**): mp 155.5—157.5 °C (H_2O) (lit.[18] mp 156—157 °C).

The organic layer of the filtrate was washed with satd. aq. $NaHCO_3$, dried over Na_2SO_4 and evaporated *in vacuo* to give diethyl malonate (1.6 g, 92% yield) (entry 5). Its identity was checked by ^{1}H-NMR spectral comparison with an authentic sample.

Entry 9——A solution of **1a** (2.6 g, 0.011 mol) in EtOH (5 ml) was added dropwise to a stirred solution of **2** (2.1 g, 0.02 mol) and triethylamine (4.5 ml, 0.032 mol) in EtOH (20 ml) at −16 °C over a period of 10 min. The reaction mixture was stirred for 1 h at −16 °C, acidified with 2 M HCl (13 ml) then concentrated *in vacuo*. After addition of water (30 ml) to the residue, the separated crystals were filtered off to give **3** (1.42 g, 68% yield).

Dithiodibutane (6a)——A solution of **1a** (2.63 g, 0.011 mol) in dichloromethane (5 ml) was added dropwise to a stirred solution of **5a** (1.80 g, 0.02 mol) and triethylamine (1.7 ml, 0.012 mol) in dichloromethane (15 ml) at −16 °C over a period of 12 min. The reaction mixture was stirred for 1 h at −16 °C, then 0.5 M HCl (10 ml) was added. The organic layer was dried over Na_2SO_4 and evaporated *in vacuo*. The residue was dissolved in hexane (50 ml), and this solution was washed with MeOH–water (4 : 1), dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by distillation under reduced pressure to give **6a** (1.73 g, 97% yield).

Dithiobis(2-hydroxyethane) (6b)——A solution of **1a** (2.63 g, 0.011 mol) in dichloromethane (5 ml) was added dropwise to a stirred solution of **5b** (1.56 g, 0.02 mol) and triethylamine (1.7 ml, 0.012 mol) in dichloromethane (15 ml) at −16 °C over a period of 10 min. After being stirred for 1 h at −16 °C, the reaction mixture was evaporated *in vacuo*. The residue was dissolved in AcOEt (30 ml) and the solution was filtered. The filtrate was evaporated *in vacuo*, and the residue was purified by silica-gel column chromatography (benzene–AcOEt) then distilled under reduced pressure to give **6b** (1.4 g, 91%).

Dithiobis(phenylmethane) (6c)——A solution of **1a** (1.3 g, 5.4 mmol) in dichloromethane (5 ml) was added dropwise to a stirred solution of **5c** (1.24 g, 10 mmol) and triethylamine (0.85 ml, 6.1 mmol) in dichloromethane (15 ml) at −16 °C over a period of 9 min. The reaction mixture was stirred for 1 h at −16 °C, then 0.5 M HCl (10 ml) was added. The organic layer was dried over Na_2SO_4 and evaporated *in vacuo*. The residual crystals were recrystallized from dichloromethane–MeOH to give **6c** (0.91 g, 74% yield).

Dithiodibenzene (**6d**), dithiobis(4-methylbenzene) (**6e**), dithiobis(4-chlorobenzene) (**6f**) and dithiobis(4-nitrobenzene) (**6g**) were obtained from the corresponding thiols (**5d—g**) in the above manner.

2,2′-Dithiobispyridine (6h)——A solution of **1a** (1.3 g, 5.4 mmol) in dichloromethane (5 ml) was added dropwise

to a stirred solution of **5h** (1.11 g, 10 mmol) and triethylamine (0.85 ml, 6.1 mmol) in dichloromethane (15 ml) at −16 °C over a period of 9 min. After being stirred for 1 h at −16 °C, the reaction solution was extracted with 2 M HCl (20 ml × 2). The aqueous layer was alkalized with 30% NaOH and extracted with dichloromethane (50 ml). The organic extract was dried over Na_2SO_4 and evaporated *in vacuo*. The residual crystals were recrystallized from dichloromethane–hexane to give **6h** (0.65 g, 59% yield).

L-Cystine (6i)——A solution of **1a** (1.3 g, 5.4 mmol) in EtOH (5 ml) was added dropwise to a stirred solution of **5i** (1.21 g, 10 mmol) in 1 M NaOH (11 ml) and EtOH (5 ml) at −16 °C over a period of 10 min. The mixture was stirred for 1 h at −16 °C, 1 M HCl (6 ml) was added, and the whole was extracted with ether. The aqueous layer was adjusted to pH 5 with 1 M NaOH and the separated crystals were filtered off to give **6i** (0.99 g, 83% yield): $[\alpha]_D^{25}$ −220.6° (c = 1.6, 1 M HCl) [lit.[21] $[\alpha]_D^{20}$ −223.4° (1 M HCl)].

Oxidized Glutathione (6j)——A solution of **1a** (0.66 g, 2.8 mmol) in EtOH (2 ml) was added dropwise to a stirred solution of **5j** (1.54 g, 5 mmol) and LiOH (0.44 g, 10.5 mmol) in EtOH (3 ml) and water (7 ml) at −16 °C over a period of 10 min. After being stirred for 1 h at −16 °C, the reaction mixture was adjusted to pH 3 with 1 M HCl (7.8 ml) and evaporated *in vacuo*. The residual syrup was powdered with EtOH and filtered. The powder was dissolved in a small amount of water, then EtOH was added to the solution. The separated powder was filtered off to give **6j**–EtOH(1 : 1) (1.48 g, 90% yield); $[\alpha]_D^{25}$ −90.9° (c = 1.1, H_2O) [lit.[33] $[\alpha]_D^{20}$ −108° (c = 2, H_2O)]. IR (KBr): 1720 (carboxyl C=O), 1635 (amide and carboxylate C=O) and 1530 cm^{-1} (amide NH). ^{1}H-NMR (D_2O) δ: 1.08 (3H, t, J = 7.0 Hz, CH_3CH_2OH), 1.88—2.70 (8H, m, $COCH_2CH_2 \times 2$), 3.00 (2H, dd, J = 13.0, 8.0 Hz, $CH_BS \times 2$), 3.27 (2H, dd, J = 13.0, 5.0 Hz, $CH_AS \times 2$), 3.63 (2H, q, J = 7.0 Hz, CH_3CH_2OH), 3.81 (2H, t, J = 6.0 Hz, $NCHCO \times 2$), and 3.93 (4H, s, $COCH_2N \times 2$) (a signal due to the methine proton of NCHCO in the cystine moiety overlapped that of HOD).

Thiamine Disulfide (6k)——A solution of **1a** (0.32 g, 1.3 mmol) in EtOH (3 ml) was added dropwise to a stirred solution of **5k** (0.90 g, 2.7 mmol) in 1 M NaOH (8 ml) and EtOH (5 ml) at −16 °C over a period of 4 min. After being stirred for 30 min at −16 °C, the reaction mixture was adjusted to pH 7 with 1 M HCl (1 ml) and extracted with ether, then the aqueous layer was evaporated *in vacuo*. After addition of EtOH (20 ml) to the residue, the solution was filtered and the filtrate was concentrated *in vacuo*. Ether (30 ml) was added to the residue and the crude crystals were filtered off and recrystallized from EtOH–ether to give **6k** (0.61 g, 81% yield).

(2*S*,2′*S*,5*R*,5′*R*)-1,1′-(3,3′-Dithiodipropionyl)bis[5-(2-hydroxyphenyl)-2-pyrrolidinecarboxylic Acid] (6l)——A solution of **1a** (0.26 g, 1.1 mmol) in dichloromethane (3 ml) was added to a solution of **5l**[34] (0.59 g, 2 mmol) and triethylamine (0.45 ml, 3.2 mmol) in dichloromethane (10 ml) at −16 °C over a period of 3 min. After being stirred for 30 min at −16 °C and for 30 min at room temperature, the reaction mixture was extracted with satd. aq. $NaHCO_3$ (10 ml). The aqueous layer was washed with ehter and acidified with 2 M HCl, then the crystals were filtered off and recrystallized from MeOH–water to give **6l** (0.55 g, 94% yield) as colorless plates: $[\alpha]_D^{25}$ +37.5° (c = 0.5, MeOH). IR (Nujol): 1715 (carboxyl C=O) and 1625 cm^{-1} (amide C=O). ^{1}H-NMR (DMSO-d_6) δ: 1.33—3.07 (16H, m, C_3-$H_2 \times 2$, C_4-$H_2 \times 2$ and $COCH_2CH_2S \times 2$), 4.30 (2H, br t, J = 6.0 Hz, C_5-H × 2), 5.00—5.50 (2H, m, C_2-H × 2), 6.43—7.23 (6H, m, aromatic H), 7.47 (d, J = 7.0 Hz) and 7.82 (d, J = 7.0 Hz) (2H, aromatic H), 9.27 (br s) and 9.50 (s) (2H, $OH \times 2$), and 11.17—13.67 (2H, br, $CO_2H \times 2$). *Anal.* Calcd for $C_{28}H_{32}N_2O_8S_2$: C, 57.13; H, 5.48; N, 4.76. Found: C, 57.02; H, 5.54; N, 4.77.

3-(Phenyldithio)propionic Acid (7)——A solution of triethylamine (2.8 ml, 0.02 mol) in dichloromethane (5 ml) was added dropwise to a stirred solution of **2** (1.06 g, 0.01 mol), **5d** (1.1 g, 0.01 mol) and **1a** (2.6 g, 0.011 mol) in dichloromethane (15 ml) at −16 °C over a period of 13 min. The mixture was stirred for 1 h at −16 °C, then 2 M HCl (10 ml) was added, and the crystals were filtered off to give **3** (0.44 g, 21% yield).

The organic layer of the filtrate was washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. A solution of the residue in ether (30 ml) was extracted with satd. aq. $NaHCO_3$ (20 ml), then the ethereal layer was washed with satd. aq. NaCl, dried over Na_2SO_4 and evaporated *in vacuo*. Methanol was added to the residual oil and the separated crystals were filtered off to give **6d** (0.25 g, 11% yield). The aqueous extract was acidified with conc. HCl and extracted with ether (30 ml). The ethereal extract was washed with water and satd. aq. NaCl, dried over Na_2SO_4 and evaporated *in vacuo*. The residual crystals were recrystallized from ether–hexane to give **7** (1.0 g, 47% yield); mp 53—55 °C (lit.[35] 57—58 °C).

Reaction of 3-Mercaptopropionic Acid (2) with Bromide 1: Ethyl Bromoacetate (1b)——The bromide **1b** (6.6 g, 0.04 mol) was added dropwise to a stirred solution of **2** (4.2 g, 0.04 mol) and triethylamine (11 ml, 0.079 mol) in dichloromethane (30 ml) at −16 °C over a period of 15 min. The reaction mixture was stirred for 1 h at −16 °C, then 2 M HCl (20 ml) was added. The organic layer was washed with water and satd. aq. NaCl, dried over Na_2SO_4 and evaporated *in vacuo* to give 3-(ethoxycarbonylmethylthio)propionic aicd (**4b**) (7.4 g, 97%) as a viscous oil. IR (film): 1723 (ester C=O) and 1708 cm^{-1} (carboxyl C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, t, J = 7.0 Hz, CH_3), 2.53—3.18 (4H, m, SCH_2CH_2CO), 3.28 (2H, s, $COCH_2S$), 4.22 (2H, q, J = 7.0 Hz, OCH_2), and 9.22 (1H, br s, CO_2H).

Ethyl α-Bromophenylacetate (1c)——The treatment of **2** with **1c**[36] in the above procedure gave 3-[α-(ethoxycarbonyl)benzylthio]propionic acid (**4c**) as a viscous oil in 77% yield. IR (film): 1728 (ester C=O) and 1707 cm^{-1} (carboxyl C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, t, J = 7.0 Hz, CH_3), 2.37—3.00 (4H, m, SCH_2CH_2CO), 4.15 (2H, q, J = 7.0 Hz, OCH_2), 4.57 (1H, s, CHS), 7.03—7.60 (5H, m, aromatic H), and 10.17 (1H, br s, CO_2H).

α-Bromo-4-chlorophenylacetonitrile (1d)——A solution of **1d**[37] (2.3 g, 0.01 mol) in dichloromethane (5 ml) was

added dropwise to a stirred solution of **2** (1.1 g, 0.01 mol) and triethylamine (3 ml, 0.022 mol) in dichloromethane (15 ml) at −16 °C over a period of 8 min. The reaction mixture was stirred for 1 h at −16 °C, then 1 M HCl (15 ml) was added, and the crystals were filtered off to give **3** (0.6 g, 55% yield). The organic layer of the filtrate was dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by silica-gel column chromatography (benzene–AcOEt) to give 3-(4-chloro-α-cyanobenzylthio)propionic acid (**4d**) (0.55 g, 22% yield) as colorless needles: mp 86—88 °C. IR (KBr): 2240 (C≡N) and 1701 cm^{-1} (carboxyl C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.45—3.22 (4H, m, SCH_2CH_2CO), 4.85 (1H, s, CHS), 7.37 (4H, s, aromatic H), and 10.63 (1H, br s, CO_2H).

Ethyl α-Bromo-4-nitrophenylacetate (1e)——A solution of **1e**[38] (5.8 g, 0.02 mol) in dichloromethane (5 ml) was added dropwise to a stirred solution of **2** (2.2 g, 0.021 mol) and triethylamine (6 ml, 0.043 mol) in dichloromethane (30 ml) at −16 °C over a period of 10 min. The mixture was stirred for 1 h at −16 °C, then 1 M HCl (40 ml) was added, and the crystals were filtered off to give **3** (1.8 g, 85% yield).

Ethyl α-Bromobenzoylacetate (1f)——The reaction of **2** with **1f**[39] according to the above procedure gave **3** in 80% yield.

Reaction of 3-Mercaptopropionic Acid (2) with Ethyl Chloromalonate (1g): Triethylamine——A solution of **1g** (2.3 g, 0.012 mol) in dichloromethane (5 ml) was added dropwise to a stirred solution of **2** (2.1 g, 0.02 mol) and triethylamine (4.5 ml, 0.032 mol) in dichloromethane (20 ml) at −16 °C. The mixture was stirred for 1 h at −16 °C and for an additional 1 h at room temperature, then 2 M HCl (10 or 13 ml) was added. The organic layer was washed with satd. aq. NaCl, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by silica-gel column chromatography ($CHCl_3$–MeOH) to give 3-[bis(ethoxycarbonyl)methylthio]propionic acid (**4a**) (2.8 g, 53% yield) as a viscous oil. IR (film): 1724 cm^{-1} (ester and carboxyl C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.30 (6H, t, J=7.0 Hz, CH_3 × 2), 2.50—3.20 (4H, m, SCH_2CH_2CO), 4.17 (1H, s, CHS), 4.23 (4H, q, J=7.0 Hz, OCH_2 × 2), and 7.77 (1H, s, CO_2H).

KOH——A solution of **1g** (1.1 g, 5.7 mmol) in EtOH (5 ml) was added dropwise to a stirred solution of **2** (1.06 g, 10 mmol) and KOH (0.9 g, 16 mmol)–water (5 ml) in EtOH (15 ml) at −16 °C. The mixture was stirred for 1 h at −16 °C and for 1 h at room temperature, then conc. HCl (1 ml) was added. The solution was concentrated *in vacuo*, then water (15 ml) and dichloromethane (15 ml) were added to the residue. The crystals of **3** (0.48 g, 46% yield) were filtered off and the organic layer of the filtrate was concentrated *in vacuo*. A solution of the residue in ether (15 ml) was extracted with satd. aq. $NaHCO_3$ (10 ml). The aqueous layer was acidified with 2 M HCl and extracted with ether (20 ml). This ethereal extract was washed with water and satd. aq. NaCl, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by silica-gel column chromatography ($CHCl_3$–MeOH) to give **4a** (0.8 g, 39% yield).

Reaction of 3-[Bis(ethoxycarbonyl)methylthio]propionic Acid (4a) with 3-Mercaptopropionic Acid (2)——A stirred solution of **2** (0.53 g, 5 mmol) and **4a** (1.32 g, 5 mmol) in EtOH (15 ml) was treated with 5 M KOH (3 ml) under ice-cooling. After the addition, the reaction mixture was stirred for 1.5 h at room temperature and concentrated *in vacuo*, then dichloromethane (20 ml) and 1 M HCl (20 ml) were added to the residual oil. The crystals were filtered off to give **3** (0.7 g, 67% yield).

The organic layer of the filtrate was washed with water, dried over Na_2SO_4 and evaporated *in vacuo* to give diethyl malonate (0.4 g, 50%).

General Procedure for Reaction of *N*-(2-Mercapto-2-methylpropionyl)-L-cysteine (9) with Ethyl Bromomalonate (1a): Entries 1—4——The bromide **1a** (33.9 g, 0.142 mol) was added dropwise to a stirred solution of **9**[40] (28.8 g, 0.129 mol) and triethylamine (38 ml, 0.272 mol) in dichloromethane (0.57, 1.5 or 3 l) at −16 or 5 °C over a period of 10 min. The mixture was stirred for 2 h at the same temperature, then 1 M HCl (270 ml) was added. The organic layer was washed with water and satd. aq. NaCl, dried over $MgSO_4$ and concentrated *in vacuo*. The residual oil was allowed to stand overnight and the separated crystals were filtered off after addition of a small amount of ether to give (4*R*)-tetrahydro-7,7-dimethyl-6-oxo-3*H*-1,2,5-dithiazepine-4-carboxylic acid (**10**) as colorless prisms: mp 175.5—177 °C (AcOEt–hexane); $[\alpha]_D^{25}$ +153.2° (c=1.0, MeOH). IR (KBr): 3244 (amide NH), 1749 and 1709 (carboxyl C=O) and 1618 cm^{-1} (amide C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.54 (3H, s, CH_3), 1.66 (3H, s, CH_3), 2.67 (1H, t, J=11.7 Hz, SCH_B), 3.40 (1H, dd, J=11.7, 4.0 Hz, SCH_A), 5.30 (1H, ddd, J=11.7, 7.4, 4.0 Hz, NCHO), 8.42 (1H, d, J=7.4 Hz, CONH), and 13.21—14.08 (1H, br, CO_2H). MS *m/e*: 221 (M^+). *Anal.* Calcd for $C_7H_{11}NO_3S_2$: C, 37.99; H, 5.01; N, 6.33. Found: C, 37.97; H, 5.06; N, 6.44.

In this procedure using pyridine or *N*,*N*-dimethylaniline instead of triethylamine, crystals of **10** could not be obtained (entries 5, 6).

Entries 7 and 8——A solution of **1a** (1.3 g, 5.4 mmol) in acetone or acetonitrile (5 ml) was added to a stirred solution of **9** (1.1 g, 4.9 mmol) and triethylamine (1.4 ml, 10 mmol) in acetone or acetonitrile (50 ml) at −16 °C over a period of 5 min. The mixture was stirred for 2 h at −16 °C, then 1 M HCl (10 ml) was added, and the organic solvent was removed *in vacuo*. The residual solution was extracted with ether (50 ml). The ethereal layer was washed with water and satd. aq. NaCl, dried over $MgSO_4$ and concentrated *in vacuo*. The residual oil was allowed to stand overnight, then the separated crystals were filtered off and washed with a small amount of ether to give **10**.

Reaction of *N*-(2-Mercapto-2-methylpropionyl)-L-cysteine (9) with Various Halides: Ethyl α-Bromobenzoylacetate (1f)——A solution of **1f** (1.4 g, 5.2 mmol) in dichloromethane (5 ml) was added dropwise to a stirred solution of **9** (1.1 g, 4.9 mmol) and triethylamine (1.4 ml, 10 mmol) in dichloromethane (50 ml) at −16 °C over a period of 5 min. The mixture was stirred for 2 h at −16 °C, then 1 M HCl (10 ml) was added, and the organic layer was treated in the

above manner to give **10** (0.45 g, 41% yield).

This procedure using ethyl α-bromoacetoacetate[41] or ethyl bromocyanoacetate[42] instead of the above halide gave **10** (28% or 32% yield).

NCS——The chloride (0.67 g, 5 mmol) was added to a solution of **9** (1.1 g, 4.9 mmol) and triethylamine (1.4 ml, 10 mmol) in portions at −16 °C over a period of 14 min. The mixture was stirred for 2 h at −16 °C, then 1 M HCl (10 ml) was added, and the organic layer was treated according to the above procedure to give **10** (0.15 g, 14% yield).

This procedure using NBS and NBA instead of NCS gave **10** in 2% and 5% yields, respectively.

General Procedure for Reaction of Dithiol (11) with Diethyl Bromomalonate (1a)——A solution of **1a** (4.0 g, 0.017 mol) in dichloromethane (10 ml) was added dropwise to a stirred solution of **11** (0.015 mol) and triethylamine (2.3 ml, 0.017 mol) in dichloromethane (160 ml) at −16 °C over a period of 10 min. The mixture was stirred for 1 h at −16 °C, then 0.5 M HCl (10 ml) was added, and the organic layer was washed with satd. aq. NaCl, dried over $MgSO_4$, and concentrated *in vacuo*. The residual oil was separated into **12** and **13** by silica-gel column chromatography (hexane–$CHCl_3$).

1,2-Dithiane (12c)——Yield 82%; bp 110 °C (18 mmHg); mp 29—30 °C (lit.[26] 30.8—31.5 °C).

1,2-Dithiepane (12d)——Yield 34%; bp 115—120 °C (13 mmHg) [lit.[26] 105 °C (14 mmHg)].

1,2-Dithiocane (12e)——Yield 10%; bp 70—75 °C (2 mmHg) [lit.[26] 65.5 °C (2 mmHg)].

1,2,8,9-Tetrathiacyclotetradecane (13d)——Yield 19%; mp 78—79 °C (hexane). IR (KBr): 1448, 1425, 1267 and 1233 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.33—2.13 (12H, m, $CH_2 \times 6$) and 2.75 (8H, t, J=6.5 Hz, $CH_2SSCH_2 \times 2$). MS *m/e*: 268 (M^+).

1,2,9,10-Tetrathiacyclohexadecane (13e)——Yield 25%; mp 47—49 °C (hexane). IR (KBr): 1459, 1434, 1408 and 1261 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.17—2.05 (16H, m, $CH_2 \times 8$) and 2.72 (8H, t, J=7.0 Hz, $CH_2SSCH_2 \times 2$). MS *m/e*: 296 (M^+).

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