(6) R. A. Abramovitch, I. Shinkai, B. W. Cue, Jr., F. A. Ragan, Jr., and J. L. Atwood, *J. Heterocycl. Chem.*, **13**, 415 (1976).
(7) R. A. Abramovitch and B. W. Cue, Jr., *J. Am. Chem. Soc.*, **98**, 1478 (1976).
(8) M. J. Abu El-Haj, *J. Org. Chem.*, **37**, 2519 (1972).
(9) (a) D. W. S. Latham, O. Meth-Cohn, and H. Suschitzky, *J. Chem. Soc., Chem. Commun.*, 1040 (1972); (b) D. W. S. Latham, O. Meth-Cohn, H. Suschitzky, and J. A. L. Herbert, *J. Chem. Soc., Perkin Trans. 1*, 470 (1977).
(10) For example, loss of NO from the molecular ion is diagnostic for a 6,6-disubstituted-1,2-oxazine (ref 6).
(11) J. B. Grutzner and R. E. Santini, *J. Magn. Reson.*, **19**, 173 (1973).
(12) K. Dimroth and H. G. Aurich, *Chem. Ber.*, **98**, 3902 (1965).
(13) The cyano band for this compound was not observed. This is not unexpected for a cyano group adjacent to electron-withdrawing, oxygen-containing moieties such as the nitro and *N*-oxide groups: N. B. Colthup, H. L. Daly, and S. E. Wiberley, "Introduction to Infrared and Raman Spectroscopy", Academic Press, New York, N.Y., 1964, p 202.
(14) The possibility that 3,3-dialkyl-3*H*-2,1,4-benzoxadiazine 4-oxides could be formed upon reaction of benzofurazan *N*-oxide with secondary nitroalkanes has been addressed by Meth-Cohn and Suschitzky (ref 9b) and ruled out by ^{13}C NMR analysis of the products obtained.

Chlorination of the Cephem Dihydrothiazine Ring. Factors Influencing Carbon-2 Substitution vs. Degradation to Isothiazoles[1]

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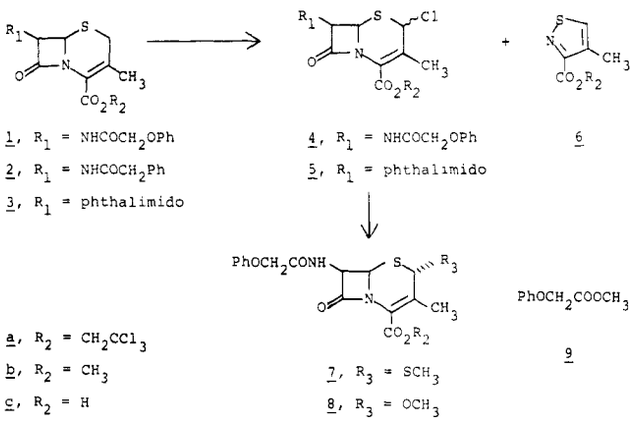
The reaction of Δ^3-cephalosporin esters with *N*-chlorosuccinimide (NCS) is described. When a 7-phenoxyacetamido- or a 7-phthalimido-Δ^3-cephem (**1a** or **3a**) is reacted with NCS, the unstable 2-chloro-Δ^3-cephem (**4a** or **5a**, respectively) can be observed in solution by NMR. Nucleophilic displacement of chloride ion in the 2-chloro derivative **4a** by methanethiol or methanol yields the 2α-methylthio- and 2α-methoxy-Δ^3-cephems **7a** and **8a**, respectively. Chlorination of 7-phenylacetamido-Δ^3-cephems **2a** and **2b** gives the isothiazoles **6a** and **6b** exclusively; **6a** is also a minor product in the chlorination of **1a**. The structure of the degradation product **6** is proven by x-ray analysis of 4-hydroxyisothiazole-3-carboxylic acid (**12**), derived from the chlorination of methyl 7-(*N*-phenylacetamido)cephalosporanate (**10**), followed by saponification.

The synthesis of 2-halo-Δ^3-cephems was undertaken to prepare a versatile intermediate for C-2 substituted cephalosporins. Methods for the introduction of alkoxy and acyloxy residues at C-2[2] involving the oxidation of sulfur in the dihydrothiazine ring cannot be used with nucleophiles susceptible to the oxidative conditions. Therefore, a substrate capable of undergoing nucleophilic substitution at C-2 was desired. Investigations by others in this area have led to the isolation and methanolysis of a 2-bromo-Δ^3-cephem and 2,3-dibromocephams, prepared by the bromination of a cephalosporin lactone[3] and Δ^2-cephems,[4] respectively. We have studied the chlorination of Δ^3-cephalosporin esters using *N*-chlorosuccinimide (NCS) and now report on the factors influencing this reaction following the initial halogenation of sulfur.

Scheme I



Results

A solution of **1a**, containing 1 equiv of NCS in deuteriochloroform, was monitored by NMR. Within 15 min the simultaneous disappearance of the NCS singlet (δ 2.94) and the AB quartet of the cephem C-2 protons (δ 3.43) was observed. The formation of an unstable C-2 substituted Δ^3-cephem, presumed to be the 2-chloro derivative **4a**, was indicated by the appearance of the resonances shown in Table I.[5] Simultaneously, a non-β-lactam component was formed having an aromatic methyl singlet (δ 2.63) and a low-field singlet (δ 8.42). After 1.5 h at ambient temperature the 2-chlorocephem **4a** had completely decomposed while the non-β-lactam component was stable to these conditions. To prove the intermediacy of a 2-chlorocephem, methanethiol was added to the reaction mixture after the NCS was consumed and gave the 2α-methylthio derivative **7a** in 33% yield[6] (Scheme I). The C-2 configuration was assigned based on long-range ^5J coupling (<1 Hz) between H-2β and H-7α and a nuclear Overhauser effect (15%) between H-2β and CH_3.[2b,8] Methanolysis of **4a** gave the 2α-methoxy derivative **8a** (identical with a sample prepared by a modification of Spry's procedure[2b] using NCS in methanol), plus equimolar amounts of the non-β-lactam compound and methyl phenoxyacetate (**9**). Cleavage of the trichloroethyl ester gave the free acid **8c**,[2b,4] which had less antimicrobial activity than the parent C-2 unsubstituted compound.

When 1 equiv of NCS was mixed with the trichloroethyl ester **2a** indeuteriochloroform, all the NCS reacted rapidly, yielding a mixture of starting material and the same non-β-lactam product observed in the reaction of **1a**. However, the desired 2-chlorocephem was not detected. The phthalimido analogue **3a** reacted slowly over a 3-h period yielding a solution of the 2-chlorocephem **5a** (Table I). None of the non-β-lactam product, formed in the chlorination of **1a** and **2a**, was observed in this reaction.

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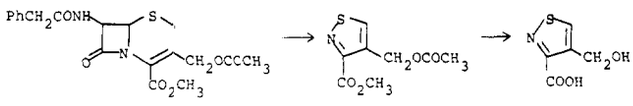
Table I. ^{1}H NMR Data of C-2 Substituted Δ^3-Cephems in $CDCl_3$

Compd	Registry no.	H-2	3-CH_3	H-6	H-7	O(S)CH_3	OCH_2CO	CH_2CCl_3
4a	64024-43-7	5.75 s	2.30 s	5.52 d (J = 5 Hz)	6.17 q (J = 5, 9 Hz)		4.67 s	5.00 m
5a	64024-44-8	5.73 s	2.28 s	5.60 d (J = 5 Hz)	6.10 d (J = 5 Hz)			5.03 AB q (J = 14 Hz)
7a	64024-45-9	4.37 s	2.28 s	5.36 d (J = 5 Hz)	6.01 m (J = <1, 5, 9 Hz)	2.28 s	4.55 s	4.88 Ab q (J = 11 Hz)
8a	64044-39-9	4.82 s	2.24 s	5.14 d (J = 4.5 Hz)	5.98 m (J = <1, 4.5, 10 Hz)	3.47 s	4.58 s	4.92 AB q (J = 12 Hz)

Scheme II



10 11 12

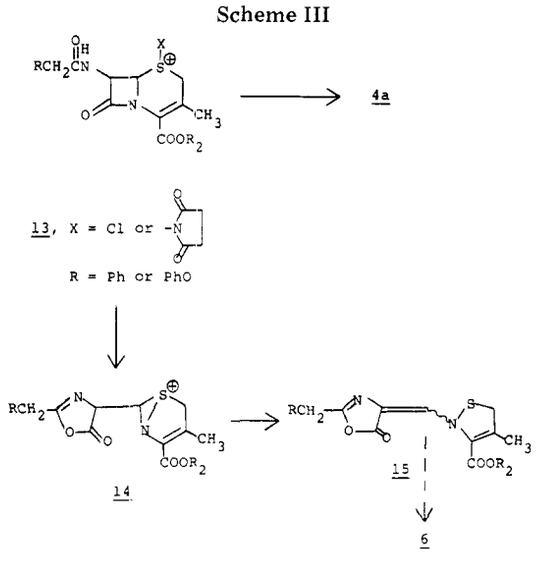
The chlorinations of **1a** and **2a** were repeated on a preparative scale giving 36 and 66% yields, respectively, of the non-β-lactam product, subsequently proven to be the isothiazole **6a.** During these reactions 2 equiv of NCS were consumed. A significant rate increase was observed when a catalytic amount of trifluoroacetic acid or sulfuric acid was added. The products **6b** and **11,** obtained from the chlorination of the methyl esters **2b** and **10,** differed only in substitution on the nuclear methyl group.

The product from **10** was a crystalline diester, which was saponified with 2 equiv of base yielding a hydroxy acid, assigned structure **12** by x-ray crystallography (Scheme II). Therefore, structures **6a, 6b,** and **11** have been assigned to the analogous non-β-lactam products. Both the ester **11** and the acid **12** exhibit two ultraviolet absorption maxima, characteristic of isothiazoles. The longer wavelength absorption of **12** (263 nm) is in agreement with the calculated value (260 nm).[10] Also, the isothiazoles exhibit coupling (0.8 Hz) between the ring proton (H-5) and the protons of the C-4 substituent.[11]

Discussion

Though all the products resulting from the acylglycyl segment of the cephem nucleus have not been identified, reasonable speculation on the origin of the isothiazole can be made (Scheme III). The reaction at sulfur by NCS would initially give a sulfonium salt **13,**[12,13] likely an intermediate common to both **4a** and **6.** The electronegativity of the positively charged sulfur in **13** would facilitate the cleavage of the β-lactam ring to form the oxazolone **14,** a common occurrence in the acid-catalyzed cleavage of penicillins.[14] The formation of a 2-chloro-Δ^3-cephem with the 7β-phenoxyacetamido residue but not with the 7β-phenylacetamido residue suggests an oxazolone intermediate. An analogy can be made with the chemistry of penicillin where the phenoxyacetyl derivative is more stable than the corresponding phenylacetamido penam under conditions where oxazolone formation is implicated in their decomposition.[15] Also, kinetic evidence indicates that electron-withdrawing substituents on the C-7 side chain of various cephalosporins slow the rate of spontaneous decomposition, presumably proceeding through intramolecular attack of the amide carbonyl on the β-lactam ring.[16] Therefore, the path leading to the 2-chlorocephem **4a** can compete with the path leading to oxazolone **14** when the nucleophilicity of the amide carbonyl is inductively reduced by the phenoxymethyl residue.

Scheme III



13, X = Cl or -N(C=O)2; R = Ph or PhO

14 15 6

The isolation of methyl phenoxyacetate (**9**) and isothiazole **6a** (1:1 ratio) after methanolysis of the reaction mixture starting with cephem **1a** is also indicative of an oxazolone intermediate. Oxazolones can behave as imino ethers and methanolysis of the imino linkage followed by hydrolysis would yield the ester **9.**[17] Further, the participation of the C-7 side chain is inferred since the phthalimido derivative **3,** which cannot form an oxazolone, does not produce the isothiazole under the reaction conditions. The mechanism of acid catalysis observed for the isothiazole formation may correspond to that proposed for the acid-catalyzed aqueous oxidation of alcohols by NCS. Presumably, NCS is protonated, which thereby increases the electrophilicity of chlorine.[18] However, in the rearrangement, acid may also catalyze the opening of the β-lactam.

The formation of the isothiazole ring may proceed by a variety of pathways. Structures **14** and **15** represent the overall result of nitrogen–sulfur bond formation and carbon–sulfur bond cleavage, respectively, leading to an isothiazoline ring.[19] From **15,** the formation of product **6** is the net result of an oxidation of the isothiazoline ring, which accounts for the second equivalent of NCS being consumed when R = phenyl, and a displacement reaction, removing the methylene oxazolone moiety. Precedent for nucleophilic displacements on 4-methylene-5-oxazolones is well documented[20] and a nucleophile present in the reaction mixture may perform the displacement on **15** or, more likely, on an oxidized form of the isothiazoline ring to give the product **6.**

In conclusion, this investigation has shown that the course of nuclear modification in cephalosporins is influenced by the nature of the C-7 amide side chain. Intervention of an oxazolone intermediate in the chlorination of cephems leads to an isothiazole and the rate of oxazolone formation is influenced by inductively changing the nucleophilicity of the amide carbonyl. When the nucleophilicity is lessened, the Pummerer-type reaction becomes competitive with S–C(6) bond cleavage and chlorination at C-2 is observed.

Experimental Section

The NMR spectra were determined on Varian nuclear magnetic resonance spectrometers (Models T-60 and XL-100-15) using tetramethylsilane as an internal standard, and chemical shifts are reported on the δ scale. Infrared spectra were recorded on Perkin-Elmer spectrometers (Models 257 and 621), and the mass spectra were obtained on an AEI-MS-902 mass spectrometer. Melting points are uncorrected.

Trichloroethyl 3-Methyl-2α-methylthio-7-(phenoxyacetamido)-3-cephem-4-carboxylate (7a) and Trichloroethyl 4-Methylisothiazole-3-carboxylate (6a). A solution of 128 mg (0.267 mmol) of cephem **1a** in 0.8 mL of deuteriochloroform was treated with 36 mg (0.267 mmol) of *N*-chlorosuccinimide (NCS). The disappearance of the NCS singlet at 2.9 ppm was monitored by NMR. After 10–15 min at ambient temperature, consumption of NCS was complete and a stream of gaseous methanethiol was bubbled through the reaction mixture for 20 min. Excess thiol was purged from the solution with nitrogen, followed by removal of solvent under reduced pressure. The mixture was separated into three bands by preparative TLC on silica gel plates developed in chloroform. Extraction yielded as oils (in order of increasing R_f) the starting cephem **1a** (28 mg), the 2α-methylthiocephem **7a** (46 mg), and the isothiazole **6a** (14 mg): IR ($CHCl_3$) 1740 (ester C=O), 1410, 1340 cm^{-1}; NMR ($CDCl_3$) δ 2.62 (doublet, J = 0.8 Hz, 3 H, CH_3), 5.07 (singlet, 2 H, CH_2CCl_3), 8.43 (multiplet, 1 H, CH); mass spectrum *m/e* 273 (molecular ion).

The 2α-methylthio cephem **7a** was precipitated as an amorphous solid (40 mg) from an ether–pentane mixture: IR ($CHCl_3$) 3410 (NH), 1790 (β-lactam C=O), 1740 (ester C=O), 1690 cm^{-1} (amide C=O); NMR (C_6D_6) δ 1.69 (singlet, 3 H, SCH_3), 2.12 (singlet, 3 H, CH_3), 3.67 (multiplet, $J_{H_2-H_7}$ < 1 Hz, 1 H, H_2), 4.07 (AB quartet, J = 14 Hz, 2 H, CH_2CO), 4.70 (AB quartet, J = 12 Hz, 2 H, CH_2CCl_3), 4.93 (doublet, $J_{H_6-H_7}$ = 5 Hz, 1 H, H_6), 5.79 (multiplet, $J_{H_2-H_7}$ = <1 Hz, $J_{H_6-H_7}$ = 5 Hz, J_{NH-H_7} = 9 Hz, 1 H, H_7), 6.62–7.20 (multiplet, 6 H, aromatic and NH); mass spectrum *m/e* 524 (molecular ion). Anal. Calcd for $C_{19}H_{19}N_2O_5S_2Cl_3$: C, 43.39; H, 3.64; N, 5.33; S, 12.20. Found: C, 44.06; H, 3.59; N, 5.36; S, 12.32.

Trichloroethyl 2α-Methoxy-3-methyl-7-(phenoxyacetamido)-3-cephem-4-carboxylate (8a). Method A. A solution of 216 mg (0.450 mmol) of cephem **1a** in 1.0 mL of deuteriochloroform was treated with 60 mg (0.450 mmol) of NCS. Formation of the 2-chlorocephem **4a** was monitored by NMR. After the disappearance of the NCS singlet (~10 min), anhydrous methanol (100 μL) was added. After 8 min the solution was poured into a mixture of methylene chloride and saturated aqueous sodium bicarbonate solution and shaken. The organic layer was separated and washed with water followed by saturated sodium chloride solution. After drying (Na_2SO_4) solvent was removed in vacuo yielding an oil (215 mg). Thin-layer chromatography of the oil on silica gel plates developed in 10:1 chloroform–ethyl acetate yielded the starting cephem **1a** (36 mg), the 2α-methoxycephem **8a** [108 mg; IR ($CHCl_3$) 3380, 1785 (β-lactam C=O), 1740 (ester C=O), 1690 cm^{-1} (amide C=O); mass spectrum *m/e* 508 (molecular ion)], and an oil (32 mg) containing a 1:1 mixture of isothiazole **6a** and methyl phenoxyacetate (**9**) proven by NMR, MS, and TLC.

On standing, the 2α-methoxycephem **8a** crystallized. The colorless needle-like crystals were triturated with an ether–pentane mixture and collected: mp 115–116.5 °C. Anal. Calcd for $C_{19}H_{19}N_2O_6SCl_3$: C, 44.76; H, 3.76; N, 5.50; S, 6.29; Cl, 20.87. Found: C, 44.61; H, 3.50; N, 5.39; S, 6.36; Cl, 20.81.

Method B. To a mixture of 200 mg (0.417 mmol) of **1a** in 5 mL of anhydrous methanol was added 56 mg (0.417 mmol) of NCS. After being stirred 2 h at room temperature, the solution gave a negative starch–KI paper test. Solvent was removed in vacuo and the crude residue was purified by preparative TLC on silica gel plates developed in chloroform. Extraction yielded the starting material (35 mg) and the 2α-methoxycephem **8a** as a foam (75 mg).

2α-Methoxy-3-methyl-7-(phenoxyacetamido)-3-cephem-4-carboxylic Acid (8c). To a solution of 511 mg (1.04 mmol) of cephem trichloroethyl ester **8a** in a mixture of anhydrous dimethylformamide (15 mL) and acetic acid (3 mL) was added 980 mg (15 mmol) of zinc dust while cooling in an ice bath and stirring. After 2 h the reaction mixture was filtered to remove excess zinc. The zinc was washed with ethyl acetate and the combined filtrate and washings were diluted with ethyl acetate. After washing three times with water, the organic layer was extracted by adding water and adjusting to pH 8.8 with base. The basic solution was separated and layered with ethyl acetate. After the aqueous layer was acidified to pH 2.8, the ethyl acetate layer was separated, washed with water, and dried (Na_2SO_4). Solvent was removed under reduced pressure, and the residue (247 mg) was recrystallized twice from a 2-propanol–hexane mixture. The product crystallized with 1 molar equiv of 2-propanol: mp 150–151 °C [lit.[4] mp 141–145 °C (acetone–hexane)]; IR (KBr) 3410, 3280, 2580, 1775 (β-lactam C=O), 1720 (acid C=O), 16[illegible] (amide C=O), 1070, 930, 755 cm^{-1}; NMR (CD_3CN) δ 1.09 (d, J = [illegible] Hz, 6 H, 2-propanol CH_3), 2.05 (singlet, 3 H, CH_3), 3.37 (singlet, 3 [illegible], OCH_3), 3.86 (septet, J = 6 Hz, 1 H, 2-propanol CH), 4.53 (singlet, 1 H, H_2), 5.01 (doublet, $J_{H_6-H_7}$ = 5 Hz, 1 H, H_6), 5.82 (quartet, $J_{H_6-H_7}$ = 5 Hz, J_{H_7-NH} = 9 Hz, 1 H, H_7), 6.6–7.8 (multiplet, 6 H, aromatic and NH). Anal. Calcd for $C_{17}H_{18}N_2O_6S \cdot C_3H_8O$: C, 54.78; H, 5.98; N, 6.39. Found: C, 54.63; H, 5.64; N, 6.41.

Trichloroethyl 4-Methylisothiazole-3-carboxylate (6a). From 1a. Compound **1a** (500 mg, 1.04 mmol) was dissolved in methylene chloride (5 mL) and NCS (278 mg, 2.08 mmol) was added while stirring at room temperature. After 2 h the reaction mixture gave a negative starch–KI paper test. Dilution of the reaction mixture with methylene chloride was followed by washing with water and then pH 7.6 phosphate buffer. Drying (Na_2SO_4), decolorization with charcoal, filtration through Celite, and removal of the solvent in vacuo yielded a crude oil (464 mg). Preparative TLC on silica gel using chloroform as the developing solvent gave the isothiazole **6a** as a foam (1[illegible]2 mg). This material was identical with that isolated in the preparation of the 2-methylthiocephem **7a**.

From 2a. The above procedure was repeated using **2a** (500 mg, 1.08 mmol) and NCS (288 mg, 2.16 mmol). In this case the reaction was exothermic giving a negative starch–KI paper test within 3 m[illegible] but the mixture was allowed to stir 1 h. After workup and chromatography the isothiazole **6a** was isolated as a foam (195 mg).

Methyl 4-Methylisothiazole-3-carboxylate (6b). To a solution of the cephem methyl ester **2b** (1.0 g, 2.89 mmol) in methylene chloride (40 mL) was added NCS (0.771 g, 5.77 mmol) and 1 drop of trifluoroacetic acid. After 1 h the reaction mixture was worked up by washing with saturated aqueous sodium bicarbonate solution, followed by water, and drying (Na_2SO_4). Solvent was removed under reduced pressure and the residual oil was purified by dry column chromatography on silica gel (1.5 × 15 in. column developed with chloroform). The product was isolated as a reddish yellow oil (293 mg). Distillation in vacuo yielded the isothiazole **6b** as a colorless crystalline solid: mp 28–29.5 °C; IR (KBr) 1710 (ester C=O), 1430, 1250, 1080 cm^{-1}; NMR ($CDCl_3$) δ 2.59 (doublet, J_{H-CH_3} = 0.8 Hz, 3 H, CH_3), 4.02 (singlet, 3 H, OCH_3), 8.39 (multiplet, 1 H, CH); λ_{max} (95% EtOH) 227 nm (ε 4400), 268 (6000); mass spectrum *m/e* 157 (molecular ion). Anal. Calcd for $C_6H_7NO_2S$: C, 45.84; H, 4.49; N, 8.91; S, 20.40. Found: C, 45.77; H, 4.30; N, 9.13; S, 20.24

Methyl 4-Acetoxymethylisothiothiazole-3-carboxylate (11). Methyl ester **10** (2.50 g, 6.20 mmol) was dissolved in methylene chloride (80 mL) and NCS (1.66 g, 12.40 mmol) was added. The mixture was allowed to stir overnight at room temperature, then washed with water, followed by pH 7.6 buffer, and dried (Na_2SO_4). The solution was decolorized with charcoal and filtered through Celite, and solvent was removed in vacuo. A combination of column chromatography and crystallization from ethyl acetate–hexane gave 0.855 g: mp 90.5–92 °C. Recrystallization yielded analytically pure **11:** 0.620 g; mp 91.5–92.5 °C; IR (KBr) 1735 (ester C=O), 1705 (ester C=O), 1440, 1350, 1130, 1085, 1035 cm^{-1}; NMR ($CDCl_3$) δ 2.14 (singlet, 3 H, CH_3), 3.98 (singlet, 3 H, OCH_3), 5.47 (doublet, J_{H-CH_2} = 0.8 Hz, 2 H, CH_2), 8.67 (multiplet, 1 H, CH); λ_{max} (95% EtOH) 227 nm (ε 4180), 262 (6260); mass spectrum m/e 215 (molecular ion). Anal. Calcd for $C_8H_9NO_4S$: C, 44.66; H, 4.22; N, 6.51. Found: C, 44.87; H, 4.05; N, 6.51.

4-Hydroxymethylisothiazole-3-carboxylic Acid (12). The isothiazole diester **11** (0.374 g, 1.74 mmol) was dissolved in a methanol (7 mL)–0.5 N aqueous sodium hydroxide (7 mL) mixture. After stirring the solution for 1.75 h at room temperature, methanol was removed by concentration in vacuo and the pH of the residual aqueous solution was adjusted to 2.5 with 6 N hydrochloric acid while cooling in an ice bath. A colorless solid crystallized, which was collected by filtration and dried: 0.180 g; mp 183.5–185 °C dec. Concentration of the filtrate under reduced pressure yielded a second crop: 0.035 g; mp 180–182 °C dec.

The first crop was recrystallized from water yielding the analytically pure hydroxy acid **12:** 0.113 g; mp 183.5–185 °C dec; IR (KBr) 3310, 3110, 2600 (br sh), 1710 (acid C=O), 1460, 1235, 1150, 1025 cm^{-1}; NMR (Me_2SO-d_6) δ 4.80 (br s, 2 H, CH_2), 8.92 (br s, 1 H, CH); λ_{max} (95% EtOH) 225 nm (ε 4190), 263 (6110); mass spectrum *m/e* 159 (molecular ion). Anal. Calcd for $C_5H_5NO_3S$: C, 37.74; H, 3.17; N, 8.80. Found: C, 37.59; H, 3.46; N, 8.72.

X-Ray Determination of Structure 12. The monoclinic crystals of **12** ($C_5H_5NO_3S$) from aqueous solution have a = 3.952 (1), b = 11.997 (7), and c = 13.21 (1) Å, β = 90.0 (1)°, d_{calcd} = 1.69 g cm^{-3}, and

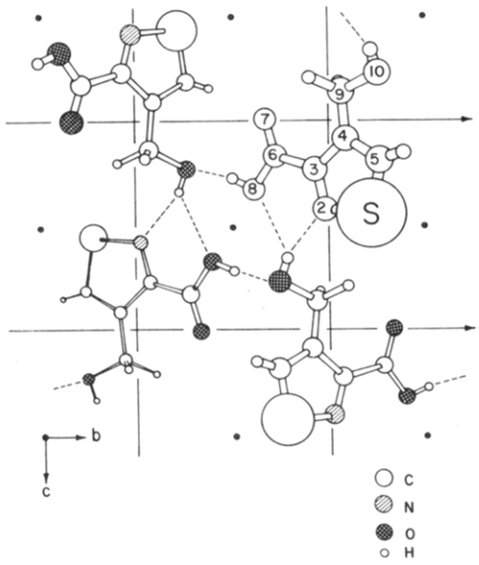


Figure 1. Crystal structure of **12.**

space group $P2_1/n$ with Z = 4; 562 "observed" intensities measured on an automatic diffractiometer (Cu Kα; λ 1.542 Å) were used for the solution and least-squares refinement of structure. Patterson and Fourier analyses revealed an atomic arrangement consistent with the 3,4-disubstituted isothiazole **12.** Refinements of the coordinates and anisotropic temperature factors, including the coordinates (but not temperature factors) of all five hydrogen atoms evident in a difference map, converged to $R = 0.06$.[21]

The heterocyclic ring is planar to within 0.004 Å and the S–N and S–C bond lengths are 1.655 (2) and 1.704 (2) Å, respectively. The carbonyl oxygen O(7) is syn to C(4) [torsional angle O(7)–C(6)–C(3)–C(4) = 1°]. There is no intramolecular hydrogen bonding; instead, O(10) adopts an anti conformation with respect to C(3) and the carboxyl group [torsional angle O(10)–C(9)–C(4)–C(3) = 179°] and is *inter*molecularly hydrogen bonded to a glide related molecule [O(8) $\cdots$ O(10) distance = 3.01 Å; O(10) $\cdots$ N(2) distance = 2.94 Å].

In addition, the carboxyl hydrogen is hydrogen bonded to O(10) of a screw-related molecule [O(8) $\cdots$ O(10) distance = 2.66 Å]. A drawing of this hydrogen-bonded network is shown in Figure 1.

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Registry No.—**1a,** 24647-47-0; **2a,** 28180-80-5; **2b,** 33465-36-0; **6a,** 64024-46-0; **6b,** 64024-47-1; **8c,** 58800-55-8; **10,** 3595-22-0; **11,** 64024-48-2; **12,** 64024-49-3; methanethiol, 74-93-1.

Supplementary Material Available: Tables of fractional coordinates, temperature factors, and interatomic angles and distances (3 pages). Ordering information is given on any current masthead page.

References and Notes

(1) Presented in part at the β-Lactam Symposium, American Chemical Society Meeting in Miniature, Stevens Institute of Technology, Hoboken, N.J. May 14, 1975.
(2) (a) R. D. G. Cooper, P. V. Demarco, C. F. Murphy, and L. A. Spangle, *J. Chem. Soc. C,* 340 (1970); (b) D. O. Spry, *Tetrahedron Lett.,* 3717 (1972); (c) D. H. Bremner, M. M. Campbell, and G. Johnson, *ibid.,* 2972 (1976).
(3) E. H. W. Bohme and J. E. Dolfini, *Chem. Commun.,* 941 (1972).
(4) A. Balsamo, P. Crotti, B. Macchia, and F. Macchia, *J. Org. Chem.,* **41,** 2150 (1976).
(5) The synthesis of simple cyclic α-chloro sulfides using NCS has been reported by D. L. Tuleen and R. H. Bennett, *J. Heterocycl. Chem.,* **6,** 115 (1969).
(6) 2α-Methylthio-Δ^3-cephems have been prepared by methylthiolation of the allylic anion of cephalosporin sulfoxides followed by reduction to the sulfide.[1,7,8] Aromatic solvent-induced shift studies[9] have proved that the C-2 methylthio moiety introduced by this procedure also has the α configuration.[1]
(7) W. H. Koster and J. E. Dolfini, U.S. Patent 3 968 109 (1976).
(8) A. Yoshida, S. Oida, and E. Ohki, *Chem. Pharm. Bull.,* **23,** 2507 (1975).
(9) P. V. Demarco and R. Nagarajan in "Cephalosporins and Penicillins: Chemistry and Biology", E. H. Flynn, Ed., Academic Press, New York, N.Y., 1972, pp 353–355.
(10) (a) D. Buttimore, D. H. Jones, R. Slack, and K. R. H. Wooldridge, *J. Chem. Soc.,* 2032 (1963); (b) D. H. Jones, R. Slack, and K. R. H. Wooldridge, *ibid.,* 3114 (1964).
(11) H. A. Staab and A. Mannschreck, *Chem. Ber.,* **98,** 1111 (1965).
(12) D. L. Tuleen and T. B. Stephens, *J. Org. Chem.,* **34,** 31 (1969).
(13) (a) E. Vilsmaier and W. Sprügel, *Justus Liebigs Ann. Chem.,* **747,** 151 (1971); (b) E. Vilsmaier, K. H. Dittrich, and W. Sprügel, *Tetrahedron Lett.,* 3601 (1974).
(14) See references cited in R. J. Stoodley, *Tetrahedron,* **31,** 2321 (1975).
(15) F. P. Doyle, J. H. C. Nayler, H. Smith, and E. R. Stone, *Nature (London),* **19,** 1091 (1961).
(16) T. Yamana and A. Tsuji, *J. Pharm. Sci.,* **65,** 1563 (1976).
(17) H. T. Clarke, J. R. Johnson, and R. Robinson, Ed., "The Chemistry of Penicillin", Princeton University Press, Princeton, N.J., 1949, pp 734–735.
(18) N. S. Srinivasan and N. Venkatsubramanian, *Tetrahedron,* **30,** 419 (1973).
(19) A related pathway has been proposed for the rearrangement of C-2 hetero-substituted cephalosporin sulfoxides: A. Yoshida, S. Oida, and E. Ohki, *Chem. Pharm. Bull.,* **23,** 2518 (1975).
(20) (a) E. Baltazzi, *Q. Rev., Chem. Soc.,* **9,** 150 (1955); (b) J. W. Cornforth in "Heterocyclic Compounds", Vol. 5, R. C. Elderfield, Ed., Wiley, New York, N.Y., 1957, Chapter 5.
(21) See paragraph at end of paper regarding supplementary material.

p-Quinobis(1,3-benzodithiole) *S*-Oxide. An Unusual Vinylogous Tetrathiafulvalene Derivative

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The purple-black title compound **9** has been synthesized from *o*-benzenedithiol in several steps, the last of which involves a novel base-catalyzed vinylogous Pummerer dehydration of a sulfoxide. Some chemical and physical properties of **9,** which may be viewed as a push–pull stabilized *p*-quinodimethane, are described.

The discovery of the high solid-state electrical conductivity of the charge-transfer complex of tetrathiafulvalene (TTF, **1**) and tetracyanoquinodimethane (TCNQ, **2**)[1] has provided the impetus for the synthesis of a variety of structural modifications of both of the above-mentioned molecules.[2]

The unknown heterocycles **3** and **4** present particularly interesting structural features, since they combine in one molecule the substituted *p*-quinodimethane system of TCNQ with the two 1,3-dithiolidine moieties of TTF. This paper describes the synthesis and some chemistry of the monosul-

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