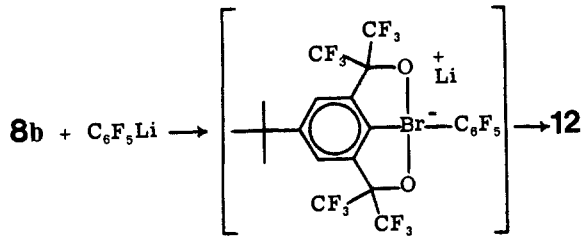
tonolysis of triaryliodinane **17**. Acidification of triaryliodinanes is known to give diaryliodonium ion and benzene.[28] The reaction of iodinane **10b** and phenyllithium is presented in Scheme IV.

Brominane **8b** forms pentafluorophenyl ether **12** upon reaction with (pentafluorophenyl)lithium. It is interesting to speculate that the formation of **12** results from a ligand–ligand coupling reaction of the pictured 12-Br-4 intermediate.



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Registry No. 1, 71401-76-8; **3**, 101697-22-7; **4b**, 101697-23-8; **5b**, 101697-24-9; **6a**, 76220-90-1; **6b**, 101697-25-0; **7a**, 76220-91-2; **7a**·2Na, 76220-93-4; **7b**, 101697-26-1; **8a**, 76220-92-3; **8b**, 101697-27-2; **9b**, 101697-28-3; **10b**, 101697-29-4; **11b**, 101697-30-7; **12**, 101697-31-8; **13**, 101697-32-9; CF_3COCF_3, 684-16-2; 9,10-dihydroanthracene, 613-31-0; anthracene, 120-12-7; tetralin, 119-64-2; napthalene, 91-20-3; thiophenol, 108-98-5; diphenyl disulfide, 882-33-7; aniline, 62-53-3; azobenzene, 103-33-3; pentafluorobenzene, 363-72-4.

Supplementary Material Available: A listing of thermal parameters, bond lengths and angles, and observed and calculated structure factors for brominane **8a** and iodinane **10b** (30 pages). Ordering information is given on any current masthead page.

Formation of Novel 1,2-Oxathietanes from 2-Chloroethyl Sulfoxide Precursors and Their Reactions in Solution, Including Formal [σ2s + σ2a] Cycloreversions and Rearrangements†

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Contribution from the Department of Chemistry, University of Alberta, Edmonton, Alberta T6G 2G2, Canada. *Received July 24, 1985. Revised Manuscript Received January 28, 1986*

Abstract: Spontaneous decomposition of antileukemic 1-[2-[(2-chloroethyl)sulfinyl]ethyl]-3-cyclohexyl-1-nitrosourea and its alkyl-substituted analogues in aqueous buffer (pH 7.0 and 37 °C) affords fragmentation products through the intermediacy of novel 1,2-oxathietanes. This was confirmed by specific deuterium labeling in the formal [σ2s + σ2a] cycloreversion products and by specific $S^{18}O$ labeling which eliminates an alternative pathway via thiirane *S*-oxide. The ^{18}O labeling also demonstrates that alternative ring opening with oxygen transfer occurs with 1,2-oxathietanes unsubstituted at the 4-position to give rearranged aldehyde. 1-[2-[(2-Chloroethyl)sulfinyl]-1,1-dimethylethyl]-3-*tert*-butyl-1-nitrosourea in aqueous buffer (pH 7.0 and 37 °C) affords products corresponding to three distinct pathways involving the formation of both 4,4-dimethyl-1,2-oxathietane and 1,2-oxathietane and the intermediacy of 4,4-dimethyl-1,2,3-oxadiazoline. Minor contribution of products from the parent 1-[2-[(2-chloroethyl)thio]ethyl]-3-alkyl-1-nitrosoureas to the extent of 5–10% occurs via in situ deoxygenation. An alternative and more convenient route to 1,2-oxathietanes was established using diazotization of (2-chloroethyl)alkyl-substituted sulfinylethylamines which provides dilute solutions of 3,3,4,4-tetramethyl-1,2-oxathietane. The latter product, which survives molecular distillation, was characterized by physical data and by the lithium aluminum hydride reduction to 2,3-dimethyl-2-mercapto-3-butanol, isopropyl alcohol, and 2-propanethiol. The thioacetone fragment from the [σ2s + σ2a] cycloreversion of the 1,2-oxathietane is trapped with reactive alkenes to give thietanes and with anthracenes to afford bicyclic thioketone adducts. There was no evidence of concomitant trapping of the acetone fragment nor of detectable chemiluminescence. Preliminary ab initio calculations at the level of SCF 6-21G and 6-31G* are in accord with spontaneous exothermic [σ2s + σ2a] cycloreversion of 1,2-oxathietane to give thioformaldehyde and formaldehyde. The thiocarbonyl fragment is expected to be more readily excited and is therefore more likely to bear the excess energy resulting in the n,π^* state for the thioketone resulting from the spontaneous cycloreversion. Preliminary calculations are in accord with this prediction. Owing to the clean aqueous decomposition of the antileukemic sulfinyl nitrosourea precursor the formation of 1,2-oxathietanes may play a physiological role in the anticancer action of the precursors.

The hitherto unkwown 1,2-oxathietanes are of both practical and theoretical interest. First, there is the analogy with the extensively studied 1,2-dioxetanes, which are of significance in bioluminescent and chemiluminescent reactions.[1] Second, these compounds are of fundamental theoretical interest because of the effects of the sulfur atom on the direction, rates, energetics, and energy distribution in the anticipated pericyclic reactions of the formal [σ2s + σ2a] type.[2] In this regard their relative structural

† Communicated in preliminary form: Lown, J. W.; Koganty, R. R. *J. Am. Chem. Soc.* **1983**, *105*, 126.

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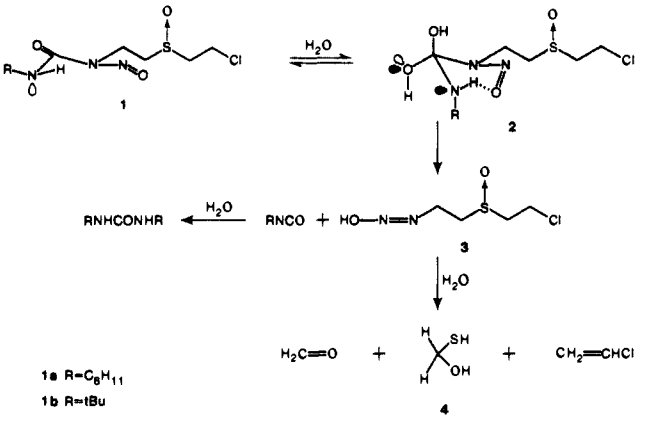
simplicity renders them accessible to sophisticated ab initio theoretical treatment.[3] Third, there is biological interest in that they were initially detected in studies on the mode of action of certain anticancer (2-chloroethyl)sulfinyl nitrosoureas.[4,5] Observation of the ability of 1,2-dioxetanes to induce pyrimidine dimers in DNA[6,7] thus raises the possibility of the cytotoxicity of modified nitrosourea precursors being, in part, due to the in vivo formation of 1,2-oxathietanes.

We report the development of mild methods of generation of these reactive novel heterocycles, the establishment of their pathways of formation using specific ^{18}O and ^{2}H labeling, and an examination of their characteristic chemical reactions. The latter include cycloreversions, rearrangements, and trapping of thiocarbonyl fragments to afford novel heterocycles. Preliminary ab initio calculations at the level of SCF 6-21G and 6-31G* assist in the interpretation of the course of the characteristic pericyclic reactions.

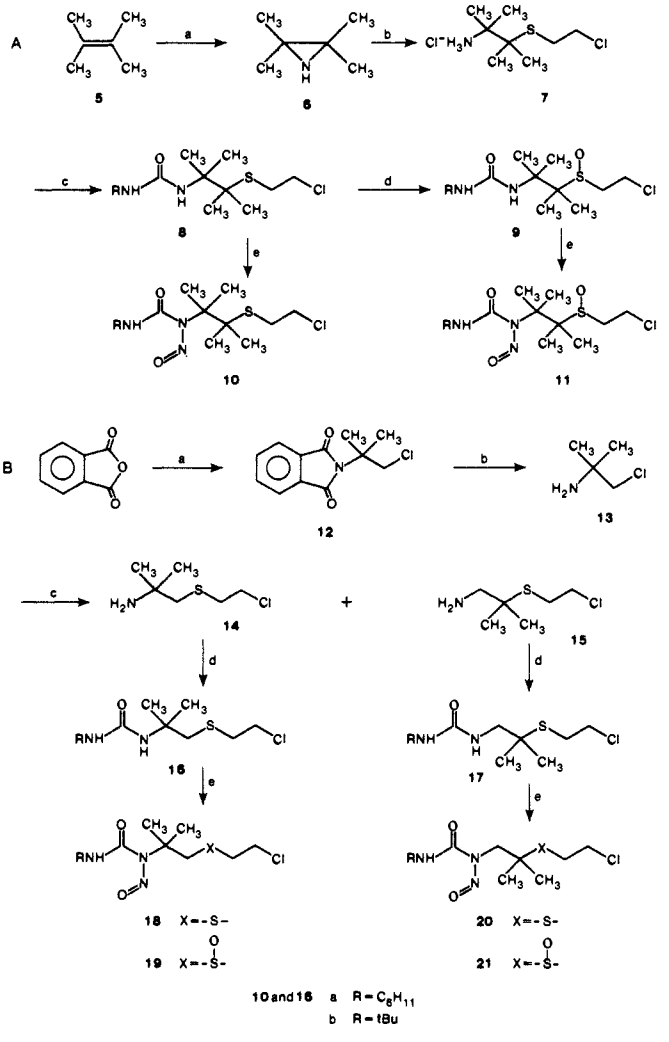
Formation of 1,2-Oxathietanes during the Stereoelectronically Controlled Aqueous Decomposition of Sulfoxide-Substituted 2-Chloroethyl Nitrosoureas. Current biochemical evidence indicates antileukemic 2-chloroethyl nitrosoureas (CENUs)[8-11] express their cytotoxicity by spontaneous decomposition under physiological conditions to generate electrophiles including 2-chloroethyl diazohydroxides which react with nucleophilic sites in sensitive cellular macromolecules including DNA.[4,5,12-15] The modified CENU 1-[2-[(2-chloroethyl)sulfinyl]ethyl]-3-cyclohexyl-1-nitrosourea (**1a**), which exhibits substantial in vivo antileukemic activity,[4a] was allowed to decompose in aqueous potassium phosphate buffer at pH 7.0 and 37 °C. The reaction proceeds via the stereoelectronically controlled intermediate **2**[4b] and the diazohydroxide **3** and affords, unexpectedly, only the fragmentation products shown (Scheme I).[5]

A number of alkyl-substituted thioethers and sulfinyl-substituted[4] nitrosoureas were prepared in order to investigate this reaction further. The synthetic procedures employed to prepare these and the corresponding sulfinyl nitrosoureas are outlined in Scheme II.[16]

Scheme I. Fragmentation Products for Decomposition of (2-Chloroethyl)sulfinyl Nitrosoureas in Aqueous Potassium Phosphate Buffer at pH 7.0 and 37 °C



Scheme II[a]



[a] Reaction conditions. A: (a) prepared by the pseudohalogen method of Closs and Brois (Closs, G. L.; Brois, S. J. *J. Am. Chem. Soc.* **1960**, *82*, 6068); (b) $HSCH_2CH_2OH$ and then $SOCl_2$ in $CHCl_3$; (c) RNCO in $CHCl_3$ at room temperature; (d) H_2O_2 in MeOH; (e) $NaNO_2$ in HCOOH at 0 °C. B: (a) $H_2NC(CH_3)_2CH_2OH$ and then $SOCl_2$ in $CHCl_3$; (b) concentrated HCl and heat; (c) KOH, $HSCH_2CH_2OH$, and then $SOCl_2$ in $CHCl_3$; (d) RNCO in $CHCl_3$ at room temperature; (e) H_2O_2 in MeOH (for **19** and **21**) followed by $NaNO_2$ in HCOOH at 0 °C.

Controlled aqueous decomposition of 1-[2-[(2-chloroethyl)-sulfinyl]-1,1,2,2-tetramethylethyl]-3-*tert*-butyl-1-nitrosourea (**22e**)

(2) Woodward, R. B.; Hoffman, R. *The Conservation of Orbital Symmetry*; Verlag Chemie: Weinheim, 1970; p 72.

(3) Snyder, J. P.; Carlsen, L. *J. Am. Chem. Soc.* **1977**, *99*, 2931.

(4) (a) Lown, J. W.; Joshua, A. V.; McLaughlin, L. W. *J. Med. Chem.* **1980**, *23*, 798. (b) The evidence for the participation of the tetrahedral intermediate includes oxygen exchange at the amide carbonyl in $H_2{}^{18}O$ (Lown, J. W.; Chauhan, S. M. S. *J. Org. Chem.* **1981**, *46*, 5309) and the fact that conformational changes of nitrosoureas in protic solvents followed by ^1H NMR (Lown, J. W.; Chauhan, S. M. S. *Tetrahedron Lett.* **1981** *22*, 401) and ^{15}N NMR spectroscopy (Lown, J. W.; Chauhan, S. M. S. *J. Org. Chem.* **1981**, *46*, 5309) as well as stereoelectronic control in the decomposition of the tetrahedral intermediates (Lown, J. W.; Chauhan, S. M. S. *J. Org. Chem.* **1983**, *48*, 3901; **1981**, *46*, 5309) uniquely interpret the formation of the observed products. In addition, in the aqueous decomposition of the closely analogous nitrosothioureas abstraction of the NH proton leads to distinctly different products from the tetrahedral intermediate pathway (Lown, J. W.; Chauhan, S. M. S. *J. Org. Chem.* **1983**, *48*, 3901).

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(14) Colvin, M.; Brundrett, R. B.; Cowens, W.; Jardine, I.; Ludlum, D. B. *Biochem. Pharmacol.* **1976**, *25*, 695.

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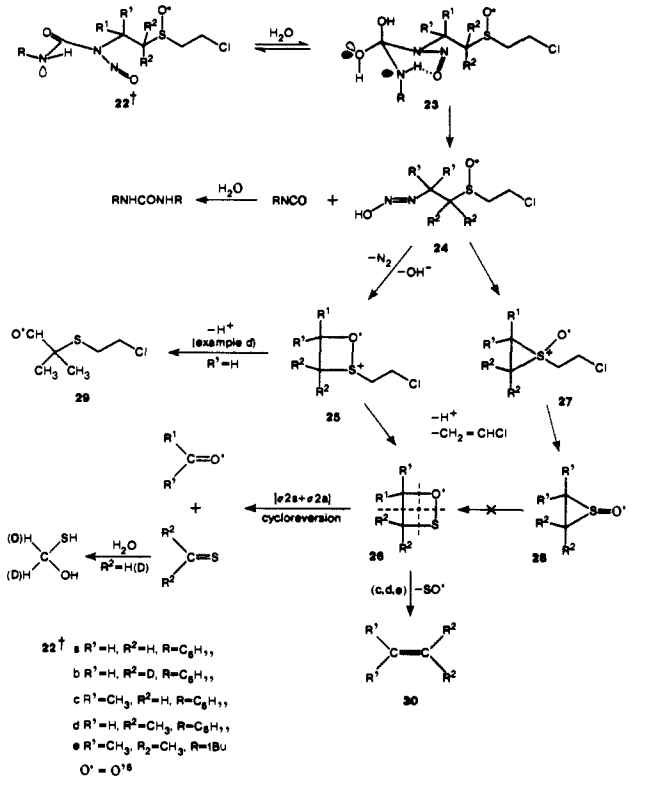
Scheme III. Pathways and Products of Decomposition of Alkyl-Substituted (2-Chloroethyl)sulfinyl Nitrosoureas **22** in Aqueous Potassium Phosphate Buffer (pH 7.0 and 37 °C) Together with the Results from Specific Isotopic Labeling

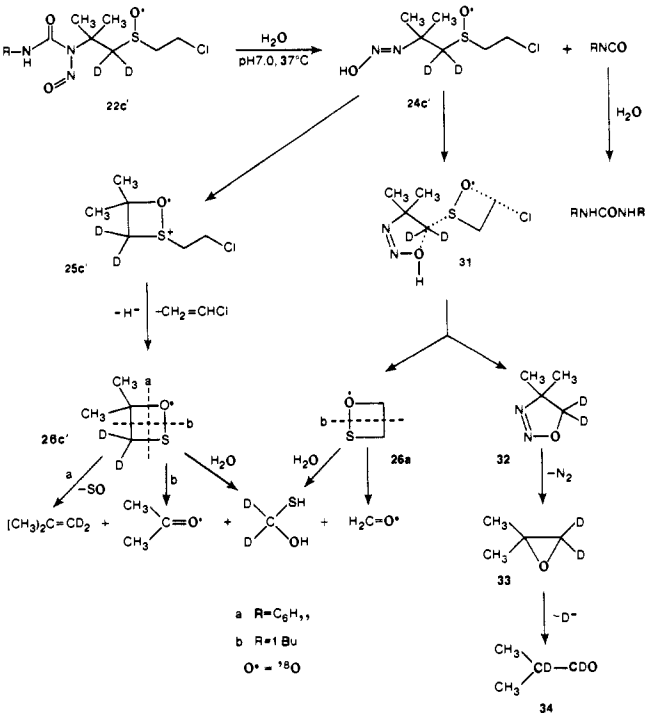


affords thioacetone, acetone, vinyl chloride, and 2,3-dimethyl-2-butene (**5**) as volatiles, as well as di-*tert*-butylurea and *tert*-butyl isocyanate. The analytical data for these and other decompositions are summarized in Table I. GC analysis of the reaction mixture permitted detection of labile 3,3,4,4-tetramethyl-1,2-oxathietane (**26**) ($R_1 = R_2 = CH_3$) with a retention time of 5.3 min, parallel GC/MS analysis of which gave the corresponding correct molecular ion of 132.

The isolation of a 1,2-oxathietane by this, and by the alternative procedures described below, together with the corresponding cycloreversion products is in accord with the decomposition pathway outlined in Scheme III. Partipation of the sulfoxide oxygen at the demand of the incipient cationic center in the diazohydroxide **24** forms the initial 1,2-oxathietane intermediate **25**. The latter eliminates vinyl chloride and a proton to give the parent 1,2-oxathietane **26**, which is then subject to one of two formal [σ2s + σ2a] cycloreversions[2] to give formaldehyde and thioformaldehyde, the latter of which is identified as the hydrate **4**. The alternative pathway via the thiirane *S*-oxides **27** or **28** followed by ring expansion to the 1,2-oxathietane prior to cycloreversion is eliminated since 1-[2-[(2-chloroethyl)sulfinyl]-

(16) Scheme IIA gives the synthesis of the 3,3,4,4-tetramethyl-1,2-oxathietane precursor. Scheme IIB shows the preparation of the isomeric 1,1- and 2,2-dimethyl counterparts. Nucleophilic ring opening of 2,2-dimethylaziridine from **13** with 2-mercaptoethanol affords a mixture of the isomeric 3- and 2-[(2-hydroxyethyl)thio]-2-methyl-2- and 1-aminopropanes which were separated chromatographically as their corresponding chloro derivatives **14** and **15**. (See: Lown, J. W.; Kganty, R. R.; Joshua, A. V. *J. Org. Chem.* **1982**, *47*, 2027.) Conversion of **14** and **15** to their respective nitrosoureas **18** and **19** and **20** and **21** proceeded normally. In general it was found to be more satisfactory to oxidize the thioethers (e.g., **8**, **16**, **17**) to the sulfoxides prior to nitrosation. This reaction was effected either with hydrogen peroxide or with *m*-chloroperbenzoic acid or when an $S^{18}O$ label was required (Scheme III) by rose bengal or methylene blue photosensitized oxidation in the presence of molecular oxygen (ref 5). The nitrosation of the ureas **16** and **17** (**a** or **b**) with sodium nitrite in formic acid proceeds regiospecifically at the less hindered positions indicated (Johnston, T. P.; McCaleb, G. S.; Opliger, P. S.; Montgomery, J. A. *J. Med. Chem.* **1966**, *9*, 862). In the case of **8** and **9** it was necessary to incorporate a *tert*-butyl *N*-substituent in order to ensure the desired regiospecificity owing to the increased steric bulk due to the two methyl groups in the side chain.

Scheme IV. Pathways and Products of Decomposition of **22c′**-*S*-^{18}O in Aqueous Potassium Phosphate Buffer (pH 7.0 and 37 °C) Illustrating the Formation of Alternative 1,2-Oxathietanes from Competing Cyclizations of 2-Chloroethyl Sulfoxide Precursors



ethyl-2,2-d_2]-3-cyclohexyl-1-nitrosourea (**22b**) affords formaldehyde and thioformaldehyde-d_2 hydrate with no deuterium scrambling.

The observation that 1-[2-[(2-chloroethyl)sulfinyl-^{18}O]-1,1-dimethylethyl]-3-cyclohexyl-1-nitrosourea (**22c**-*S*-^{18}O) affords acetone-^{18}O and thioformaldehyde among the volatile products establishes that the transfer of oxygen from the sulfoxide group to the carbonyl fragment occurs intramolecularly.

The major reaction pathway is therefore via the 1,2-oxathietane **26**, leading to carbonyl and thiocarbonyl fragments as well as alkene **30** and sulfur monoxide by the alternative formal [σ2s + σ2a] cycloreversion as shown in Scheme III. It should be noted however that cheletropic[2] loss of sulfur monoxide from a thiirane *S*-oxide **28** cannot be ruled out as a possible source of the alkene **30**.

Alternative Ring Opening of 1,2-Oxathietane. 1-[2-[(2-Chloroethyl)sulfinyl]-2,2-dimethylethyl]-3-cyclohexyl-1-nitrosourea (**22d**) decomposes in pH 7.0 buffer at 37 °C to give 2-[(2-chloroethyl)thio]-2-methylpropanal (**29**) as a minor product together with small amounts of 1-[(2-chloroethyl)thio]-2-methylpropene (**37**), 1-[(2-hydroxyethyl)thio]-2-methylpropene (**39**), *tert*-butyl isocyanate, and *tert*-butylurea in addition to the major cycloreversion products of formaldehyde and thioacetone. Isolation of the aldehyde **29** is in accord with formation of the 3,3-dimethyl-2-(2-chloroethyl)-1,2-oxathietanium species **25** ($R_1 = H$, $R_2 = CH_3$) which undergoes proton loss at position 4 and breakage of the O–S bond with transfer of oxygen to carbon to yield **29**.

The corresponding reaction of 1-[2-[(2-chloroethyl)sulfinyl-^{18}O]-2,2-dimethylethyl]-3-cyclohexyl-1-nitrosourea (**22d**-*S*-^{18}O) to afford 2-[(2-chloroethyl)thio]-2-methylpropanal-^{18}O (**29**-^{18}O) is also in accord with the suggested pathway via a four-membered heterocyclic intermediate.

Formation of Alternative 1,2-Oxathietanes by Competing Cyclizations of 2-Chloroethyl Sulfoxide Precursors. Decomposition of 1-[2-[(2-chloroethyl)sulfinyl-^{18}O]-1,1-dimethyl-2,2-dideuterioethyl]-3-*tert*-butyl-1-nitrosourea (^{2}**2c′**-*S*-^{18}O) in potassium phosphate buffer at pH 7.0 and 37 °C affords the products bearing the isotopic labels shown in Scheme IV.

The nature and spectrum of products obtained from the aqueous decomposition of **22c′** require the intermediacy of two different

Table I. Products from Controlled Decomposition of Sulfinyl Nitrosoureas in Phosphate Buffer (pH 7.2) at 37 °C

source	dec prod	GC retention time, min	% theoretical yield	m/z (rel intensity, fragments)
(**21**) 1-[2-[(2-chloroethyl)sulfinyl]-2,2-dimethylethyl]-3-*tert*-butyl-1-nitrosourea	vinyl chloride	1.5	1–5	64 (M + 2, 1.2), 62 (M^+, 3.9), 27 (M − Cl, 100)
	2-methylpropene	2.1	≃5	56 (M^+, 100), 41 (60), 26 (19)
	tert-butylurea[a]			173 (MH^+, 6), 158 (45), 100 (100), 99 (30), 85 (8), 57 (60)
	tert-butyl isocyanate[b]	2.6	30	99 (M^+, 90), 84 (20), 73 (100), 57 (82)
	thioacetone	3.3	≃15	74 (M^+, 29), 59 (100), 45 (52), 44 (60)
	1-[(2-chloroethyl)thio]-2-methylpropene (**37**)	24.5	4.8	152 (M + 2, 8), 150 (M^+, 26), 115 (M − Cl, 19), 101 (M − CH_2Cl, 100), 88 (42), 69 (15), 46 (60), 45 (52)
	1-[(2-hydroxyethyl)thio]-2-methylpropene (**39**)	29.5	2–3	132 (M^+, 22), 114 (M − H_2O, 28), 101 (M − CH_2OH, 100), 88 (38), 47 (38), 46 (27), 45 (42)
(**22a**) 1-[2-[(2-chloroethyl)-sulfinyl]ethyl]-3-cyclohexyl-1-nitrosourea	vinyl chloride	1.5	1–5	64 (M + 2, 1.2), 62 (M^+, 3.9), 27 (M − Cl, 100)
	thioformaldehyde hydrate	2.4	15–28	64 (100), 48 (52), 47 (30)
(**22b**) 1-[2-[(2-chloroethyl)-sulfinyl]-2,2-dideuterioethyl]-3-cyclohexyl-1-nitrosourea	vinyl chloride	1.6	5–10	64 (M + 2, 1.2), 62 (M^+, 3.9), 27 (M − Cl, 100)
	thioformaldehyde-d_2	2.4	15–25	66 (100), 50 (55), 47 (30)
(**22c'**-2,2-d_2-S-^{18}O) 1-[2-[(2-chloroethyl)sulfinyl-^{18}O]-1,1-dimethyl-2,2-dideuterioethyl]-3-cyclohexyl]-1-nitrosourea	thioformaldehyde-d_2 hydrate	1.5	0–5	64 (M + 2, 1.2), 62 (M^+, 3.9), 27 (M − Cl, 100)
	1-chloro-1-deuterio-2-methyl-1-propene	1.9	2.4	93 (M + 2, 9.5), 91 (M^+, 29), 78 (5.3), 76 (16.6)
	1,1-dideuterio-2-methyl-1-propene	2.2	5.8	58 (M^+, 100), 43 (M − CH_3, 41), 41 (62)
	thioformaldehyde-d_2 hydrate	3.0	10–12	66 (M^+, 100), 50 (52), 44 (21)
	acetone-^{18}O	4.0	10–15	60 (M^+ 27), 45 (M − CH_3, 100), 30 (29)
	tert-butyl isocyanate[a]	4.5	20–30	99 (M^+, 88), 84 (M − CH_3, 20), 57 (100), 43 (20)
	1,1-dideuterio-2-methylpropene oxide	5.5	1–2	74 (M^+, 3), 59 (M − CH_3, 100), 43 (28)
	isobutyraldehyde-d_1	7.5	trace	73 (M^+, 21), 58 (M − CH, 11), 43 (M − CDO, 100)
(**22d**-S-^{18}O) 1-[2-[(2-chloroethyl)-sulfinyl]-^{18}O]-2,2-dimethylethyl]-3-cyclohexyl-1-nitrosourea	vinyl chloride	1.5	2–5	64 (M + 2, 1.2), 62 (M^+, 3.9), 27 (M − Cl, 100)
	2-methylpropene	2.1	5–8	56 (M^+, 100), 41 (60), 26 (19)
	thioformaldehyde	2.4	2–4	64 (100), 48 (52), 47 (30)
	thioacetone	3.5	≃12	74 (M^+, 29), 59 (100), 45 (52), 44 (60)
	2-[(2-chloroethyl)thio]·2-methylpropanol-^{18}O (**29**)	27.5	5–10	170 (M + 2, 6.5), 168 (M^+, 21), 139 (13.8), 137 (M − $CH^{18}O$, 42), 133 (M − Cl, 9), 119 (M − CH_2Cl, 100), 88 (43), 74 (26), 46 (41), 45 (43)
	2,3-dimethyl-2-butene	1.2	5–8	84 (M^+, 22), 69 (M − CH_3, 61), 55 (12), 41 (100)
(**22e**-S-^{18}O) 1-[2-[(2-chloroethyl)-sulfinyl-^{18}O]-1,1,2,2-tetramethylethyl]-3-*tert*-butyl-1-nitrosourea	vinyl chloride	1.5	2–4	64 (M + 2, 1.2), 62 (M^+, 3.9), 27 (M − Cl, 100)
	acetone-^{18}O	2.9	12–20	60 (M^+, 22), 45 (M − CH_3, 100), 30 (19)
	thioacetone	3.3	12–20	74 (M^+, 29), 59 (100), 45 (52), 44 (66)
	3,3,4,4-tetramethyl-1,4-oxathietane (**26e**)	4.1	trace	134 (M^+, 6), 119 (M − CH_3, 4), 116 (M − ^{18}O, 19), 84 (100), 74 (8), 60 (19)
	2,2,3,3-tetramethyl-1,4-oxathiane (**42**)	34	1–3	160 (M^+, 28), 145 (M − CH_3, 16), 100 (100), 85 (48), 84 (60), 60 (68), 47 (60), 46 (29), 45 (42)

[a] *tert*-Butylurea is found in the decompositions reactions and has been identified by chemical ionization mass spectrum using NH_3 as reagent gas [b] *tert*-Butyl isocyanate is found in the reactions as one of the products.

1,2-oxathietanes formed from competing pathways from the intermediate diazohydroxide **24'** in Scheme IV. The major pathway, accounting for ca. 75% (estimated from relative yields of products) of the reaction, is via the 4,4-dimethyl-1,2-oxathietane species **25c'**. In accord with this mechanistic interpretation it was observed that the 1-[2-[(2-chloroethyl)sulfinyl]-2,2-dimethylethyl]-3-cyclohexyl-1-nitrosourea (**22d**) after controlled aqueous decomposition affords both 2,2-dimethyloxirane **33** and isobutyraldehyde **34**. This is consistent with the intermediacy of a 5,5-dimethyl-1,2,3-oxadiazoline[17] isomeric with **32**.

Compounds **22a–e** and similar (2-chloroethyl)sulfinyl derivatives show no tendency to undergo spontaneous intramolecular displacement of chloride in polar aprotic media. Therefore it seems plausible that the 1,2-oxathietanes **26** are formed only as a result of intramolecular participation of the diazohydroxide moiety in intermediate **31** or similar reactive species.

Competing Direct Sulfoxide Deoxygenation Pathway. The above normal reactions leading to 1,2-oxathietanes are complicated to a minor extent by pathways involving direct deoxygenation of the sulfoxide group. The latter group is evidently susceptible to deoxygenation in one of the intermediates (possibly the diazohydroxide **24**) to the extent of ~5–10% of the overall reaction. Therefore minor amounts of aqueous decomposition products are observed, corresponding to the parent thioether nitrosourea (see Scheme V).[18,19]

In the case of 1-[2-[(2-chloroethyl)sulfinyl]-1,1,2,2-tetramethylethyl]-3-*tert*-butyl-1-nitrosourea (**11b**) similar minor deoxygenation occurs with consequent sulfur-assisted hydrolysis of the terminal chloro group via species **40**.[20] Intramolecular hydroxyl group participation in the decomposition of **41** affords the 2,2,3,3-tetramethyl-1,4-oxathiane (**42**) (Scheme Vb).

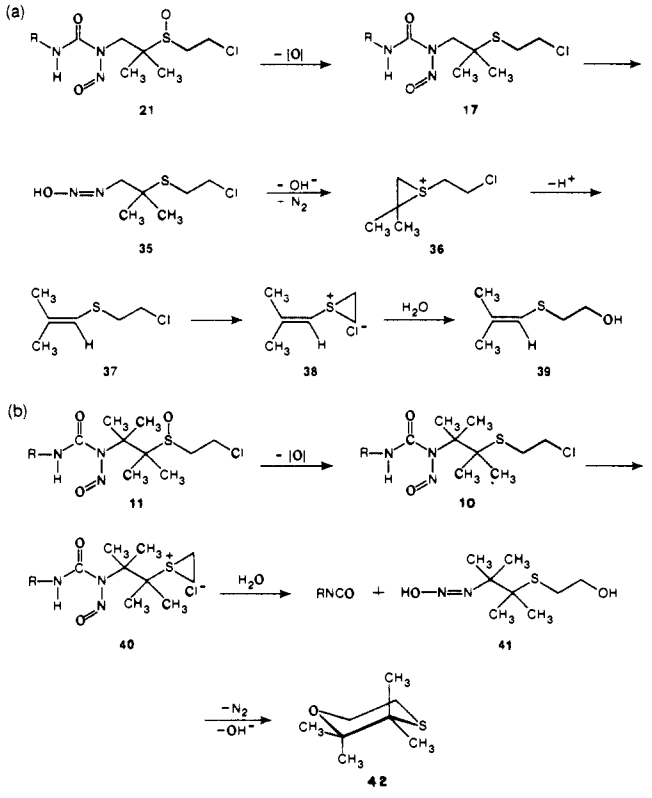
(17) The intermediacy of the latter species in the aqueous decomposition of 2-chloroethyl nitrosoureas has previously been demonstrated with specific $N^{18}O$ labeled compounds (Lown, J. W.; Chauhan, S. M. S. *J. Org. Chem.* **1982**, *47*, 851. See also: Johnston, T. P.; McCaleb, G. S.; Opliger, P. S.; Montgomery, J. A. *J. Med. Chem.* **1966**, *9*, 892).

(18) In view of the relatively minor contribution of the deoxygenation pathways illustrated in Schemes Va and Vb (~5–10%) it was difficult, because of analytical limitations of detection, to determine the nature of the oxygen acceptor from the sulfoxide group. One or more of the readily oxidizable products, such as aldehydes, are possible candidates. Similarly one cannot, with confidence, designate the precise sulfinyl species from which oxygen is transferred. However since the sulfinyl nitrosoureas are stable in aprotic solvents in the presence of mild reductants, the minor deoxygenation pathways may involve reactive intermediates such as **24**.

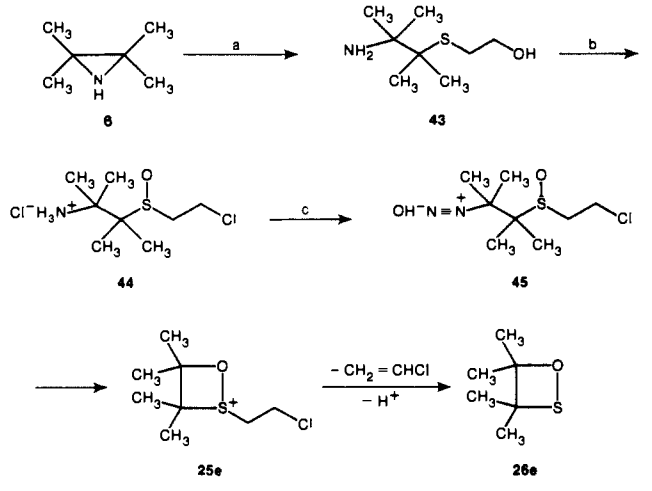
(19) Removal of the oxygen from **21**, for example, permits participation of the sulfur in **17** to form two distinct thiiranium species **36** and **38**, leading to the thioether side products **37** and **39**, respectively (Scheme Va). This facile neighboring-group participation by sulfur has been confirmed previously by deuterium labeling experiments. (See Lown et al., ref 17.)

(20) Proton loss cannot occur in the intermediate tetramethylthiiranium species **36** to give an alkene comparable to **33**. Hydrolysis of the thiiranium species occurs instead, and after generation of the diazohydroxide, intramolecular participation in the decomposition of the latter affords 2,2,3,3-tetramethyl-1,4-oxathiane (**42**).

Scheme V. Pathways and Products from the Minor Contribution (5–10%) of the Sulfur Deoxygenation Followed by Decomposition of the Thioether Diazohydroxides To Give Rearranged Products



Scheme VI[a]

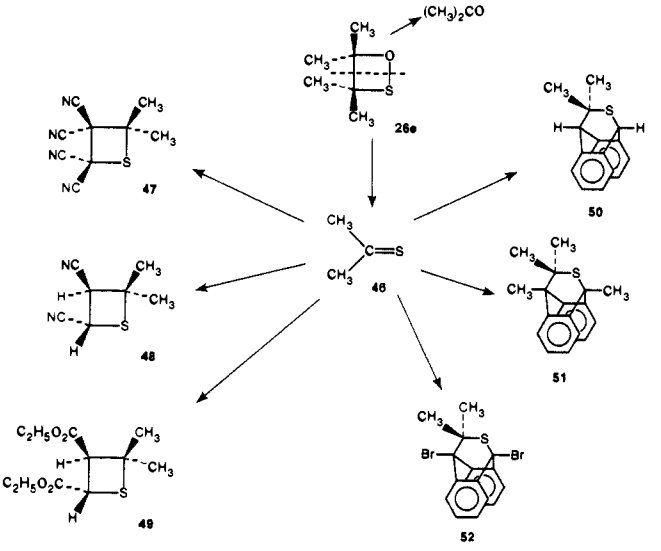


[a] Reaction conditions: (a) $HSCH_2CH_2OH$; (b) $SOCl_2$ in $CHCl_3$ and then H_2O_2 in MeOH; (c) $NaNO_2$ and HCl at 0 °C.

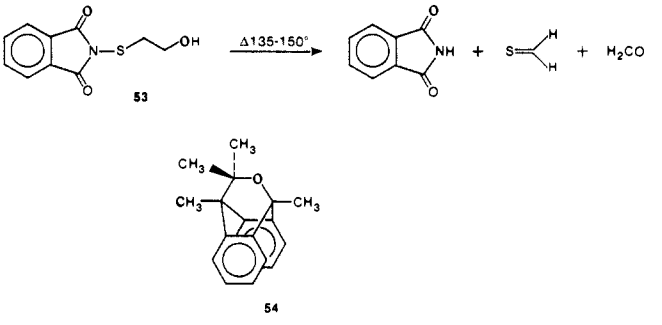
Alternative Generation of 1,2-Oxathietanes via Diazotization and Characterization of 3,3,4,4-Tetramethyl-1,2-oxathietane. A more direct method of preparation of the 1,2-oxathietanes is by diazotization of the amine precursor. Careful diazotization of **44** using sodium nitrite in aqueous formic acid at 0 °C with added dichloromethane permits the preparation of a dilute dichloromethane solution of 3,3,4,4-tetramethyl-1,2-oxathietane (**26e**) (Scheme VI), which is identical in GC behavior and MS properties with that prepared from sulfinyl nitrosourea **22e**.

The extract following the diazotization of 2-[(2-chloroethyl)-sulfinyl]-1,1,2,2-tetramethylethylamine hydrochloride at −10 °C was rapidly dried, cooled to −25 °C, and vacuum distilled at 0.5 mmHg. High-resolution mass spectral examination of the distillate confirmed the composition of the 3,3,4,4-tetramethyl-1,2-oxathietane (26e) (m/z 132.0588 (calcd for $C_6H_{12}OS$, 132.0609)) and its characteristic fragments (117 (M − CH_3), 116 (M − O), 84

Scheme VII. Sulfur Heterocycles Formed from Reaction of Thioacetone (**46**) (Generated from Spontaneous Formal [σ2s + σ2a] Thermal Cycloreversion of 3,3,4,4-Tetramethyl-1,2-oxathietane (**26e**)) and by [π2a + π2a] Cycloaddition with Reactive Alkenes and [π2a + π4a] Cycloaddition with Anthracene as Dienes



Scheme VIII. Generation of Thioformaldehyde by Flash Vacuum Pyrolysis of *N*-[(2-Hydroxyethyl)thio]phthalimide (**53**)



(M − SO), and 74 [$(CH_3)_2C{=}S$]). The dichloromethane solution exhibits peaks in the ^1H NMR spectrum at δ 0.98 [s, 6 H, S-C-$(CH_3)_2$] and 1.18 [s, 6 H, $OC(CH_3)_2$], and the IR shows bands at 910 and 810 cm^{-1} attributed to –C–O–S–. The UV absorption spectrum shows maxima at 258 and 265 extending to 320 nm although the extinction coefficients cannot be assigned with confidence. The absorption at 430 nm that appears slowly upon storage is tentatively ascribed to the thioacetone fragment.[21]

The 3,3,4,4-tetramethyl-1,2-oxathietane was further characterized by its reduction with lithium aluminum hydride. This yielded 2,3-dimethyl-2-mercapto-3-butanol, isopropyl alcohol, and 2-propanethiol in 8%, 68%, and 24% yields, respectively.

The dichloromethane solution of the 1,2-oxathietane at −20 °C is sufficiently stable to permit exploration of the chemical reactions of this novel heterocycle (see below).

Formal [σ2s + σ2a] Cycloreversions of Tetramethyl-1,2-oxathietanes and Trapping of Thiocarbonyl Fragments. Treatment of a dilute solution of tetramethyl-1,2-oxathietane **26e** in methylene chloride at −20 °C with tetracyanoethylene affords 2,2,3,3-tetracyano-4,4-dimethylthietane (**47**) resulting from [2 + 2] cycloaddition to the thioacetone derived from the cycloreversion (Scheme VII). Similar reaction of **26e** with fumaronitrile gives the corresponding *trans*-2,3-dicyano-4,4-dimethylthietane (**48**).[22] An additional reaction of **26e** with the olefinic trapping agent

(21) Thioketones or thioaldehydes are not normally isolable unless they are severely hindered sterically. (a) Okazaki, R.; Ishii, A.; Fukuda, N.; Oyama, H.; Inamoto, N. *J. Chem. Soc., Chem. Commun.* **1982**, 1187. (b) Vedejs, E.; Perry, D. A. *J. Am. Chem. Soc.* **1983**, *105*, 1683.

(22) Maleonitrile cyclizes spontaneously to pyrazine and therefore cannot be used to test the possible stereospecificity of the [2 + 2] cycloaddition trapping of the thiocarbonyl compounds.

diethyl fumarate gives *trans*-2,3-dicarboethoxy-4,4-dimethylthietane (**49**). Reaction of tetramethyl-1,2-oxathietane **26e** with anthracene, 9,10-dimethylanthracene, and 9,10-dibromoanthracene affords the [π4s + π2s] cycloadducts of thioacetone, **50**, **51**, and **52**, respectively (Scheme VII). In the representative case of **51** both ^{13}C and ^{1}H NMR spectroscopies as well as MS were used for characterization. Authentic samples of thiocarbonyl compounds for comparison with the products from 1,2-oxathietanes were prepared from the phthalimide derivative **53** (Scheme VIII). Flash thermolysis of **53**[23] at 135–150 °C and condensation of the volatile products in a cold trap containing the addend (e.g., tetracyanoethylene or an anthracene) afforded cleanly the corresponding adducts of thioformaldehyde.

Preliminary Consideration of the Energetics of 1,2-Oxathietane Decomposition. The second fragment from the cycloreversion of 1,2-oxathietane **26e** is acetone. In principle, and by analogy with 1,2-dioxetanes,[1] this could be produced in an excited state and therefore might be capable of [π2s + π2s] or [π4s + π2s] cycloadditions.[2] In order to test for this possible reactivity an authentic sample of the 1:1 adduct of photoexcited acetone with 9,10-dimethylanthracene **54** was prepared. However there was no evidence for the formation of **54** during the reaction of **26e** with 9,10-dimethylanthracene to form **51**. A number of interpretations are possible at this stage of our investigations of this new heterocyclic system. Either the 1,2-oxathietane system does not release either fragment in an excited state in contrast to the 1,2-dioxetanes[1] or the energy distribution in the unsymmetrical fragmentation favors the lower lying and more readily excited thiocarbonyl fragment. Whether the potential energy surface of 1,2-oxathietane cycloreversion does or does not cross that of the singlet-triplet states of either thioacetone or acetone remains to be determined from detailed ab initio calculations. The only pertinent calculations reported to date are on the parent 1,2-oxathietane molecule at the CNDO/B level and yielded the optimized geometry and relative energy.[24] Our own preliminary calculations at the SCF 6-21G level indicate, after geometry optimization, an energy of −550.119 20 au for the 1,2-oxathietane and destabilization relative to the formal [σ2s + σ2a] fragments with an energy of −431.4162 au for thioformaldehyde and of −113.6971 au for formaldehyde for a total of −550.1133 au. Our continuing theoretical studies are now directed toward including configuration interaction and polarization functions for the sulfur and oxygen atoms. Among the factors to be considered in connection with the latter calculations is the intrinsic chemical reactivity of thiocarbonyl compounds in the ground state.[25] The results of critical experimental tests invoking stereochemical criteria together with more detailed ab initio theoretical treatment of this system will be reported in due course together with consideration of a possible diradical pathway compared with a concerted process.

Experimental Section

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. The ^{1}H NMR spectra of the intermediates were recorded on a Varian HA-100 or a Bruker WH-200 or WH-400 spectrometer. Mass spectra were determined on an Associated Electrical Industries (AEI-MS-9) double-focusing high-resolution mass spectrometer with ionization energies at 70 eV. Peak measurements were made by comparison with perfluorotributylamine at a resolving power of 15 000 on an AEI-MS-50 mass spectrometer. GC analyses were performed on a Hewlett-Packard 5840A analytical gas chromatograph equipped with a flame ionization detector. GC/MS analyses were performed on an AEI-MS-12 spectrometer. Infrared spectra were recorded on a Nicolet 7199 FT spectrophotometer, and only the principal absorptions are reported when appropriate.

Preparation of Sulfinyl Nitrosourea Precursors. 3-[(2-Chloroethyl)thio]-2,3-dimethyl-2-butylamine Hydrochloride (7). A solution of 1.18 g (10 mmol) of thionyl chloride in 5 mL of chloroform was added dropwise to a stirred solution of 0.8 g (5 mmol) of 3-[(2-hydroxyethyl)thio-2,3-dimethyl-2-aminobutane[16] in 5 mL of chloroform cooled to 0 °C. Stirring was continued at room temperature for 12 h and then a gentle reflux was maintained during a final 30 min. The solvent and excess of thionyl chloride were removed in vacuo, and the residue was taken up in 10 mL of methanol and decolorized with Norit. The residue remaining after removal of the solvent was recrystallized from chloroform/petroleum ether (1:1) and afforded **7** as a pink crystalline solid: 1.0 g (80% yield); mp 96–97 °C; ^{1}H NMR ($CDCl_3$) δ 1.4–1.7 (m, 12 H), 2.8–3.1 (m, 2 H, SCH_2), 3.3–3.7 (m, 2 H, CH_2Cl), 8.45–9.55 (brs, 3 H, NH_3^+Cl); MS, *m/z* (relative intensity) 195 (M^+, 5), 160 (M − Cl, 28), 146 (M − CH_2Cl, 19), 116 (100). Anal. Calcd for $C_8H_{18}NSCl\cdot HCl$: C, 41.6; H, 8.2; N, 6.1. Found: C, 41.8; H, 8.1; N; 6.1.

***N*-(2-Hydroxy-1,1-dimethylethyl)phthalimide.** A mixture of 7.4 g (50 mmol) of phthalic anhydride and 4.5 g (50 mmol) of 2-amino-2-methylpropanol was heated at 160–180 °C for 30 min and then poured into cold water. The product was taken up in chloroform (30 mL) and dried (Na_2SO_4) and the solvent removed in vacuo, affording the phthalimide: 10.0 g (95% yield); ^{1}H NMR ($CDCl_3$) δ 1.6 (s, 6 H, $2CH_3$), 3.4 (br s, 1 H, OH), 3.92 (s, 2 H, CH_2), 7.4–7.9 (m, 4 H, aryl); MS, *m/z* (relative intensity) 219 (M^+, 8), 188 (M − 31, 100), 173 (38), 146 (48), 145 (32), 76 (58).

***N*-(2-Chloro-1,1-dimethylethyl)phthalimide (12).** Thionyl chloride (7.0 g, 60 mmol) was added dropwise to a solution of 8.76 g (40 mmol) of *N*-(2-hydroxy-1,1-dimethylethyl)phthalimide in 75 mL of chloroform, and the mixture was refluxed for 4 h. The excess of solvent and thionyl chloride were removed under vacuum. The residue was dissolved in 200 mL of ether, washed with water, and dried (Na_2SO_4), and the solvent was removed in vacuo, leaving 9.0 g (95% yield) of **12** as a white crystalline solid which was purified by recrystallization from ether: mp 58–60 °C; ^{1}H NMR ($CDCl_3$) δ 1.8 (s, 6 H, $2CH_3$), 4.08 (s, 2 H, CH_2), 7.6–7.9 (m, 4 H, aryl); MS, *m/z* (relative intensity) 239 (M + 2, 6), 237 (M^+, 19), 202 (62), 188 (100), 173 (18), 146 (42), 145 (29), 76 (72). Anal. Calcd for $C_{12}H_{12}ClNO_2$: C, 60.6; H, 5.1; N, 5.9. Found: C, 60.5; H, 5.2; N, 6.0.

1-Chloro-2-methyl-2-propylamine Hydrochloride (13). A mixture of 9.0 g (38 mmol) of *N*-(2-chloro-1,1-dimethylethyl)phthalimide (**12**) and 2.5 g (50 mmol) of hydrazine hydrate in 100 mL of 95% ethanol was heated under reflux for 45 min. The solution was cooled and the precipitated phthalazinedione collected. The solution was diluted with 100 mL of ether, filtered, and saturated with dry hydrogen chloride. The solvents were removed under vacuum, and the residual solid was purified by recrystallization from $CHCl_3$ to give **13** (4.5 g, 80% yield) as an off-white hygrosopic solid: ^{1}H NMR (Me_2SO-d_6) δ 1.36 (s, 6 H, $2CH_3$), 4.21 (s, 2 H, CH_2Cl), 8.1 (brs, 3 H, NH_3^+); MS, *m/z* (relative intensity) 105 (M − HCl, 3.5), 70 (M − Cl, 100), 69 (58), 54(72).

3-[(2-Chloroethyl)thio]-2-methyl-2-aminopropane Hydrochloride (14). A mixture of 3.9 g (60 mmol) of 85% KOH and 2.35 g (30 mmol) of 2-mercaptoethanol in 5 mL of water and 2 mL of ethanol was heated under reflux for 30 min. A solution of 4.3 g (30 mmol) of 1-chloro-2-methyl-2-propylamine hydrochloride[23] (**13**) in 10 mL of ethanol was added slowly to the refluxing solution, and the mixture was stirred for another 30 min, cooled, and filtered. The filtrate was cooled to 0 °C, neutralized with concentrated HCl, and filtered. The solvents were removed under vacuum, the brown residue was taken up in 100 mL of chloroform, 4.8 g (40 mmol) of thionyl chloride was added slowly, and the mixture was heated under reflux for 6 h. The solvents and excess of thionyl chloride were removed under vacuum, the residue was taken up in methanol and decolorized with charcoal, and the product was further purified by column chromatography (silica, 5% MeOH in $CHCl_3$), affording **14** (2.8 g, 46% yield) as an off-white solid: mp 115–118 °C; ^{1}H NMR ($CDCl_3$) δ 1.54 (s, 6 H, $2CH_3$), 2.92–3.13 (m, 4 H, CH_2SCH_2–), 3.73 (t, J = 8 Hz, 2 H, CH_2Cl), 8.57 (brs, 3 H, NH_3^+. Anal. Calcd for $C_6H_{15}Cl_2NS$: C, 35.8; H, 7.3; N, 6.8. Found: C, 36.1; H, 7.2; N, 6.4.

2-[(2-Chloroethyl)thio]-2-methylpropylamine Hydrochloride (15). A solution of 1.95 g (25 mmol) of 2-mercaptoethanol and 3.25 g (50 mmol) of KOH in 5 mL of water was heated under reflux for 30 min until it turned yellow, and a solution of 3.6 g (25 mmol) of 2-chloro-2-methylpropylamine hydrochloride in 10 mL of ethanol was added slowly. The mixture was cooled to room temperature, stirred for 1 h, and filtered, and

(23) Similar flash pyrolysis of an *N*-phthalimide derivative has been reported by: Davis A. P.; Whitham, G. H. *J. Chem. Soc., Chem. Commun.* **1981**, *741*. Mild thermolysis is reported by: Kirby, G. W.; Lochead, A. W. *J. Chem. Soc., Chem. Commun.* **1983**, 1325.

(24) The 1,2-oxathietanes belong to the family of cyclic sulfenates or sultenes, examples of which have been discussed by: Astrologes, G. W.; Martin, J. C. *J. Am. Chem. Soc.* **1977**, *99*, 4390. Block, E.; Wall, A.; Zubieta, J. *J. Am. Chem. Soc.* **1985**, *107*, 1783 and references therein. CNDO/B calculations on 1,2-oxathietane and other sultenes were reported, ref 3.

(25) (a) Baldwin, J. E.; Lopez, R. C. G. *J. Chem. Soc., Chem. Commun.* **1982**, 1029. (b) Baldwin, J. E.; Lopez, R. C. G. *Tetrahedron* **1983**, *39*, 1487. (c) Vedejs, E.; Eberlein, T. H.; Varie, D. L. *J. Am. Chem. Soc.* **1982**, *104*, 1445.

(26) Gudkova, A. S.; Ostapchuk, G. M.; Petrosyan, I. V.; Reutov, O. A. *Dokl. Akad. Nauk SSSR* **1970**, *194*, 660.

the filtrate was neutralized with concentrated HCl. The filtered solution was evaporated to dryness in vacuo, the residue was dissolved in 50 mL of chloroform, and thionyl chloride (3 g, 25 mmol) was added. Workup by the procedure described above afforded **15** as a white crystalline hygroscopic solid: 2.5 g (50% yield); mp 93–96 °C; ^{1}H NMR ($CDCl_3$) δ 1.19 (s, 6 H, $2CH_3$), 2.7 (t, J = 7.5 Hz, 2 H, $-SCH_2$), 3.42 (s, 2 H), 3.7 (t, J = 7.5 Hz, 2 H, $-CH_2Cl$), 7.8 (br, 3 H); MS, m/z (relative intensity) 167 (M − HCl, 2.5), 132 (60), 118 (100), 103 (48), 102 (69).

3-[(2-Hydroxyethyl)thio]-2,3-dimethyl-2-aminobutane (43). A mixture of 0.99 g (10 mmol) of tetramethylaziridine **6** and 0.78 g (10 mmol) of 2-mercaptoethanol was stirred mechanically at 60–70 °C under reflux for 10 h. Fractionation of the colorless heavy oil yielded the amine **43**: 0.8 g (45% yield); bp 120–124 °C/0.1 mm; ^{1}H NMR ($CDCl_3$) δ 1.25 [s, 6 H, $(CH_3)_2CS$], 1.4 [s, 6 H, $(CH_3)_2C-N$], 1.38 (brs, 3 H, H_2N + OH), 2.76–3.0 (m, 2 H), 3.7–4.0 (m, 2 H, $-CH_2O-$); MS, m/z 177 (M^+).

3-[(2-Chloroethyl)sulfinyl]-2,3-dimethyl-2-aminobutane Hydrochloride (44). A solution of 2.31 g (20 mmol) of the corresponding thioether compound in 15 mL of methanol containing 1 mL of 30% H_2O_2 was stirred at room temperature for 6 h. The solution was evaporated to dryness, the residue was taken up in $CHCl_3$, and the solution was dried ($MgSO_4$) and concentrated to yield **44** as an amorphous white powder: 2.4 g (95% yield); mp 120–125 °C; ^{1}H NMR ($CDCl_3$) δ 1.16 (s, 3 H, CH_3-C-SO), 1.68 [s, 6 H, $(CH_3)_2C-N$], 1.86 (s, 3 H, CH_3-C-SO), 2.8–3.04 (m, 1 H, CHSO), 3.1–3.26 (m, 1 H, CHSO), 3.92–4.04 (m, CH_2Cl), 8.54 (brs, 3 H); CIMS (NH_3, m/z 248 (M^+).

General Procedure for the Preparation of Thioether-Substituted 2-Chloroethyl Ureas. A solution (or suspension where appropriate) of 10 mmol of the appropriate substituted 2-[(2-chloroethyl)thio]ethylamine hydrochloride in 50 mL of $CHCl_3$ was treated with 10 mmol of triethylamine followed by the dropwise addition of *tert*-butyl isocyanate with cooling if necessary.[16] The reaction mixture was stirred for 4 h, washed with water, and dried (Na_2SO_4), and the solvent was removed. Analytical samples were prepared by recrystallization from (1:1) $CHCl_3$/petroleum ether. The following ureas were prepared in this manner.

1-[2-[(2-Chloroethyl)thio]-1,1,2,2-tetramethylethyl]-3-*tert*-butylurea (8): white solid (83% yield); mp 123–125 °C; ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 9 H, *t*-Bu), 1.42 [s, 6 H, $SC(CH_3)_2$], 1.54 [s, 6 H, $(CH_3)_2C-N$], 2.92 (t, J = 8 Hz, SCH_2), 3.65 (t, J = 8 Hz, CH_2Cl), 4.7 (s, 1 H, NH), 5.3 (s, 1 H, NH); CIMS (NH_3), m/z 295 (MH^+).

1-[2-[(2-Chloroethyl)thio]ethyl]-3-*tert*-butylurea: white crystalline powder (90% yield); mp 57–58 °C; ^{1}H NMR ($CDCl_3$) δ 1.36 (s, 9 H, *t*-Bu), 2.7 (*t*, ^1J = 6 Hz, 2 H, SCH_2), 2.9 (t, ^2J = 8 Hz, 2 H, SCH_2), 3.34 (dt, ^1J = 6, ^3J = 6 Hz, $NHCH_2$), 3.65 (t, ^2J = 8 Hz, 2 H, CH_2Cl), 4.96 (s, 1 H, NH), 5.36 (t, ^3J = 6 Hz, 1 H, NH); CIMS (NH_3), m/z 238 (MH^+). Anal. Calcd for $C_9H_{19}ClN_2OS$: C, 45.3; H, 8.0; N, 11.7. Found: C, 45.6; H, 8.2; N, 11.9.

1-[2-[(2-Chloroethyl)thio]-1,1-dimethylethyl]-3-*tert*-butylurea (16): white solid (68% yield); mp 72–74 °C; ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 9 H, *t*-Bu), 1.35 [s, 6 H, $C(CH_3)_2$], 2.9 (t, J = 8 Hz, 2 H, SCH_2), 3.08 (s, 2 H, CH_2S), 3.66 (t, J = 8 Hz, 2 H, CH_2Cl), 4.42 (brs, 2 H, NH); CIMS (NH_3), m/z 267 (MH^+).

1-[2-[(2-Chloroethyl)thio]-2,2-dimethylethyl]-3-*tert*-butylurea (17): yellow semisolid (50% yield); ^{1}H NMR ($CDCl_3$) δ 1.25 (s, 9 H, *t*-Bu), 1.3 (s, 6 H, $2CH_3$), 2.84 (t, J = 8 Hz, 2 H, SCH_2), 3.48 (brs, 2 H, CH_2), 3.6 (t, J = 8 Hz, 2 H, CH_2), 4.78 (s, 1 H, NH), 4.86 (t, J = 6 Hz, 1 H, NH); MS, m/z (relative intensity) 266 (M^+, 23), 231 (M − Cl, 70), 217 (58), 100 (82), 99 (100), 57 (48).

General Procedure for Preparation of Sulfinyl Ureas. (a) Using *m*-Chloroperbenzoic Acid. A solution of 3 mmol of the urea in 20 mL of $CHCl_3$ was cooled to 0 °C, and 3.2 mmol of *m*-chloroperbenzoic acid was gradually introduced with continuous stirring. Stirring was continued for 4 h and the solution kept at 0 °C for 10 h. The $CHCl_3$ solution was washed with 10% aqueous $NaHCO_3$ (3 × 10 mL) and dried (Na_2SO_4). Removal of the solvent in vacuo afforded the sulfinyl urea, which was purified by recrystallization.

The following compounds were prepared by this method.

1-[2-[(2-Chloroethyl)sulfinyl]-1,1,2,2-tetramethylethyl]-3-*tert*-butylurea (9): white solid (95% yield); mp 120–122 °C; ^{1}H NMR ($CDCl_3$) δ 1.14 (s, 3 H, CH_3C-S), 1.3 (s, 9 H, *t*-Bu), 1.4 (s, 3 H, CH_3C-S), 1.58 (s, 3 H, $N-C-CH_3$), 1.62 (s, 3 H, $N-C-CH_3$), 2.84–3.06 (m, 2H, SCH_2, 3.86–3.98 (m, 2 H, CH_2Cl), 4.32 (brs, 1 H, NH), 5.84 (s, 1 H, NH); CIMS (NH_3), m/z 311 (MH^+); IR ($CHCl_3$) ν_{max} 3355, 2965, 1650, 1680, 1030 cm^{-1}. Anal. Calcd for $C_{13}H_{27}N_2O_2SCl$: C, 50.3; H, 8.7; N, 9.2. Found: C, 50.6; H, 8.4; N, 8.8.

1-[2-[(2-Chloroethyl)sulfinyl]-1,1-dimethylethyl]-3-*tert*-butylurea: white powder (69% yield); mp 166–168 °C; ^{1}H NMR ($CDCl_3$) δ 1.28 (s, 9 H, *t*-Bu), 1.5 [s, 6 H, $(CH_3)_2$], 2.8 (d, J = 13 Hz, 1 H, CHS), 3.26 (m, 2 H, SCH_2), 3.86 (d, J = 13 Hz, 1 H, CH-S), 3.92 (m, 2 H, CH_2Cl), 4.0–6.0 (brs, 2 H, NH); IR (film) ν_{max} 3420, 1730, 1520, 1065 cm^{-1}; CIMS (NH_3), m/z 283 (MH^+). Anal. Calcd for $C_{11}H_{23}ClN_2O_2S$: C, 46.7; H, 8.1; N, 9.9. Found: C, 46.9; H, 8.2; N, 9.9.

(b) Using Singlet Oxygen for Specific ^{18}O Labeling. A solution of 2 mmol of the urea and 10 mg of rose bengal in 50–75 mL of methanol was placed in a cylindrical Pyrex reactor with a water cooling jacket and a sintered glass dispersion tube. The $^{18}O_2$ gas bulb outlet tube was connected to the reactor inlet via a short high-vacuum tube. The inlet tube of the $^{18}O_2$ gas bulb was connected to a 100-mL syringe filled with deoxygenated CCl_4. The solution in the reactor was thoroughly deoxygenated by repeated cycles of high-vacuum evacuation followed by saturation with high-purity N_2 gas. The reactor was then connected to the $^{18}O_2$ bulb and evacuated thoroughly, and the reactor outlet was closed. The seal of the $^{18}O_2$ outlet tube was broken, and the contents allowed to equilibrate with the reactor atmosphere. The remaining $^{18}O_2$ in the gas bulb was displaced into the reactor by forcing in CCl_4 with the syringe. The reaction mixture was irradiated with two 200-W light bulbs for 4 h. The solution was evaporated to dryness, and the residual solid was subjected to chromatography on silica gel with $CHCl_3$ as eluent. The products were pure sulfoxides with yields of 85–90%. Mass spectral analysis of the ureas confirmed that the ^{18}O isotope incorporation was >95%. No detectable oxygen exchange takes place during the subsequent N-nitrosation of the urea sulfoxide. The following compound was prepared by this procedure, together with **22a-*S*-^{18}O** and **22d-*S*-^{18}O**.

1-[2-[(2-Chloroethyl)sulfinyl-^{18}O]-2,2-dideuterioethyl]-3-*tert*-butyl-1-nitrosourea[5] (1b-2,2-d_2-*S*-^{18}O). White powder (90% yield); mp 110–112 °C; ^{1}H NMR ($CDCl_3$) δ 1.36 (s, 9 H, *t*-Bu), 2.91–3.2 (m, 2 H, SCH_2), 3.72 (m, 2 H, CH_2Cl), 3.98 (d, J = 6 Hz, 2 H, NCH_2), 4.98 (brs, 1 H, NH), 5.7 (t, J = 6 Hz, 1 H, $NHCH_2$). Anal. Calcd for $C_9H_{17}D_2ClN_2{}^{16}O^{18}OS$: C, 41.8; H(D), 8.1; N, 10.8. Found: C, 42.1; H(D), 8.4; N, 10.5.

General Procedure for Nitrosation of Sulfinyl Ureas. A solution of 2–3 mmol of sulfinyl urea in 5 mL of 97% formic acid was cooled to 0 °C, and 8–10 mmol of solid sodium nitrite was added slowly in portions.[17] The temperature was maintained at <5 °C for 4 h. The solution was diluted with 10 mL of water and extracted with $CHCl_3$ (3 × 10 mL). The combined extracts were washed with aqueous sodium bicarbonate and dried ($MgSO_4$), and the solvent was removed in vacuo. The nitrosoureas were purified by chromatography on silica gel or Florisil using $CHCl_3$ as eluent. The yields are in the vicinity of 70–85%, and the nitrosoureas are stored under anhydrous conditions at 0 °C.

The following nitrosoureas were prepared in this way.

1-[2-[(2-Chloroethyl)sulfinyl]ethyl]-3-*tert*-butyl-1-nitrosourea (1b): pale yellow solid (65% yield); mp 48–50 °C; ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 9 H, *t*-Bu), 2.52 (t, ^1J = 8 Hz, 2 H, SCH_2), 2.82 (t, J = 8 Hz, 2 H, CH_2S), 3.56 (t, ^2J = 8 Hz, 2 H, NCH_2), 3.94 (t, ^2J = 8 Hz, 2 H, CH_2Cl), 6.8 (brs, ^{1}H, NH); CIMS (NH_3), m/z 284 (MH^+).

1-[2-[(2-Chloroethyl)thio]-1,1,2,2-tetramethylethyl]-3-*tert*-butyl-1-nitrosourea (10): thick oil (68% yield); ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 9 H, *t*-Bu), 1.52 [s, 6 H, $(CH_3)C-S$], 1.62 [s, 6 H, $(CH_3)_2$, C-N], 2.78 (t, J = 8 Hz, 2 H, SCH_2), 3.78 (t, J = 8 Hz, 2 H, CH_2Cl), 6.8 (brs, 1 H, NH); IR (film) ν_{max} 3430, 2930, 2845, 1720, 1520 cm^{-1}; ClMS (NH_3), m/z 324 (MH^+).

1-[2-[(2-Chloroethyl)sulfinyl]-1,1,2,2-tetramethylethyl]-3-*tert*-butyl-1-nitrosourea (11): pale yellow oil (75% yield); ^{1}H NMR ($CDCl_3$) δ 1.12 (s, 3 H, CH_3-C-S), 1.28 (s, 9 H, *t*-Bu), 1.42 (s, 3 H, CH_3-C-S), 1.58 (s, 3 H, $N-C-CH_3$), 1.62 (s, 3 H, $N-C-CH_3$, 2.84–3.08 (m, 2 H, SCH_2), 3.86–4.0 (m, 2 H, CH_2Cl), 4.22 (brs, 1 H, NH); lR ($CHCl_3$) ν_{max} 3355, 2960, 1640, 1575, 1040 cm^{-1}; CIMS (NH_3), m/z 340 (MH^+).

1-[2-[(2-Chloroethyl)thio]-1,1-dimethylethyl]-3-*tert*-butyl-1-nitrosourea (18): yellow oil (65% yield); ^{1}H NMR ($CDCl_3$) δ 1.48 (s, 9 H, *t*-Bu), 1.58 [s, 6 H, $N-C(CH_3)_2$], 2.9 (s, J = 6 Hz, 2 H, SCH_2), 3.04 (s, 2 H, CH_2S), 3.64 (t, J = 6 Hz, 2 H, CH_2Cl), 4.5–6.0 (b, 1 H, NH); IR ($CHCl_3$) ν_{max} 3420, 1730, 1520, 1065 cm^{-1}; ClMS (NH_3), m/z 296 (MH^+).

1-[2-[(2-Chloroethyl)thio]-2,2-dimethylethyl]-3-*tert*-butyl-1-nitrosourea (20): yellow oil (65% yield); ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 9 H, *t*-Bu), 1.52 [s, 6 H, $(CH_3)_2$], 2.98 (t, J = 8 Hz, 2 H, SCH_2), 3.72 (t, J = 8 Hz, 2 H, CH_2Cl), 4.12 (s, 2 H, NCH_2), 6.78 (brs, 1 H, NH); IR (film) ν_{max} 3415, 2925, 2845, 1725, 1520 cm^{-1}; CIMS (NH_3), m/z 296 (MH^+).

1-[2-[(2-Chloroethyl)sulfinyl]-2,2-dimethylethyl]-3-*tert*-butyl-1-nitrosourea (21): yellow crystalline solid (90% yield); mp 72–74 °C; ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 9 H, *t*-Bu), 1.64 (s, 3 H, CH_3), 1.7 (s, 3 H, CH_3), 3.16 (m, 2 H, SCH_2), 3.96 (m, 2 H, CH_2Cl), 4.18 (s, 2 H, NCH_2), 7.2 (brs, 1 H, NH); IR ($CHCl_3$) ν_{max} 3420, 1735, 1520, 1035 cm^{-1}; CIMS (NH_3), m/z 312 (MH^+).

1-[2-[(2-Chloroethyl)sulfinyl-^{18}O]-2,2-dideuterioethyl]-3-cyclohexyl-1-nitrosourea (22b-*2,2-d*$_2$-*S*-^{18}O): pale yellow crystalline solid (85% yield); mp 48–50 °C; ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 9 H, *t*-Bu), 2.85 (t, J = 7 Hz, 2 H, SCH_2), 3.9 (t, J = 7 Hz, 2 H, CH_2Cl), 4.2 (s, 2 H,

NCH_2), 6.86 (s, 1 H, NH); IR (film) ν_{max} 3420, 1728, 1446, 1065 cm^{-1}.

General Procedure for Analysis of Aqueous Decomposition Products of Sulfinyl Nitrosoureas in Buffer. Solutions of the sulfinyl nitrosoureas (~25 mg, 0.1 mmol/mL) in 0.5–1.0 mL of 40 mM potassium phosphate buffer (pH 7.2) in 3-mL air-tight Reactivials equipped with Teflon septums were thermostated at 37 °C. Samples of the gaseous fractions were withdrawn at intervals with a 2-mL hypodermic syringe and were injected into the Hewlett-Packard gas chromatograph fitted with a 6-ft 10% Carbowax 20M 80–100 WAW-DMCS 5830 column maintained at an oven temperature of 45 °C and a flow rate of 22 mL/min. The column was heated at 70 °C to detect aldehydes and vinyl chloride and was heated further at a rate of 5 deg/min up to 120 °C to detect the thioethers and the corresponding 2-hydroxyethyl compounds. The aqueous layer was extracted with 200–500 mL of Spectrograde CH_2Cl_2, dried ($MgSO_4$), and concentrated. A volume of 0.1 μL was used in a typical GC analysis with a temperature program of 60–150 °C range and a gas flow rate of 22 mL/min. The remaining aqueous mother liquor was evaporated to dryness, and the residue was analyzed by CIMS using NH_3 as reagent gas. Components of volatile gases and the CH_2Cl_2 extracts were identified by GC/MS using similar experimental conditions.

3,3,4,4-Tetramethyl-1,2-oxathietane (26e). A solution of 2-[(2-chloroethyl)sulfinyl]-1,1,2,2-tetramethylethylamine hydrochloride (2 mmol) in 5 mL of 2 N hydrochloric acid was cooled to −10 °C, and 2 mmol of solid sodium nitrite was added slowly in portions. The temperature was maintained at <−10 °C for 2 h, and then the solution was extracted with precooled ether (3 × 10 mL). The combined extracts were washed with aqueous sodium bicarbonate, dried ($MgSO_4$), and cooled to −25 °C. The ether was removed in vacuo at <−20 °C and the residue vacuum distilled at 0.5 mmHg to afford pure 3,3,4,4-tetramethyl-1,2-oxathietane (**26**) as a pale yellow oil (ca. 85% yield): ^1H NMR ($CDCl_3$) δ 0.98 [s, 6 H, S—C(CH_3)$_2$], 1.18 [s, 6 H, O-C(CH_3)$_2$]; IR (film) ν_{max} 2950, 2915, 2850, 1720, 1095, 1070, 910, 810 cm^{-1}; MS, *m/z* (relative intensity) 132.0588 (M^+, 10, calcd for $C_6H_{12}OS$, 132.0609), 117 (4, $M^+ - CH_3$), 116 (17, $M^+ - O$), 84 (100, $M^+ - SO$), 74 [8, $(CH_3)_2C{=}S$]; UV (CCl_4) λ_{max} 258, 265, 320 nm (slow appearance of a band at 430 nm attributed to $(CH_3)_2C{=}S$). The retention time in gas chromatography using a Hewlett-Packard 5840A gas chromatograph with a 10% Carbowax column and a helium flow rate of 22 mL/min at 60 °C was 5.3 min.

Trapping of Thiocarbonyl Fragment from 1,2-Oxathietane Cycloreversion by Cycloaddition Reactions. A solution of 3,3,4,4-tetramethyl-1,2-oxathietane (ca. 1 mmol) in 10 mL of dry CH_2Cl_2 at ≥−10 °C was treated with a precooled solution of addend (1 mmol) in 5 mL of CH_2Cl_2 at −10 °C. The solution was stirred for 1 h and allowed to warm to 0 °C. The temperature was slowly raised to 50–60 °C and the solution stirred for a further 30 min. The residue obtained after evaporation of the solvent was chromatographed on silica gel using $CHCl_3$ as eluent. The following products were obtained in this way.

(a) Trapping with Alkenic Addends. 2,2,3,3-Tetracyano-4,4-dimethylthietane (47): yellow oil (90% yield); ^1H NMR ($CDCl_3$) δ 1.8 (s, 6 H, CH_3); IR ($CHCl_3$) ν_{max} 2242, 2236 cm^{-1}; MS, *m/z* (relative intensity) 202 (M^+, 3.5), 1.76 (M − CN, 5.2), 128 (1.8), 100 (54), 84 (81), 59 (63), 58 (100), 42 (76).

***trans*-2,3-Dicyano-4,4-dimethylthietane (48)**: yellow solid (15% yield); mp 143–145 °C dec; ^1H NMR ($CDCl_3$) δ 1.78 [s, 6 H, $(CH_3)_2$], 2.8 (m, 2 H); IR ($CHCl_3$) ν_{max} 2248, 2242 cm^{-1}; CIMS (NH_3), *m/z* 153 (MH^+, 5.2), 126 (MH^+ − HCN, 29), 111 (9), 74 (6), 59 (100), 58 (46).

***trans*-2,3-Dicarbethoxy-4,4-dimethylthietane (49)**: pale brown semisolid (15% yield); ^1H NMR ($CDCl_3$) δ 1.2–1.5 (m, 6 H, CH_3CH_2), 1.78 [s, 6 H, $(CH_3)_2$], 2.16 (d, *J* = 6 Hz, 1 H, $CHCOOC_2H_5$), 2.3 (d, *J* = 6 Hz, 1 H, $CHCOOC_2H_5$), 4.05–4.5 (m, 4 H, CH_3CH_2); MS, *m/z* (relative intensity) 246 (M^+, 46), 218 (58), 174 (100), 156 (42), 112 (19), 74 (18), 56 (58).

(b) Trapping with Diene Addends. Thioacetone Adduct with Anthracene. 50: yellow solid (20% yield); mp 198–201 °C, ^1H NMR (Me_2SO-d_6) δ 1.72 [s, 6 H, $(CH_3)_2$], 2.2 (s, 1 H, CHS), 2.41 (s, 1 H, CH), 7.18–7.28 (m, 4 H, aryl), 7.82–8.1 (m, 4 H, aryl); MS, *m/z* (relative intensity) 221 (0.6, M − CH_3), 194 (2.67), 193 (3.7), 178 (9.3), 167 (100), 165 (15.5), 89 (2.5); CIMS (NH_3), *m/z* 237 (MH^+).

Thioacetone Adduct with 9,10-Dimethylanthracene. 51: yellow solid (90% yield); mp 188–190 °C; ^1H NMR (Me_2SO-d_6) δ 1.76 [s, 6 H, $(CH_3)_2$], 1.98 [s, 3 H, S–C(CH_3)], 2.18 [s, 3 H, C(CH_3)], 7.16–7.28 (m, 4 H, aryl), 7.82–8.05 (m, 4 H, aryl); ^{13}C NMR (Me_2SO-d_6) δ 16.87 [S–C–(CH_3)$_2$], 22.96 (C–CH_3), 25.31 (C–CH_3), 38.55 (C–CH_3), 58.12 [–C(CH_3)$_2$], 66.29 (–S–C–CH_3), 123.96–131.47 (aryl); MS, *m/z* (relative intensity) 265 (1.9, M − CH_3), 238 (1.4), 223 (29), 207 (45), 204.0931 (69.8, calcd for $C_{13}H_{16}S$, M − C_6H_4, 204.0973), 189.0702 (30.4, calcd for $C_{12}H_{13}S$, 189.0738), 178 (11), 177.0688 (5.6, calcd for $C_{11}H_{13}S$, 177.0731), 101.0391 (100, calcd for C_5H_9S, 101.0425), 100 (49), 41 (1.8), 58 (100); CIMS (NH_3), *m/z* 281(MH^+).

Thioacetone Adduct with 9,10-Dibromoanthracene. 52: brown solid (35% yield); mp 198–204 °C; ^1H NMR ($CDCl_3$) δ 1.95 [s, 6 H, $(CH_3)_2$], 7.2–8.0 (m, 8 H, aryl); MS, *m/z* (relative intensity) 331, 329 (M − Br, 29, 30), 253, 255 (100, 98), 238, 240 (15, 13), 159 (68), 115(42).

Generation of Thioformaldehyde from Flash Vacuum Pyrolysis of *N*-[(2-Hydroxyethyl)thio]phthalimide (53). Flash pyrolysis of **53** was carried out at 120 °C under vacuum with trapping of the volatile products in a cold trap, containing the alkene or diene addend, at liquid N_2 temperatures. When the mixture was allowed to warm to room temperature 1:1 adducts were isolated identical with those obtained from the 1,2-oxathietane.

Reduction of 3,3,4,4-Tetramethyl-1,2-oxathietane with Lithium Aluminum Hydride. A 15-mL volume of a solution of the 1,2-oxathietane in ether (ca. 1 mM) was cooled to 0 °C and treated with lithium aluminum hydride (0.25 g, 6.5 mmol) in portions with continuous stirring. The pale yellow solution immediately turned colorless. The solution was heated under gentle reflux for 1 h, then cooled to 0 °C, and treated cautiously with 10% aqueous ammonium chloride solution. The precipitates were collected in a small Soxhlet thimble and continuously extracted with ether. The combined extracts were analyzed by GC/MS using a 6-ft 10% Carbowax column, and the following products were identified. (i) 2,3-Dimethyl-2-mercapto-3-butanol (8% yield): retention time 16.5 min, MS, *m/z* (relative intensity) 116.0625 (6.5, calcd for $C_6H_{12}S$, M − H_2O, 116.0660), 101.0412 (41, calcd for C_5H_9S, M − H_2O − CH_3, 101.0425), 45 (100). (ii) 2-Propanethiol (24% yield): retention time 4.3 min; MS, *m/z* (relative intensity) 76.0318 (M^+, 12.5, calcd for C_3H_8S, 76.0347), 75.0261 (M^+ − H, 0.4, calcd for C_3H_7S, 75.0267), 74.0168 (0.2, M^+ − 2H, calcd for C_3H_6S, 74.0190). (iii) Isopropyl alcohol (68% yield): retention time 5.9 min; MS, *m/z* (relative intensity) 60.0632 (M^+, 4.5, calcd for C_3H_8O, 60.0549), 59.0522 (M^+ − H, 1.5, calcd for C_3H_7O, 59.0547), 58.0444 (M^+ − 2H, 1.5, calcd for C_3H_6O, 58.0469), 45 (M − CH_3, 100).

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