Thiono Compounds. 1. Interactions of Monoatomic Sulfur, Including Insertion into S–H Bonds

Lamar Field,* J. Valerie Ravan,[1,2] John D. Dunkel,[2] John A. Waites,[2] and David W. White[2]

Department of Chemistry, Vanderbilt University, Nashville, Tennessee 37235

Norman E. Heimer

Department of Chemistry, University of Mississippi, University, Mississippi 38677

Robert A. Neal

Center in Environmental Toxicology, Department of Biochemistry, Vanderbilt University School of Medicine, Nashville, Tennessee 37232

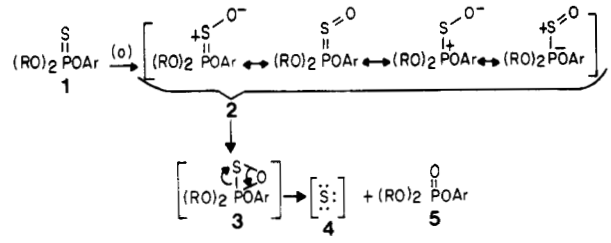
Received June 29, 1982

Possible traps for monoatomic sulfur were assessed by determining the reduction in yields of cyclohexanethiol (6) when carbonyl sulfide was photolyzed in cyclohexane containing the potential trap; the identity of 6 was confirmed by GC/MS and other means. Reduction of the yield of 6 by benzene, triethylamine, acetic acid, acetonitrile, and ethanol indicates undesirability of lone pair and π systems in the assessment procedure. In order of promise as traps, compounds tested were n-Bu_3SnH > $(n$-$C_5H_{11}S)_2 \approx$ RSH > $(EtO)_3SiH$ > $Et_3SiH \approx$ cyclohexane. Insertion of sulfur was demonstrated with two thiols, chosen as members of one of the most promising classes, by identity with authentic samples of derivatives of the hydrodisulfides generated; this result points to the chemical feasibility of postulated insertions of monoatomic sulfur in biological reactions and also suggests promise of the other potential traps for further study.

Many widely used compounds with thione functions (=S) exhibit toxic properties (induction of neoplasia, bone-marrow depression, damage to liver or lung tissue, and inhibition of certain enzymes).[3] Among the most studied is the insecticide parathion (1), which inhibits cytochrome P-450,[3] an enzyme that modifies xenobiotics. This inhibition is attributed to attack by monoatomic sulfur (4), formed as shown in Scheme I.[3] Scheme I also was invoked for peroxy acid models, the sequence being formation of an *S*-oxide (2), closure to a phosphoxathiirane (3), and loss of monoatomic sulfur (4) to give paraoxon (5).[3] With a cytochrome P-450 system and 1 in vitro, sulfur (4) was shown to bind to the cytochrome P-450 molecule by double labeling experiments with ^{35}S and ^{14}C, with relatively little binding of ^{14}C; similar results were obtained with liver microsomes and 1 labeled with ^{35}S and ^{32}P.[3] That 4 reacted as singlet sulfur, $S(^1D)$, was concluded from subsequent release of SCN^- by CN^-, which indicated that part of the sulfur was bound to cytochrome P-450 as a hydrodisulfide (RSSH), formed through insertion of $S(^1D)$ into the S–H bond of a cysteine residue in the cytochrome P-450 molecule.

Much has been learned about monoatomic sulfur in the gas phase,[4] but little has been reported about reactions in solution.[4b,5] The biologically relevant states of monoatomic sulfur are the singlet and the triplet, $S(^3P)$. Both add to alkenes to give episulfides, but only $S(^1D)$ inserts into C–H bonds.[4a] To explore the biological relevance of monoatomic sulfur, we sought traps that by lack of effect in reactions of interest would argue against participation of monoatomic sulfur, while involvement would point to (although not prove) its participation. Thiols were of special interest, since failure of monoatomic sulfur (generated by known means) to insert in the SH group would argue against chemical feasibility of the insertion proposed for cytochrome P-450, while occurrence of insertion would support it. This paper describes a procedure for assessing possibilities as traps (and interferences from functional groups), establishes that with thiols as traps insertion of sulfur does indeed occur to give hydrodisulfides, and suggests by inference that several other compounds compared with thiols also are promising as traps.

Scheme I[a]



[a] R = Et; Ar = 4-O_2NPh.

Elegant work by Gollnick, Leppin, and Schomburg provided a good basis for the desired generation of $S(^1D)$ in solution by photolysis of carbonyl sulfide (COS) in cyclohexane.[5a,b,g] Since these authors reported insertion of $S(^1D)$ into cyclohexane to give cyclohexanethiol (6, eq 1),[5a,b,g] cyclohexane seemed a suitable reference material

$$C_6H_{12} + COS \xrightarrow{h\nu} \underset{6}{C_6H_{11}SH} + CO \qquad (1)$$

against which potential traps could compete. They concluded that photolysis of a saturated solution of COS in cyclohexane gives 6 from gas chromatographic (GC) retention times (only), and we therefore confirmed their conclusion by GC peak enhancement with authentic 6 and

(1) Stephen Harris Cook Memorial Fellow, Summer, 1981.
(2) Undergraduate research program, Vanderbilt University.
(3) Neal, R. A. *Rev. Biochem. Toxicol.* **1980**, *2*, 131–171.
(4) (a) For the latest of several reviews, see Strausz, O. P. In "Sulfur in Organic and Inorganic Chemistry"; Senning, A., Ed.; Marcel Dekker: New York, 1972; Vol. 2, pp 1–12. (b) For the most complete review, see Gunning, H. E.; Strausz, O. P. *Adv. Photochem.* **1966**, *4*, 143–194.
(5) (a) Gollnick, K.; Leppin, E. *J. Am. Chem. Soc.* **1970**, *92*, 2217. (b) Leppin, E.; Gollnick, K. *Ibid.* **1970**, *92*, 2221. (c) Leppin, E.; Gollnick, K. *Chem. Ber.* **1970**, *103*, 2571. (d) Luria, M.; Treinin, A. *J. Phys. Chem.* **1968**, *72*, 305. (e) Sato, S.; Miyamoto, H.; Hirokami, S.; Tsunashima, S. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 754. (f) Sidhu, K. S.; Csizmadia, I. G.; Strausz, O. P.; Gunning, H. E. *J. Am. Chem. Soc.* **1966**, *88*, 2412. (g) Leppin, E.; Gollnick, K.; Schomburg, G. *Chromatographia* **1969**, *2*, 535.

0022-3263/82/1947-4651$01.25/0

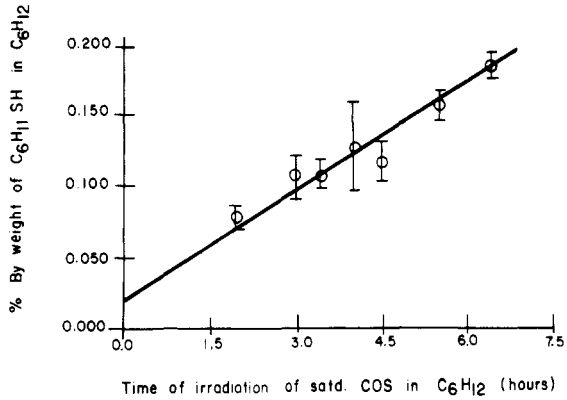


Figure 1. Percent by weight of cyclohexanethiol in cyclohexane after photolysis of saturated solutions of COS in cyclohexane (least-squares plot; standard deviations shown by vertical lines; correlation coefficient 0.969).

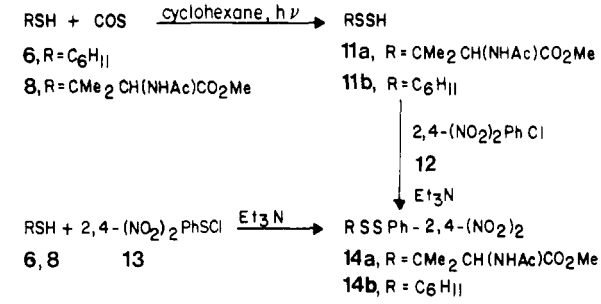
by identity of GC mass spectra of the product and **6** (as well as by evidence described below developed in other connections).

In order to determine the optimum time of photolysis, we investigated several methods as analyses for **6**. When the photolyzed solution was shaken with aqueous KI_3 and back titrated with thiosulfate, the identity of the product was confirmed as a thiol, but this method was quantitatively unpromising. When the solution was shaken with aqueous $Hg(CN)_2$, a TLC spot resulted that was consistent with that of the authentic mercuric thiolate of **6**; however, use of $Hg(CN)_2$ was unsatisfactory as a gravimetric method. A GC method proved satisfactory, on the other hand, with Ellman's method for thiols as a check.[6] Values for **6** by the GC and Ellman methods agreed reasonably (although conceivably either value may reflect a little hydrodisulfide that decomposed on GC columns to **6**).

Figure 1 shows a plot of the mean of GC and Ellman analyses for the weight percent of **6** produced in cyclohexane as a function of the time of photolysis. The mean of the standard deviations was ca. 11%, indicating that the method should point usefully to traps that can effect the marked reductions in **6** desired of much better competitors than cyclohexane for $S(^1D)$. The optimum time of photolysis appeared to be 6 h (after ca. 6.5 h, values deviated from linearity). Reasonable reliability was confirmed by agreement of predicted (Figure 1) and found values for the weight percent of **6** of 0.178 and 0.185%, respectively, after 6 h of photolysis. In later work, as the intensity of the UV sources decreased it was necessary to extend the time of photolysis by the ratio of the original and new intensities. The overall range of values for the weight percent of **6** after 6 h (or the appropriate prorated time) was 0.125–0.187%.

In the hope of circumventing sparing solubility of certain potential traps in cyclohexane, as well as for a guideline to groups that would be unsuitable in traps, we assessed the effects of a 1:5 molar ratio of possible cosolvent to cyclohexane. Yields of **6** were reduced 8% by ethanol, 44% by acetonitrile, 56% by acetic acid, and 100% by triethylamine; at only 1 mol %, benzene led to 63% reduction and triethylamine to 40–46% reduction. These results are consistent with earlier ones where ethanol, acetonitrile, and benzene were used neat and where the effects were attributed to catalysis of the change of $S(^1D)$ to $S(^3P)$,[5a,b,7] "probably by charge-transfer interactions".[5a] Acetone also reduced the yield but by a quantitatively uncertain amount. DMF and HMPA proved too sparingly soluble in cyclohexane to be useful cosolvents.

Scheme II



The potential of compounds as traps was assessed by introducing 1 mol % into cyclohexane before saturation with COS and photolysis. Beforehand, to assure stability, potential traps were exposed to COS alone and to UV alone under otherwise usual conditions. Changes in IR spectra with COS alone ruled out 9-borabicyclo[3.3.1]nonane and mercuric bis(cyclohexanethiolate), and changes with UV alone ruled out 1-adamantanethiol and 1,3-dithiane. Several other possibilities proved to be too sparingly soluble in cyclohexane to warrant trial: methimazole, hexamethylenetetramine, tosylmethyl isocyanide, and Me_2SO. The reduction in weight percent of **6** by the possible traps remaining then showed the following order of relative effectiveness (with percent reduction from duplicate experiments in parentheses): tri-*n*-butylstannane (**7**; 83, 83) > di-*n*-pentyl disulfide (47–58) ≈ methyl 2-

n-Bu_3SnH (**7**) $HSCMe_2CH(NHAc)CO_2Me$ (**8**)

$(EtO)_3SiH$ (**9**) Et_3SiH (**10**)

acetamido-3-mercapto-3-methylbutanoate (**8**; 47, 53; at 0.3–0.4 mol % in saturated solution) > triethoxysilane (**9**; 18, 35) > triethylsilane (**10**; 0, 0) ≈ cyclohexane. Whether the reductions by **7** and **9** resulted from deactivation of $S(^1D)$ to $S(^3P)$ rather than competitive insertion was not established, although competitive insertion is the probable explanation, since a "crude estimate of the relative rates for Si–H to C–H insertion gives a value of ca. 50 per bond"[4b] and since C, Si, and Sn seem likely to show behavior common to the same periodic group.

The postulated insertion of $S(^1D)$ into the S–H bond of cytochrome P-450 discussed above lent special interest to determining whether insertion into the S–H bond of thiol traps does indeed occur (Scheme II). Additional interest lay in the fact that sulfur is not in the periodic group with C, Si, and Sn. For this study, **8** affords a carboxy-blocked *N*-acylcysteine as a model for the cysteine moiety that presumably is the trap for monoatomic sulfur in cytochrome P-450; we have already reported the synthesis of the expected insertion product (**11a**) and a derivative of it (**14a**).[8] A saturated solution of **8** in cyclohexane therefore was saturated with COS and then irradiated (Scheme II). The product **11a**, mixed with considerable residual **8** (NMR), was converted to the 2,4-dinitrophenyl disulfide **14a**. This **14a** had the same TLC R_f value as authentic **14a**, obtained from the thiol **8** by using the sulfenyl chloride **13** (Scheme II),[8] and was separated by preparative TLC (other TLC fractions appeared to be **6**, **8**, and the trisulfide corresponding to **8**; a little material insoluble in the TLC solvent appeared to be sulfur). Identity of the isolated and authentic samples of **14a** was

(6) Ellman, G. L. *Arch. Biochem. Biophys.* **1959**, *82*, 70.
(7) Leppin, E.; Gollnick, K. *J. Am. Chem. Soc.* **1971**, *93*, 2848.
(8) Heimer, N. E.; Field, L.; Neal, R. A. *J. Org. Chem.* **1981**, *46*, 1374.

shown by comparison of R_f values, melting point/mixture melting point, and IR spectra; the sulfide from the reaction of **8** and **12** differed significantly from **14a** in IR spectrum and melting point (256–259 °C vs. 161–163 °C for **14a**). A duplicate experiment gave the same result, in contrast to a control experiment with omission of COS that gave no indication whatever of **14a**.

Insertion of sulfur into the S–H bond of **6** also was demonstrated, by reaction with **12** of the hydrodisulfide **11b** produced along with the thiol **6** when COS was irradiated in cyclohexane. The unsymmetrical disulfide derivative was shown to be **14b**.[9]

The possibility that the insertion leading to **11b**, as well as to **11a**, involved monoatomic sulfur in the form of $S(^3P)$ rather than of $S(^1D)$ cannot be dismissed at this point, although it seems unlikely. Also, the suggestion of a reviewer that some form of elemental sulfur photochemically generated may have contributed to the conversion of the thiols to the hydrodisulfides cannot be dismissed nor, indeed, can possible involvement of intermediates (e.g., S_2, discussed in ref 5a). Of course, such processes might intervene biologically as well. With respect to the use of thiols for assessing possible participation of monoatomic sulfur (and related species mentioned) in a reaction, *lack* of the effects discussed should afford useful evidence for *lack* of participation. The same can be said of the other compounds that reduced the conversion of cyclohexane to **6** [n-Bu_3SnH, $(n$-$C_5H_{11}S)_2$, and R_3SiH], although these probably should be considered only promising as traps until studied further.

The SH insertions that produced **11a** and **11b** are consistent with chemical feasibility of the proposed insertion of a monoatomic form of sulfur into an S–H bond of cytochrome P-450. Whether such a reaction in fact accounts for the entry of sulfur into cytochrome P-450 in the biotransformation of compounds like parathion (**1**) remains to be seen.

Experimental Section

Melting points are corrected and were determined with a Thomas-Hoover stirred-liquid apparatus or with a Köfler hot-stage micro melting point apparatus (so specified). IR spectra were obtained by using NaCl plates or KBr pellets with a Perkin-Elmer 727 spectrometer, GC/MS results were obtained with a Hewlett-Packard Model 5985 mass spectrometer (1-m column of 12% OV-101 on Gas Chrom Q), and NMR spectra were obtained with a JEOL JNM-MH-100 spectrometer using Me_4Si as an internal standard. Solvents were removed under reduced pressure using a rotary-flask evaporator. Qualitative TLC was done with Eastman Chromagram sheets of Type 13181 silica gel, and preparative TLC was done with Whatman PLK5F linear-K precoated silica gel (80 Å) plates.

Gas chromatography was done principally using a Shimadzu Model 3-PF flame-ionization detector instrument with a 6-ft glass column packed with 9.25% Apiezon-L on 45–60 mesh Chromosorb P; temperature of column, 140 °C; injection port ca. 200 °C; He carrier gas, flow rate, 23 mL/min. Before each series of uses, the septum was changed, and the column was purged for at least 24 h at a He pressure of ca 2 psi. Early work was done with a Carle Basic Model 9500 flame-ionization detector chromatograph using a 9-ft stainless-steel column and 5% SE30 on Gas Chrom Q (80–100 mesh; SE30 was superior for separating **6** to DC 500, Carbowax, or Chromosorb 101); He carrier-gas flow, 40 mL/min; column temperature normally 132 °C.

Cyclohexane (purchased in large amount of the same lot number) and dodecane were Aldrich Spectrograde. COS (Matheson) was used from lecture bottles within about a year. Methyl 2-acetamido-3-mercapto-3-methylbutanoate (**8**)[8] and 1-adamantanethiol (mp 99–101 °C; lit.[10] mp 102–104 °C) were prepared as reported. Tri-n-butylstannane was kindly provided by Dr. T. L. Macdonald and N. Narasimhan. All other materials were best commercial grades.

Photolysis of Carbonyl Sulfide (COS) in Cyclohexane. (a) Procedures. Photolyses were carried out in cyclohexane containing dodecane as a GC standard (99 g/1 g) using a Hanovia 100-W low-pressure Hg arc lamp, which was lighted 20 min before photolysis; the peak lamp output reportedly was at ca. 2537 Å, one of the absorbance peaks for COS. UV intensity was monitored with a Blak-Ray UV meter, Model J-225 (Ultra-violet Products, Inc.); where necessary, the time of photolysis was prorated to 6 h at a (frequent) lamp intensity of 19 $\mu W \times 100/cm^2$ at 20-cm distance [e.g., with a lamp at 8–13 $\mu W \times 100/cm^2$, the time was $19/(8–13) \times 6$ h]. For each photolysis, 25 mL of the stock solution in a 25-mL quartz flask was purged and saturated by passing COS during 5 min of vigorous bubbling from a sparger (the concentration of a saturated solution of COS in cyclohexane at 25 °C is 0.684 M; ref 5a). The flask was sealed with a wired-on septum cap and placed 5-cm from the UV lamp (front of lamp to front of flask). The solution was slowly stirred magnetically during photolysis and was kept at ca. 20–25 °C by a stream of air passed through Tygon tubing immersed in ice (rapid stirring causes undue loss of COS). After 6 h (or other appropriate periods for Figure 1), aliquots were removed and kept tightly stoppered at 0 °C until analyzed. The weight percent of **6** in photolyzed reaction mixtures was determined after a 1-μL GC injection by comparing the ratio of the peak area (triangulation) of **6**/dodecane with a standard plot of this ratio vs. weight percent of **6**; the standard plot was prepared by using appropriate weights of **6** with 1 g of dodecane and enough cyclohexane to make 100 g and was linear up to ca. 1 wt % of **6**. In the GC analyses for **6** after photolysis, no dodecanethiol was detected. For the Ellman analysis,[6] a 0.01 M solution of Ellman's reagent in pH 7.0 phosphate buffer (μ = 0.1) was used. The reaction mixture comprised 3 mL of pH 8.0 phosphate buffer, 6.8 mL of deionized H_2O, 200 μL of the solution of reagent, and 10 μL of sample; the small sample size obviated the need for phase-separation techniques. The mixture was shaken for ca. 5 min until a yellow color fully developed, after which the absorbance was read at 412 nm (Bausch and Lomb Spectronic 20 spectrophotometer) by using an identical blank, except for the 10-μL sample. Absorbance was correlated with the weight percent of **6** by using a plot based on the usual standard mixtures of **6** in cyclohexane–dodecane. To obtain Figure 1, we plotted the means of mean values of the weight percent of **6** by GC and Ellman analysis from three experiments vs. time of irradiation.

(b) Results. In confirmation of the identity of **6**, two GC peaks that resulted after the photolysis of COS in cyclohexane had retention times of 1.3 and 1.9 min; comparison with a 1% standard of **6** in cyclohexane identified these as cyclohexane and **6** (retention times 1.3 and 1.9 min, respectively); pure **6** enhanced the 1.9-min peak. For further confirmation, a typical product was subjected to GC/MS (injection at 80 °C, programmed for 8 °C/min to 210 °C; He flow, 20 mL/min). After cyclohexane, **6** was identified at a retention time of 8.6 min by comparison with the mass spectrum of authentic **6**.

Assessment of Interferences and of Potential Traps. In order to learn whether MeCN, EtOH, AcOH, and benzene could be used as cosolvents, we saturated a mixture of 1 molar proportion to 5 of cyclohexane (containing dodecane) with COS, photolyzed it for the appropriate time, and then analyzed it as described under (a) above. The percent reduction was determined as for traps (see below); results are given in previous paragraphs. Et_3N also was studied, to assess its lone-pair effect. AcOH was removed before GC analysis by washing with aqueous $NaHCO_3$, and Et_3N was removed by washing with aqueous HCl.

In assessing potential traps, stability of the compounds to COS alone and UV alone under the otherwise standard procedure of (a) above first was established by lack of change in the IR spectra; stability of **7** also was checked by TLC and NMR. With stable compounds, the procedure of (a) then was followed, except that 1 mol % (except for **8**), based on cyclohexane, of the compound was introduced before passage of COS. At the end of the standard

(9) Tanner, D. D.; Brownlee, B. G. *Can. J. Chem.* **1973**, *51*, 3366.

(10) Khullar, K. K.; Bauer, L. *J. Org. Chem.* **1971**, *36*, 3039.

period, GC was used to determine the weight percent of 6 present and the percent reduction reported above was calculated as 100 - [weight percent of 6 (from plot) with the trap present] × 100/[weight percent of 6 (plot) in the absence of the trap]. The maximal concentration of 8 was 0.3–0.4 mol % rather than the usual 1 mol %; some variation in results is attributable to crystallization from the (still supersaturated) solution prepared by dissolving 8, allowing the solution to cool briefly, and decanting from solid 8.

Insertion of Monoatomic Sulfur into Methyl 2-Acetamido-3-mercapto-3-methylbutanoate (8) and Isolation of Methyl 2-Acetamido-3-[(2,4-dinitrophenyl)dithio]-3-methylbutanoate (14a). A solution of 1.00 g of 8 prepared at ca. 85 °C in 100 mL of cyclohexane (containing dodecane) was allowed to cool briefly until 8 that crystallized had settled, and the solution then was decanted from the 8; ca. 80% (ca. 0.8 g, 4 mmol, 0.4 mol %) remained in solution. COS was bubbled into the solution in a quartz flask as usual for 5 min, and the solution then was irradiated for 6 h (UV intensity measure, 8.4 μW × 100/cm²). Since a previous experiment showed that standing after photolysis for 1–2 days led to polysulfides corresponding to 8 (R_f 0.4, EtOAc), a characteristic of the hydrodisulfide **11a**,[8] cyclohexane was removed under reduced pressure without heat, and the residue was dissolved in 12 mL of MeOH containing 100 μL of Et_3N and 100 mg of **12**. After 30 min, 2 drops of HCl were added to neutralize the amine (light yellow crystals appeared), and the mixture was concentrated to dryness under reduced pressure. The residue was dissolved in a minimum of EtOAc (a little precipitate appeared to be sulfur), and the solution was filtered and subjected to preparative TLC using 6:4 acetone–petroleum ether. The band of **14a**, identified by its previously established position as the middle of three bands, was removed and extracted with EtOAc. Removal of the EtOAc yielded a yellow-orange oil, which was suspended in Et_2O at 0 °C overnight. Yellow crystals that appeared were recrystallized (twice) to constant melting point from EtOAc to give 12 mg of **14a** (also 12 mg, with the same properties, in a confirming experiment). In comparisons of this **14a** with authentic **14a**,[8] IR spectra were congruent, melting points and mixture melting points were identical (161–163 °C, Köfler; lit.[8] mp 161–163 °C), and R_f values (Eastman 13181) were the same in either EtOAc (R_f 0.63) or $CHCl_3$ (R_f 0.28). In a control experiment where UV only was omitted, no **14a** whatever could be detected.

Insertion of Monoatomic Sulfur into Cyclohexane and Isolation of 1-(Cyclohexyldithio)-2,4-dinitrobenzene (14b). After photolysis of 25 mL of standard cyclohexane (dodecane) with COS as usual, except that the solution from the trapping experiment with **10** is referred to (**10** having been shown to have a negligible effect), cyclohexane was removed under reduced pressure. The residual oil was dissolved in MeOH, and **12** (100 mg) was added, followed by 50 μL of Et_3N. After 1 h, TLC (1:9 EtOAc–pentane) showed a spot with R_f 0.55, the same as that of authentic **14b**. Cyclohexane was removed under reduced pressure, and the residue was separated by preparative TLC to give 8 mg of **14b**. This **14b** had the same R_f value and mp (109–112 °C) as authentic **14b** (mp 113.5–114.5 °C), which was prepared from cyclohexanethiol and the sulfenyl chloride **13** (lit.[9] mp 114.5–115.5 °C).[9] The melting point of this **14b** was undepressed by the authentic **14b**, and IR spectra of the two were congruent ($CHCl_3$, 1-mm cell).

Acknowledgment. This investigation was supported by PHS Grant ES 00267 to the Center in Environmental Toxicology in the School of Medicine, Vanderbilt University, awarded by the National Institute of Environmental Health Sciences, DHHS, and in the latter phases by PHS Grant CA 30321, awarded by the National Cancer Institute, DHHS. We thank D. E. Pearson, J. B. Tellinghuisen, and E. Dawson for helpful conversations.

Registry No. 6, 1569-69-3; 7, 688-73-3; 8, 39239-85-5; 9, 998-30-1; 10, 617-86-7; 11a, 83151-19-3; 11b, 83115-77-9; 12, 97-00-7; 14a, 76480-13-2; 14b, 51245-66-0; C_6H_{12}, 110-82-7; COS, 463-58-1; monoatomic sulfur, 7704-34-9.

Reaction of 1-Bromoadamantane with Diphenylphosphide and Diphenylarsenide Ions by the $S_{RN}1$ Mechanism. Facile Nucleophilic Substitution at the Bridgehead Position[1]

Roberto A. Rossi,* Sara M. Palacios, and Ana N. Santiago

Departamento de Quimica Orgânica, Facultad de Ciencias Quimicas Universidad Nacional de Côrdoba, Est 32, 5000 Côrdoba, Argentina

Received December 11, 1981

The photostimulated reaction of 1-bromoadamantane (**1**) with diphenylphosphide (**2**) and diphenylarsenide (**6**) ions in liquid ammonia afforded good yields of the substitution products, together with small amounts of adamantane (**4**) and 1,1′-biadamantyl (**5**) as byproducts. The reaction of **1** with **2** in the dark did not occur, but stimulation with solvated electrons gives a small amount of the substitution product and **5**, with a large amount of **4**. The photostimulated reaction of **1** with **2** is inhibited by *p*-dinitrobenzene and di-*tert*-butyl nitroxide. All these results suggest that these reactions occur by the $S_{RN}1$ mechanism of substitution, where radical and radical anions are intermediates.

It is well-known that 1-halosubstituted bridgehead compounds are very unreactive toward nucleophilic substitution reactions. The low reactivity shown in S_N1 reactions was attributed to the strain arising from the formation of a carbonium ion at the bridgehead position. The structure of the bicyclic system precludes adoption of a planar geometry around the cationic carbon and requires a great activation energy for the ionization step. The S_N2 mechanism is also precluded because the direct displacement of the halogen atom with inversion of configuration is impossible.[2]

Different adamantyl intermediates have been suggested in nucleophilic substitution reactions such as ion pairs,[3] radical anions,[4] or simply radicals.[5] There is also a report

(1) Research supported in part by the Consejo Nacional de Investigaciones Cientificas y Tecnicas and the Subsecretaria de Ciencia y Tecnologia, Argentina. Presented in part at the Segunda Reunión Argentina de Fisico Quimica Orgânica, Villa Giardino, 1981.

(2) See, for example: Barlett, P. B.; Knox, L. H. *J. Am. Chem. Soc.* **1939**, *61*, 3184. Schleyer, P. v. R.; Nicholas, R. D. *Ibid.* **1961**, *83*, 2700.
(3) Perkins, R. R.; Pincock, R. E. *Tetrahedron Lett.* **1975**, 943; Takeuchi, K.; Kato, Y.; Moriyama, T.; Okamoso, K. *Chem. Lett.* **1981**, 935.

0022-3263/82/1947-4654$01.25/0