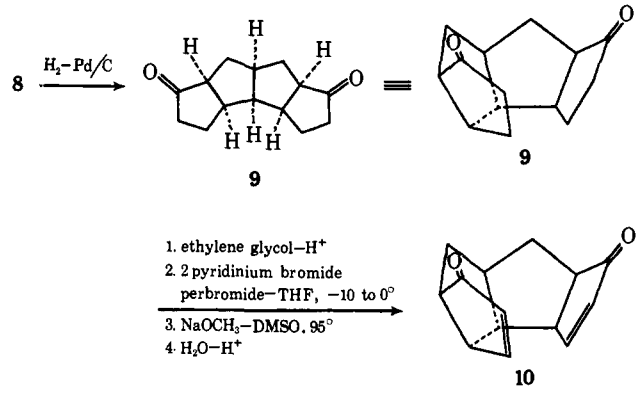
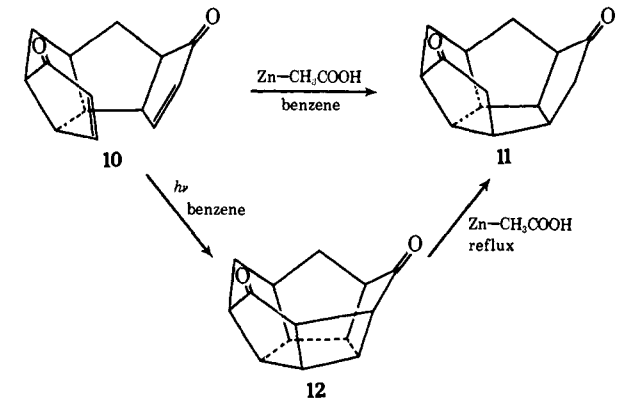
Chart III

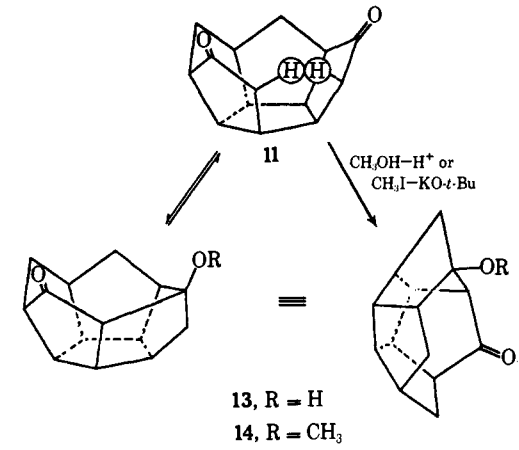


λ max 228 (ε 13,000) and 321 mμ (110);[14] nmr ($CDCl_3$) δ 7.85 (2 H, d of d, J = 6 and 3 Hz, HC=C–C=O), 6.03 (2 H, d of d, J = 6 and 2 Hz, C=CH–C=O), 3.7 (2 H, m), 2.9 (4 H, m), 1.9 (2 H, m), and 1.4 ppm (2 H, m). Catalytic hydrogenation of **10** regenerates **9** cleanly; thus both compounds have the same configuration at the central ring fusion.

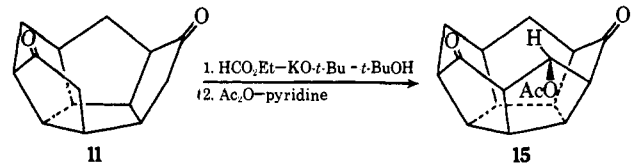
Trans-skeletal reductive coupling within **10** is brought about by treatment with zinc and acetic acid.[15] Although this is the most direct method for the conversion of **10** to **11**, for practical reasons the transformation is better carried out instead by way of photochemical closure[16] of **10** to the norperistylane **12** (90%; mp >260° dec; ir (CCl_4) λ 5.79 μ) and subsequent reductive cleavage of **12** to **11** (85%) with zinc in refluxing acetic acid.[17]



Numerous recrystallizations of **11** fail to improve its indistinct melting point (210–226° dec) or change its spectral properties [ir (CCl_4) λ 2.98 and 5.79 μ; nmr ($CDCl_3$) hydroxyl proton (exchangeable, position concentration dependent), no absorption attributable to hydrogen on carbon-bearing oxygen]. Apparently diketone **11** equilibrates readily with the isomeric hydroxy ketone **13**, the product of internal aldol cyclization. In a related process, probably *via* an intermediate hemiketal, reaction of **11** with acidic methanol gives cleanly the methoxy ketone **14**: mp 68.5–69.5°; ir (CCl_4) 5.79 μ, no hydroxyl absorption; nmr ($CDCl_3$) δ 3.33 ppm (3 H, s), no other low-field absorption. The same methoxy ketone is produced on treatment of **11** with methyl iodide and base. The driving force for these closures (to a norbornane derivative) must certainly derive from relief of crowding of the inside methylene hydrogens α to the carbonyl functions of **11**.



Completion of the synthesis of the peristylane system from **11** requires introduction of the fifteenth carbon atom and closure of the sixth ring. Both are accomplished by treating **11** with ethyl formate in *tert*-butyl alcohol containing potassium *tert*-butoxide. The hydroxyperistylane so formed is not isolated as such but is taken on directly to the corresponding acetate **15**:



mp 169–173° dec with loss of acetic acid; ir (CCl_4) λ 5.74 and 8.15 μ; nmr ($CDCl_3$) δ 5.70 (1 H, singlet, 2.5 Hz wide at half-height) and 2.02 (3 H, s). The spin coupling (*ca.* 1 Hz) of the proton on carbon-bearing acetate to the vicinal protons indicates a dihedral angle between them of about 100° and leads to the assignment of configuration shown.

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(14) *Cf. cis*-bicyclo[3.3.0]oct-2-en-4-one: ir ($CHCl_3$) λ 5.87 and 6.29 μ; uv (95% EtOH) λ max 224 (ε 11,400) and 319 mμ (40).

(15) See J. Wiemann, P.-F. Casals, and S. Risse (*Bull. Soc. Chim. Fr.*, 1281 (1963)) for examples of intermolecular reductive coupling of enone systems.

(16) P. E. Eaton, *Accounts Chem. Res.*, 1, 50 (1968).

(17) For another example of a cleavage of this sort, see E. Wenkert and J. E. Yoder, *J. Org. Chem.*, 35, 2986 (1970).

Photochemistry of Disulfides. I. Carbon–Sulfur Cleavage in the Photosensitized Decomposition of Simple Disulfides

Sir:

There is clear evidence that cystine residues are primary targets in the photochemical inactivation of enzymes.[1] In addition, the photochemistry of some

(1) Reviews: K. C. Smith and P. C. Hanawalt, "Molecular Photo-

proteins and peptides involves energy transfer from tyrosyl and tryptophanyl to cystyl.[1,2] A complete analysis of these photobiological problems is inhibited by the gaps in our understanding of the fundamental details of the photochemistry of disulfides. Previous studies of simple systems have emphasized the direct photolysis (254 nm) and the formation of thiyl radicals by S–S bond cleavage.[3] Quantum yields for S–S cleavage in the liquid phase are not known. The use of radical scavengers in the gas phase gives a quantum yield of about 1.4 for the formation of thiyl radicals[4] from methyl disulfide. Carbon–sulfur cleavage is also recognized,[5] but the quantitative significance of this process has been studied only in the gas phase;[6] a quantum yield for C–S cleavage of 0.1 to 0.3 has been reported for methyl disulfide.[6b] Photosensitized decompositions of simple disulfides are reported only for aromatic hydrocarbons[7] and Hg($^3P_1$) as sensitizers.[8]

We report that the photodecomposition of simple disulfides can be effected with a variety of typical organic photosensitizers. A system for the quantitative determination of C–S cleavage is developed and C–S cleavage is shown to be an important process for some disulfides.

The benzophenone sensitized photolysis of *tert*-butyl disulfide in deoxygenated benzene was studied in detail; photolysis gives isobutane, isobutene, and *tert*-butyl tri- and tetrasulfides.[9] Benzophenone is not consumed. The ratios of disulfide lost to isobutane (~2.5) and isobutene (~2.7) formed at *low* conversions[10] are compatible with eq 1 and 2 as the major pathways for the formation of products.[11] The perthiyl radicals, *tert*-$C_4H_9S_2\cdot$, apparently combine to give the observed tetrasulfide.

$$(t\text{-}C_4H_9S\text{-})_2 \xrightarrow[h\nu]{Ph_2CO} t\text{-}C_4H_9\cdot + t\text{-}C_4H_9S_2\cdot \quad (1)$$

$$(t\text{-}C_4H_9S\text{-})_2 + t\text{-}C_4H_9\cdot \longrightarrow t\text{-}C_4H_{10} + (CH_3)_2C{=}CH_2 + t\text{-}C_4H_9S_2\cdot \quad (2)$$

Tetrasulfides are known to disproportionate photochemically to di- and trisulfides.[5b] Our experiments give no measure of the role of S–S cleavage; the stoichiometry, however, is also compatible with some S–S cleavage to thiyl radicals, followed by thiyl and perthiyl combination as an alternative route to trisulfide. Equation 2 has analogy in the chemistry of sulfides[12] and is directly supported by the observation that phenyl radicals (from phenylazotriphenylmethane) react with *tert*-butyl disulfide to give equivalent yields of benzene and isobutene. Isobutane is not formed in this reaction. The benzophenone sensitized photolysis of *tert*-butyl disulfide in carbon tetrachloride gives *tert*-butyl chloride, confirming the importance of C–S cleavage and the formation of *tert*-butyl radicals (eq 1). *tert*-Butyl chloride accounts for ~90% of the disulfide lost at low conversions. A small amount of chloroform (~10%, based on disulfide lost) balances the stoichiometry (eq 3 and 4). The remaining $\cdot CCl_3$ radicals and the perthiyl radicals are presumably consumed by coupling reactions.

$$t\text{-}C_4H_9\cdot + CCl_4 \longrightarrow t\text{-}C_4H_9Cl + \cdot CCl_3 \quad (3)$$

$$\cdot CCl_3 + (t\text{-}C_4H_9S\text{-})_2 \longrightarrow HCCl_3 + [(CH_3)_2C{=}CH_2] + [t\text{-}C_4H_9S_2\cdot] \quad (4)$$

A variety of sensitizers with different excited states, energies, and lifetimes are effective. Thus, acetophenone, benzophenone, 2-methylanthraquinone (2-MAQ), benzil, and biacetyl (all n,π^* sensitizers[13]), and triphenylene and 2-acetylnaphthalene (π,π^* sensitizers[13]) mediate the formation of C–S cleavage products. In addition, the fluorescent emission from triphenylene (EPA, ~300°K) and the phosphorescent emission from benzophenone (EPA, 77°K) and biacetyl (benzene, ~300°K) are quenched by *tert*-butyl disulfide. Benzyl disulfide quenches both fluorescence and phosphorescence from biacetyl (benzene, ~300°K); cyclohexyl and *n*-hexyl disulfides were shown to quench biacetyl phosphorescence (benzene, ~300°K). In all cases, the extent of quenching is a function of the disulfide concentration. It is clear that these quenching phenomena can give useful information about the photosensitized reactions of disulfides.

The use of efficient scavengers for the *tert*-butyl radicals formed in the initial C–S cleavage isolates this process (eq 1) and permits its quantitative description. The quantum yields for the formation of *tert*-butyl products from the benzophenone-sensitized photolyses of *tert*-butyl disulfide in two different scavenging systems are in agreement; CCl_4 solvent ($\phi_{RCl} = 0.33$) and 0.1 *M* *tert*-C_4H_9SH in C_6H_6 ($\phi_{RH} = 0.34$),[14] The identical quantum yields with two different scavenger systems demonstrate that mercaptan functions only as a radical scavenger and is not involved in the photochemical reaction. In addition, a benzophenone-sensitized control photolysis of *tert*-butyl mercaptan in benzene gives only traces of isobutane ($\phi_{RH} \sim 0.006$).

biology," Academic Press, New York, N. Y., 1969, p 85f; J. K. Setlow, "Comprehensive Biochemistry," M. Florkin and E. H. Stotz, Ed., Elsevier, Amsterdam, 1967, Chapter V; A. D. McLaren, *Enzymologia*, 37, 18 (1969); Yu. A. Vladimirov, D. I. Roshchupkin, and E. E. Fleshenko, *Photochem. Photobiol.*, **11**, 227 (1970).

(2) T. K. Rathinasamy and L. G. Augenstein, *Biophys. J.*, **8**, 1275 (1968); K. Dose, *Photochem. Photobiol.*, **6**, 437 (1967); **8**, 331 (1968); J. W. Longworth, *ibid.*, **7**, 587 (1968); R. Cowgill, *Biochem. Biophys. Acta*, **140**, 37 (1967); S. Arian, M. Benjamini, J. Feitelson, and G. Stein, *Photochem. Photobiol.*, **12**, 481 (1970).

(3) Reviews: E. Block, *Quart. Rep. of Sulfur Chem.*, **4**, 283 (1969); L. Bateman, C. Moore, and M. Porter, *J. Chem. Soc.*, 2866 (1958); A. Parker and N. Kharasch, *Chem. Rev.*, **59**, 583 (1959).

(4) P. M. Rao, J. A. Copeck, and A. R. Knight, *Can. J. Chem.*, **45**, 1369 (1967).

(5) (a) W. Haines, G. Cook, and J. Ball, *J. Amer. Chem. Soc.*, **78**, 5213 (1956); (b) B. Milligan, D. Rivett, and W. Savige, *Aust. J. Chem.* **16**, 1020 (1963); (c) R. N. Haszeldine and J. M. Kidd, *J. Chem. Soc.*, 3219 (1953).

(6) (a) A. B. Callear and D. R. Dickson, *Trans. Faraday Soc.*, **66**, 1987 (1970); (b) H. Ogoro and T. Inaba, *J. Chem. Soc., Jap., Ind. Chem. Sect.*, **72**, 114 (1969).

(7) V. Krongauz, *Dokl. Akad. Nauk SSSR*, **132**, 1136 (1960); C. Walling and R. Rabinowitz, *J. Amer. Chem. Soc.*, **81**, 1137 (1959).

(8) A. Jones, S. Yamashita, and F. P. Lossing, *Can. J. Chem.*, **46**, 833 (1968).

(9) D. Grant and J. Van Wazer, *J. Amer. Chem. Soc.*, **86**, 3012 (1964).

(10) The stoichiometric details of these photolyses are complicated by secondary photolyses of the polysulfide products at high conversions.

(11) Isobutane and isobutene are not formed by the disproportionation of *tert*-butyl radicals since 2,2,3,3-tetramethylbutane could not be detected (15% of that required by the known disproportion/combination ratio would have been observed): S. F. Nelsen and P. D. Bartlett, *ibid.*, **88**, 137 (1966).

(12) J. A. Kampmeier, R. P. Geer, A. J. Meskin, and R. M. D'Silva, *ibid.*, **88**, 1257 (1966); J. Hepinstall and J. A. Kampmeier, unpublished observations.

(13) "Energy Transfer and Organic Photochemistry," Techniques of Organic Chemistry, Vol. XIV, A. A. Lamola and N. J. Turro, Ed., Wiley, Interscience, New York, N. Y., 1969, p 194f.

(14) All quantum yields are limiting quantum yields since they are not increased by increases in disulfide or mercaptan concentration. They are minimum quantum yields for C–S cleavage since only those alkyl radicals which escape cage return are counted.

Table I. Quantum Yields for C–S Cleavage[a] of RSSR

R	Sensitizer	ϕ_{RH}[b]
t-C_4H_9	Ph_2CO	0.34
$PhCH_2$	$PhCOCH_3$	0.26 ± 0.003 (3 DF)
	Ph_2CO	0.21 ± 0.003 (10 DF)
	2-MAQ	0.17 ± 0.005 (5 DF)
c-C_6H_{11}	Ph_2CO	~0.007
n-C_6H_{13}	Ph_2CO	~0.001

[a] In purified, deoxygenated benzene 0.1 M in the corresponding mercaptan as a radical scavenger. Limiting quantum yields are reported.[14] Photolysis conditions were carefully adjusted so that <2% of the incident light is absorbed by the disulfides; [RSSR] ~ 0.4 M. Several actinometers were used; results for different actinometers are in good agreement. All hydrocarbon yields were determined gas chromatographically. Neither gas chromatographic nor uv analyses give any indication of important reactions other than C–S cleavage in any of these photolyses; uv analyses demonstrate that none of the sensitizers is consumed. Solvents and reactants were carefully purified by appropriate methods; purity was, in general, monitored by gas chromatography. [b] Precision stated as standard deviation of the mean; DF = degrees of freedom.

The use of mercaptan as a radical scavenger was applied to the photosensitized decomposition of several other disulfides. Quantum yields for C–S cleavage product, ϕ_{RH}, for a series of sensitizers and disulfides are reported in Table I.

It is clear that C–S cleavage is an important process in some cases and that the quantitative details are a function of both disulfide structure and sensitizer. The fate of the missing quanta is not known. A considerable body of qualitative evidence suggests that some are accounted for by S–S cleavage.[3,4] Unfortunately, there is no presently established method for quantitatively monitoring S–S cleavage in solution. An alternative possibility is that some "excited" disulfides return to ground state. Finally, cage recombination of the primary fragments can simply reverse the photochemical cleavage.[14] It is important to note that, in the absence of thiyl radical traps, S–S cleavage is apparently followed by the recombination of thiyl radicals to regenerate disulfide.[15] Thus, it is reported that direct photolysis (254 nm) of neat ethyl disulfide gives no apparent loss of disulfide, even though there is evidence for the formation of thiyl radicals.[15] Cyclohexyl and n-hexyl disulfides give comparable results; alkanes are formed in low yields by C–S cleavage, but the main characteristic of the photolyses is that there is no other apparent reaction. Thus, only alkanes are detected by gas chromatographic or ultraviolet analyses, sensitizer is not consumed, and (within the limits of the gas chromatographic analyses) neither mercaptans nor disulfides are consumed.[16]

In summary, these data qualitatively demonstrate the interaction of a variety of excited states with simple disulfides. C–S cleavage is clearly established as an important process in the photochemistry of *tert*-butyl and benzyl disulfides. Results for cyclohexyl and hexyl disulfides suggest that C–S cleavage may not be generally important when less stable alkyl fragments are formed. Nevertheless, these data provide the first quantitative details on the photosensitized decomposition of disulfides in solution. It will clearly be interesting to apply this method to the photodecomposition of cystine. Carbon–sulfur cleavage has been qualitatively identified in the direct photolysis of cystine.[17] Carbon–sulfur cleavage further provides an entry to the details of the interaction of sensitizers with disulfides; such a study will be reported in a separate paper.

Acknowledgment. This work was supported by a Public Health Service Grant, CA-06535, from the National Cancer Institute.

(15) K. Sayamol and A. R. Knight, *Can. J. Chem.*, **46**, 999 (1968).

(16) Since these analyses focus on the loss of starting materials at low conversion to hydrocarbon, the small amounts of disulfides consumed by C–S cleavage would not be detected. Any significant, unsuspected reaction which consumes disulfides would, however, have been observed.

(17) W. Forbes and W. Savige, *Photochem. Photobiol.*, **1**, 1 (1962).

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Structural Studies on Penicillin Derivatives. VIII. A Possible Model Biosynthetic Route to Penams and Cephems

Sir:

In previous publications[1-4] we described some of our investigations on the penicillin sulfoxide systems, in particular the mechanism of its rearrangement to a deacetoxycephem. In the original discovery of this rearrangement, Morin, *et al.*,[5] postulated that the reaction pathway proceeds through a sulfenic acid, a functionality of fleeting existence in aliphatic chemistry. Proof of its intermediacy was obtained by both ourselves[3] and other workers[6] using deuterium exchange techniques. We have also reported[4] that the penicillin sulfenic acid **1** is generated thermally from the sulfoxide **2** and can be trapped by reduction to thiol **3** using trimethyl phosphite. Subsequently, an intramolecular condensation product **4** of the intermediate thiol was isolated in high yield. Further interception of **3** was achieved[7] by acetic anhydride when the *S*-acetyl derivative **5** was isolated.

The thiazoline–azetidinone such as **4** is a derivative of L-cysteinyl-D-dehydrovaline and thus represents a model for a possible intermediate in the biosynthesis of penicillin and cephalosporin antibiotics (see Scheme I). In such a speculative biosynthetic pathway, the cysteine moiety may be protected either as a derivative of α-aminoadipic acid[8] or by attachment to a protein surface. The proposed course of events subsequent to protection of the cysteine moiety would be amidation with L-valine, followed by β-lactam ring closure (see Scheme I). The resulting derivative **7** is

(1) R. D. G. Cooper, P. V. Demarco, J. C. Cheng, and N. D. Jones, *J. Amer. Chem. Soc.*, **91**, 1408 (1969).
(2) R. D. G. Cooper, P. V. Demarco, and D. O. Spry, *ibid.*, **91**, 1528 (1969).
(3) R. D. G. Cooper, *ibid.*, **92**, 5010 (1970).
(4) R. D. G. Cooper and F. L. José, *ibid.*, **92**, 2575 (1970).
(5) (a) R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavagnino, W. B. Scanlon, and S. L. Andrews, *ibid.*, **85**, 1896 (1963); (b) *ibid.*, **91**, 1401 (1969).
(6) D. H. R. Barton, F. Comer, D. C. T. Greig, G. Lucente, P. G. Sammes, and W. G. E. Underwood, *Chem. Commun.*, 1059 (1970).
(7) L. D. Hatfield, J. W. Fisher, F. L. Jose, and R. D. G. Cooper, *Tetrahedron Lett.*, 4897 (1970).
(8) This amino acid appears to play a key role in the biosynthesis of β-lactam antibiotics.[9]
(9) S. C. Warren, G. G. F. Newton, and E. P. Abraham, *Biochem. J.*, **103**, 891 (1967).