IR: 1740 (s). ^{1}H NMR (500 MHz): δ 0.88 (s, 3), 0.90 (d, 3, J = 6.6), 1.00 (d, 3, J = 6.4), 1.21-1.44 (m, 8), 1.52-1.92 (m, 10), 2.00-2.07 (m, 1), 2.14 (dd, 1, J = 10.5, 7.3), 2.44 (ddd, 1, J = 16.4, 10.9, 4.4), 2.51 (ddd, 1, J = 16.4, 11.4, 6.4), 2.73 (d, 1, J = 4.9), 2.74 (d, 1, J = 14.2), 3.25 (dt, 1, J = 14.2, 3.0), 3.67 (s, 3). ^{13}C NMR (125 MHz): δ 20.98, 21.33, 22.67, 25.37, 25.79, 26.06, 27.02, 28.54, 28.70, 31.01, 32.56, 36.60, 36.99, 37.90, 41.58, 41.69, 47.17, 47.98, 51.33, 51.49, 62.89, 72.17, 174.50. Anal. Calcd for $C_{23}H_{37}NO_2$: C, 76.83; H, 10.37; N, 3.90. Found: C, 76.93, H, 10.35; N, 3.90.

Method B. A solution of amino alcohol **28** (42.0 mg, 0.127 mmol in 10 mL of acetone) was stirred in a 25-mL round-bottomed flask, cooled by an ice/water bath, as 1 drop of concd H_2SO_4 was added. Celite (250 mg) was added, followed by 5 drops of Jones reagent. After 30 min, the slurry was diluted with 10 mL of acetone, and 20 drops 2-propanol were added to consume excess oxidant. After 15 min, the mixture was filtered through a plug of Celite (2.5 g), eluting with acetone, and the filtrate was concentrated. The residue was transferred to a 25-mL round-bottomed flask with methanol and concentrated. This material was dissolved in 15 mL of absolute methanol, the flask was equipped with a reflux condenser, and the solution was heated at reflux with a hot oil bath. After 1 h, the cooled reaction mixture was combined with 10 mL of a 2 M aqueous K_2CO_3 solution, and the mixture was concentrated. The condensate was diluted with 15 mL of water and extracted with CH_2Cl_2 (3 × 20 mL). The extracts were washed with 10 mL of brine, which was back-extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic extracts were dried, filtered, and concentrated. The crude product was purified by column chromatography on silica (10 g), eluting with 10:90:5 ether-hexanes-triethylamine, to provide 63.5 mg (73%) of methyl homodaphniphyllate as a colorless solid, mp 88-90 °C, identical by ^{1}H NMR and TLC mobility with the material prepared by method A.

Acknowledgment. This work was supported by a research grant from the National Science Foundation (CHE-84-18437) and by fellowships granted to R.B.R. by Smith, Kline, and French Research Laboratories (administered by the ACS Division of Organic Chemistry) and Pfizer, Inc. We are indebted to Professor S. Yamamura for authentic samples of daphnilactone A and methyl homodaphniphyllate.

Registry No. (±)-**4**, 104115-43-7; (±)-**6**, 111795-09-6; (±)-**7**, 138285-48-0; (±)-**11**, 53229-93-9; **13** (1-ene isomer), 74036-88-7; (±)-**13** (2-ene isomer), 138260-30-7; (±)-**14a**, 138260-33-0; (±)-**14b**, 111794-96-8; (±)-**14c**, 138260-32-9; (±)-**14d**, 138260-31-8; (±)-**15a**, 138260-36-3; (±)-**15b**, 111795-08-5; (±)-**15c**, 138260-35-2; (±)-**15d**, 138260-34-1; (±)-**16**, 111794-99-1; (±)-**17a** (isomer 1), 138260-41-0; (±)-**17a** (isomer 2), 138260-42-1; (±)-**17b** (isomer 1), 111795-01-8; (±)-**17b** (isomer 2), 111795-10-9; (±)-**17c** (isomer 1), 138260-39-6; (±)-**17c** (isomer 2), 138260-40-9; (±)-**17d** (isomer 1), 138260-38-5; (±)-**17d** (isomer 2), 138260-37-4; (±)-**18a**, 138260-44-3; (±)-**18b**, 138332-64-6; (±)-**18c**, 138260-43-2; (±)-**18d**, 118893-20-2; (±)-**19c**, 138260-45-4; (±)-**19d**, 118893-21-3; (±)-**22c**, 138260-46-5; (±)-**22d**, 118893-22-4; (±)-**23**, 118893-23-5; (±)-**24**, 118893-24-6; (±)-**26**, 138260-47-6; (±)-**28**, 104154-53-2; (±)-S5, 138260-48-7; (±)-S6, 138260-49-8; (±)-S7, 138260-50-1; (±)-S9, 138260-51-2; (±)-S10, 138260-52-3; (±)-S11, 138260-53-4; (±)-S12, 138260-54-5; (±)-S13, 138260-55-6; S14, 138260-56-7; (±)-S15, 138260-57-8; (±)-S16, 138260-58-9; S17, 138260-59-0; S18, 138260-60-3; S19, 138260-61-4; (±)-S20, 111794-97-9; (±)-S21, 111794-98-0; (±)-S22 (isomer 1), 111794-93-5; (±)-S22 (isomer 2), 111794-95-7; S24, 111794-94-6; (±)-S25, 138260-62-5; (±)-S26, 138260-63-6; (±)-S27 (isomer 1), 138260-64-7; (±)-S27 (isomer 2), 138260-65-8; S28, 138260-66-9; $ClCH_2C(CH_3)=CH_2$, 563-47-3; MeI, 74-88-4; $PhCH_2NH_2$, 100-46-9; $MeNH_2$, 74-89-5; δ-valerolactone, 542-28-9; homogeranyl iodide, 22339-13-5; homoprenyl iodide, 43161-11-1.

Supplementary Material Available: Discussion and experimental details on support studies dealing with the preparation of tricyclic lactam ethers analogous to lactone ethers **18**, details on the X-ray structural determination of compound **18a**, ^{1}H NMR spectra of synthetic and natural daphnilactone A and methyl homodaphniphyllate, and the ^{1}H NMR spectrum of compounds **24** and **28** (26 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and may be ordered from the ACS; see any current masthead page for ordering information.

β-(*N*,*N*-Dialkylamino)ethyl Arylthiosulfonates: New Simulants for *O*-Ethyl *S*-[2-(Diisopropylamino)ethyl] Methylphosphonothioate

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β-(*N*,*N*-Dialkylamino)ethyl arylthiosulfonates **2**, new simulants for the hydrolysis and oxidation chemistry of VX (**1**), are prepared in good yield by reaction of a potassium arylthiosulfonate with a 2-chloroethylamine. Alkaline hydrolysis of **2** results in cleavage of the S-S bond to give sulfinic acids and disulfides. Like VX, oxidation of **2** by *N*-sulfonyloxaziridine **12** occurs exclusively on nitrogen to give the corresponding amine oxide which subsequently undergoes a Cope elimination reaction affording the vinyl sulfide **14**.

The development of simple, but effect methods for the detoxification (decontamination) of toxic organophosphorus compounds is a goal of considerable practical importance because these compounds appear in the environment as pesticides and as chemical warfare agents.[1] The decontamination of VX (*O*-ethyl *S*-[2-(diisopropylamino)ethyl] methylphosphonothioate) (**1**), a chemical warfare nerve agent, generally involves conditions that are themselves corrosive and/or harmful to the environment, i.e., hydrolysis with caustic alkaline solutions and/or oxidation with hypochlorite.[2,3] Simple hydrolysis results in multiple products, some of which are as toxic as VX itself. A recent study of the oxidative chemistry of VX, by Yang and co-workers, revealed that it can be detoxified by oxidation followed by hydrolysis.[4] An impediment to the

(1) For leading references see: Hammond, P. S.; Forster, J. S.; Lieske, C. N.; Durst, H. D. *J. Am. Chem. Soc.* **1989**, *111*, 7860.

(2) Harris, B. C.; Shanty, F.; Wiesman, W. J. *Kirk-Othmer Encyclopedia of Chemical Technology*, 3rd ed.; John Wiley and Sons; New York, 1978; Vol. 5, pp 394-416. Epstein, J.; Bauer, V. E.; Saxe, M.; Demek, M. M. *J. Am. Chem. Soc.* **1956**, *78*, 4068.

(3) For other methods see: Epstein, J.; Kaminski, J. J.; Bodor, N.; Enever, R.; Sowa, J.; Higuchi, T. *J. Org. Chem.* **1978**, *43*, 2816. Kenley, R. A.; Lee, G. C.; Winterle, J. S. *J. Org. Chem.* **1985**, *50*, 40. Bodor, N.; Radhakrishman, B. In *Proceedings of the U.S. Army Chemical Research, Development and Engineering Center Scientific Conference on Chemical Defense Research*; Rausa, M., Ed. CRDEC-SP-88013; April 1988; pp 81-86. Truhaut, R. C. R. *Acad. Sci. Paris* **1985**, *3*, 67.

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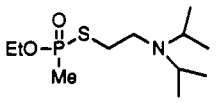
Table I. Synthesis of β-(Dialkylamino)ethyl Arylthiosulfonates 2 for 15 h

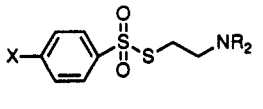
entry	p-XCHSO$_2$SK	ClCH$_2$CH-$_2$NR$_2$	condns base/solvent	% yield of 2
1	3a (X = CH$_3$)	4 (R = Me)	t-BuOK/dioxane	(2a) 5
2			t-BuOK/DMSO	9
3			pyridine	7
4			MeONa/MeOH	20
5			EtONa/EtOH	30
6			t-BuOK/t-BuOH	40
7			t-BuOK/t-BuOH/ Adogen-464[a]	75
8		4 (R = Pr^i)	t-BuOK/t-BuOH	(2c) 70
9			t-BuOK/t-BuOH/ Adogen-464[a]	86
10	3b (X = F)	4 (R = Me)	t-BuOK/t-BuOH	(2b) 35
11			t-BuOK/t-BuOH/ Adogen-464[a]	55
12		4 (R = Pr^i)	t-BuOK/t-BuOH	(2d) 45
13			t-BuOK/t-BuOH/ Adogen-464[a]	64

[a] Adogen-464, 0.5% by weight added.

development of more efficient and environmentally safe methods for the decontamination of VX, 1, has been the lack of suitable simulants that both mimic its hydrolysis and oxidation chemistry and are nontoxic. In this context we describe the preparation and chemistry of β-(N,N-dialkylamino)ethyl arylthiosulfonates 2, new and potentially useful simulants for VX (1).



1 (VX)

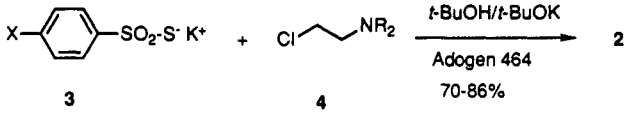


2a, X=R=Me
b, X=F, R=Me
c, X=Me, R=Pr^i
d, X=F, R=Pr^i

Results and Discussion

Two factors suggest that the thiosulfonate (RSO$_2$SR) moiety would be a useful mimic of the physical and chemical properties of the phosphonothioate unit in VX (1) and other phosphothioates. First, the sulfonyl group has an electronic configuration and polarity similar to that of the phosphate group. Second, both the reaction of thiosulfonates[5] and VX[4,6] with nucleophiles results in cleavage of the S–S and P–S bonds, respectively. Furthermore, thiosulfonates are generally solids having low toxicity and vapor pressures.

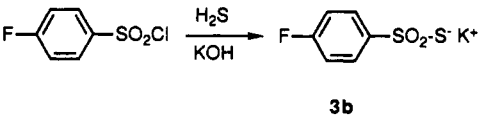
Our synthesis of β-(dialkylamino)ethyl arylthiosulfonates 2 follows that of Dunbar and co-workers, involving the reaction of a metal arylthiosulfonate 3 with an appropriate (2-chloroethyl)dialkylamine 4.[7] Initial attempts to prepare 2a by treatment of potassium p-toluenethiosulfonate (3a) with 2-chloro-N,N-dimethylethylamine (4) afforded only



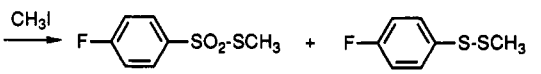
3 4 2

5–10% yield of the desired product 2a under a variety of conditions (Table I, entries 1–3). Yields were improved to 20–40% on addition of the hydrochloride of 4 to an equimolar amount of 3a in alkaline alcohol (Table I, entries 4–6). The highest yields of 2 were realized using 2-methyl-2-propanol/potassium tert-butoxide and the phase-transfer catalyst Adogen 464 affording 2a in better than 75% yield. β-Aminoethyl p-fluorobenzenethiosulfonates 2b–d were prepared in a similar manner. These results are summarized in Table I.

Potassium p-fluorobenzenethiosulfonate (3b), required for the synthesis of 2b and 2d, was prepared in ca. 40–60% yield by treatment of the p-fluorobenzenesulfonyl chloride with alkaline hydrogen sulfide according to the general procedure of Uhlenbroek and Koopmans.[8] Compound 3d was characterized by treatment of the crude reaction mixture with iodomethane to give a 60:40 mixture of methyl p-fluorobenzenethiosulfonate (5) and methyl p-fluorophenyl disulfide (6). Thiosulfonate 5 gave a satisfactory elemental analysis and had spectral properties consistent with its structure. Disulfide 6, previously reported,[9] was characterized by GC/MS and ^{1}H NMR. The absorption of the methyl protons in 6 appear at δ 2.5 ppm upfield from those of 5 (δ 3.1). The ratio of 5/6 improved to 80:20 on reducing the amount of H$_2$S. Apparently, hydrogen sulfide reduces the sulfonyl chloride and/or 3b producing the aryldithiolate anion (ArSS$^-$).



3b



5 6

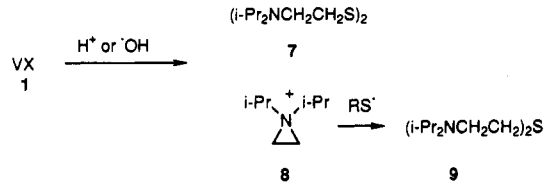
Thiosulfonates 2a and 2c, prepared from N,N-dimethyl 2-chloroethylamine, were isolated as oils, whereas 2b and 2d, prepared from N,N-diisopropyl chloroethylamine, were obtained as low-melting solids. The new β-aminoethyl arylthiosulfonates gave satisfactory elemental analysis and had spectral properties consistent with their structures.

To determine how well β-aminoethyl arylthiosulfonates 2 simulate the chemistry of VX, the hydrolysis and oxidation of these new compounds were explored.

Hydrolysis. Epstein, Callahan, and Bauer reported the hydrolysis kinetics of phosphonothioates including VX in dilute aqueous solution.[6] In acid solutions (up to pH ca. 7) and in more alkaline solutions (pH >10) VX reportedly undergoes exclusive cleavage of the P–S bond to give bis(diisopropylamino) disulfide 7. At intermediate pH ranges of 7–10 bis[(diisopropylamino)ethyl] sulfide (9) was also obtained. Air oxidation of the initially formed β-(isopropylamino)ethyl mercaptide ion (RS$^-$) afforded disulfide 7. Sulfide 9 is thought to result from attack of the mercaptide ion on an ethyleneimmonium ion 8 formed by intramolecular displacement of the phosphonothiolate group. While subsequent studies, for the most part, confirmed these results, Yang and co-workers made the important observation that hydrolysis of the ethoxy phosphate bond also occurs producing S-[2-(diisopropylamino)ethyl] methylphosphonothioic acid, nearly as toxic as VX.[4]

Treatment of 2 with 5% hydrochloric acid (pH 2.0) for 48 h followed by evaporation of the clear aqueous solvent afforded a semisolid. The ^{1}H NMR spectra of the solid suggests that hydrochloride 10 was formed as indicated by

(4) Yang, Y-C.; Szafraniec, L. L.; Beaudry, W. T.; Rohrbaugh, D. K. *J. Am. Chem. Soc.* **1990**, *112*, 6621.
(5) For a review on the chemistry of thiosulfonates see: (a) Kice, J. C. *Adv. Phys. Org. Chem.* **1980**, *17*, 65. (b) Isenberg, N., Grdinic, M. *Int. J. Sulfur Chem.* **1973**, *8*, 307.
(6) Epstein, J.; Callahan, J. J.; Bauer, V. E. *Phosphorus* **1974**, *4*, 157.
(7) Dunbar, J. E.; Tarnowski, B. H. *J. Heterocycl. Chem.* **1967**, *4*, 339.
(8) Uhlenbroek, J. H.; Koopmans, M. J. *Rec. Trav. Chim.* **1957**, *76*, 657.
(9) Latypova, V. Z.; Chichirov, A. A.; Zhuikok, V. V.; Yakovleva, O. G.; Vinokurova, R. I.; Ustyugova, I. A.; Kargin, Yu. M. *Zh. Olshch. Kim.* **1989**, *59*, 1344; *Chem. Abstr.* **1989**, *111*, 220906a.



the downfield shift of the methyl and isopropyl methyl by ca. 1.1 ppm. Indeed, the formation of **10** was confirmed by reisolation of **2** in 70–80% yield on neutralization (Scheme I).

Hydrolysis of **2** with 20% sodium hydroxide (pH ca. 11) for 48 h gave a 40–45% isolated yield of sodium *p*-tolyl or *p*-fluorobenzene sulfinates **11** and disulfide **7**, identified by comparison with an authentic sample prepared independently. In neither case was sulfide **9** detected, suggesting that ethyleneimmonium ion **8** is not formed from **2** under these conditions.

The hydrolysis of organophosphorous esters is generally thought to involve attack by the nucleophile at the tetrahedral phosphorus atom[1] and is consistent with the products formed on hydrolysis of VX.[4,6] By contrast, detailed studies by Kice on the hydrolysis of thiosulfonates have shown that nucleophiles attack at the divalent sulfur atom.[5,10] For VX simulant **2** this results in the formation of the observed sulfinate anion ($ArSO_2^-$) and an intermediate sulfenic acid (RSOH) (eq 1). Sulfenic acids are

$$\underset{\mathbf{2}}{ArSO_2SR} + HO^- \rightarrow ArSO_2^- + RSOH \qquad (1)$$

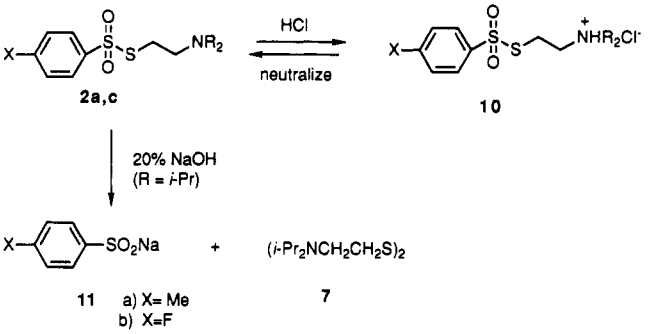
$$2RSOH \rightarrow RS(O)SR + H_2O \qquad (2)$$

highly reactive species which generally dimerize to thiosulfinates (RS(O)SR) (eq 2).[11] However, under our reaction conditions the sulfenic acid is apparently reduced to mercaptide (RS^-) which on air oxidation gives disulfide **7**.

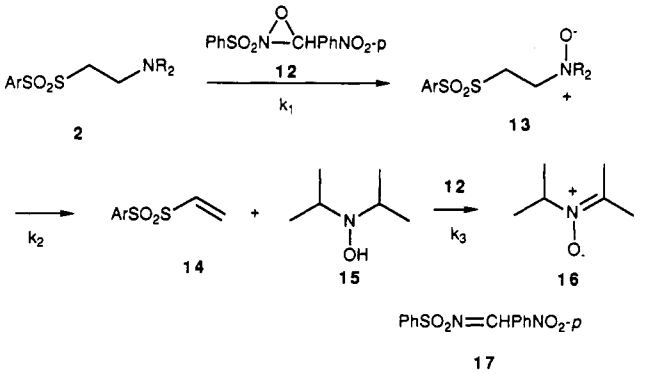
Oxidation. Yang et al.[4] in their studies of the oxidation of VX employed as one of their oxidants 2-(phenylsulfonyl)-3-(*p*-nitrophenyl)oxaziridine (**12**), an aprotic and neutral oxidizing reagent developed in our laboratory.[12] The reaction profile for the oxidation of VX by this reagent was monitored, and the products were identified by ^{31}P and ^{13}C NMR spectroscopy. Oxidation is rapid, resulting in initial formation of the *N*-oxide **13** (Ar = $EtOP(O)CH_3$–) which undergoes a Cope elimination reaction to give *O*-ethyl *S*-vinyl methylphosphonothioate **14** (Ar = $EtOP(O)CH_3$–). For complete oxidation, 2 equiv of **12** were required because the hydroxyl amine **15**, presumably involved in the formation of **13**, is oxidized at a faster rate than is VX (Scheme II). After 5 h less than 10% of VX remained.[4]

Treatment of **2c** with 1 equiv of **12** resulted in complete consumption of the oxidant within 1 h. Monitoring the progress of the oxidation by ^1H NMR, however, indicated that only 50% of **2c** had been oxidized as evidenced by the presence of isopropyl methyl protons at δ 0.98 ppm as well as by TLC analysis. The slow appearance of the vinyl protons at δ 5.6 and 6.4 ppm is indicative of the formation of *S*-vinyl *p*-methylbenzenesulfonylthioate (**14c**). With 2 equiv of **12** the simulant **2c** was consumed within 2 h affording the vinyl sulfide **14c** in 65–68% yield. The vinyl sulfide, isolated as an oil, was characterized by ^1H NMR and GC–mass spectrometry.

Scheme I



Scheme II[a]



[a] Key: (a) Ar = *p*-tolyl, R = Me; (b) Ar = *p*-FPh, R = Me; (c) Ar = *p*-tolyl, R = Pr^i; (d) Ar = *p*-F-Ph, R = Pr^i.

As observed for the oxidation of VX, the simulant **2c** undergoes exclusive oxidation at the more nucleophilic nitrogen atom by **12** to give amine oxide **13**. It is worth mentioning that the thiosulfonate **5** is not oxidized by **12** under these conditions. In both these reactants the bivalent sulfur atom is deactivated toward electrophilic oxidation as a result of its close proximity to the sulfonyl group. Rapid disappearance of the oxidant **12** and the gradual appearance of the vinyl proton absorptions of **14c**, i.e., $k_1 > k_2$, is evidence that **13** slowly eliminates *N*,*N*-dialkylhydroxylamine via a Cope elimination reaction. Two equivalents of oxidant are necessary for complete oxidation of VX simulant **2c** because the hydroxyl amino **15** is an "α-effect" nucleophile.[13] For this reason it is oxidized at a much faster rate than is **2c**: $k_3 \gg k_1 > k_2$ (Scheme I).

The complexity of the ^1H NMR and ^{13}C NMR spectra precludes definitive assignment of the absorptions due to *N*-oxide **13c**. In addition to the proton absorptions of **2b**, **13c**, **14c**, and sulfonimine **17** (the reduction product of **12**), absorptions at δ 2.15 (singlet) and at δ 1.2 ppm (J = 0.2 Hz) are also present. These absorptions are assigned to nitrone **16** resulting from oxidation of the intermediate hydroxy amine **15** by **12** (Scheme I). Recent studies by Zajac et al. have shown that oxidation of secondary amines by 2 equiv of *N*-sulfonyloxaziridine **12** gives nitrones in good yield.[14] Furthermore, treatment of diisopropylamine with 2 equiv of **12** resulted in the immediate and quantitative formation of a product whose ^1H NMR spectra is identical to those attributed to nitrone **16**. A possible explanation for the disappearance of **2c** after 20 h following oxidation with only 1 equiv of **12** is reaction with **15** and/or **16**.

(10) Kice, J. L.; Rogers, T. E. *J. Am. Chem. Soc.* **1974**, *96*, 8009.
(11) For leading reference to the chemistry of sulfenic acids see: Davis, F. A.; Jenkins, L. A.; Billmers, R. L. *J. Org. Chem.* **1986**, *51*, 1033.
(12) For a review on the oxygen-transfer reactions of *N*-sulfonyloxaziridines see: Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, *45*, 5703.
(13) For leading references to "α-effect" nucleophiles see ref 11.
(14) Zajac, W. W., Jr.; Walters, T. R.; Darcy, M. G. *J. Org. Chem.* **1988**, *53*, 5856.

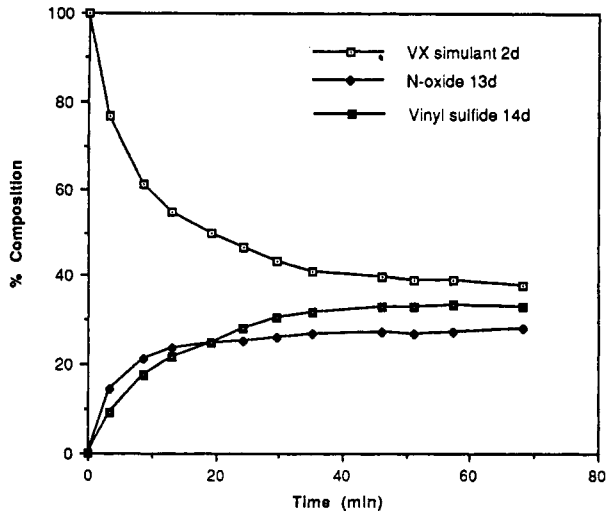


Figure 1. Oxidation of β-(diisopropylamino)ethyl *p*-fluorobenzenethiosulfonate (**2d**) with 1.0 equiv of oxaziridine **12** at 35 °C in $CDCl_3$.

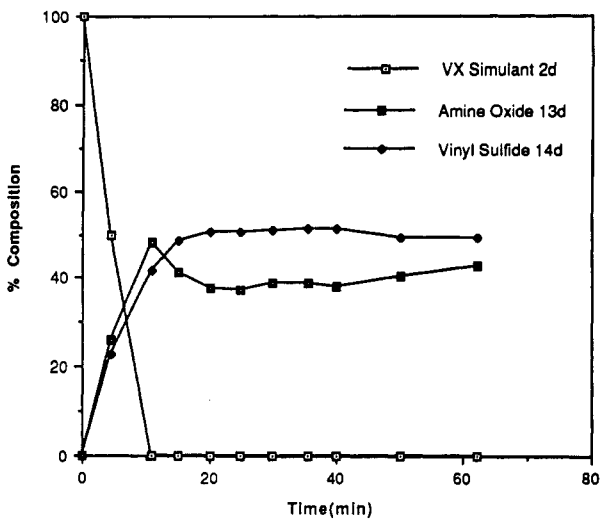


Figure 2. Oxidation of β-(diisopropylamino)ethyl *p*-fluorobenzenethiosulfonate (**2d**) with 2.0 equiv of oxaziridine **12** at 35 °C in $CDCl_3$.

It was not possible to accurately monitor the progress of the oxidation by proton or carbon NMR because of the complexity of the spectra. Consequently the oxidation of VX simulant **2d** by **12** was explored and the reaction progress followed by ^{19}F NMR spectroscopy. Treatment of **2d** (δ - 104.9) with 1 equiv of **12** results in an immediate reaction and complete consumption of the oxidant within 1 h. After a few minutes two new absorptions, one upfield at δ -111.1 ppm and one downfield at δ -103.2 ppm relative to **2d**, appear with a corresponding decrease in the signal at δ -104.9 ppm due to **2d** (Figure 1). We attribute the upfield absorption at δ -111.1 ppm to the vinyl sulfide **14d** by correlation of the integrated intensity of vinyl protons in the ^1H NMR spectra with the integrated intensity of the absorption at δ -111.1 in the ^{19}F NMR spectra. Consequently, the downfield absorption at δ -103.2 ppm is assigned to the *N*-oxide **13d**, which, over the next 60 min, slowly increases along with the vinyl sulfide (Figure 1).

Simulant **2d** is completely consumed in less than 10 min on oxidation with 2 equiv of **12**, and the *N*-oxide and vinyl sulfide reached a steady state after about 15 min (Figure 2). Over the next 5 h the 1:1 ratio of the *N*-oxide and vinyl sulfide did not change. Heating at 60 °C for 5 h, however, did result in an increase in the concentration of the vinyl sulfide to 65:35 at the expense of the *N*-oxide. For reasons which are unclear *N*-oxide **13d** appears to be more resistant to the Cope elimination reaction than is *N*-oxide **13c**.

The *N,N*-dimethyl simulants **2a** and **2b** are completely oxidized within 5 min to the corresponding *N*-oxides **13** on treatment with only 1 equiv of **12**. The *N,N*-dimethyl *N*-oxides are stable under these conditions and failed to eliminate to the vinyl sulfide **14** after 20 h. Similar results were observed by Yang and co-workers for oxidation of the dimethyl derivatives of **1** with **12**.[4] The greater stability of **13** (R = Me) compared to **13** (R = isopropyl) is attributed to steric acceleration of the Cope reaction by the bulkier isopropyl groups.

Toxicity. Aquatic toxicity testing of **2c** followed current ASTM and EPA guidelines.[15] All of the toxic effects to daphnia and fish were observed within the first 24 h. Using the EPA scoring criteria VX-simulant **2c** is ranked 5.0 on a scale of 0–9, with VX being ranked 9.0 as the most toxic. Precautions should be exercised in handling this new VX simulant.

Conclusions

β-(*N,N*-Dialkylamino)ethyl arylthiosulfonates **2** are useful simulants of the hydrolysis and oxidation chemistry of VX. For example, alkaline hydrolysis of **2** and VX result in cleavage of the S–S and P–S bonds, respectively. Under acid conditions these simulants form stable hydrochlorides. Oxidation takes place exclusively at the nitrogen atom to afford the amine oxide which is also observed for VX. These new simulants, **2**, are prepared in good yield by the phase-transfer-catalyzed reaction of a potassium arylthiosulfonate with 2-chloro-*N,N*-dimethyl- or diisopropylethylamine.

Experimental Section

Details concerning the recording of spectra, the analytical instruments used, the determination of melting points, elemental analyses, and the purification of solvents (freshly distilled) have been previously described.[16] ^{19}F NMR spectra were recorded on a JEOL FX90Q (84.6 MHz) in ppm (δ) upfield from internal fluorotrichloromethane.

Potassium *p*-Fluorobenzenethiosulfonic Acid (3b). A modification of the procedure reported by Uhlenbroek and Koopmans was used to prepare this compound.[8] In a 100-mL three-necked flask equipped with a magnetic stirring bar and thermometer was placed 6.3 g (0.11 mol) of potassium hydroxide in 12 mL of water. Hydrogen sulfide (H_2S) gas was passed through the solution for approximately 5–10 min. It is important to note that if a saturated solution of H_2S was used (i.e., constant weight) yields were reduced (see below). *p*-Fluorobenzenesulfonyl chloride (Aldrich), 9.5 g (0.04 mol), was added at such a rate that the internal temperature was maintained at 20–25 °C. After stirring for 3 h at 20–25 °C a clear yellow solution resulted and the evolution of hydrogen sulfide had ceased as indicated by the lack of bubbles. The solution was filtered, cooled to 5 °C in an ice bath and, on addition of a 0 °C solution of 17 g of potassium chloride dissolved in 50 mL of water, a precipitate resulted. The precipitate was filtered to give approximately 2.2 g of crude potassium *p*-fluorobenzenethiosulfonic acid (**3b**). After the filtrate was cooled for 3 at 0 °C the precipitated salt was collected and dried under vacuum to give 6.9 g (60%) of **3b**; mp >230 °C. The purity of this material was determined as indicated below.

Methyl *p*-Fluorobenzenethiosulfonate (5). In a flame-dried 10-mL flask equipped with a magnetic stirring bar was placed

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0.47 g of the crude potassium *p*-fluorobenzenethiosulfonic acid, 1.3 mL of iodomethane, and 5 mL of anhydrous DMF. After the solution was stirred for 16 hrs, 10 mL of water was added and the reaction mixture extracted with CH_2Cl_2 (2 × 10 mL). The organic solution was washed with 10 mL of 0.1 M $Na_2S_2O_3$ solution and 10 mL of water and dried over anhydrous $MgSO_4$. Removal of the solvent under vacuum gave a white solid which was purified by preparative TLC (silica gel G) eluting with CH_2Cl_2 to give **5** and **6**.

Thiosulfonate **5** was crystallized from CH_2Cl_2–*n*-pentane to give 0.23 g (54%) of **5**; mp 68–9 °C; IR (KBr) 1130, 1320 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.1 (s, 3 H, Me), 7.2–7.3 (m, 2 H, Ar), 7.9–8.0 (m, 2 H Ar); ^{19}F NMR ($CDCl_3$) δ −103.5; MS/EI *m/e* (relative intensity) 206 (M, 15), 159 (80), 95 (100). Anal. Calcd for $C_7H_7FO_2S_2$: C, 40.77; H, 3.39. Found: C, 40.39; H, 3.77.

Methyl *p*-Fluorophenyl Disulfide (6).[9] Isolated as a low-melting solid; ^1H NMR ($CDCl_3$) δ 2.5 (s, 3 H, Me), 7.3 (m, 2 H, Ar), 7.9 (m, 2 H, Ar); ^{19}F NMR ($CDCl_3$) δ −103.1; MS/EI *m/e* (relative intensity) 174 (M, 10), 159 (20), 95 (100).

General Procedure for Preparation of VX Simulants 2. In a 100-mL single-necked flask, equipped with a magnetic stirring bar, were placed equivalent amounts, typically 18 mmol, of the potassium salt of *p*-tolylthiosulfonic acid (**3a**) (Aldrich) or *p*-fluorobenzenethiosulfonic acid (**3b**), potassium *tert*-butoxide, 2-(dimethylamino)ethyl chloride hydrochloride (Aldrich Chemical Co.) or 2-(diisopropylamino)ethyl chloride hydrochloride (Fluka Chemical Co.), and Adogen 464 (2–3 drops) in 30 mL of 2-methyl-2-propanol. The reaction was stirred vigorously for 15–18 h at room temperature under argon and quenched by addition of 100 mL of cold water. The solution was extracted with methylene chloride (3 × 25 mL) and the organic solvent washed with water (2 × 25 mL) and dired over anhydrous $MgSO_4$. Removal of the solvent on the rotary evaporator afforded crude **2**.

***β*-(Dimethylamino)ethyl *p*-toluenethiosulfonate (2a)**: oil, 75% yield; IR (KBr) 1140, 1322 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.17 (s, 6 H, NMe), 2.46 (s, 3 H, *p*-MePh), 2.55 (t, 2 H, CH_2, J = 7 Hz), 3.1 (t, 2 H, CH_2, J = 7 Hz), 7.35 (d, 2 H, aryl, J = 9 Hz), 7.83 (d, 2 H, aryl, J = 9 Hz); ^{13}C NMR ($CDCl_3$) δ 21.49, 33.68, 44.67, 57.06, 126.69, 129.57, 141.41, 144.46; MS/EI *m/e* (relative intensity) 260 (M + 1, 50), 104 (50), 58 (100). Anal. Calcd for $C_{11}H_{17}NO_2S_2$: C, 50.94; H, 6.61. Found: C, 50.60; H, 6.80.

***β*-(Dimethylamino)ethyl *p*-fluorobenzenethiosulfonate (2b)**: oil, 55% yield; IR (thin film) 1201, 1365 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.21 (s, 6 H, NMe), 2.61 (t, 2 H, CH_2N, J = 6 Hz), 3.19 (t, 2 H, CH_2S, J = 6 Hz), 7.4 (m, 2 H), 7.99 (m, 2 H); ^{19}F ($CDCl_3$) δ −104.9; MS/EI *m/e* (relative intensity) 263 (M, 10), 165 (70), 58 (100). Anal. Calcd for $C_{10}H_{14}FNO_2S_2$: C, 45.62; H, 5.32. Found: C, 45.40; H, 5.10.

***β*-(Diisopropylamino)ethyl *p*-toluenethiosulfonate (2c)**: mp 45 °C, 86% yield; IR (KBr) 1133, 1310 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (d, 12 H, Me, J = 6 Hz), 2.54 (s, 3 H, *p*-MePh), 2.71 (t, 2 H, CH_2, J = 6 Hz), 2.91 (m, 2 H, CH), 3.1 (t, 2 H, CH_2S, J = 6 Hz), 7.35 (d, 2 H, aryl, J = 7 Hz), 7.85 (d, 2 H, aryl, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 20.67, 20.70, 36.92, 43.44, 48.06, 126.88, 129.63, 141.93, 144.28; MS/EI *m/e* (relative intensity) 315 (M, 10), 114 (100), 72 (45). Anal. Calcd for $C_{15}H_{25}NO_2S_2$: C, 57.14; H, 7.93. Found: C, 56.92; H, 7.66.

***β*-(Diisopropylamino)ethyl *p*-fluorobenzenethiosulfonate (2d)**: mp 47–48 °C; 64% yield; IR (thin film) 1138, 1322 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (d, 12 H, Me, J = 6 Hz), 2.72 (t, 2 H, CH_2, J = 6 Hz), 2.93 (m, 2 H, CH), 3.15 (t, 2 H, CH_2S, J = 6 Hz), 7.23 (d, 2 H, aryl), 8.1 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 20.75, 37.23, 43.25, 47.99, 116.14, 116.50, 129.62, 129.77; ^{19}F ($CDCl_3$) δ −104.9; MS/EI *m/e* (relative intensity) 302 (M + 1, 30), 304 (40), 114 (100). Anal. Calcd for $C_{14}H_{22}FNO_2S_2$: C, 52.60; H, 6.89. Found: C, 52.70; H, 7.20.

General Procedure for Alkaline Hydrolysis of VX Simulants 2. To 1.6 mmol of **2c** and **2d** was added 25 mmol of 20% NaOH (5 mL), the mixture was stirred for 48 h, 10 mL of saturated NaCl solution added, and the mixture was extracted with ether (2 × 15 mL). After drying, removal of the solvent gave 40–45% of **7** as an oil identified by comparison of its spectra data with a sample prepared independently.

The aqueous portion was acidified to pH 5–6 by addition of 17% HCl and the solution extracted with methylene chloride. After drying, removal of the solvent gave 40–45% of sulfinic acids **11** identified by comparison of their mp and ^1H NMR spectra with authentic samples: **11a** (40%) mp 84–86 °C (lit.[17] mp 89 °C); **11b** (46%) mp 46–7 °C (lit.[18] mp 43–44 °C); IR (KBr) 3400, 1600, 1500, 1360 cm^{-1}; ^{H} NMR ($CDCl_3$) δ 7.17 (m, 2 H), 7.76 (m 2 H), 8.71 (bs 1 H).

Synthesis of Authentic Bis[2-(diisopropylamino)ethyl] Disulfide (7b). 2-(Diisopropylamino)ethyl chloride hydrochloride (Fluka, 5 g, 25 mmol) was treated with 1.9 g (25 mmol) of thiourea and 2.0 g (50 mmol) of NaOH in 5 mL of water for 5 h. After the aqueous reaction mixture was saturated with NaCl the solution was extracted with ether and dried, the solvent removed, and the residue distilled, bp 40 °C (1 mm), to give 3 g (74%) of 2-(diisopropylamino)ethanethiol as a colorless oil: ^1H NMR δ ($CDCl_3$). 1.10 (d, 12 H, J = 7 Hz), 2.52 (m, 2 H) 2.65 (m, 2 H) 3.00 (m, 2 H). The thiol, 0.65 g (4.6 mmol), was stirred with 0.18 g (4.6 mmol) of NaOH and 0.75 g (6.6 mmol) of KI in 2 mL of H_2O for 2 h. After dilution with 10 mL of H_2O the solution was extracted with ether and dried. Removal of solvent and distillation, bp 100–5 °C (5 mm), gave 0.52 g (80%): ^1H NMR ($CDCl_3$) δ 1.01 (d, 12 H, J = 7 Hz), 2.7 (br s, 8 H), 3.01 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 20.87, 40.51, 45.78, 49.35. Anal. Calcd for $C_{16}H_{36}N_2S_2$: C, 59.63; H, 11.80. Found: C, 59.59; H, 11.62.

General Procedure for Acid Hydrolysis of VX Simulants 2. Simulant **2**, 0.4 mmol, was added to 5 mL of 5% HCl. The mixture was stirred at 25 °C for 48 h and the aqueous solvent evaporated with a minimum of heating to afford the semisolid hydrochloride salts of **2**. Hydrochloride of **10a** (75%): white solid, mp 178–180 °C dec; ^1H NMR ($CDCl_3$) δ 2.4 (m, 6 H) 2.9 (s, 3 H), 3.5 (br s, 4 H), 7.4 (m, 2 H) 7.9 (m, 2 H), 12 (bs, 1 H). **10c** (70%): semisolid; ^1H NMR ($CDCl_3$) δ 1.5 (dd, 12 H), 2.5 (s, 3 H) 3.5 (m, 6 H), 7.4 (d, 2 H), 7.8 (m, 2 H), 11.7 m (bs, 1 H). **10d** (83%): white solid, mp 175–178 °C; ^1H NMR ($CDCl_3$) δ 1.55 (m, 12 H), 3.6 (m, 6 H), 7.37 (m, 2 H), 7.9 (m, 2 H).

Treatment of the hydrochlorides **10** with 2% cold NaOH solution followed by extraction with CH_2Cl_2 (2 × 10 mL) and drying gave **2a–d** in 70–85% isolated yields.

General Procedure for Oxidation of VX Simulants 2. Equimolar amounts of oxaziridine **12** and the VX simulant **2**, typically 0.1–0.18 mmol, were placed in a 5-mm NMR tube in 1 mL of $CDCl_3$, and the tube was shaken. For fluorine compounds **2b** and **2d** a drop of $CFCl_3$ as internal standard was added. The ^{19}F NMR spectra were recorded every 5 min involving 30 scans with a relaxation time of 5 s. When the oxidant **12** had been consumed, as indicated by the disappearance of the oxaziridine proton at ca. δ 5.6 ppm, 1 additional equiv of **12** was added.

Amine oxide **13a**: ^1H NMR ($CDCl_3$) aliphatic region δ 2.5 (s, 3 H), 2.6 (s, 6 H), 3.1 (m, 2 H), 3.4 (m, 2 H). Amine oxide **13b**: ^1H NMR ($CDCl_3$) aliphatic region δ 2.7 (s, 6 H), (t, 2 H), 3.21 (t, 2 H), 3.73 (t, 2 H). ^{19}F NMR ($CDCl_3$) δ −103.2. Amine oxide **13d** ^{19}F NMR ($CDCl_3$) δ −103.2.

Isolation of Vinyl Arylthiosulfonates (14). After the oxidation was complete the reaction mixture was diluted to 50% with *n*-pentane, filtered, and evaporated to dryness on the rotary evaporator without heating and the residue dissolved in 2 mL of *n*-pentane. The *n*-pentane-soluble portion was evaporated to dryness to afford the vinyl sulfides which were purified by TLC (silica gel G) eluting with CH_2Cl_2. **14c** (oil) (63%): R_f 0.7; ^1H NMR ($CDCl_3$) δ 2.45 (s, 3 H), 5.7 (d, J = 7 Hz, 1 H), 5.8 (d, J = 5 Hz, 1 H), 6.6 (m, 1 H), 7.8 (d, J = 7.5, 2 H); MS/EI, *m/e* (relative intensity) 214 (M, 20), 155 (30), 91 (100). **14d** (volatile oil) (10%): ^1H NMR ($CDCl_3$) δ 5.6 (d, J = 7 Hz, 1 H), 5.85 (d, J = 6 Hz, 1 H) 6.6 (m, 1 H), 7.2 (m, 2 H), 7.9 (m, 2 H); ^{19}F NMR ($CDCl_3$) δ −111.1; MS/EI *m/e* (relative intensity) 218 (M, 33), 159 (25), 95 (100).

Oxidation of Diisopropylamine by 12. Diisopropyl amine, 6 mg (0.06 mmole), and 18 mg (0.06 mmole) of **12** were dissolved separately in 1.0 mL of $CDCl_3$ and mixed and the ^1H NMR spectra taken. The proton NMR spectra indicates the presence of a 1:1 mixture of diisopropylamine and nitrone **16** by integration of the isopropyl protons in the amine and **16** appearing at δ 1.0 and 1.3 ppm. Complete oxidation to **16** results on addition of a second equivalent of **12**: ^1H NMR of ($CDCl_3$) δ 1.3 (d, 6 H, J = 6 Hz),

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2.15 (s, 6 H), 4.5 (m, 1 H, CH); MS/EI m/e (relative intensity) 115 (M, 10), 77 (100), 55 (70).

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Registry No. **2a**, 139131-28-5; **2b**, 139131-29-6; **2c**, 139131-30-9; **2d**, 139131-31-0; **3a**, 28519-50-8; **3b**, 139131-32-1; **5**, 139131-33-2; **7b**, 65332-44-7; **10a**, 139131-34-3; **10c**, 139131-35-4; **10d**, 139131-36-5; **11a**, 824-79-3; **11b**, 824-80-6; **13a**, 139131-37-6; **13b**, 139131-38-7; **13d**, 139131-39-8; **14c**, 139131-40-1; **14d**, 139131-41-2; **16**, 94143-77-8; VX, 50782-69-9; 2-(dimethylamino)ethyl chloride hydrochloride, 4584-46-7; 2-(diisopropylamino)ethyl chloride hydrochloride, 4261-68-1; *p*-fluorobenzenesulfonyl chloride, 349-88-2.

Supplementary Material Available: ^{1}H NMR spectra of hydrochlorides **10a**, **10c**, and **10d**, vinyl sulfides **14c** and **14d**, and nitrone **16** (7 pages). Ordering information is given on any current masthead page.

Asymmetric Oxidation of Simple Selenides to Selenoxides in High Enantiopurity. Stereochemical Aspects of the Allyl Selenoxide/Allyl Selenenate Rearrangement

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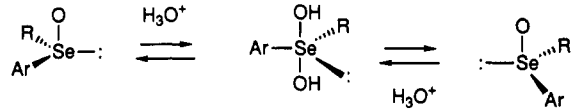
For the first time simple alkyl aryl selenoxides of high enantiomeric purity (90–95% ee) and well-defined stereochemistry are available via the asymmetric oxidation of selenides using (+)- or (−)-*N*-(phenylsulfonyl)-(3,3-dichlorocamphoryl)oxaziridine [**4**, [3,3-dichloro-1,7,7-trimethyl-2′-(phenylsulfonyl)spiro[bicyclo[2.2.1]heptane-2,3′-oxaziridine]]]. These nonracemic selenoxides, which are more stable in solution than in the solid state, exhibit high configurational stability as long as acid and moisture are excluded. Complete racemization occurs within minutes on addition of trace amounts of acid and water. The asymmetric oxidation of (*E*)- and (*Z*)-aryl cinnamyl selenides **11** and **12** with oxaziridine (+)-**4** affords optically active 1-phenyl allyl alcohol (**15**) via a concerted [2,3] sigmatropic selenoxide–selenenate rearrangement. The extent of 1 → 3 chirality transfer (41–62% ee) as well as the endo/exo transition state geometry is highly dependent on the structure of the allylic selenide.

Until recently, simple chiral selenoxides were little studied, being first reported by us in 1983.[1,2] This is in contrast to chiral sulfoxides which have been known since the mid-1920s[3] and have played pivotal roles in studies of the origins of molecular recognition and in asymmetric synthesis.[4] Optically active diaryl selenoxides have been prepared by chromatographic resolution on chiral columns (12–66% ee),[5,6] and by oxidation with *tert*-butyl hypochlorite in the presence of (−)-2-octanol (1.0% ee).[7] Oxidation of prochiral selenides with enantiopure *N*-sulfonyloxaziridines (up to 13%)[2] and with the Sharpless reagent (7–40% ee)[8] gives enantiomerically enriched alkyl aryl selenoxides. Microbial oxidation of selenides to selenoxides, however, failed.[9] Resolution of racemic selenoxides by complexation with chiral diols and by kinetic resolution with chiral sulfonamides (6–10% ee)[1] has also been described.[10] In addition, diastereomeric selenoxides have been prepared by oxidation of steroidal[11] and nonracemic [2.2]paracyclophane-substituted selenides.[12]

The principal difficulty in studying and preparing chiral selenoxides in high enantiomeric purity is their configurational lability. In earlier studies we demonstrated that chiral alkyl arylselenoxides racemize in the presence of moisture via the formation of an achiral hydrate **1** which



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is strongly acid catalyzed.[1,2] Bulky ortho substituents were shown to slow the rate of racemization by sterically inhibiting the formation of **1**. Subsequent studies by Shimizu et al. confirmed these results and established that the rate-limiting step is protonation of the selenoxide oxygen.[13] These same workers succeeded in preparing enantiomerically pure (−)-4-(methoxycarbonyl)phenyl 2,4,6-triisopropylphenyl selenoxide, which is air-stable, by fractional

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