Large-Ring Cyclic Disulfide Diamides[1]

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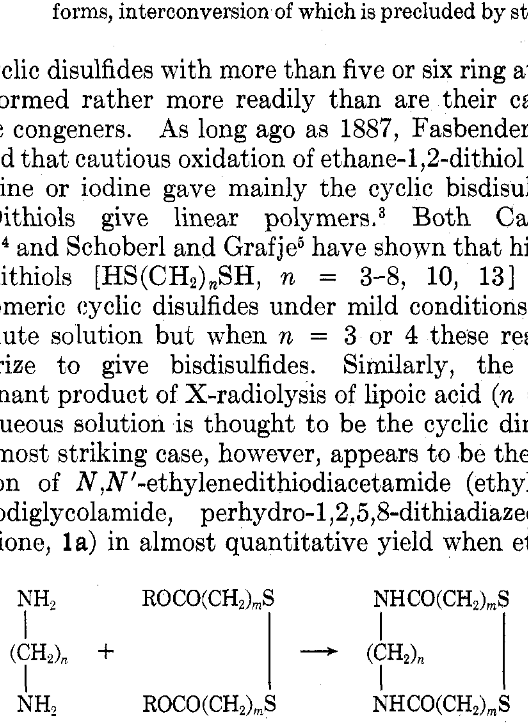
Unsubstituted 10-, 11-, and 13-membered ring cyclic disulfide diamides result in good to excellent yields from reaction of ethylenediamine and trimethylenediamine with esters of dithiodiacetic and 3,3′-dithiodipropionic acid in the absence of solvent. The procedure fails to give the desired products even from very simple substituted diamines and dithio diesters, however. Oxidation of the appropriate dithiols proved to be a satisfactory alternative route, good yields of ethylenedithiodiacetamide, its 2-methyl derivative, and what is probably its *N*,*N*′-dimethyl derivative being obtained. Ethylenedithiodiacetamide appears to exist in two diastereoisomeric forms, interconversion of which is precluded by steric hindrance.

Cyclic disulfides with more than five or six ring atoms are formed rather more readily than are their carbocyclic congeners. As long ago as 1887, Fasbender[2] reported that cautious oxidation of ethane-1,2-dithiol with bromine or iodine gave mainly the cyclic bisdisulfide. 1,1-Dithiols give linear polymers.[3] Both Calvin, *et al.*,[4] and Schoberl and Grafje[5] have shown that higher α,ω-dithiols [$HS(CH_2)_nSH$, $n = 3$–8, 10, 13] give monomeric cyclic disulfides under mild conditions and in dilute solution but when $n = 3$ or 4 these readily dimerize to give bisdisulfides. Similarly, the predominant product of X-radiolysis of lipoic acid ($n = 3$) in aqueous solution is thought to be the cyclic dimer.[6] The most striking case, however, appears to be the formation of *N*,*N*′-ethylenedithiodiacetamide (ethylenedithiodiglycolamide, perhydro-1,2,5,8-dithiadiazecine-4,9-dione, **1a**) in almost quantitative yield when ethylenediamine is mixed with a dithiodiacetate ester in the absence of solvent.[7] Plausibly, major controlling factors are the preferred cis dihedral configuration about the disulfide group and the lack of freedom of rotation within the amide group of the intermediate acyclic monoamide. We now report the preparation of further large-ring disulfide diamides of the same sort.

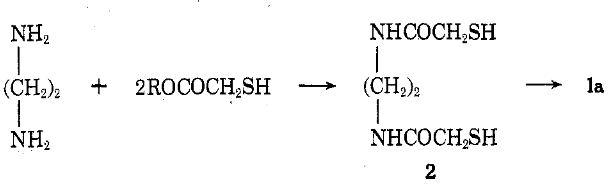


1a, $n = 2; m = 1$
b, $n = 3; m = 1$
c, $n = 3; m = 2$

The simple 11- and 13-membered ring disulfides (**1b**, **1c**) were obtained just as was **1a** by mixing equimolar amounts of trimethylenediamine with dimethyl dithiodiacetate or dimethyl 3,3′-dithiodipropionate in the absence of solvent. Each reaction was moderately exothermic, each reaction mixture set solid in due course, and yields of recrystallized products were good (60–70%). Low-resolution mass spectra of the dithiodiacetamides (**1a**,**1b**) showed no masses (other than ^{34}S isotope peaks) above those expected for the molecular ions at 206 and 220 daltons. The dithiodipropionamide (**1c**) however, gave additional small peaks up to M + 32. A high-resolution spectrum of **1c** showed conclusively that the M + 32 peak at 280 daltons contained an additional atom of sulfur. Presumably it corresponds to the cyclic trisulfide present as impurity. Repeated crystallization failed to remove this impurity completely, although a satisfactory elemental analysis was obtained. The trisulfide (if such it be) does not result from trisulfide impurity in the dithiodipropionate starting material, since this methyl ester analyzed satisfactorily and exhibited no M + 32 peak in the mass spectrum. It must arise from some relatively deep-seated reorganization of the disulfide group. A product analogous to **1c**, presumed to be largely the 12-membered ring compound (**1**, $n = 2$; $m = 2$) resulted from reaction of ethylenediamine with dimethyl dithiodipropionate. This also exhibited a marked M + 32 peak.

Attempts to extend the above procedure to substituted diamines and disulfide diesters revealed that cyclic diamide formation is most sensitive to slight steric hindrance. Neither reaction of dimethyl 2,2′-dithiodipropionate with ethylenediamine nor even of propylenediamine with dimethyl dithiodiacetate gave the desired products. In the latter case, a modest amount of a 2-substituted imidazoline may have been formed. Both *N*,*N*′-dimethyl- and *N*,*N*′-diethylethylenediamines with 3,3′-dithiodipropionate esters gave brown tars, a foul stench, and no desired product. The disulfide bond is known to be reactive toward primary and secondary amines, and it seems that cyclic amide formation depends upon a nice balance of steric and electronic factors.

An alternative route to the desired disulfides is oxidation of the corresponding dithiols (**2**). While the control afforded by the cisoid disulfide dihedral is lacking in this approach, the two amide groups present in the dithiol would seem to offer a good measure of conformational restriction. In any event, reaction of ethylenediamine with methyl mercaptoacetate (2 mol) readily afforded the dithiol **2** (82% yield, characterized as its bis-*S*-dinitrophenyl derivative, mp 245°), which, upon oxidation with iodine solution, gave, immediately



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[1] Financial support from the National Institute of General Medical Sciences, Public Health Service, Research Grant GM 16477, is gratefully acknowledged.

[2] H. Fasbender, *Ber.*, **20**, 460 (1887).

[3] T. L. Cairns, G. L. Evans, A. W. Larchar, and B. C. McKusick, *J. Amer. Chem. Soc.*, **74**, 3982 (1952).

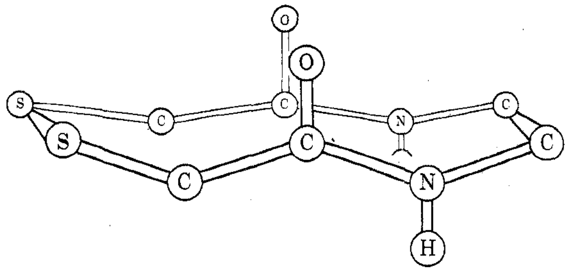
[4] J. A. Barltrop, P. M. Hayes, and M. Calvin, *J. Amer. Chem. Soc.*, **76**, 4348 (1954).

[5] A. Schoberl and H. Grafje, *Justus Liebigs Ann. Chem.*, **614**, 66 (1958).

[6] T. C. Owen and A. C. Wilbraham, *J. Amer. Chem. Soc.*, **91**, 3365 (1969).

[7] T. C. Owen and J. M. Fayadh, *J. Org. Chem.*, **35**, 3198 (1970).

and in excellent yield (80%), disulfide **1a** identical in melting point, mixture melting point, and mass spectrum with material prepared by the earlier procedure. The dithiol **2** proved to be unusually sensitive to air oxidation also. However, to our consternation, the product of aerial oxidation melted at 245°, in sharp contrast to the melting point (215°) of the earlier products. A mixture of the two substances, from which the lower melting one was selectively extracted by warm dimethylformamide, resulted when the dithiol was oxidized with aqueous hydrogen peroxide. The higher melting product analyzed satisfactorily for cyclic disulfide. Its mass spectrum was essentially identical with that of the lower melting one, showing, in particular, no masses above the 206–208 isotopic pair, so that it is unlikely to be a dimer or oligomer. Yet its melting point, its solubility (it is much less soluble even than **1a**, dissolves only in boiling DMF or DMSO, and could not be recrystallized owing to polymerization under such vigorous conditions), and its X-ray powder pattern all show it to be quite different from the earlier product. Both gave back the dithiol (characterized as the DNP derivative) upon reduction with mercaptoethanol. The two may perhaps be just different crystalline modifications of the same substance or, despite the mass spectral data, one may be a polymer. However, models show that the ten-membered ring is a trapezoid in which the amide planes occupy the long, nonparallel sides and that these planes are sterically precluded from rotating through the plane of the trapezoid. Thus, two diastereoisomeric structures (**3**, **4**) are possible, in one of which (**3**) the amide carbonyl groups are cis and in the other (**4**) trans to each other.



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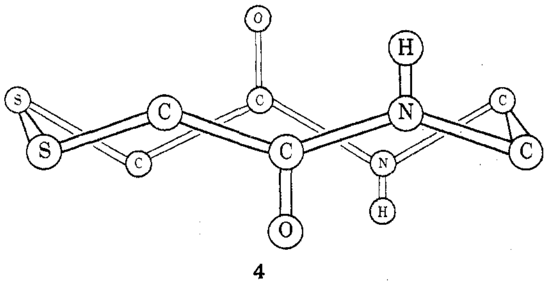

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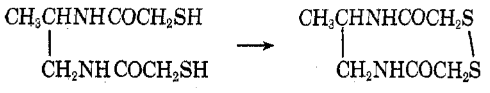
We suggest that our two products may well be such isomers. For the present, we refer to the lower melting form as α-ethylenedithiodiacetamide and to the higher melting as the β form.

Propylenediamine reacted much more sluggishly with methyl mercaptoacetate than did ethylenediamine. Nevertheless, the desired dithiol **5** was obtained as a yellow oil [consistent nmr spectrum, bis-S-dinitrophenyl derivative mp 214–219°, uv λ_{max} 337 nm (ϵ_{max} 25,350)] which, upon oxidation with iodine or with hydrogen peroxide, gave the desired cyclic disulfide **6** in good yield.

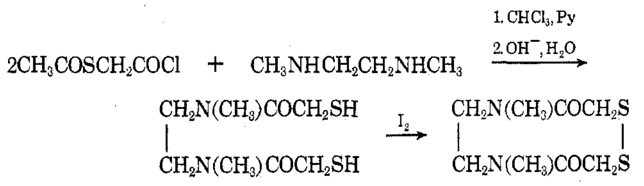


$$\begin{array}{l} CH_3CHNHCOCH_2SH \\ \;| \\ CH_2NHCOCH_2SH \end{array} \longrightarrow \begin{array}{l} CH_3CHNHCOCH_2S \\ \;| \qquad\qquad\quad \backslash \\ CH_2NHCOCH_2S \end{array}$$

5 **6**

Elemental analysis, mass spectrum, and nmr and ir spectra were entirely consistent with the cyclic monomer structure. In contrast with the unsubstituted compounds **1a–1c**, **6** proved to be quite soluble in water and the common polar solvents. No evidence for different forms of **6** has been observed, although the product from iodine oxidation did appear to have a slightly higher melting point than did that from oxidation with peroxide.

Attempts to prepare N,N′-dialkyl derivatives of ethylene dithiodiacetamide in the same manner failed completely. Only partial diminution of ester carbonyl and development of amide carbonyl bands in the infrared spectrum occurred when appropriate diamines were heated for prolonged periods with methyl mercaptoacetate. The reaction of acetylthioacetyl chloride with N,N′-dimethylethylenediamine proceeded smoothly, however, to give, after alkaline hydrolysis of thioester groups, a liquid product exhibiting properties consistent with its being the desired dithiol **7**.



$$2CH_3COSCH_2COCl + CH_3NHCH_2CH_2NHCH_3 \xrightarrow[2.\ OH^-,\ H_2O]{1.\ CHCl_3,\ Py}$$

$$\begin{array}{l} CH_2N(CH_3)COCH_2SH \\ \;| \\ CH_2N(CH_3)COCH_2SH \end{array} \xrightarrow{I_2} \begin{array}{l} CH_2N(CH_3)COCH_2S \\ \;| \qquad\qquad\qquad\quad | \\ CH_2N(CH_3)COCH_2S \end{array}$$

7 **8**

This, upon oxidation with iodine followed by continuous extraction with chloroform, afforded a colorless oil. The product, which may be the disulfide **8**, has stubbornly refused to crystallize and has not given acceptable elemental analytical data, presumably because of persistent retention of solvent. Its nmr spectrum is consistent with structure **8**, however, and its mass spectrum shows the expected isotopic molecular ion pair (m/e 234, 236) and no significant higher masses.

Experimental Section[8]

Materials. Dimethyl Dithiodiacetate.—A mixture of p-toluenesulfonic acid (1.0 g), dithiodiacetic acid (31 g, 0.170 mol), and methanol (110 ml) was heated under reflux for 4 hr. Methanol was removed under reduced pressure, chloroform (200 ml) was added to the oily residue, the solution was washed with aqueous $NaHCO_3$ (5%, 75 ml × 3) and water, dried ($MgSO_4$), and evaporated, and the residue was distilled under vacuum to give dimethyl dithiodiacetate as a colorless liquid: 24.3 g (68%); bp 109–114° (1.5 mm);[9] nmr ($CDCl_3$) τ 6.38 (s, 4 H, 2 SCH_2) and 6.24 (s, 6 H, 2 $COOCH_3$).

Dimethyl 3,3′-dithiodipropionate was similarly prepared: 63% yield; bp 148–152° (1.2 mm); nmr (CCl_4) τ 7.18 (symmetrical octet, 8 H, SCH_2CH_2CO) and 6.30 (s, 6 H, 2 $COOCH_3$).

N,N′-Ethylenebismercaptoacetamide (2).—Ethylenediamine

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[8] Melting points are uncorrected. Elemental analyses were by Galbraith Laboratories, Knoxville, Tenn. Mass spectra were by Florida State University, Tallahassee, Fla. A Perkin-Elmer Model 137 G spectrophotometer was used for ir spectra. Proton magnetic resonance spectra were determined with Varian A-60 and JEOL 100 instruments using tetramethylsilane as an internal standard.

[9] T. S. Price and D. F. Twiss, J. Chem. Soc., 1645 (1908).

(3.6 g, 60 mmol) was added slowly to stirred, ice-cooled methyl mercaptoacetate (12.8 g, 120 mmol) and the mixture then was heated at 100° for 1.5 hr. Overnight, the product solidified. Trituration with cold EtOH gave crude **2** (10.25 g, 82%, mp 135–139°). Pure **2**, white needles from hot EtOH, had mp 138–139°; nmr (D_2O) τ 6.41 (s, 4 H, 2 $COCH_2$), 6.55 (s, 4 H, 2 NCH_2). *Anal.* Calcd for $C_6H_{12}O_2S_2N_2$: C, 34.59; H, 5.82. Found: C, 34.72; H, 5.94.

Bis-*S*-dinitrophenyl Derivative of 2.—Crude **2** (0.62 g), $NaHCO_3$ (1 g), and fluoro-2,4-dinitrobenzene (1.3 g) in water (20 ml) were stirred for 2 hr and filtered, and the product was washed with ethanol, gave a yellow solid (1.32 g, 76%). Recrystallization from EtOH gave pale yellow crystals, mp 245–247°. *Anal.* Calcd for $C_{18}H_{16}N_6O_{10}S_2$: C, 40.00; H, 2.96. Found: C, 39.84; H, 3.17.

***N*,*N*′-Ethylenedithiodiacetamide (1a), α Form. A. From Ethylenediamine and Dimethyl Dithiodiacetate.**—The melting point of the product prepared by the published procedure[7] was raised to 213–215° (72% yield) by careful recrystallization from fairly hot (90–95°) dimethylformamide.

B. From *N*,*N*′-Ethylenebismercaptoacetamide.—The dithiol **2** (2.0 g) was stirred with water (75 ml) for 1 hr. The solution was separated from a moderate amount (0.38 g, 18%) of insoluble white solid (β form, mp 244.5–246°) and treated with I_2–KI solution (0.1 *N*) until a faint yellow color persisted. The precipitate (1.39 g, 69%), recrystallized from dimethylformamide, had mp 214–216, undepressed upon admixture with material from procedure A. Spectra (ir, mass) and elemental analysis were as previously reported.[7]

***N*,*N*′-Ethylenedithiodiacetamide (1a), β Form.**—A brisk stream of air was blown over a solution of the dithiol **2** (0.9 g) in EtOH (10 ml) containing ethylenediamine (1 drop) until the solvent had evaporated. The residue, washed with water, hot EtOH, and hot (90°) dimethylformamide, afforded the β form of **1a** as a white powder (0.75 g, 83%), mp 245–246.5°, identical in all respects with the initial precipitate in procedure B above and with the less soluble product from peroxide oxidation (below). *Anal.* Calcd for $C_6H_{10}N_2O_2S_2$: C, 34.95; H, 4.85. Found: C, 34.87; H, 4.95. The mass spectrum (50 eV) was very similar indeed to that of the α form.[7] Oxidation (overnight) of an aqueous solution of dithiol **2** with the requisite amount of 3% H_2O_2 gave, in 50% yield, a white precipitate which, after washing with hot EtOH, had mp 220–227°. Repeated extraction of this solid with hot (90°) dimethylformamide left a residue having mp 242–245°. Crystalline powder, mp 213–215° after recrystallization, was deposited by the first dimethylformamide extract.

Characterization of α- and β-Ethylenedithiodiacetamides by Reduction.—Either disulfide (0.2 g), heated with mercaptoethanol (0.5 ml) on the steam bath overnight, dissolved in part. Dilution of the mixtures with warm EtOH (2–3 ml), filtration, partial evaporation, and chilling afforded the crude solid dithiol **2**, which was converted directly into its bis-*S*-dinitrophenyl derivative as described above. The overall yield from the α disulfide was 0.23 g (43%); from the β form, 0.18 g (34%). The melting points were undepressed upon admixture with authentic material.

***N*,*N*′-Trimethylenedithiodiacetamide (1b).**—The exothermic reaction between trimethylenediamine (1.41 g, 19 mmol) and dimethyl dithiodiacetate (4.00 g, 19 mmol) was moderated by means of an ice–water bath. The resulting oil, kept at 25° for 2 hr and then heated at 100° for 1.5 hr, solidified upon cooling. Trituration with ethanol followed by recrystallization from EtOH–dimethylformamide mixture gave a pale yellow solid (2.5 g, 62%), mp 164–165°. *Anal.* Calcd for $C_7H_{12}N_2O_2S_2$: C, 38.18; H, 5.45. Found: C, 38.37; H, 5.47. The mass spectrum (70 eV) showed *m/e* 220 (^{32}S ion) with minor peaks (~8%) at 222 (^{34}S ion) and 221 (^{32}S, ^{13}C–^{2}H ion); ir (Nujol) 1640 cm^{-1}.

***N*,*N*′-Trimethylene-3,3′-dithiodipropionamide (1c).**—Addition of trimethylenediamine (0.64 g, 8.6 mmol) to dimethyl 3,3′-dithiodipropionate (2.00 g, 8.4 mmol) gave a light brown, viscous oil which, after standing for 1.5 hr at 25° and refrigeration overnight, solidified. Trituration with EtOH gave a pale yellow solid (1.77 g, 85%). Recrystallization from hot (90°) dimethylformamide gave a white product (1.39 g, 67%), mp 181–183°. *Anal.* Calcd for $C_9H_{16}O_2N_2S_2$: C, 43.52; H, 6.51. Found: C, 43.31; H, 6.66. The mass spectrum (70 eV) showed *m/e* 248 (^{32}S ion) with additional peaks (10, 10, 15, and 5% intensity, respectively) at 249 (^{32}S, ^{13}C–^{2}H ion), 250 (^{34}S ion), 280 (M + 32 ^{32}S ion), and 284; high-resolution mass spectrum, measured masses *m/e* 248.0656 and 280.0373; calcd mass for $C_9H_{16}O_2N_2S_2$, 248.0652; and for $C_9H_{16}O_2N_2S_3$, 280.0373; ir (Nujol) 1635 cm^{-1}.

***N*,*N*′-Propylenebismercaptoacetamide (5) and *N*,*N*′-Propylenedithiodiacetamide (6).**—Methyl mercaptoacetate (8.0 g, 75 mmol) was heated with propylenediamine (2.8 g, 37.5 mmol) at 100° for 5 hr, the disappearance of ester (1735 cm^{-1}) and development of amide (1640 cm^{-1}) carbonyl bands being followed by ir. Removal of a trace of volatile matter under reduced pressure gave the dithiol **5** as a yellow oil [6.88 g (82%), ir 2510 (SH), 1635 cm^{-1}], a portion (0.46 g, 2.0 mmol) of which was converted into its bis-*S*-dinitrophenyl derivative by stirring a solution in water (20 ml) containing $NaHCO_3$ (0.53 g, 6.3 mmol) with fluoro 2,4-dinitrobenzene (0.82 g, 4.4 mmol) for 2 hr at 25°. The yellow precipitate, crystallized from EtOH (20 ml), had mp 227–229°; uv (acetone) λ_{max} 337 nm (ϵ_{max} 25,350). Oxidation of the dithiol **5** (3.25 g, 14 mmol) in water (75 ml) with hydrogen peroxide (3%, 18 ml, 16 mmol), overnight, followed by continuous extraction with $CHCl_3$, gave the disulfide **6** as a white solid (2.24 g, 69%), recrystallized from $CHCl_3$, mp 189–191°. Oxidation of another portion (2.88 g, 12.5 mmol) with I_2–KI solution (0.1 *N*, 130 ml, 13 mmol) followed by continuous extraction with $CHCl_3$ gave pale yellow solid (2.10 g, 73%), recrystallized from $CHCl_3$, mp 188–189°. *Anal.* Calcd for $C_7H_{12}N_2O_2S_2$: C, 38.18; H, 5.45. Found: C, 38.01; H, 5.56. The mass spectrum (70 eV) showed *m/e* 220 (^{32}S ion) with minor peaks (~8%) at 222 (^{34}S ion) and 221 (^{32}S, ^{13}C–^{2}H ion); ir (Nujol) 1635 cm^{-1}. It is noteworthy that **6**, in sharp contrast to the unsubstituted cyclic disulfide diamides, is moderately soluble in water and the common solvents.[10]

***N*,*N*′-Dimethyl-*N*-*N*′-ethylenebismercaptoacetamide (7) and Presumed *N*,*N*′-Dimethyl-*N*,*N*′-ethylenedithiodiacetamide (8).**—A solution of *N*,*N*′-dimethylethylenediamine (1.35 g, 15 mmol) in pyridine (2.70 g, 34 mmol) was added slowly to an ice-cooled solution of acetylthioacetyl chloride (5.16 g, 33 mmol) in $CHCl_3$ (15 ml). The milky solution was heated under reflux for 2 hr, kept at 5° overnight, and filtered, and the filtrate was washed successively with 3 *N* HCl, water, and 5% $NaHCO_3$, dried ($MgSO_4$), and evaporated under reduced pressure to give the crude bisacetylthioacetamide as a colorless oil (4.10 g, 85%), ir 1690 (–COS–), 1640 cm^{-1} (–CONH–). Selective hydrolysis of thiolester groups was effected with NaOH (1.02 g) in water (7.2 ml) at 65° during 4.5 hr with stirring. Extraction with $CHCl_3$ followed by evaporation gave crude *N*,*N*′-dimethyl-*N*,*N*′-ethylenebismercaptoacetamide (**7**) as a colorless oil (2.2 g, 62% overall), ir 1640 (–CONH–), 2530 cm^{-1} (–SH). The bis-*S*-dinitrophenyl derivative, prepared as usual and recrystallized from EtOH, had mp 195–197°, uv (acetone) λ_{max} 335 nm (ϵ_{max} 21,700). *Anal.* Calcd for $C_{20}H_{20}N_6O_{10}S_2$: C, 42.25; H, 3.52. Found: C, 42.38; H, 3.63. The crude dithiol (2.00 g, 8.5 mmol), dissolved in water (60 ml), was treated with 0.1 *N* I_2–KI until a faint yellow color persisted. Continuous extraction with $CHCl_3$ followed by evaporation gave presumed *N*,*N*′-dimethyl-*N*,*N*′-ethylenedithiodiacetamide as a colorless oil (1.50 g, 74%) which did not crystallize. The mass spectrum (70 eV) showed *m/e* 234 (^{32}S ion) with minor peaks (~8%) at 236 (^{34}S ion) and 235 (^{32}S, ^{13}C–^{2}H ion); nmr ($CDCl_3$) τ 6.86 (s, 6 H, 2 CH_3N)), 6.41 (s, 4 H), and 6.20 (s, 4 H).

Registry No.—**1a,** 25286-76-4; **1b,** 37709-50-5; **1c'** 37818-76-1; **2,** 692-93-3; **2** (bis-*S*-dinitrophenyl), 37709-97-0; **5,** 37709-98-1; **5** (bis-*S*-dinitrophenyl), 37709-99-2; **6,** 37710-00-2; **7,** 37709-09-4; **7** (bis-*S*-dinitrophenyl), 37709-10-7; **8,** 37709-11-8; dimethyl dithiodiacetate, 1665-64-1; dimethyl 3,3′-dithiodipropionate, 15441-06-2; ethylenediamine, 107-15-3; methyl mercaptoacetate, 2365-48-2; trimethylenediamine, 109-76-1; acetylthioacetyl chloride, 10553-78-3; *N*,*N*′-dimethylethylenediamine, 108-00-9; bisacetylthioacetamide, 37709-13-0.

Acknowledgment.—We thank Dr. R. G. Stevenson, Jr., of the Department of Geology, University of South Florida, for providing X-ray powder patterns of α- and β-ethylenedithiodiacetamides.

(10) NOTE ADDED IN PROOF.—Mol wt (osmometric in DMF) 240 (calcd 220) confirms the monomeric nature of this disulfide.