# Organic Disulfides and Related Substances. 38. Some Disulfide and Trisulfide Sulfinate Salts as Antiradiation Drugs[1]

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The trisulfide disulfinate $[NaO_2S(CH_2)_4S]_2S$ (**2**) is an antiradiation drug which is atypical in having no nitrogen function. At low dose levels of 37.5 and 18.8 mg/kg intraperitoneally (ip), **2** protected respectively about 82 and 35% of lethally irradiated mice. By the oral route (po), 150 mg/kg of **2** protected about 73%, and 75 mg/kg protected about 20%. The $LD_{50}$ either ip or po exceeded 900 mg/kg. Although a 2,3-diacetoxy analog **3** was inactive, cyclic disulfide and trisulfide sulfinate analogs showed promise. Among these, a sulfinate moiety is related to a di- or trisulfide moiety in the sense of 1,8 in a naphthyl system (**4, 5**), 2,2′ in a biphenyl system (**6–9**), and $\alpha,\alpha'$ in an *o*-xylyl system (**10, 11**). The 1,8-naphthyl disulfide sulfinate **4** was not tested biologically because a marked neighboring group effect of $-SO_2Na$ on -SS- caused rapid cyclization to the parent disulfide dioxide **14**; the corresponding trisulfide **5** was more stable but only slightly protective. Other analogs lacking the coplanarity of **4** also were more stable. The biphenyl compounds **6** and **7** were quite active ip (e.g., **7** led to 90% survival at 4.6 mg/kg, with $LD_{50}$ = 130 mg/kg, although protection with **6** and **7** at the doses given po was only fair). Dichloro counterparts **8** and **9** offered no advantages over **6** and **7**. The xylylene compounds **10** and **11** were roughly comparable to each other by ip and po routes (e.g., given ip, **10** led to 93–100% survival at 75 mg/kg, with $LD_{50}$ > 950 mg/kg; given po, **10** gave 100% survival at 600 mg/kg, with $LD_{50}$ > 900 mg/kg). Compounds **7** and **11** join **2** as promising antiradiation drugs that lack the usual nitrogen function. The fact that sulfinate salts show activity, both ip and po, suggests that the $-SO_2Na$ moiety deserves more attention in medicinal chemistry. Hydration of sulfinate salts often made analytical characterization difficult. Confirmatory evidence for typical structures is given.

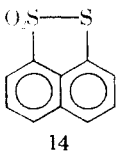
The disulfide sulfinate salt **1** showed promise as an antiradiation drug.[2,3] Results with the trisulfide disulfinate **2** were particularly attractive as a new lead because **2** lacks the nitrogen function common to most antiradiation drugs; hence nitrogen-associated toxic effects would be precluded.[3] Compounds **1** and **2** not only provide excellent protection at doses well below toxic levels by the ip route but also are active po. A 2,3-diacetoxy analog **3** also was reported earlier.[4] Although **3** later proved to be negligibly active (see below), results with **1** and **2** prompted us to synthesize cyclic analogs.

$AcNH(CH_2)_2SS(CH_2)_4SO_2Na$ (**1**) $\quad [NaO_2S(CH_2)_4S]_2S \cdot 2H_2O$ (**2**)

$[NaO_2SCH_2CH(OAc)CH(OAc)CH_2S]_2S \cdot H_2O$ (**3**)

**Chemistry.** Di- and trisulfides were sought that would have the sulfinate moiety in a 1,8 relationship on a naphthyl system (**4, 5**), a 2,2′ relationship on a biphenyl system (**6** and **7**, and their 4,4′-chloro analogs **8** and **9**), and an $\alpha,\alpha'$ relationship on the *o*-xylyl system (**10** and **11**). 2-Acetamidoethanethiol (**12**) was used as its thiolate salt (**13**) for making the disulfides **6, 8,** and **10**; other thiols, of course, may lead to better activities than the model **12**.

We prepared the cyclic analog **4** of **1** (eq 1), but it recyclized so rapidly in solution to **14** that **4** was not tested as a drug (eq 1);[4] presumably coplanarity of the $NaO_2S$- and -SS- moieties in **4** greatly enhances a neighboring-group attack of $-SO_2Na$ on the -SS- bond.[4]



**14**

$\xrightleftharpoons{AcNH(CH_2)_2SNa\,(13)}$ $NaO_2SRSS(CH_2)_2NHAc \cdot H_2O$ (**4**) (1)

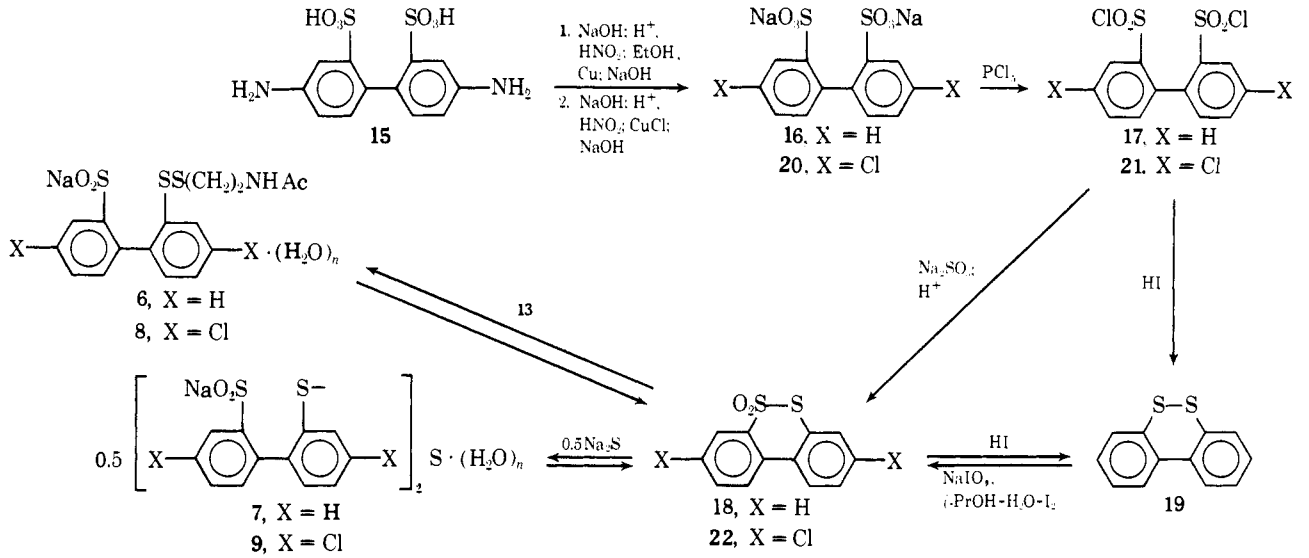
$\xrightleftharpoons{0.5Na_2S}$ $0.5[NaO_2SRS]_2S \cdot 2\text{–}5H_2O$ (**5**) (2)

R = 1,8-$C_{10}H_6$

The trisulfide **5** could be obtained in methanol, however, by adding $Na_2S$ to the dioxide **14** (eq 2). Ether then precipitated $5 \cdot 5H_2O$ (90%), which could be purified only by reprecipitation. Like sulfinate salts reported earlier,[3,4] **5** is quite hygroscopic and readily acquires enough moisture to give hydrates (without contact with water per se, except from $Na_2S \cdot 9H_2O$). Hydration, and perhaps also the difficulty of purifying the sensitive **5**, precluded good elemental analysis for a single hydrated species. NMR spectra of **5** and other sulfinates discussed seemed unlikely to be satisfactory because the NMR spectrum of such a compound begins to change almost as soon as it is dissolved owing to recyclization.[4] Ir spectra (particularly, strong $-SO_2Na$ absorption at ~960 and 1020 $cm^{-1}$), however, and conversion of water-insoluble **14** to the highly water-soluble salt **5** reassure one as to the identity of **5**; reaction of 2 mol of **14** (eq 2), rather than only one, was evidenced by absence of **14** after the reaction. The same comments about hydration, spectra, and structure can be made about other sulfinate salts discussed below (cf. Experimental Section).

Scheme I shows the synthesis of biphenyl analogs **6** and **7**, as well as of chlorobiphenyl analogs **8** and **9**; **8** and **9** were synthesized because of the profound influence halogen substituents may have on biological activity.[5] Synthesis of the requisite disulfide dioxide was reported by Barber and Smiles,[6] through a sequence that involved copper-induced coupling of sodium 2-iodobenzenesulfonate to give **16**, followed by the sequence **16** → **17** → dioxide **18** (Scheme I). Attempts to repeat this preparation of **16** gave unpromising results (cf. also ref 7), but we were able to synthesize **18** by the sequence in Scheme I of **15** (1) → **16** → **17** → **18**. The acid corresponding to salt **16** was obtained by adapting an earlier method;[7] the (more soluble) disodium salt of **15** was diazotized, after which deamination and neutralization led to **16**. Use of hypophosphorous acid for deamination gave lower yields of **16** in less clean reactions, and separation of phosphate salts proved difficult. The disulfonyl chloride **17**, obtained from **16** using $PCl_5$,[6] showed appropriate ir bands and good agreement with earlier melting points.[6,7] The dioxide **18** was obtained by reducing **17** and acidifying,[6] presumably via the disulfinic acid. **18** had an appropriate elemental analysis and ir spectrum but at first had the previously unreported constant melting point of 115–116°; later, only melting points of a different form (mp

**Scheme I**




125–126°)[6] could be obtained. As Scheme I shows, the structure of 18 was confirmed by reducing it with HI to the disulfide 19 and then reoxidizing to 18 by a recent procedure for oxidizing disulfides to the 1,1-dioxides (Scheme I).[4,8] The structure of 19 in turn was confirmed by reducing disulfonyl chloride 17 using HI.

For synthesis of the disulfide sulfinate 6, dioxide 18 was cleaved with the thiolate salt 13 of 2-acetamidoethanethiol (12, Scheme I). The ir spectrum was consistent with structure 6. The trisulfide 7 was prepared as a highly hygroscopic hexahydrate by adding $Na_2S$ to dioxide 18 in methanol. Ether then precipitated 7, which was purified by reprecipitation. As with the naphthyl trisulfide sulfinate 5, hydration and the difficulty of purifying the sensitive 7 precluded good elemental analysis. Also as with 5, however, ir spectra and conversion of water-insoluble 18 to a highly water-soluble salt 7 substantiated the identity of 7.

For synthesis of the chloro analogs 8 and 9, the sequence was that of the unsubstituted series except for use of the Sandmeyer reaction instead of deamination, i.e., 15 (2) → 20 → 21 → 22 → 8 or 9 (Scheme I). The success of this sequence further confirms the structures of the unsubstituted series. Both 8 and 9 were very hygroscopic and were isolated as hydrates particularly difficult to obtain as single hydrated species.

Hydration was more of a problem with trisulfide disulfinates than with disulfide sulfinates, perhaps because of two sulfinate moieties per molecule rather than one. Complications in analytical characterization besides hydration may be partial solvation by methanol (since the only purification found was to precipitate the salts from methanol using ether), as well as cyclization or disproportionation prior to final precipitation from methanol.

Comparison of the relative ease of cyclization of some of the salts, according to the reverse sense of eq 1 and 2, was possible by extracting the dioxides at various times from aqueous solutions of the salts. The results suggest that the ease of reversion is 4 > 5 > 6 ~ 7. The naphthyl series thus does indeed cyclize faster than the biphenyl series (our impression from our earlier work,[4] though only qualitative, is that the xylyl compounds 10 and 11 probably cyclize more slowly than either of the other series). The disulfides cyclize somewhat more readily than the trisulfides, but explanations for this behavior at present would be speculative.

**Biological Results.** Table I shows some new results with 1 for comparison, together with new results at lower doses for 2. The surprising inactivity of 3 suggests a marked effect of substitution on activity (Table I). As mentioned, 4 was not tested because of the extreme ease of cyclization. Although 5 seemed sufficiently more stable than 4 to be a feasible drug, it afforded only slight protection (Table I), perhaps because of its strongly basic pH in solution or of a lower solubility that affected absorption.

Our conclusions as to the cause of the great reactivity of 4 suggested that stability might be enhanced in other systems if the sulfinate and di- or trisulfide moieties were less constrained to be coplanar. This thought led to the biphenyl counterparts 6 and 7. Table I shows that 6 and 7 were quite active when administered ip and fair when given po. With 6 given ip, toxic deaths occurred at high doses following irradiation, while somewhat lower doses produced severe liver damage. At doses that did not produce liver damage, protection was apparent by both ip and po routes. The trisulfide 7 led to side effects like those with 6, and the two seemed roughly comparable. Perhaps lower doses of 6 would have led to further increases of activity like those seen with 7; perhaps also, activities of both 6 and 7 by the oral route would improve at lower doses.

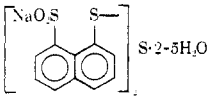
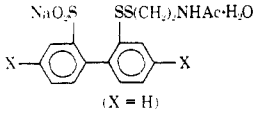
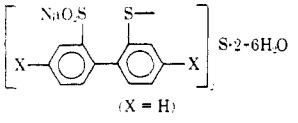
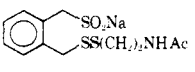
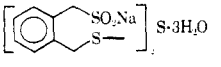
The dichloro disulfide 8 was more toxic and less promising at low doses than its hydrogen counterpart 6. The dichloro trisulfide 9 was roughly comparable to 8. Hence, 8 and 9 offer no advantages over the hydrogen prototypes 6 and 7.

As discussed above, the $\alpha,\alpha'$-*o*-xylene analogs 10 and 11, available from earlier work,[4] qualitatively seemed to recyclize less readily to the dioxide than did the naphthyl or biphenyl counterparts. Table I shows that they afford promising protection after both ip and po administration and are roughly comparable to each other. The po activity, however, seems superior to that of 6 and 7.

Conceivably, the protective activities of 1–3 and 5–11 may result from products of rapid chemical reaction and/or rapid biotransformation rather than from 1–3 or 5–11 per se. Possible reaction products (with parenthetical comment about probable activity) include 2-acetamidoethyl disulfide (inactive),[3] cyclic disulfide dioxides (activity unlikely because of sparing solubility), sulfide ion (unlikely, since 3 is inactive), disulfide bissulfinates (at least one is active),[3] thiolate ion (2-mercaptoethylamine is active but insufficiently so to account for many of the present activities; Table I, footnote e), or hydrodisulfide ions.

In summary, 1, 2, 6, 7, 10, and 11 are promising antiradiation drugs that protect at low doses ip, although only 1, 2, 10, and 11 seem significantly protective po. Compounds 7

Table I. Protection of Mice against γ Radiation by Disulfide and Trisulfide Sulfinate Salts

| Compd | Structure | $LD_{50}$, mg/kg[a] | Test dose, mg/kg[b] | Vehicle[c] | pH of soln admin[d] | Survival, 30 days, %[e] |
|---|---|---|---|---|---|---|
| 1[f] | $AcNH(CH_2)_2SS(CH_2)_4SO_2Na$ | 694–800 ip | 185 ip | NaCl | 7.0 | 67[f] |
| | | | 90 ip | NaCl | 7.0 | 33[f] |
| | | | 45 ip | NaCl | 7.0–7.1 | 33–40[f] |
| | | 1050 po | 278 po | $H_2O$ | 7.0 | 100 |
| 2[g] | $[NaO_2S(CH_2)_4S]_2S \cdot 2H_2O$ | >950 ip | 37.5 ip | NaCl | 6.3–7.0 | 73, 80, 93 |
| | | | 18.8 ip | NaCl, $H_2O$ | 6.3–7.1 | 30–40 |
| | | | 9.4 ip | $H_2O$ | 7.1 | 0 |
| | | >900 po | 150 po | $H_2O$ | 6.6 | 73 |
| | | | 75 po | NaCl, $H_2O$ | 6.3–6.6 | 13–27 |
| | | | 37.5 po | NaCl | 6.3 | 13 |
| 3[g] | $[NaO_2SCH_2CH(OAc)CH(OAc)CH_2S]_2S \cdot H_2O$ | >900 ip | 300 ip | $H_2O$ | 7.0 | 0 |
| | | | 150 ip | $H_2O$ | 7.0 | 7 |
| | | >900 po | 600 po | $H_2O$ | 7.3 | 7 |
| | | | 300 po | $H_2O$ | 7.0 | 0 |
| 5[h] |  | 135 ip | 75 ip | Mc/Tw | 9.2 | 20[i] |
| | | | 50 ip | Mc/Tw | 8.3 | 18 |
| | | | 37.5 ip | Mc/Tw | 9.2 | 10 |
| | | | 25 ip | Mc/Tw | 8.3–8.7 | 10–30 |
| | | | 12.5 ip | Mc/Tw | 8.7 | 10 |
| | | >600 po | 500 po | Mc/Tw | 9.0 | 10 |
| 6[h] |  | >600 ip[j] | 300 ip | $H_2O$ | 6.5 | 0[i] |
| | | | 250 ip | $H_2O$ | 6.5 | 40[k] |
| | | | 125 ip | $H_2O$ | 6.5 | 10[k] |
| | | | 80 ip | NaCl | 6.5 | 50[k] |
| | | | 40 ip | NaCl | 6.5 | 70 |
| | | >900 po | 500 po | $H_2O$ | 7.0 | 0 |
| | | | 250 po | $H_2O$ | 7.0 | 30 |
| 7[h] |  | 130 ip[j] | 100 ip | NaCl | 5.9 | 0 |
| | | | 50 ip | NaCl | 5.9 | 0 |
| | | | 40 ip | NaCl | 6.0 | 10[k] |
| | | | 20 ip | NaCl | 6.0 | 80 |
| | | | 10 ip | NaCl | 6.0 | 70 |
| | | | 9.2 ip | NaCl | 6.0 | 90 |
| | | | 5.0 ip | NaCl | 5.5 | 70 |
| | | | 4.6 ip | NaCl | 5.2 | 90 |
| | | | 2.5 ip | NaCl | 5.5 | 10 |
| | | >900 po | 500 po | $H_2O$ | 6.0 | 20 |
| | | | 250 po | $H_2O$ | 5.8–6.0 | 30–40 |
| | | | 125 po | $H_2O$ | 5.8 | 30–40 |
| 8[h] | 6, with X = Cl; $\cdot 3H_2O$ | 200 ip[j] | 100 ip | NaCl | 6.7 | 50[k] |
| | | | 50 ip | NaCl | 6.7 | 0 |
| | | | 25 ip | NaCl | 5.3 | 0 |
| | | >1000 po | 1000 po | $H_2O$ | 8.0 | 40 |
| | | | 500 po | $H_2O$ | 8.0 | 10 |
| 9[h] | 7, with X = Cl; $\cdot 3H_2O$ | 125 ip[j] | 100 ip | NaCl | 6.5 | 67[k] |
| | | | 50 ip | NaCl | 6.3–6.5 | 10–20[k] |
| | | | 20 ip | NaCl | 6.5 | 0 |
| | | | 10 ip | NaCl | 6.5 | 0 |
| | | >900 po | 500 po | $H_2O$ | 6.5 | 30 |
| | | | 250 po | $H_2O$ | 6.5 | 0 |
| 10[g] |  | >950 ip | 300 ip | $H_2O$ | 7.2 | 93 |
| | | | 150 ip | $H_2O$ | 7.2 | 100 |
| | | | 75 ip | $H_2O$ | 7.2 | 93–100 |
| | | | 37.5 ip | $H_2O$ | 7.2 | 20 |
| | | >900 po | 600 po | $H_2O$ | 7.4 | 100 |
| | | | 300 po | $H_2O$ | 7.4 | 33 |
| 11[h,l] |  | 750 ip | 446 ip | $H_2O$ | 5.7 | 100 |
| | | | 223 ip | $H_2O$ | 5.7 | 100 |
| | | | 200 ip | $H_2O$ | 5.7 | 80 |
| | | | 100 ip | $H_2O$ | 5.7 | 80 |
| | | | 50 ip | $H_2O$ | 5.7 | 20 |
| | | >800 po | 800 po | $H_2O$ | 5.7 | 90 |
| | | | 400 po | $H_2O$ | 5.7 | 0 |

*Footnotes to Table I*

[a]Approximate $LD_{50}$ for the compound in nonirradiated mice; ip = intraperitoneal administration, po = oral administration. [b]Test doses were administered 15 min before irradiation when ip and 15–30 min before when po. Doses shown are the milligrams per kilograms of free acid calculated to correspond to the salt actually used. [c]Physiological saline solution (NaCl) or $H_2O$ was used as vehicle for soluble agents; Mc/Tw (a suspending medium consisting of 0.2% methylcellulose, 0.4% Tween-80, and 0.9% NaCl) was used for sparingly soluble agents. [d]Unadjusted. Change of the natural pH of the salt solution seemed likely to induce cyclization to the parent disulfide dioxide (cf. ref 4). [e]For comparison, 2-mercaptoethylamine had an ip $LD_{50}$ of 250 mg/kg and afforded 100% survival at an ip dose level of 150 mg/kg; po, it had an $LD_{50}$ of 625 mg/kg and afforded 73% survival at a dose of 300 mg/kg. [f]These results, included for comparison, are considered better than those of ref 3. The ip results were obtained using lethal radiation of 950 rads at 30–40 rads/min from a $^{60}Co$ source. The po result was obtained using 975 rads (230 rads/min) from $^{60}Co$. [g]Procedures were those of ref 3 (975 rads, 230 → 200 rads/min, $^{60}Co$ source). [h]Irradiation using $^{137}Cs$ at a dose of 849 rads and dose rate of 141.5 → 139.6 rads/min. [i]Deaths attributed to toxicity of drug. [j]At doses near the $LD_{50}$, mice showed severe liver damage. [k]Survivors showed hepatitis and ascites. [l]Changes may have occurred in 11 during 22 months of storage, before it could be tested, even though it was kept at −20° meanwhile.

and **11** thus join **2** in sharing the noteworthy lack of nitrogen present in most significantly active antiradiation drugs. Of the group in Table I, however, **1** and **2** seem the most promising. It is worth adding that the activity, both ip and po, of the sulfinate salts reported in Table I suggests that the $-SO_2Na$ moiety deserves more attention than it has received in medicinal chemistry.

## Experimental Section

Melting points, determined in capillary tubes using a Thomas-Hoover liquid-bath apparatus, are corrected. Decomposition points of the sulfinate salts, usually done at a temperature increase ~3–4°/min, were not very helpful (shrinking, darkening) and often varied by 10–15°. Ir spectra were obtained using KBr pellets and a Beckman Model IR10 spectrophotometer; bands reported were at least of medium intensity. TLC spots were obtained using Brinkmann F-254 precoated sheets of silica gel (0.25 mm) on Al and were developed by exposure to $I_2$ vapor in a sealed container. Elemental analyses were by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Where analyses are indicated only by symbols of the elements, analytical results for those elements were within +0.4% of the theoretical values.

Procedures for testing antiradiation agents described earlier were used,[9] with the following modifications. Mice were female inbred Charles River strain 8–9 weeks old, weighing 25–30 g, from the Walter Reed Animal Colony. Groups of ten were treated ip or po with maximum tolerated doses of drugs (ca. $LD_0$ from a toxicity estimate, usually ca. ½ to ⅔ of the $LD_{50}$), as well as lower doses. Solutions or suspensions of the drugs were freshly prepared prior to testing (the pH was not adjusted to obviate conversion to disulfide dioxides; cf. ref 4). The volumes (milliliters) of drug solutions injected did not exceed 2% of mouse body weight (in grams). Drugs were administered ip 15 min before exposure of mice to whole body irradiation lethal to controls (849 rads) or po 15–30 min prior to exposure. The mice were irradiated in a specially designed small-animal $^{137}Cs$ γ irradiator which had a dose rate that ranged from 140.9 to 139.6 rads/min during the irradiations. Equal numbers of vehicle-injected control mice were irradiated simultaneously with the treated mice and thereafter housed jointly. mortality was recorded over a 30-day period. Mice were given food and $H_2O$ ad libitum. The drinking $H_2O$ contained 15 ppm of $Cl_2$ to suppress growth of *Pseudomonas aeruginosa*.[10] The principles of laboratory animal care as promulgated by the National Society for Medical Research were observed throughout.

**Disodium 8,8′-Trithiobis(1-naphthalenesulfinate) (5).** A solution of commercial $Na_2S·9H_2O$ (2.9 mmol) in MeOH (5 ml) was added *slowly* to the dioxide **14** (1.30 g, 5.80 mmol)[4] in MeOH (25 ml) at 25° with good stirring during 30 min. The pH of the mixture went below 7 at first but soon rose to 7. After the addition was complete, the clear solution (pH 7) showed only one spot for **5** by TLC (1:1 MeOH–$Me_2CO$) and none for **14** (a control spot of **14** was well resolved from **5**). Addition of $Et_2O$ (600 ml) at 0° gave a white precipitate. Most of the solvent was decanted, after which drying at 0.1 mm gave 1.60 g (90%, calculated as $5·5H_2O$) of white **5**, mp ~233–235° dec. This **5** was dissolved in a little MeOH, and a small amount of dry $Et_2O$ was added until cloudiness occurred. A colorless clear solution resulted upon removal of the small amount of precipitate by centrifugation as quickly as possible. Dry $Et_2O$ again was added to this solution until appearance of white precipitate was complete. Decantation and drying at 0.1 mm for 24 hr at ~25° gave 1.30 g of **5**, mp ~233–235° dec. TLC showed one spot (1:1 MeOH–$Me_2CO$); ir ~3400 ($H_2O$), ~1640 ($H_2O$), 1020 and 960 ($SO_2^-$), and 760 $cm^{-1}$. Anal. [($C_{20}H_{12}Na_2O_4S_5·5H_2O$ → $C_{20}H_{12}Na_2O_4S_5·2H_2O$, after rigorous drying) $H_2O$: calcd, 8.82; found, 8.27] ($C_{20}H_{12}Na_2O_4S_5·2H_2O$) C, S; H: calcd, 2.86; found, 2.39.

**Disodium 2,2′-Biphenyldisulfonate (16).** 4,4′-Diamino-2,2′-biphenyldisulfonic acid (**15**, 34.4 g, 100 mmol)[†] was suspended in $H_2O$ (300 ml) and neutralized with a solution of NaOH (150 ml). Diazotization then was carried out between −5 and −2° by adding $NaNO_2$ (17.2 g, 250 mmol) in $H_2O$ (100 ml) to the cold solution, followed slowly (45 min) by dilute $H_2SO_4$ (concentrated acid, 40 ml, and ice, 200 g). The bisdiazonium salt that separated within 15 min was kept at −3 to −5° for 1 hr (it decomposes above ca. −1°) and then was rapidly separated by filtration. It was dried between filter papers and added to absolute EtOH (400 ml). On addition of Cu powder (1.0 g), the bisdiazonium salt decomposed (2 hr). The solution then was evaporated to dryness, and the residue was dissolved in $H_2O$, neutralized with 10% NaOH, boiled with charcoal, filtered, and evaporated to dryness: yield of **16**, 14.3 g (40%).

**2,2′-Biphenyldisulfonyl Chloride (17).** In a procedure based on an undetailed one of Barber and Smiles,[6] very finely powdered **16** (8.90 g, 24.9 mmol) was intimately mixed with $PCl_5$ (15.6 g, 74.9 mmol), and the reaction mixture was heated at 100° for 6 hr. After 1 hr more at ~25°, the mixture was decomposed with crushed ice. The white product that resulted was removed by filtration and was recrystallized (without being dried) from AcOH to give **17** as needles (5.20 g, 60%): mp 142–143° (lit. mp 138°,[6] 142–144°[7]). This **17** showed strong ir bands at 1180 and 1370 $cm^{-1}$ ($SO_2Cl$).

**Dibenzo[*c,e*]-*o*-dithiin 5,5-Dioxide (18) from 17.** In a procedure based on an undetailed one of Barber and Smiles,[6] the disulfonyl chloride **17** (3.50 g, 10.0 mmol) was mixed with $Na_2SO_3$ (6.3 g, 50 mmol) in 100 ml of $H_2O$, and the reaction mixture was heated under reflux with good stirring for 6 hr. The mixture then was acidified with concentrated HCl to a pH of ~1 and was further heated for ~15 min. The reaction mixture then was allowed to stand at ~25° for 2 hr, during which white **18** gradually separated. Filtration and recrystallization from EtOH gave **18** as white needles (1.00 g, 40%): mp 115–116° (lit.[6] mp 128°). An analytically pure sample of constant mp 115–116° was obtained after three recrystallizations from EtOH. This **18** showed ir bands at 1460–1440, 1420, 1310 ($SSO_2$), 1150 ($SSO_2$), 750, and 700 $cm^{-1}$. Anal. ($C_{12}H_8O_2S_2$) C, H, S. Later preparations had a constant melting point of 125–126° and, thereafter, we never encountered the lower melting form again.

**Reduction of Dioxide 18 to Dibenzo[*c,e*]-*o*-dithiin (19).** As reported without detail,[6] the dioxide **18** (1.00 g, 4.02 mmol) was dissolved in AcOH (10 ml), and HI (3 ml, sp gr 1.7) was added dropwise during 15 min with stirring of the reaction mixture at 60–70°. $I_2$ separated immediately. The reaction mixture was stirred for 12 hr at 60–70° and then was poured into cold $H_2O$ (200 ml). The $I_2$ present was destroyed with a solution of sodium thiosulfate. Filtration and recrystallization from glacial AcOH yielded **19** as shining yellow needles (0.60 g, 69%): mp 112–113° (lit.[6] mp 113°). This **19** was identical in all respects (mp, mmp, and ir) with the authentic disulfide **19** obtained by reduction of **17** with HI. Formation of disulfide **19** was evidenced by the disappearance of ir bands at 1310 and 1150 $cm^{-1}$ ($SSO_2$) from the dioxide **18**. Anal. ($C_{12}H_8S_2$) C, H, S.

**Oxidation of Disulfide 19 to Dioxide 18.** An aqueous solution of $NaIO_4$ (2.50 g, 11.7 mmol, in 20 ml of $H_2O$) was added gradually to a solution of disulfide **19** (1.00 g, 4.63 mmol) in *i*-PrOH (25 ml) containing a crystal of $I_2$. The reaction mixture then was stirred at

[†]The 4,4′-diamino-2,2′-biphenyldisulfonic acid (**15**) was from Distillation Products Industries. The purity was stated to be 70%. The assumption was made that the impurity was inert, and actual weights used were (weights of **15** reported)/0.7.

80° for 4 hr, $I_2$ was destroyed with aqueous sodium thiosulfate, solvent was removed, and the residue was extracted with $CHCl_3$. Removal of $CHCl_3$ gave 0.70 g (61%) of dioxide 18 which was recrystallized from EtOH: mp 125–126°. This 18 was identical in all respects (mp, mmp, and ir) with 18 obtained from reduction of 17 with $Na_2SO_3$.

**Reduction of 17 to 19 with HI.** In an adaptation of a reported procedure,[7] 17 (3.51 g, 10.0 mmol) was dissolved in AcOH (20 ml) and HI (5 ml, sp gr 1.7) was added during 20 min with stirring at 50–60°. The mixture was stirred (12 hr, 50–60°) and poured into cold $H_2O$ (200 ml), and $I_2$ was destroyed as usual. Filtration and recrystallization from glacial AcOH yielded 19 (1.01 g, 47%), mp 112–113° (lit.[7] mp 113–114°).

**Sodium 2′-(2-Acetamidoethyldithio)-2-biphenylsulfinate (6).** The dioxide 18 (1.24 g, 5.00 mmol) was suspended in MeOH (10 ml) and was mixed intimately with 2-acetamidoethanethiol (12, 0.595 g, 5.00 mmol).[11] This mixture was cooled to 0°. A solution of NaOMe from 0.115 g of Na (5.00 mmol) and 10 ml of MeOH also was cooled to 0° and then was added dropwise (10 min) to the solution of 18 with stirring. The resulting solution at first dropped to pH ~4 but then became slightly basic. A large excess of $Et_2O$ (400 ml) was added to precipitate the sulfinate salt 6. The ethereal layer was decanted, and the residue was redissolved in ~3 ml of MeOH. Centrifugation and decantation gave a clear solution, to which 100 ml of $Et_2O$ was added. White 6 precipitated. Decantation and drying of this 6 at 0.1 mm for 24 hr at ~25° gave 1.40 g (69%, calculated as $6{\cdot}H_2O$) of white 6: mp ~194–196° dec. TLC showed one spot (1:1 MeOH–$Me_2CO$). Additional TLC spots appeared after 6 had been dissolved for a few minutes in $H_2O$ or (longer) in MeOH; ir 3240, 1640, 1540, 1430, 1300, 1040, 970, 750, and 690 $cm^{-1}$. Anal. [$(C_{16}H_{16}NNaO_3S_3{\cdot}H_2O)$ $H_2O$: calcd, 4.42; found, 5.02] ($C_{16}H_{16}NNaO_3S_3$; anhydrous, after rigorous drying) C, H, S.

**Disodium 2′,2′-Trithiobis(2-biphenylsulfinate) (7).** A solution of commercial $Na_2S{\cdot}9H_2O$ (2.50 mmol) in MeOH (10 ml) was added slowly to a suspension of dioxide 18 (1.24 g, 5.00 mmol) in MeOH (20 ml) at 0–5° with good stirring during 10 min. After addition was complete (the pH then was 7), the reaction mixture showed one somewhat diffuse and irregular spot for sulfinate salt 7 by TLC (1:1 MeOH–$Me_2CO$). Addition of $Et_2O$ (400 ml) at 0° gave a white precipitate. As much as possible of the solvent was decanted, after which drying at 0.1 mm gave 1.93 g (113%, calculated as $7{\cdot}6H_2O$) of 7 as a white powder: mp ~186–188° dec. This 7 was dissolved in MeOH (~5 ml) and a small amount of $Et_2O$ was added until cloudiness began to appear. A colorless clear solution then resulted upon removal of the small amount of precipitate by centrifugation as quickly as possible. Dry $Et_2O$ again was added to the decanted clear solution until appearance of a white precipitate was complete. Decantation and drying at 0.1 mm for 24 hr at ~25° gave 1.81 g (106%, calculated as $7{\cdot}6H_2O$) of 7: mp ~186–188° dec. TLC showed one spot (1:1 MeOH–$Me_2CO$). Additional spots appeared a few minutes after 7 had been dissolved in $H_2O$ or (longer) in MeOH; ir 3300, 1620, 1450, 1420, 1010, 960, and 750 $cm^{-1}$. Anal. [$(C_{24}H_{16}Na_2O_4S_5{\cdot}6H_2O \rightarrow C_{24}H_{16}Na_2O_4S_5{\cdot}2H_2O$, after rigorous drying) $H_2O$] ($C_{24}H_{16}Na_2O_4S_5{\cdot}2H_2O$) H; C: calcd, 47.22; found, 47.91. S: calcd, 26.23; found, 25.39.

**4,4′-Dichloro-2,2′-biphenylsulfonyl Chloride (21).** The diaminodisulfonic acid 15 (34.4 g, 100 mmol)† was converted to the bisdiazonium salt as for 16. This salt was separated by filtration as before and was gradually added in many portions (30 min) to a freshly prepared solution of 30 g of commercial CuCl in 100 ml of concentrated HCl. The reaction mixture was warmed until evolution of $N_2$ ceased (2 hr). Filtration, evaporation to dryness, and extraction with absolute EtOH afforded the required dichlorodisulfonic acid, which was neutralized with NaOH to give 21.3 g (50% yield) of the crude disodium salt 20.

Very finely powdered 20 (8.54 g, 20.0 mmol) was intimately mixed with $PCl_5$ (12.48 g, 60.0 mmol). Subsequent steps of heating (100°, 6 hr), standing, treatment with ice, and recrystallization from AcOH were carried out as in the preparation of 17: yield of 21 as white amorphous powder, 7.1 g (85%); mp 128–129°; strong ir bands at 1180 and 1370 $cm^{-1}$. Anal. ($C_{12}H_6Cl_4O_4S_2$) C, H, S.

**3,8-Dichlorodibenzo[*c,e*]-*o*-dithiin 5,5-Dioxide (22).** The dichlorodisulfonyl chloride 21 (4.2 g, 10.0 mmol) was reduced as for 18 from 17 except that 7.5 g (59.5 mmol) of $Na_2SO_3$ was used. Recrystallization from EtOH gave 22 as a yellow powder (1.40 g, 44%): mp 225–226°; ir 1580, 1450, 1320, 1140, 870, 820, and 680 $cm^{-1}$. Anal. ($C_{12}H_6Cl_2O_2S_2$) C, H, Cl, S.

**Sodium 2′-(2-Acetamidoethyldithio)-4,4′-dichloro-2-biphenylsulfinate (8).** Essentially as for the conversion of 18 to 6, a mixture of dioxide 22 (0.63 g, 2.0 mmol) and the thiol 12 (0.24 g, 2.0 mmol)[11] was cooled in MeOH (10 ml) to 0°. Cold methanolic NaOMe from Na (46.0 mg, 2.0 mmol) and MeOH (10 ml) was added, and 8 was isolated as before: 0.74 g (73% yield, calculated as $8{\cdot}3H_2O$). One reprecipitation in the usual way led to still impure 8; hence, the reprecipitated product was dissolved again in MeOH (5 ml) and enough $Et_2O$ was added to precipitate an estimated 20% of 8. After centrifugation, the mother liquor was separated and was diluted with more $Et_2O$ to precipitate an estimated 60% of the original 8 (the mother liquor containing the remaining 20% of the crude 8, after centrifugation, then was discarded). 8 then was dried at 0.1 mm for 24 hr: mp ~280–282°; ir 3400, 1640, 1580, 1550, 1450, 1200, 1030, 970, and 820 $cm^{-1}$. Anal. [$(C_{16}H_{14}Cl_2NNaO_3S_3{\cdot}3H_2O \rightarrow C_{16}H_{14}Cl_2NNaO_3S_3{\cdot}H_2O$, after rigorous drying) $H_2O$: calcd, 7.03; found, 6.57] ($C_{16}H_{14}Cl_2NNaO_3S_3{\cdot}H_2O$) C, H; Cl: calcd, 14.91; found, 13.80.

**Disodium 2′,2′-Trithiobis(4,4′-dichloro-2-biphenylsulfinate) (9).** As in the conversion of 18 to 7, a solution of commercial $Na_2S{\cdot}9H_2O$ (2.50 mmol) in MeOH (10 ml) was added to 22 (1.58 g, 5.0 mmol) suspended in MeOH (20 ml) at 0–5°. Precipitation from MeOH with $Et_2O$ gave 1.40 g (73%, calculated as $9{\cdot}3H_2O$) of white powdery 9. A second fractional reprecipitation was carried out as described for 8, and the latter white powder was dried at 0.1 mm for 24 hr: mp ~220–225° dec; ir 3380, 1630, 1580, 1440, 1380, 1230, 1030, 970, 820, and 780 $cm^{-1}$. Anal. [$(C_{24}H_{12}Cl_4Na_2O_4S_5{\cdot}3H_2O \rightarrow C_{24}H_{12}Cl_4Na_2O_4S_5$, after rigorous drying) $H_2O$: calcd, 7.13; found, 6.56] ($C_{24}H_{12}Cl_4Na_2O_4S_5$) Cl; C: calcd, 40.23; found, 41.12. H: calcd, 1.68; found, 2.39.

**Relative Ease of Cyclization.** A solution of 5.00 g of 5, 6, or 7 in 100 ml of $H_2O$ at ~25° was extracted periodically with $CHCl_3$. Evaporation of the extract and drying to constant weight gave the dioxide 14 or 18, the cumulative yields of which (calculated on the basis of equations like 1 or 2) are shown in Table II. The dioxides were identified by mixture melting point and ir. Owing to the uncertainty as to the extent of hydration of 5, 6, or 7, the results should be considered only as approximations.

**Table II.** Yields of Dioxides (14 or 18) by Cyclization of Disulfide and Trisulfide Sulfinate Salts (~25°)

| Compd | Conversion to dioxide in hr of standing, % | | | |
|---|---|---|---|---|
| | 0.17 hr | 4 hr | 8 hr | 16 hr |
| 4[a] | 43[a] | 59[a] | 69[a] | 77[a] |
| $5 \cdot 5H_2O$[b] | 23 | 35 | 41 | 45 |
| $6 \cdot H_2O$[b] | 15 | 25 | 32 | 36 |
| $7 \cdot 6H_2O$[b] | 14 | 24 | 30 | 34 |

[a] Previous results, entered for comparison (ref 4). Compound 4 never could be obtained quite pure. The calculations are based on anhydrous 4; to the extent 4 actually was hydrated, the percent yields would be even greater. [b] The product apparently ordinarily in hand prior to rigorous drying.

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