Synthesis and Reactions of *N*-Sulfonylamines

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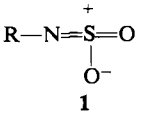
Abstract: *N*-Sulfonylamines, a new heterocumulene system, have been synthesized by the action of triethylamine on sulfamoyl chlorides. *N*-Sulfonylethylamine and *N*-sulfonylbenzamide have been prepared in solution and intercepted with amines to give sulfamides or with nucleophilic olefins to give 1,2-thiazetidine 1,1-dioxides when the reactions were carried out under conditions which did not favor ring opening. In several cases, ring openings occurred leading to β-substituted vinylsulfonamides or other acyclic products. Neither *N*-sulfonylethylamine nor *N*-sulfonylbenzamide could be isolated from solution as the former underwent exothermic polymerization at room temperature in the absence of a trapping agent, while the latter rearranged to phenyl isocyanate upon warming to room temperature. Ethyl(carboxysulfamoyl)triethylammonium hydroxide, inner salt, was synthesized from carbethoxysulfamoyl chloride and treated with amines and alcohols as well as with 1-vinyl-2-pyrrolidinone. The inner salt reacted at 60° with tetramethylallene to give 2-carbethoxy-3,3-dimethyl-4-isopropylidene-1,2-thiazetidine 1,1-dioxide and 2,3-dihydro-2,2-dimethyl-3-isopropylidene-6-ethoxy-1,4,5-oxathiazine 4,4-dioxide and in another reaction gave a 1:1 adduct with hexamethylbicyclo[2.2.0]hexa-2,5-diene, the structure of which was firmly established. *N*-Sulfonylethylamine and ethyl(carboxysulfamoyl)triethylammonium hydroxide inner salt reacted with *N*,*N*-dimethylaniline giving sulfanilamides in fair yields.

Investigations of the chemistry of heterocumulenes spanning more than a century (beginning with isocyanates in 1848) have greatly contributed to the area of academic and industrial synthetic organic chemistry. The chemical importance of this class of compounds may be recognized if one considers the ambivalent nature (below) of the heterocumulene linkage where (a) nucleophilic, (b) electrophilic, and (c) electrocycloaddition reactions are possible. (X, Y or Z may be O, N, NR, S and SO.)

$$-X=Y=\ddot{Z} \longleftrightarrow -\bar{X}-Y\equiv\overset{+}{Z}$$

The studies reported herein are concerned with the synthesis of a new heterocumulene, the *N*-sulfonylamines (**1**), which are isoelectronic with sulfenes and otherwise closely related to *N*-sulfinylamines and might be expected to show similar reactivity and stability.[1,2]



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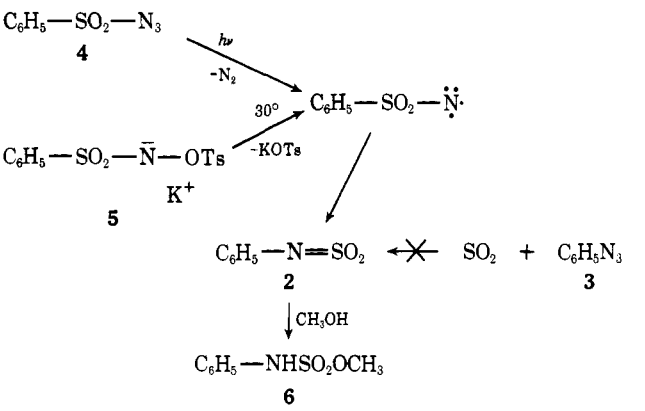
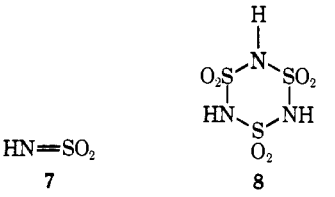
A reported attempt to generate *N*-phenylsulfonylamine (**2**) from the thermal or photochemical decomposition of phenyl azide (**3**) in liquid sulfur dioxide failed.[3] However **2** has been proposed as an intermediate in the Curtis and Lossen rearrangement of **4** and **5**, respectively, in methanol.[4] In both cases, the interposition of **2** was inferred since the rearrangements provided methyl *N*-phenylsulfamate (**6**) when methanol was used as the solvent.

It has been reported that when ammonia is passed into an anhydrous solution of sulfur trioxide in nitromethane approximately one-fourth of the sulfur trioxide is converted into sulfimide (**7**) as evidenced by the isolation of the cyclic trimer **8**.[5]



4 **5** **2** **3** **6**



7 **8**

An attractive approach to a general *N*-sulfonylamine synthesis which has precedence in the preparation of other heterocumulenes would involve dehydrohalogenation of an appropriate sulfamoyl chloride. Presently, we wish to describe the details of the successful application of this method.

Ethylsulfamoyl chloride (**9**) was prepared by the interaction of ethylamine hydrochloride and sulfuryl chloride in diethyl ether solution.[6]

The sulfamoyl chloride reacts rapidly with 1 equiv of triethylamine in toluene solution at −78° to afford a nearly quantitative yield of precipitated triethylamine hydrochloride. Filtration at this temperature provides a solution of *N*-sulfonylethylamine (**10**), a species which undergoes a mildly exothermic polymerization upon

(1) The names sulfurylamine and azasulfene have been ascribed to structure 1. However, *N*-sulfonylamine is the name currently preferred and used for indexing by the Chemical Abstracts Service and is more consistent with the naming of related heterocumulenes.

(2) A portion of this study has been reported in preliminary communications. G. M. Atkins, Jr., and E. M. Burgess, *J. Amer. Chem. Soc.*, **89**, 2502 (1967); **90**, 4744 (1968).

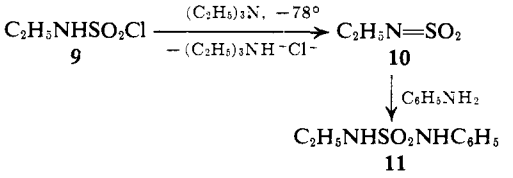
(3) T. Nagai, K. Yamamoto, and N. Tokura, *Bull. Chem. Soc. Jap.*, 40, 408 (1967).

(4) W. Lwowski and E. Scheiffele, *J. Amer. Chem. Soc.*, **87**, 4359 (1965).

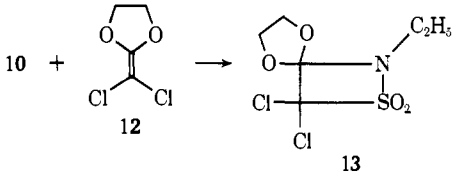
(5) R. Appel and M. Goehring, *Z. Anorg. Allg. Chem.*, 271, 171 (1953).

(6) N. C. Hansen, *Acta Chem. Scand.*, 17, 2141 (1963).

warming. Successful interception of **10** was accomplished by the addition to this solution at −78° of a nucleophile such as aniline which resulted in the production of *N*-phenyl-*N'*-ethylsulfamide (**11**) whose yields (20–50%) varied with the age of the filtrate.

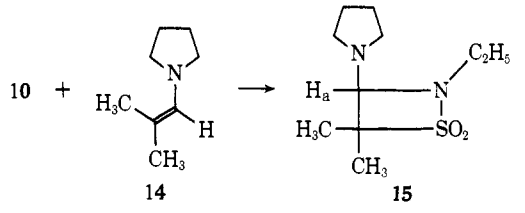


When *N*-sulfonylethylamine was generated in the presence of 2-(dichloromethylene)-1,3-dioxolane,[7] 4,4-dichloro-3,3-ethylenedioxy-2-ethyl-1,2-thiazetidine 1,1-dioxide (**13**), mp 74–75°, was isolated in 85% yield.



The nmr spectrum ($CDCl_3$, 60 MHz) of **13** displayed an ethyl group at δ 3.28 (quartet, J = 7 Hz, 2 H) and 1.33 (triplet, J = 7 Hz, 3 H) and the dioxolane moiety at 4.27 (multiplet, 4 H) while the mass spectrum showed ions at m/e 262 (M^+), 154 ($C_4H_4O_2Cl_2^+$), and 107 ($C_2H_5NSO_2^+$) with accompanying proper chlorine isotopic combination ions where applicable. No ions resulting from 1,2 and 3,4 bond cleavage were visible and the proposed orientation of the cycloadduct rests upon mechanistic considerations.

In a related reaction, **10** was found to react with the pyrrolidine enamine of isobutyraldehyde (**14**) to afford a good yield of 4,4-dimethyl-2-ethyl-3-(*N*-pyrrolidino)-1,2-thiazetidine 1,1-dioxide (**15**).

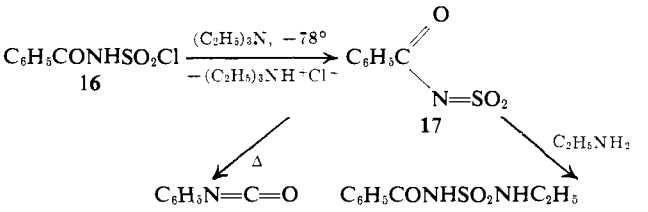


Since attempts to purify **15** for complete analysis were unsuccessful, the structural assignment is based in large part on its nmr spectrum (C_6H_6, 60 MHz). Signals centered at δ 2.75 (4 H) and 1.78 (4 H) as multiplets, 3.22 (quartet, 2 H), 1.28 (triplet, 3 H), and 1.57 (singlet, 6 H) were present along with a singlet at 3.66 (1 H) for H_a. Chromatography of **15** over Florisil led to hydrolysis and the formation of α-(ethylsulfamoyl)isobutyraldehyde identified as its 2,4-dinitrophenylhydrazone.

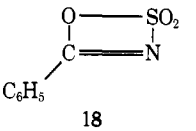
While *N*-sulfonylethylamine appeared to have reacted smoothly with strongly nucleophilic olefins such as ketene acetals and enamines, it did not react with ethyl vinyl ether, an olefin of more moderate nucleophilicity. In order to extend the scope of reactions of this new heterocumulene, it therefore became desirable to prepare substituted *N*-sulfonylamines of greater electrophilicity. In this connection *N*-sulfonylbenzamide (**17**) would be a suitable candidate for study.

(7) S. M. McElvain and M. J. Curry, *J. Amer. Chem. Soc.*, 70, 3781 (1948).

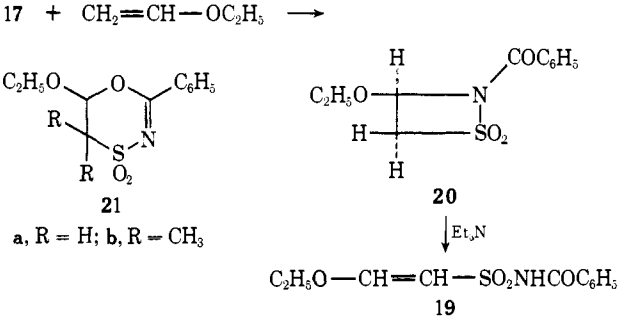
Benzoylsulfamoyl chloride (**16**) was prepared by decarboxylation of the mixed anhydride derived from chlorosulfonyl isocyanate and benzoic acid.[8] When **16** was mixed with triethylamine in THF solution at −78°, a quantitative precipitate of triethylamine hydrochloride formed and was removed by filtration. Treatment of the resulting solution of *N*-sulfonylbenzamide (**17**) at −78° with ethylamine afforded *N*-ethyl-*N'*-benzoylsulfamide in a 66% yield. When



the solution of **17** at −78° was allowed to warm to room temperature, rearrangement to phenyl isocyanate occurred. Aside from the uniqueness of this latter transformation it provides partial evidence that the species present at low temperatures is in fact **17** and not the valence isomer **18** whose intermediacy is implicated in the decomposition of sulfamoyl chlorides to give nitriles in DMF.[9]



Generation of **17** in the presence of ethyl vinyl ether and excess triethylamine gave *N*-benzoyl-β-ethoxyvinylsulfonamide (**19**), mp 135–136°. However, when these same reactants were mixed under conditions of limited triethylamine, a cycloadduct, mp 87–88°, was obtained in 70% yield. The structural assignment as 2-benzoyl-3-ethoxy-1,2-thiazetidine 1,1-dioxide (**20**) is consistent with the ir absorption at 1705 cm^{-1} (C=O) and the nmr ($CDCl_3$, 60 MHz) spectrum consisting of multiplets centered at δ 5.93 (1 H) and 3.79 (2 H) for H_3 and H_4 accompanied by the ethoxyl and aromatic pattern. Decoupling of the heterocyclic ring protons revealed an ABX system with $|J_{3,4}|_{trans}$ = 9 Hz, $|J_{3,4}|_{cis}$ = 3 Hz, and $|J_{4,4}|$ = 14 Hz.

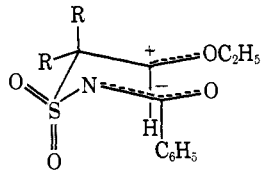


A trace amount of an isomer, mp 130–132°, was isolated from the cycloaddition reaction and may have structure **21a** based on a 1605-cm^{-1} (C=N) absorption observed in the ir spectrum. Treatment of **20** with triethylamine in benzene at 30° leads to ring opening

(8) A. Dorlas in Houben-Wedyl's "Methoden der Organischen Chemie," Vol. 8, E. Muller, Ed., Georg Thieme Verlag, Stuttgart, 1952, p 700.

(9) G. Lohaus, *Chem. Ber.*, 100, 2719 (1967).

and conversion to **19**. When **17** is allowed to react with isobutenyl ethyl ether[10] the only cycloadduct isolated is the oxathiazine **21b**, mp 98–99°, which displayed an unexceptional nmr spectrum and an ir absorption at 1600 cm^{-1} (C=N). The incongruence in the cycloaddition mode resulting from β substitution of the vinyl ether may be rationalized if the common intermediacy of a dipolar ion, **22**, is invoked. The



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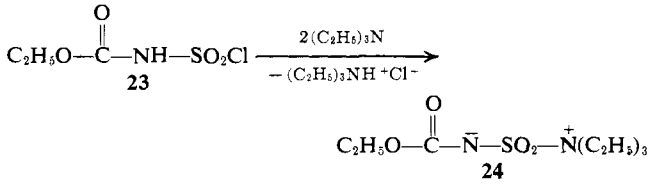
staggered conformation shown minimizes interactions about the C–S bond but maximizes the 1,4-bonding distance and may represent the ion configuration leading to 1,6-cyclization when R = CH_3. Conversely, 1,4 cyclization may be permitted only when R = H from an attainable eclipsed configuration.

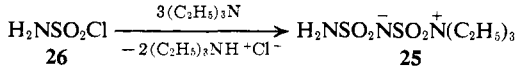
It was observed that the partition of **17** between rearrangement and capture by olefins became the predominate reaction path with decreasing nucleophilicity of the olefin. In order to probe further the cycloadditive reactivity of *N*-sulfonylamines a more rigid system was needed. It was anticipated that the heterocumulene produced from the dehydrohalogenation of **23** derived from the addition[11] of chlorosulfonyl isocyanate to ethanol would have less proclivity toward Curtis rearrangement.

When **23** was treated with 2 equiv of triethylamine in benzene at 30°, a quantitative yield of precipitated triethylamine hydrochloride was collected and, in addition, a colorless crystalline compound was isolated which analyzed for the *N*-sulfonylamine–triethylamine adduct, (carboxysulfamoyl)triethylammonium hydroxide, inner salt, ethyl ester (**24**).

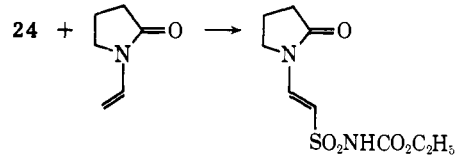


The structure of **24** was established by examination of its infrared and nmr spectra and by its subsequent reactions with nucleophiles. The infrared spectrum showed no vibrations characteristic of N–H bonds, and the carbonyl stretching frequency was of unusually low energy (1685 cm^{-1}) as compared to that for a normal urethane C=O linkage. The nmr spectrum (C_6H_6, 60 MHz) showed absorptions for one *O*-ethyl group as a quartet (2 H) at δ 4.29 and a triplet (3 H) at δ 1.28 and for three equivalent *N*-ethyl groups as a quartet (6 H) at δ 3.29 and a triplet (9 H) at δ 1.15.

Subsequently, another *N*-sulfonylamine–triethylamine adduct (**25**) has been reported to result from the sulfonyl chloride **26** and excess triethylamine in acetonitrile at −40°.[12]



The inner salt, upon treatment with water, gave a monohydrate which reverted to **24** on gentle heating under reduced pressure. This hydrate displayed water protons as a single broad absorption in the nmr spectrum ($CDCl_3$, 60 MHz) at δ 8.38 and the carbonyl absorption in the infrared at 1720 cm^{-1} is intermediate in energy between that of the inner salt (1685 cm^{-1}) and those values found for the grouping $C_2H_5OCONHSO_2$– (1740–1755 cm^{-1}).[13] In addition, **24** reacted with aniline and isopropyl alcohol to give *N*-carbethoxy-*N'*-phenylsulfamide and isopropyl carbethoxysulfamate, respectively. When a mixture of **24** and 1-vinyl-2-pyrrolidinone in acetonitrile was heated to 50° a reaction occurred which provided a vinylsulfonamide (**26**), mp 149–151°, which gave a consistent nmr and ir spectrum. None of the expected 1,2-thiazetidine 1,1-dioxide cycloadduct was isolated and it may be concluded that the triethylamine present promoted the prototropy of the dipolar intermediate.



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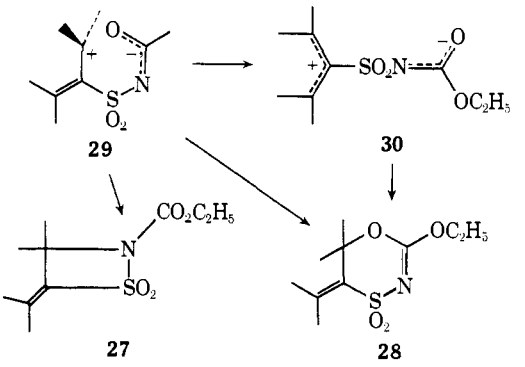
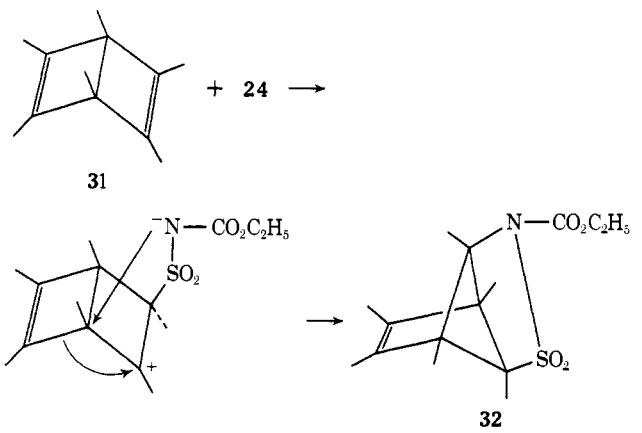
Tetramethylallene reacted with **24** at 60° in acetonitrile to give a 60% yield of two isomeric cycloadducts in a ratio of 3:17. To the major adduct, mp 81–82°, was assigned the 2,3-dihydro-2,2-dimethyl-3-isopropylidene-6-ethoxy-1,4,5-oxathiazine 4,4-dioxide structure **27** based on the observed nmr ($CDCl_3$, 60 MHz) signals at δ 4.40 (quartet, J = 7 Hz, 2 H), 1.38 (triplet, J = 7 Hz, 3 H), 2.35 and 2.04 (singlets, 3 H), and 1.81 (singlet, 6 H) and C=N infrared absorption at 1615 cm^{-1}. The minor component, mp 150–151°, exhibited infrared C=O absorption at 1725 cm^{-1} and nmr ($CDCl_3$, 60 MHz) signals at δ 4.42 (quartet, J = 7 Hz, 2 H), 1.35 (triplet, J = 7 Hz, 3 H), 2.10 and 1.91 (singlets, 3 H), and 1.76 (singlet, 6 H) and was considered to be 2-carbethoxy-3,3-dimethyl-4-isopropylidene-1,2-thiazetidine 1,1-dioxide (**28**). The divergent distribution of adducts in this case may be ascribed to the formation of two conformationally and electronic distinct dipolar intermediates. Electrophilic attack at the allenic central[14] carbon atom produces a nonallylic but tertiary cation containing dipole, **29**, which can close to give either **27** or **28**. Rotation of **29** gives an allylic cation, **30**, whose orbital alignment will only permit ring closure to **28**. Under similar conditions no reaction was observed with allene.

Admixture of equivalent amounts of hexamethylbicyclo[2.2.0]hexa-2,5-diene (**31**) and **24** in acetonitrile solution at 60° resulted in the formation of a 1:1 cycloadduct, mp 140–141°, in which the urethan function was intact as evidenced by an infrared carboxyl absorption at 1730 cm^{-1}. The nmr signals (60 MHz)

(10) M. G. Voronkov, *J. Gen. Chem. USSR*, 20, 2131 (1950).
(11) Reference 8, p 699.
(12) R. Appel and R. Helwerth, *Angew. Chem.*, **79**, 937 (1967).
(13) The sulfur trioxide–trimethylamine inner salt is relatively stable to hydrolysis. W. Traube, H. Zander, and H. Gaffron, *Ber.*, **57**, 1045 (1924).
(14) This orientation has been observed in other heterocumulene-tetramethylallene cycloadditions. E. J. Moriconi and J. F. Kelley, *J. Amer. Chem. Soc.*, **88**, 3657 (1966).



in $CDCl_3$ for the methyl groups appeared as singlets at δ 1.73 (6 H), 1.49 (3 H), 1.28 (3 H), and 1.25 (6 H) with no additional splitting in benzene as a solvent or at 100 MHz. These findings are consistent with a symmetrical tricyclic framework for the adduct and this conclusion is substantiated by the isolation of a dihydro derivative, mp 157–158°, upon catalytic hydrogenation which displayed an nmr ($CDCl_3$, 60 MHz) sharp doublet at δ 1.09 (6 H) and quartet at δ 2.05 (2 H) as well as singlets at δ 1.18 (9 H) and 1.62 (3 H). On this basis structure **32** is assigned to the cycloadduct and its genesis results from initial bonding of the electrophile to the less-hindered exo surface of **31** with subsequent or concomitant 4,5 bond migration.[15]



The inner salt (**24**) was capable of electrophilic aromatic substitution of *N*,*N*-dimethylaniline and only the para isomer, *N*,*N*-dimethyl-*N'*-carbethoxysulfanilamide,[16] was produced. *N*-Sulfonylethylamine (**10**) generated in the presence of *N*,*N*-dimethylaniline gave only *N*,*N*-dimethyl-*N'*-ethylsulfanilamide while *N*-sulfonylbenzamide (**17**) afforded the corresponding ortho- and para-substituted sulfanilamide in a ratio of 4:6, albeit in low yield.

Experimental Section[17]

***N*-Sulfonylethylamine. Generation of *N*-Sulfonylethylamine (10).** Ethylsulfamoyl chloride (**9**) (3.85 g, 0.0268 mol) in 10 ml of toluene was added dropwise under nitrogen over a 5-min period to a solution of 8 ml of triethylamine in 35 ml of toluene at −78°. The solution was stirred at −78° for 30 min and then filtered at this temperature into a flask containing 5 ml of aniline. The precipitate of triethylamine hydrochloride, after washing with several portions of benzene and drying under reduced pressure, weighed 3.6 g (98.5%). A portion of ether (250 ml) was added to the above filtrate and this solution was extracted with three 50-ml portions of 6 *M* hydrochloric acid. The ether layer was washed with 25 ml of water and then dried over anhydrous magnesium sulfate. Filtration and evaporation of the solvent under reduced pressure gave a yellow oil which was chromatographed over 40 g of alumina. The fraction obtained using 1:1 (v/v) ether–chloroform as an eluent gave 1.098 g (20.5%) of a colorless oil which solidified on cooling. Recrystallization from benzene–hexane gave colorless crystals of *N*-ethyl-*N'*-phenylsulfamide (**11**): mp 72–72.5°; ir ($CHCl_3$) 3320 (N–H), 2990, 1605, 1495, 1355 and 1155 cm^{-1} (SO_2–N); nmr ($CDCl_3$) δ 7.75 (s, 1 H), 7.30–6.80 (m, 5 H), 5.49 (broad, t, 1 H, J = 6 Hz), 2.95 (m, 2 H), and 0.93 (t, 3 H, J = 7 Hz); mass spectrum (70 eV) *m/e* (relative intensity) 200 (100).

Compound **11** was also prepared by allowing ethylsulfamoyl chloride and aniline to react directly.

In another example, the same procedure was used except that after addition of the ethylsulfamoyl chloride the mixture was stirred at −78° for only 15 min before filtering. In this case 54% of **11** was isolated as previously described, but only 92% of the theoretical amount of triethylamine hydrochloride was collected.

In yet another example, the aniline was omitted in the receiving flask during filtration. As the filtrate which contained *N*-sulfonylethylamine (**10**) was allowed to warm to room temperature, an exothermic polymerization occurred. Evaporation of the solvent yielded a light yellow oil which could be precipitated from a chilled ethanol solution. Filtration gave a polymer in the form of a white powder having no definitive melting point but which began to soften at 110°.

Reaction with 2-(Dichloromethylene)-1,3-dioxolane (12). Ethylsulfamoyl chloride (6.46 g, 0.0450 mol) in 10 ml of benzene was added dropwise under nitrogen over a 2-hr period to a stirred solution containing 7.20 g (0.0465 mol) of 2-(dichloromethylene)-1,3-dioxolane (**12**) and 8.6 ml of triethylamine in 25 ml of benzene at ambient temperatures. After the addition the mixture was stirred overnight at ambient temperatures. The precipitate of triethylamine hydrochloride was removed by filtration, and the solvent was evaporated under reduced pressure leaving a residual dark red-brown oil. Removal of the last traces of solvent at 0.1 mm pressure caused the oil to solidify. Recrystallization from carbon tetrachloride gave 10.1 g (85.6%) of crude 4,4-dichloro-3,3-ethylenedioxy-2-ethyl-1,2-thiazetidine 1,1-dioxide (**13**) as off-white plates. Another recrystallization from carbon tetrachloride solution after decoloration with charcoal gave **13** as colorless plates: mp 74–75°; ir ($CHCl_3$) 2995, 1460, 1340, 1170, 1135, and 890 cm^{-1}; nmr ($CDCl_3$) δ 4.27 (m, 4 H), 3.28 (q, 2 H, J = 7 Hz), and 1.33 (t, 3 H, J = 7 Hz); mass spectrum (70 eV) *m/e* (relative intensity) 262 (5), 154 (46), 107 (42).

The ions in the mass spectrum at *m/e* 262 and 154 had accompanying $(M + 2)^+$ and $(M + 4)^+$ signals in proportions corresponding to the isotopic combinations of two chlorine atoms.

Anal. Calcd for $C_6H_9Cl_2NO_4S$: C, 27.49; H, 3.47; N, 5.34; S, 12.23. Found: C, 27.62; H, 3.53; N, 5.41; S, 11.98.

Reaction with Isobutyraldehyde Pyrrolidine Enamine (14). Ethylsulfamoyl chloride (3.44 g, 0.0240 mol) in 10 ml of benzene was added dropwise under nitrogen over 40 min to a solution of 3.285 g (0.0285 mol) of the pyrrolidine enamine of isobutyraldehyde and 4 ml of triethylamine in 20 ml of benzene at ambient temperatures. The mixture was stirred for an additional 30 min after which time the precipitate of triethylamine hydrochloride was removed by filtration and the solvent was evaporated from the filtrate under reduced pressure. After the last traces of solvent were removed at 0.1 mm pressure, the residual red, oily, impure 4,4-dimethyl-2-ethyl-3-(*N*-pyrrolidino)-1,2-thiazetidine 1,1-dioxide (**15**) displayed the following nmr spectrum: (benzene) δ 3.66 (s, 1 H), 3.22 (q, 2 H, J = 7 Hz), 3.00–2.51 (m, 4 H), 1.94–1.62 (m, 4 H), 1.57 (s, 6 H), and 1.28 (t, 3 H, J = 7 Hz).

After attempts to crystallize **15** were unsuccessful, the oil was chromatographed over Florisil (40 g). Elution with benzene gave α-(ethylsulfamoyl)isobutyraldehyde as a yellow oil (2.99 g) which was judged to be pure by tlc (benzene). The spectral data are as follows: ir (liquid film) 3340 (N–H), 3000, 2890 and 2750 (weak), 1740 (C=O), and 1450, 1335 and 1170 cm^{-1} (SO_2–N); nmr (ben-

(15) Attack by other electrophiles on the endo face appears as a result of electronic considerations. L. A. Paquette and G. R. Krow, *Tetrahedron Lett.*, 2133 (1968); L. A. Paquette, *ibid.*, 2139 (1968).

(16) Belgium Patent 622,214 (1963); *Chem. Abstr.*, **59**, 12710*d* (1963).

(17) Melting points are uncorrected and the microanalyses were performed by Huffman Laboratories, Wheatridge, Colo. Infrared spectra were obtained using either a Perkin-Elmer Model 137 or Model 457 spectrometer fitted with sodium chloride optics. The nmr spectra were determined with a Varian A-60 spectrometer. (TMS internal standard) and mass spectra were measured on either a LKB-9000 or Varian M-66 spectrometer. Thin layer chromatography was performed using silica gel G (E. Merck AG, Darmstadt).

zene) δ 9.76 (s, 1 H), 3.18 (q, 2 H, J = 7 Hz), 1.52 (s, 6 H), and 1.17 (t, 3 H, J = 7 Hz).

Treatment of the above product with an ethanolic solution of 2,4-dinitrophenylhydrazine and sulfuric acid gave, after recrystallization from ethyl acetate, bright yellow needles of the 2,4-dinitrophenylhydrazone: mp 186.5–187.5°; ir (Nujol mull) 1625 cm^{-1} (C=N).

Reaction with *N,N*-Dimethylaniline. Ethylsulfamoyl chloride (3.06 g, 0.0213 mol) in 10 ml of benzene was added dropwise under nitrogen to a stirring solution containing 2.58 g (0.0213 mol) of *N,N*-dimethylaniline at ambient temperatures. After addition was complete, 150 ml of water was added to the benzene solution, and the aqueous layer was acidified with concentrated hydrochloric acid. The mixture was extracted with five 50-ml portions of ether. The combined ether extracts were washed with 50 ml of water and dried over anhydrous magnesium sulfate. Evaporation of solvent under reduced pressure gave 2.30 g (47.4%) of *N,N*-dimethyl-*N'*-ethylsulfanilamide as off-white needles. An analytical sample was obtained which had: mp 160–162°; ir ($CHCl_3$) 3355 (N-H), 2970, 1600, 1505, 1370, 1315, and 1150 cm^{-1}; nmr (DMSO-d_6) δ 7.25 (m, 4 H), 3.63 (broad, s, 1 H), 3.01 (s, 6 H), 2.59 (q, 2 H, J = 7 Hz), and 1.01 (t, 3 H, J = 7 Hz).

Anal. Calcd for $C_{10}H_{16}N_2O_2S$: C, 52.60; H, 7.08; N, 12.27; S, 14.07. Found: C, 52.43; H, 6.95; N, 12.36; S, 14.12.

***N*-Sulfonylbenzamide. Generation of *N*-Sulfonylbenzamide (17).** Benzoylsulfamoyl chloride (**16**) (1.00 g, 0.00456 mol) in 10 ml of THF was added dropwise under nitrogen over a 10-min period to a solution of 5 ml of triethylamine in 20 ml of THF at −78°. The mixture was stirred at −78° for 8 hr and then filtered at that temperature into a flask containing 5 ml of anhydrous ethylamine. The precipitate of triethylamine hydrochloride weighed 605 mg (96%). Evaporation of the solvent from the filtrate gave a light yellow oil which was chromatographed over silica gel (10 g). Elution with chloroform and recrystallization from chloroform–hexane gave colorless needles (685 mg, 66%) of *N*-benzoyl-*N'*-ethylsulfamide (**18**): mp 158–159°; ir ($CHCl_3$) 3400 (N-H), 3000, 1700 (C=O), 1605, 1455, 1360, and 1160 cm^{-1}.

Anal. Calcd for $C_9H_{12}N_2O_3S$: C, 47.35; H, 5.31; N, 12.27; S, 14.04. Found: C, 47.12; H, 5.31; N, 12.12; S, 14.12.

Compound **18** was also prepared by allowing benzosulfamoyl chloride and anhydrous ethylamine to react directly.

In another example, the ethylamine was omitted in the receiving flask during filtration. The filtrate was allowed to warm to 30° and stand at that temperature for several hours. Evaporation of solvent at reduced pressure gave a colorless liquid having an infrared spectrum identical with that of an authentic sample of phenyl isocyanate.

Reaction with Ethyl Vinyl Ether in Excess Triethylamine. Benzoylsulfamoyl chloride (5.0 g, 0.0228 mol) in 10 ml of DME was added dropwise under nitrogen over a 2-hr period to a solution containing 3.58 g (0.0498 mol) of ethyl vinyl ether and 3.0 g (0.0297 mol) of triethylamine in 20 ml of benzene at ambient temperatures. After the addition, the mixture was stirred at ambient temperatures for 12 hr, and the precipitate of triethylamine hydrochloride was removed by filtration. The solvent was evaporated from the filtrate under reduced pressure to provide a dark yellow oil which was chromatographed over silica gel (70 g). Elution with benzene gave a light yellow oil (3.27 g) which was crystallized from benzene–hexane solution giving colorless needles of *N*-benzoyl-β-ethoxyvinylsulfonamide (**19**): mp 135–136°; ir ($CHCl_3$) 3290, 3095, 2990, 1710 (C=O), 1625 (C=C), 1610, 1450, 1340, and 1150 cm^{-1}; nmr ($CDCl_3$) δ 7.85–7.30 (m, 7 H), 5.92 (d, 1 H, J = 12 Hz), 3.89 (q, 2 H, J = 7 Hz), and 1.27 (t, 3 H, J = Hz); mass spectrum (70 eV) *m/e* (relative intensity) 255 (0.24), 191 (1.4), 105 (82), 88 (100), 60 (40).

Anal. Calcd for $C_{11}H_{13}NO_4S$: C, 51.74; H, 5.14; N, 5.49; S, 12.56. Found: C, 51.69; H, 5.32; N, 5.51; S, 12.95.

Reaction with Ethyl Vinyl Ether in Limited Triethylamine. Triethylamine (0.462 g, 0.00456 mol) in 5 ml of benzene was added dropwise under nitrogen over a 25-min period to a solution containing 1.00 g (0.00456 mol) of benzosulfamoyl chloride and 2.6 g of ethyl vinyl ether in 20 ml of benzene–DME (1:1 v/v) at ambient temperatures. The mixture was stirred at ambient temperatures for 90 min after the addition was complete, and then the precipitate of triethylamine hydrochloride was removed by filtration. Evaporation of the solvents under reduced pressure gave a brown solid residue. Recrystallization from benzene–hexane provided colorless needles (820 mg, 71%) of 2-benzoyl-3-ethoxy-1,2-thiazetidine 1,1-dioxide (**20**): mp 87–88°; ir ($CHCl_3$) 2905, 1705 (C=O), 1450, 1350, and 1165 cm^{-1} (SO_2-N); nmr ($CDCl_3$) δ 8.20–7.30 (m, 5 H), 5.93 (m, 1 H), 4.38–3.20 (m, 2 H), 4.15 (q, 2 H, J = 7 Hz), and 1.38 (t, 3 H, J = 7 Hz); mass spectrum (70 eV) *m/e* (relative intensity) 255 (0.8), 150 (0.5), 104 (100).

Decoupling of the heterocyclic ring protons in the nmr revealed the theoretical 15 lines for the ABX system with J_{AB} = 14 Hz, J_{AX} = 9 Hz, and J_{BX} = 3 Hz (H_A trans to H_X).

Anal. Calcd for $C_{11}H_{13}NO_4S$: C, 51.74; H, 5.14; N, 5.49; S, 12.56. Found: C, 51.81, 51.87; H, 5.43, 5.32; N, 5.52; S, 12.55.

A small amount (approximately 5 mg) of colorless needles crystallized from the filtrate obtained from the first recrystallization of **20**. Although an insufficient amount was obtained for complete analysis, this material appeared to be an isomer of **20**, 2,3-dihydro-2-ethoxy-6-phenyl-1,4,5-oxathiazine 4,4-dioxide (**21**): mp 130–132°; ir ($CHCl_3$) 2985, 1605 (C=N), 1570, 1440, 1335, 1155, and 1105 cm^{-1}.

Reaction with Isobutenyl Ethyl Ether.[18] Triethylamine (0.462 g, 0.00456 mol) in 5 ml of dry benzene was added dropwise over a 30-min period to a solution containing 1.0 g (0.00456 mol) of benzoylsulfamoyl chloride and 3.60 g (0.0360 mol) of isobutenyl ethyl ether in 20 ml of benzene–DME (1:1, v/v) at ambient temperature. The mixture was stirred overnight at ambient temperature after the addition was complete. The precipitate of triethylamine hydrochloride (0.530 g, 90%) was removed by filtration and the filtrate concentrated under reduced pressure to give a viscous oil, part of which solidified on scratching. The oily crystalline mass was then spread over a porous plate and allowed to stand overnight in a vacuum desiccator. The solid (mp 89–96°) which formed was removed and recrystallized from benzene and hexane to give colorless needles (50%) of 3,3-dimethyl-2-ethoxy-6-phenyl-1,4,5-oxathiazine 4,4-dioxide (**21b**): mp 98–99°; ir ($CHCl_3$) 1600 (C=N), 1570 (C=C), 1325 (SO_2), and 1175 cm^{-1} (SO_2); nmr ($CDCl_3$) δ 8.10 (m, 2 H), 7.55 (m, 3 H), 5.71 (s, 1 H), 4.02 (m, 2 H), 1.56 (s, 3 H), 1.42 (s, 3 H), and 1.39 (t, 3 H, J = 6.9 Hz); mass spectrum (70 eV) *m/e* (relative intensity) 175 (54), 105 (100), 100 (45), 77 (30).

Anal. Calcd for $C_{13}H_{17}NO_4S$: C, 55.11; H, 6.05; N, 4.94; S, 11.31. Found: C, 55.13; H, 6.09; N, 4.91; S, 11.40.

Conversion of 20 to 19. Compound **20** (30 mg) was dissolved in 10 ml of benzene containing 0.4 ml of triethylamine, and the solution was allowed to stand at ambient temperatures overnight. Evaporation of the solvent under reduced pressure gave a colorless oil which was chromatographed over silica gel (5 g). Elution with absolute ethanol gave colorless crystals (19 mg) which were identical with **19** by mixture melting point and infrared spectra comparisons.

Reaction with *N,N*-Dimethylaniline. Benzoylsulfamoyl chloride (3.0 g, 0.0137 mol) in 10 ml of DME was added dropwise under nitrogen at ambient temperatures to a solution containing 3.31 g (0.0273 mol) of *N,N*-dimethylaniline in 20 ml of benzene. The solution was stirred for 2 hr at ambient temperatures and then poured into 150 ml of dilute aqueous hydrochloric acid. This mixture was extracted with four 75-ml portions of ether. The extracts were combined, washed with 30 ml of water, and dried over anhydrous magnesium sulfate. Filtration and evaporation of solvent under reduced pressure gave a residue which was recrystallized from absolute ethanol providing 326 mg of off-white crystals. The nmr (DMSO-d_6) of this material showed, in addition to aromatic (δ 8.16–6.73) and nitrogen-bound protons (δ 4.43, broad), two singlets at δ 3.08 and 2.99 in an area ratio of approximately 4:6 indicating a mixture of ortho- and para-substituted products. Recrystallization from a dilute ethanol solution gave large colorless needles (35 mg) of *N,N*-dimethyl-*N'*-benzoylsulfanilamide: mp 158–159°; ir (KBr) 3255 (N-H), 2920, 1685 (C=O), 1590, 1495, 1335, 1150, and 820 cm^{-1}.

Anal. Calcd for $C_{15}H_{16}N_2O_3S$: C, 59.20; H, 5.31; N, 9.21; S, 10.53. Found: C, 59.25; H, 5.25; N, 9.09; S, 10.43.

(Carboxysulfamoyl)triethylammonium Hydroxide, Inner Salt, Ethyl Ester. Carbethoxysulfamoyl chloride (**23**) (3.75 g, 0.0200 mol) in 10 ml of benzene was added dropwise under nitrogen over a 30-min period to a solution containing 5.0 g (0.0495 mol) of triethylamine in 25 ml of benzene at ambient temperatures. After the addition was complete, the precipitate of triethylamine hydrochloride was removed by filtration, and the solvent was evaporated under reduced pressure giving a colorless oil which solidified on standing. Recrystallization from benzene solution gave colorless crystals (4.10 g, 81%) of (carboxysulfamoyl)triethylammonium hydroxide, inner salt, ethyl ester (**24**); mp 66–69°; ir ($CHCl_3$) 2990, 1685 (C=O), 1460, 1260, and 1105 cm^{-1}; nmr (benzene) δ 4.29 (q, 2 H, J = 7 Hz), 3.29 (q, 6 H, J = 7 Hz), 1.28 (t, 3 H, J = 7 Hz), and 1.15 (t, 9 H, J = 7 Hz).

(18) We are indebted to Dr. W. Michael Williams for this experiment.

Anal. Calcd for $C_9H_{20}N_2SO_4$: C, 42.82; H, 8.00; N, 11.10; S, 12.70. Found: C, 42.74; H, 7.85; N, 11.11; S, 12.71.

Monohydrate of 24. When **24** was dissolved in benzene containing 1% water and allowed to stand for several hours at ambient temperatures, a crystalline precipitate formed which upon filtration gave the monohydrate of **24** as transparent plates: mp 89–90°; ir ($CHCl_3$) 3410, 2980, 1720 (C=O), 1465, 1435, 1270, and 1035 cm^{-1}; nmr ($CDCl_3$) δ 8.38 (broad, s, 2 H), 4.14 (q, 2 H, J = 7 Hz), 3.30 (q, 6 H, J = 7 Hz), 1.37 (t, 9 H, J = 7 Hz), and 1.23 (t, 3 H, J = 7 Hz).

It was possible to convert the monohydrate to **24** by gentle heating under vacuum. In one example, **24** was dissolved in water and allowed to stand for several hours at 25°. Evaporation of the water under reduced pressure at 45–50° gave **24** displaying the same melting point and infrared spectrum as before hydration.

Reaction with Aniline. Compound **24** (2.00 g, 0.00792 mol) was dissolved in 10 ml of benzene. Upon addition of 2 ml of aniline an exothermic reaction occurred. The benzene solution was added to 100 ml of dilute hydrochloric acid, and this mixture was extracted with four 75-ml portions of ether. The combined ether extracts were washed with 50 ml of water and dried over anhydrous magnesium sulfate. Filtration and evaporation of solvent under reduced pressure, followed by recrystallization of the residue from a benzene solution, gave 1.77 g (92%) of colorless needles of *N*-carbethoxy-*N'*-phenylsulfamide: mp 140–141° (lit.[19] mp 140–141°); ir ($CHCl_3$) 3380 (N–H), 3000, 1745 (C=O), 1600, 1475, 1430, 1350, and 1160 cm^{-1}; nmr (acetone) δ 9.06 (broad, s 1 H), 7.50–7.21 (m, 5 H), 4.22 (q, 2 H, J = 7 Hz), 3.23 (s, 1 H), and 1.23 (t, 3 H, J = 7 Hz).

Reaction with Isopropyl Alcohol. Compound **24** (1.0 g) was dissolved in 10 ml of isopropyl alcohol containing 3 ml of benzene and then allowed to stand overnight at ambient temperatures. Evaporation of the solvents under reduced pressure gave a colorless oil which was dissolved in 60 ml of dilute hydrochloric acid and extracted with four 50-ml portions of ether. After the ether extracts were dried over anhydrous magnesium sulfate, the ether was evaporated giving isopropyl carbethoxysulfamate as a colorless oil: ir ($CHCl_3$) (N–H), 2990, 1755 (C=O), 1465, 1435, 1370, and 1165 cm^{-1}; nmr ($CDCl_3$) δ 8.72 (s, 1 H), 5.05 (m, 1 H), 4.28 (q, 2 H, J = 7 Hz), 1.41 (d, 6 H, J = 6 Hz), and 1.30 (t, 3 H, J = 7 Hz).

This compound was also prepared by allowing carbethoxysulfamoyl chloride and isopropyl alcohol to react directly.

Reaction with 1-Vinyl-2-pyrrolidinone. Compound **24** (0.9171 g, 0.00363 mol) and 1-vinyl-2-pyrrolidinone (0.462 g, 0.00408 mol) were dissolved in 10 ml of acetonitrile and allowed to stand in a flask fitted with a calcium chloride drying tube for 13 hr at 30°. At the end of that time, tlc ($CHCl_3$) indicated little or no reaction. The flask was then fitted with a reflux condenser and the solution was heated at 50° for 18 hr. At the end of this time, tlc ($CHCl_3$) indicated the disappearance of **24** and only a small amount of residual 1-vinyl-2-pyrrolidonone in comparison to a new polar compound. The solvent was evaporated under reduced pressure yielding a clear red oil which was then dissolved in 50 ml of dilute hydrochloric acid. The acid solution was extracted with three 40-ml portions of chloroform, and the combined chloroform extracts were dried over anhydrous sodium sulfate. Evaporation of solvent under reduced pressure gave, after recrystallization from chloroform–hexane, colorless needles (478 mg, 50.3%) of *N*-carbethoxy-β-(1-pyrrolidin-2-one)vinylsulfonamide (**26**): mp 149–151°; ir ($CHCl_3$) 3450 (N–H), 1750 (C=O), 1635 (C=C), 1390, 1340, and 1140 cm^{-1}; nmr ($CDCl_3$) δ 8.11 (d, 1 H, J = 14 Hz), 5.98 (d, 1 H, J = 14 Hz), 4.26 (q, 2 H, J = 7 Hz), 3.61 (t, 2 H, J = 7 Hz), 2.60–2.11 (m, 4 H), and 1.29 (t, 3 H, J = 7 Hz).

Anal. Calcd for $C_9H_{14}N_2O_5S$: C, 41.21; H, 5.39; N, 10.68; S, 12.22. Found: C, 40.88; H, 5.41; N, 10.45; S, 12.10.

Reaction with *N,N*-Dimethylaniline. Compound **24** (335 mg) was dissolved in 10 ml of benzene containing 1.0 ml of *N,N*-dimethylaniline and allowed to stand at ambient temperatures overnight during which time a colorless precipitate was deposited from the benzene solution. To this mixture was added 30 ml of water, and it was then acidified with concentrated hydrochloric acid. This mixture was then extracted with three 25-ml portions of ether, and the combined ether extracts were dried over anhydrous magnesium sulfate. Evaporation of solvent under reduced pressure gave colorless needles (130 mg, 36%) of *N,N*-dimethyl-*N'*-carbethoxysulfanilamide. An analytical sample was prepared by recrystallization from chloroform–benzene: mp 184–190° (lit.[8] mp 192–194°); ir ($CHCl_3$) 3390 (N–H), 3010, 1740 (C=O), 1600, 1470, 1340, and 1150 cm^{-1}; nmr (DMSO-d_6) δ 7.10 (m, 4 H), 3.95 (q, 2 H, J = 7 Hz), 3.54 (broad, s, 1 H), 2.93 (s, 6 H), and 1.10 (t, 3 H, J = Hz).

Anal. Calcd for $C_{11}H_{16}N_2O_4S$: C, 48.51; H, 5.93; N, 10.29; S, 11.77. Found: C, 48.24; H, 5.85; N, 10.33; S, 11.56.

In another example, 5.0 g (0.0266 mol) of carbethoxysulfamoyl chloride in 10 ml of benzene was added dropwise under nitrogen over a 1-hr period at ambient temperatures to a solution of 6.45 g (0.0580 mol) of *N,N*-dimethylaniline in 15 ml of benzene. The solution was stirred at ambient temperatures for 2 hr after the addition was completed and was then poured into 300 ml of dilute hydrochloric acid. This mixture was extracted with five 100-ml portion of ether. The combined ether extracts were washed with 30 ml of water and dried over anhydrous magnesium sulfate. Filtration and evaporation of solvent under reduced pressure gave 4.38 g (60.7%) of *N,N*-dimethyl-*N'*-carbethoxysulfanilamide.

Reaction with Tetramethylallene. Compound **24** (0.50 g, 0.00198 mol) and tetramethylallene (0.38 g, 0.00396 mol) were dissolved in 3 ml of acetonitrile in a flask fitted with a reflux condenser and a calcium chloride drying tube. The solution was heated at 60° for 3 hr. Evaporation of solvent under reduced pressure gave a red oil which was chromatographed over Florisil (9 g). Elution with benzene–chloroform (1:1, v/v) gave 228 mg of colorless crystals which were shown by glc to be a mixture of two compounds, **27** (15%) and **28** (85%). The major component of the mixture was purified by repeated recrystallization from benzene–hexane solution providing colorless needles of 2,3-dihydro-2,2-dimethyl-3-isopropylidene-6-ethoxy-1,4,5-oxathiazine 4,4-dioxide (**28**): mp 81–83°; ir ($CHCl_3$) 2985, 1615 (C=N), 1460, 1330, and 1130 cm^{-1}; nmr ($CDCl_3$) δ 4.40 (q, 2 H, J = 7 Hz), 2.35 (s, 3 H), 2.04 (s, 3 H), 1.81 (s, 6 H), and 1.38 (t, 3 H, J = 7 Hz); mass spectrum (70 eV) *m/e* (relative intensity) 247 (2), 232 (57), 202 (4), 160 (100).

Anal. Calcd for $C_{10}H_{17}NO_4S$: C, 48.60; H, 6.89; N, 5.67; S, 12.95. Found: C, 48.54; H, 6.91; N, 5.72; S, 13.07.

Compounds **27** and **28** could also be separated by glc on a silicone rubber column. The mixture was separated in this way giving 2-carbethoxy-3,3-dimethyl-4-isopropylidene-1,2-thiazetidine 1,1-dioxide (**27**) as colorless needles: mp 150–151°; ir ($CHCl_3$) 2980, 1725 (C=O), 1695 (C=C), 1440, 1370, 1315, and 1160 cm^{-1}; nmr ($CDCl_3$) δ 4.42 (q, 2 H, J = 7 Hz), 2.10 (s, 3 H), 1.91 (s, 3 H), 1.76 (s, 6 H), and 1.35 (t, 3 H, J = 7 Hz); mass spectrum (70 eV) *m/e* (relative intensity) 247 (0.5), 232 (100), 202 (5), 176 (2), 160 (100).

The molecular formula of **27** was confirmed by exact mass determinations: found for $C_{10}H_{17}NO_4S$ $(M)^+$ 247.086 (calcd 247.088); found for $C_9H_{14}NO_4S$ $(M - 15)^+$ 232.062 (calcd 232.064).

Attempted Reaction with Allene. A bomb with a capacity of 250 ml was charged with a solution of 7.40 g of **24** in 40 ml of acetonitrile. After the bomb was cooled to −78° and evacuated to 25 mm, 10 g of allene was passed into the bomb which was then rocked for 6 hr at 65–70°. After cooling and venting the bomb, the contents, a clear red solution, were removed. Evaporation of solvent under reduced pressure gave a red solid residue which was shown by infrared and nmr spectra and by tlc to be only slightly contaminated **24**. The nmr spectrum showed no absorptions for protons resulting from the incorporation of allene.

Reaction with Hexamethylbicyclo[2.2.0]hexa-2,5-diene (31). Compound **24** (1.206 g, 0.00458 mol) and 3.0 g of hexamethylbicyclo[2.2.0]hexa-2,5-diene (**31**) were dissolved in 4 ml of acetonitrile–benzene (1:1, v/v) and heated at 60° for 3 hr in a flask fitted with a reflux condenser and calcium chloride drying tube. Cooling and evaporation of solvents under reduced pressure gave a residue comf posed of two separated oils. The lower layer was a dark red viscous oil while the upper layer was colorless. On standing at 0.-mm pressure, the colorless oil crystallized. A portion (700 mg) o1 these colorless crystals was removed from the flask manually with a spatula. Recrystallization from benzene–hexane gave colorless crystals of an adduct (**32**): mp 140–141.5°; ir ($CHCl_3$) 2980, 1730 (C=O), 1440, 1325, 1300, and 1145 cm^{-1}; nmr ($CDCl_3$) δ 4.36 (q, 2 H, J = 7 Hz), 1.73 (s, 6 H), 1.49 (s, 3 H), 1.40 (t, 3 H, J = 7 Hz), 1.28 (s, 3 H), and 1.25 (s, 6 H); nmr (benzene) δ 4.32 (q, 2 H, J = 7 Hz), 1.66 (s, 3 H), 1.51 (s, 6 H), 1.30 (t, 3 H, J = 7 Hz), 1.27 (s, 6 H), and 1.25 (s, 3 H); mass spectrum (70 eV) *m/e* (relative intensity) 313 (0.2), 268 (3), 149 (89).

Anal. Calcd for $C_{15}H_{23}NO_4S$: C, 57.48; H 7.41; N, 4.47; S, 10.23. Found: C, 57.24; H, 7.54; N, 4.25; S, 10.00.

Hydrogenation of Adduct 32. Compound **32** (0.305 g, 0.00094 mol) in 50 ml of ethanol was hydrogenated at 40 psi over 0.2 g of 10% Pd/C for 24 hr in a Parr shaker. The catalyst was removed

(19) R. Graf, German Patent 940,292 (1956); *Chem. Abstr.*, **52**, 14667*c*.

and the solvent was evaporated under reduced pressure and the oily residue crystallized on standing. Four recrystallizations from benzene–hexane gave 0.1 g (30%) of a dihydro adduct as colorless needles: mp 157.5–158.5°; ir ($CHCl_3$) 1730 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.09 (d, 6 H), 2.05 (g, 2 H), 1.18 (s, 9 H), 1.62 (s, 3 H), 1.40 (t, 3 H, J = 7 Hz), and 4.36 (q, 2 H, J = 7 Hz); mass spectrum (70 eV) m/e 315.

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Disulfide Stereochemistry. Conformations and Chiroptical Properties of L-Cystine Derivatives[1]

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Abstract: Successive N-methylation of L-cystine (L-CySSCy (**1**)) reverses the relative magnitudes of the vicinal coupling constants and chemical shifts of the anisochronous methylene hydrogens on passing from di- to tetramethylcystine. These pmr results indicate that the most stable staggered ethanic rotamer with anti sulfur and carboxylate residues for **1** is succeeded by the rotamer with anti sulfur and methylated ammonium groups. For the same series of compounds, the composite circular dichroism (CD) of the disulfide absorption at >240 nm changes sign from negative to positive upon N-methylation, permitting estimation of contributions to optical activity by each rotamer due to perturbation of the disulfide chromophore by the asymmetric centers. Upon passing from water and methanol to longer chain alcoholic solvents, the disulfide CD of alkyl ester dihydrochlorides of **1** also changes sign from negative to positive, suggesting a similar change in rotamer preference. Acylation and amidation of **1** produce only minor effects on vicinal coupling constants and CD, indicating only small influences of these substituents on rotamer distribution. Mixed disulfides such as L-$CySSC_2H_5$ yield coupling constants and CD curves similar to that of **1**. These results among others indicate no significant restriction on the conformation of **1** due to endocyclic interactions. The relatively high optical rotatory properties of **1** and derivatives in solution are due not to endocyclic interactions nor to biasing of screw sense in the disulfide bond but rather to unequal populations of three staggered rotamers. From an examination of (−)-(9*S*,10*S*)-*trans*-hexahydro-2,3-benzodithiin and crystals of **1**, a negative long wavelength CD sign is associated with M disulfide chirality for dihedral angles less than 90°. The utility of the long wavelength CD in assigning M disulfide chirality and monitoring conformational changes is demonstrated for the naturally occurring cyclopentapeptide malformin A.

Two decades have passed since a rekindling of interest in the high optical rotation of L-cystine (L-CySSCy (**1**)) relative to L-cysteine (L-CySH (**2**)) and other amino acids. A postulate[3] that endocyclic interactions composed of hydrogen bonds make **1** more akin to the cyclic amino acid L-proline than to the less strongly rotatory acyclic amino acids followed an earlier suggestion[4] of ". . . forces which very severely restrict the freedom or orientation of groups . . ." in **1**. When the proposal of endocyclic interactions appeared, it was quickly countered by the point that proximity of an asymmetric center to a disulfide bond is sufficient to produce increased D-line rotation.[5] As increasingly more sophisticated instrumentation has become available, optical rotatory dispersion[6–10] and circular dichroism[10–12] data have been reported for **1**.

The disulfide bond is potentially an inherently dissymmetric chromophore, for the normal disulfide dihedral angle is near 90°, and in the presence of a chiral center, some degree of preference for M (left-handed) or P (right-handed)[13] disulfide chirality must be induced.[6] In such an instance, two contributions considered additive to optical activity are present, that of the potentially chiral chromophore and that of the chromophore perturbed by the asymmetric center. In L-cystine, the last contribution may in turn be considered the sum of weighted contributions according to the relative

(1) Abstracted from the Doctoral Dissertation of Jeremiah P. Casey, University of Virginia, 1968. The research was supported by grants from the National Science Foundation.

(2) NDEA Fellow, 1964–1967; Tennessee Eastman Fellow, 1967–1968.

(3) L. Fieser, *Recl. Trav. Chim. Pays-Bas*, **69**, 410 (1950).

(4) W. Kauzmann and H. Eyring, *J. Chem. Phys.*, **9**, 41 (1941). The 15-fold greater temperature dependence of the molar rotation for 1 over **2** is often cited as evidence for endocyclic interactions. Normalized to the molar rotation of the respective amino acids, however, the temperature coefficient for 1 is only half that for **2**.

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