Novel Substituted 1,2-Oxathietanes from Competing Cyclizations of 2-Chloroethyl Sulfoxide Precursors. Observation of Vinylogous 1,4-Halogen Participation in 1,2-Oxathietane Generation

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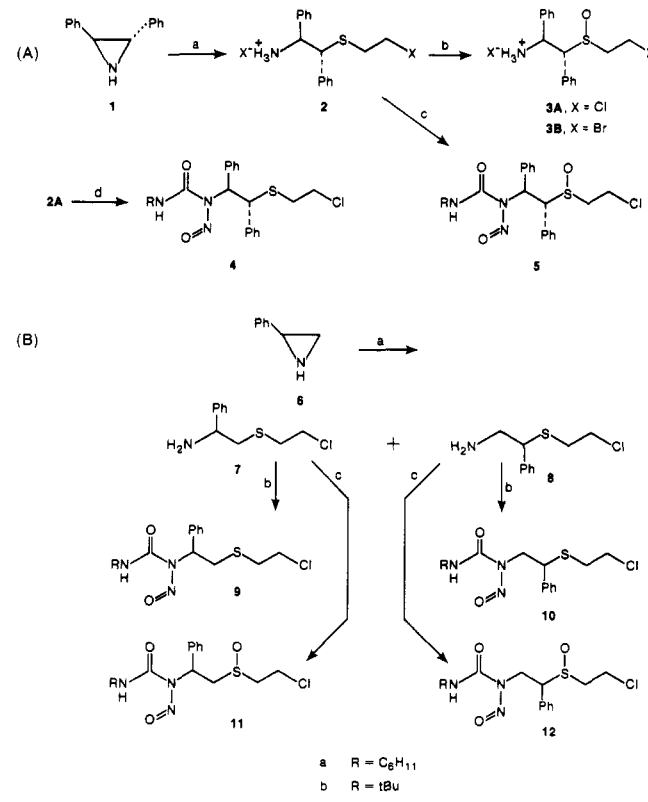
Spontaneous ambient temperature decomposition of 1-[2-[(2-chloroethyl)sulfinyl]-*threo*-1,2-diphenylethyl]-3-*tert*-butyl-1-nitrosourea in aqueous buffer (pH 7.0) affords fragmentation products corresponding to the formation of 1,2-oxathietane and *trans*-3,4-diphenyl-1,2-oxathietane. The former is formed in a reaction involving 1,4-chlorine participation with migration of chlorine over three bonds, substitution, and concomitant formation of (*E*)-1-chlorostilbene. That the halogen is involved in a tightly bound intramolecular reaction is corroborated by the lack of exchange of chlorine in the presence of excess bromide ion. Aqueous diazotizations of 2-[(2-bromoethyl)thio]-1,2-*threo*-diphenylethylamine hydrobromide and 2-[(2-bromoethyl)sulfinyl]-1-phenylethylamine hydrobromide afford among their products of controlled decomposition, (*Z*)-1-bromostilbene and (*E*)- and (*Z*)-2-bromostyrenes, respectively. These examples confirm the tightly controlled nature of the 1,4-halogen-transfer process. Aqueous decomposition of sulfinylamine precursors, which are not subject to steric hindrance at the carbon α to the sulfinyl group, e.g, following diazotization of 2-[(2-chloroethyl)sulfinyl]-1-phenylethylamine hydrochloride, affords fragmentation products corresponding to the participation of three separate pathways. These involve the formation of 4-phenyl-1,2-oxathietane, 1,2-oxathietane, and 4-phenyl-1,2,3-oxadiazoline, respectively. These reactions provide further examples of 1,4-halogen participation with migration resulting in conformationally controlled formation of (*E*)- and (*Z*)-2-chlorostyrenes from the chloro precursor and (*E*)- and (*Z*)-2-bromostyrenes from the corresponding bromo compound.

1,2-Oxathietanes[1,2] are novel heterocycles which are of practical and theoretical interest owing to their analogy with the more extensively studied 1,2-dioxetanes.[3] Because they were originally established as intermediates in the decomposition of anticancer sulfinyl(2-chloroethyl)-nitrosoureas[1,2,4] under physiological conditions there is the added interest of a possible biological role for this reactive heterocycle.

We recently described the generation of simple 1,2-oxathietanes both from sulfinylnitrosourea precursors and, more conveniently, from diazotization of appropriate sulfinyl amines[1,2] by processes similar to those shown in Schemes II and III, respectively. 3,3,4,4-Tetramethyl-1,2-oxathietane was isolated and characterized, and its chemistry was explored. In those reports we described the characteristic formal [σ2s + σ2a] cycloreversion[5] of 1,2-oxathietanes to reactive thiocarbonyls and ketones or aldehydes together with, in appropriate cases, their conversion to ring-opened thioether aldehydes by intramolecular oxygen transfer.[1,2]

(2-Chloroethyl)nitrosoureas have been shown to express their anticancer effects by reacting directly with cellular DNA causing, inter alia, interstrand cross-links and alkylation of bases.[4] Our recent results indicate that the reactive thiocarbonyl fragments from the cycloreversion of 1,2-oxathietanes bind covalently to DNA bases. The possibility that this may account for the anticancer action of sulfinyl(2-chloroethyl)nitrosoureas[1,2,4] is under investigation. Further exploration of the chemical characteristics of these novel heterocycles appeared warranted.

Scheme I[a]



[a] Reaction conditions: (A) a KOH, $HSCH_2CH_2OH$ then $SOCl_2$ or $SOBr_2$, $CHCl_3$; b *m*-CPB; c RNCO, CH_2Cl_2, then *m*-CPB, then $NaNO_2$ HCOOH; d RNCO, CH_2Cl_2 then $NaNO_2$, HCOOH; (B) a KOH, $HSCH_2CH_2OH$ then $SOCl_2$, $CHCl_3$; b RNCO, CH_2Cl_2, then $NaNO_2$, HCOOH; c RNCO, CH_2Cl_2 then *m*-CPB, then $NaNO_2$, HCOOH.

Therefore, we now report the formation of novel substituted 1,2-oxathietanes by competing cyclization reactions of bifunctional sulfoxide precursors. These reactions involve novel intramolecular transfer to both oxygen and halogen.

(1) Lown, J. W.; Koganty, R. R. *J. Am. Chem. Soc.* **1983**, *105*, 126.
(2) Lown, J. W.; Koganty, R. R. *J. Am. Chem. Soc.* **1986**, in press.
(3) (a) Kopecky, K. R.; Filby, J. E.; Mumford, C.; Lockwood, P. A.; Ding, J. Y. *Can. J. Chem.* **1975**, *53*, 1103. (b) Richardson, W. H.; Montgomery, F. C.; Yelvington, M. B.; O'Neal, H. E. *J. Am. Chem. Soc.* **1974**, *96*, 7525. (c) White, E. H.; Wildes, P. D.; Weicko, J.; Doshan, H.; Wei, C. C. *J. Am. Cehm. Soc.* **1973**, *95*, 7050. (e) Adam, W. in *Chemical and Biological Generation of Excited States*; Adam, W., Cilento, G., Eds.; Academic: New York, 1982; Chapter 4 and references therein.
(4) Lown, J. W.; Joshua, A. V.; McLaughlin, L. W. *J. Med. Chem.* **1980**, *23*, 798.
(5) Woodward, R. B.; Hoffman, R. *The Conservation of Orbital Symmetry*; Verlag Chemie: Weinheim, 1970; p 72.

0022-3263/86/1951-2116$01.50/0

Table I. Products from Controlled Decomposition of Sulfinylnitrosoureas in Potassium Phosphate Buffer (pH 7.2) at 37 °C and from Diazotization of Sulfinylamines at 0 °C[a]

source	products	GC t_2, min	theor yield, %	m/z (rel intensities, fragments)
1-[2-[(2-chloroethyl)sulfonyl]-*threo*-1,2-diphenylethyl]-3-*tert*-butyl-1-nitrosourea	vinyl chloride	1.8	5–10	64 (M + 2, 1.2), 62 (M^+, 39), 27 (M – Cl, 100)
	thioformaldehyde hydrate	3.2	2–6	66 (M^+, 100), 50 (52), 44 (21)
	thiobenzaldehyde	17.5	trace	122 (M^+, 15), 77 (M – CHS, 100), 45 (46)
	benzaldehyde	21.1	10–12	106 (M^+, 100), 105 (M – H, 97), 77 (89), 51 (40)
	(*E*)-stilbene	37.0	≃5	180 (M^+, 79), 179 (68), 165 (48), 89 (100), 77 (62), 76 (20), 51 (19)
	(*E*)-chlorostilbene	44.5	5–10	216 (M + 2, 4.8), 214 (M^+, 15), 179 (M – Cl, 100), 178 (M – HCl, 4.8), 101 (17), 77 (47)
2-[(2-chloroethyl)sulfinyl]-1-phenylethylamine hydrochloride	vinyl chloride	1.5	2	64 (M + 2), 62 (M^+, 3.9), 27 (100)
	thioformaldehyde hydrate	3.2	trace	66 (M^+, 100), 50 (52), 44 (21)
	styrene	19.0	2–6	104 (M^+, 100), 76 (4), 74 (5), 27 (7)
	styrene oxide	21.5	≃2	120 (M^+, 30), 119 (23), 92 (M – CO, 28), 91 (100), 90 (30), 65 (16)
	benzaldehyde	23.0	15–20	106 (M^+, 100), 105 (97), 77 (89), 51 (40)
	(*E*)-2-chlorostyrene[b]	26.5	8–10	140 (M + 2, 20), 138 (M^+, 63), 103 (100), 102 (16), 77 (43), 51 (50), 50 (22)
	(*Z*)-2-chlorostyrene[b]	28.0	2–3	140 (M + 2, 9), 138 (M^+, 29), 103 (100), 102 (16), 77 (46), 51 (52), 50 (23)
	phenylacetaldehyde	31.5	2–3	120 (M^+, 28), 119 (1), 92 (23), 91 (100), 65 (13)
2-[(2-chloroethyl)sulfinyl]-2-phenylethylamine hydrochloride	vinyl chloride	1.5	2–5	64 (M + 2, 1.2), 62 (M^+, 3.9), 27 (M – Cl, 100)
	thioformaldehyde hydrate	3.0	≃2	66 (M^+, 100), 50 (52), 44 (21)
	thiobenzaldehyde	18.0	10–20	122 (M^+, 15), 77 (M – CHS, 100), 45 (46)
	styrene	19.5	2–4j	104 (M^+, 100), 76 (4), 74 (5), 27 (7)
	styrene oxide	22.0	≃2	120 (M^+, 30), 119 (23), 92 (28), 91 (100), 90 (30), 65 (16)
	phenylacetaldehyde	30.0	trace	120 (M^+, 27), 119 (1), 92 (21), 91 (100), 65 (14)
2-[(2-bromoethyl)sulfinyl]-*threo*-1,2-diphenylethyl]-3-*tert*-butyl-1-nitrosourea[c]	(*Z*)-1-bromostilbene	31.4	6–12	260 (M + 2, 51), 258 (M, 50), 179 (100), 178 (M – HBr, 53), 77 (12.5)
2-[(2-bromoethyl)sulfinyl]-2-phenylethylamine hydrobromide[c]	(*Z*)-2-bromostyrene	22.1	2–5	184 (M + 2, 25), 182 (M, 23.3), 103 (M – Br, 100), 77 (21.6), 51 (30)
	(*E*)-2-bromostyrene	22.9	7–11	184 (M + 2, 70.8), 182 (M^+, 72.6), 103 (M – Br, 100), 77 (C_6H_5, 39.4)

[a] *tert*-Butyl isocyanate is a common product in all nitrosourea reactions. *tert*-Butylurea is similarly identified in all the reactions by chemical ionization mass spectrometry using NH_3 as reagent gas. [b] (*E*)- and (*Z*)-β-Chlorostyrenes were confirmed by their characteristic mass fragmentation pattern. [c] The other products observed in common with the corresponding 2-chloroethyl precursors are not shown.

Synthesis of 1,2-Oxathietane Precursors. An examination of the effects of conjugating aryl substituents in the precursors on the formation and subsequent reactions of 1,2-oxathietanes was undertaken.

The synthesis of 1-[2-[(2-chloroethyl)sulfinyl]-*threo*-1,2-diphenylethyl]-3-*tert*-butyl(and cyclohexyl)-1-nitrosourea (**5a,b**) from *trans*-2,3-diphenylaziridine[1] (**1**) is outlined in Scheme IA.

Synthesis of the isomeric 1-[2-[(2-chloroethyl)-sulfinyl]-1-(and 2)phenylethyl]-3-*tert*-butyl(and cyclohexyl)-1-nitrosoureas obtained from the precursor **6** is outlined in Scheme IB. Nucleophilic opening of 2-phenylaziridine **6** with 2-mercaptoethanol affords an isomeric mixture of 2-[(2-hydroxyethyl)thio]-(1-(and 2)-phenylethylamines. Reaction of the later with thionyl chloride gives a mixture of **7** and **8** which were separated chromatographically. Treatment of each of the latter with *tert*-butyl or cyclohexyl isocyanate followed by reaction with sodium nitrite in formic acid afforded regiospecifically nitrosated[7] thioether ureas **9** and **10**; respectively.

The corresponding sulfinyl nitrosoureas **11** and **12** were prepared similarly except for the intervening S-oxidation with *m*-chloroperbenzoic acid, hydrogen peroxide, or oxidation with singlet oxygen.[8]

Results

Aqueous Decomposition of Phenyl-Substituted Sulfinylnitrosoureas. Decomposition of 1-[2-[(2-chloroethyl)sulfinyl]-*threo*-1,2-diphenylethyl]-3-*tert*-butyl-1-nitrosourea (**5Ab**) in phosphate buffer (pH 7.0) and 37 °C affords the following volatile products identified by GC–MS: stilbene, benzaldehyde, thiobenzaldehyde,[9] thioformaldehyde hydrate **19**[8] and formaldehyde (the latter two products arising from 1,2-oxathietane (**17**), (*Z*)-1-chlorostilbene (**18**), and *tert*-butyl isocyanate (Table I). CIMS revealed the formation of *tert*-butylurea. A similar experiment performed in the presence of 5 molar equiv of sodium bromide gives exactly the same spectrum of products including (*Z*)-1-chlorostilbene[10] (Scheme II).

(6) Ittah, Y.; Sasson, Y.; Shahak, I.; Tsaroom, S.; Blum, J. *J. Org. Chem.* **1978**, *43*, 4271.

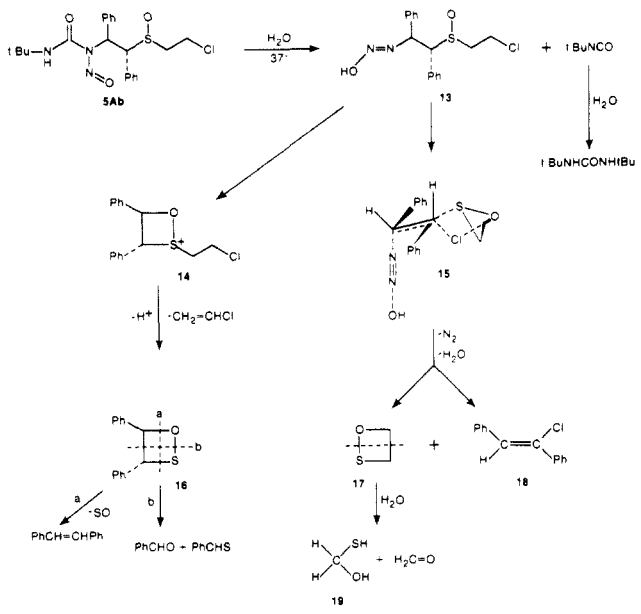
(7) Johnston, T. P.; McCaleb, G. S.; Opliger, P. S.; Montgomery, J. A. *J. Med. Chem.* **1966**, *9*, 892.

(8) Oxidation of the thio ether group with *m*-chloroperbenzoic acid or hydrogen peroxide is equally appropriate while selective photosensitized S-oxidation with molecular oxygen in the presence of rose bengal or methylene blue is convenient for ^{18}O labeling.[1,2]

(9) In general, thioaldehydes, with the exception of a few highly hindered and less reactive examples (Okazaki, R.; Ishii, A.; Fukuda, N.; Oyama, H.; Inamoto, N. *J. Chem. Soc., Chem. Commun.* **1982**, 1187), form hydrates readily when generated in aqueous media.

(10) (a) Closs, G. L.; Brois, S. J. *J. Am. Chem. Soc.* **1960**, *82*, 6068. (b) Ittah, Y.; Sasson, Y.; Shahak, I.; Tsaroom, S.; Blum, J. *J. Org. Chem.* **1978**, *43*, 4271.

Scheme II[a]



[a] Pathways and products of decomposition of 1-[2-[(2-chloroethyl)sulfinyl]-*threo*-1,2-diphenylethyl]-3-*tert*-butyl-1-nitrosourea (**5Ab**) in aqueous potassium phosphate buffer (pH 7.0) and 37 °C.

The behavior of alternative 1,2-oxathietane precursors was also examined. Thus [2-(2-chloroethyl)sulfinyl]-1,2-*threo*-diphenylethylamine hydrochloride when subjected to aqueous diazotization conditions affords stilbene, benzaldehyde, thiobanzaldehyde, thioformaldehyde hydrate, formaldehyde, and (*Z*)-1-chlorostilbene.[10] As in the previous example addition of several molar equivalents of sodium bromide has no detectable effect in that (*Z*)-1-chlorostilbene is still formed.

In contrast, similar diazotization of [2-(2-bromoethyl)-sulfinyl]-1,2-*threo*-diphenylethylamine hydrobromide affords the same spectrum of products except (*Z*)-1-bromostilbene is formed. The control "exchange" experiments, i.e., in the presence of excess sodium chloride, did not affect the formation of (*Z*)-1-bromostilbene.

Similarly 2-[(2-chloroethyl)sulfinyl]-2-phenylethylamine hydrochloride when subjected to aqueous diazotization conditions affords styrene, thiobenzaldehyde,[9] formaldehyde, thioformaldehyde hydrate,[9] vinyl chloride, and 1-chlorostyrene. Addition of several molar equivalents of sodium bromide has no detectable effect, in that (*Z*)-1-chlorostyrene was still formed.

In contrast the behavior of the 2-[(2-chloroethyl)-sulfinyl]-1-phenylethylamine hydrochloride (**20A**) is significantly different. Diazotization of **20A** and examination of the decomposition products by GC–MS confirmed styrene, benzaldehyde, thioformaldehyde hydrate, formaldehyde, and (*E*)- and (*Z*)-2-chlorostyrenes (**28** and **29**)[11] (in a ratio of 70:30) as well as 2-phenyloxirane[12] (**30**), and phenylacetaldehyde (**31**).[12]

As in the previous experiments, addition of 5 molar equiv of sodium bromide has no effect in that (*E*)- and (*Z*)-2-chlorostryenes (**28** and **29**) are formed in the same ratio (70:30) (Scheme III).

Aqueous diazotization of 2-[(2-bromoethyl)sulfinyl]-1-phenylethylamine hydrobromide (**20B**) affords the same spectrum of products except that (*E*)- and (*Z*)-2-bromostyrenes are formed (in a ratio of 72:28). A control experiment in the presence of excess chloride ion did not effect exchange of the halogen in the bromostyrenes.

Discussion

The aryl-substituted sulfinylnitrosoureas exhibit quite different chemistry upon spontaneous decomposition in aqueous buffer compared with their alkyl-substituted counterparts.[1,2] The products from the decomposition of 1-[[2-[(2-chloroethyl)sulfinyl]-*threo*-1,2-diphenyl]ethyl]-3-*tert*-butyl-1-nitrosourea (**5Ab**) require the intermediacy of two different 1,2-oxathietanes (Scheme II). The products (*E*)-stilbene, benzaldehyde, and thiobenzaldehyde are in accord with the two alternative [σ2s + σ2a] cycloreversions of the *trans*-3,4-diphenyl-1,2-oxathietane (**16**) formed from the diazohydroxide **13** via intermediate **14**. The comparable contribution of the phenyl substituted 1,2-oxathietanes **16** and **27** to the overall decomposition of the alternative precursors is better indicated by the comparable yields of benzaldehyde (Table I) than by thiobenzaldehyde owing to the well-known reactivity and instability of thioaldehyde.[13]

Ab initio calculations at the level of SCF6-21G, after geometry optimization, predict an energy of −550.119 20 au for 1,2-oxathietane. The energies of the fragments from the alternative [σ2s + σ2a] cycloreversions were calculated as −472.169 46 au for sulfur monoxide and −77.948 0 au for ethylene for a total of −550.117 5 au; compared with −436.416 2 au for thioformaldehyde and −113.697 1 au for formaldehyde for a total of −550.113 3 au. Thus the alternative cycloreversions are predicted to be comparable in energy and certainly fragments from both reactions are observed in the case of **16** and **27**. Analytical difficulties may account for the lack of detection of ethylene from what is already a minor pathway of **17**. Extended calculations now in progress and designed to incorporate configuration interaction as well as polarization functions and the contribution of the sulfur 3d orbitals may reveal a distinct preference in the alternative spontaneous cleavage modes of the parent 1,2-oxathietane.

The additional fragmentation products, thioformaldehyde hydrate[8] **19**, and formaldehyde require the intermediacy of the alternative 1,2-oxathietane (**17**).

However the new product (*Z*)-1-chlorostilbene (**18**)[14] indicates a different mechanism is operating compared with the reactions of alkyl-substituted precursors[1,2] and implies migration of the chlorine atom over three bonds. There are several precedents for halogen participation involving migration of the halogen atom over three bonds and initiated by a good leaving group via a five-membered halogen-bridged intermediate.[15] The intermediates involved in these 1,4-halogen transfers may be regarded as "vinylogues" of the bridged halonium species investigated by Peterson[15] and independently by Olah.[16] Thus conjugative interaction by the stilbene or styrene double bond is interposed between the participating chlorine and diazonium leaving group. Examples of 1,4-participation leading to migration of chlorine to an incipient double bound leading to a preferred *E* product stereochemistry

(11) Compared with authentic *E* and *Z* chlorostyrene.

(12) Identified by comparison with authentic samples commercially available for Aldrich Chem. Co.

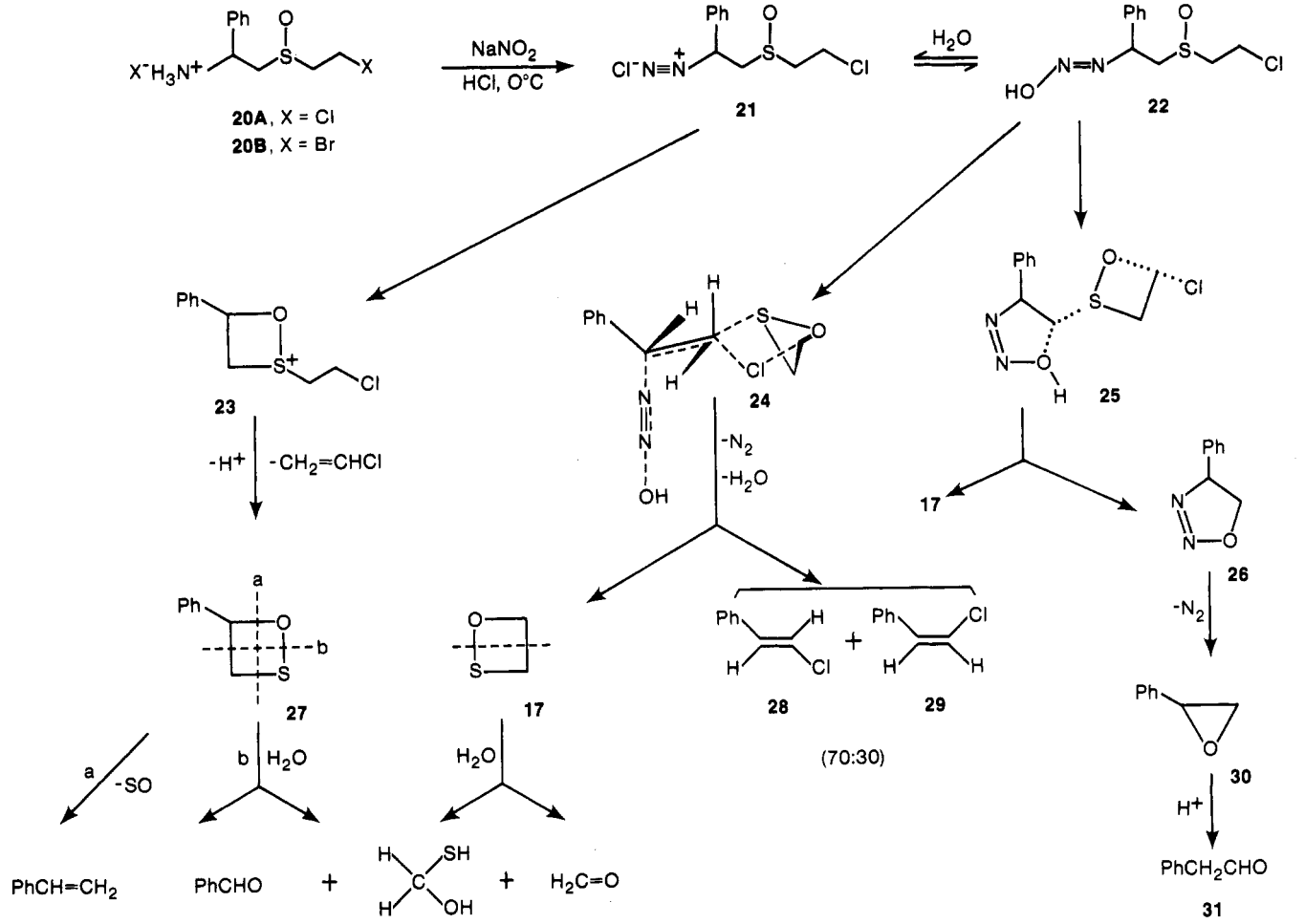
(13) Thioaldehydes or thio ketones are very reactive and are not normally isolable unless they are severely hindered sterically. Reference 9 and Vedejs, E.; Perry, D. A. *J. Am. Chem. Soc.* **1983**, *105*, 1683.

(14) (*Z*)-1-Chlorostilbene **17** together with phenyloxirane **28**, phenylacetaldehyde **29** and (*E*)- and (*Z*)-2-chlorostyrenes (**26** and **27**) were identified by their GC retention times, compared with authentic samples and their characteristic MS fragmentation patterns quoted in the *Eighth Peak Index of Mass Spectra*; Mass Spectrometry Data Centre: Reading, UK, 1974, Volume I, Table I.

(15) For a review, see: Peterson, P. E. *Acc. Chem. Res.* **1971**, *4*, 407 and references therein.

(16) Olah, G. A.; DeMember, J. R. *J. Am. Chem. Soc.* **1970**, *92*, 718.

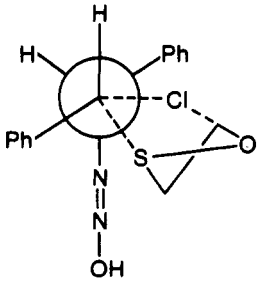
Scheme III[a]



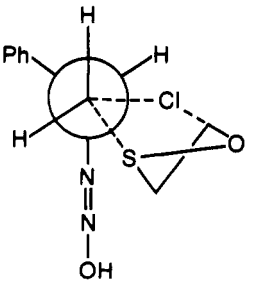
[a] Pathways and products of aqueous decomposition resulting from the diazotization of 2-[2-haloethyl)sulfinyl]-2-phenylethylamine hydrohalides **20** (A and B) at 0 °C.

have also been reported.[17] Addition of a large excess of bromide ion to the reaction medium had no effect in that (*Z*)-1-chlorostilbene is still the only halogenated product. the chloro group is, therefore, transferred in a tightly bound nonexchangeable and evidently conformationally controlled manner.

The results suggest an intermediate of the type **15** is formed at the demand of the incipient diazonium group.[15] Collapse of **15** to form **17** and **18** may be subject to conformational control rationalized in terms of the Newman projection **32**.



32



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The results, together with the observation of (*Z*)-1-chlorostilbene among the products of the diazotization of [2-(2-chloroethyl)thio]-1,2-*threo*-diphenylethylamine hydrochloride, suggest initial formation of diazohydroxide **13** which undergoes a conformational change dictated by loss of nitrogen which results in the formation of **15** and a concomitant intramolecular 1,4-chlorine transfer to give **17** and **18**. The fact that a similar 1,4-bromine transfer occurs from **5Bb** and with no halogen exchange again suggests a tightly bound halogen during the transfer.

The contrasting behavior of alkyl- and aryl-substituted sulfinylnitrosoureas or sulfinylethylamines suggested a direct influence of the nature of the substituents on the course of the reaction. The fact that no halo-substituted alkene is detected from alkyl-substituted sulfinylnitrosoureas,[1,2] in contrast to **5Ab**, suggests that a contributing factor is that the double bond character in the stilbene moiety in the transition state **15** from **13** (or the styrene moiety from **21** in Scheme III stabilized by conjugation with the aryl groups) is relatively well-developed. This evidently favors the halogen transfer and the formation of **18** or **28** and **29**. Comparison of the relative yields of products shown in Scheme II suggests that decompsotion via intermediate **14** accounts for ca. 75% of the reaction compared with ca. 25% contributed by the pathway leading to **17** and **18**.

The rather unusual chemistry posed by intermediate **13** receives support from the observed behavior of the monophenyl-substituted precursor **20A** (Scheme III). The spectrum of products obtained from **20A**, in fact, corresponds to the participation of three separate pathways (Scheme III).

(17) Peterson, P. E.; Duddey, E. *J. Am. Chem. Soc.* **1963**, *85*, 2865; **1966**, *88*, 4990. Peterson, P. E.; Bopp, R. J.; Ajo, M. M. *J. Am. Chem. Soc.* **1970**, *92*, 2834.

First, participation of the sulfinyl oxygen in the initially formed diazonium ion **21** forms **23**, from which elimination of vinyl chloride generates the 4-phenyl-1,2-oxathietane (**27**). Products were identified[14] corresponding to the two alternative formal [σ2s + σ2a][5] cycloreversion reactions of **27**.

Second the observation of formaldehyde and (*E*)- and (*Z*)-2-chlorostyrenes[12] (in a ratio of 70:30) is in accord with the formation of a second 1,2-oxathietane (**17**) via the intermediates **22** and **24**. As in the previous example the suggestion of a tightly controlled intramolecular 1,4-chlorine shift was supported by the lack of exchange of the chlorine substituent in the presence of excess bromide ion. The predominant formation of (*E*)-2-chlorostyrene suggests conformational control in the transition state from **24** as in the Newman projection **33**. The formation of (*E*)- and (*Z*)-2-bromostyrenes in a ratio of 72:28 from the corresponding aqueous decomposition of **20B** suggests a similar mechanism and conformational control in the 1,4-migration of the bromine.

Third, the observation of 2-phenyloxirane (**30**)[12] and phenylacetaldehyde (**31**)[12] is in accord with the intermediacy of the 4-phenyl-1,2,3-oxadiazoline intermediate (**26**)[18] with concomitant formation of 1,2-oxathietane (**17**).

It appears plausible that the contribution of the pathway via the 1,2,3-oxadiazoline[18] is permitted in **20** as in Scheme III, but precluded in **5**, as in Scheme II, for reasons of steric hindrance offered by the phenyl group in the latter case.

In addition halo-substituted olefins (i.e., products of 1,4-halogen transfer[15]) are formed readily from aryl-substituted precursors from **5Ab** and **20** but are not detected from the alkyl substituted precursors.[1,2] It is plausible that the intramolecular transfer and substitution of halogen requires the conjugation provided by the aryl substituents in the intermediates **15** and **24**.[15]

In conclusion, the examples investigated in this report confirm the facile generation of alternative and novel 1,2-oxathietanes by competing pathways under mild conditions from at least two different types of precursors. These examples also demonstrate the marked effect of the nature of the substituents in the sulfinylnitrosourea or (aminoethyl)sulfinyl precursors on the course of the reactions. Aryl substituents, by providing conjugative stabilization, promote a vinylogous 1,4-halogen participation with migration of chlorine over three bonds in a conformationally controlled manner.

Additional novel chemistry involved in both the formation and reactions of 1,2-oxathietanes, and including the reaction of thiocarbonyl fragments with DNA bases that may be relevant to the anticancer activity of the precursors, together with interpretation of their characteristic reactions by ab initio calculations will be reported in due course.

Experimental Section

Melting points were determined on a Fisher–Johns apparatus and are uncorrected. The IR spectra were recorded on a Nicolet 7199 F.T. spectrophotometer, and only the principal sharply defined peaks are reported. The PMR spectra were recorded on Varian HA-100, Bruker WH-200, or WH-400 spectrometers. The spectra were recorded on approximately 5–15% (w/v) solutions, depending upon the spectrometers, in appropriate deuterated solvents with tetramethylsilane as internal standard. Wherever possible, and where overlap of signals did not interfere, the positions of the individual protons in particular regioisomers were assigned. EI mass spectra were determined on an Associated Electrical Industries (AEI) MS-9 double-focusing high-resolution mass spectrometer. The peak measurements were made by comparison with perfluorotributylamine at a resolving power of 15000. Kiesel gel DF-5 (Camag, Switzerland) and Eastman Kodak precoated sheets were used for thin-layer chromatography.

2-[(2-Chloroethyl)thio]-1,2-diphenylethylamine Hydrochloride (2). A solution of 1.95 g (10 mmol) of *trans*-2,3-diphenylaziridine[6] and 1.2 g (15 mmol) of 2-mercaptoethanol in 15 mL of methanol was heated under reflux for 24 h. The solvent and excess of 2-mercaptoethanol were removed in vacuo affording 2.5 g (90% yield) of the thioethanol derivative which was used without further purification: ^{1}H NMR ($CDCl_3$) δ 1.75 (br s, 2 H, NH_2), 2.38 (t, 2 H, J = 6 Hz, SCH_2), 3.1 (br s, 1 H, OH), 3.48 (t, 2 H, J = 6 Hz, CH_2O), 4.0 (d, 1 H, J = 4 Hz, SCHPh), 4.28 (d, 1 H, J = 4 Hz, CHN), 7.3 (s, 10 H, Ar).

The crude product was dissolved in 25 mL of $CHCl_3$ and saturated with dry HCl with cooling. Thionyl chloride (1.8 g, 15 mmol) was added dropwise, and the mixture was refluxed for 15 h. The solvent and excess of reagent were removed in vacuo, and the residual solid recrystallized from $CHCl_3$ affording **2** as a white crystalline solid mp 205–208 °C: ^{1}H NMR δ (Me_2SO-d_6) 2.6 (t, 2 H, J = 6 Hz, SCH_2), 3.5 (t, 2 H, J = 6 Hz, CH_2Cl), 4.67 (d, 1 H, J' = 9 Hz, C*H*Ph), 4.95 (d, 1 H, J' = 9 H, C*H*Ph), 7.4 (br s, 10 H, Ar), 9.0 (br s, 3 H, exch. $^+NH_3$; CIMS (NH_3), m/z (rel intensity) 294 [(MH^+ + 2 – HCl), 3.8], 292 [(MH^+ – Cl), 10.4], 277 (NH_3, 9.7), 275 (NH_3, 26.8), 256 (Cl, 100), 228 (4.3), 196 (3.5).

1-[2-[(2-Chloroethyl)thio]-1,2-diphenylethyl]-3-*tert*-butylurea. A solution of 0.33 g (1 mmol) of *tert*-butyl isocyanate and 0.1 g (1 mmol) of triethylamine in 20 mL of $CHCl_3$ was refluxed for 6 h. Then the $CHCl_3$ layer was thoroughly washed and dried. Removal of the solvent gave a solid which was purified by recrystallization from ethyl acetate/pentane as a white fibrous solid 0.34 g (87% yield) mp 186–188 °C: ^{1}H NMR ($CDCl_3$) δ 1.2 (s, 9 H, *t*-Bu), 2.64 (t, 2 H, J = 9 Hz, CH_2), 3.42 (t, 2 H, J = 9 Hz, CH_2), 4.34 (br s, 2 H, CH, NH), 5.2 (br s, 2 H, CH, NH), 7.24 (br s, 10 H, Ar); CIMS (NH_3) m/z (rel intensity) 391 (MH^+). Anal. Calcd for $C_{21}H_{27}ClN_2OS$: C, 64.6; H, 6.9; N, 7.2. Found: C, 65.0; H, 7.1; N, 6.9.

1-[2-[(2-Chloroethyl)sulfenyl]-1,2-diphenylethyl]-3-*tert*-butyl-1-nitrosourea (4b). A solution of 0.195 g (0.5 mmol) of the above urea and 0.1 mL of (0.09 mmol) of 30% (w/v) H_2O_2 in 2 mL of MeOH was stirred at room temperature for 4 h. The solvent and excess of reagent were removed under vacuum, and the residual solid was recrystallized from (1:1) ethyl acetate/petroleum ether as a white powder 0.17 g (83%) mp 96–100 °C: ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 9 H, *t*-Bu), 2.7 (t, 2 H, J = 6.5 Hz, SCH_2), 3.68 (t, 2 H, J = 6.5 Hz, CH_2Cl), 4.72 (d, 1 H, J' = 9 Hz, CHS), 4.98 (d, 1 H, J' = 9 Hz, NC*H*), 5.6 (br, 2 H, exch NH), 7.4 (br s, 10 H, Ar); IR (film) ν_{max} 3425, 2920, 2845, 1725, 1490, 1025 cm^{-1}; CIMS (NH_3), m/z (rel intensity) 407 (MH^+). Anal. Calcd for $C_{21}H_{26}ClN_3O_2S$: C, 61.9; H, 6.6; N, 6.9. Found: C, 62.2; H, 6.9; N, 6.5.

1-[2-[(2-Chloroethyl)sulfinyl]-1,2-diphenylethyl]-3-*tert*-butyl-1-nitrosourea (5b). A solution of 0.2 g (0.5 mmol) of the sulfinylurea in 1 mL of 97% formic acid was cooled to 0 °C, and 0.14 g (2 mmol) of sodium nitrite was gradually added with stirring. Stirring was continued for a further 6 h. Then the mixture was diluted with 15 mL of water and extracted with $CHCl_3$ (3 × 20 mL).

Concentration of the dried ($MgSO_4$) extract and column chromatography (silica gel, $CHCl_3$) gave (**10a**) as a yellow waxy solid 0.15 g (69% yield), mp 68–73 °C: ^{1}H NMR ($CDCl_3$) δ 1.5 (s, 9 H, *t*-Bu), 2.88 (m, 2 H, SCH_2), 3.8 (m, 2 H, CH_2Cl), 5.08 (d, 1 H, J = 8 Hz, SCH), 5.62 (d, 1 H, J = 8 Hz, NC*H*), 7.0 (br, 1 H, exch NH), 7.35 (m, 10 H, Ar); IR (film) ν_{max} 3430, 2915, 2845, 1725, 1520, 1495, 1035 cm^{-1}; CIMS (NH_3), m/z (rel intensity) 400 (MH^+ – Cl), 386 (MH^+ – CH_2Cl).

2-[(2-Chloroethyl)thio]-1-phenylethylamine Hydrochloride (7) and 2-[(2-Chloroethyl)thio]-2-phenylethylamine Hydrochloride (8). A solution of 5.95 g (0.05 mol) of 2-phenylaziridine and 7.8 g (0.1 mol) of 2-mercaptoethanol in 25 mL of methanol was heated under reflux for 15 h. The solvent and excess of 2-mercaptoethanol were removed in vacuo. The residual viscous oil was dissolved in 50 mL of $CHCl_3$ and cooled to 0 °C, and 9.5 g (80 mmol) of thionyl chloride was added dropwise during about 1 h. A gentle reflux was maintained for

(18) 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.

4 h. The solvent and excess of reagent were removed under vacuum, and the residue was taken up in $CHCl_3$/MeOH (1:1) and decolorized with charcoal. The solvents were removed in vacuo, and the residue upon column chromatography (silica gel, $CHCl_3$ with 10% MeOH) afforded first the 1-phenyl isomer **7**, 6.05 g (48% yield), mp 153–154 °C: ^{1}H NMR (Me_2SO-d_6) δ 2.62–2.96 (m, 2 H, SCH_2), 3.3 (d, 2 H, CH_2S, J = 8 Hz), 3.56 (m, 2 H, CH_2Cl), 4.48 (t, 1 H, ArCH, J = 8 Hz), 7.40 (m, 5 H, aryl), 8.44 (br s, 3 H, $^+NH_3$); MS, m/z (rel intensity) 217 (M^+ + 2), 215 (M^+ – HCl), 180 (M – Cl, 28), 166 (M – CH_2Cl, 100), 165 (29), 119 (63), 118 (29), 77 (43).

Further elution afforded the 2-phenyl isomer **8**, 1.5 g (12% yield) mp 56–60 °C: ^{1}H NMR (Me_2SO-d_6) δ 2.4–2.66 (m, 1 H, SCH), 2.9–3.5 (m, 6 H, CH_2Cl, SCH_2, CH_2), 3.94 (dd, ArCH, ^1J = 10.5 Hz, ^2J = 2 Hz), 7.1–7.32 (m, 5 H, Ar), 8.42 (br s, 3 H, NH_3^+); MS, m/z (rel intensity) 217 (M + 2), 215 (M^+ – HCl, 15), 180 (M – Cl, 32), 166 (M – CH_2Cl, 100), 165 (26), 119 (20), 118 (8), 77 (46), 51 (9).

2-[(2-Chloroethyl)sulfinyl]-1-phenylethylamine Hydrochloride (20A). A solution of 0.2 g (0.8 mmol) o 2-[(2-chloroethyl)thio]-1-phenylethylamine hydrochloride (**7**) and 0.2 mL (1.7 mmol) of 30% hydrogen peroxide in 1 mL of methanol was stirred at room temperature for 4 h. Upon removal of the solvent the product was obtained as a white crystalline solid, 0.2 g (90% yield) mp 140–145 °C: ^{1}H NMR ($CDCl_3$) δ 2.76–2.94 (m, 1 H, SCH), 3.12–3.28 (m, 1 H, SCH), 3.5–3.68 (m, 1 H, CHS), 3.7–4.0 (m, 3 H, CH_2Cl and CHS), 4.52–4.66 (m, 1 H, NC*H*) 7.46 (s, 5 H, Ar), 8.32 (br s, 3 H, $-NH_3^+$); MS, m/z (rel intensity) CIMS (NH_3); 232 (MH^+ – HCl), 197 (MH^+ – Cl, 100), 183 (MH^+ – CH_2Cl, 56), 120 (68), 119 (27), 118 (33), 90 (28), 76 (42).

1-[2-[(2-Chloroethyl)sulfinyl]-1-phenylethyl]-3-*tert*-butylurea. A solution of 0.13 g (0.5 mmol) of the appropriate sulfoxide, 0.05 g (0.5 mmol) of *tert*-butyl isocyanate, and 0.06 g (0.6 mmol) of triethylamine in 5 mL of $CHCl_3$ was heated under reflux for 30 min. The cooled solution was washed thoroughly with water and dried (Na_2SO_4), and the solvent was removed under vacuum. The residual solid was recrystallized from $CHCl_3$ to give the urea 0.15 g (95% yield) mp 101–105 °C: ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 9 H, *t*-Bu), 2.8–3.3 (m, SCH_2, 2 H), 3.5–4.05 (m, 4 H, CH_2Cl and CH_2S), 4.62–4.78 (m, 1 H, NCH), 5.2 (br s, 1 H, NH), 5.66 (br, 1 H, NH), 7.41 (s, 5 H, Ar); MS CIMS (NH_3), 331 (MH^+, 16), 296 (MH – Cl, 15), 282 (MH^+ – CH_2Cl, 53), 231 (100), 100 (57), 90 (40). Anal. Calcd for $C_{15}H_{23}ClN_2O_2S$: C, 54.5; H, 7.0; N, 8.5. Found: C, 55.0; H, 7.3; N, 8.2.

1-[2-[(2-Chloroethyl)sulfinyl]-1-phenylethyl]-3-*tert*-butyl-1-nitrosourea (11b). A solution of 0.15 g (0.45 mmol) of the urea in 97% formic acid was cooled to 0 °C and treated with 0.1 g (1.5 mmol) of sodium nitrite in portions over about 30 min. After the addition was completed, stirring was continued for another 1 h, then diluted to 10 mL with water, and extracted with $CHCl_3$ (3 × 15 ml). The combined extracts were dried (Na_2SO_4) and the solvent was removed. The residual heavy yellow oil was chromatographied (florisil, $CHCl_3$) to afford **16b** 0.145 g (92% yield) as an oil: ^{1}H NMR ($CDCl_3$) δ 1.41 (s, 9 H, *t*-Bu), 2.88–3.38 (m, 2 H, SCH_2), 3.62–4.2 (m, 4 H, CH_2Cl, CH_2S), 4.82–4.96 (m, 1 H, NCH), 6.82 (br s, NH), 7.52 (s, 5 H, Ar); IR ν_{max} ($CHCl_3$), 3418, 1728, 1455, 1060 cm^{-1}; CIMS (NH_3), m/z 360 (MH^+).

2-[(2-Chloroethyl)sulfinyl]-2-phenylethylamine Hydrochloride. A solution of 0.2 g (0.8 mmol) of 2-[(2-chloroethyl)-thio]-2-phenylethylamine hydrochloride (**8**) and 0.2 mL (1.7 mmol) of 30% hydrogen peroxide in 1 mL of methanol was stirred at room temperature for 5 h. Upon removal of the solvent the product 2-[(2-chloroethyl)sulfinyl]-2-phenylethylamine hydrochloride a white crystalline powder was obtained, 0.2 g (90% yield) mp 138–143 °C: ^{1}H NMR ($CDCl_3$) δ 2.72–2.91 (m, 1 H, SCH_2), 3.09–3.22 (m, 1 H, SCH_2), 3.8–4.22 (m, 4 H, CH_2Cl and NCH_2), 4.38–4.42 (m, 1 H, PhCHS), 7.43 (m, 5 H, Ar), 8.3 (br s, 3 H, $^+NH_3$).

1-[2-[(2-Chloroethyl)sulfinyl]-2-phenylethyl]-3-*tert*-butylurea. This compound was prepared by a similar procedure to that described above for the 1-phenyl isomer and was obtained as a crystalline solid mp 110–113 °C: ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 9 H, *t*-Bu), 2.78–3.28 (m, 2 H, SCH_2), 3.5–4.16 (m, 4 H, CH_2Cl, NCH_2), 4.32–4.43 (m, 1 H, PhC*H*), 5.1 (br s, 1 H, N*H*), 5.56 (br, 1 H, exch NH) 7.44 (s, 5 H, Ar); CIMS (NH_3), 331 (MH^+). Anal. Calcd for $C_{15}H_{23}ClN_2O_2S$: C, 54.5; H, 7.0; N, 8.5. Found: C, 54.6; H, 7.1; N, 8.2.

1-[2-[(2-Chloroethyl)sulfinyl]-2-phenylethyl]-3-*tert*-butyl-1-nitrosourea (12b). Regiospecific nitrosation as described for the 1-phenyl isomer affords a waxy solid: ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 9 H, *t*-Bu), 3.81–3.36 (m, 2 H, SCH_2), 3.48–4.12 (m, 4 H, CH_2Cl and NCH_2), 4.6–4.71 (m, 1 H, PhCH), 7.47 (s, 5 H, Ar); IR ν_{max} ($CHCl_3$) 3428, 1730, 1450, 1062 cm^{-1}.

2-[(2-Hydroxyethyl)thio]-*threo*-1,2-diphenylethylamine. A solution of *trans*-2,3-diphenylaziridine[6] (0.975 g, 5 mmol) and 2-mercaptoethanol (3.12 g, 40 mmol) in 20 mL of absolute methanol was heated under reflux for 48 h with exclusion of moisture. The solvent was removed in vacuo, and the evaporation was repeated following addition of dichloromethane (3 × 50 mL) affording 2-[(2-hydroxyethyl)thio]-*threo*-1,2-diphenylethylamine as a pale yellow oil 1.0 g (73% yield): ^{1}H NMR ($CDCl_3$) δ 1.85 (br, 2 H, NH_2), 2.3 (t, 2 H, SCH_2, J = 6 Hz), 3.15 (br, 1 H, OH), 3.4 (t, 2 H, CH_2O, J = 6 Hz), 3.95 (d, 1 H, J = 8.8 Hz), 4.2 (d, 1 H, J = 8.8 Hz), 7.3 (m, 10 H, aryl); IR (film) 3240, 3280 cm^{-1} (OH, NH_2); CIMs (NH_3) (rel intensity) 274 (MH^+, 98), 257 (MH – OH, 100), 197 (15), 196 (90.5), 172 (22.5).

2-[(2-Bromoethyl)thio]-*threo*-1,2-diphenylethylamine Hydrobromide. A solution of 2-[(2-hydroxyethyl)**thio**]-*threo*-1,2-diphenylethylamine (1.0 g, 2.8 mmol) in 10 mL of methanol at 0 °C was acidified to pH 2.0 by dropwise addition of 48% hydrobromic acid. The mixture was diluted with dichloromethane (30 mL), and the solution was evaporated to dryness. The residual solid was dried in vacuo over P_2O_5 for 24 h 1.1 g (85% yield): ^{1}H NMR (Me_2SO-d_6) δ 2.60 (m, 2 H, SCH_2), 3.25 (m, 2 H, CH_2O), 4.37 (d, 1 H, J = 8.5 Hz), 4.52 (d, 1 H, J = 8.5 Hz), 7.37 (m, 10 H), 8.35 (br, 3 H, exch NH_3^+Br).

A solution of freshly distilled thionyl bromide (0.517 g, 2.5 mmol) in 10 mL of dry benzene was added to a stirred solution of the hydrobromide (0.706 g, 2 mmol) in 40 mL of benzene at 0 to –5 °C. After a further 1 h at 0 to –5 °C, the mixture was stirred at ambient temperature overnight. The resulting precipitate was collected, washed with hexane, and then recrystallized from chloroform to give the bromoethyl hydrobromide as a yellow crystalline solid mp 193–195 °C, 0.5 g (60% yield): ^{1}H NMR δ (Me_2SO-d_6) δ 2.4 (m, 2 H, CH_2S), 3.2 (m, 2 H, CH_2Br), 4.6 (d, 1 H, CHS, J = 8.5 Hz), 4.80 (1 H, *CH*NH_2, J = 8.8 Hz), 7.5 (m, 10 H, Ph), 8.4 (br, exch 3 H, NH_3^+Br); IR ν_{max} (Nujol) 2840 cm^{-1} (NH_3^+Br); CIMS (NH_3), m/z (rel intensity) 338 (MH^{+2} – HBr, 6.3), 336 (M^+ – HBr, 6.4), 256 (100), 196 (92.4), 195 (2.9), 194 (4.3), 180 (1.4), 179 (0.3), 106 (2.0).

2-[(2-Bromoethyl)sulfinyl]-*threo*-1,2-diphenylethylamine Hydrobromide. To a stirred solution of 2-[(2-bromoethyl)-thio]-*threo*-1,2-diphenylethylamine hydrobromide (0.41 g, 1 mmol) in 2 mL of methanol was added a 30% solution of hydrogen peroxide (0.226, 2 mmol), and the mixture was stirred at room temperature for 48 h. The solvent was removed in vacuo, and the residual solid was recrystallized from benzene–hexane to give the pure product 0.4 g (92% yield) mp 170 °C: ^{1}H NMR ($CDCl_3$) δ 2.65 (m, 2 H, CH_2S), 3.3 (m, 2 H, CH_2Br), 5.0 (d, 1 H, J = 8.8 Hz, *CH*S), 5.5 (d, 1 H, J = 8.8 Hz, $CHNH_2$), 7.3 (m, 10 H, Ph), 8.6 (br s, exch NH_3^+Br); IR (Nujol) 1012 cm^{-1} (SO); CIMS (NH_3), m/z (rel intensity) 354 [(MH^{+2}) – HBr, 23.1], 352 (M^+ – HBr, 23.1), 335 (30.5), 272 (62.9), 256 (54.4), 196 (100), 106 (25.2).

2-[(2-Bromoethyl)thio]-1-phenylethylamine Hydrobromide. A solution of 2-phenylaziridine[6] (1.19 g, 10 mmol) and 2-mercaptoethanol (3.14 g, 40 mmol) in 40 mL of methanol was heated under reflux for 48 h. The solvent was removed in vacuo, the residue was dissolved in 15 mL of methanol, and the solution acidified with 48% hydrobromic acid to pH 2.0. Dichloromethane (20 mL) was added, and the precipitate was collected and washed with hexane to remove excess of 2-mercaptoethanol. The pure isomer 2-[(2-hydroxyethyl)thio]-1-phenylethylamine was obtained by column chromatography (silica gel, 10% methanol in ethyl acetate 0.554 g (56% yield), mp 56–60 °C: ^{1}H NMR (Me_2SO-d_6) δ 2.8–3.1 (m, 4 H, CH_2SCH_2), 3.3–3.4 (br, 1 H, exch OH), 3.45–3.5 (m, 2 H, CH_2O), 5.4 (m, 1 H, CHPh), 7.3–7.4 (m, 5 H, Ar), 8.02–8.1 (br, 3 H, exch NH_3^+).

A solution of the above compound (0.554 g, 2 mmol) in 25 mL of dry CH_2Cl_2 at –10 °C was treated with thionyl bromide (0.52 g, 2.5 mmol). The mixture was then stirred for 15 h at room temperature. The solvent was removed in vacuo, and the crude material was recrystallized from a $CHCl_3$/MeOH mixture to provide the pure bromo compound as a yellow solid 0.49 g (59%

yield), mp 139–142 °C: ^{1}H NMR (Me_2SO-d_6) δ 3.1 (m, 2 H, SCH_2), 3.6–3.8 (m, 4 H, SCH_2CH_2Br), 5.4 (m, 1 H, CHPh), 7.4–7.6 (m, 5 H, Ar), 8.35 (br, 3 H, exch, NH^+_3); IR (Nujol) ν_{max} 2960 cm^{-1} (NH_3); CIMS (NH_3), m/z (rel intensity) 262 [(MH + 2) – HBr], 260 (MH^+ – HBr).

2-[(2-Bromoethyl)sulfinyl]-1-phenylethylamine Hydrobromide. A stirred solution of 1-phenyl-2-[(2-bromoethyl)-thio]ethylamine hydrobromide (0.339 g, 1 mmol) in 2 mL of dry methanol was treated with a solution of 30% H_2O_2 (0.226 g, 2 mmol). The mixture was then stirred for 48 h. The solvent was removed in vacuo, and the crude material was recrystallized from chloroform to give the pure product as a yellow crystalline solid 0.3 g (84% yield), mp 96–100 °C: ^{1}H NMR ($CDCl_3$) δ 2.9–3.2 (m, 6 H, $CH_2SOCH_2CH_2Br$), 5.1 (m, 1 H, $CHPh(CH_2)$, 7.1 (m, 5 H, Ph), 8.1 (s, 3 H, exch $NH_3^+Br^-$); IR (Nujol) ν_{max} 1040 (s), 2912–3029 cm^{-1} ($NH_3^+Br^-$); MS, m/z (rel intensity) 196 (M^+ – HBr – Br).

General Procedure for Analysis of Aqueous Decomposition Products of Sulfinylnitrosoureas in Buffer or from Diazotization Reactions. Solutions of the sulfinylnitrosoureas ~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. In the case of the amino precursors diazotization was carried out at 0 °C. At intervals samples of the gaseous fractions were withdrawn with a hypodermic syringe and analyzed by GC HP-5890 and the Hewlett-Packard GCMS with mass selective detector Model 5920 as described previously. Similar reaction conditions were employed but in the presence of 5 molar equiv of sodium bromide or sodium chloride where appropriate in the control reactions examining for possible halide exchange.

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Six-Membered Ring-Fused Thiirene *S*-Oxides. Synthesis, Characterization, and Reactivity

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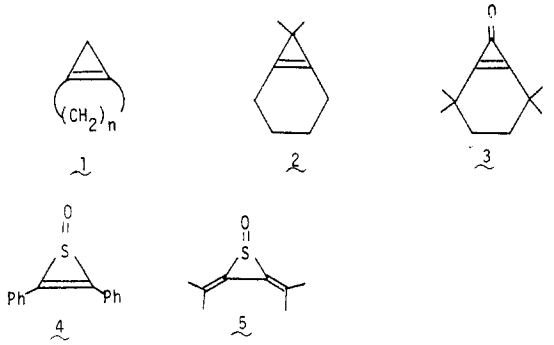
Alkyl-substituted thiirene *S*-oxides fused to six-membered rings have been synthesized by [2 + 4] cycloaddition of thiiranoradialene *S*-oxide with 4-substituted-1,2,4-triazoline-3,5-diones and to singlet oxygen. The fused thiirene *S*-oxides reacted with methanol or *p*-nitrophenyl isonitrile to afford products resulting from C–S bond cleavage. The distorted π-bond of a thiirene *S*-oxide released its strain in a cycloaddition with furan to yield a propellane thiirene *S*-oxide.

The bicyclo[*n*.1.0] olefin system **1** is of interest because of its unusual electron system.[1,2] The two reported examples of this system in which $n = 4$ are the annelated cyclopropene **2**, which has been observed only below –35 °C,[2a] and cyclopropenone **3**,[2n] which has been isolated.



1 2 3 4 5

There are no reports of this system in which $n < 4$, and the six-membered ring may be the lower limit for a cyclopropene fused to another ring.

Diphenylthiirene *S*-oxide (**4**) has been prepared by a modified Ramberg–Backlund reaction of bis(bromobenzyl) sulfone with triethylamine,[3] but alkyl-substituted thiirene *S*-oxides have not been reported. Recently, the authors synthesized the first hetero[3]radialene, thiiranoradialene *S*-oxide (**5**).[4] Although there has been considerable study of [2 + 4] cycloadditions of radialenes with dienophiles as a route to fused ring systems, no successful example is reported for [3]radialene[5] or its analogues.[6] This cycloaddition would provide a route to the highly strained bicyclo[4.1.0] olefins with a double bond at the bridge. We here describe the synthesis and properties of some six-membered ring-fused thiirene *S*-oxides.

Results and Discussion

Synthesis of Fused Thiirene *S*-Oxides. When **5** was treated with an equimolar amount of 4-methyl-1,2,4-triazoline-3,5-dione (MTAD) in CH_2Cl_2 at room temperature, the red color of MTAD rapidly disappeared and a single product **6a** was obtained as colorless crystals in quantitative yield.[7] Likewise, **5** added to 4-phenyl-1,2,4-triazo-

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