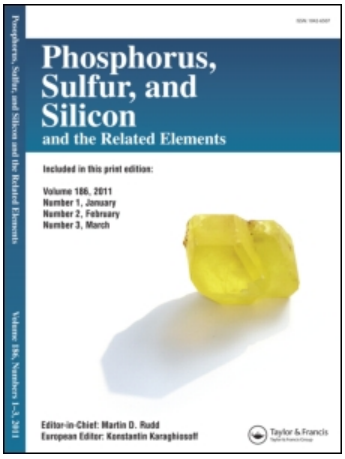

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SULFINIC ACIDS AND RELATED COMPOUNDS. 22. DERIVATIVES OF 2-HYDROXYETHANE SULFINIC ACID[1,2]

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SULFINIC ACIDS AND RELATED COMPOUNDS. 22. DERIVATIVES OF 2-HYDROXYETHANE-SULFINIC ACID[1,2]

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Sodium 2-hydroxyethanesulfinate (**3**) could be converted to the unstable methyl ester **8** by acidification followed by reaction with diazomethane (although the acid **4**, itself, could not be isolated as reported). The ester **8** was esterified with 2,2'-dithiodiacetyl dichloride (**10**) to afford the desired convergent synthesis of a disulfide bissulfinate ester (**11**), but **11** was even less stable than **8**; efforts to esterify the sulfinate salt **3** with **10** to give a more stable sulfinate salt counterpart (**12**) of the ester **11** were unpromising. The salt **12** also was sought by reduction of a sulfonyl chloride **13**, which was obtained by coupling **10** with 2-hydroxyethanesulfonyl chloride (**2**) and for which the structure was confirmed by reaction with *p*-bromoaniline; **12** evidently was obtained, but greater purity could not be obtained than ca. 83–95%. In other reactions, 2-hydroxyethanesulfonyl chloride (**2**) reacted with *p*-bromoaniline, and the hydroxysulfonanilide (**6**) produced could be esterified with **10** to give **9** by use of special conditions.

Key words: Disulfides, 2-hydroxyethanesulfinic acid; 2-hydroxyethanesulfonyl chloride; sulfinic acids; sulfinic-acid esters; sulfinic-acid salts.

INTRODUCTION

Di- and trisulfides of the general structure $RS_nR'SO_2Na$ are promising agents for reducing otherwise lethal effects of ionizing radiation in mammals, particularly since they lack the nitrogen function common to most antiradiation drugs.[3] Because of much improved prospects of flexibility, possibilities of convergent syntheses of such agents have attracted our interest. Such syntheses should make it possible to connect one molecule containing a di- or trisulfide function through a link such as a carboxylate ester with another molecule containing a sulfinate function. Convergent approaches of this kind should greatly enhance capabilities for substitutional and functional variation in each of the components.

RESULTS AND DISCUSSION

An attractive access to a convergent synthesis was implied in the recent availability of sodium 2-hydroxyethanesulfinate (**3**),[4] since it should be possible to link **3** through a carboxylate function to a disulfide like **10** to afford disulfide

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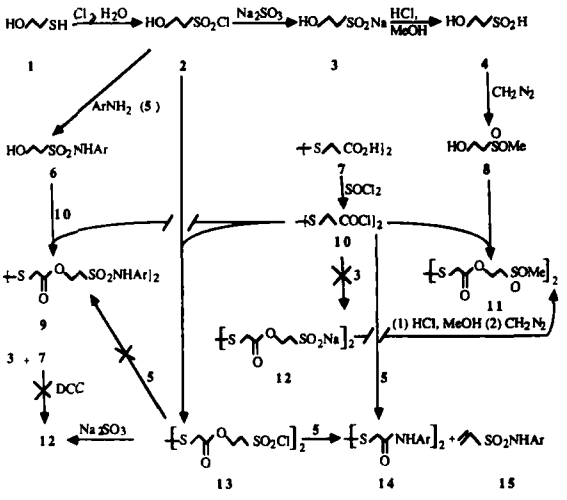


SCHEME 1[a]

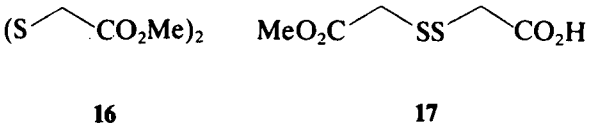
[a]Ar = p-BrC_6H_4

sulfinates such as the salt **12** or the counterpart ester **11** (Scheme 1). As it turned out, low yields and instabilities of **11** and **12** make the alkane series rather unattractive as drugs. In consequence of the research, however, a considerable amount was learned about the chemistry of 2-hydroxyalkanesulfinates, a scarcely known class, and report of these results is the major focus of this paper.

The sulfonyl chloride **2**, intriguingly the first compound that is both an alcohol and a sulfonyl chloride,[4] was prepared by oxidizing **1** with Cl_2 essentially as reported.[4] King and Hillhouse reduced the sulfonyl chloride **2** to the sulfinate salt (**3**), which they did not isolate but acidified to give the acid **4**.[4] We were unable to isolate the sulfinic acid **4** from the reaction mixture by the method reported,[4] although after acidification a solution of the salt **3** (vide infra) in CD_3OD gave NMR spectra with the values reported for **4** (we also were unable to isolate the acid **4** from our isolated **3** as a starting material). As further evidence for the identity of the salt **3**, our **3** isolated after reduction of the chloride **2** had the same properties reported by King and Hillhouse for **3** which they obtained by neutralizing their acid (**4**). We confirmed the identity of **3**, after acidifying it with methanolic HCl, by esterifying the acid (**4**) with diazomethane to give the ester (**8**). The ester **8** was rather unstable, but analysis was possible by high-resolution mass spectrometry of a sample shown to be pure by TLC.

For the convergent synthesis of **11** (Scheme 1), the acid chloride **10** was allowed to react with the ester **8**. The product (**11**) was obtained in 9% yield but was even less stable than **8** and therefore lacked promise as a practical antiradiation agent. NMR spectra pointed to a reason for the low yield of **11**, apart from instability of the **11**, by pointing to the presence of **16–18** in the crude product (**16** was confirmed by comparison).

To our surprise, **16** and **17** appeared to result from the reaction of **10** with two molecules of MeOH (for **16**), or one of MeOH and another of H_2O (for **17**); **18** appeared to result from the desired preliminary reaction of one molecule of **8**



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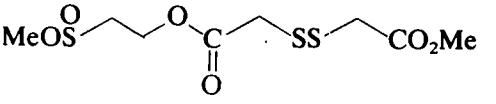

18

but followed by reaction of MeOH with the remaining —COCl function. The attack of H_2O can be understood as arising from a trace of moisture in the starting materials, but the surprising involvement of MeOH seems best understood as arising from condensation polymerization of **8** to liberate MeOH, perhaps via 1,2-ethanesultine (cf. Reference 4 for the analogous sultone); a comparably dilute solution of MeOH was shown to be capable of reacting thus (i.e. NMR and TLC showed that 39 mg of MeOH in 30 mL of CH_2Cl_2 was completely converted to **16** within 0.5 h by 130 mg of **10,** the equivalent amount).

Since the sulfinate salt **12** seemed likely to be more stable than the ester **8**, it was sought by reaction of the acid chloride **10** with the salt **3**. This effort was unpromising,[2] perhaps because of the virtual insolubility of **3** in all solvents tried, or because H_2O could not be entirely removed from **3**, and/or because HCl produced attacked the sulfinate function or the disulfide linkage. Attempted reaction of the acid **7** with **3**, with *N,N'*-dicyclohexylcarbodiimide (DCC) as a coupling reagent, also was quite unpromising (furthermore the DCC caused a persistent skin rash in one of us).

Synthesis of **12** finally was sought by reaction of **10** with the sulfonyl chloride **2**, with the intent of forming the sulfonyl chloride **13** and then of reducing this **13** to **12** (Scheme 1). The sulfonyl chloride (**13**) was obtained in 84% yield. To confirm the identity of **13**, the initial sulfonyl chloride **2** was converted through the *p*-bromosulfonanilide **6** (26% yield) to the condensation product **9** (48% yield), with the presumption that this sequence would represent an independent synthesis of **9**, which we then expected to prepare straightforwardly from the sulfonyl chloride **13**. However, **13** and *p*-bromoaniline did not react to give **9**. Instead, cleavage occurred to give **14** and **15** in yields respectively of 44% and 19% (Scheme 1). Nevertheless, this result of course confirms the structure of **13**; since **13** clearly was a chemical entity and not a mixture, both **14** and **15** in effect must have been linked initially. The **14** may have been formed from **13** by conventional cleavage of an ester (**13**) to an amide (**14**) and the **15** by an equally conventional E2 elimination of a carboxylate ion before or after formation of the sulfonamide [a reviewer suggested (and we concur) that a sulfene may have played a role and cited J. F. King *et al.*, *Can. J. Chem.*, **66**, 1109 (1988)].

Efforts to reduce the sulfonyl chloride **13** to the sulfinate salt **12** with Na_2SO_3 were less satisfactory than hoped. Evidently the conditions needed to reduce **13** to **12** also led to attack on the disulfide bond. Along with the water-soluble products, a polymeric precipitate amounting to about 10–30% of the mass of the **13**, frequently was obtained. NMR indicated a maximum content in the

water-soluble products of 70% of **12**, which could only be increased to a maximum of 83–95% by a very wasteful reprecipitation. The impurities probably were the Bunte salt and thiolate produced as shown by Equation (1), which represents a long known equilibrium.[5] Three NMR singlets were observed for the product;

$$RSSR + Na_2SO_3 \rightleftharpoons RSNa + RSSO_3Na \quad (1)$$

the estimates for the maximum content of **12** of 70%–95% were based on the ratio of the largest of these, shown to be **12** as described in the Experimental, to the total of all three.

EXPERIMENTAL

General details of instrumentation, procedure, etc. were as reported earlier,[1] with the following additions: TLC was done on Whatman K6F (as well as on K5F) plates; flash chromatography was done with ca. 50 g of silica gel per g of product in a 4 × 45-cm column; mass spectra were obtained with a VG 70-250 GC-MS instrument (resolving power, 10,000) in the EI exact mass mode at 70 eV with a direct introduction probe and consecutively averaged scans; they were kindly provided by Prof. B. J. Sweetman (Department of Pharmacology; funds provided by the NIH, Division of Research Resources Grant RR 01688).

Preparation of 2-hydroxyethanesulfonyl chloride (2) and reduction to sodium 2-hydroxyethanesulfinate (**3**). Much as reported,[4] Cl_2 was passed into a solution of 0.43 mol (30 mL) of 2-mercaptoethanol (**1**) in 100 mL of H_2O during ca. 30 min, after which the solution gave an immediate purple color with KI-starch paper; ice cooling was used to keep the temperature below 50°C. Benzene extracts (4 × 50 mL) were discarded,[4] and the aqueous solution was saturated with NaCl and extracted with CH_2Cl_2 (10 × 40 mL). The CH_2Cl_2 extracts were combined, dried ($MgSO_4$), and concentrated to give 12.6 g (20%) of **2** as a colorless liquid: n^{28}D 1.4950 (lit.[4] n^{25}D, 1.4902); IR, ^{1}H NMR and ^{13}C NMR spectra agreed with reported values for **2**.

The sulfonyl chloride (**2**) was reduced to sodium 2-hydroxyethanesulfinate (**3**), through a procedure based on one for reducing methanesulfonyl chloride,[6] by adding a solution of 15.9 g (126.2 mmol) of Na_2SO_3 and 5.30 g (63.1 mmol) of $NaHCO_3$ in 100 mL of H_2O during 15 min to 9.00 g (62.2 mmol) of H_2O-soluble **2** at 25°C with stirring. After 2.5 h more of stirring, the solution was washed twice with 40 mL of CH_2Cl_2 and freeze dried to a white solid, which usually contained ca. 5–20% of the sulfonic acid salt, $HO(CH_2)_2SO_3Na$, by NMR [δ 3.40 (t, 2H), 3.15 (t, 2H)]. This solid was stirred at 25°C for 0.5 h with 100 mL of MeOH, inorganic salt was removed by filtration, the MeOH solution was concentrated to ca. 20 mL, and 150 mL of Et_2O was added. Drying of the gummy precipitate obtained at 0.2 torr for ca. 48 h gave 4.20 g (51% if pure) of **3** as white powder (shown by elemental analysis, however, still to contain some inorganic salt and a little sulfonic acid salt): ^{1}H NMR (D_2O) δ 3.88 (t, 2H), 2.57 (t, 2H) [lit. for **3** from the neutralization of the acid **4**,[4] δ 3.91 (t, 2H), 2.58 (t, 2H)]; ^{13}C NMR (D_2O) 70.51, 63.66. Attempted conversion of the **3** to 2-hydroxyethanesulfinic acid (**4**), as reported,[4] led only to a trace of gum; however, when **3** was dissolved in CD_3OD and acidified with a little methanolic HCl the ^{1}H NMR spectrum agreed with reported values for **4** [δ (CD_3OD) 3.94 (t, 2H), 2.99 (t, 2H); lit.[4] δ (D_2O) 4.01 (t, 2H), 3.04 (t, 2H).

Methyl 2-hydroxyethanesulfinate (***8***). In an esterification based on a reported procedure,[7] sodium 2-hydroxyethanesulfinate (**3**; 2.50 g, 18.9 mmol) was dissolved in MeOH (25 mL), 15 mL of 1.33 N-methanolic HCl (20.0 mmol) was added, and the mixture was stirred for 5 min. An ethereal solution of diazomethane at 0° then was added in 1-mL portions until a pale yellow color persisted. Inorganic salt was removed by filtration, the yellow color of CH_2N_2 was discharged with a few drops of AcOH, accumulated moisture was removed by drying over $MgSO_4$, and solvent was evaporated to leave 0.80 g of **8** as a pale yellow liquid. TLC (3% MeOH in $CHCl_3$) indicated a complex mixture (6–8 spots, developed with I_2 vapor) but with a major spot at R_f 0.20. Flash chromatography with 3% MeOH in $CHCl_3$ and collection of the fraction with a TLC R_f of 0.20 led to 0.70 g (30%) of **8** as colorless liquid; TLC indicated that the **8** slowly began to decompose after ca. 48 h at ca. 25°C but was stable for at least a month at 0°C: IR (neat) 3450 (s, b), 2950, 2900, 1460, 1395, 1300, 1210, 1110 (s, b), 1060 (s), 980 (s, b), 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.19–4.03 (m, 2H), 3.83 (s, 3H);

3.10–3.02 (m, 1H), 2.97–2.89 (m, 1H), 2.65 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 59.08, 55.75, 54.96; MS (EI), exact mass found 124.0189, $C_3H_8O_3S$ requires 124.0194; MS m/z (relative intensity) 124.(27), 80 (95), 79 (100), 65 (66), 63 (69).

2,2'-Dithiodiacetyl dichloride (**10**). Thionyl chloride (20.0 g, 168 mmol) was added to a solution of 2,2'-dithiodiacetic acid (**7**; 14.0 g, 76.8 mmol) in dioxane (20 mL), and the solution was heated under reflux for 4 h. Excess $SOCl_2$ and solvent were removed at aspirator pressure, and the dark brown liquid was distilled using a short-path (1 cm) still; **10** has been reported, in unstated yield, by the use of PCl_5:[8] yield of **10** as yellow liquid, 10.0 g (59%): bp 135–140°C (2.0 torr), lit.[8] bp 92–93°C (0.03 torr); IR (neat) 3550, 2970 2940, 1900, 1780 (s, b), 1390, 1360 (s), 1250, 1170 (s), 1000–950 (s, b), 850, 740, 690 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.06 (s), lit.[8] ^{1}H NMR (acetone-d_6), δ 4.38; ^{13}C NMR ($CDCl_3$) δ 169.70, 51.90. The **10** was stable at 0°C under N_2 for at least a month, but at 25°C without N_2 decomposition began in ca. 2 days.

Bis-2-(methoxysulfinyl)ethyl 2,2'-dithiodiacetate (**11**). A solution of 0.10 g (1.26 mmol) of pyridine in 20 mL of CH_2Cl_2 was added during 5 min to a solution of 0.13 g (0.59 mmol) of 2,2'-dithiodiacetyl dichloride (**10**) and 0.15 g (1.21 mmol) of methyl 2-hydroxyethanesulfinate (**8**) in 30 mL of CH_2Cl_2 kept at 0°C. After 1 h of stirring at ca. 25°C, the mixture was washed with 50 mL of H_2O and then dried over $MgSO_4$. Removal of solvent left 0.12 g of gum, indicated by TLC to be a complex mixture. Preparative TLC with 3:7 EtOAc-CH_2Cl_2 gave a fraction with R_f 0.33 that contained 20 mg (9%) of **11** as a yellow gum; extra TLC spots developed after only 24 h at ca. 25°C: IR (neat) 2950, 1740 (s), 1460, 1390, 1280 (s, b), 1120 (s, b), 1060, 980 (s, b), 880, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.53–4.48 (m, 2H), 3.79 (s, 3H), 3.57 (s, 2H), 3.16–2.98 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 168.90, 58.48, 55.89, 54.98, 41.02; MS, *m/z* (relative intensity): 394 [4; M^+, in the absence of perfluorokerosene (PFK); an exact mass was not obtainable because of PFK interference at *m/z* 394], 362 (80), 315 (34), 270 (70), 197 (9), 182 (11), 119 (66), 79 (100). ^{1}H NMR, ^{13}C NMR, and TLC all show that **11** is a single compound; whether **11** is a racemic or meso product (two chiral sulfinate moieties) is unknown; presumably the other diastereomer remained in the "complex mixture."

Anal. Calcd for $C_{10}H_{18}O_8S_4$: C, 30.44; H, 4.60; S, 32.51. Found: C, 30.52; H, 4.76; S, 34.03.

Several efforts to condense the acyl halide **10** with **3** (as the salt counterpart of the ester **8**) led only to mixtures that showed complex NMR spectra with no indication of significant amounts of **12**.

Bis-2-(chlorosulfonyl)ethyl 2,2'-dithiodiacetate (**13**). A solution of 2.00 g (25.3 mmol) of pyridine in 5 mL of CH_2Cl_2 was added during 15 min to a solution of 2.70 g (12.3 mmol) of 2,2'-dithiodiacetyl dichloride (**10**) and 3.60 g (24.9 mmol) of 2-hydroxyethanesulfonyl chloride (**2**) in 40 mL of CH_2Cl_2 at 0°C. The resulting yellow solution was stirred for 0.5 h at 0°C and for 2.5 h at 25°C, was washed with brine, and was dried. Removal of solvent left 4.50 g (84%) of **13** as a sticky brown liquid, which decomposed during TLC and therefore was analyzed and used as prepared: IR (neat) 3000 (b), 1720 (s, b), 1360 (s), 1250 (s, b), 1160 (s, b), 1040, 760, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.73 (t, 2H), 4.08 (t, 2H), 3.64 (s, with two small shoulders, 2H).

Anal. Calcd for $C_8H_{12}Cl_2O_8S_4$: C, 22.07; H, 2.78; S, 29.46. Found: C, 22.62; H, 2.93; S, 29.71.

N-(p-bromophenyl)-2-hydroxyethanesulfonamide (**6**). A solution of 10.7 g (62.2 mmol) of *p*-bromoaniline in 60 mL of CH_2Cl_2 was added during 15 min to one of 4.50 g (31.1 mmol) of 2-hydroxyethanesulfonyl chloride (**2**) in 50 mL of CH_2Cl_2, and the mixture was stirred for 24 h. The precipitate of amine salt then was removed by filtration, and the solution was washed with 10% aqueous HCl (20 mL) and H_2O (2 × 50 mL). Drying and removal of solvent gave 2.5 g of pale purple oil. The oil was dissolved in warm CH_2Cl_2 (15 mL) and pentane was added to incipient turbidity. After 24 h at ca. 25°C, 2.30 g (26%) of **6** was collected as a soft white solid: mp 94–95°C; R_f, 0.50 (2:3 EtOAc-CH_2Cl_2); IR 3440 (s), 3150, 3050, 2950, 1590, 1500, 1400, 1335 (s), 1290, 1220, 1160, 1138 (s), 1060, 1010, 960, 840–820 (b), 740 cm^{-1}; ^{1}H NMR ($CDCl_3$), δ 7.46–7.43 (d, 2H, 9Hz), 7.15–7.12 (d, 2H, 9Hz), 6.71 (s, b, 1H), 4.13–4.07 (q, 2H), 3.25 (t, 2H), 2.38 (t, 1H); ^{13}C NMR (acetone-d_6) δ 138.61, 132.94, 123.14, 117.53, 57.18, 54.07.

Anal. Calcd for $C_8H_{10}BrNO_3S$: C, 34.30; H, 3.60; N, 5.00; S, 11.45. Found: C, 34.12; H, 3.88; N, 4.71; S, 11.55.

Bis-2-(p-bromophenylaminosulfonyl)ethyl 2,2'-dithiodiacetate (**9**). A solution of N-(*p*-bromophenyl)-2-hydroxyethanesulfonamide (**6**; 0.30 g, 1.07 mmol) and 2,2'-dithiodiacetyl dichloride (**10**; 0.40 g, 1.83 mmol) in 20 mL of CH_2Cl_2 was allowed to stand at ca. 25°C under N_2 for one week, with gentle swirling once or twice each day; when stirring was vigorous, or when pyridine was used under various conditions, a complex mixture resulted and yields were only ca. 5%. The solution then was washed with 10% aqueous HCl (20 mL) and H_2O (2 × 50 mL). After the solution had been dried,

TLC (3% MeOH in CH_2Cl_2) indicated a complex mixture, but a major spot was present at R_f 0.28. Solvent was removed, and the brown gummy residue (0.70 g) was subjected to preparative TLC with 3% MeOH in CH_2Cl_2. The fraction with R_f 0.28 was a viscous yellow liquid (0.18 g, 48% of **9**), which slowly crystallized from $CHCl_3$ (in which **9** was very sparingly soluble) during ca. one week to give solid **9**; the **9** could be kept without change at 0°C for more than two years: mp 95–97°C; IR (neat) 3300 (s), 2950, 1740 (s), 1590, 1495, 1460, 1400, 1340, 1280, 1220, 1140 (s, b), 1080, 1010, 920, 820, 720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.59 (s, 2H), 7.49–7.46 (d, 4H), 7.23–7.20 (d, 4H), 4.60 (t, 4H), 3.61 (s, 4H), 3.49 (t, 4H); ^{13}C NMR ($CDCl_3$) δ 169.69, 135.73, 132.75, 122.13, 118.44, 59.56, 49.75, 41.73.

Anal. Calcd for $C_{20}H_{22}Br_2N_2O_8S_4$: C, 34.00; H, 3.14; N, 3.97; S, 18.15. Found: C, 33.54; H, 2.86; N, 3.54; S, 18.04.

Reaction of the coupled ester-sulfonyl chloride ***13*** *with p-bromoaniline* (**5**). In the effort to convert **13** to the independently synthesized sulfonamide **9**, a solution of 0.14 g (1.77 mmol) of pyridine in 10 mL of CH_2Cl_2 was added to one of 0.40 g (0.92 mmol) of the ester-sulfonyl chloride **13** and 0.63 g (3.66 mmol) of *p*-bromoaniline (**5**) in 100 mL of CH_2Cl_2. The solution was stirred for 24 h, washed with 10% aqueous HCl (20 mL), H_2O (2 × 50 mL), and dried. Removal of solvent left 0.42 g of brown oil. Preparative TLC with 4:1 CH_2Cl_2-EtOAc gave two major fractions, I and II.

(*a*) *Fraction I, N-(p-bromophenyl)ethenesulfonamide* (***15***). Fraction, I, which proved to be **15**, had R_f 0.82 and amounted to 0.090 g (19%) of pale brown gum: IR (neat) 3275 (b), 3050, 1580, 1480 (s), 1450, 1380 (s), 1320 (s, b), 1220, 1150 (s), 1070, 1000, 960, 920, 820, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.45–7.42 (d, 2H, J = 9 Hz), 7.08–7.05 (d, 2H, J = 9 Hz), 6.66 (s, b, 1H), 6.59–6.50 (dd, 1H, J = 17 and 9 Hz), 6.31–6.25 (d, 1H, J = 16.5 Hz), 6.01–5.97 (d, 1H, J = 10 Hz); ^{13}C NMR ($CDCl_3$) δ 135.49, 135.03, 132.56, 128.69, 122.65, 118.59.

Anal. Calcd for $C_8H_8BrNO_2S$: C, 36.65; H, 3.08; N, 5.34; S, 12.23. Found: C, 36.53; H, 3.15; N, 5.05; S, 12.12.

(*b*) *Fraction II, N,N'-bis(p-bromophenyl)-2,2'-dithiodiacetamide* (***14***). Fraction II, which proved to be **14**, had R_f 0.63 and amounted to 0.20 g (44%) of **14** as a white solid: mp 188–189°C (lit.[9] mp, 188–190°C); IR 3250 (b), 3200, 3120, 3060, 1675, 1640 (s), 1610 (s), 1585, 1540 (s), 1480 (s), 1390, 1370, 1320, 1240, 1180, 1120, 1070, 1005, 950, 820 (s) cm^{-1}; ^1H NMR (CD_3OD) δ 7.52–7.49 (d, 2H, J = 8 Hz), 7.44–7.41 (d, 2H, J = 8 Hz), 4.60 (s, b, NH), 3.66 (s, 2H).

Anal. Calcd for $C_{16}H_{14}Br_2N_2O_2S_2$: C, 39.20; H, 2.88; N, 5.72. Found: C, 39.27; H, 2.85; N, 5.77.

The structure of **14** was confirmed by an independent synthesis in which a solution of *p*-bromoaniline (**5**; 0.63 g, 3.66 mmol) in CH_2Cl_2 (40 mL) was added dropwise to one of the acyl halide **10** (0.20 g, 0.91 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred for 2 h, and the resulting suspension was shaken twice with 10 mL of 10% aqueous HCl and twice with 50 mL of H_2O. The solid was removed by filtration, and a solution in EtOAc was dried and then concentrated; yield of **14** as white solid, 0.40 g (89%): mp 188–189°C, undepressed by the **14** obtained from **13**; the TLC R_f and ^1H NMR spectrum were identical with those of **14** from **13**.

Reduction of the coupled ester-sulfonyl chloride ***13*** *with* Na_2SO_3. A solution of 4.18 g (33.2 mmol) of sodium sulfite in 40 mL of H_2O was added slowly (15 min) to a suspension of 3.90 g (8.96 mmol) of the ester-chloride **13** in 50 mL of H_2O, and the mixture was stirred vigorously at 50°C for 1 h; in similar experiments (especially on larger scale), ca. 10–30% of the mass of **13** sometimes then was present as insoluble and presumably polymeric product. The light brown solution (stench) was washed with CH_2Cl_2(2 × 40 mL) and freeze dried. The tan solid obtained was dissolved in 50 mL of MeOH, inorganic salts were removed by filtration, the solution was concentrated to ca. 25 mL, and Et_2O (ca. 150 mL) was added until no more precipitate appeared. The precipitate was removed by filtration and dried at 0.2 torr; yield of solid, 2.00 g [54%, calculated as disodium bis-2-sulfinoethyl 2,2'-dithiodiacetate (**12**)]. The ^1H NMR spectrum (D_2O) had δ 4.45 (t),* 3.93 (s),* 3.80 (s), 3.70 (s) and 2.68 (t);* as will be shown, the asterisked values are attributable to **12**, and the ratio of integrals for δ 3.93:3.80:3.70 was 7:2:1, consistent with a content for **12** of (7) (100)/10 = 70%; the triplets not reported appeared to be embedded in those at δ 2.68 and 4.45. In an effort to purify this crude **12**, the product was redissolved in 15 mL of MeOH and five fractions were precipitated by adding 20 mL of Et_2O successively for each. Fraction 5 (200 mg, ca. 5% yield) showed the integrals corresponding to the singlets at δ 3.93:3.80:3:70 to be 15:1:2, consistent with a content of **12** of (15)(100)/18 = 83%. Attempts to remove the peaks of δ 3.80 and 3.70 completely were unsuccessful despite great losses.

That the largest singlet at δ 3.93, which was used to calculate content of 70–83% of **12**, did in fact arise from **12** was shown by conversion of similarly prepared **12** (95% content of **12**) to the ester **11** (reported above) in a high yield, as predicted from the high content of **12**. Thus 0.100 g (0.23 mmol)

of the 95% **12** was dissolved in 5 mL of MeOH. Methanolic HCl (0.20 mL of 3.5 N; 0.70 mmol) was added, followed by use of ethereal diazomethane and other procedures essentially as for the preparation of **8**. Preparative TLC as with **11** then gave one spot of four at R_f 0.34, which afforded 75 mg (82%) of **11** as yellow gum; the TLC R_f value and the ^{1}H NMR spectrum of this **11** were identical with those of **11** prepared from **8** and **10**, as described above. Hence the ^{1}H NMR spectrum of **12** in D_2O is δ 4.45 (t, 2H), 3.93 (s, 2H), 2.68 (t, 2H).

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