tone, 765-43-5; cyclopropyl ethyl ketone, 6704-19-4; cyclopropyl α-ethoxyethyl ketone, 25111-29-9; cyclopropyl α-ethoxyethyl ketone (semicarbazone), 25111-30-2; 1-methylcyclopropyl ethyl ketone, 25111-31-3; 1-methylcyclopropyl 1-ethoxyethyl ketone, 25111-32-4; cyclobutyl isopropyl ketone, 25111-33-5; α-ethoxyethyl cyclobutyl ketone, 25111-34-6; α-ethoxyethyl cyclopentyl ketone, 25111-35-7; cyclohexyl ethyl ketone, 1123-86-0; α-ethoxyethyl cyclohexyl ketone, 25111-37-9; α-ethoxyethyl cyclohexyl ketone (semicarbazone), 25111-38-0; cyclopropyl ethyl acyloin, 25111-39-1.

# Organic Disulfides and Related Substances. XXIX. Studies in the Chemistry of Sulfenamides[1a-c]

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A variety of sulfenamides, $R^1SNR^2R^3$, were prepared and generalizations were sought for the chemical and physical properties of the class. Of syntheses studied, the smoothest was through reaction of sulfenyl chlorides with amines or amides. Thermal stability decreased from $R^1$ = *n*-butyl to 2-acetamidoethyl, suggesting an anchimeric effect in the latter; it decreased also with enhanced basicity of $NR^2R^3$ [*e.g.*, for $R^1 = AcNH(CH_2)_2$, stability for $R^2 + R^3$ = phthaloyl > $R^2 = R^3$ = alkyl], presumably because of an increased rate of proton transfer. The sulfenamides studied were quite stable to light. In their spectra, the predominant EI fragmentation reactions were C–S and N–S cleavage, with or without hydrogen rearrangement depending upon the nature of $R^1$, $R^2$, and $R^3$; ir and Raman spectra showed no useful characteristic absorption for the S–N bond. In their chemical reactions, sulfenamides with electrophiles characteristically gave products consistent with attack on $NR^2R^3$, followed by nucleophilic cleavage of the S–N bond (*e.g.*, with an alkyl or sulfonyl halide, carbon disulfide, and an isothiocyanate); however, with isocyanates and electron-deficient alkenes the preferred course seemed to be for elimination reactions, which can be formulated as concerted ones. The general pattern of nucleophilic attack was followed in conversion of sulfenamides by thiols to disulfides. In their biological properties, inactivity of several sulfenamides as antiradiation drugs indicated that $NR^2R^3$ may not be a promising latentiating group for radioprotective thiols.

Sulfenamides, which have the generalized structure **1** of eq 1, have been known for many years, but we are

$$R^1SCl + HNR^2R^3 \longrightarrow R^1SNR^2R^3 + HCl \quad (1)$$

**3** → **1**, **4–17**

$$\downarrow {}^1/_2Cl_2$$

$${}^1/_2R^1SSR^1$$

**2**

$R^1 = AcNHCH_2CH_2$ (for **2–11**)

**4**, $R^2$ = H; $R^3$ = *p*-$C_6H_4CO_2Me$
**5**, $R^2$ = H; $R^3$ = 2-benzothiazolyl
**6**, $R^2 = R^3 = C_2H_5$
**7**, $R^2 + R^3 = (CH_2)_5$
**8**, $R^2 + R^3 = (CH_2)_2O(CH_2)_2$
**9**, $NR^2R^3$ = 1-benzimidazolyl
**10**, $R^2 + R^3$ = *o*-phthaloyl
**11**, $R^2$ = H; $R^3$ = *p*-$CH_2C_6H_4SO_2$
**12**, $R^1 = C_2H_5$; $R^2 + R^3 = (CH_2)_5$
**13**, $R^1$ = *n*-$C_4H_9$; $R^2 + R^3 = (CH_2)_5$
**14**, $R^1$ = *t*-$C_4H_9$; $R^2 + R^3 = (CH_2)_5$
**15**, $R^1 = C_2H_5$; $R^2 = R^3 = C_2H_5$
**16**, $R^1$ = *t*-$C_4H_9$; $R^2 = R^3 = C_2H_5$
**17**, $R^1$ = *t*-$C_4H_9$; $R^2$ = H; $R^3 = C_6H_5$

unaware of any effort to develop a unified theory of their chemistry.[2] Because of the possibility that the $NR^2R^3$ function might be an effective latentiating group for medicinally useful thiols,[3] we had occasion to prepare a variety of sulfenamides for testing as antiradiation drugs. Investigation thus became possible of the chemistry of typical sulfenamides in the hope of developing concepts useful for rationalizing and predicting chemical and physical properties of this class of compounds.

**Preparation.**—As a thiol, 2-acetamidoethanethiol was chosen because both it[3a] and the corresponding amine[3b] afford protection against ionizing radiation. As eq 1 shows, its disulfide (**2**) was converted to the sulfenyl chloride (**3**), which then was allowed to react with amines or amides to give the sulfenamides, **1**. This method was preferred to two others tried. Aminolysis of an acetamidoethanethiolsulfonate ($R^1SO_2SR^1$), which is an equilibrium reaction,[4] gave no pure, isolable sulfenamides; the product ratio was the same after 4 days as after 0.5 hr by tlc. Although this method often succeeds,[4] the properties of the acetamido products are not suited to the usual technique. The sulfenyl thiocyanate route[5] gave poor yields; thus crude **8** was obtained in only 30% yield (*vs.* 86% from **3**) and even then showed a strong –SCN band at 2200 $cm^{-1}$ which could not be removed by washing with water. Furthermore, the preparation of 2-acetamidoethanesulfenyl thiocyanate was difficult because of its solubility properties.

The sulfenyl chloride, **3**, was obtained in quite variable yields, usually about 60%, by chlorinolysis of the disulfide in methylene chloride at temperatures in the range of −40 to −25° (eq 1). A lower temperature did not increase the yield of **3**; for example, **10** was

(1) (a) Paper XXVIII: L. Field and P. M. Giles, Jr., *J. Med. Chem.*, **13**, 317 (1970). (b) This investigation was supported by the U. S. Army Medical Research and Development Command, Department of the Army, under Research Contracts No. DA-49-193-MD-2030 and DADA17-69-C-9128. (c) Presented in part at the Symposium on Organosulfur Chemistry, 157th National Meeting of the American Chemical Society, Minneapolis, Minn., April 14–18, 1969 (Abstracts, Paper ORGN 26), and at the Third International Cork Mechanisms Conference, University College, Cork, Ireland, Sept 29–Oct. 3, 1969. (d) To whom inquiries should be addressed.

(2) For reviews see (a) N. Kharasch, S. Potempa, and H. L. Wehrmeister, *Chem. Rev.*, **39**, 304 (1946); (b) E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. I, Chemical Publishing Co., Inc., New York, N. Y., 1958, p 279; (c) E. Riesz, *Bull. Soc. Chem. Fr.*, 1449 (1966).

(3) For discussions, see (a) L. Field, A. Ferretti, R. R. Crenshaw, and T. C. Owen, *J. Med. Chem.*, **7**, 39 (1964); (b) L. Field, B. J. Sweetman, and M. Bellas, *ibid.*, **12**, 624 (1969).

(4) J. E. Dunbar and J. H. Rogers, *J. Org. Chem.*, **31**, 2842 (1966).

(5) H. Lecher and F. Holschneider, *Ber.*, **57**, 755 (1924).

obtained in 70% yield by preparing **3** at −35° and in 45% yield at −50°.

Sulfenamides then were generated by adding the cold solution of **3** to excess amine in methylene chloride (**6–8**) or to equivalent amounts of the amine or amide with triethylamine added as the acid scavenger. The only exception to this method was with **10**, where potassium phthalimide was used. With ammonia or the primary amines ethyl glycinate and 1-aminoadamantane, reaction of **3** was unpromising. The first two sulfenamides could not be isolated, but their water solubility probably was a contributing reason; a little material was obtained using ammonia which had a promising ir spectrum, but it decomposed extensively in 3 days. The crude product from 1-aminoadamantane (73% yield) also could not be purified because of extensive decomposition. With primary aromatic or heterocyclic amines, the reaction was more satisfactory. Considerable loss occurred with **4** (55% crude yield to 11% pure), but it may be attributed at least partly to the need for chromatography since **5**, which crystallized well, was obtained pure in 63% yield. With secondary amines, crude yields of 55–103% for **6–8** dropped only to 29–51%; the possibly beneficial effect of structure was complemented, however, by the ease of removing the amine impurity by washing with water and by evaporation. Benzimidazole was included among the secondary amines because the amine function is part of a ring and because it protects against; ionizing radiation *per se*.[6]

1-Benzylpiperazine gave crude sulfenamide in 103% yield but, although tlc and nmr indicated good purity, a satisfactory analysis could not be obtained; marked darkening at 50° during a few minutes suggested notable heat sensitivity. With phthalimide, **10** was obtained in 45% yield. With *p*-toluenesulfonamide, a low yield of 21% **11** probably mainly reflects difficulties in purification. With succinimide, no pure sulfenamide; was obtained. Composition of all of the sulfenamides **4–11** was assured by elemental analysis, and the structures were confirmed by ir, nmr, and mass spectrometry (the mass spectrum of **11** could not be obtained however, because of decomposition during attempted volatilization).

Some impressions gained from the foregoing syntheses and purifications deserve mention. Strong basicity of the amine ($R^2R^3NH$ of eq 1) led to products that were frequently more difficult to purify since they decomposed at temperature above 60° (darkening of products) and slowly even at *ca.* 25° (*e.g.*, strong amine odor from **6** after a week). The sulfenamide derived from isobutylamine could not be purified by short-path distillation (0.05 mm, <80°), as were **6–8**, because of decomposition. The less basic aryl or heterocyclic counterparts were more easily handled, probably in part because they were crystalline. Secondary alkylamines succeeded better than primary ones of similar basicity, and difficulties with products from 1-benzylpiperazine and to a lesser extent benzimidazole and 2-aminobenzothiazole probably were caused by the second basic function. The less basic phthalimide derivative **10** worked best. These observations suggest that lower basicity and a higher degree of substitution of the amine facilitate synthesis and purification, as does sparing solubility (with **5**, **9**, and **10**). Our impression as to the $R^1S$ moiety is that the known compounds[7] where $NR^2R^3$ is 1-piperidyl and where $R^1$ was ethyl (**12**), *n*-butyl (**13**), or *t*-butyl (**14**) were roughly comparable to one another in ease of preparation and purification (yields of 55–90%), and that **12–17** were markedly superior in stability and ease of purification to compounds where $R^1$ was 2-acetamidoethyl. These impressions led us to study qualitatively the rates of decomposition of some typical sulfenamides.

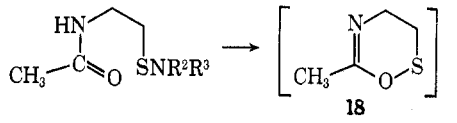
**Stability toward Heat and Light.**—Comparison of some thermal stabilities are shown in Table I. Two

TABLE I
COMPARISON OF THERMAL STABILITIES OF TYPICAL SULFENAMIDES, $R^1SNR^2R^3$ (1)

| Compd | $R^1$ | $R^2$, $R^3$ | Temp, °C | Time, min | Estimated decomposition, % |
|---|---|---|---|---|---|
| **5** | $AcNH(CH_2)_2$ | 2-Benzothiazolyl, H | 155 | 20 | >80 |
| **8** | $AcNH(CH_2)_2$ | $-(CH_2)_2O(CH_2)_2-$ | 140 | 20 | >80 |
| **10** | $A(cNHCH_2)_2$ | *o*-Phthaloyl | 155 | 20 | <20 |
| **13** | *n*-Butyl | $-(CH_2)_5-$ | 140 | 80 | <5 |
| **16** | *t*-Butyl | Et, Et | 100 | 4 days | ~0 |

factors decreased the thermal stability: (1) the presence in $R^1$ of a group capable of anchimeric participation in cleavage of the S–N bond (thus **13** and **16** are more stable than **5**, **8**, or **10**); (2) increased basicity of the nitrogen atom of $NR^2R^3$ (thus **10** is more stable than **5** or **8**). Two additional factors noted by others are worth adding: (3) an increased number of substituents on the nitrogen increases the stability,[8,9] a point consistent with the greater ease mentioned above of preparing pure sulfenamides from secondary than from primary amines; (4) substitution of electron-withdrawing substituents into $R^1$ also increases the thermal stability; thus a 5-carbomethoxy- or 5-acetyl-2-thiazolesulfenamide is more stable than the 5-methyl derivative.[8]

Products from the decomposition of **5**, **8**, and **10** always included the amine ($R^2R^3NH$), suggesting that the reaction shown in eq 2 might play a major role in thermal decomposition through anchimeric participation of the acetamido group, although we could find no evidence of the heterocycle **18**. It is tempting to conclude that the greater stability of the phthalimide derivative **10** results from the decreased ability of the nitrogen atom to remove a proton from the amide group to give phthalimide and **18** as required by eq 2. Analysis




of the residue from decomposition of **8** by glpc and mass spectrometry showed only morpholine and N-acetylmorpholine; apparently the sulfur fragment is not volatile. Prolonged heating of the diethylamino com-

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TABLE II

RELATIVE INTENSITIES OF PRODUCT IONS FROM COMPETING FRAGMENTATION REACTIONS IN THE EI MASS SPECTRA OF SULFENAMIDES, $R^1SNR^2R^3$

| | | | | | Eq 3 | | Eq 4, | Eq 5 | | Eq 6, |
|---|---|---|---|---|---|---|---|---|---|---|
| Compd | $R^1$ | $R^2$, $R^3$ | $M^+$ | M − 1 | $R^1$ [M − $SNR^2R^3$] | $SNR^2R^3$ [M − $R^1$] | HSN$R^2R^3$ [M − ($R^1$ − 1)] | $NR^2R^3$ [M − $R^1S$] | $R^1S$ [M − $NR^2R^3$] | $HNR^2R^3$ [M − ($R^1S$ − 1)] |
| 4[a] | $AcNH(CH_2)_2$ | *p*-$C_6H_4CO_2Me$, H | 4 | <1 | 6 | <1 | <1 | 3 | 4 | 61 |
| 5 | $AcNH(CH_2)_2$ | 2-Benzothiazolyl, H | 2 | <1 | 18 | <1 | 1 | 4 | 22 | 100 |
| 6 | $AcNH(CH_2)_2$ | $C_2H_5$, $C_2H_5$ | 2 | <1 | 26 | 2 | <1 | 100 | 4 | 1 |
| 7 | $AcNH(CH_2)_2$ | $(CH_2)_5$ | 12 | <1 | 100 | 5 | 3 | 40 | 5 | 9 |
| 8 | $AcNH(CH_2)_2$ | $(CH_2)_2O(CH_2)_2$ | 13 | <1 | Y[b] | 14 − X[c] | 3 | 100 − Y[b] | X[c] | 16 |
| 9 | $AcNH(CH_2)_2$ | 1-Benzimidazolyl | 2 | <1 | 7 | <1 | <1 | 7 | Y[b] | 100 − Y[b] |
| 10[d] | $AcNH(CH_2)_2$ | *o*-Phthaloyl | 2 | <1 | 16 | 2 | 1 | <1 | 10 | 55 |
| 12[e] | $C_2H_5$ | $(CH_2)_5$ | 68 | 42 | 54 | 68 | 14 | 52 | 44 | 14 |
| 13 | *n*-$C_4H_9$ | $(CH_2)_5$ | 35 | 4 | 29 | 31 | 16 | 100 | 3 | 64 |
| 14 | *t*-$C_4H_9$ | $(CH_2)_5$ | 25 | <1 | 86 | 25 | 100 | 10 | 3 | 2 |
| 16[f] | *t*-$C_4H_9$ | $C_2H_5$, $C_2H_5$ | 19 | <1 | 38 | 10 | 57 | 2 | 1 | 2 |
| 17 | *t*-$C_4H_9$ | $C_6H_5$, H | 15 | <1 | 59 | 4 | 100 | 31 | 15 | 60 |

[a] The base peak is *m/e* 120 corresponding to the metastable loss of 31 (OMe) from *m/e* 151 (*p*-$H_2NC_6H_4CO_2Me$). [b] These two fragments fall at the same nominal mass, total intensity 100%. [c] These two fragments fall at the same nominal mass, total intensity 14%. [d] The base peak is at *m/e* 117 and may correspond to heterocycle **18**. [e] The base peak is *m/e* 55, presumably a fragment from the piperidine ring. [f] The base peak is *m/e* 90 corresponding to the metastable loss of 15 ($CH_3$) from *m/e* 105.

pound **6** followed by glpc and mass spectrometric analysis resulted in detection of five volatile products. Three of these seemed identifiable from the mass spectra (*cf.* Experimental Section): N,N-diethylacetamide, presumably from reaction of diethylamine with **6** (amide interchange), N,N-diethylthioacetamide, and N,N-diethyl-N′-acetylthioglycinamide, $AcNHCH_2C(S)NEt_2$. Tlc analysis suggested that other (nonvolatile) products also were formed, but these were not investigated. Under these same conditions the *t*-butyl compound **16** was essentially unchanged.

The trends in thermal stability of sulfenamides thus resemble those suspected from the synthesis and seem to be for improved stability of sulfenamides containing the more weakly basic amine moieties or containing $R^1S$ groups unlikely to afford anchimeric assistance to cleavage of the S–N bond; with $R^1S$=$AcNHCH_2CH_2S$, elimination of the amine moiety and subsequent amide-transfer reactions are likely.

All of the sulfenamides seemed quite stable to light. In ambient light over a period of several months we saw no changes in sulfenamides **4–17** which would suggest adverse effects. For example, the refractive indices of **7** and **8** did not differ significantly whether they were stored for 1 month in ambient light or in the dark. An attempt to photolyze N-(*t*-butylthio)-N,N-diethylamine (**16**) in cyclohexane–cyclohexene failed to change the sulfenamide (glpc), and 75% of the **16** was recovered. However, light reportedly does accelerate the rate of decomposition of thiazolesulfenamides.[9]

**Spectra.**—Nmr spectra were done routinely. The only noteworthy feature was with the carbomethoxyphenylsulfenamide (**4**), in which half of the aromatic $A_2B_2$ system, presumably those protons *ortho* to the nitrogen, were shifted downfield 26 Hz relative to the corresponding protons in the amine. This shift (probably reflecting decreased electron density on nitrogen, and hence in the aromatic ring) parallels the reported decreased basicity of sulfenamides.[10] This effect could arise from $p\pi$–$d\pi$ bonding between nitrogen and sulfur.

The EI mass spectra of 12 sulfenamides were studied to determine the fragmentation reactions responsible for their mass spectra. As shown by Table II, $R^1$ of $R^1SNR^2R^3$ was primary alkyl, tertiary alkyl, or 2-acetamidoethyl, while $R^2R^3$ comprised alkyl, aryl, or heterocyclic groups. Examination of the data of Table II suggests that there are four predominant fragmentation reactions: C–S cleavage (eq 3), C–S cleavage with hydrogen rearrangement (eq 4), S–N cleavage (eq 5), and S–N cleavage with hydrogen rearrangement to the nitrogen fragment (eq 6).

$$R^1SNR^2R^3 \longrightarrow R^{1(\cdot \text{ or } +)} + SNR^2R^{3(+ \text{ or } \cdot)} \quad (3)$$

$$\longrightarrow (R^1 - H) + H(SNR^2R^3)\cdot^+ \quad (4)$$

$$\longrightarrow R^1S^{(\cdot \text{or} +)} + NR^2R^{3(+ \text{ or } \cdot)} \quad (5)$$

$$\longrightarrow (R^1S - H) + HNR^2R^3\cdot^+ \quad (6)$$

Eq 3 shows the most consistently important fragmentation reaction, C–S cleavage with the charge remaining on the $R^1$ fragment. That the relative abundance of the charged fragment containing no heteroatom [*i.e.*, of $(R^1)^+$ in **12–14**, **16**, and **17**] is greater than that of $(SNR^2R^3)^+$ probably results from the slower rate of decomposition of $(R^1)^+$ ion relative to the $(SNR^2R^3)^+$ fragment. Another notable feature, the decreased abundance of $(SNR^2R^3)^+$ when $R^1$ = $AcNHCH_2CH_2$, can be attributed to relatively greater stability of the 2-acetamidoethyl carbonium ion than of $(SNR^2R^3)^+$. Examination of the relative intensities of the ions in the mass spectrum of **4** as a function of electron energies suggests that the *m/e* 86 ion, $(AcNHCH_2CH_2)^+$ or an isomer, is probably cyclic since its abundance (%Σ) shows an increase as the electron energy is lowered (1.6%$\Sigma^{40}$ at 18 eV to a maximum of 18%$\Sigma^{40}$ at *ca.* 14 eV), the same behavior shown by McLafferty-type rearrangement ions in the spectrum. The mass spectrum of 2-acetamidoethyl disulfide (**2**) also shows this C–S cleavage reaction giving an intense *m/e* 86 ion. Labeling of **2** by washing with deuterium oxide caused the *m/e* 86 ion to shift to *m/e* 87 in accordance with the assigned structure. Presumably, substitution of any group in $R^1$ which will stabilize a carbonium ion will similarly decrease the relative intensity of $(SNR^2R^3)^+$ with respect to that seen with simple alkyl groups.

(10) R. T. Major and L. H. Peterson, *J. Amer. Chem. Soc.*, **78**, 6181 (1956).

Eq 4, C–S cleavage with hydrogen rearrangement, can be seen from Table II to play a role, but it is important only when $R^1$ does not contain the acetamido moiety of **4–10**. The relative abundance of $(HSNR^2R^3)\cdot^+$ increases with an increasing number of $\beta$-hydrogen atoms (*cf.* *t*-butyl > ethyl ~ *n*-butyl, Table II), suggesting a preference for transfer of a $\beta$-hydrogen atom over transfer from other locations. (The structure $HSNR^2R^3$ implies only that the hydrogen atom has been transferred to $SNR^2R^3$ and that it probably is bound to sulfur or nitrogen.)

Eq 5, cleavage of the S–N bond, does not give intense ions in all of the spectra, although such ions are seen to some extent in all spectra. The $(NR^2R^3)^+$ fragment may be formed by any of three routes: simple S–N bond cleavage (eq 5), simple C–S cleavage (eq 3) followed by loss of a sulfur atom, or C–S cleavage with hydrogen rearrangement (eq 4) followed by loss of 33 (SH). The absence of metastable ions for any of these secondary fragmentations reactions did not allow decision among these possibilities. Except with **4**, **5**, **9**, **10**, and **16**, $(NR^2R^3)^+$ is significantly intense. In all of these except **16**, competitive fragmentation reactions probably prevail (eq 6). With **16**, further decomposition of $(NR^2R^3)^+$ may explain its low abundance since only one bond needs to be broken to produce a mass loss whereas in the cyclic amine two bonds must be broken for a mass loss other than hydrogen. In the cleavage of the S–N bond (eq 5) with formation of $(R^1S)^+$, the ions from **8** and **9** at *m/e* 118 may be doublets and therefore deceptively large. The $R^1S^+$ ion from **12**, *m/e* 61, probably is correctly assigned since the *m/e* 63 ion is more than large enough to account for the expected contribution from the $^{34}S$ isotope (6% of *m/e* 61).

Eq 6, showing N–S cleavage with hydrogen rearrangement, leads to ions of relative intensity exceeding 20% only in **4**, **5**, **9**, **10**, **13**, and **17**. Of these, only **13** lacks an unsaturated substituent on nitrogen. The high intensity of $(HSNR^2R^3)\cdot^+$ from **13** may result from the ease of hydrogen transfer from the $\gamma$ carbon to nitrogen with simultaneous formation of two neutral fragments, thioformaldehyde and propene. The other compounds (**4**, **5**, **9**, **10**, and **17**) have unsaturated groups that should allow a McLafferty-type rearrangement.

Summarization in terms of structures also is informative. All of the sulfenamides show molecular ions (except **11**, where only *p*-toluenesulfonamide could be seen). The 2-acetamidoethyl derivatives (**4–10**) characteristically show lower intensity molecular ions than the unsubstituted compounds (**12–14**, **16**, and **17**), and ions at *m/e* 86 of moderate to high intensity corresponding to C–S cleavage with retention of the charge on the $R^1$ fragment. With the acetamidoethyl compounds, S–N cleavage either with or without rearrangement dominates the spectra (eq 5 and 6). Cleavage of the S–N bond occurs predominantly without hydrogen rearrangement when the nitrogen substituents are alkyl (eq 5); however, with unsaturated substituents on nitrogen, cleavage with hydrogen rearrangement predominates (eq 6). The S-*n*-alkylsulfenamides, **12** and **13**, show all four fragmentation reactions (eq 3–6); however, the S-*t*-alkyl derivatives (**14**, **16**, and **17**) show predominantly C–S cleavage with and without rearrangement (eq 3 and 4), except for **17** in which the aromatic ring allows S–N cleavage with hydrogen rearrangement (eq 6).

We also examined the ir and laser-Raman spectra of several sulfenamides to determine whether there is an easily recognized characteristic frequency for the S–N bond. Seven simple sulfenamides were chosen for the ir studies: **12–15**, **17**, morpholine sulfide (**19**), and piperidine sulfide (**20**). Compounds **19** and **20** were chosen for help in seeking characteristic bands because any characteriestic frequency seen with the simple sulfenamides should be modified in **19** and **20** by coupling of the two S–N modes owing to the common sulfur atom. Raman spectra of four of these simple sulfenamides were determined; the laser-Raman spectra of **5**, **10**, and **11** could not be determined because of fluorescence, although the compounds were pure by ordinary criteria. Ir bands in common seemed either weak, without Raman counterparts, or with counterparts in **19** and **20** which seemed to rule out their being characteristic for S–N stretching (*cf.* Experimental Section). There appears to be no strong, consistent band present throughout the series that is not assignable to other portions of the molecule. The ir or Raman spectra thus do not seem to afford a good diagnostic tool for detection of sulfenamides. An incidental point is that a band at *ca.* 830 $cm^{-1}$ previously assigned to S–N stretching in piperidine polysulfides[11] may result instead from piperidine ring vibrations, since the authors state that it is present in piperidine sulfide (**20**) as well, where one might expect the S–N stretching frequencies to be different owing to coupling because of the common sulfur atom.

**Reactions with Electrophiles.**—Sulfenamides (**1**) are unstable to acids.[12] For example, N-sulfenyl protecting groups are removed in peptide synthesis using hydrogen chloride, which results in formation of sulfenyl chlorides,[12a] and eq 7 provides a basis for iodo-

$$R^1SNR^2R^3 + HX \longrightarrow RSX + HNR^2R^3 \qquad (7)$$

metric determination of **1**.[13,14] Boron trichloride[15] and diborane[16] also cleave **1**, although amine sulfides reportedly form complexes with boron trifluoride.[17] It seems likely that the instability of **1** to acids results from coordination of an electrophilic species with the nitrogen lone pair, followed by displacement of the protonated nitrogen fragment, $HNR^2R^3$, by nucleophilic attack on sulfur. With this in mind as a principle for electrophiles in a general sense, reaction of **1** with electrophiles seemed likely to result in S–N cleavage and in formation of a variety of sulfenyl derivatives.

Methyl iodide reacted as such an electrophile. Thus N-(*n*-butylthio)piperidine (**13**) or N-(ethylthio)piperidine (**12**) gave *n*-butyl or ethyl disulfide, iodine, and presumably N,N-dimethylpiperidinium iodide (eq 8).

$$\begin{array}{ccccc} [R^1SN(CH_3)R^2R^3]^+I^- & \longrightarrow & [R^1SI] & + & CH_3NR^2R^3 \\ \uparrow & & \downarrow & & \downarrow CH_3I \\ R^1SNR^2R^3 + CH_3I & & {}^1/_2R^1SSR^1 + {}^1/_2I_2 & & (CH_3)_2N^+R^2R^3I^- \end{array} \qquad (8)$$

(11) C. N. R. Rao, R. Venkataraghavan, and T. R. Kasturi, *Can. J. Chem.*, **42**, 36 (1964).
(12) (a) L. Zervas, D. Borovas, and E. Gazis, *J. Amer. Chem. Soc.*, **85**, 3660 (1963). (b) H. Rheinboldt and F. Mott, *Ber.*, **72**, 668 (1939).
(13) O. Foss, *Acta Chem. Scand.*, **1**, 307 (1947).
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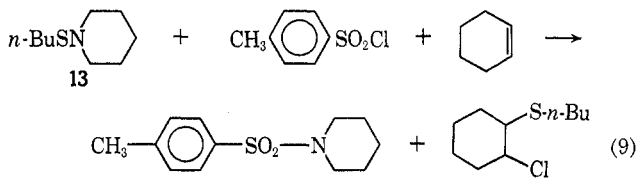
(15) H. Nöth and G. Mikulaschek, *ibid.*, **97**, 709 (1964).
(16) H. Nöth and G. Mikulaschek, *ibid.*, **94**, 634 (1961).
(17) A. B. Burg and H. W. Woodrow, *J. Amer. Chem. Soc.*, **76**, 219 (1954).

*n*-Butyl disulfide was identified by ir, nmr, and glpc comparison with an authentic sample, and 102% of the iodine required by eq 8 was titrated after 1 hr with **12** at room temperature.

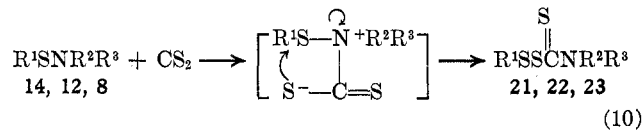
Reaction of N-(*n*-butylthio)piperidine (**13**) with *p*-toluenesulfonyl chloride, in the presence of cyclohexene as a trap for the sulfenyl chloride, gave as the only major products N-tosylpiperidine and 2-chlorocyclohexyl *n*-butyl sulfide (eq 9). These products were



(9)

identified by glpc mass spectrometric analysis and comparison of their mass spectra with those of authentic materials.

Carbon disulfide, considered as an electrophile, should react with sulfenamides to give trithiopercarbamates, as shown by eq 10. Blake has reported products from



(10)

**14, 21**, $R^1 = t\text{-}C_4H_9$; $R^2 + R^3 = (CH_2)_5$
**12, 22**, $R^1 = C_2H_5$; $R^2 + R^3 = (CH_2)_5$
**8, 23**, $R^1 = AcNH(CH_2)_2$; $R^2 + R^3 = (CH_2)_2O(CH_2)_2$

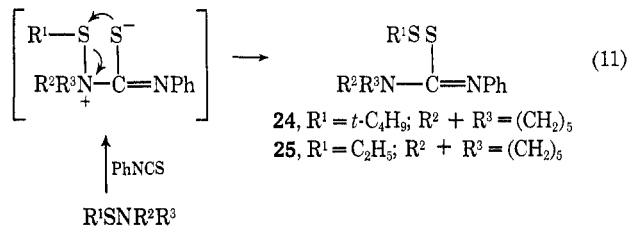
this type of reaction to be disulfides and tetrasubstituted thiuram disulfides;[18] these probably resulted from disproportionation of the primary product in the case of a N,N-disubstituted sulfenamide. The products reported from carbon disulfide and a monosubstituted sulfenamide were an isothiocyanate and a thiol[9,18] (decomposition). 2-Benzothiazolesulfenamide did not react.[9]

Reaction of N-(*t*-butylthio)piperidine (**14**) with carbon disulfide was very slow but gave **21** in 50% yield. The structure of **21** was assigned from its spectra and was confirmed by a reported independent synthesis from the appropriate dithiocarbamate and 2-methylpropane-2-sulfenyl chloride.[19] Reaction of N-(ethylthio)piperidine (**12**) was very fast and exothermic, possibly because of much less shielding with $R^1$ = Et than with $R^1$ = *t*-Bu; **22** resulted in 95% yield (eq 10). Although **22** was an oil which was difficult to purify, presumably because of disproportionation, the ir spectrum clearly showed the thioamide function, the nmr spectrum demonstrated the presence of ethyl and piperidyl groups, and the mass spectrum gave a molecular ion with the proper isotope distribution. The base peak in the spectrum was at *m/e* 128, as with **21**, and must result from loss of the ethyl group and two sulfur atoms. The acetamidosulfenamide **8** also reacted rapidly with carbon disulfide, giving **23** in 100% yield. The spectra of **23** were consistent with expectations.

(18) E. S. Blake, *J. Amer. Chem. Soc.*, **65**, 1267 (1943). After the presentation of our work as is mentioned in ref 1c and the submission of the present paper, a report appeared by J. E. Dunbar and J. H. Rogers that also described the new reaction of carbon disulfide with sulfenamides, but with other sulfenamides than those discussed here [*J. Org. Chem.*, **35**, 279 (1970)].

(19) C. M. Himel and L. O. Edmonds, U. S. Patent 2,792,394 (1957); *Chem. Abstr.*, **52**, 1282 (1958).

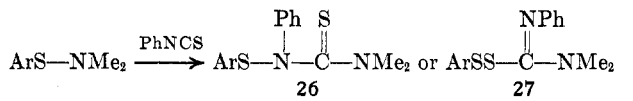
The general principle suggested for reaction of electrophiles predicts that isothiocyanates should react according to eq 11. As with carbon disulfide, reactions reported with isothiocyanates have varied with the



(11)

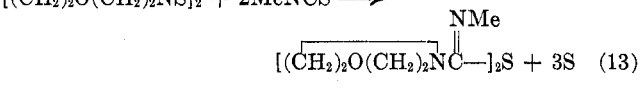
**24**, $R^1 = t\text{-}C_4H_9$; $R^2 + R^3 = (CH_2)_5$
**25**, $R^1 = C_2H_5$; $R^2 + R^3 = (CH_2)_5$

degree of nitrogen substitution. N,N-dimethylperchlorobenzenesulfenamide reportedly gave the N-sulfenylthiourea **26** (eq 12),[20] instead of isomer **27** that



(12)

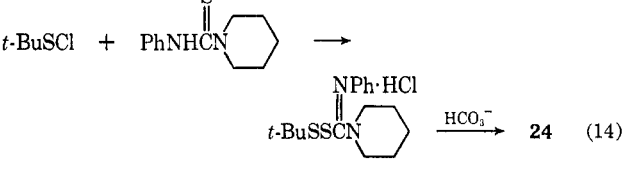
one would expect. Morpholine disulfide with methyl isothiocyanate gave the formamidine sulfide of eq 13,[21]



(13)

which could be formed reasonably by loss of sulfur from the type of product predicted by eq 11. 2-Benzothiazolesulfenamide and an isothiocyanate gave 2-benzothiazolyl disulfide,[9] presumably from the initial product, and *o*-nitrobenzenesulfenamide gave *o*-nitrophenyl disulfide.[22]

We found that N-(*t*-butylthio)piperidine (**14**) reacted very slowly with phenyl isothiocyanate. The reaction was nearly complete only after 1 month (by ir). It gave a low melting solid, **24** (eq 11). The ir and mass spectrum supported the assigned structure. The ir spectrum showed a strong band at 1590 $cm^{-1}$ (>C=NPh), and the mass spectrum showed the correct molecular weight with the expected enhancement of the M + 2 peak due to two sulfur atoms and the base peak at *m/e* 187 corresponding to loss of the *t*-butyl group and two sulfur atoms. An independent synthesis gave identical **24** (eq 14). Both formation of a hydrochlo-



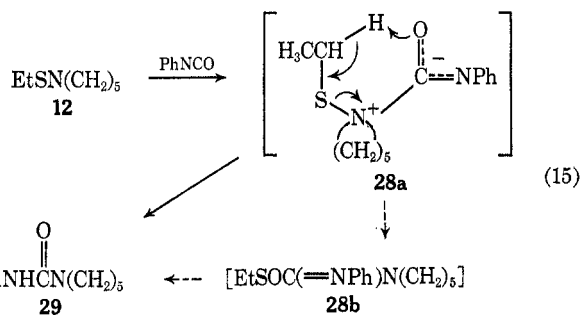
(14)

ride salt of **24** and the failure of **24** to oxidize iodide to iodine further argue against formulation as the isomeric N-sulfenylthiourea. As with carbon disulfide, the ethyl derivative **12** reacted much faster than **14**; reaction was complete by ir in 5 min. The product (**25**) apparently disproportionated more readily than **24**, a characteristic of resistance noted before with *t*-

(20) G. Oertel, H. Malz, and H. Holtschmidt, *Chem. Ber.*, **97**, 891 (1964).
(21) R. W. Saville, *ibid.*, 2880 (1958).
(22) F. Kurzer and W. Tertiuk, *ibid.*, 1571 (1958).

butyl disulfides.[23] The structure of **25** follows from its spectra and (like **24**) from its failure to oxidize iodide ion to iodine. The ir spectrum of **25** shows a strong band at 1590 $cm^{-1}$ (>C=NPh) and the nmr spectrum shows phenyl, ethyl, and piperidyl groups. The mass spectrum shows the expected molecular ion with the expected enhancement of the M + 2 peak, and also a base peak at *m/e* 187 resulting from loss of the ethyl group and two sulfur atoms.

Reaction of N-(ethylthio)piperidine (**12**) with phenyl isocyanate in principle should give **28b** (eq 15), probably an unstable compound. Sulfenamides derived

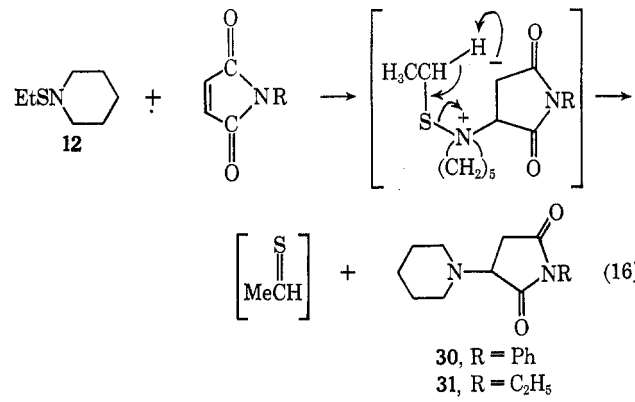



(15)

from ammonia have been reported to react with aryl isocyanates to give the N-sulfenylureas;[9,24,25] hydrogen transfer from nitrogen in an intermediate like **28a** must occur. With N-alkyl substituted sulfenamides, the product is the urea derivative of the amine,[9,24] the sulfur fragment being lost. This result has been explained by D'Amico as resulting from a thiol-catalyzed decomposition of the sulfenamide.[24] Reaction of **12** with phenyl isocyanate at 90° for 3 days gave **29** as the only isolable product, along with much dark, intractable material; the identity of **29** was confirmed by independent synthesis from piperidine and phenyl isocyanate. Presumably either **28a** or **28b** decomposes by abstraction of a hydrogen atom $\alpha$ to sulfur to give the urea and thioacetaldehyde, the latter undergoing further reactions to give the dark color. We prefer this mechanism *via* **28a** to **29** to that of D'Amico since we have no evidence for decomposition of **12** under the reaction conditions. It should be noted that the isocyanate reaction (eq 15) proceeds more slowly than the isothiocyanate reaction (eq 11).

Having in mind the previously mentioned general principle, we attempted to prepare sulfenyl acetates by treating **12** with acetic anhydride. Others have used acetic anhydride to convert 2-aminothiazolesulfenamides to the corresponding 5-thiazolyl sulfides[26] and N-monoalkylsulfenamides to bisthioamines, $(R^1S)_2NR^2$.[27] Glpc and mass spectrometric analysis of the products obtained from **12** showed only N-acetylpiperidine and ethyl disulfide, but ethanesulfenyl acetate would be expected to be quite unstable.

With electron-rich olefins (vinyl ethers) and cyclic olefins (cyclohexene), **13** failed to react in 4 days at 100°, as determined by the absence of change in the intensity of the olefinic protons relative to other peaks in the nmr spectrum. With electron-deficient olefins, eliminations resembling that of eq 15 occurred. Qualitatively, the rate of reaction seemed to follow the degree of electron deficiency (tetracyanoethylene > N-ethyl- or N-phenylmaleimide > ethyl acrylate). The reaction with N-phenylmaleimide was studied because of the ease of monitoring the reaction by nmr and uv. Reaction of N-phenylmaleimide with N-(ethylthio)piperidine (**12**) at 90° for 16 hr gave as the only isolable product the compound resulting from addition of piperidine to N-phenylmaleimide (eq 16). The formation of **30** may be




(16)

a concerted process which requires the presence of $\alpha$-hydrogens, since the *n*-butyl derivative **13** reacts similarly with N-ethylmaleimide, while the *t*-butyl derivative **14** reacts much more slowly (3 days at 90° gave only a trace of **30**, although this result also could be attributed to the larger *t*-butyl group, as with eq 10 and 11). A stepwise mechanism seems less likely since **12** and **16** showed no decomposition after 16 hr at 90°. The adduct **30** (47% yield from **12**) was identical with **30** obtained from piperidine and N-phenylmaleimide.

Ethyl acrylate and N-(ethylthio)piperidine (**12**) reacted to 60% completion only after 3 days at 77°. Analysis of the product mixture still later by glpc and mass spectrometry showed the presence of both **12** and a new compound with mol wt 185 (**32**). Analogy with eq 16 suggested that **32** was ethyl $\beta$-(1-piperidyl)-propionate (eq 17). The mass spectrum of **32** showed

$$\underset{\mathbf{12}}{EtSN(CH_2)_5} + CH_2{=}CHCO_2Et \longrightarrow \underset{\mathbf{32}}{(CH_2)_5NCH_2CH_2CO_2Et} + [CH_3CHS] \quad (17)$$

only one intense ion, *m/e* 100, corresponding to loss of piperidine from the molecular ion. An ir spectrum of the reaction mixture after nearly complete reaction was very similar to that of the proposed propionate. Preparative tlc ultimately gave **32** identical with the adduct of piperidine and ethyl acrylate.[28] No pure sulfur-containing fragment could be identified.

The general pattern suggested at the outset for reaction with electrophiles thus seems to be borne out with disubstituted sulfenamides in that attack first occurs upon the nitrogen. Thereafter, if a counterion has been expelled (*e.g.*, halide) it attacks the sulfur, effecting nucleophilic displacement of the nitrogen fragment. If an internal charge center has been developed, however, it is now clear that this may not *only* attack $SR^1$ (as in eq 10, 11) but in other situations may give the effect of abstracting a proton from $R^1S$ (as in eq 15–17).

(23) L. Field, A. Ferretti, and T. C. Owen, *J. Org. Chem.*, **29**, 2378 (1964).
(24) J. J. D'Amico, *ibid.*, **26**, 3436 (1961).
(25) F. Kurzer, *J. Chem. Soc.*, 3360 (1953).
(26) E. Hoggarth, *ibid.*, 110 (1947).
(27) J. C. Conly, U. S. Patent 2,860,142; *Chem. Abstr.*, **53**, 7199 (1959).
(28) E. Philippi and E. Galter, *Monatsh. Chem.*, **51**, 253 (1929).

Although the foregoing reactions seem best formulated as being heterolytic, it certainly would be unwise to assert that homolysis does not play a role. One is particularly dubious about ruling out homolysis in the elimination reactions in view of the more vigorous conditions used. Further study on the possible involvement of homolysis would be worthwhile.

One further reaction of an electrophilic nature should be added for the sake of completeness, that of carbonyl compounds (eq 18).[24,29] This reaction works well for

$$R_2CO + R^1SNH_2 \longrightarrow R_2C = NSR^1 + H_2O \qquad (18)$$

benzaldehyde and acetone,[29] but with cyclohexanone and dicarbonyl compounds thioalkylation may occur.[24]

**Reactions with Nucleophiles.**—Reactions of sulfenamides with nucleophiles seem to proceed in a straightforward manner. Thus Grignard reagents,[30] thiols,[31] and amines[9,32] effect displacement on sulfur to give sulfides, disulfides, and sulfenamides respectively. The general reaction seems to be that of eq 19.

$$R^1SNR^2R^3 + (Nu)^- \longrightarrow RS(Nu) + R^2R^3N^- \qquad (19)$$

Nucleophilic attack of one sulfenamide on another seemed likely to result in metathesis (eq 20). How-

$$R^1SNR^2R^3 + R^4SNR^5R^6 \rightleftharpoons R^1SNR^5R^6 + R^4SNR^2R^3 \qquad (20)$$

ever, when the ethyl and *t*-butylsulfenamides **12** and **16** were heated either neat or with amine or thiol catalysts no change occurred in up to 16 hr at 90°. In a similar experiment, **16** was heated with piperidine for 12 days at 90° with no metathesis evident. Although no amine or sulfenamide exchange took place in these experiments, the lack of reaction may have resulted from the steric effect of the *t*-butyl group.

Interest in the chemistry of disulfides prompted us to examine nucleophilic displacement on the acetamidoethyl derivatives **5** and **10** to evaluate their use for the synthesis of unsymmetrical disulfides. Reaction of **10** with 2-acetamidoethanethiol, with triethylamine as a catalyst, gave the symmetrical disulfide **2** in 93% yield. No reaction occurred in the absence of triethylamine. Reaction of **5** or **10** with *p*-toluenethiol proceeded rapidly, in the absence of base, to give 2-*p*-tolyldithio-1-acetamidoethane (**33**) in about 61–70% yield; however, the product from **10** contained some phthalimide and was difficult to purify. An unsuccessful effort was made to develop a general method for preparing unsymmetrical disulfides by a similar route using N-tosyloxyphthalimide. If reaction of the tosyloxyphthalimide with a thiol gave a sulfenamide, reaction with a second thiol should give the unsymmetrical disulfide and phthalimide. This method failed because α-toluenethiol did not react with N-tosyloxyphthalimide. An elegant capitalization along similar lines has been reported recently by Mukaiyama and Takahashi.[33] They prepared a sulfenamide by reaction of one thiol with diethyl azodicarboxylate and then converted this sulfenamide in 75–90% yield to unsymmetrical disulfides using a second thiol.[33] In our experience, a highly nucleophilic aminothiol may behave poorly in this synthesis owing to attack of the first thiol on the sulfenamide as it forms, thus leading to a symmetrical disulfide in the first stage.

**Biological Properties.**—Toxicities and antiradiation activities of typical products are being evaluated by means outlined earlier.[3] Preliminary results indicate that none of the sulfenamides and related products led to significant protection in mice against ionizing radiation.[34] Results thus far suggest therefore that $NR^2R^3$ is surprisingly unpromising as a latentiating group for biologically active thiols.

## Experimental Section[35]

**Materials.**—Preparations were performed as reported for N-phenymaleimide,[36] 2-acetamidoethyl disulfide (**2**),[37] N-(*t*-butylthio)piperidine (**14**),[7] N-(*n*-butylthio)piperidine (**13**),[7] N-(ethylthio)piperidine (**12**),[7] N-(*t*-butylthio)aniline (**17**),[7] and N-(ethylthio)diethylamine (**15**).[10] Satisfactory melting points or analysis by glpc or nmr were obtained for all the above-listed compounds. Morpholine sulfide (**19**) and piperidine sulfide (**20**) were gifts from J. L. Richards, to whom we are grateful. All other materials were purchased and used without purification.

**2-Acetamidoethanesulfenyl Chloride (3).**—Illustratively, a solution of 2.00 g (8.48 mmol) of 2-acetamidoethyl disulfide (**2**) in 75 ml of $CH_2Cl_2$ was cooled to −35°. Chlorine (0.4 ml, 8.8 mmol), previously collected in a Dry Ice–acetone cooled vessel, was allowed to evaporate during 15 min into the stirred solution. After 10 min, the amount of **3** was determined by iodometric titration;[38] 2 ml of the solution of **3** required 3.39 ml of 0.0731 *N* sodium thiosulfate solution (0.248 meq) (55% yield). Reasonable stability of **3** was found at −35°, since titration at intervals up to 2.5 hr gave the same result. In the preparation of sulfenamides, however, the amount of sulfenyl chloride specified is simply twice the number of mols of disulfide used, the assumption being made that the yield was theoretical from the disulfide as the limiting reagent.

**General Procedure for Synthesis of Sulfenamides. A.**—The **3** from *ca.* 2 g (8.5 mmol) or 4 g (17 mmol) of **2** and an equimolar quantity of $Cl_2$, 0.4 ml (8.8 mmol) or 0.8 ml (17.6 mmol), was

(29) J. A. Barltrop and K. J. Morgan, *J. Chem. Soc.*, 3072 (1957).

(30) H. Gilman and C. C. Vernon, *Recl. Trav. Chim. Pays-Bas*, **48**, 743 (1929).

(31) A. Fontana, F. Marchiori, L. Moroder, and E. Scoffone, *Tetrahedron Lett.*, 2985 (1966).

(32) L. H. Howland, U. S. Patent 2,382,793; *Chem. Abstr.*, **40**, 368 (1946).

(33) T. Mukaiyama and K. Takahashi, *Tetrahedron Lett.*, 5907 (1968).

(34) We are indebted for these evaluations to Drs. D. P. Jacobus, T. R. Sweeney, and E. A. Steck, and Miss Marie Grenan, all of the Walter Reed Army Institute of Research, Washington, D. C. Preliminary $ALD_{50}$[b] results (mg/kg) for compounds follow: **5**, 240; **6**, 475; **8**, 130; **10**, 45; **11**, 150; **13**, 75; **14**, 430; **21**, 800; **23**, 60; **24**, > 300. Thus far, **5** has led only to 17% survival at 180 mg/kg (0% at 90) and **23** only to 7% survival at 30 mg/kg (0% at 15). The other compounds just mentioned were completely inactive when tested at *ca.* 0.3–0.6 × $ALD_{50}$. Other compounds remain to be tested.

(35) Melting points are corrected, and boiling points are uncorrected. Elemental analyses were by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Mass spectra were obtained with an LKB Model 9000 instrument, operating at 70 eV, source temperature 250°, and accelerating potential 3.5 kV, unless specified otherwise, using either direct-inlet or gas chromatographic (glass, 6-ft 1% SE-30 on a Gas Chrom Q column) inlet systems; the instrument was obtained through Science Development Program Grant GU-2057 from the National Science Foundation; we are indebted to Mr. Charles Wetter for these spectra. In the mass spectra, peaks of relative intensity lower than 5% are reported only for products of eq 3, 4, 5, or 6, or elsewhere when thought important. Ir spectra were obtained using a Beckman Model IR-10 with films of liquids and KBr pellets of solids; absorptions are given in $cm^{-1}$, "s" signifying strong (other reported were medium). Glpc analyses were obtained using a 6-ft stainless-steel 10% SE-30 on Chromosorb P column, injection port 250°, detector 220°, column temperature 130–170°. Nmr spectra were obtained with a Varian Model A-60 with TMS as internal standard in $CCl_4$ unless otherwise noted. Raman spectra were obtained with a Cary Model 81 instrument. We thank the National Science Foundation for departmental grants GP-1683 and GP-6932 respectively toward purchase of the latter two instruments. Unless otherwise stated, reactions were done at room temperature. Moist extracts were dried using the anhydrous reagent specified, and solvents were evaporated at reduced pressure with a rotary evaporator. Short-path distillations were done in a conventional falling-drop apparatus with a path length of *ca.* 1–2 cm or less.

(36) M. P. Cava, A. A. Deana, K. Muth, and M. J. Mitchell, *Org. Syn.*, **41**, 93 (1961).

(37) L. Field, T. C. Owen, R. R. Crenshaw, and A. W. Bryan, *J. Amer. Chem. Soc.*, **83**, 4414 (1961).

(38) N. Kharasch and M. M. Wald, *Anal. Chem.*, **27**, 996 (1955).

added slowly (*ca.* 0.3 hr) to a solution of the amine or amide, 17 or 34 mmol, in $CH_2Cl_2$ at $-20 \pm 10°$. Either an excess of the amine was used (usually *ca.* 2.5 mol of total amine/mol RSCl) or $Et_3N$ was present (*ca.* 1.5 mol/mol RSCl). The solution was stirred for 1.5 hr during which time it warmed to *ca.* 25°; it was then washed with water to remove amine salts or excess amine, dried ($MgSO_4$ or $Na_2SO_4$), and evaporated to dryness under reduced pressure. Crude products then were purified by column chromatography, short-path distillation, or recrystallization (*vide infra*).

**B. Applications of Procedure A. N-(2-Acetamidoethylthio)-*p*-carbomethoxyaniline (4).**—The crude product from 5.1 g (34 mmol) of methyl *p*-aminobenzoate by A (55% **4** by nmr analysis) was chromatographed over Florisil in $CHCl_3$ to give 1.0 g (11% yield). Two recrystallizations from ethyl acetate gave mp 98–100°; nmr ($CDCl_3$) $\delta$ 2.00 (s, 3, $CH_3C(=O)N$), 2.70 (m, 2, $CH_2$–S), 3.50 (m, 2, $CH_2$–NH), 3.85 (s, 3, $CH_3O$), 6.45 (s, 1, NH Ar), 7.10 (m, 3, 2ArH and Ac NH), and 7.90 (m, 2, 2ArH); mass spectrum *m/e* (rel intensity) 270 (0.3), 269 (0.7), 268 (4), 182 (0.2), 152 (6), 151 (61), 150 (3), 121 (9), 120 (100), 118 (4), 92 (31), 91 (5), 87 (7), 86 (6), 84 (9), 72 (15), 65 (25), 64 (5), 63 (6), 60 (8), 45 (20), 44 (9), 43 (100), and 42 (9).

*Anal.* Calcd for $C_{12}H_{16}N_2O_3S$: C, 53.71; H, 6.01; N, 10.44. Found: C, 53.58; H, 6.01; N, 10.42.

**N-(2-Acetamidoethylthio)-2-aminobenzothiazole (5).**—The $CH_2Cl_2$ solution from A (17 mmol of **2**) after the water wash and before drying, was chilled at 5° for 3 hr and filtered: yield of **5**, 5.1 g (56%), mp 140–141° (dec). Partial evaporation of the filtrate and chilling gave an additional 0.6 g (7%) of **5**, mp 140–142° (dec). Recrystallization from EtOH–$H_2O$ gave pure **5**: mp 142–143°; nmr ($C_5D_5N$) $\delta$ 2.05 (s, 3, $CH_3C(=O)N$), 3.15 (m, 2, $CH_2S$), 3.80 (m, 2, $CH_2NH$), 7.0–8.0 (m, *ca.* 4, Ar), 8.57 (s, $w_{1/2}$ 14 Hz, 1, $NHCH_2$), and 8.74 (s, 1, NHS); mass spectrum *m/e* (rel intensity) 269 (0.2), 268 (0.2), 267 (2), 182 (1), 152 (5), 151 (13), 150 (100), 149 (4), 123 (21), 122 (6), 118 (22), 117 (2), 109 (6), 96 (22), 86 (18), 76 (5.4), 75 (12), 72 (5.3), 69 (13), 60 (18), 45 (7), 44 (13), 43 (33), and 42 (5).

*Anal.* Calcd for $C_{11}H_{13}N_3OS_2$: C, 49.35; H, 4.89; N, 15.69; S, 23.95. Found: C, 49.29; H, 4.91; N, 15.63; S, 24.09.

**N-(2-Acetamidoethylthio)-N,N-diethylamine (6).**—The crude product from $Et_2NH$ (excess) and the **3** from 8.5 mmol of **2**, 1.78 g (55%) of a pale yellow oil, $n^{25}D$ 1.4905, was chromatographed over Florisil in benzene. A middle fraction, the fourth of seven ($n^{25}D$ 1.4913), was analyzed. Crude **6** also was purified by short-path distillation (70°, 0.08 mm) to give pure **6**: $n^{25}D$ 1.4899 (*ca.* 70% yield in distillation, net yield 39%); nmr (neat) $\delta$ 1.12 (t, 6, $CH_3CH_2$), 1.95 (s, 3, $CH_3C(=O)N$), 2.9 (m, 6, $CH_2$–$CH_3$ and $CH_2$–S), 3.35 (m, 2, $CH_2$–NH), and 8.20 (m, 1, $NHCH_2$); mass spectrum *m/e* (rel intensity) 192 (0.07), 191 (0.4), 190 (2), 118 (4), 104 (2), 86 (26), 73 (1), 72 (100), 58 (7), 56 (6), 44 (32), 43 (29), and 42 (20).

*Anal.* Calcd for $C_8H_{18}N_2OS$: C, 50.49; H, 9.43; N, 14.72; S, 16.85. Found: C, 50.77; H, 9.52; N, 14.41; S, 17.05.

**N-(2-Acetamidoethylthio)piperidine (7).**—The crude **7** from **3** (34 mmol, theory) and excess piperidine was obtained in 103% yield (7.0 g, $n^{28}D$ 1.5125). A 6.0-g portion was purified by short-path distillation (80°, 0.08 mm) to give 3.0 g (51%) of pure **7**: $n^{28}D$ 1.5160; nmr $\delta$ 1.48 (m, 6, $-(CH_2)_3-$), 1.95 (s, 3, $CH_3C(=O)N$), 2.5–3.1 (m, 6, $-(CH_2)_2N$ + $-CH_2S$), 3.45 (m, 2, $CH_2$–NH), and 7.81 (m, 1, $NHCH_2$); mass spectrum *m/e* (rel intensity) 204 (0.7), 203 (2), 202 (12), 119 (3), 118 (5), 117 (3), 116 (5), 87 (6), 86 (100), 85 (9), 84 (40), 83 (5), 60 (9.5), 56 (10), 55 (20), 44 (44), 43 (30), 42 (27), and 41 (9).

*Anal.* Calcd for $C_9H_{18}N_2OS$: C, 53.43; H, 8.97; N, 13.84; S, 15.85. Found: C, 53.24; H, 8.72; N, 13.69; S, 15.91.

**N-(2-Acetamidoethylthio)morpholine (8).**—The crude **8** from **3** (*ca.* 34 mmol theory) by A, 6.0 g (86%) of pale yellow oil $n^{28}D$ 1.5154, was purified by short-path distillation (80°, 0.1 mm) to give a slightly yellow oil: 2.0 g (29%); $n^{28}D$ 1.5150; nmr $\delta$ 1.96 (s, 3, $CH_3C(=O)N$), 2.9 (m, 6, $-CH_2NS$ + $-CH_2S$), 3.1–3.8 (m, 6, $CH_2O$ + $CH_2NH$), and 7.88 (m, 1, $NHCH_2$); mass spectrum *m/e* (rel intensity) 206 (0.7), 205 (2), 204 (13), 119 (3) 118 (14), 88 (7), 87 (16), 86 (100), 76 (6), 72 (8), 57 (30), 56 (47), 55 (7), 54 (40), 42 (18), and 41 (6).

*Anal.* Calcd for $C_8H_{16}N_2O_2S$: C, 47.05; H, 7.89; N, 13.72; S, 15.70. Found: C, 46.96; H, 7.79; N, 13.62; S, 15.49.

**N-(2-Acetamidoethylthio)benzimidazole (9).**—The crude **9** from **3** (34 mmol theory) and 4.0 g (34 mmol) of benzimidazole was crystallized from acetone to give 2.2 g of white needles (28%). Partial evaporation of the solvent gave an additional 1.2 g, total yield 42%. Two recrystallizations from acetone gave **9** of mp 118–121° (dec); nmr ($CDCl_3$) $\delta$ 1.92 (s, 3, $CH_3C(=O)N$), 2.8–3.7 (m, 4, $NCH_2CH_2S$), 7.1–7.9 (m, 5, 4ArH + NH), and 8.02 (s, 1, $-N=CH-N-$); mass spectrum *m/e* (rel intensity) 237 (0.2), 236 (0.5), 235 (2.0), 119 (21), 118 (100), 117 (7), 91 (26), 90 (11), 86 (7), 76 (5), 65 (14), 64 (15), 63 (52), 59 (5), 52 (6), 44 (7), and 43 (25).

*Anal.* Calcd for $C_{11}H_{13}N_3OS$: C, 56.14; H, 5.57; N, 17.86; S, 13.63. Found: C, 56.13; H, 5.67; N, 17.82; S, 13.42.

**N-(2-Acetamidoethylthio)phthalimide (10).**—The crude **10** from 31.4 g (170 mmol) of the potassium salt of phthalimide and **3** (176 mmol) was crystallized from MeOH to give 20.0 g (45%) of **10**, mp 144–149°. Concentration of mother liquor gave 9.0 g of phthalimide. Recrystallization from MeOH gave pure **10**: mp 149–150°; nmr ($CDCl_3$) $\delta$ 2.08 (s, 3, $CH_3C(=O)N$), 3.0 (m, 2, $CH_2S$), 3.4 (m, 2, $CH_2NH$), 6.85 (s, $w_{1/2}$ 20 Hz, 1, NH), and 7.9 (m, 4, ArH); mass spectrum *m/e* (rel intenstiy) 266 (0.1), 265 (0.2), 264 (2), 205 (17), 179 (1), 178 (2), 160 (8), 149 (7), 148 (68), 147 (55), 130 (31), 119 (6), 118 (10), 117 (100), 105 (7), 104 (51), 103 (17), 102 (69), 86 (16), 84 (20), 77 (56), 76 (66), 75 (37), 74 (15), 72 (13), 60 (29), 59 (5), 58 (15), 50 (30), and 44 (24).

*Anal.* Calcd for $C_{12}H_{12}N_2O_3S$: C, 54.58; H, 4.58; N, 10.61; S, 12.14. Found: C, 54.91; H, 4.63; N, 10.46; S, 12.33.

**N-(2-Acetamidoethylthio)-*p*-toluenesulfonamide (11).**—The solution of crude **11** from **3** (34 mmol theory) and 5.8 g (34 mmol) of *p*-toluenesulfonamide (using $Et_3N$) was washed with a solution of 3.2 g (80 mmol) of NaOH in 100 ml of $H_2O$. The aqueous layer then was cooled and brought to pH 4 with 50% AcOH. The resulting solid was removed by filtration and dried to give 6.3 g (64%) of crude **11**,[39] mp 99–120°.

The solid was chromatographed over silica gel (Baker 60–200 mesh; 180 g) in EtOAc to give 2.1 g (21%) of **11**. Recrystallizations from $Me_2CO$ gave pure **11**: mp 120.5–121°; nmr ($CDCl_3$) $\delta$ 1.97 (s, 3, $CH_3C(=O)N$), 2.41 (s, 3, $CH_3Ar$), 3.2–3.9 (m, 4, $NCH_2CH_2S$), 5.32 (s, $w_{1/2}$ = 13 Hz, 1, $NHSO_2$), 6.9 (s, $w_{1/2}$ = 25 Hz, 1, $NHC(=O)-$), 7.30 (m, 2, 2 ArH), and 7.80 (m, 2, 2 ArH).

*Anal.* Calcd for $C_{11}H_{16}N_2O_3S_2$: C, 45.81; H, 5.59; N, 9.71; S, 22.23. Found: C, 45.89; H, 5.52; N, 9.56; S, 21.88.

**N-(*t*-Butylthio)-N,N-diethylamine (16).**—2-Methyl-2-propanesulfenyl chloride, from chlorination of *t*-butyl disulfide at *ca.* 25°, was added dropwise to excess diethylamine in petroleum ether at 5°. The resulting mixture was washed twice with water and distilled (20-cm Vigreux column) to give pure **16**: bp 48° (8.0 mm); $n^{28}D$ 1.4479; nmr $\delta$ 1.08 (t, 6, $CH_3CH_2$), 1.20 (s, 9, $(CH_3)_3$), and 2.97 (q, 4, $CH_2$ $CH_3$).

*Anal.* Calcd for $C_8H_{19}NS$: C, 59.56; H, 11.87. Found: C, 59.36; H, 11.91.

**Thermolysis.**—Thermolyses were carried out on neat samples in open vessels (**5**, **8**, **10**, and **13**) for the time shown in Table I, or for 4 days in a sealed ampoule (**6** and **16**). Analysis of the products was accomplished by tlc (acetone, Brinkmann F-254 precoated analytical plates) for acetamidoethyl derivatives and are qualitative estimates based on visually estimated spot intensities. Volatile products from **6**, **8**, and **13** were analyzed by glpc and mass spectrometry. **N-(*n*-butylthio)piperidine (13**, 1.00 g) after 20 min at 140° showed no new peaks or change in the ratio of the original peak heights of **13** and *n*-butyl disulfide in the sample used as a standard. Further heating (1 hr) caused slight darkening but no change by glpc analysis. **N-(2-Acetamidoethylthio)phthalimide (10**, 10 mg) after 20 min at 155° gave a nearly colorless residue. Tlc analysis, by comparison with **10** and phthalimide, showed a large spot corresponding to **10** and only a trace of phthalimide.

**N-(2-Acetamidoethylthio)morpholine (8**, 10 mg), after 20 min at 140° gave a dark residue. Tlc analysis by comparison with pure **8** showed only a small spot corresponding to **8** and other spots not identified. Glpc and mass spectrometric analysis starting at 40° and programming for an increase of 10°/min, showed only the presence of morpholine and N-acetylmorpholine, mol wts (ms) 87 and 129 respectively. **N-(2-Acetamidoethylthio)-2-aminobenzothiazole (5**, 10 mg) after 20 min at 155° left a dark residue. Tlc analysis by comparison with **5** and 2-aminobenzothiazole showed only a trace of **5** and a large spot corresponding to 2-aminobenzothiazole.

(39) This separation of **11** was based on information on the physical properties of compounds like **11** kindly supplied to us by Professor Robert B. Scott of the University of Mississippi.

**N-(2-Acetamidoethylthio)-N,N-diethylamine** (**6**, 2.00 g), in a sealed ampoule was heated at 100° for 4 days. Tlc analysis of the reaction mixture showed only a small portion of the mixture to be **6**. Glpc–mass spectrometric analysis, starting at 60°, programmed at 5°/min to 230°, showed five volatile products.

Spectral data for the products follow. The first product, N,N-diethylacetamide [*m/e* (rel intensity) 115 (22), 100 (18), 86 (4), 72 (16), 58 (100), 44 (34), 43 (34) and 30 (22)], was identified by comparison of its mass spectrum with that reported.[40] The yield of the second product was small and it could not be identified. The third product [*m/e* (rel intensity) 131 (81), 130 (17), 102 (17), 72 (16), 70 (30), 61 (44), 59 (67), 58 (15), 56 (10), 44 (100), 42 (68), and 30 (12)] showed a molecular ion at *m/e* 131; the intensity of *m/e* 133 (4% of 131) suggested the presence of a sulfur atom; loss of 29 ($C_2H_5$) and 72 ($NEt_2$) as well as presence of a strong peak at *m/e* 59, $(CH_3CS)^+$, are consistent with assignment as N,N-diethylthioacetamide. The fourth product, also the glpc peak of largest intensity, had the mass spectrum *m/e* (rel intensity) 188 (34), 154 (10), 129 (18), 116 (39), 88 (75), 82 (30), 72 (65), 60 (67), 56 (55), 54 (22), 44 (43), 43 (100), 42 (37), and 30 (78); it showed a molecular ion at *m/e* 188; *m/e* 190 (5% of *m/e* 188) suggests a sulfur atom. The presence of intense ions at *m/e* 30 ($CH_2NH_2^+$), 43 ($CH_3CO^+$), and 60 ($CH_3C(=O)NH_3^+$) suggest the presence of an N-substituted acetamide. The *m/e* 72 ($Et_2N^+$) ion suggests that the second nitrogen is present as an N,N-diethyl group. Thus N,N-diethyl-N′-acetylthioglycinamide, $AcNHCH_2C(S)NEt_2$, seems a good possibility since similar compounds have been observed in the decomposition of α-ketosulfenamides.[41] The fifth component of the mixture was not assigned a structure: mass spectrum *m/e* (rel intensity) 150 (23), 120 (38), 87 (63), 86 (20), 72 (100), 56 (80), 44 (87), 43 (76), 42 (33), and 30 (23). Under the same conditions (4 days, 100°), **16** was recovered unchanged ($n^{28}D$ = 1.4485).

**Attempted Photolysis.**—In a quartz vessel, N-(*t*-butylthio)-N,N-diethylamine, **16** (2.00 g), in 500 ml of cyclohexane and 10 ml of cyclohexene was irradiated for 18 hr using a 100-W Hanovia lamp. Partial evaporation of the solvent (total residual wt, 2.4 g), followed by glpc and mass spectrometric analysis showed the presence of only starting material. Complete evaporation (80° at *ca.* 15 mm) gave 1.5 g (75%) of **16**, which was identified by its ir spectrum.

**Mass Spectra.**—Mass spectra were obtained using the direct-inlet system for **2** and **4–10** and using the glpc-inlet system for **12–14**, **16**, and **17**. In the latter case, reported intensity values were from two identical scans.

Mass spectra, *m/e* (rel intensity), not reported above follow: **12**, 145 (68), 144 (42), 118 (4), 117 (14), 116 (68), 104 (10), 89 (14), 88 (7), 87 (7), 85 (14), 84 (52), 83 (13), 62 (16), 61 (44), 60 (21), 59 (10), 58 (5), 57 (20), 56 (30), 55 (100), 54 (14), 53 (9), 47 (13), 46 (10), 45 (14), 44 (21), 43 (18), 42 (65), 41 (45), 40 (43), and 29 (54); **13**, 173 (35), 172 (4), 117 (16), 116 (31), 89 (3), 86 (13), 85 (64), 84 (100), 75 (7), 62 (12), 61 (18), 60 (17), 59 (8), 57 (29), 56 (32), 55 (88), 54 (12), 53 (9), 47 (16), 46 (10), 45 (16), 44 (16), 43 (23), 42 (64), 41 (68), and 40 (5); **14**, 173 (25), 118 (11), 117 (100), 116 (25), 89 (3), 84 (10), 75 (8), 62 (7), 61 (15), 60 (11), 59 (17), 58 (5), 57 (86), 56 (23), 55 (45), 54 (7), 53 (7), 46 (5), 45 (7), 44 (8), 43 (36), 42 (38), 41 (97), and 40 (7); **16**, 161 (19), 105 (57), 104 (10), 90 (100), 89 (1), 76 (10), 74 (2), 73 (2), 62 (8), 61 (6), 59 (8), 58 (14), 57 (38), 56 (10), 48 (5), 46 (7), 44 (13), 42 (34), and 41 (46); **17** (70 eV), 181 (15), 127 (5), 126 (8), 125 (100), 124 (4), 97 (6), 93 (60), 92 (31), 89 (15), 80 (6), 79 (15), 77 (17), 66 (21), 65 (26), 63 (5), 57 (59), and 56 (18); (12 eV), 181 (68), 127 (5), 126 (8), 125 (100), 105 (60), 57 (9), and 56 (15).

**Ir and Raman Spectra.**—All compounds were done neat. The most noteworthy absorptions in $cm^{-1}$ were as follows. For **EtSN(CH₂)₅** (**12**), ir spectrum 685, 860, 930 (s), 1040 (s), 1060, 1100, 1050, 1220 (s), 1270, and 1375 and Raman spectrum 525, 635, 660, 690, 840 (s), 1040 (s), 1060, and 1270 were obtained. For ***n*-BuSN(CH₂)₅** (**13**): ir 685, 860, 930 (s), 1040 (s), 1060, 1100, 1150, 1225 (s), 1270 (s), 1295, and 1370. For ***t*-BuSN(CH₂)₅** (**14**): ir 860, 925 (s), 950, 1040 (s), 1060 (s), 1100, 1160 (s), 1220 (s), 1260, and 1365 (s). For **EtSNEt₂** (**15**): ir 690, 728 (s), 1175, and 1380; Raman 525, 770, 790 (s), 1010 (s), 1036, and 1214. For ***t*-BuSNHPh** (**17**): ir 690 (s), 750 (s), 890, 1165, 1175, 1240, 1290, and 1365. For **morpholine sulfide** (**19**): ir 680, 930 (s), 950, 1060, 1100 (s), 1260, 1300, and 1365; Raman 370, 480, 600 (s), 680 (s), 850 (s), 1030 (s), 1055, 1210, and 1305. For **piperidine sulfide** (**20**): ir 450, 670, 820, 850, 910, 930, 1030, 1100, 1150, 1210 (s), 1270, 1295, 1340, and 1365; Raman 552 (s), 675 (s), 840 (s), 1050 (s), 1150, 1219, 1260, 1273, 1290, and 1436. For the other sulfenamides (**4-11**, **16**), the ir spectra showed no unexpected features and did not need to be added to the typical spectra above.

**Reactions of Sulfenamides with Electrophiles. A. With Methyl Iodide.**—A solution of 0.83 g (4.8 mmol) of **13** (slightly contaminated with *n*-butyl disulfide) in 2 ml of MeI was allowed to stand overnight; the reaction mixture darkened rapidly. Titration of the mixture in EtOH–$H_2O$ with 42.0 ml of 0.073 *N* $Na_2S_2O_3$ showed 3.06 mequiv (64%) of iodine. The titrated solution was evaporated to near dryness, diluted with water, and extracted with $CH_2Cl_2$, yield 0.54 g (126%) of *n*-butyl disulfide, identified by ir, nmr, and glpc-peak enhancement. Similarly, 87.0 mg (0.503 mmol) of **13** in 1 ml of MeI gave 0.376 mequiv of $I_2$ (75%). A solution of 125 mg (0.86 mmol) of **12** in 1 ml of MeOH and 1 ml of MeI, allowed to stand for 1 hr, gave 0.88 mequiv (102%) of $I_2$.

**B. With *p*-Toluenesulfonyl Chloride.**—An equimolar mixture of **13** (1.73 g, 10 mmol) and *p*-toluenesulfonyl chloride (1.90 g, 10 mmol) in 10 ml of cyclohexene was allowed to stand for 15 days. Analysis of the product mixture by glpc and mass spectrometry, starting at 100°, programmed at 10°/min, showed the principal products to be 1-*p*-toluenesulfonylpiperidine [mass spectrum *m/e* (rel intensity) 239 (25), 238 (20), 155 (24), 92 (13), 91 (67), 85 (6), 84 (100), 83 (36), 65 (25), 63 (7), 57 (6), 56 (14), and 55 (31)], which had a mass spectrum identical with that of the product prepared by reaction of piperidine with *p*-toluenesulfonyl chloride,[42] and 2-chlorocyclohexyl *n*-butyl sulfide [mass spectrum *m/e* (rel intensity) 208 (3.1), 207 (1.5), 206 (8.3), 171 (8.1), 129 (9.1), 116 (6.0), 91 (5.4), 88 (5.4), 82 (9.5), 81 (100), 79 (25), 75 (9.8), 73 (6.8), 71 (7.2) 67 (14), and 61 (10.2)], which had a mass spectrum identical with that of an authentic sample. For the preparation of authentic **2-chlorocyclohexyl *n*-butyl sulfide**, *n*-butyl disulfide (17.8 g, 0.1 mol) in petroleum ether was chlorinated with 0.1 mol of $Cl_2$ at −30°, and the product then was added to excess cyclohexene. Removal of solvent left pale yellow oil; distillation (90–91°, 1.2 mm) gave 8.4 g (20%); glpc and mass spectrometry showed the presence of both *cis* and *trans* isomers.

*Anal.* Calcd for $C_{10}H_{19}ClS$: C, 58.04; H, 9.26. Found: C, 57.88; H, 9.20.

**C. With Carbon Disulfide.**—For the reaction of **N-(*t*-butylthio)piperidine** (**14**), 2.7 g (16 mmol) of **14** in 10 ml of ether was added to 20 ml of $CS_2$. The mixture slowly turned yellow. It was let stand until the reaction was complete (*ca.* 21 days), as determined by weight gain after removal of solvent. The product was recrystallized from methanol by dissolution at *ca.* 50° and then chilling in Dry Ice: yield of colorless **21**, 2.00 g (50%); mp 56–57°; nmr ($CDCl_3$) δ 1.35 (s, 9), 1.74 (m, 6), 4.19 (m, 4); mass spectrum *m/e* (rel intensity) 251 (0.3), 250 (1), 249 (2), 130 (5), 129 (8), 128 (100), 84 (12), 77 (8), 72 (39), 69 (60), 59 (11), 57 (29), 56 (25), 55 (17), 53 (5), 45 (7.6), 42 (18), and 41 (90). Independent synthesis of **21** was achieved by treating piperidinium N-pentamethylene dithiocarbamate in water with 2-methyl-2-propanesulfenyl chloride in petroleum ether, essentially as reported;[43] recrystallization of the crude **21** (MeOH) gave **21** in 60% yield. Further recrystallization gave colorless **21** having constant mp 59–61° and an ir spectrum identical with that of the previous reaction product.

*Anal.* Calcd for $C_{10}H_{19}NS_3$: C, 48.15; H, 7.68. Found: C, 48.24; H, 7.57.

With **N-(Ethylthio)piperidine** (**12**), addition of $CS_2$ (10 ml) to 1.00 g of **12** (6.9 mmol) resulted in rapid evolution of heat. After 0.5 hr, evaporation of excess $CS_2$ left 1.44 g (95% yield) of bright yellow oil ($n^{27}D$ 1.6284), which gave only one spot on tlc (3:1 heptane–benzene, silica gel). Short-path distillation (70°, 0.1 mm), gave 1.30 g of **22**, $n^{27}D$ 1.6274. In another experiment a solution of 4.00 g (27.6 mmol) of **12** in 50 ml of dry ether was added dropwise to 30 ml of $CS_2$. The solution became yellow

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(42) L. G. Groves, E. E. Turner, and G. I. Sharp, *J. Chem. Soc.*, 512 (1929).

(43) C. M. Himel and L. O. Edmonds reported **21**, but without melting point or analysis.[19]

and after 2 hr the solvent was evaporated to give 5.90 g (97%) of yellow oil, $n^{27}$D 1.6275. Short-path distillation (80°, 0.05–0.1 mm) gave $n^{26}$D 1.6259. Another distillation (60°, 0.025 mm) gave $n^{26}$D 1.6257; nmr $\delta$ 1.35 (t, 3, $CH_3CH_2$), 1.80 (s, $w_{1/2}$ = 7 Hz, 6, $(CH_2)_3$), 2.90 (q, 2, $CH_2CH_3$), and 4.20 (s, $w_{1/2}$ = 11 Hz, 4, $CH_2N$); mass spectrum *m/e* (rel intensity) 223 (0.4), 222 (0.7), 221 (2.5), 220 (4), 130 (5), 129 (9), 128 (100), 93 (17), 84 (20), 77 (20), 76 (10), 72 (80), 70 (6), 69 (72), 67 (7), 65 (7), 64 (19), 61 (12), 60 (12), 59 (25), 58 (18), 56 (51), 55 (24), 54 (13), 53 (10), 46 (15), 45 (45), 43 (7), 42 (40), and 41 (100).

*Anal.* Calcd for $C_8H_{15}NS_3$: C, 43.40; H, 6.83. Found: C, 43.63; H, 7.00.

With **N-(2-Acetamidoethylthio)morpholine** (**8**) a solution of **8**, 0.35 g (1.7 mmol), in $CH_2Cl_2$ was added dropwise to 1 ml of $CS_2$. After the initial exothermic reaction, the yellow mixture was let stand for 0.5 hr. Removal of the solvent gave 0.48 g (100%) of crystalline **23**, mp 86–89°. Two recrystallizations from EtOAc gave **23** having constant mp 96–98°; ir 3270, 3100, 1645, 1550, 1420, 1220 cm$^{-1}$; mass spectrum *m/e* (rel intensity) 282 (0.4), 281 (0.4), 280 (2.4), 195 (3), 163 (5), 132 (5), 131 (8), 130 (100), 118 (8), 87 (9), 86 (66), 77 (5), 76 (29), 75 (6), 60 (15), 59 (7), 57 (10), 56 (10), 45 (6), 44 (12), 43 (30), and 42 (8).

*Anal.* Calcd for $C_9H_{16}N_2O_2S_3$: C, 38.54; H, 5.75; S, 34.30. Found: C, 38.73; H, 5.87; S, 34.13.

**D. With Phenyl Isothiocyanate.—N-(*t*-Butylthio)piperidine** (**14**, 1.90 g, 10.9 mmol) and PhNCS (1.47 g, 10.9 mmol) were allowed to stand until change ceased in the ir spectrum (30 days). A small portion of the oil ($n^{26}$D 1.5774) was purified by short-path distillation (65°, 0.002 mm) to give an oil ($n^{26}$D 1.5890), which crystallized when seeded with a crystal from the still. The undistilled product was recrystallized twice from heptane using these seeds (Dry Ice cooling) to give **24**: yield, 1.8 g (54%); constant mp 39–41°; ir 1610, 1590, 1490, 1450, 1390, 1370, 1225, 1175, 1160, 1115, 1000, 750, and 690 cm$^{-1}$; nmr $\delta$ 1.22 (s, 9), 1.67 (s, $w_{1/2}$ = 4 Hz, 6 $(CH_2)_3$), 3.5 (s, $w_{1/2}$ = 10 Hz, 4, $CH_2N$), and 6.7–7.5 (m, 5); mass spectrum *m/e* (rel intensity) 308 (0.2), 219 (4), 188 (15), 187 (100), 131 (14), 77 (20), 69 (7), 57 (8), and 55 (7).

*Anal.* Calcd for $C_{16}H_{24}N_2S_2$: C, 62.29; H, 7.84; S, 20.80. Found: C, 62.23; H, 7.81; S, 20.65.

For the independent synthesis of **24**, 2-methyl-2-propanesulfenyl chloride from *t*-butyl disulfide (39 mmol) and 1.8 ml of liquid $Cl_2$ (39 mmol) in 75 ml of petroleum ether at 25° was added dropwise to 17.2 g of N-phenyl-N′-pentamethylenethiourea (78 mmol) in 150 ml of 1:1 $CH_2Cl_2$–$Et_2O$ at 5°, and the mixture was stirred at 5° for 1 hr. The solution then was washed with 35% HCl and then water, and the organic layer then was evaporated to dryness to give 16.0 g of the HCl salt of **24** (60%), mp 140–141°; recrystallization from benzene gave an analytical sample, mp 140–141°.

*Anal.* Calcd for $C_{16}H_{25}ClN_2S_2$: C, 55.71; H, 7.30. Found: C, 56.10; H, 7.29.

A suspension of the hydrochloride (3.44 g, 10.0 mmol) was neutralized with 2 equiv of aqueous $Na_2CO_3$. Immediate extraction with $Et_2O$, evaporation, and recrystallization (heptane, Dry Ice–acetone bath) gave 2.30 g (75%) of **24**, mp 39–41°. The ir spectrum was identical with that of **24** obtained from the isothiocyanate reaction.

**N-(Ethylthio)piperidine** (**12**, 0.29 g, 2.0 mmol) and PhNCS (0.27 g, 2.0 mmol) were allowed to stand for 1 day, even though by ir analysis the reaction is complete in 5 min. The product (**25**) then was purified by short-path distillation (65°, 0.002 mm) to a constant refractive index of $n^{26}$D 1.6108; yield 0.44 g, 79%; nmr ($CDCl_3$) $\delta$ 1.08 (t, 3, $CH_3$), 1.3–1.9 (s, $w_{1/2}$ = 5 Hz, 6, $(CH_2)_3$), 2.48 (q, 2, $CH_2CH_3$), 3.50 (s, $w_{1/2}$ = 10 Hz, 4, $CH_2N$), and 6.5–7.4 (m, 5, Ph); ir 1610, 1590 (>C=N), 1500; mass spectrum *m/e* (rel intensity) 280 (0.3), 219 (5), 188 (14), 187 (100), 131 (12), 119 (5), 109 (5), 84 (6), 77 (18), 69 (9), 55 (7), 51 (6), 42 (5), and 41 (18).

*Anal.* Calcd for $C_{14}H_{20}N_2S_2$: C, 59.96; H, 7.19; S, 22.86. Found: C, 60.16; H, 7.24; S, 23.03.

**E. With Phenyl Isocyanate.**—Phenyl isocyanate (2.16 g, 18.2 mmol) and N-(ethylthio)piperidine, **12**, (2.64 g, 18.2 mmol) were heated on a steam bath (*ca.* 90°) for 3 days. The dark crystalline mass was then triturated with $CCl_4$. Crystalline material was removed and recrystallized from $CCl_4$ to give 2.14 g (58%) of white crystals identified by nmr as N-pentamethylene-N′-phenylurea (**29**), mp 167–171°, lit.[44] mp 171–172°; the ir spectrum was identical with that of **29** prepared from PhNCO and piperidine.[44]

**F. With Olefins.—N-Phenylmaleimide** (86 mg, 0.5 mmol) and **N(ethylthio)piperidine**, (**12**, 73 mg, 0.5 mmol) were heated at 90° for 16 hr. The mixture at first became light red. It then turned very dark and the maleate chromophore (*ca.* 220 mμ) disappeared. Upon dissolution of the product in $CCl_4$, 60 mg (47%) of dark N-phenyl-2-(1-piperidino)succinimide, **30**, crystallized, mp 130–131°. Recrystallization ($CCl_4$) gave still dark **30**, mp 130–131°. Tlc and ir showed this **30** to be identical with colorless **30**, mp 133–135° (dec), obtained by mixing equimolar amounts of N-phenylmaleimide and piperidine: nmr ($CDCl_3$) $\delta$ 1.52 (s, $w_{1/2}$ = 9 Hz, 6, $(CH_2)_3$), 2.1–3.1 (m, 6, $CH_2N$ + $CH_2C(=O)$), 3.87 (m, 1, $NCHC(=O)$), and 7.33 (m, 5, ArH); ir (Nujol) 1700 (s), 1595, 1500, 1165, 770, 750, and 695 cm$^{-1}$; mass spectrum *m/e* (rel intensity) 258 (3), 175 (5), 138 (8), 119 (10), 112 (6), 111 (72), 110 (16), 96 (45), 91 (11), 85 (6), 84 (100), 83 (8), 82 (12), 77 (8), 70 (7), 69 (12), 68 (8), 64 (8), 57 (7), 56 (13), 55 (40), 54 (20), and 51 (5).

*Anal.* Calcd for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02. Found: C, 69.68; H, 7.03.

For the reaction of **N-ethylmaleimide**, 125 mg (1.00 mmol), and 173 mg (1.00 mmol) of **N-(*n*-butylthio)piperidine** (**13**) were dissolved in 0.5 ml of $CCl_4$. After 10 hr at 100°, the reaction, based on the intensity of the nmr peak at 6.70 $\delta$, appeared *ca.* 50% complete. Partial purification by preparative tlc (Brinkmann precoated plates, silica gel F-254; $Me_2CO$) and analysis by glpc and mass spectrometry showed the presence of **13** and a second compound presumed to be N-ethyl-$\alpha$-(1-piperidyl)-succinimide (**31**): mass spectrum *m/e* (rel intensity) 210 (8), 181 (5), 138 (10), 111 (30), 96 (50), 84 (100), and 55 (60).

For the reaction of **ethyl acrylate** with **N-(ethylthio)piperidine** (**12**), equimolar amounts were combined in an nmr tube, and the progress of the reaction was determined by comparing the integral ratio of the total of olefinic protons, with that of the $CH_2O$ group. After 3 days at 77°, the reaction was *ca.* 60% complete. Glpc and mass spectrometric analysis of the reaction mixture, after standing 2 weeks more at *ca.* 25° showed the presence of a new compound [mass spectrum *m/e* (rel intensity) 185 (3), 101 (6), 100 (100), 98 (5), 84 (5), 56 (5), 55 (9), 42 (10), and 41 (9)] presumed to be ethyl $\beta$-(1-piperidyl)propionate (**32**). Comparison of the ir spectrum of either the crude product or of **32** purified by preparative glpc with that of **32** prepared by addition of piperidine to ethyl acrylate[28] showed both to be identical with it; its picrate had mp 124–126° (lit.[45] mp 131.5°).

**G. With Acetic Anhydride.**—Acetic anhydride (0.45 g, 4.5 mmol) and **N-(ethylthio)piperidine** (**12**, 0.62 g, 4.3 mmol) were mixed and the progress of the reaction was followed by glpc. After 3 hr, the reaction appeared to be *ca.* 50% complete, and the products were analyzed by glpc and mass spectrometry. In addition to **12**, the other products seen evidently were ethyl disulfide (mass spectrum mol wt 122) and N-acetylpiperidine (mass spectrum mol wt 127). Acetic anhydride and **N-(*t*-butylthio)-piperidine** (**14**) were mixed and the extent of reaction determined by glpc. No reaction occurred at *ca.* 25° in up to 3.5 hr. Heating at 90° for 0.5 hr apparently gave *ca.* 50% reaction. The products determined by distillation at 50–120° (*ca.* 25 mm) and infrared analysis were *t*-butyl disulfide and N-acetylpiperidine.

**Reactions of Sulfenamides with Nucleophiles.—N-(2-Acetamidoethylthio)phthalimide** (**10**, 264 mg, 1 mmol) was added to 120 mg (1.01 mmol) of 2-acetamidoethanethiol in 10 ml of MeOH and 80 μl of $Et_3N$. Four days later the solution gave a negative nitroprusside test and was evaporated to dryness. Two washes with EtOH left 100 mg (68%) of phthalimide, mp and mmp 227–229°. The EtOH washes were evaporated and the residue was triturated with benzene to give 220 mg (93%) of **2**, mp 87–89° (lit.[37] mp 92–93°), identified by comparison of its ir spectrum with that of **2**.

**N-(2-Acetamidoethylthio)-2-aminobenzothiazole** (**5**, 0.22 g, 0.82 mmol) suspended in 25 ml of $CH_2Cl_2$ was allowed to react with *p*-thiocresol (0.100 g, 0.80 mmol). After the **5** had completely dissolved, the solution was washed twice with 20-ml portions of 10% HCl, dried, and evaporated to dryness to give 0.14 g (70%) of 2-(*p*-tolyldithio)-1-acetamidoethane (**33**); this **33** was pure by tlc and was identified by comparison of its ir spectrum with that of authentic material.[37]

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**N-(2-Acetamidoethylthio)phthalimide** (**10**, 0.78 g, 3.0 mmol) in 5 ml of $CH_2Cl_2$ was allowed to react with *p*-**thiocresol** (0.36 g, 2.9 mmol). After a brief exothermic reaction, phthalimide precipitated and was removed by filtration. The filtrate was evaporated to dryness, and the residue was crystallized from benzene to give 0.43 g (61%) of **33** slightly contaminated (ir) with phthalimide; the ir spectrum was similar to that of authentic **33**, and tlc using 1:1 heptane–acetone separated a major product identical with authentic **33**.

**Attempted Equilibration of Two Sulfenamides.**—A 1:1 mixture of **12** and **16** was heated at 90° for 16 hr. Glpc analysis (10-ft column of 10% SE-30 on Gas Chrom Q at 160°) showed the presence of only **12** and **16**.

**Registry No.**—**4**, 25116-48-7; **5**, 25116-49-8; **6**, 25116-50-1; **7**, 25116-51-2; **8**, 25116-52-3; **9**, 25116-53-4; **10**, 25158-14-9; **11**, 25116-54-5; **12**, 25116-55-6; **13**, 25116-56-7; **14**, 3060-70-6; **16**, 25116-77-2; **17**, 25116-78-3; **19**, 5038-11-9; **20**, 25116-80-7; **21**, 25110-35-4; **22**, 25110-36-5; **23**, 25110-37-6; **24**, 25110-38-7; **24** HCl, 25110-39-8; **25**, 25110-40-1; **30**, 25110-41-2.

# Photoaddition of Diphenylacetylene to Tetrahydro-2-quinolones[1]

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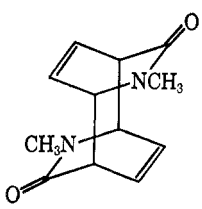
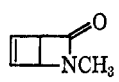
Diphenylacetylene has been observed to undergo photocycloaddition to a series of cycloalkano-2-pyridones **4** at 3500 Å to give the pentacyclic lactams **8**, the cyclobutene derivatives **16**, and the insoluble dimer **7**. Formation of **8** probably proceeds *via* the Diels–Alder adduct (4 + 2 addition) followed by photoreorganization. The pentacyclic lactams were highly labile to aqueous acid and base reverting back to starting materials, whereas the N-methyl derivatives were smoothly rearranged in methanolic acid to benzamides, **11**. Irradiation of **8** at 2537 Å resulted in rearrangement to the cyclobutene systems, **16**, a hitherto unknown photolytic reaction. This behavior was found to be general for a series of cycloalkano-2-pyridones containing various alkyl substitution and ring size.

Investigation of the photochemical behavior of simple 2-pyridones has been limited to the formation of dimers, **1**,[3–5] and valence isomers, **2**.[6] Recently,[7] the cycloaddition of olefins to the related carbostyril system has resulted in the cyclobutane derivative, **3**. Thermally induced cycloadditions to pyridones have also been observed in a few instances.[8–10] However, no photocycloadditions to pyridones have been described.[2] In view of the ready availability[11] of a series of cycloalkanopyridones, **4**, obtained by oxidative cyclization of cyano ketones, **5**, it was convenient to examine the photocycloaddition reaction with a suitable unsaturated substrate, *e.g.*, diphenylacetylene.



**1**



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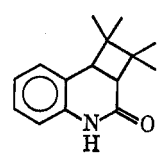

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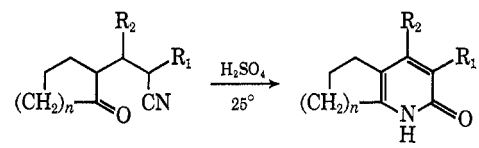
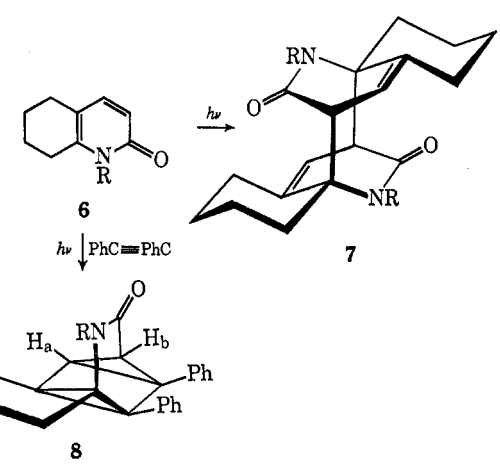


**5** **4**

$R_1$ = H, Me
$R_2$ = H, Me
$n$ = 1-3

## Results and Discussion

**Dimer Formation.**—When a methanol–hexane solution of the 2-quinolone, **6** (R = H), and diphenylacetylene was irradiated (Pyrex) for 15 hr a crystalline material deposited along the walls of the vessel. The quantity of solid product was observed to increase with increasing exposure to the light source. The elemental analysis and mass spectrum under all practical ionizing conditions were identical with those of the starting material; yet the infrared spectrum displayed a single nonconjugated lactam band at 1660 $cm^{-1}$ (Nujol) unlike the two strong bands (1653, 1625 $cm^{-1}$) present in **6** (R = H). Further, the melting point at various heat-



**6** **7**

**8**

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(2) Taken from the Ph.D. Dissertation of P. Singh, June 1969. Preliminary accounts have already appeared (a) A. I. Meyers and P. Singh, *Chem. Commun.*, 576 (1968); (b) A. I. Meyers and P. Singh, *Tetrahedron Lett.*, 4073 (1968).

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