Organic Disulfides and Related Substances. 46. Derivatives of 2-(Benzylsulfinyl)ethanethiol[1]

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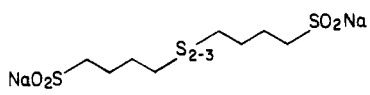
In a further study of the little known class of mercapto sulfoxides and their derivatives 2-(benzylsulfinyl)-ethanethiol (**9a**) could be kept only for minutes at ca. 25 °C in CH_2Cl_2, but the key intermediate, *S*-[2-(benzylsulfinyl)ethyl] *p*-toluenethiosulfonate (**17**), was quite stable; **17** was prepared by reaction of 2-(benzylsulfinyl)ethyl chloride (**7**) with sodium *p*-toluenethiosulfonate (**10**). Reaction of the thiosulfonate **17** with Na_2S under usual conditions gave 2-(benzylsulfinyl)ethyl disulfide (**8**), rather than the expected trisulfide (**11**), but a two-phase reaction with dilute solutions protected the trisulfide and led to **11** (69% yield); aqueous Na_2S converted **11** to **8**. Reaction of **17** with a thiol, RSH, under usual conditions gave only the symmetrical disulfide, RSSR, but unsymmetrical disulfides could be obtained at −70 °C [$PhCH_2S(O)(CH_2)_2SSR''$ with R'' = *p*-ClC_6H_4 (**12**), Ph (**13**), *p*-MeC_6H_4 (**14**), C_6H_{11} (**15**), and $(CH_2)_4SS(CH_2)_2S(O)CH_2Ph$ (**16**)]. Solutions of **12–16** resisted change for 21–66 h in the dark, for 19–66 h in ambient light, for 7–11 h in refluxing EtOAc (dark), and for 19–36 h in refluxing EtOH (dark); in UV light, however, reaction began in 7–20 min. The order of increasing resistance to change, under all conditions, was **12** < **16** ≲ **13** < **14** < **15**. The di- (**8**) and trisulfide (**11**) were much more resistant than any of the unsymmetrical disulfides under all conditions. Neighboring group effects of the –S– and –S(O)– functions appeared to play a role in several instances.

Di- and trisulfinate salts of structure **1**, as well as disulfide sulfinates of structure **2**, are of considerable interest



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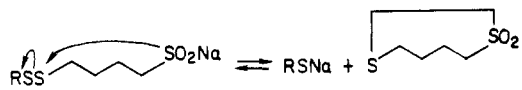
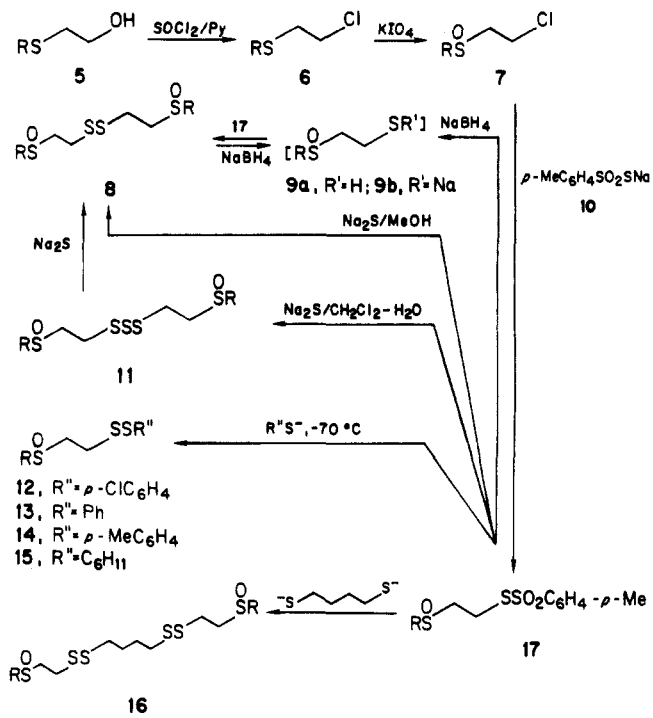
for protection against ionizing radiation.[2] Unfortunately, sulfinate salts often show variable hydration and present analytical problems;[2b,3] they also may be difficult to prepare and may be unstable over long periods.[2a] An important feature in the radioprotective activity of compounds like **1** and **2** seems likely to be the neighboring group capability of the $-SO_2Na$ group, as illustrated in eq 1.[2c] Since sulfinyl groups are well known to be capable



2 (1)

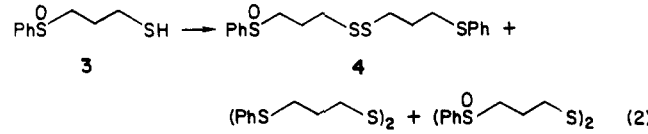
of neighboring group participation,[4] the possibility was attractive that –S(O)– might be advantageously substituted for $-SO_2Na$ in antiradiation candidates. A second motivation for study of the requisite derivatives envisioned of mercaptoalkyl sulfoxides lay in extending the chemistry of this class, which has been unknown until recently.[5] Earlier work on mercapto sulfoxides showed that 3-(phenylsulfinyl)propanethiol (**3**) underwent rapid oxidation–

Scheme I[a]



[a] R = $PhCH_2$.

reduction at ca. 25 °C to give chiefly **4** (eq 2), along with the other two products shown in eq 2.[5] The present paper



3 **4** (2)

reports the results of changing the aryl group of **3** to an aralkyl group and of shortening the chain; however, since the target thiol, 2-(benzylsulfinyl)ethanethiol (**9a**), proved too reactive to be studied readily, the main concern of the paper is with the derivatives of **9a** shown in Scheme I.

The key compound for preparation of the desired derivatives of **9a** was the thiosulfonate **17**. An attempt to synthesize **17** by converting **5** to the tosylate as the first

(1) (a) Paper 45: Srivastava, P. K.; Field, L. *J. Chem. Eng. Data*, in press. (b) This investigation was supported by the U. S. Army Medical Research and Development Command, Department of the Army, under Research Contracts Nos. DAMD17-79-C-9039 and DAMD17-85-C-5181; this paper has been designated as Contribution No. 1768 to the U. S. Army Drug Development Program. (c) We thank Prof. N. E. Heimer of the University of Mississippi for helpful suggestions.

(2) (a) Klayman, D. L.; Copeland, E. S. In *Kirk-Othmer Encyl. Chem. Technol., 3rd Ed*, **1982**, *19*, 813–814. (b) Srivastava, P. K.; Field, L.; Grenan, M. *J. Med. Chem.* **1975**, *18*, 798. (c) Bowman, G. T.; Clement, J. J.; Davidson, D. E., Jr.; Eswarakrishnan, V.; Field, L.; Hoch, J. M.; Musallam, H. A.; Pick, R. O.; Ravichandran, R., Srivastava, P. K. *Chem.-Biol. Interact.*, in press.

(3) Field, L.; Hanley, W. S.; McVeigh, I. *J. Med. Chem.* **1971**, *14*, 995.

(4) (a) Oae, S. In "Organic Chemistry of Sulfur"; Oae, S., Ed.; Plenum Press: New York, 1977; pp 430–431. (b) Block, E. "Reactions of Organosulfur Compounds"; Academic Press: New York, 1978, pp 168–171.

(5) Field, L.; Bowman, G. T. *J. Org. Chem.* **1981**, *46*, 2771.

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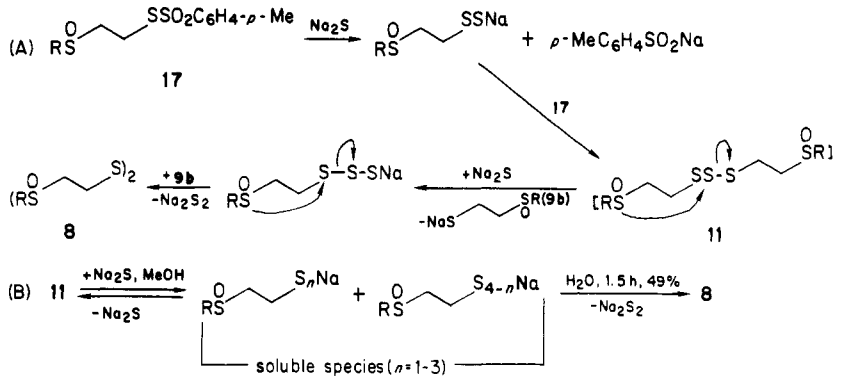
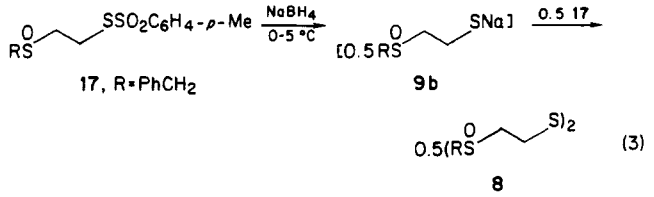
Scheme II[a]



[a] R = $PhCH_2$.

step led mainly to polymer(attributable to enhanced reactivity of the tosylate by a neighboring group effect of the sulfide function). The alternative of Scheme I through the chloride **6** was successful, however. The chlorosulfoxide **7** did not react satisfactorily with sodium *p*-toluenethiosulfonate (**10**) in MeOH (KI catalysis) or in MeCN (18-crown-6 catalysis), but did react in warm DMF with KI catalysis to afford pure **17** (50% yield; reaction temperatures much in excess of 60–80 °C led to a mush from which pure **17** could not be obtained satisfactorily).

Synthesis of the thiol **9a** first was attempted by reduction of the thiosulfonate **17** with $NaBH_4$ (Scheme I). The product isolated (without acidification), however, was the disulfide **8**. Air oxidation of the thiolate salt **9b** seems much less probable as an explanation of the formation of **8** than thioalkylation of **9b**, as it formed, by the thiosulfonate **17** (eq 3); loss by oxidation–reduction, as described for **9a** below, also is a possible explanation, however.



(3)

On the other hand, the thiol **9a** could be obtained by reducing the disulfide **8** with $NaBH_4$, acidifying, isolating the mercuric thiolate, and then treating with H_2S. The **9a** had an initial weak IR absorption for SH at ca. 2600 cm^{-1}, which disappeared in ca. 5–10 min. In a subsequent experiment done to confirm and quantify this result, the **9a** again disappeared rapidly; a considerable amount probably disappeared in an estimated 5 min before titration with standard KI_3 could be done to show a yield of 58%. After 5 min more, the yield of **9a** had decreased to 33%, and after 100 min only 13% remained (the loss, unlike the earlier result with **3**,[5] did not give a first-order plot). In several experiments with **9a**, TLC always showed three spots (one of which had the R_f value of **8**), as would be expected if **9a** behaved like the mercaptopropyl phenyl sulfoxide (**3**). The disappearance of **9a** thus seems best explained by concurrent oxidation of –SH and reduction of –S(O)–, essentially as reported for **3** (cf. eq 2).[5] However, the disappearance of **9a** occurred far more rapidly than with **3**, which had a half-life at room temperature of 5.0–5.8 h. In any event, the rapid disappearance of **9a** led us to work with derivatives acquired by means that did not involve the free thiol.

The trisulfide **11** first was sought by reaction of the thiosulfonate **17** with Na_2S in MeOH (Scheme I), essentially according to our usual procedures.[6] The actual product, however, was the disulfide **8** (56% yield). Since we have not had problems with disulfide formation in this way previously, the sulfoxide moiety seems likely to have been involved in the formation of **8**, perhaps through activation by the neighboring group effect suggested by the arrows in Scheme IIA. In substantiation of the formation and subsequent reaction of the trisulfide **11** (Scheme IIA), when **11** was allowed to react in MeOH with Na_2S, soluble species resulted (Scheme IIB). But when the MeOH was evaporated and replaced by H_2O, the pure (insoluble) disulfide **8** separated (49% yield). An implication of Scheme II is that the trisulfide **11** might be isolable if it were kept at low concentration and were removed from the reaction before it could be destroyed by Na_2S. Such protection of **11** seems to have been afforded by use of a dilute two-phase system, since reaction of Na_2S in water with **17** in CH_2Cl_2 at low concentrations gave the trisulfide **11** in 69% yield. Since the di- and trisulfide have similar R_f values, **8** is difficult to remove as a contaminant from **11**; fortunately, use of dilute solutions with CH_2Cl_2 as a solvent minimized this problem.

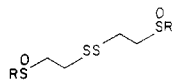
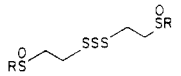
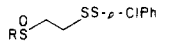
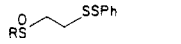
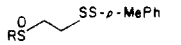
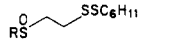
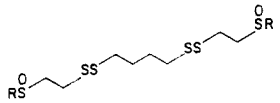
In preparing unsymmetrical disulfide–sulfinate salts of structure **2**, our usual procedure has been to add methanolic NaOMe to 1,2-dithiane 1,1-dioxide and the appropriate thiol (RSH) in MeOH at ca. 0 °C; when the reaction was complete (10–15 min), the salt **2** was precipitated with ether.[1a] A similar reaction of *p*-toluenethiolate ion with the thiosulfonate **17** at 0 °C gave only the two symmetrical disulfides, **8** and di-*p*-tolyl disulfide. Nevertheless, unsymmetrical disulfides (**12–16**) could be obtained when methanolic solutions of the thiolates were added to **17** in MeOH at –70 °C (the more stable cyclohexyl disulfide, **15**, was prepared at –15 °C). When the reaction was complete after 20–80 min (loss of **17** by TLC), the mixture was diluted with water. Evaporation of an extract and chromatography then gave **12–16** as solids in yields of 42–72%. An effort to prepare an unsymmetrical trisulfide similarly, i.e., $PhS(O)(CH_2)_2SSS$-*t*-Bu, by reaction of **17** with *tert*-butyl hydrodisulfide (*t*-BuSSH)[7] was unpromising; the product when subjected to repeated TLC separations gave three spots each time.

The disulfides **12–16** were reasonably stable as solids (by TLC), although they were kept in the dark at –70 °C as a precaution (without change, during several months); for example, **13** and **14** were unchanged after at least a month under ambient conditions.

Resistance of **8**, **11**, and **12–16** to change in solution was investigated under various conditions that one might wish

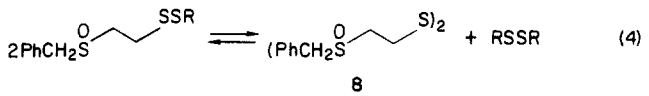
(6) Cf. ref. 2b and earlier papers there referred to.
(7) Aycock, D. F.; Jurch, G. R. *J. Org. Chem.* **1974**, *44*, 569.

Table I. Relative Stabilities of Di- and Trisulfide Products[a]

compd no.	structure[c]	time of first change in TLC[b] (1) dark	(2) ambient light	(3) UV,[d] min	(4) EtOAc, 77 °C[e]	(5) EtOH, 78 °C[e]
8		>1 week	>1 week	78	>60	>60
11		>1 week	>1 week	52	>60	>60
12		21	19	7	7	19
13		44	44	13	8	20
14		57	60	18	8	22
15		66	66	20	11	36
16		38	36	13	7	20

[a] As assessed by the first indication of change in TLC behavior of solutions in CH_2Cl_2, EtOAc, or EtOH. Except where otherwise indicated, experiments were done at room temperature (ca. 28 °C). [b] In hours, unless otherwise stated. For the nature of the change, see the Experimental Section. [c] R = $PhCH_2$. [d] Irradiated as explained in the Experimental Section. [e] In the dark.

to use in working with them, the time being noted at which TLC first showed a change (Table I). The disulfide **8** was more resistant than the trisulfide **11**, although both were considerably more resistant than the unsymmetrical disulfides **12–16**. In the case of **8** and **11**, only the resistance to change was of interest, and the products were not studied further. Changes in **12–16** no doubt represent disproportionation (eq 4), since in the experiments of Table



(4)

8

I TLC always showed the symmetrical disulfide **8** and one new spot corresponding to RSSR of eq 4 (with **12** and **14**, illustratively, the new spot was shown to be the other symmetrical disulfide).

The following conclusions can be drawn from the results of Table I: (1) Ambient light has a negligible effect (cf. columns 1 and 2), although UV irradiation has a very marked one (column 3). (2) Heat in the dark in EtOAc acclerates change, although the effect of structure is much less marked than at ca. 25 °C (cf. column 4 with columns 1–3). (3) Substitution of EtOH for EtOAc markedly enhanced the resistance. This effect is particularly interesting since other unsymmetrical disulfides have disproportionated more readily in polar than in nonpolar solvents.[8,9] It seems consistent with a normal neighboring group acceleration of disproportionation by the –S(O)– function, akin to that suggested in Scheme II, which has been diminished by a hydrogen-bonding interaction with the EtOH. Blocking of the neighboring-group effect of –S(O)– by hydrogen bonding has been noted elsewhere.[4b] (4) The effectiveness of the group attached to $PhCH_2S(O)(CH_2)_2$ as a leaving group seems to play a key role. Thus under all conditions (columns 1–5), among the aryl groups the electron-withdrawing Cl (Hammett σ_p 0.227)[10] diminishes resistance, the electron-donating Me (σ_p–0.170) enhances it, and H (of **13**) has an intermediary effect. This outcome is what one would expect if the electron-donating –S(O)– function is facilitating cleavage of the SS bond (cf. Scheme II); it is worth adding that in a similar situation where $-SO_2Na$ led to disproportionation, $-SO_2CH_2Ph$ did not.[9] The bis(disulfide) **16** appears to have about the same resistance as the phenyl disulfide **13**. The cyclohexyl group, providing $C_6H_{11}S$ as probably much the poorest leaving group, confers the greatest resistance to change by a considerable margin (cf. **15** in columns 1–5).

Overall, the order of resistance remains surprisingly much the same, irrespective of whether disproportionation is induced photochemically or thermally, although in another series this change virtually inverted the order.[11] In general, it appears that the order of increasing resistance to change, whether in the dark, light, or with heat will be about as follows: **12 < 16 ≲ 13 < 14 < 15 < 11 < 8.**

Experimental Section

Melting points were determined using a Thomas-Hoover stirred-liquid apparatus and are corrected. NMR spectra, reported in parts per million (δ), are ^1H spectra obtained in $CDCl_3$ with a JEOL Model JNM-MH-100 spectrometer with Me_4Si as an internal standard. Owing to the chirality of the –S(O)– function, the NMR singlet one might otherwise expect for $-CH_aH_bS(O)-$ sometimes appeared as a doublet of doublets; on the other hand, the coupling constants often were such that this doublet of doublets appeared to be a triplet (in confirmation, for example, a 400-mHz spectrum of **14** separated an apparent such triplet at δ 4.08–3.76 into a clear doublet of doublets); hence the actual *appearance* of the 100-mHz spectrum is reported, without regard to relative intensities or theoretical expectation. IR spectra were obtained with a Perkin-Elmer Model 727 spectrometer; strong peaks are so indicated (s)- others were medium or weak. Elemental analyses were done by Galbraith Laboratories. Moist extracts usually were dried over anhydrous $MgSO_4$, and solvents then were removed with a rotary-flask evaporator under reduced pressure. TLC was performed on Eastman Chromagram silica gel plates (catalog no. 13181), with visualization by I_2 vapor or UV. 2-(Benzylthio)ethanol (**5**), prepared as reported,[12] except with standing overnight rather than with heating (yield 88% and 79%, respectively), had n^{25}_D 1.5736 (lit.[12] n^{20}_D 1.5755). Sodium *p*-

(8) Field, L.; Buckman, J. D. *J. Org. Chem.* **1968**, *33*, 3865.
(9) Khim, Y. H.; Field, L. *J. Org. Chem.* **1972**, *37*, 2714.
(10) Gordon, A. J.; Ford, R. A. "The Chemist's Companion"; Wiley-Interscience: New York, 1972, pp 145–146.
(11) Field, L.; Parsons, T. F.; Pearson, D. E. *J. Org. Chem.* **1966**, *31*, 3550.
(12) Étlis, V. S.; Grobov, L. N. *Zh. Org. Khim.* **1969**, *5*, 685 [*J. Org. Chem. USSR* **1969**, *5*, 671 (Engl. Transl.)].

toluenethiosulfonate (**10**) was prepared from *p*-toluenesulfonyl chloride by adaptation of a procedure for methanesulfonyl chloride.[13] All other compounds not reported below were commercial ones.

Benzyl 2-Chloroethyl Sulfoxide (7). In lieu of inconvenient methods,[14] **5** was converted to **6** by adding $SOCl_2$ (119 g, 1.00 mol) slowly to 136 g (0.81 mol) of **5** and 63.7 g of pyridine (0.81 mol) with vigorous stirring at 0 °C. The mixture was stirred for 4 h more and poured into 1500 mL of H_2O. An Et_2O extract was washed well with H_2O, dried, and concentrated. Distillation gave 129.9 g (86%) of benzyl 2-chloroethyl sulfide (**6**): bp 150–156 °C (15 torr); n^{25}_D 1.5665 (lit.[15] n^{25}_D 1.5712); NMR δ 7.28 (s, 5 H), 3.68 (s, 2 H), 3.64–3.40 (t, 2 H), 2.88–2.62 (t, 2 H); IR (neat) 3000, 1600, 1480 (s), 1440 (s), 1310, 1280, 1250, 1200, 1180, 1060, 1010, 900, 760, 680 (s) cm^{-1}. Care should be used with **6** since it penetrates the skin[16] and since similar compounds are vesicants[16] and are mutagenic;[17] however, **6** caused only slight redness on the skins of **3** rats during 3 days,[18] although we found that the vapors caused headaches and itching of exposed forearms. The sulfide **6** was converted to benzyl 2-chloroethyl sulfoxide (**7**) with KIO_4 (62% yield):[19] mp 91–93 °C; lit.[19] mp 91 °C; the **7** had appropriate spectra and analysis (C, H, S). *m*-Chloroperoxybenzoic acid also effectively oxidized **6** to **7** (71% yield); IR 1020 cm^{-1}.

***S*-[2-(Benzylsulfinyl)ethyl] *p*-Toluenethiosulfonate (17).** A mixture of 40.5 g (200 mmol) of **7**, 73.8 g (351 mmol) of **10**, and 0.25 g of KI (catalyst) in 250 mL of DMF was stirred at 60–80 °C for 6 h. The mixture was poured into ca. 1400 mL of H_2O, and a $CHCl_3$ extract was washed well with H_2O, dried, and concentrated to a liquid, which crystallized in ca. 1 h. Recrystallization from MeOH gave 35.7 g (50%) of **17**: mp 111–113 °C; NMR δ 7.86–7.66 (d, 2 H), 7.46–7.22 (d, 7 H), 4.20 (s, 2 H), 3.44–3.08 (t, 2 H), 3.06–2.84 (m, 2 H), 2.44 (s, 3 H); IR (Nujol) 2900 (s), 1580, 1500, 1460 (s), 1380, 1360, 1320 (s), 1125 (s), 1070, 1025 (s), 925, 800, 680, 640 cm^{-1}. Anal. Calcd for $C_{16}H_{18}O_3S_3$: C, 54.20; H, 5.12; S, 27.13. Found: C, 53.99; H, 4.98; S, 26.91.

Studies of 2-(Benzylsulfinyl)ethanethiol (9a). (a) Attempted Preparation by Reduction of the Thiosulfonate 17, with Isolation of the Disulfide 8. $NaBH_4$ (0.037 g, 0.98 mmol) was added to a solution of 0.35 g (0.99 mmol) of **17** in 50 mL of MeOH with stirring at 0–5 °C. After 20 min, ca. 250 mL of H_2O was added, and the mixture was extracted with CH_2Cl_2. Since the isolation of the product took only ca. 20 min, air oxidation of the thiol **9a** is highly improbable as an explanation of the formation of **8**. Drying and evaporation led to 0.15 g (76%) of bis-2-(benzylsulfinyl)ethyl disulfide (**8**), which was recrystallized from MeOH to give 0.13 g (66%) of **8**: mp 147–148 °C; for spectra, see the preparation of **8** described below (spectra of the two products were congruent). Anal. Calcd for $C_{18}H_{22}O_2S_4$: C, 54.23; H, 5.56, S, 32.18. Found: C, 54.12; H, 5.51; S, 31.99.

(b) Preparation of 9a by Reduction of the Sulfinyl Disulfide 8. A solution of 0.80 g (2.01 mmol) of **8** and 0.20 g (5.3 mmol) of $NaBH_4$ was heated under reflux for 2 h and then was acidified with dilute HCl to pH 7. A solution of 0.50 g (1.98 mmol) of $Hg(CN)_2$ in 10 mL of MeOH was added, with a few drops of H_2O, and solid was allowed to separate overnight. Solvent was decanted, the solid was washed with water and suspended in 10 mL of CH_2Cl_2, and H_2S was passed. The black precipitate of HgS was removed by centrifugation, and 1-mL aliquots of the solution were titrated with 0.100 N standard KI_3. The time between the treatment with H_2S and the first titration, during which **9a** presumably was disappearing, was about 5 min. The time of titration, the mL required of KI_3 (extrapolated to the total 10 mL of solution) and the % yield of **9a** were as follows: 0 min, 23.0 mL, 58%; 5 min, 13.0 mL, 33%; 15 min, 9 mL, 23%; 45 min, 7.0 mL, 18%; 90 min, 6.0 mL, 15%; 100 min, 5.0 mL 13%.

Bis(2-(benzylsulfinyl)ethyl) Disulfide (8). A solution of $Na_2S·9H_2O$ (0.12 g, 0.50 mmol) in 5 mL of MeOH was added with stirring to one of 0.35 g (0.99 mmol) of the thiosulfonate **17** in 25 mL of MeOH at 0–5 °C. The mixture at first became clear yellow but after 25–30 min became turbid, and ca. 250 mL of H_2O was added. A CH_2Cl_2 extract was dried and concentrated to give a white solid, which after recrystallization from EtOH amounted to 0.11 g (56%) of **8**: mp 147–149 °C; R_f 0.66 (15% MeOH in Me_2CO); NMR δ 7.22 (s, 10 H), 4.22–3.88 (t, 4 H), 3.20–2.88 (m, 8 H); IR (KBr), 3050, 2950, 1600, 1500, 1450, 1410, 1260, 1140, 1100, 1070, 1025 (s), 760 (s), 690 (s) cm^{-1}. Anal. Calcd for $C_{18}H_{22}O_2S_4$: C, 54.23; H, 5.56; S, 32.18. Found: C, 53.80; H, 5.38; S, 32.32.

Bis(2-(benzylsulfinyl)ethyl) Trisulfide (11). A solution of 1.80 g (7.49 mmol) of $Na_2S·9H_2O$ in 400 mL of H_2O was added with stirring during 5 min to one of 5.31 g (15.0 mmol) of **17** in 300 mL of CH_2Cl_2 at 0–5 °C. After 10 min, the organic layer was separated, washed with H_2O, dried, and concentrated. The white solid that resulted was recrystallized from MeOH and MeOH/H_2O to give 2.21 g (69%) of **11**: mp 143–144 °C; R_f 0.71 (15% MeOH in Me_2CO); NMR δ 7.36 (s, 10 H), 4.20–3.88 (t, 4 H), 3.32–2.80 (m, 8 H); IR (KBr) 2950, 1490, 1450, 1410, 1100, 1070, 1020 (s), 760, 690 (s) cm^{-1}. Anal. Calcd for $C_{18}H_{22}O_2S_5$: C, 50.19; H, 5.14; S, 37.22. Found: C, 50.07; H, 5.16; S, 37.51.

That the trisulfide **11** was a probable intermediate in the conversion of the thiosulfonate **17** to the disulfide **8**, as described above, was shown by stirring a solution of 0.10 g (0.23 mmol) of **11** with 0.06 g (0.25 mmol) of $Na_2S·9H_2O$ in 15 mL of MeOH for 20 min at 0 °C. The resulting clear yellow solution was concentrated at ca 25 °C to a solid. Addition of 15 mL of H_2O then gave a clear solution. Within ca. 1.5 h, however, equilibration of the soluble species (cf. Scheme II) to give sparingly soluble **8** led to a considerable amount of precipitate, which was extracted with CH_2Cl_2; yield of **8**, 0.045 g (49%); mp 146–149 °C; depressed to 136–137 °C by **11** (mp 144–145 °C) but undepressed by **8** (mixture mp 146–149 °C); the NMR spectra of this **8** was congruent with that of authentic **8**. Evidently the formation of **8** is thermodynamically favored over that of **11**.

Preparation of Unsymmetrical Disulfides (12–16). (a) 2-(Benzylsulfinyl)ethyl *p*-Chlorophenyl Disulfide (12). The general procedure for **12–16** will be illustrated for **12**, with differences being specified for **13–16**: *p*-Chlorobenzenethiol (1.45 g, 10.0 mmol) was dissolved in a solution of 0.23 g (10.0 mmol) of Na in 20 mL of MeOH. This solution was added dropwise to a solution of 3.54 g (10.0 mmol) of the thiosulfonate **17** in 50 mL of MeOH with stirring at −70 °C. When TLC showed absence of the **17** (20 min for **12**), the mixture was poured into ca. 250 mL of H_2O. A CH_2Cl_2 extract was washed several times with H_2O and dried. Removal of the $MgSO_4$ and evaporation of the CH_2Cl_2 gave a white solid, which was chromatographed using 100% EtOAc on a 3 × 28-cm column of silica gel (J. T. Baker cat. no. 7024-2). Removal of solvent from the fraction that had a TLC R_f of 0.57 (EtOAc) gave 2.46 g (72%) of **12**: mp 69–70 °C; NMR 7.40–6.96 (m, 9 H), 4.00–3.68 (t, 2 H), 3.12–2.68 (m, 4 H); IR (KBr) 2950, 1460, 1400, 1380, 1260, 1090, 1020 (s), 900, 800, 760, 700 cm^{-1}. Anal. Calcd for $C_{15}H_{15}ClOS_3$: C, 52.54; H, 4.40; S, 28.05. Found: C, 52.77; H, 4.58; S, 27.82.

(b) 2-(Benzylsulfinyl)ethyl Phenyl Disulfide (13). Thiophenol (1.10 g, 10.0 mmol) and Na with **17** after 35 min at −70 °C and 10 min at 25 °C, after chromatography (5 × 16 cm column), gave a fraction of R_f 0.49 that yielded 2.28 g (72%) of **13**: mp 90–91 °C; NMR δ 7.44–6.84 (m, 10 H), 3.96–3.68 (t, 2 H), 3.20–2.60 (m, 4 H); IR (KBr) 3050, 2950, 1580, 1470, 1280, 1060, 1020 (s), 930, 730, 680 cm^{-1}. Anal. Calcd for $C_{15}H_{16}OS_3$: C, 58.40; H, 5.22; S, 31.18. Found: C, 58.67; H, 5.11; S, 31.18.

(c) 2-(Benzylsulfinyl)ethyl *p*-Tolyl Disulfide (14). *p*-Toluenethiol (2.48 g, 20.0 mmol) and Na (0.46 g, 20.0 mmol) in 50 mL of MeOH with 7.08 g (20.0 mmol) of **17** in MeOH (50 mL) after 80 min at −70 °C, addition to H_2O (1 L), and chromatography (5.5 × 16 cm column) as before gave a fraction of R_f 0.54 that yielded 4.04 g (63%) of **14**: mp 97–99 °C; NMR δ 7.50–7.20 (m, 9 H), 4.08–3.76 (t, 2 H), 3.20–2.72 (m, 4 H), 2.32 (s, 3 H); IR (KBr)

(13) Buckman, J. D.; Pera, J. D.; Raths, F. W. *Can. Pat.* 867787, 1971; *Chem. Abstr.* **1971**, *75*, 5242. Details of our adaptation are given in: Harmon, J. P., Ph.D. Dissertation Vanderbilt University, May 1985, pp 114–115.

(14) (a) Wood, J. L.; Rachele, J. R.; Stevens, C. M.; Carpenter, F. H.; du Vigneaud, V. *J. Am. Chem. Soc.* **1948**, *70*, 2547; (b) Patterson, W. I.; du Vigneaud, V. *J. Biol. Chem.* **1935**, *111*, 393.

(15) Stirling, C. J. M. *J. Chem. Soc.* **1957**, 3597.

(16) Nagy, S. M.; Golumbic, C.; Stein, W. H.; Fruton, J. S.; Bergman, M. *J. Gen. Physiol.* **1946**, *29*, 441.

(17) Stevens, C. M.; Mylroie, A. *Biochim. Biophys. Acta* **1952**, *8*, 325.

(18) We thank Dr. W. M. Mitchell of the Dept. of Pathology, Vanderbilt School of Medicine, for this evaluation.

(19) Colonna, S.; Stirling, C. J. M. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2120.

3050-2900, 1500, 1460, 1420, 1080, 1020 (s), 940, 800, 760, 700 cm^{-1}. Anal. Calcd for $C_{16}H_{18}OS_3$: C, 59.58; H, 5.62; S, 29.82. Found: C, 59.89; H, 5.57; S, 30.03.

(d) 2-(Benzylsulfinyl)ethyl Cyclohexyl Disulfide (15). Cyclohexanethiol (1.16 g, 10.0 mmol) and Na in 10 mL of MeOH reacted with 10 mmol of **17** in MeOH (25 mL) in only 6 min at −15 °C. After the procedure of (a) as usual, chromatography (5.5 × 8 cm column) gave a fraction of R_f 0.53 that yielded 2.20 g (70%) of **15**: mp 66-67 °C; NMR δ 7.36 (s, 5 H), 4.04 (s, 2 H), 3.00 (s, 4 H); 2.08-1.00 (m, 11 H); IR (KBr) 3050, 2950 (s), 1600, 1500, 1460 (s), 1420, 1270, 1200, 1030 (s), 940, 750, 700 (s). Anal. Calcd for $C_{15}H_{22}OS_3$: C, 57.28; H, 7.05; S, 30.58. Found: C, 57.23; H, 7.17; S, 30.42.

(e) 1,4-Bis[[2-(benzylsulfinyl)ethyl]dithio]butane (16). 1,4-Butanedithiol (1.22 g, 10.0 mmol) and Na (0.46 g, 20 mmol) in 50 mL of MeOH reacted with 7.08 g (20.0 mmol) of **17** in 50 mL of MeOH at −70 °C in 30 min. Delivery into ca. 300 mL of H_2O, extraction, and chromatography (5.5 × 8 cm column) as usual then gave a fraction of R_f 0.31 that yielded 2.17 g (42%) of **16**: mp 113-115 °C; NMR δ 7.80 (s, 10 H), 4.20-3.88 (t, 4 H), 3.20-2.80 (m, 8 H), 2.80-2.48 (m, 4 H), 1.84-1.56 (m, 4 H); IR (KBr) 2950, 2900, 1600, 1500, 1440, 1400, 1300, 1180, 1140, 1100, 1060, 1030 (s), 940, 760, 740, 700 (s) cm^{-1}. Anal. Calcd for $C_{22}H_{30}O_2S_6$: C, 50.93; H, 5.83; S, 37.08. Found: C, 51.05; H, 5.77; S, 37.07.

Resistance To Change of 8, 11, and 12-16. The results in columns 1-3 of Table I were obtained at room temperature (ca. 28 °C) using solutions of 0.1 mmol of the disulfide **8**, the trisulfide **11**, and the unsymmetrical disulfides **12-16** in 10 mL of CH_2Cl_2. For column 1 (dark), samples were kept in foil-wrapped containers. Samples for column 2 (ambient light) were treated similarly but were not foil-wrapped. Samples for column 3 (UV) were irradiated in Pyrex flasks (that touched one another in a circle) by a 100-W Hanovia Model 30620 UV lamp placed 18 cm below the flasks; the temperature of the flasks was ca. 28 °C. Each solution was sampled frequently enought to permit estimation within ca. 5-10% of the time at which TLC first showed a spot other than that of the starting material. TLC was done with 100% EtOAc or (8, 11) 15% MeOH in Me_2CO. For columns 4 and 5, solutions of 0.1 mmol in either EtOAc (bp 77 °C) or EtOH (bp 78 °C) were heated under reflux in foil-wrapped flasks.

Since only the resistance to change was sought with **8** and **11**, the products from **8** and **11** were not studied further (after UV irradiation was well advanced, two new spots were seen for **8** and three for **11**). The disulfides **12-16** showed only the three spots expected for disproportionation (plus traces of a fourth spot). That these three spots corresponded to the starting material and the two symmetrical disulfides was confirmed, illustratively, with **12** and **14**; after reaction (column 3) was well advanced, TLC comparison with authentic samples showed one spot to be **12** or **14**, the second to be **8**, and the third to be di-*p*-chlorophenyl or di-*p*-tolyl disulfide.

Registry No. **5**, 3878-41-9; **6**, 4332-51-8; **7**, 54623-96-0; **8**, 101544-07-4; **9a**, 101544-08-5; **10**, 3753-27-3; **11**, 101544-09-6; **12**, 101544-10-9; **13**, 101544-11-0; **14**, 101544-12-1; **15**, 101544-13-2; **16**, 101544-14-3; **17**, 101544-06-3; *p*-chlorobenzenethiol, 106-54-7; thiophenol, 108-98-5; *p*-toluenethiol, 106-45-6; cyclohexanethiol, 1569-69-3; 1,4-butanedithiol, 1191-08-8.

Selective, Oxophilic Imination of Ketones with Bis(dichloroaluminum) Phenylimide[1]

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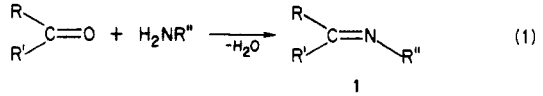
Bis(dichloroaluminum) phenylimide, which can be readily prepared from ethylaluminum dichloride and aniline, is shown to be a highly selective iminating agent for aldehydes, ketones, and acid chlorides. Especially the transformation of α,β-unsaturated ketones into anils can be achieved exclusively, without any detectable amount of the usual conjugate addition of the amine to the C=C linkage. This oxophilic iminating agent functions in the complete absence of water and thus obviates the tendency of α,β-unsaturated ketimines to rearrange, in the presence of water, into the corresponding β-aminoalkyl ketones. The reasons for the failure of previous attempts to synthesize chalcone anil from chalcone and aniline are analyzed in terms of kinetic and thermodynamic factors.

The formation of N-substituted imines (**1** in eq 1) from



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primary amines and aldehydes or ketones plays a pivotal role in chemical transformations as diverse as the synthesis of azaaromatic heterocycles[2] and the biosynthesis of amino acids.[3] The preparation of imines in vitro becomes progressively more difficult as one passes from aldehydes to ketones and as one employes aromatic, rather than aliphatic, amines.[4] Over 120 years ago, Schiff showed that aldimine formation from aromatic amines is base-catalyzed.[5] For the most difficult case, ketimines bearing two or more aromatic groups (**1**: R,R″ = aromatic), Reddelien found that a combination of proton and Lewis acids ($ArNH_2$–HCl–$ZnCl_2$) proved to be an effective iminating catalyst.[6] The use of acidic or basic catalysis, however, coupled with the slower rates of ketiminations, can lead to extensive side reactions, such as aldol condensations or competitive 1,4-additions to α,β-unsaturated ketones. Under Reddelien's conditions of imination, for example, acetophenone and aniline produce a large proportion of dypnone anil (**2**, eq. 2)[7] while chalcone (**3**) yields only one

(1) Part 5 of the series "Rearrangements of Heterocyclic Compounds". Part 4: Eisch, J. J.; Noels, A. F. *J. Org. Chem.* **1976**, *41*, 1461.
(2) Joule, J. A.; Smith, G. F. "Heterocyclic Chemistry", 2nd ed.; Van Nostrand Reinhold: New York, 1978, pp 74-80.
(3) Snell, E. E.; Braunstein, A. E.; Severin, E. S.; Torchinsky, Yu. M. "Pyridoxal Catalysis: Enzymes and Model Systems"; Wiley: New York, 1968.
(4) Layer, R. W. *Chem. Rev.* **1963**, *63*, 493.
(5) Schiff, H. *Ann. Chem. Pharm.* **1864-5**, *131*, 118.
(6) Reddelien, G. *Ber. Dtsch. Chem. Ges.* **1913**, *46*, 2721.
(7) Eisch, J. J., unpublished studies, 1976.

0022-3263/86/1951-1848$01.50/0