sulfones are deazosulfonated under nearly identical conditions.

Work is now in progress to study the reactivity of nucleophiles derived from the fourth and the fifth families of the periodic chart.

Experimental Section

General Method. All the known compounds cited in this paper have been fully characterized through melting point, ^{1}H NMR, MS, and thin-layer chromatography. Tolyl arylazo sulfones have been synthesized according to Ahern.[8] New tolyl arylazo sulfones **2a**,**c**,**d**,**f**,**j**,**k**,**m**,**o** gave satisfactory elemental analysis (C, ± 0.27; H, ± 0.25) and significant characterization data are given below.[12] Sodium methaneselenolate was obtained from methaneselenol and sodium methoxide in methanol solution. Dry sodium methaneselenolate was obtained after elimination of the methanol under reduced pressure. The lithium salt of methane-, butane- and benzeneselenol were prepared from commercial methyl-, butyl-, or phenyllithium in hexane solution and elemental selenium in tetrahydrofuran suspension. After elimination of the solvents under reduced pressure, the residual solids were dissolved in acetonitrile. The trimethylsilyl derivative of methanetellurol was generated in situ from commercial methyllithium in ether, elemental tellurium in tetrahydrofuran suspension, and trimethylsilyl chloride. The following procedures are representative.

Synthesis of *o*-(Methoxycarbonyl)selenoanisole (3a). A mixture of 3.18 g (10 mmol) of **2a**, 50 mg of 18-crown-6, 1.18 g (10 mmol) of sodium methaneselenolate, and 150 mL of acetonitrile was stirred for 8 h at room temperature. The reaction mixture was poured into water (300 mL) and extracted with ether (3 × 100 mL). The mixed organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography using a mixture of $CHCl_3$–C_6H_6 (15:85) as eluent.

Synthesis of 4-Bromotelluroanisole (6n). To a suspension of 1.27 g (10 mmol) of elemental tellurium in 60 mL of THF was added 11 mmol of methyllithium in ether solution in 10 min at room temperature. The excess of methyllithium was destroyed by adding 1 mL of propanone. Trimethylsilyl chloride (1.09 g, 1.27 mL) was added in one portion and the mixture allowed to stand for 10 min. Volatile materials were eliminated under reduced pressure before redissolving the solid residue obtained in 120 mL of acetonitrile. After addition of 50 mg of 18-crown-6 and 3.49 g of **2n** and being stirred during 8 h at room temperature, the reaction mixture was poured into water (300 mL) and extracted with ether (3 × 100 mL). The mixed organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography using a mixture of $CHCl_3$–C_6H_6 (15:85) as eluent.

Registry No. **2a**, 105230-44-2; **2b**, 26788-89-6; **2c**, 105230-45-3; **2d**, 105230-46-4; **2e**, 105230-47-5; **2f**, 105230-48-6; **2g**, 38568-60-4; **2h**, 105230-49-7; **2i**, 60095-84-3; **2j**, 105230-50-0; **2k**, 95765-82-5; **2l**, 60095-87-6; **2m**, 105230-51-1; **2n**, 33604-66-9; **2o**, 105230-52-2; **2p**, 33604-67-0; **3a**, 78377-06-7; **3b**, 4346-64-9; **3c**, 105230-53-3; **3d**, 3757-99-1; **3e**, 1694-00-4; **3f**, 105230-54-4; **3g**, 43022-52-2; **3h**, 105230-55-5; **4a**, 105230-56-6; **4b**, 28622-61-9; **4e**, 10520-57-7; **4g**, 105230-58-8; **4h**, 86297-09-8; **4i**, 105230-59-9; **4j**, 105230-60-2; **4k**, 105230-61-3; **5b**, 1132-39-4; **5e**, 105230-62-4; **5g**, 6343-83-5; **5l**, 65848-40-0; **5m**, 105230-63-5; **6a**, 105230-64-6; **6b**, 872-89-9; **6n**, 28192-39-4; **6o**, 32294-61-4; **7b**, 1202-36-4; **7g**, 79424-71-8; **7l**, 79424-69-4; **7m**, 105230-65-7; **7d**, 56950-00-6; CH_3SeLi, 50491-55-9; CH_3SeNa, 37773-10-7; BuSeLi, 55163-69-4; PhSeLi, 52251-58-8; $Me_3SiTeCH_3$, 34117-12-9; PhTeLi, 52251-60-2; Te, 13494-80-9; CH_3Li, 917-54-4; Me_3SiCl, 75-77-4; 1,4-bis(phenylselenyl)benzene, 71672-72-5.

(13) In this paper the periodic group notation in parentheses is in accord with recent actions by IUPAC and ACS nomenclature committees. A and B notation is eliminated because of wide confusion. Group IA and IIA become groups 1 and 2. The d-transition elements comprise groups 3 through 12, and the p-block elements comprise groups 13 through 18. (Note that the former Roman number designation is preserved in the last digit of the new numbering: e.g., III → 3 and 13.)

Thioimidate *N*-Oxides: Nitrones of Thio Esters

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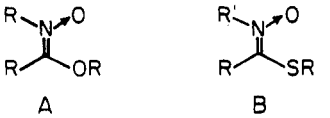
A group of three *C*-phenyl and three *C*-alkyl thioimidate *N*-oxides (nitrones of thio esters) was prepared by S-alkylation of *N*-alkylthiohydroxamic acids with methyl or ethyl iodide followed by basification of the resulting hydriodide salts. An X-ray crystallographic analysis of *S*-methyl *N*-methylthiobenzimidate *N*-oxide (**9Z**) established the *Z* stereochemistry for the more stable isomer. The ^{1}H NMR, ^{13}C NMR, IR, and UV spectral properties of the thio ester nitrones are reported. The *E*/*Z* stereochemistry of the *C*-alkyl derivatives is tentatively assigned on the basis of NOE measurements, long-range coupling, and chemical shift correlations. Thermal equilibration in bromobenzene-d_5 at 80 °C gave the following *E*/*Z* ratios: *C*-phenyl, 5:95; *C*-methyl, 46:54; *C*-ethyl, 53:47; *C*-isopropyl, 83:17. The equilibrium values are rationalized in terms of a balance between electronic stabilization and steric destabilization of the *Z* isomers. Hydrolysis of **9Z** in aqueous acid at 100 °C gave *S*-methyl thiobenzoate and *N*-methylhydroxylamine, whereas basic hydrolysis at 100 °C afforded *N*-methylbenzohydroxamic acid as the principal initial product.

The chemistry of nitrones derived from aldehydes and ketones has been extensively explored[1] since the first members of this family of dipolar compounds were reported.[2] In contrast, nitrones of esters (imidate *N*-oxides, A) and thio esters (thioimidate *N*-oxides, B) have appeared only infrequently in the recent literature. The preparation



A B

and dipolar cycloaddition reactions of the cyclic analogues, oxazoline and oxazine *N*-oxides, have been described,[3] and

(1) (a) Stamm, H. In *Methodicum Chimicum*; Korte, F., Ed.; Academic: New York, 1975; Vol. 6, pp 329–401. (b) Breuer, E. In *The Chemistry of Amino, Nitroso, and Nitro Compounds and their Derivatives*; Patai, S., Ed.; Wiley: Chichester, West Sussex, 1982; Part 1, pp 459–564. (c) Rundel, W. In *Methoden der Organischen Chemie (Houben-Weyl)*; Mueller, E., Ed.; Georg Thieme: Stuttgart, 1968; Vol. 10/4, pp 309–448. (d) Delpierre, G. R.; Lamchen, M. *Q. Rev.* **1965**, *19*, 329–348. (e) Hamer, J.; Macaluso, A. *Chem. Rev.* **1964**, *64*, 473–495.

(2) Dittrich, M.; Pinner, A. *Chem. Ber.* **1890**, *23*, 3589–3608.

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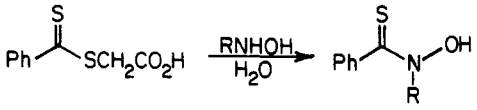
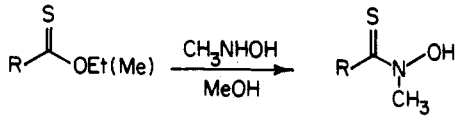
the formation of a related 2-methoxypyrroline *N*-oxide is mentioned in a review.[4] The first acyclic imidate *N*-oxides were prepared in low yield recently in our laboratory by condensation of benzamide acetal with *N*-methylhydroxylamine.[3c] To our knowledge there exist only two isolated reports of thioimidate *N*-oxides in the literature.[5] This paper presents a new, general synthesis of thioimidate *N*-oxides via S-alkylation of thiohydroxamic acids[6] as well as physical and chemical characteristics of this new family of nitrones.

Syntheses. Since thioamides undergo facile alkylation on sulfur to form thioimidates and thioalkyl iminium ions,[7] it seemed likely that *N*-alkylthiohydroxamic acids[6] would undergo similar S-alkylation to afford salts of thioimidate *N*-oxides. The requisite *N*-alkylthiohydroxamic acids (**2**, **3**, **5a–c**) were prepared by thioacylation of the appropriate *N*-alkylhydroxylamine. Reaction of *N*-methyl- and *N*-benzylhydroxylamines with *S*-(thiobenzoyl)thioglycolic acid (**1**)[8] in water at pH 7 and room temperature afforded *N*-methyl- and *N*-benzylbenzothiohydroxamic acids (**2** and **3**) in 83% and 71% yield, respectively. *O*-Ethyl thio-



1

2, R = CH_3 (83%)
3, R = $PhCH_2$ (71%)

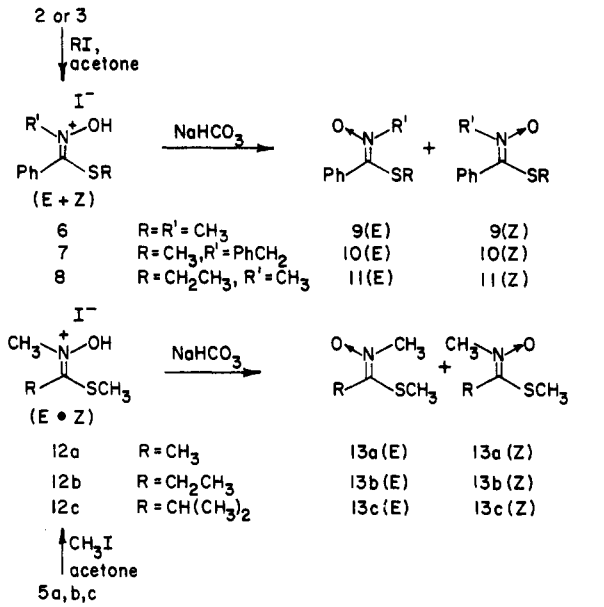


4a, 4b, 4c

5a, R = CH_3 (54%)
5b, R = CH_3CH_2 (55%)
5c, R = $(CH_3)_2CH$ (30%)

acetate (**4a**) and thiopropionate (**4b**, 71%) were prepared by ferric chloride catalyzed sulfhydrolysis of ethyl orthoacetate and orthopropionate.[9] Reaction of isobutyronitrile imino ether hydrochloride[10] with hydrogen sulfide in quinoline[11] gave *O*-methyl thioisobutyrate (**4c**) in 78% yield. The alkyl series of *N*-alkylthiohydroxamic acids **5a–c** was obtained by thioacylation of *N*-methylhydroxylamine with thio esters **4a–c** in methanol at room temperature for 4.5–48 h.[11b,12]

S-Alkylation of the *N*-alkylthiohydroxamic acids was accomplished by reaction with 3 equiv of methyl iodide in acetone[13] at room temperature for 2–48 h or 3 equiv of ethyl iodide in refluxing acetone for 10 h. The resulting nitrone hydriodide salts were obtained in most cases as crystalline solids that crystallized from solution either during the reaction or afterwards upon addition of ether. Hydroiodide **12a** crystallized during the reaction as a single pure isomer which is assigned the *Z* stereochemistry. The other five hydriodide salts were obtained as mixtures of *E* and *Z* isomers. Analysis of the progress of the alkylations by ^1H NMR spectroscopy revealed that the *E*/*Z* ratio was time dependent during and/or subsequent to the reaction. In general, the proportion of the apparently less stable hydriodides was higher in the earlier stages of the reaction. The ratios of the *C*-alkyl salts changed while the reactions were in progress while the *C*-phenyl salts **6** and **7** underwent equilibration more slowly following completion of the alkylations. The following *E*/*Z* ratios attained after 21 days (12 h for **7**) at room temperature appear to represent final equilibrium values: *E*/*Z* ratio for **6**, 35:65; **7**, 25:75 (12 h); **12b**, 5:95; **12c**, 1:99. However, some uncertainty remains whether the slower equilibrations of **6** and **7** were actually complete. In any case, the time dependence of the *E*/*Z* ratio of the hydriodide salts offers a way to obtain altered proportions of the *E* and *Z* nitrone isomers.



The free thio ester nitrones were liberated from the hydriodides with aqueous sodium bicarbonate (or carbonate) and were isolated by extraction with dichloromethane. The *E*/*Z* ratio of the resulting nitrone before crystallization was the same as that of its hydriodide precursor in each case. Five of the thio ester nitrones crystallized readily as the pure *Z* isomers. The one exception was **13c** (R = isopropyl) which was isolated after partial equilibration as a liquid with a 32:68 *E*/*Z* ratio. The *C*-phenyl nitrones were stable in the open atmosphere, whereas the alkyl series **13a–c** proved to be quite hygroscopic. The crystalline *C*-methyl and *C*-ethyl thio ester nitrones **13a** and **13b** were best isolated by filtration in a glovebag to avoid rapid deliquescence. The absorption of water by the *C*-alkyl nitrones is evidently a physical hydration of the *N*-oxide rather than hydrolysis since **13aZ** was shown to be stable in D_2O solution at room temperature for 72 h and all three compounds could be isolated

(3) (a) Lee, T. D.; Keana, J. F. W. *J. Org. Chem.* **1976**, *41*, 3237–3241. (b) Ashburn, S. P.; Coates, R. M. *Ibid.* **1984**, *49*, 3127–3133. (c) Ashburn, S. P.; Coates, R. M. *Ibid.* **1985**, *50*, 3076–3081. (d) Hendrickson, J. B.; Pearson, D. A. *Tetrahedron Lett.* **1983**, *24*, 4657–4660.

(4) Zbaida, S.; Brewer, E., unpublished results cited in ref 1b pp 528–529.

(5) (a) Kerr, D. A.; Wilson, D. A. *J. Chem. Soc. C* **1970**, 1718–1725. (b) Pennings, M. L. M.; Reinhoudt, D. N. *J. Org. Chem.* **1982**, *47*, 1816–1823.

(6) Walter, W.; Schaumann, E. *Synthesis* **1971**, 111–130.

(7) Walter, W.; Voss, J. In *The Chemistry of Amides*; Zabicky, J., Ed.; Interscience: London, 1970; pp 383–475.

(8) *S*-(Thiobenzoyl)thioglycolic acid (**1**) is available from Aldrich Chemical Co. It may also be prepared by the following literature procedure: Kurzer, F.; Lawson, A. *Organic Syntheses*, Wiley: New York, 1973; Collect. Vol. V, pp 1046–1049.

(9) Ohno, A.; Koizumi, T.; Tsuchihashi, G. *Tetrahedron Lett.* **1968**, 2083–2085.

(10) McElvain, S. M.; Venerable, J. T. *J. Am. Chem. Soc.* **1950**, *72*, 1661–1669.

(11) (a) Renson, M.; Bidaine, J. *Bull. Soc. Chim. Belg.* **1961**, *70*, 519–535. (b) Mizukami, S.; Nagata, K. *Chem. Pharm. Bull.* **1966**, *14*, 1249–1255.

(12) Corey, E. J.; Wright, S. W. *Tetrahedron Lett.* **1984**, 2639–2640.

(13) (a) Peak, D. A.; Stansfield, F. *J. Chem. Soc.* **1952**, 4067–4075. (b) Walter, W.; Ruback, W.; Meese, C. O. *Chem. Ber.* **1980**, *113*, 171–182.

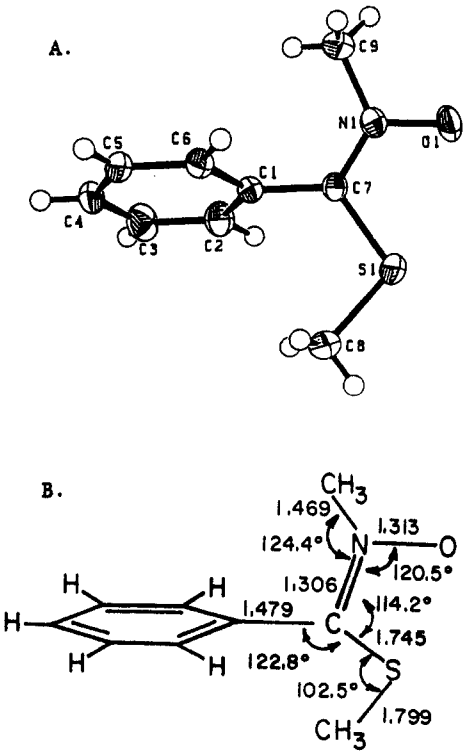


Figure 1. (A) An ORTEP plot showing the structure of *C*-phenyl thio ester nitrone **9Z** in the solid state from a single-crystal X-ray analysis. (B) A conformational depiction of **9Z** in the solid state showing the bond lengths and bond angles of the nitrone group.

by aqueous extractions. Furthermore the *C*-phenyl nitrone **9Z** was unaffected after heating in water at 100 °C for 7.7 h.

The high polarity of the nitrones was evident from their behavior upon thin layer chromatographic analysis. The R_f values of **9Z**, **10Z**, **11Z**, and **13aZ** on silica gel with 1:1 ethanol/ethyl acetate were as follows: 0.11, 0.50, 0.40, and 0.10, respectively. Nitrone **9Z** could be purified efficiently by flash chromatography on silica gel with 1:1 ethanol/ethyl acetate as eluant, and the *E* and *Z* proportions of **13c** could be enriched by chromatography on silica gel.

A potentiometric titration gave a value of 2.30 ± 0.02 for the pK_a of hydriodide **6Z**. Unfortunately the only pK_a data available for nitrones[14] were measured in acetonitrile (benzaldehyde *N*-methylnitrone, $(pK_a)_{AN} = 8.26$).[14b] Since the value of ΔpK_a for transfer of protic acids from water to acetonitrile varies widely ($\Delta pK_a = +4.9$ to $+16.5$),[15] a precise comparison cannot be made at this time. However, if pyridinium ion ($\Delta pK_a = +7.16$)[15] is considered a suitable model, **6Z** would be one pK_a unit more acidic than protonated aldonitrones in acetonitrile. Thioimidate *N*-oxide **6Z** is 4.12 p*K* units less basic than the corresponding thioimidate (pK_a 6.42 in H_2O),[16] a difference similar to that between pyridine and pyridine *N*-oxide ($\Delta pK_a = -4.38$ in H_2O).[17]

Structure and Stereochemistry. An X-ray crystallographic analysis was performed on the nonhygroscopic, *C*-phenylnitrone **9Z** in order to verify the structure, to establish unequivocally the stereochemistry, and to obtain bond length and bond angle information. An ORTEP drawing (A)[18] and a conformational representation (B) showing the principal bond lengths and bond angles around the nitrone are presented in Figure 1. The phenyl ring is twisted into an almost orthogonal relationship to the plane of the nitrone function ($\phi = 65.6°$). On the other hand, the methyl group on sulfur is almost coplanar ($\phi = 13.6°$) with the nitrone group and anti to nitrogen. This conformation allows delocalization of nonbonded electrons on sulfur into the C=N group and avoids steric interactions between the *S*-methyl and the *N*-oxide oxygen.

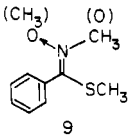
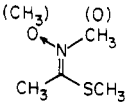
The somewhat longer C=N bond length (1.306 Å) compared to that of the *N*-methylnitrone of 4-chloro-2,6-dimethylbenzaldehyde (1.299 Å)[19] in which the substituted benzene ring is also twisted out of conjugation may be attributed to a slight decrease in double bond character in the former resulting from the electronic interaction with the sulfur atom. The C=N—O bond angle (120.5°) is smaller than the corresponding angle (124.6–125.3°)[19,20] of *N*-methylnitrones of aryl aldehydes (including the same twisted 4-chloro-2,6-dimethylbenzaldehyde nitrone). The S—C=N bond angle (114.2°) is also contracted, whereas the Ph—C=N and C=N—CH_3 bond angles (123.0° and 124.4°) are correspondingly expanded. These deformations are evidently a consequence of an attractive interaction between sulfur and oxygen and steric repulsion between the phenyl and *N*-methyl groups. The S···O interatomic distance of 2.72 Å is considerably less than the sum of the S and O van der Waals radii (3.25 Å).[21] Similar attractive nonbonded S···O interactions have been observed in X-ray crystal structures of two *o*-nitrophenyl sulfides (S···O interatomic distances = 2.44 and 2.64 Å),[22] albeit in a five-atom array rather than the four-atom relationship in **9Z**. Since the thermal *E*/*Z* equilibrations to be discussed later indicate at most a relatively small thermodynamic stabilization of the *Z* isomers, the resemblance to the hypervalent bonding of 10-S-3 sulfuranes is probably rather remote.[23]

The *E*/*Z* stereochemistry of the other two *C*-phenyl nitrones **10** and **11** can be assigned with confidence on the basis of ^1H NMR chemical shift comparisons with **9** as well as the results of the thermal equilibrations (see below). However, the *E*/*Z* assignments for the three *C*-alkyl nitrones (**13a–c**) must be regarded as tentative since they are based on small nuclear Overhauser enhancements, long-range coupling, and rather tenuous chemical shift correlations.

Spectral Properties. ^1H and ^{13}C NMR chemical shifts and chemical shift differences for two representative thio ester nitrones (**9** and **13a**) are presented in Table I. The δ_H values for the *N*-alkyl and *C*-alkyl groups of the nitrones exhibit rather consistent trends for the *E* and *Z* isomers. The chemical shifts for the ortho aromatic protons (δ 7.38–7.66) in **9Z**, **10Z**, and **11Z** indicate that the phenyl group is twisted out of conjugation in solution as it is in

(14) (a) Bren, V. A.; Medyantseva, E. A.; Minkin, V. I. *Org. React. (N.Y., Engl. Transl.)* **1968**, *5*, 413–415. (b) Bren, V. A.; Medyantseva, E. A.; Andreeva, I. M.; Minkin, V. I. *J. Org. Chem. USSR (Engl. Transl.)* **1973**, *9*, 790–792.
(15) Coetzee, J. F. *Prog. Phys. Org. Chem.* **1967**, *4*, 45–92.
(16) Kjellin, G.; Sandstroem, J. *Acta Chem. Scand.* **1973**, *27*, 209–217.
(17) Kondratov, V. K.; Novikov, E. G. *Russ. J. Phys. Chem. (Engl. Transl.)* **1971**, *45*, 1259–1261.
(18) Johnson, C. K. "ORTEP-II: A Fortran Thermal Ellipsoid Plot Program"; ORNL-3794; Oak Ridge National Laboratory: Oak Ridge, TN, 1971.
(19) Jensen, K. G.; Jerslev, B. *Acta Crystallogr., Sect. B* **1969**, *25B*, 916–925.
(20) (a) Folting, K.; Lipscomb, W. N.; Jerslev, B. *Acta Crystallogr.* **1964**, *17*, 1263–1275; *Acta Chem. Scand.* **1963**, *17*, 2138–2139. (b) Bachechi, F.; Zambonelli, L. *Acta Crystallogr., Sect. B* **1975**, *31B*, 2499–2501. (c) Brown, J. N.; Trefonas, L. M. *Ibid.* **1973**, *29*, 237–241.
(21) Pauling, L. *The Nature of the Chemical Bond*; Cornell University: Ithaca, NY, 1960; pp 260–262.
(22) (a) Korp, J. D.; Bernal, I.; Miller, R. F.; Turley, J. C.; Williams, L.; Martin, G. E. *J. Cryst. Mol. Struct.* **1978**, *8*, 127–140. (b) Hamilton, W. C.; LaPlaca, S. J. *J. Am. Chem. Soc.* **1964**, *86*, 2289–2290.
(23) (a) Perkins, C. W.; Martin, J. C.; Arduengo, A. J.; Lau, W.; Alegria, A.; Kochi, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 7753–7759. (b) Perkins, C. W.; Wilson, S. R.; Martin, J. C. *Ibid.* **1985**, *107*, 3209–3218.

Table I. ^1H and ^{13}C NMR Chemical Shifts and Chemical Shift Differences for the *E* and *Z* Isomers of *C*-Phenyl and *C*-Methyl Thio Ester Nitrones 9 and 13a[a]

		δ_H			δ_C			
		C-R	SCH_3	NCH_3	C-R	SCH_3	NCH_3	C=N
 9	*E*	7.79–7.88[b]	2.09	4.10	131.59[c]	17.56	51.71	142.87
	Z	7.45–7.57[b]	1.88	3.51	130.85[c]	15.01	48.27	150.10
	$\Delta\delta_{E\rightarrow Z}$	−0.55	−0.21	−0.59	−0.74	−2.55	−3.44	+7.23
 13a	*E*[d]	2.36	2.43	3.85	16.34	17.86	48.72	150.29
	Z[d]	2.28	2.34	3.72	14.36	16.56	47.03	146.21
	$\Delta\delta_{E\rightarrow Z}$	−0.08	−0.09	−0.13	−1.98	−1.30	−1.69	−4.08

[a] In $CDCl_3$. [b] Ortho hydrogens of C_6H_5. [c] Ipso carbon of C_6H_5. [d] Assignment of *E* and *Z* configuration to **13a** isomers is tentative (see text).

the solid state of **9Z**. The ortho protons in the *N*-methylnitrone (*Z* isomer) of benzaldehyde and other unhindered *C*-arylnitrones resonate at relatively low field (δ_H 8.16–8.28) owing to the proximity of the *N*-oxide in the planar, conjugated conformation.[24] Consequently the upfield shift of the *N*-alkyl and *S*-alkyl groups in **9Z**, **10Z**, and **11Z** can be attributed to the shielding influence from the π-electrons of the twisted benzene ring. The downfield shifts ($\Delta\delta$ +0.3–0.5) of the peaks for the α-protons of the *C*-alkyl groups in the hydriodide salts **12a–c** compared to the corresponding nitrones presumably reflect the increased positive charge at the iminium carbon.

Long-range coupling (J = 1.2 Hz) is observed between the *N*-methyl and *C*-methyl groups in the ^1H NMR spectrum of the **13a** isomer exhibiting the lower field *N*-methyl absorption (δ_H 3.85). Such homoallylic coupling between groups lying across C=N double bonds has been reported for cyclic nitrones,[25] imines,[26] imidates,[27] and thioimidates.[28] The fact that the five-bond coupling between two trans methyl groups (^5J = 1.2–1.5 Hz) is invariably larger than it is between cis methyl groups (^5J = 0.4–0.9 Hz) is consistent with the *E* stereochemical assignment for the **13a** isomer exhibiting long-range coupling. The width at half-height of the *N*-CH_3 and *C*-CH_3 singlets ($W_{1/2}$ = 2.2 Hz) from the other isomer (**13aZ**) indicates $J \leq 0.5$ Hz.

Attempts were made to detect nuclear Overhauser effects in the ^1H NMR spectra of **13a–c** as mixtures of *E* and *Z* isomers in order to obtain more evidence regarding the stereochemistry about the C=N double bond. Although quite small NOEs would be expected for the *N*-methyl and the α-proton(s) of the *C*-alkyl groups in the *Z* isomers, enhancements as low as 1–4% can be detected by the difference NOE method[29] and an NOE of 4.4% has been used to assign the rotomeric configuration of *N*-amino-*N*-methylthioacetamide.[29b]

NOE difference spectra were measured on relatively dilute solutions (0.05 M in $CDCl_3$) in order to minimize the possibility of intermolecular NOEs owing to dimer formation.[30] The small NOEs observed between the *N*-CH_3 and *C*-alkyl groups of **13aZ** (1.0–1.2 ± 0.3%) and **13bZ** (2.7–3.4 ± 0.3%) are consistent with the stereochemical assignments. The corresponding *E* isomers (**13aE** and **13bE**) exhibited negligible or small negative enhancements (−0.5 to −0.7%) between the *N*-methyl and *C*-alkyl groups.

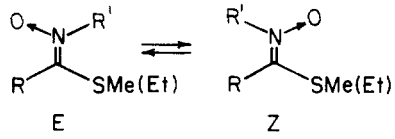
The ^{13}C NMR chemical shifts for the iminyl carbon of the nitrones range from δ_c 142.9 (**9E**) to 151.9 (**13cZ**). The upfield shift from the position of the iminyl carbon in thioimidates (*S*-methyl *N*-methylthiobenzimidate, $\delta_{C=N}$ 166.7 (*E*) and 166.0 (*Z*))[31] presumably reflects an increased charge density at carbon in the nitrones from the nitrosonium ylide resonance contributor.[32] The iminyl carbon invariably appears 20–30 ppm upfield in the ^{13}C NMR spectra of nitrones compared to its position in spectra of the corresponding imines.[3c,33] A 10 ppm upfield shift of the ^{13}C NMR peak for C-2 in pyridine *N*-oxide is similarly attributed to nitrosonium carbanion resonance forms.[34] On the other hand, the ^{13}C NMR absorptions for the iminyl carbons of the hydriodide salts (three *E* and five *Z*) are shifted downfield (δ_C 176.3–187.6) with respect to their shifts in the thio ester nitrones.

The IR spectra ($CHCl_3$, Me_2SO, and KBr) of the thio ester nitrones exhibit C=N and N–O stretching vibrations in the same regions as those of aldo and keto nitrones.[1a] The bands for the C=N group appear at 1540–1560 cm^{-1} for the *C*-phenylnitrones and at 1576–1580 cm^{-1} for the *C*-methyl and *C*-ethyl analogues. The *N*-oxide stretching vibrations appear in the range 1222–1281 cm^{-1}.

The UV spectrum (MeOH) of *Z* nitrones **9–11** and **13a** show maxima at 273–277 (ϵ_{max} 8200–11 000) and 262 nm (ϵ_{max} 11 700), respectively. Evidently the thioalkyl substituents are responsible for the shift of these presumed $\pi \rightarrow \pi^*$ transitions to longer wavelength with respect to those of *C*,*N*-dialkylnitrones (λ^{ROH} 229–236 nm)[24a,35] and the phenyl-twisted *N*-methylnitrone of acetophenone (λ_{max}

(24) (a) Koyano, K.; Susuki, H. *Tetrahedron Lett.* **1968**, 1859–1864. (b) Koyano, K.; Suzuki, H. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 3306–3309. (c) Grubbs, E. J.; Milligan, R. J.; Goodrow, M. H. *J. Org. Chem.* **1971**, *36*, 1780–1785. (d) Arumugam, N.; Manisankar, P.; Sivasubramanian, S.; Wilson, D. A. *Magn. Reson. Chem.* **1985**, *23*, 246–249.
(25) Black, D. St. C.; Brown, R. F. C.; Dunstan, B. T.; Sternhell, S. *Tetrahedron Lett.* **1974**, 4283–4284.
(26) (a) Kyba, E. P. *Tetrahedron Lett.* **1973**, 5117–5120. (b) Findeisen, K.; Heitzer, H.; Dehnicke, K. *Synthesis* **1981**, 702–704.
(27) Meese, C. O.; Walter, W.; Berger, M. *J. Am. Chem. Soc.* **1974**, *96*, 2259–2260.
(28) Walter, W.; Meese, C. O. *Chem. Ber.* **1976**, *109*, 922–946.
(29) (a) Hall, L. D.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1980**, *102*, 5703–5711. (b) Eggert, H.; Nielsen, P. H. *Tetrahedron Lett.* **1981**, 4853–4854.
(30) Schilling, G.; Klosterhalfen, B. *Org. Magn. Reson.* **1979**, *12*, 605–606.
(31) Walter, W.; Ruback, W.; Meese, C. O. *Org. Magn. Reson.* **1978**, *11*, 612–616.
(32) Arumugam, N.; Manisankar, P.; Sivasubramanian, S.; Wilson, D. A. *Org. Magn. Reson.* **1984**, *22*, 592–596.
(33) (a) Albright, T. A.; Freeman, W. J. *Org. Magn. Reson.* **1977**, *9*, 75–79. (b) Olah, G. A.; Donovan, D. J. *J. Org. Chem.* **1978**, *43*, 860–865.
(34) (a) Cushley, R. J.; Naugler, D.; Ortiz, C. *Can. J. Chem.* **1975**, *53*, 3419–3424. (b) Anet, F. A. L.; Yavari, I. *J. Org. Chem.* **1976**, *41*, 3589–3591. (c) Günther, H.; Gronenborn, A. *Heterocycles* **1978**, *11*, 337–345.
(35) (a) Kaminsky, L. S.; Lamchen, M. *J. Chem. Soc. B* **1968**, 1085–1087. (b) Elsworth, J. F.; Lamchen, M. *J. Chem. Soc. C* **1968**, 2423–2427.

Table II. *E*/*Z* Ratios of Nitrones Resulting from Thermal Equilibrations[a]



cmpd	R	R′	*t*, °C	*E*–*Z* ratio[b] initial	final
9	Ph	Me	80	0:100	5:95
			147	47:53	8:92[c]
			156	0:100	8:92[d]
10	Ph	$PhCH_2$	80	0:100	7:93
11	Ph	Me[e]	80	0:100	12:88
13a	Me	Me	80	0:100	46:54
13b	Et	Me	80	6:94	53:47
			80	6:94	50:50
13c	iPr	Me	80	42:58	83:17
			25	20:80	76.24[f]
			25	92:08	75:25[f]

[a] 98–107 mM in C_6D_5Br at 80 °C unless specified otherwise. [b] Error estimated at ±1–2%. [c] Neat liquid. [d] Melt. [e] *S*-Ethyl instead of *S*-methyl. [f] In $CDCl_3$ at 25 °C.

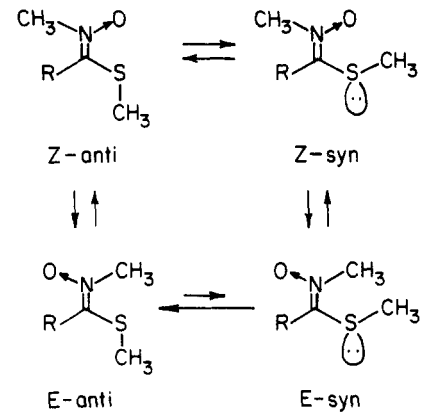
258 nm).[36] The fully conjugated *C*-phenyl-*N*-methylnitrone shows λ^{ROH} 288–292 nm.[24a,36,37]

Reactions. Thermal equilibrations of the thio ester nitrones were carried out in order to evaluate the relative thermodynamic stabilities of the *E* and *Z* isomers (Table II). The approach to equilibrium was monitored closely by ^1H NMR spectroscopy both during the initial phase as the isomer ratios were changing (0.5–8 h) and for long periods (25–52 h) after the ratios had stabilized. All six nitrones were equilibrated in bromobenzene-d_5 at 80 °C. In addition, *C*-phenylnitrone **9** was equilibrated in the melt at 147 and 156 °C and *C*-isopropylnitrone **13c** was equilibrated in chloroform-*d* at 25 °C over 24 days. The latter equilibria were approached from both directions.

It is apparent that the *C*-phenylnitrones are considerably more stable in the *Z* configuration (88–95% *Z* at 80 °C), whereas the *E* and *Z* isomers of the *C*-methyl- and *C*-ethylnitrones are of about equal stability (54–47% *Z* at 80 °C). The *C*-isopropylnitrone equilibrates in favor of the *E* isomer (83% *E* in C_6D_5Br at 80 °C, 75–76% *E* in $CDCl_3$ at 25 °C).

The relative stabilities of the *E* and *Z* thio ester nitrones will be influenced by conformational equilibria of the substituents, steric interactions, and electronic effects. The anti and syn conformers shown below arise from rotation about the C–S bond. We assume that the *S*-methyl (or *S*-ethyl) groups will always reside in the plane of the nitrone in order to allow maximum delocalization of a sulfur nonbonding electron pair with the nitrone. Conformers arising from rotation about the R–C, NCH_2–Ph (in **10**), and SCH_2–CH_3 (in **11**) bonds may also play a role.

Since *N*-methylnitrones of aldehydes are invariably more stable in the *Z* form (R and *N*-CH_3 groups anti),[1a,38] it is clear that the NCH_3···R steric interactions are greater than the NO···R interactions and in this regard the *Z* thio ester nitrones should be destabilized with respect to the *E* isomers. The NCH_3···SCH_3 interaction in the *E*-syn conformer is similar to a 1,3-diaxial interaction between methyl groups on a cyclohexane ring, albeit attenuated to some extent by the longer C–S and S–CH_3 bonds. Consequently, the *E* isomers will presumably exist predominantly in the *E*-anti conformation. The *Z*-anti and *E*-anti conformers are both destabilized by R···SCH_3 interactions while the *Z*-syn conformer is destabilized by the NO···SCH_3 interaction. The *E* isomer of the three *C*-phenylnitrones may be destabilized by repulsion between the π-electrons of the twisted phenyl group and the *N*-oxide.[38b]



An n → σ* electronic interaction between a nonbonded electron pair on sulfur and the C=N group should stabilize the two syn conformers in a manner similar to thio esters.[39] The attractive S–O interaction revealed by the X-ray structure of **9Z** should stabilize the *Z*-anti conformers to some extent. The resonance interaction of the sulfur substituent with the nitrone generates sulfonium–*N*-oxide dipolar character. The separation of the resultant charges and net dipole moment should be less in the *Z* conformers which should therefore be stabilized with respect to their *E* counterparts. The enhanced stability of the *s*-cis conformers of α-diazo aldehydes and ketones[40] as well as *cis*-1,2-dihaloethylenes[41] has been attributed to a similar electrostatic stabilization of the cis forms. Alternatively, the energy difference may be explained by a conjugative destabilization of the trans forms.[42]

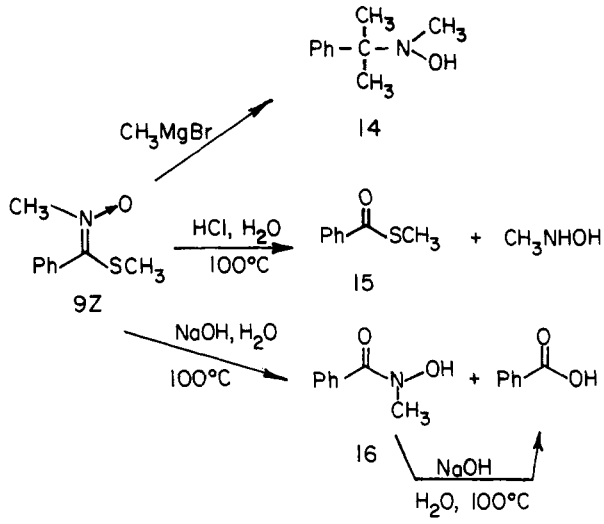
The relative stabilities of the *E* and *Z* thio ester nitrones can be rationalized in terms of a balance between electronic stabilization and steric destabilization of the *Z*-isomers. In the absence of the NCH_3···R steric interaction, we assume that the *Z* isomer is inherently more stable than the *E* isomer owing to weak attractive S···O interaction (*Z*-anti conformer), n → σ* interaction (*Z*-syn conformer), and/or minimization of charge separation. However, as the *C*-R substituent becomes larger, the increased NCH_3···R steric interaction counteracts the electronic stabilization of the *Z* isomer. Since the van der Waals radius of a methyl group (2.0 Å) is larger than the half-thickness of a benzene ring (1.7Å),[21] the twisted-Ph···NCH_3 steric interaction should be less than the NCH_3···CH_3 interaction. Thus, the relative stability order of the *Z* isomers, Ph > Me ≥ Et > *i*-Pr, follows the order of increasing steric size of the *C*-R substituent. If this interpretation is valid, the equilibrium for the corresponding thioformate nitrone (R = H) should greatly favor the *Z* isomer.

(36) Kubota, T.; Yamakawa, M.; Mori, Y. *Bull. Chem. Soc. Jpn.* **1963**, *36*, 1552–1563.
(37) Thesing, J.; Sirrenberg, W. *Chem. Ber.* **1958**, *91*, 1978–1980.
(38) (a) Boyle, L. W.; Peagram, M. J.; Whitham, G. H. *J. Chem. Soc. B* **1971**, 1728–1733. (b) Bjørgo, J.; Boyd, D. R.; Neill, D. C.; Jennings, W. B. *J. Chem. Soc., Perkin Trans. 1* **1977**, 254–259.
(39) Exner, O.; Jehlička, V.; Firl, J. *Collect. Czech. Chem. Commun.* **1971**, *36*, 2936–2943. (b) Staeglich, P.; Thimm, K.; Voss, J. *Liebigs Ann. Chem.* **1974**, 671–689. (c) Pelinghelli, M. A.; Tiripicchio, A.; Tiripicchio-Camellini, M. *Cryst. Struct. Commun.* **1974**, *3*, 159–162.
(40) (a) Kaplan, F.; Meloy, G. K. *J. Am. Chem. Soc.* **1966**, *88*, 950–956. (b) Kessler, H.; Rosenthal, D. *Tetrahedron Lett.* **1973**, 393–396.
(41) (a) Epiotis, N. D. *J. Am. Chem. Soc.* **1973**, *95*, 3087–3096. (b) Epiotis, N. D.; Sarkanen, S.; Bjorkquist, D.; Bjorkquist, L.; Yates, R. *Ibid.* **1974**, *96*, 4075–4084.
(42) Bingham, R. C. *J. Am. Chem. Soc.* **1976**, *98*, 535–540.

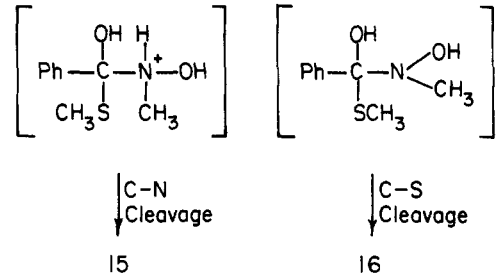
Since the separation of charges and dipole moment in the *E* isomer should be larger than they are in the *Z*, one might have expected that the proportion of the *E* isomer at equilibrium would be increased in more polar solvents. However, the *E*/*Z* ratio in melt equilibrations of **9** at 147 and 156 °C proved to be quite similar (8:92) to that observed in bromobenzene (5:95). The melt should constitute a highly polar medium owing to the high concentration of *N*-oxide groups. Furthermore, heating **9Z** in dimethyl sulfoxide-d_6 at 100 °C also resulted in apparent equilibration to a 6:94 *E*/*Z* ratio along with some hydrolysis of the nitrone.

Equilibrium *E*/*Z* ratios for a similar series of *S*-methyl *N*-methyl thioimidates in benzene-d_6 at 38 °C have been reported.[13b,28] The proportion of the *E* isomer (corresponds to *Z* isomer of the nitrones) at equilibrium in the *C*-alkyl series decreased as follows: R = Me, 76%; R = Et, 57%; R = *i*-Pr, 37%.[28] This similar trend also presumably reflects a destabilization of the *E* isomer from an increasing NCH_3···R steric interaction. The lower proportion of *E* found for the C-phenyl thioimidate (63%) may be attributed to some degree of conjugation of the phenyl group with the C=N group in this less crowded environment.

Since the thioimidate *N*-oxides may be regarded as analogues of thio esters, we expected that nucleophilic substitution of the *S*-alkyl group could be accomplished. Reaction of nitrone **9Z** with excess methylmagnesium bromide in THF–CH_2Cl_2 at 0 °C gave hydroxylamine **14** in 59% yield. A mechanism consisting of Grignard addition, thiolate elimination to give the *N*-methylnitrone of acetophenone, and a second Grignard addition seems likely for this reaction. The addition of Grignard reagents to aldo and keto nitrones is well-known.[1]



The hydrolysis of **9Z** was carried out under acidic and basic conditions. Although the nitrone proved to be remarkably stable in water (no change after 7.7 h at 100 °C), hydrolysis with 2.1 equiv of HCl in water at 100 °C for 2 h gave methyl thiobenzoate (**15**, 81%) and *N*-methylhydroxylamine (50%). Hydrolysis of **9Z** with 2 equiv of NaOH in water at 100 °C for 2.5 h gave a mixture of benzoic acid (68%) and *N*-methylbenzohydroxamic acid (**16**, 20%). Control experiments demonstrated that **15** is completely hydrolyzed under the basic reaction conditions and that **16** undergoes substantial hydrolysis to benzoic acid (73%). When the basic hydrolysis of **9Z** was interrupted at low conversion (20 min), the proportion of hydroxamic acid **16** in the product was increased to 83%. Thus, the predominant, if not exclusive, product formed under basic conditions is **16**, which undergoes subsequent



base-catalyzed hydrolysis to benzoic acid. It is apparent that acidic conditions favor C–N bond cleavage by protonation of nitrogen in the tetrahedral intermediate, whereas basic conditions favor C–S bond cleavage to form the more stable thiolate anion in a manner similar to the hydrolytic behavior of acyclic *N*,*N*-dialkyl imidates and thioimidates.[43]

Experimental Section

Melting points were determined on a Thomas Hoover capillary melting point apparatus or on a Reichert (Austria) micro cover glass melting point apparatus. All melting and boiling points are uncorrected. IR spectra were obtained with an IBM instruments IR/32 FTIR spectrometer or a Model 137 Perkin-Elmer infracord spectrophotometer calibrated with a polystyrene film (1603 cm^{-1}). ^1H NMR spectra were recorded on a Varian Associates Model EM 390 (90 MHz) or Model XL-200 (200 MHz) NMR spectrometer. Broad-band proton-decoupled ^{13}C NMR spectra were recorded at 50.3 MHz on a Varian Associates Model XL-200 NMR spectrometer or at 90.5 MHz on a Nicolet Model NT-360 NMR spectrometer. UV spectra were recorded on a Perkin-Elmer Lambda 3 UV–vis spectrophotometer. Low-resolution electron-impact (LR-EI) mass spectra were obtained on a Varian-MAT CH-5 spectrometer, and high-resolution electron-impact (HR-EI) peak matching was performed on a Varian-MAT 731 mass spectrometer. Elemental analyses were performed by J. Nemeth and associates at the University of Illinois microanalytical laboratory.

Thin-layer chromatographic (TLC) analyses were carried out on Brinkmann plastic sheets coated with a 0.25-mm layer of silica gel incorporating a (UV 254) fluorescent indicator. Visualization was effected with short (254 nm) UV light and/or by spraying with a phosphomolybdic acid reagent solution (a 7% solution of phosphomolybdic acid, 48-hydrate in 1:19 concentrated sulfuric acid–95% ethyl alcohol). Gas chromatographic (GC) analyses were carried out on a Varian Model 3700 gas chromatograph equipped with a flame ionization detector. A glass column (6.3 mm by 3.6 m) packed with 3% OV-17 on Gas Chrom Q was used with a helium flow rate of ca. 30 mL/min. Flash chromatographic separations[44] were performed under elevated pressure in glass columns on Woelm silica gel purchased from Universal Scientific or from EM Science. The weight ratio of silica gel to mixture was in the range 75–110 to 1.

Dry acetone, diethyl ether, and absolute ethyl and methyl alcohols were used as received. Tetrahydrofuran was dried by distillation from sodium benzophenone ketyl under a nitrogen atmosphere immediately before use. All thiohydroxamic acids synthesized gave a positive ferric chloride test—the formation of intensely colored (purple, violet, or greenish) solutions with the following test reagent: 10% ferric chloride hexahydrate in 0.7 N hydrochloric acid.[45]

N-Methylhydroxylamine hydrochloride was purchased from Aldrich Chemical Company. *N*-Benzylhydroxylamine was pre-

(43) (a) Smith, V. F., Jr.; Schmir, G. L. *J. Am. Chem. Soc.* **1975**, *97*, 3171–3177 and references cited therein. (b) Chaturvedi, R. K.; MacMahon, A. E.; Schmir, G. L. *Ibid.* **1967**, *89*, 6984–6993. (c) Chaturvedi, R. K.; Schmir, G. L. *Ibid.* **1969**, *91*, 737–746.

(44) (a) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925. (b) Jarvis, B. B.; Midiwo, J. O. *Aldrichimica Acta* **1980**, *13*, 42.

(45) Sandler, S. R.; Karo, W. *Organic Functional Group Preparations*; Academic: New York, 1972; Vol. 3, p 412–413.

pared by the sodium cyanoborohydride reduction of *syn*-benzaldoxime[46] at pH 3 in anhydrous methanol as described by Borch and co-workers.[47] The yield was 27.0 g (49%), mp 54–55 °C (lit.[47] 58–59 °C). The hydrochloride salt was obtained by dissolving 18.4 g (0.149 mol) of *N*-benzylhydroxylamine in about 100 mL of dichloromethane, cooling the resulting solution in an ice bath, and bubbling hydrogen chloride gas through it for 10 min. Filtration and drying over calcium chloride under reduced pressure afforded 17.7 g (74%) of the hygroscopic salt: mp 103–104 °C (lit.[48] 105–107 °C); ^{1}H NMR (Me_2SO-d_6) δ 4.28 (s, 2 H, CH_2), 7.37 (m, 3 (Me_2SO-d_6) meta and para aryl H's), 7.53 (m, 2 H, ortho aryl H's), 11.85 (br s, 3 H, NH_2 and OH).

Hydrogen sulfide gas was dried by passage through a drying tower packed with 4-Å molecular sieves and calcium sulfate. The effluent stream from the reaction flask was passed through a series of traps consisting of an empty back-up, a 20% aqueous sodium hydroxide, and a 10% aqueous lead tetraacetate solution and finally into a large bath containing an aqueous Chlorox solution. Before workup of a reaction involving hydrogen sulfide, a stream of nitrogen gas was passed through the reaction mixture for 0.5–1 h to expel any dissolved hydrogen sulfide. Subsequent removal of solvent was done by simple distillation in the hood.

***N*-Hydroxy-*N*-methylbenzenecarbothioamide (2)** was prepared from 19.65 g (90.0 mmol) of *S*-(thiobenzoyl)thioglycolic acid (1)[8] and 8.40 g (99.0 mmol) of *N*-methylhydroxylamine hydrochloride according to the procedure of Jensen et al.[49] The pH of the cold, aqueous solution was adjusted to 7, the ice bath was removed, and the mixture was stirred vigorously until its color changed from orange to tan (15–20 min). The product was then isolated as described.[49] Distillation under reduced pressure yielded 12.5 g (83%) of *N*-hydroxy-*N*-methylbenzenecarbothioamide (2), bp 101–102 °C (0.35 mm), as a yellow, disagreeably smelling liquid. The ^{1}H NMR spectral data for the product are identical with those reported in the literature.[50]

***N*-Hydroxy-*N*-(phenylmethyl)benzenecarbothioamide (3)** was prepared as described above for **2** by using 4.95 g (40.2 mmol) of *N*-benzylhydroxylamine and 5.67 g (26.7 mmol) of *S*-(thiobenzoyl)thioglycolic acid (1) in 31 mL (31 mmol) of 1 N aqueous sodium hydroxide. The solution (pH 8–9) was stirred at room temperature for 1 h and extracted with four portions of ether. The combined ether extracts were washed three times each with dilute hydrochloric acid and water and were dried ($MgSO_4$). Evaporation of the filtrate and crystallization of the remaining oil with cyclohexane–anhydrous ether afforded two crops of the thiohydroxamic acid as a greenish yellow solid. The combined yield was 4.60 g (71%), mp 54–59 °C. A second recrystallization gave the analytically pure material as colorless plates: mp 63–65 °C (lit.[51] mp 59–60 °C); IR ($CHCl_3$) 3021 (CH), 1522 (CN) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.96 (s, 2 H, CH_2), 7.08–7.50 (m, 5 H, $CH_2C_6H_5$), 7.36 (s, 5 H, C_6H_5C=S), 10.68–10.97 (variable, exchangeable with D_2O) (br s, 1 H, OH); ^{13}C NMR ($CDCl_3$) δ 56.40 (CH_2), 126.93 and 127.49 (2 C each, meta and ortho C's in C_6H_5C=S), 128.40 (para C of C_6H_5 in NCC_6H_5), 128.63 and 128.81 (2 C each, ortho and meta C's in NCC_6H_5), 130.01 (para C of C_6H_5 in C_6H_5C=S), 133.48 (C-1 of C_6H_5 in NCC_6H_5), 138.1 (C-1 of C_6H_5 in C_6H_5C=S), 183.60 (C=S); TLC R_f 0.54 (1:1, EtOAc–hexane).

Anal. Calcd for $C_{14}H_{13}NOS$: C, 69.09; H, 5.40; N, 5.76; S, 13.18. Found: C, 68.96; H, 5.36; N, 5.68; S, 13.10.

***O*-Ethyl thioacetate (4a)**[52] was prepared by a modification of the literature procedure.[9] A suspension of 0.33 g (2.0 mmol) of ferric chloride in 100.35 g (0.600 mol) of triethyl orthoacetate was stirred magnetically and cooled at 0 °C as hydrogen sulfide gas was bubbled into the mixture at a rate of 11–14 mL/min for 13 h. The ferric chloride was filtered, and the filtrate (containing an estimated 58.0 g of 4a by GC) was fractionally distilled under nitrogen through a 20-cm Vigreux column. Three fractions were collected: A, 75.2 g (bp 73–74 °C); B, 3.81 g (bp 90–99 °C); C, 22.5 g (bp 99–100 °C). GC analysis indicated that each fraction consisted of a mixture of thionoacetate **4a**, ethyl acetate, ethanol, and an unidentified impurity in the following ratios: A (1.0:0.20:0.85:0); B (1.0:0.19:0.05:0.10); C (1.0:0.02:0:0.15). Only fraction C, 22.5 g (36%), boiling at 99–100 °C (lit.[9] bp 105–109 °C) was used in subsequent reactions.

***O*-Ethyl thiopropionate (4b)**[52] was synthesized from 0.33 g (2.0 mmol) of ferric chloride and 109.0 g (0.600 mol) of triethyl orthopropionate in the same manner described above for **4a** (0 °C, 5 h, 9–12 mL/min). Fractional distillation afforded four fractions A, 45.8 g (bp 74–76 °C); B, 19.3 g (bp 76–77 °C); C, 2.3 g (bp 76–110 °C); D, 50.5 g (bp 122–123 °C). Each fraction consisted of a mixture of thiono ester **4b**, ethyl propionate, ethanol, and an unidentified impurity in the following GC ratios: A (1.0:0.12:0.82:0); B (1.0:0.23:0.80:0); C (1.0:0.56:0.64:0.05); D (1.0:0.13:0:0.17). Fraction D, 50.5 g (71%), bp 122–123 °C (lit.[53] bp 129–30 °C), contained a product of satisfactory purity and was used in subsequent reactions.

***O*-Methyl thioisobutyrate (4c)**[52] was prepared in two steps from isobutyronitrile following published procedures for related compounds.[11] Methyl iminoisobutyrate hydrochloride was prepared from isobutyronitrile as described by McElvain and Venerable.[10] The yield of the salt was 216.5 g (79%): mp 117–119 °C dec; ^{1}H NMR ($CDCl_3$) δ 1.31 (d, 6 H, J = 7.0 Hz, 2 CCH_3), 3.26 (septet, 1 H, J = 7.0 Hz, CH), 4.31 (s, 3 H, OCH_3), 11.59 (br s, 1 H, NH_2). A heterogeneous mixture of 20.7 g (0.150 mol) of methyl iminoisobutyrate hydrochloride in 74.8 mL (0.64 mol) of quinoline was stirred mechanically and cooled at 0 °C as dry hydrogen sulfide was bubbled through the suspension at a rate of 17–21 mL/min for 2.0 h. Nitrogen gas was passed through the reaction mixture for ca. 1 h, after which several volumes of anhydrous ether were added. The precipitated ammonium chloride was filtered, the filtrate was extracted six times with 6 N hydrochloric acid and three times with water, and the ether phase was dried ($MgSO_4$). Distillation of the filtrate under nitrogen afforded 13.9 g (78%) of *O*-methyl thioisobutyrate (**4c**) as a pale greenish yellow strong-smelling liquid, bp 118–120 °C (lit. bp 119–121 °C,[54] 120 °C[55]), that was of satisfactory purity by ^{1}H NMR spectroscopy.

Fractional distillation of the product in the presence of quinoline as suggested in the literature,[11a] resulted in an increase in the proportion of the isomeric *S*-methyl thioisobutyrate which was difficult to separate from **4c**.

***N*-Hydroxy-*N*-methylethanethioamide (5a)** was prepared from *O*-ethyl thioacetate (**4a**) as described by Corey and Wright[12] for similar compounds. *N*-Methylhydroxylamine was generated in 150 mL of anhydrous methanol from 40.8 g (0.48 mol) of *N*-methylhydroxylamine hydrochloride and 26.0 g (0.48 mol) of sodium methoxide as prescribed by LeBel and Hwang[56] and was added, under nitrogen, to a solution of 20.8 g (0.20 mol) of **4a** in 100 mL of methanol. The resulting solution was stirred under nitrogen at room temperature for 4.5 h. The solution was acidified (pH <4) with dilute aqueous hydrochloric acid, saturated with sodium chloride, and extracted four times with chloroform. The combined chloroform extracts were dried ($MgSO_4$) and the solvent was removed by simple distillation. Vacuum distillation afforded 11.4 g (54%) of the known[57] thiohydroxamic acid **5a**, bp 42.0–42.5 °C (0.20 mm), as a colorless, disagreeably smelling liquid: IR (neat) 1555 (CN), 1382 (CCH_3 deformation), 1253 (N–OH) cm^{-1}; UV (MeOH) λ_{max} 269 (ϵ 12 360), 208 sh (ϵ 5682) nm; ^{1}H NMR ($CDCl_3$) δ 2.55 (s, 3 H, CCH_3), 3.61 (s, 3 H, NCH_3), 10.42–10.87 (variable,

(46) Crawford, R. J.; Woo, C. *Can. J. Chem.* **1965**, *43*, 1534–1544.
(47) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897–2904.
(48) Nakajima, M.; Anselme, J.-P. *J. Org. Chem.* **1983**, *48*, 1444–1448.
(49) Jensen, K. A.; Buchardt, O.; Christophersen, C. *Acta Chem. Scand.* **1967**, *21*, 1936–1941.
(50) Murray, K. S.; Newman, P. J.; Gatehouse, B. M.; Taylor, D. *Aust. J. Chem.* **1978**, *31*, 983–992.
(51) Prabhakar, S.; Lobo, A. M.; Santos, M. A.; Rzepa, H. S. *Synthesis* **1984**, 829–831.
(52) The exposure and handling of thio esters **4a–c** should be kept to a miminum since they smoke on contact with air[11a] and may form explosive mixtures with the latter. Scheithauer, S.; Mayer, R. In *Topics in Sulfur Chemistry*; Senning, A., Ed.; Georg Thieme: Stuttgart, GFR, 1979; Vol. 4, pp 101, 283–284.
(53) Reynaud, P.; Moreau, R. C. *Bull. Soc. Chim. Fr.* **1964**, 2999–3002.
(54) Uhlemann, E.; Mueller, H. *J. Prakt. Chem.* **1965**, *30* (4), 163–172.
(55) Vermeer, P.; Meijer, J.; Bos, H. J. T.; Brandsma, L. *Recl. Trav. Chim. Pays-Bas* **1974**, *93*, 51–53.
(56) LeBel, N.; Hwang, D. *Org. Synth.* **1978**, *58*, 106–112.
(57) Walter, W.; Schaumann, E. *Liebigs Ann. Chem.* **1971**, *743*, 154–166.

exchangeable with D_2O) (br s, 1 H, OH); ^{13}C NMR ($CDCl_3$) δ 26.95 (CCH_3), 38.59 (NCH_3), 179.39 (C=S); TLC R_f 0.43 (1:1 EtOAc–hexane); GC t_R (70–250 °C at 20 °C/min) 5.20 min.

Anal. Calcd for C_3H_7NOS: C, 34.26; H, 6.72; N, 13.32; S, 30.49. Found: C, 34.30; H, 6.77; N, 13.44; S, 30.48.

N-Hydroxy-N-methylpropanethioamide (5b) was prepared from 23.6 g (0.20 mol) of *O*-ethyl thiopropionate (**4b**) as described for **5a** (25 °C, 22 h). Distillation of the crude product under reduced pressure afforded 13.0 g (55%) of **5b**, bp 77–78 °C (3.20 mm), as a colorless, disagreebly smelling liquid: IR (neat) 1553 (CN), 1393 (CCH_3 deformation), 1258 (N–OH) cm^{-1}; UV (MeOH) λ_{max} 269 (ϵ 11 000), 203 sh (ϵ 5790) nm; ^1H NMR ($CDCl_3$) δ 1.31 (t, 3 H, J = 7.5 Hz, CH_3CH_2), 2.71 (q, 2 H, J = 7.5 Hz, CH_3CH_2), 3.60 (s, 3 H, NCH_3), 10.71 (variable, exchangeable with D_2O) (br s, 1 H, OH); ^{13}C NMR ($CDCl_3$) δ 12.85 (CH_2CH_3), 31.99 (CH_2CH_3), 38.16 (NCH_3), 185.53 (C=S); TLC R_f 0.46 (1:1 EtOAc–hexane); GC t_R (70–250 °C at 20 °C/min) 5.58 min.

Anal. Calcd for C_4H_9NOS: C, 40.30; H, 7.62; N, 11.75; S, 26.90. Found: C, 40.60; H, 7.75; N, 11.52; S, 27.14.

N,2-Dimethyl-N-hydroxy-1-propanethioamide (5c) was prepared according to the procedure given for **5a** from 3.85 g (32.6 mmol) of *O*-methyl thioisobutyrate (**4c**), 6.95 g (81.6 mmol) of *N*-methylhydroxylamine hydrochloride, and 4.41 g (81.6 mmol) of sodium methoxide in a total volume of 15 mL of anhydrous methanol. After 50 h at room temperature, the crude product, contaminated with an estimated 0.73 g (19%) of unreacted **4c** and a small amount of methyl isobutyrate (^1H NMR), was isolated and purified by distillation under reduced pressure. The analytically pure thiohydroxamic acid **5c** was obtained as a colorless, strong-smelling liquid: yield, 1.29 g (30%); bp 49–50 °C (0.67 mm); IR (neat) 1548 (CN), 1385 and 1362 (*i*-Pr CCH_3 deformations), 1254 (N–OH) cm^{-1}; UV (MeOH) λ_{max} 270 (ϵ 10 700), 208 sh (ϵ 4300) nm; ^1H NMR ($CDCl_3$) δ 1.27 (d, 6 H, J = 6.6 Hz, 2 CCH_3), 3.04 (septet, 1 H, J = 6.6 Hz, CH), 3.64 (s, 3 H, NCH_3), 10.98 (variable, exchangeable with D_2O) (br s, 1 H, OH); ^{13}C NMR ($CDCl_3$) δ 22.08 (2 CCH_3), 34.56 (CH), 37.95 (NCH_3), 190.50 (C=S); TLC R_f 0.47 (1:1 EtOAc–hexane); GC t_R (70–250 °C at 20 °C/min) 5.65 min.

Anal. Calcd for $C_5H_{11}NOS$: C, 45.07; H, 8.34; N, 10.51; S, 24.07. Found: C, 45.09; H, 8.38; N, 10.48; S, 23.75.

When the reaction was carried out in refluxing methanol under nitrogen, the starting material was completely consumed in 2 h. However, poor yields of **5c** were obtained, evidently owing to a competing side reaction producing methyl isobutyrate.

N-[(Methylthio)phenylmethylene]methanamine N-Oxide Hydriodide (6). A solution of 4.52 g (27.0 mmol) of *N*-hydroxy-*N*-methylbenzenecarbothioamide (**2**) and 5.13 mL (81.0 mmol) of methyl iodide in 18 mL of acetone was stirred under nitrogen at room temperature for 4.5 h. The color of the solution changed from light yellow to brown, and a dense white solid precipitated after about 2.5 h. An identical reaction carried out in acetone-d_6 was followed by ^1H NMR spectroscopy. The spectra revealed that the alkylation was clean and that the isomer ratio at 4.5 h was E/Z = 57:43.

At the end of the 4.5-h period, 36–48 mL of anhydrous ether was added to the heterogeneous reaction mixture, and the hydriodide salt was filtered and washed with several small portions of anhydrous ether containing a trace of acetone. The combined yield of the white crystalline solid from two crops was 7.28 g (87%); E/Z = 57:43. The first crop (7.02 g) of hydriodide **6** had the following properties: mp 117–120 °C dec; IR (KBr) 3360 (OH), 2600 (OH), 1622 (C=N, *Z*), 1590 (C=N, *E*) cm^{-1}; IR ($CHCl_3$) 2920 (CH, OH), 2590 (OH), 1605 (C=N, *E* + *Z*) cm^{-1}; UV (MeOH) λ_{max} 272 (ϵ 6610), 218 (ϵ 21 100) nm. **6Z**: ^1H NMR ($CDCl_3$) δ 2.17 (s, 3 H, SCH_3), 3.75 (s, 3 H, NCH_3), 7.39–7.79 (m, 5 H, C_6H_5), 9.5–10.5 (s, 1 H, OH); ^1H NMR (D_2O, TSP[58]) δ 1.93 (s, 3 H, SCH_3), 3.45 (s, 3 H, NCH_3); ^1H NMR (acetone-d_6) δ 2.20 (s, 3 H, SCH_3), 3.74 (s, 3 H, NCH_3); ^{13}C NMR ($CDCl_3$) δ 17.22 (SCH_3), 48.33 (NCH_3), 127.00 (2 meta C), 127.30 (C-1 of C_6H_5), 129.59 (2 ortho C), 132.89 (para C), 184.07 (C=N). **6E**: ^1H NMR ($CDCl_3$) δ 2.35 (s, 3 H, SCH_3), 4.13 (s, 3 H, NCH_3), 7.39–7.79 (m, 5 H, C_6H_5), 9.5–10.5 (s, 1 H, OH); ^1H NMR (D_2O, TSP[58]) δ 2.06 (s, 3 H, SCH_3), 3.94 (s, 3 H, NCH_3); ^1H NMR (acetone-d_6) δ 2.38 (s, 3 H, SCH_3), 4.09 (s, 3 H, NCH_3); ^{13}C NMR ($CDCl_3$) δ 18.77 (SCH_3), 47.82 (NCH_3), 127.04 (2 meta C), 128.45 (2 ortho C), 130.68 (para C), 133.08 (C-1 of C_6H_5), 183.16 (C=N).

Anal. (*E* + *Z*) Calcd for $C_9H_{12}NIOS$: C, 34.96; H, 3.92; N, 4.53; S, 10.37; I, 41.04. Found: C, 35.00; H, 3.92; N, 4.47; S, 10.23; I, 41.30.

The reaction was much slower in anhydrous ether. After 4 days at room temperature, 4.23 g (76%) of hydriodide **6** (E/Z = 0:100) and 0.66 g (22%) of unreacted thiohydroxamic acid **2** were isolated. Pure **6Z** isolated from this reaction had the following properties: mp 127–130 °C dec (sealed capillary); IR (KBr) 3355 (OH), 1620 (C=N) cm^{-1}; IR ($CHCl_3$) 2900 (CH, OH), 1590 (C=N) cm^{-1}; UV (MeOH) λ_{max} 272 (ϵ 10 788), 217 (ϵ 29 445) nm. The ^1H and ^{13}C NMR chemical shifts are identical with the ones given above.

Anal. (*Z*) Calcd for $C_9H_{12}NIOS$: C, 34.96; H, 3.92; N, 4.53; S, 10.37; I, 41.04. Found: C, 35.05; H, 3.71; N, 4.68; S, 10.57; I, 41.36.

It was clear from the ^1H NMR spectra of the reaction carried out in acetone-d_6 that isomer **6E** predominated in the early stages of the reaction (e.g., E/Z = 1.4:1.0 after 2.0 h) but that the proportion of **6Z** increased after the reaction was complete. The following data illustrate the time dependency of the E/Z ratio: 0.8 h (1.3:1.0); 11.7 h (1.3:1.0); 28.5 h (0.4:1.0).

Stability of Hydriodide 6 in Water. Solutions of thioimidate *N*-oxide hydriodides **6Z** and **6** (E/Z = 57:43) in deuterium oxide were allowed to stand at room temperature and their ^1H NMR spectra were recorded over a 23-day period. In both cases the hydriodide was reisolated in pure form from water by extraction with dichloromethane. In addition, the conversion of **6E** into the *Z* isomer was observed: 0 h (57:43); 5 days (30:70); 23 days (16:84).

pK_a Determination for Hydriodide 6. A solution of 0.1661 g (0.5372 mmol) of **6Z** in 30 mL of distilled water was titrated with 0.1000 N standard aqueous sodium hydroxide. The Beckmann Zeromatic IV pH meter used to follow the titration was calibrated immediately before use with standard buffer solutions at pH 4.00 and 7.00. The pK_a value was determined as the pH value at half the equivalence volume. A second determination was carried out and an average pK_a value of 2.30 ± 0.01 was obtained. The pure free nitrone **9Z**, mp 147–150 °C, was recovered from the basic aqueous solution by extraction with chloroform and trituration with pentane.

N-[(Methylthio)phenylmethylene]benzenemethanamine N-oxide hydriodide (7) was prepared according to the procedure given for **6** with the following modifications. After 10 h at 25 °C [E/Z = 23:77, ^1H NMR (acetone-d_6)] 2 mL of dry acetone was added to the clear and dark-brown reaction solution. Evaporation at *room temperature* under reduced pressure afforded 2.15 g (93%) of hydriodide **7** (E/Z = 5:95) as a brown free-flowing solid that was of suitable purity (^1H NMR) for use in subsequent reactions. Hydriodide **7** (E/Z = 5:95) is best stored in a freezer, since it turned gummy within hours at room temperature. The ^1H NMR spectrum of the gum indicated the presence of 5–10% of *S*-methyl thiobenzoate. The spectral properties of the product are as follows. **7Z**: ^1H NMR ($CDCl_3$) δ 2.14 (s, 3 H, SCH_3), 5.20 (s, 2 H, CH_2), 7.17–7.26 (unsym dd, 2 H, meta aryl H's in $NCH_2C_6H_5$), 7.32–7.41 (unsym t, 3 H, ortho and para aryl H's in $NCH_2C_6H_5$), 7.44–7.56 (unsym dd, 2 H, meta aryl H's in C_6H_5C=N), 7.68–7.78 (unsym t, 3 H, ortho and para aryl H's in C_6H_5C=N), 10.00 (br s, 1 H, OH); ^1H NMR (acetone-d_6) δ 2.20 (s, 3 H, SCH_3), 5.27 (s, 2 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 16.96 (SCH_3), 63.79 (CH_2), 127.31, 127.39, 129.05, 129.46, 130.40, 130.55, 130.68, 132.88 (Ar C's), 182.2 (C=N). **7E**: ^1H NMR ($CDCl_3$) δ 2.38 (s, 3 H, SCH_3), 5.68 (s, 2 H, NCH_2) [the peaks from the aromatic protons were obscured by those of the *Z* isomer]; ^1H NMR (acetone-d_6) δ 2.40 (s, 3 H, SCH_3), 5.75 (s, 2 H, CH_2).

Recrystallization of the brown solid (E/Z = 5:95) from chloroform afforded analytically pure **7Z** (albeit with poor recovery) as a white crystalline solid: mp 112–114 °C dec. Its ^1H and ^{13}C NMR chemical shifts were identical with the ones given in the preceding paragraph.

Anal. Calcd for $C_{15}H_{16}NOSI$: C, 46.76; H, 4.19; N, 3.64; S, 8.32; I, 32.94. Found: C, 46.62; H, 3.86; N, 3.60; S, 8.53; I, 32.95.

An identical run carried out in acetone-d_6 and monitored by ^1H NMR spectroscopy showed the reaction to be clean and provided the following E/Z ratios: 1.0 h (0.6:1.0); 5 h (0.5:1.0); 12 h (0.3:1.0).

N-[(Ethylthio)phenylmethylene]methanamine N-Oxide Hydriodide (8). A solution of 1.00 g (6.0 mmol) of thio-

(58) Sodium 3-(trimethylsilyl)propionate-2,2,3,3-d_4.

hydroxamic acid **2** and 1.50 mL (18.0 mmol) of ethyl iodide in 4 mL of acetone was heated at reflux for 10 h with exclusion of moisture. Addition of ether to the dark-brown solution failed to precipitate **8**. Concentration on the rotatory evaporator left 2.7 g of a dark liquid. The ^1H NMR ($CDCl_3$) spectrum indicated the presence of **8** (E/Z = 5.4:94.6) and *S*-ethyl thiobenzoate (see preparation of nitrone **11** below) as the major and minor components of this liquid. **8Z**: δ 1.20 (t, 3 H, J = 8.1 Hz, CH_2CH_3), 2.57 (q, 2 H, J = 8.1 Hz, CH_2CH_3), 3.69 (s, 3 H, NCH_3), 7.35–7.55 (m, 3 H, meta and para aryl H's), 7.57–7.79 (m, 2 H, ortho aryl H's), 10.78–11.28 (variable) (br s, 1 H, OH). **8E**: δ 4.15 (s, 3 H, NCH_3), 10.78–11.28 (br s, 1 H, OH). The other resonances from the *E* isomer were obscured by peaks from the predominant *Z* isomer and from *S*-ethyl thiobenzoate.

***N*-[(Methylthio)phenylmethylene]methanamine *N*-Oxide (9).** A solution of 0.65 g (2.1 mmol) of hydriodide **6** (E/Z = 59:41) in 15 mL of water and 15 mL of dichloromethane were placed in a separatory funnel. Solid sodium carbonate was added in small portions, and the funnel was shaken vigorously each time after effervescence had subsided. When effervescence no longer occurred upon carbonate addition, a slight excess of the base was added. The aqueous layer was saturated with sodium chloride and extracted with four 10-mL portions of dichloromethane. Drying ($MgSO_4$) of the combined organic layers and concentration at *room temperature* on the rotatory evaporator afforded 0.42 g of a colorless liquid, which consisted of the free nitrone **9** (E/Z = 57:43) and residual dichloromethane. Trituration with 1:1 pentane–ether at room temperature precipitated 0.18 g (47%) of **9Z** as a white crystalline solid, mp 148–150 °C. Concentration of the colorless filtrate on the rotatory evaporator at *room temperature* afforded an additional 0.17 g (46%) of nitrone **9** (E/Z = 89:11) as a clear and colorless liquid. **9Z**: ^1H NMR ($CDCl_3$) δ 1.88 (s, 3 H, SCH_3), 3.51 (s, 3 H, NCH_3), 7.21–7.34 (m, 2 H, meta aryl H's), 7.45–7.57 (m, 3 H, ortho and para aryl H's); ^1H NMR (D_2O, DSS[59]) δ 1.94 (s, 3 H, SCH_3), 3.45 (s, 3 H, NCH_3); ^{13}C NMR ($CDCl_3$) δ 15.01 (SCH_3), 48.27 (NCH_3), 128.94 (2 meta C), 129.47 (2 ortho C), 130.32 (para C), 130.85 (C-1 of C_6H_5), 150.10 (C=N). **9E**: ^1H NMR ($CDCl_3$) δ 2.09 (s, 3 H, SCH_3), 4.10 (s, 3 H, NCH_3), 7.34–7.45 (m, 3 H, meta and para aryl H's), 7.79–7.88 (dd, 2 H, J = 8.6 Hz, ortho aryl H's); ^{13}C NMR ($CDCl_3$) δ 17.56 (SCH_3), 51.71 (NCH_3), 128.37 (2 meta C), 129.80 (2 ortho C), 129.42 (para C), 131.59 (C-1 of C_6H_5), 142.87 (C=N).

A similar run was carried out by using 3.09 g (10.0 mmol) of hydriodide **6Z**. Recrystallization from 1:1 pentane–ether yielded 1.65 g (91%) of free nitrone **9Z**, mp 149–151 °C, as white crystals: IR (KBr) 1555 (C=N), 1235 (N–O) cm^{-1}; IR (Me_2SO) 1563 (C=N), 1248 (N–O) cm^{-1}; IR ($CHCl_3$) 1552 (C=N), 1222 (N–O) cm^{-1}; UV (MeOH) λ_{max} 273 (ϵ 8200) nm; its ^1H NMR and ^{13}C NMR spectral data are identical with the ones given above; MS (70 eV) m/e (relative intensity) 181 (39.2, M^+), 180 (36.0, M – H), 164 (22.7, M – OH), 121 (100.0, $C_6H_5C{\equiv}S$), 118 (66.7, C_8H_8N), 77 (61.3, C_6H_5). The empirical formulas for the ions at m/e 181, 121, and 118 were confirmed by HR-EI peak matching. The TLC R_f values were as follows: 0.45 (EtOH), 0.30 (1:1 EtOH–EtOAc).

Anal. (*Z*) Calcd for $C_9H_{11}NOS$: C, 59.62; H, 6.13; N, 7.73; S, 17.69. Found: C, 59.65; H, 5.95; N, 7.88; S, 17.55.

***N*-[(Methylthio)phenylmethylene]benzenemethanamine *N*-oxide (10)** was prepared in the same manner from 1.57 g (4.1 mmol) of hydriodide **7Z**. Trituration of the amber, viscous liquid residue with pentane provided 0.83 g (78%) of nitrone **10Z**, the ^1H NMR spectrum of which showed it to be pure. Recrystallization from pentane–dichloromethane afforded an analytically pure sample: mp 125–127 °C; IR (KBr) 1540 (C=N), 1250 (N–O) cm^{-1}; IR (Me_2SO) 1545 (C=N), 1241 (N–O) cm^{-1}; IR ($CHCl_3$) 1542 (C=N), 1270 (N–O) cm^{-1}; UV (MeOH) λ_{max} 277 (ϵ 11 000) nm; ^1H NMR ($CDCl_3$) δ 1.84 (s, 3 H, CH_3), 4.84 (s, 2 H, CH_2), 7.14–7.34 (m, 7 H, 2 meta aryl H's of C_6H_5C=N and 5 aryl H's of $NCH_2C_6H_5$), 7.39–7.61 (m, 3 H, ortho and para H's); ^{13}C NMR ($CDCl_3$) δ 14.87 (CH_3), 64.06 (CH_2), 128.12 (para C in $NCH_2C_6H_5$), 128.28 (2 meta C in $NCH_2C_6H_5$), 128.49 (2 ortho C in $NCH_2C_6H_5$), 129.29 (2 meta C in C_6H_5C=N), 129.35 (2 ortho C in C_6H_5C=N), 130.37 (para C in C_6H_5C=N), 130.47 (C-1 of C_6H_5 in $NCH_2C_6H_5$), 133.84 (C-1 of C_6H_5 in C_6H_5C=N), 150.16 (C=N); MS (70 eV), m/e (relative intensity) 257 (3.5, M^+), 240 (1.6, M – OH), 211 [5.2, M – (H_2C=S)], 210 (2.3, M – CH_3S), 194 (8.6, $C_6H_5C{\equiv}NCH_2C_6H_5$), 121 (27.3, $C_6H_5C{\equiv}S$), 91 (100.0, C_7H_7), 77 (68.9, C_6H_5); TLC R_f 0.50 (1:1 EtOH–EtOAc).

Anal. Calcd for $C_{15}H_{15}NOS$: C, 69.99; H, 5.89; N, 5.44; S, 12.46. Found: C, 69.63; H, 6.01; N, 5.31; S, 12.34.

The ^1H NMR spectrum of **10E** was observed when a chloroform-*d* solution of **10Z** was equilibrated at 80 °C to a 6:94 ratio of the *E* and *Z* isomers: **10E**, δ 2.04 (s, 3 H, CH_3), 5.62 (s, 2 H, CH_2). The aromatic protons were obscured by those of the *Z* isomer.

***N*-[(Ethylthio)phenylmethylene]methanamine *N*-oxide (11)** was liberated from 2.7 g of the crude hydriodide **8** (E/Z = 5:95, contaminated with *S*-ethyl thiobenzoate) in 20 mL of chloroform as described previously for **9**. Slow treatment of the residual tan liquid with pentane precipitated 0.54 g (46%, from **2**) of nitrone **11Z**, mp 120–124 °C, as colorless crystals. The filtrate was evaporated and purified by flash chromatography starting with 1:9 ethyl acetate–hexane and ending with 1:1 ethanol–ethyl acetate. *S*-Ethyl thiobenzoate,[60] 0.20 g (20%), was isolated from the least polar fraction (EtOAc–hexane, 30%), and an additional 0.06 g (5%) of nitrone **11Z** was obtained from the most polar fraction (1:1 EtOH–EtOAc). Recrystallization from pentane–dichloromethane afforded analytically pure **11Z**: mp 127–129 °C; IR (KBr) 1555 (C=N), 1235 (N–O) cm^{-1}; IR ($CHCl_3$) 1560 (C=N), 1224 (N–O) cm^{-1}; UV (MeOH) λ_{max} 273 (ϵ 8400) nm; ^1H NMR ($CDCl_3$) δ 1.10 (t, 3 H, J = 7.4 Hz, CH_2CH_3), 2.30 (q, 2 H, J = 7.4 Hz, CH_2CH_3), 3.49 (s, 3 H, NCH_3), 7.17–7.40 (m, 2 H, meta aryl H's), 7.40–7.61 (m, 3 H, ortho and para aryl H's); ^{13}C NMR ($CDCl_3$) δ 14.39 (CH_2CH_3), 26.02 (CH_2CH_3), 48.11 (NCH_3), 128.98 (2 meta C), 129.34 (2 ortho C), 130.30 (para C), 131.23 (C-1 of C_6H_5), 149.55 (C=N); MS (70 eV), m/e (relative intensity) 195 (18.7, M^+), 194 (5.9, M – H), 178 (14.9, M – OH), 121 (85.8, $C_6H_5C{\equiv}S$), 118 (100.0, $C_6H_5C{\equiv}NMe$), 77 (46.8, C_6H_5), 29 (2.8, C_2H_5); TLC R_f 0.40 (1:1 EtOH–EtOAc).

Anal. Calcd for $C_{10}H_{13}NOS$: C, 61.49; H, 6.72; N, 7.17; S, 16.42. Found: C, 61.54; H, 6.73; N, 7.20; S, 16.16.

Isomer **11E** was observed when a chloroform-*d* solution of **11Z** was equilibrated at 80 °C to a 7:93 ratio of *E* and *Z* isomers: ^1H NMR δ 1.11 (t, 3 H, J = 7.5 Hz, CH_2CH_3), 2.44 (q, 2 H, J = 7.5 Hz, CH_2CH_3), 4.07 (s, 3 H, NCH_3); the aromatic protons were obscured by those of the major isomer *Z*.

***N*-[1-(Methylthio)ethylidene]methanamine *N*-oxide hydriodide (12a)** was prepared as described above for hydriodide **6**. Reactions carried out at 25 °C for 2.0 and 10.5 h afforded 1.74 (76%) and 2.18 g (95%), respectively, of **12a** (E/Z = 0:100). The white crystalline solid that precipitated during the reaction was collected and washed with anhydrous ether. The first crop had the following properties: mp 122–124 °C dec; IR (Me_2SO) 3340 (OH), 3200 (OH), 1625 (C=N) cm^{-1}; UV (MeOH) λ_{max} 262 (ϵ 8450), 218 (ϵ 16 500) nm; ^1H NMR (Me_2SO-d_6) δ 2.64 (s, 6 H, SCH_3 and CCH_3), 3.80 (s, 3 H, NCH_3), 8.08–10.99 (br s, 1 H, OH); ^{13}C NMR (Me_2SO-d_6) δ 14.69 (CCH_3), 19.11 (SCH_3), 45.44 (NCH_3), 177.22 (C=N). Although hydriodide **12aZ** was apparently reasonably stable in the atmosphere, its exposure and handling were kept to a minimum.

Anal. Calcd for $C_4H_{10}NOSI$: C, 19.44; H, 4.09; N, 5.67; S, 12.98; I, 51.35. Found: C, 19.27; H, 4.07; N, 5.72; S, 12.67; I, 51.70.

An identical run carried out in acetone-d_6 and monitored by ^1H NMR spectroscopy gave the following E/Z ratios: 0.5 (1.0:0.3) and 1.0 h (1.0:0.7). The ^1H NMR data for the two isomers in acetone-d_6 are as follows. **12aE**: δ 2.80 (s, 3 H, $W_{1/2}$ = 3.1 Hz, CCH_3), 2.92 (s, 3 H, SCH_3), 3.84 (q, 3 H, J = 1.1 Hz, NCH_3), 10.04 (variable) (br s, 1 H, OH). **12aZ**: δ 2.73 (s, 3 H, SCH_3), 2.80 (s, 3 H, CCH_3), 4.05 (s, 3 H, NCH_3), 10.04 (variable) (br s, 1 H, OH). The *Z* isomer precipitated from the reaction medium after 1.0 h.

***N*-[1-(Methylthio)propylidene]methanamine *N*-oxide hydriodide (12b)** was prepared in the same manner as **6** at 25 °C for 4.0 h. The clear, brown-red solution was concentrated at *room temperature* on the rotatory evaporator, and residual acetone and methyl iodide were removed by entrainment with dichloromethane. The brown residue was treated with anhydrous ether

(59) Sodium 2,2-dimethyl-2-silapentane-5-sulfonate.

(60) Takeda, K.; Tsuboyama, K.; Yamaguchi, K.; Ogura, H. *J. Org. Chem.* **1985**, *50*, 273–275.

and left in the freezer overnight. The precipitated brown solid was collected in a *glovebag* and washed with anhydrous ether to yield hydriodide **12b** as a brown, free-flowing solid. The ^{1}H NMR spectrum revealed an E/Z ratio of 8:92 and showed the purity of the product to be satisfactory. The yield was 8.72 g (88%): mp 84–89 °C dec; IR ($CHCl_3$) 2880 (OH, CH), 2550 (OH), 1595 (C=N), 1195 (N–OH) cm^{-1}; UV (MeOH) λ_{max} 266 (ϵ 7000), 217 (ϵ 19 000) nm. **12bZ**: ^{1}H NMR ($CDCl_3$) δ 1.40 (t, 3 H, J = 7.5 Hz, CH_2CH_3), 2.72 (s, 3 H, SCH_3), 3.05 (q, 2 H, J = 7.5 Hz, CH_2CH_3), 4.06 (s, 3 H, NCH_3), 9.98–10.42 (br s, 1 H, OH); ^{1}H NMR (acetone-d_6) δ 1.33 (t, 3 H, CH_2CH_3), 2.76 (s, 3 H, SCH_3), 3.11 (q, 2 H, CH_2CH_3), 4.06 (s, 3 H, NCH_3); ^{13}C NMR ($CDCl_3$) δ 11.27 (CH_2CH_3), 16.01 (SCH_3), 26.33 (CH_2CH_3), 46.97 (NCH_3), 186.30 (C=N). **12bE**: ^{1}H NMR ($CDCl_3$) δ 1.40 (t, 3 H, J = 7.5 Hz, CH_2CH_3), 2.89 (s, 3 H, SCH_3), 3.14 (q, 2 H, J = 7.5 Hz, CH_2CH_3), 3.93 (s, 3 H, NCH_3), 9.98–10.42 (br s, 1 H, OH); ^{1}H NMR (acetone-d_6) δ 1.33 (t, 3 H, CH_2CH_3), 2.94 (s, 3 H, SCH_3), 3.09 (q, 2 H, CH_2CH_3), 3.89 (s, 3 H, NCH_3); ^{13}C NMR ($CDCl_3$) δ 11.52 (CH_2CH_3), 16.84 (SCH_3), 26.62 (CH_2CH_3), 47.09 (NCH_3), 187.58 (C=N).

Anal. (E + Z) calcd for $C_5H_{12}NOSI$: C, 22.99; H, 4.64; N, 5.36; S, 12.28; I, 48.59. Found: C, 22.66; H, 4.77; N, 5.28; S, 11.80; I, 48.94.

A run carried out in acetone-d_6 and monitored by ^{1}H NMR spectroscopy gave the following E/Z ratios: 0.6 h (1.0:0.4); 1.1 h (1.0:1.0); 4.1 h (1.0:4.7); 28 h (1.0:5.2); 21 days (1.0:19.8).

***N*-[2-Methyl-1-(methylthio)propylidene]methanamine *N*-oxide hydriodide (12c)** was prepared as described for **12b**. Two reactions carried out at 25 °C for 15 h and 2 days afforded 0.66 g (80%) of **12c** (E/Z = 48:52) and 0.70 g (84%) of **12c** (E/Z = 39:61), respectively. In both cases the hydriodide was obtained as a brown viscous liquid that did not crystallize on standing in ether containing a trace of chloroform in the freezer overnight. Approximately 0.04 g (10%) of unreacted thiohydroxamic acid **5c** was present in the product from the 15-h run. The spectroscopic properties of **12c** as determined on the oils are as follows. **12cZ**: ^{1}H NMR ($CDCl_3$) δ 1.44 (d, 6 H, J = 6.8 Hz, 2 CCH_3), 2.98 (s, 3 H, SCH_3), 3.36 (septet, 1 H, J = 6.8 Hz, CH), 4.06 (s, 3 H, NCH_3), 9.91–10.01 (br s, 1 H, OH); ^{1}H NMR (acetone-d_6) δ 1.38 (d, 6 H, 2 CCH_3), 2.92 (s, 3 H, SCH_3), 3.61 (septet, 1 H, CH), 4.05 (s, 3 H, NCH_3). **12cE**: ^{1}H NMR ($CDCl_3$) δ 1.51 (d, 6 H, J = 7.0 Hz, 2 CCH_3), 2.88 (s, 3 H, SCH_3), 3.50 (septet, 1 H, J = 7.0 Hz, CH), 4.03 (s, 3 H, NCH_3), 9.91–10.01 (br s, 1 H, OH); ^{1}H NMR (acetone-d_6) δ 1.44 (d, 6 H, 2 CCH_3), 2.87 (s, 3 H, SCH_3), 3.61 (septet, 1 H, CH), 3.99 (s, 3 H, NCH_3).

The assignment of the ^{13}C NMR chemical shifts to particular carbon atoms was done on the basis of the multiplicity pattern in the ^{1}H-coupled ^{13}C NMR spectrum. However, the following assignments are tentative and one or more may actually be reversed. **12cE**: δ 20.2 (2 CH_3C), 23.6 (SCH_3), 34.7 (CH), 48.6 (NCH_3), 185.6 (C=N). **12cZ**: δ 19.0 (2 CH_3C), 24.3 (SCH_3), 34.1 (CH), 47.4 (NCH_3), 176.3 (C=N).

A run carried out in acetone-d_6 and monitored by ^{1}H NMR spectroscopy provided the following E/Z ratios: 0.7 h (1.0:0.4); 4.7 h (1.0:0.5); 28 h (1.0:1.6); 21 days (1.0:99). No decomposition was evident either after 28 h or after 21 days.

NOTE: All manipulations of the following crystalline thioimidate *N*-oxides **13a** and **13b** were carried out under nitrogen in a glovebag.

***N*-[1-(Methylthio)ethylidene]methanamine *N*-oxide (13a)** was liberated from 2.01 g (8.1 mmol) of hydriodide **12aZ** by the same procedure described for nitrone **9**. Since the product is hygroscopic and water soluble, the aqueous carbonate phase was extracted with ten 15-mL portions of dichloromethane. Drying ($MgSO_4$) of the combined dichloromethane layers followed by concentration at *room temperature* on the rotary evaporator left a clear and colorless residual liquid. Slow trituration with pentane precipitated nitrone **13aZ** as a white crystalline solid that was collected and washed in a *glovebag*. The combined yield from two crops was 0.61 g (63%). The product was recrystallized from pentane–dichloromethane or benzene–dichloromethane. The first crop (0.44 g, 45%) had the following properties: mp 118–119 °C dec (sealed capillary); IR ($CHCl_3$) 1580 (C=N), 1247 (N–O) cm^{-1}; UV (MeOH) λ_{max} 262 (ϵ 11 700) nm; ^{1}H NMR ($CDCl_3$) δ 2.28 (s, 3 H, $W_{1/2}$ = 2.2 Hz), 2.34 (s, 3 H, SCH_3), 3.72 (s, 3 H, $W_{1/2}$ = 2.2 Hz, NCH_3); ^{1}H NMR (D_2O, DSS[59]) δ 2.37 (s, 3 H, CCH_3), 2.41 (s, 3 H, SCH_3), 3.64 (s, 3 H, NCH_3); ^{13}C NMR ($CDCl_3$) δ 14.36 (CCH_3), 16.56 (SCH_3), 47.03 (NCH_3), 146.21 (C=N); MS (70 eV), m/e (relative intensity) 119 (36.5, M$^+$), 102 (40.0, M – OH), 73 [14.4, M – (H_2C=S)], 59 (100.0, CH_3C≡S), 56 (84.6, CH_3C≡NCH_3), 43 (34.8, CH_3N=CH_2); TLC R_f 0.10 (1:1 EtOH–EtOAc). The ^{1}H NMR spectrum of **13aZ** in deuterium oxide showed no sign of equilibration or hydrolysis after several days at room temperature.

Anal. Calcd for C_4H_9NOS: C, 40.30; H, 7.63; N, 11.75; S, 26.90. Found: C, 40.08; H, 7.58; N, 11.60; S, 26.64.

The *E* isomer was generated in solution by partial equilibration of **13aZ** in chloroform-*d* at 80 °C. The ^{1}H NMR spectrum recorded on the mixture provided the following data for **13aE**: ^{1}H NMR ($CDCl_3$) δ 2.36 (q, 3 H, J = 1.2 Hz, CCH_3), 2.43 (s, 3 H, SCH_3), 3.85 (q, 3 H, J = 1.2 Hz, NCH_3); ^{13}C NMR ($CDCl_3$) δ 16.34 (CCH_3), 17.86 (SCH_3), 48.72 (NCH_3), 150.29 (C=N).

***N*-[1-(Methylthio)propylidene]methanamine *N*-oxide (13b)** was liberated from 6.01 g (23.0 mmol) of hydriodide **12b** (E/Z = 08:92) by the procedure described for **13a**. The yield of nitrone **13b** (E/Z = 07:93) was 2.43 g (80%) of colorless hygroscopic crystals that were handled in a glovebag. The analytically pure first crop (2.24 g, $E + Z$) exhibited the following properties: mp 66–69 °C (sealed capillary); IR ($CHCl_3$) 1576 (C=N), 1281 (N–O) cm^{-1}; **13bZ**: ^{1}H NMR ($CDCl_3$) δ 1.20 (t, 3 H, J = 7.6 Hz, CH_3CH_2), 2.35 (s, 3 H, SCH_3), 2.62 (q, 2 H, J = 7.6 Hz, CH_3CH_2), 3.72 (s, 3 H, NCH_3); ^{13}C NMR ($CDCl_3$) δ 11.52 (CH_2CH_3), 13.43 (SCH_3), 22.83 (CH_2CH_3), 46.04 (NCH_3), 151.06 (C=N); **13bE**: ^{1}H NMR ($CDCl_3$) δ 1.19 (t, 3 H, J = 7.6 Hz, CH_3CH_2), 2.40 (s, 3 H, SCH_3), 2.78 (q, 2 H, J = 7.6 Hz, CH_3CH_2), 3.87 (s, 3 H, NCH_3); ^{13}C NMR ($CDCl_3$) δ 9.37 (CH_2CH_3), 15.72 (SCH_3), 23.91 (CH_2CH_3), 49.00 (NCH_3), 147.55 (C=N); MS (70 eV), m/e (relative intensity) 133 (65.8, M$^+$), 116 (36.9, M – OH), 87 [19.1, M – (H_2C=S)], 73 (100.0, CH_3CH_2C≡S), 70 (59.3, CH_3CH_2C≡NCH_3), 45 (66.6, CH_3N=O). The ^{13}C NMR chemical shifts for CH_3CH_2 and SCH_3 of both the *E* and *Z* isomers were assigned by using the coupling patterns in the hydrogen-coupled ^{13}C NMR spectrum.

Anal. ($E + Z$) Calcd for $C_5H_{11}NOS$: C, 45.07; H, 8.34; N, 10.51; S, 24.07. Found: C, 45.02; H, 8.13; N, 10.55; S, 23.84.

***N*-[2-Methyl-1-(methylthio)propylidene]methanamine *N*-oxide (13c)** was liberated from 0.70 g (2.5 mmol) of crude **12c** (E/Z = 39:61) that was contaminated with small amounts of unreacted thiohydroxamic acid **5c**, methyl iodide, and *S*-methyl thioisobutyrate. The oil was dissolved in 15 mL of water and the contaminants were removed by two extractions with ether. Solid sodium bicarbonate was added in small portions to a mixture of the aqueous solution and 15 mL of dichloromethane in a separatory funnel as described previously. Nitrone **13c** (E/Z = 32:68) was isolated as a clear liquid: yield, 0.20 g (53%); IR (neat) 1647, 1518 (C=N), 1381 and 1362 (CH_3 deformations), 1258 (N–O) cm^{-1}. **13cZ**: ^{1}H NMR ($CDCl_3$) δ 1.23 (d, 6 H, J = 7.0 Hz, 2 CCH_3), 2.49 (s, 3 H, SCH_3), 3.07 (septet, 1 H, J = 7.0 Hz, CH), 3.78 (s, 3 H, NCH_3); ^{13}C NMR ($CDCl_3$) δ 14.21 (SCH_3), 19.81 (2 CCH_3), 32.64 (CH), 49.02 (NCH_3), 151.85 (C=N). **13cE**: ^{1}H NMR ($CDCl_3$) δ 1.15 (d, 6 H, J = 7.0 Hz, 2 CCH_3), 2.33 (s, 3 H, SCH_3), 3.78 (septet, 1 H, J = 7.0 Hz, CH), 4.06 (s, 3 H, NCH_3); ^{13}C NMR ($CDCl_3$) δ 18.41 (SCH_3), 18.88 (2 CCH_3), 31.39 (CH), 50.65 (NCH_3), 151.50 (C=N); MS (70 eV), m/e (relative intensity) 147 (33.0, M$^+$), 132 (5.22, M – CH_3), 130 (22.6, M – OH), 101 [11.5, M – (H_2C=S)], 100 (15.8, M – CH_3S), 87 (32.2, *i*-PrC≡S), 84 (31.9, *i*-PrC≡NCH_3), 83 (43.8, C_5H_9N), 61 (20.5, C_2H_5S), 43 (39.8, C_3H_7), 42 (100.0, C_2H_4N). The empirical formulas for the ions at m/e 83, 61, and 42 were confirmed by HR-EI peak matching. A gas chromatogram showed one peak at t_R 6.19 min for both isomers (70–250 °C at 20 °C/min). The ^{13}C NMR chemical shifts were unambiguously assigned on the basis of their respective multiplicity patterns in the hydrogen-coupled ^{13}C NMR spectrum.

Anal. Calcd for $C_6H_{13}NOS$: C, 48.93; H, 8.92; N, 9.51; S, 21.78. Found: C, 48.85; H, 9.04; N, 9.52; S, 21.57.

Attempts to induce crystallization of one or both isomers of nitrone **13c** were not successful. However, *E*-rich (E/Z = 92:08) and *Z*-rich (E/Z = 20:80) fractions were obtained by flash chromatography on silica gel of 0.46 g of a mixture consisting mainly of **13c** (E/Z = 57:43) and some thiohydroxamic acid **5c**. The weight ratio of silica gel to mixture was 82:1. The column was eluted with 1:1 ethanol–ethyl acetate and 10-mL fractions were collected. The *E*-rich mixture (0.13 g) was obtained from

fractions 7–11 and the *Z*-rich mixture (0.10 g) was found in fractions 13–24.

Single-Crystal X-ray Structure Determination of Nitrone 9Z. Crystals suitable for X-ray diffraction analysis were obtained by recrystallization of nitrone **9Z** from dichloromethane–pentane. The crystal used for data collection was a colorless, transparent prism with well-formed faces, edges and corners, and measured 0.6 × 0.7 × 0.8 mm. Lattice constants and intensity data were measured at 298 K and λ = 0.71069 Å (Mo K$\bar{\alpha}$) on a Syntex $P2_1$ automated four-circle diffractometer equipped with a graphite crystal monochromator. Data collection was attempted only to $2\theta < 55.0°$. A total of 4993 reflections were collected (one form, $\pm hkl$), yielding 4236 unique intensities and 3063 reflections with $I > 2.58\sigma(I)$. This set of reflections was used in the structure solution and refinement. Data reduction included corrections for background, Lorentz, and polarization effects, and anomalous dispersion effects. No absorption or extinction corrections were applied. Systematic absences for $h0$, $k = 2n + 1$, and $h0l$, $l = 2n + 1$ unambiguously indicated the space group to be $P2_1/c$ (C_{2h}^5). Cell data: monoclinic; a = 18.374 (4) Å, b = 8.362 (1) Å, c = 12.206 (2) Å, β = 91.28 (1)°, V = 1874.9 (5) Å^3, ρ_c = 1.284 g cm^{-3}; Z = 8.

The structure was solved by direct methods (MULTAN),[61] and calculations were performed on the DEC VAX 11/780 computer system at the University of Illinois. Correct positions for 22 of the 24 non-hydrogen atoms were deduced from the *E*-map. After one cycle of refinement, a difference Fourier map gave positions for the remaining two non-hydrogen atoms and subsequent least-squares-difference Fourier calculations revealed positions for all of the hydrogen atoms.[62] In the final cycle of least squares, all positional parameters were refined, anisotropically for the non-hydrogen atoms and isotropically for the hydrogen atoms. Refinement converged at R = 0.036 (R_w = 0.043). The final difference Fourier map was featureless (highest peak = 0.24 e/Å^3). A weighted mean aromatic carbon–carbon bond length of 1.387 Å and a carbon–hydrogen bond length of 0.93 Å provided an additional measure of confidence in the solution.

NOE Measurements on *C*-Alkylnitrones 13a–c. Solutions (0.050 M) of **13a–c** in chloroform-*d*, containing tetramethylsilane as an internal reference, were degassed by using several freeze–pump–thaw cycles and the NMR tubes were sealed under reduced pressure. All experiments were carried out at 20.5 ± 0.5 °C on a Varian XL-200 (200 MHz) FT-NMR spectrometer under the control of Varian XL-series data system. A delay–pulse–acquisition (D1–PW–AT) sequence and a homonuclear decoupling modulation were used in conjunction with a 90° pulse width of 11 μs. The digital resolution of the acquisition processor was less than or equal to 0.2 Hz. The decoupler low power (DLP = 21–23) and the delay (D1 = 10 s) values used were chosen to provide signal saturation through long decoupling times and low decoupler power in order to achieve the best irradiation selectivity possible. A line broadening of 1.0–2.0 Hz was used to ensure complete signal cancellation, especially of methyl singlets.

The isomer of **13a** (*E*/*Z*, 36:64) which exhibits the higher field *N*-methyl absorption gave positive NOEs of 1.2 ± 0.3% at the *N*-methyl peak (irradiation at *C*-CH_3) and 1 ± 0.1% at the *C*-methyl peak (irradiation at *N*-methyl). The other isomer showed only small negative enhancements (−0.5 to −0.7%) at the *N*-methyl and *C*-methyl groups, possibly owing to the long-range coupling between them. Similarly, irradiation at the higher field *N*-methyl peak in the spectrum of **13b** (*E*/*Z*, 28:72) produced a 2.7 ± 0.3% NOE at the *C*-CH_2 quartet and irradiation at the *C*-CH_2 frequency resulted in a 3.4 ± 0.2% NOE at the *N*-methyl singlet. The isomer assigned the *E* stereochemistry exhibited negligible or negative enhancements when the same irradiations were carried out. Unfortunately superposition of peaks and the multiplicity of the *C*-CH absorption (heptet) precluded measurement of the corresponding NOEs for **13c** (*E* + *Z*).

Thermal Equilibration of Nitrone 9Z. A solution of 37.7 mg (0.208 mmol) of nitrone **9Z** in 2.0 mL of bromobenzene-d_5 was heated at 80 ± 1 °C under nitrogen. Small aliquots (20–50 μL) were withdrawn and diluted with about 0.3–0.4 mL of chloroform-*d*, and their ^{1}H NMR spectra were recorded. The relative proportions of **9E** and **9Z** were determined by comparing the intensities of the NCH_3 and SCH_3 signals, and the approach to equilibrium was followed for several half-lives. The equilibrium ratio (*E*/*Z* = 5:95 ± 1) was calculated by averaging several values obtained after equilibrium had been established. The equilibrations of the remaining nitrones **10**, **11**, and **13a–c** in bromobenzene-d_5 (98.2–107 mM) at 80 °C were carried out in the same way (Table II). No peaks other than those of the *E* and *Z* isomers were evident in any of the ^{1}H NMR spectra except in those of **10** (NCH_2Ph). The solutions remained colorless and clear with the exception of that of **13a**, which acquired a light pink color. However, no extraneous peaks were detected in the spectra of **13a**. Only one hydrolysis product, *S*-methyl thiobenzoate, was observed in the equilibration of **10Z** after equilibrium had been established. The ratio of *S*-methyl thiobenzoate to the minor isomer **10E** at various times was as follows: 8 h (0.6:1.0); 24 h (2:1); 54 h (6.4:1.0).

The equilibration of **9Z** was also carried out in the absence of solvent at 156 °C [$(E/Z)_{eq}$ = 8:92] and in dimethyl sulfoxide-d_6 at 100 °C [$(E/Z)_{eq}$ = 6:94]. In this last solvent, the equilibration was accompanied by significant hydrolysis leading to *S*-methyl thiobenzoate and *N*-methylbenzohydroxamic acid (**16**). The ratio $(E/Z)_{eq}$ = 8:92 was obtained from the equilibration of **9** (*E*/*Z* = 47:53) in the absence of solvent at 147 °C. Equilibrations of nitrones **10Z** (*N*-Bz) and **11Z** (*S*-Et) carried out in chloroform-*d* at 80 °C afforded an *E*/*Z* equilibrium ratio of 6:94 and 7:93, respectively. The equilibrations of **13c** (*E*/*Z* = 92:08) and **13c** (*E*/*Z* = 20:80) in chloroform-*d* at 25 °C over 24 days converged to the same equilibrium *E*/*Z* ratio of 76:24.

***N*-Hydroxy-*N*,α,α-trimethylbenzenemethanamine (14).** A 5-mL (15.5 mmol) portion of 3.1 M methylmagnesium bromide in ether was stirred under nitrogen and cooled in an ice bath as a solution of 0.54 g (3.0 mmol) of **9Z** in 11 mL of dry tetrahydrofuran–dichloromethane (8:3) was added dropwise over ca. 15 min. Stirring was continued for 30 min at 0 °C, after which the reaction solution was poured onto a mixture of 5 mL of concentrated sulfuric acid and 100 g of crushed ice. The layers were swirled well and the aqueous phase was extracted with three 25-mL portions of ether.

The remaining aqueous layer was covered with 25 mL of ether and small portions of solid sodium carbonate were added until the effervescence ceased. The aqueous phase was extracted three times with ether. Drying (Na_2SO_4) of the combined ether extracts and concentration afforded a residual yellowish liquid that crystallized within a few minutes. Recrystallization from petroleum ether, bp 30–60 °C, afforded 0.30 g (59%) of the hydroxylamine product **14** as white crystals in three crops. The first crop was analytically pure and provided the following data: mp 91–93 °C; IR (KBr) 3145 (OH), 3030 (CH), 2940 (CH), 2860 (CH), 757 and 700 (C_6H_5) cm^{-1}; IR ($CHCl_3$) 3530 (OH), 3160 (OH), 3020 (CH), 2940 (CH), 2840 (CH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.52 (s, 6 H, 2 CCH_3), 2.40 (s, 3 H, NCH_3), 7.14–7.53 (m, 5 H, C_6H_5), 7.80 (br s, 1 H, OH); ^{13}C NMR ($CDCl_3$) δ 41.03 (2 CCH_3), 64.38 (NCH_3), 126.43 (2 ortho C), 126.82 (para C), 128.20 (2 meta C), 145.50 (1 ipso C); TLC R_f 0.41 (1:1 EtOAc–hexane).

Anal. Calcd for $C_{10}H_{15}NO$: C, 72.67; H, 9.17; N, 8.48. Found: C, 72.83; H, 9.13; N, 8.40.

Acid Hydrolysis of Nitrone 9Z. A solution of 0.54 g (3.0 mmol) of **9Z** and 0.52 mL (6.2 mmol) of concentrated hydrochloric acid in 10 mL of water was heated at reflux under nitrogen for 2.0 h, and the reaction progress was monitored by TLC (EtOAc). The cooled solution was saturated with sodium chloride and extracted with five portions of chloroform. The combined chloroform extracts were dried ($MgSO_4$) and concentrated on the rotatory evaporator to give 0.37 g (81%) of *S*-methyl thiobenzoate (**15**) as a pale yellow liquid. The identity and purity of the thio ester product were established by comparing its ^{1}H NMR spectrum [δ 2.46 (s, 3 H, SCH_3), 7.36–7.56 (m, 3 H, meta and para aryl H's), 7.90–8.02 (dd, 2 H, J = 7.5 Hz, J' = 2.4 Hz, ortho aryl H's)] with the ^{1}H NMR spectral data reported in the literature.[63]

(61) Main, P.; Fiske, S. J.; Hull, S. E.; Lessinger, L.; Germain, G.; Declercq, J.-P.; Woolfson, M. M. "MULTAN 80, A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data"; Universities of York, England, and Louvain-la-Neuve, Belgium, 1980.

(62) Sheldrick, G. M. "SHELX 76, A Program for Crystal Structure Determination"; University Chemical Laboratory: Cambridge, England, 1976.

The ^1H NMR spectrum and TLC plates did not show any trace of unreacted **9Z**, hydroxamic acid **16**, or benzoic acid, which would arise from further hydrolysis of *S*-methyl thiobenzoate.

The remaining aqueous layer was filtered and evaporated to dryness. Absolute ethyl alcohol was added, and the precipitated sodium chloride was filtered. The evaporation–precipitation procedure was repeated once more and the new filtrate was evaporated to dryness. The residual slush was triturated with absolute ethanol–anhydrous ether and allowed to stand in the freezer overnight. The precipitated solid was collected and dried in a desiccator over drierite ($CaSO_4$) for 2 days, providing 0.12 g (50%) of *N*-methylhydroxylamine hydrochloride as white hygroscopic crystals, mp 87–89 °C.

Alkaline Hydrolysis of Nitrone 9Z. *Caution*: The following reaction should be carried out in a well-ventilated hood since methanethiol is generated as a byproduct. A solution of 0.54 g (3.0 mmol) of **9Z** and 1.2 mL (6.0 mmol) of 5 N aqueous sodium hydroxide in 10 mL of water was heated at reflux under nitrogen for 2.5 h. The cooled reaction mixture was extracted four times with ethyl acetate. Evaporation of the ethyl acetate extracts afforded a trace amount of unreacted nitrone. The remaining aqueous layer was acidified to pH 1–2 with 6 N hydrochloric acid and extracted five times with dichloromethane. Drying (Na_2SO_4) of the combined extracts and concentration afforded 0.60 g of an off-white solid consisting of 0.25 g (68%) of benzoic acid and 0.09 g (20%) of *N*-methylbenzohydroxamic acid (**16**) on the basis of a comparison of its ^1H NMR spectrum with that of authentic **16** (see below) and benozic acid.[64] The spectrum exhibited the following peaks: δ 3.41 (s, 1.4 H, NCH_3 of **16**), 7.36–7.68 (7-line m, 7.8 H, meta and para H's of PhCOOH and all Ar H's from **16**), 8.06 (dd, 3.4 H, J = 8.3 Hz, ortho H's of PhCOOH), 11.65 (br s, 2.4 H, OH from **16** and PhCOOH). Attempts to separate **16** from benzoic acid either by bicarbonate extraction or by flash chromatography were not successful. The ^1H NMR spectrum also indicated the absence of any unreacted **9Z** or *S*-methyl thiobenzoate (diagnostic peak, SCH_3 singlet at δ 2.43).

An identical run was carried out, during which 1.7-mL aliquots were removed after 20, 40, and 150 min. The products were isolated by extraction as described above. Analysis of the ^1H NMR spectra of the aliquots provided the percent yield of benzoic acid and the molar ratio of **16** to benzoic acid in each: 20 min (9%; 1.0:0.20); 40 min (20%, 1.0:0.40); 150 min (90%; 1.0:3.23).

Alkaline Hydrolysis of *N*-Methylbenzohydroxamic Acid (16). A solution of 0.91 g (6.0 mmol) of **16** and 1.6 mL (8.0 mmol) of 5 N sodium hydroxide in 18.6 mL of water was heated at reflux under nitrogen for 2.5 h. The cooled solution was acidified with 2 N hydrochloric acid and extracted four times with chloroform. Drying ($MgSO_4$) of the combined chloroform extracts and concentration afforded an off-white solid contsisting of 0.53 g (73%) of benzoic acid and 0.20 g (22%) of unreacted *N*-methylbenzohydroxamic acid (**16**) according to ^1H NMR spectroscopy.

***N*-Hydroxy-*N*-methylbenzamide (16)** was prepared by an adaptation of literature procedures for similar compounds.[65] An aqueous solution of *N*-methylhydroxylamine was prepared under nitrogen by adding 9.44 g (0.113 mol) of *N*-methylhydroxylamine hydrochloride to a solution of 14.5 g (0.137 mol) of sodium carbonate in 164 mL of water and was covered with 50 mL of ether. The heterogeneous mixture was stirred magnetically and cooled in an ice–salt bath, as 19.7 g (0.140 mol) of benzoyl chloride in 50 mL of anhydrous ether was added dropwise over 14 min. The mixture was stirred and cooled for an additional 30 min, after which 45 mL of 20% sodium hydroxide was added. The aqueous layer (pH 12) was neutralized to pH 7 with 6 N hydrochloric acid, saturated with sodium chloride, and extracted five times with chloroform. Drying ($MgSO_4$) and concentration under reduced pressure afforded 12.6 g (74%) of the known[66] *N*-methylbenzohydroxamic acid (**16**) as a tan, viscous liquid (purity, ca. 96% by ^1H NMR): ^1H NMR ($CDCl_3$) δ 3.31 (s, 3 H, CH_3), 7.29–7.45 (m, 3 H, meta and para aryl H's), 7.45–7.65 (m, 2 H, ortho aryl H's), 9.15 (br s, 1 H, OH); ^{13}C NMR ($CDCl_3$) δ 38.40 (CH_3), 127.93 and 128.30 (2 C each, ortho and meta C's), 130.69 (para C), 132.93 (C-1 of C_6H_5), 168.65 (C=O).

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Registry No. **1**, 942-91-6; **2**, 89861-45-0; **3**, 95096-10-9; **4a**, 926-67-0; **4b**, 924-45-8; **4c**, 5140-89-6; **5a**, 32117-77-4; **5b**, 105183-86-6; **5c**, 105183-87-7; (*E*)-**6**, 105205-45-6; (*Z*)-**6**, 105183-88-8; (*E*)-**7**, 105183-90-2; (*Z*)-**7**, 105183-91-3; (*E*)-**8**, 105183-92-4; (*Z*)-**8**, 105183-93-5; (*E*)-**9**, 105183-94-6; (*Z*)-**9**, 105183-89-9; (*E*)-**10**, 105183-96-8; (*Z*)-**10**, 105183-95-7; (*E*)-**11**, 105183-97-9; (*Z*)-**11**, 105183-98-0; (*E*)-**12a**, 105183-99-1; (*Z*)-**12a**, 105205-46-7; (*E*)-**12b**, 105184-00-7; (*Z*)-**12b**, 105184-01-8; (*E*)-**12c**, 105184-02-9; (*Z*)-**12c**, 105184-03-0; (*E*)-**13a**, 105184-05-2; (*Z*)-**13a**, 105184-04-1; (*E*)-**13b**, 105184-06-3; (*Z*)-**13b**, 105184-07-4; (*E*)-**13c**, 105184-08-5; (*Z*)-**13c**, 105184-09-6; **14**, 105184-10-9; **15**, 5925-68-8; **16**, 2446-50-6; *N*-methylhydroxylamine hydrochloride, 4229-44-1; *N*-benzylhydroxylamine, 622-30-0; triethyl orthoacetate, 78-39-7; ethyl acetate, 141-78-6; triethyl orthopropionate, 115-80-0; ethyl propionate, 105-37-3; isobutyronitrile, 78-82-0; methyl iminoisobutyrate hydrochloride, 39739-60-1; *S*-methyl thioisobutyrate, 42075-42-3; methyl isobutyrate, 547-63-7; methyl iodide, 74-88-4; ethyl iodide, 75-03-6; *S*-ethyl thiobenzoate, 1484-17-9; methylmagnesium bromide, 75-16-1; benzoic acid, 65-85-0; benzoyl chloride, 98-88-4.

Supplementary Material Available: Tables of final atomic coordinates (Table III), thermal parameters (Table IV), and bond lengths and bond angles (Table V) for thioimidate *N*-oxide **9Z** (3 pages). Ordering information is given on any current masthead page.

(63) (a) Rullkoetter, J.; Budzikiewiz, H. *Org. Mass Spectrom.* **1976**, *11*, 44–52. (b) Skinner, J. F.; Markgraf, J. H. *J. Mol. Struct.* **1975**, *28*, 177–183.

(64) "The Aldrich Library of NMR Spectra", 2nd ed.; Pouchert, C. J., Ed.; Aldrich Chemical: Milwaukee, 1983; Vol. 2, p 182c.

(65) (a) Gupta, V. K.; Tandon, S. G. *J. Indian Chem. Soc.* **1969**, *46*, 831–834. (b) Said, I. Md., Ph.D. Thesis, University of Illinois, 1977.

(66) Monzyk, B.; Crumbliss, A. L. *J. Org. Chem.* **1980**, *45*, 4670–4675.