cephem-4-carboxylic Acid (20d).—**19d** (1.265 g, 2.99 mmoles) was reduced with PCl_3 (2.1 ml, 24.0 mmoles) in DMF (21 ml) at −35° (45 sec) and worked up as described above. The acidic fraction (439 mg, 36%) in EtOH was converted into the Na salt with NaOAc (88.3 mg) in MeOH. The pptd Na salt of **20d** was recrystd from MeOH-EtOH: ir (mull) 1765, 1730, 1655, 1605, 1530 cm^{-1}; uv max (MeOH) 295 nm (ϵ 11,400); nmr (DMSO-d_6) δ 1.98 (3 H, s), 3.78 (2 H, s), 4.85 (1 H, d, J = 12 Hz), 5.07 (1 H, d, J = 5 Hz), 5.21 (1 H, d, J = 12 Hz), 5.27 (1 H, s), 5.47 (1 H, s), 5.57 (1 H, d/d, J = 5 Hz, J = 8 Hz).[15]

Chemistry of Cephalosporin Antibiotics. 24. 2-Thiomethyl- and 2-Thiomethylenecephalosporins

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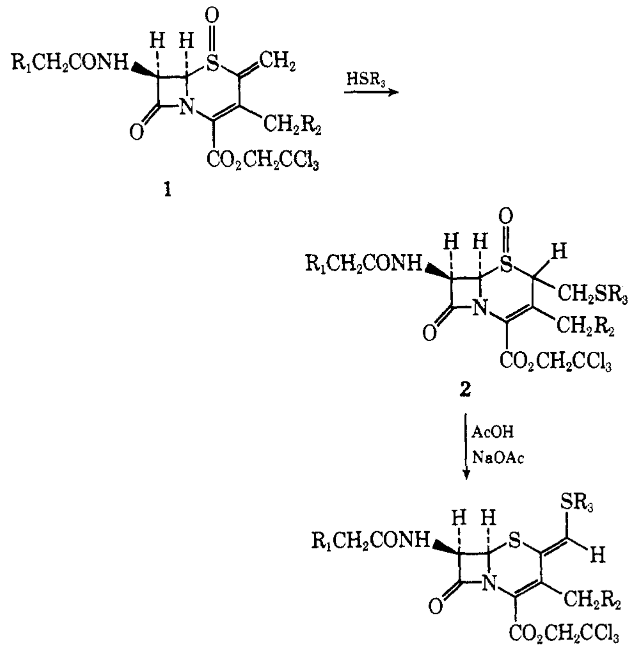
2-Methylenecephalosporin sulfoxide trichloroethyl esters, **1**, were treated with a variety of thiols to give the corresponding 2-thiomethyl adducts **2**. These compounds are stable, but lose the elements of H_2O in HOAc–NaOAc to give 2-thiomethylene esters **3**. Deesterification and sulfoxide reduction of compound type **2** and deesterification of **3** gave the corresponding 2-thiomethyl- and 2-thiomethylenecephalosporins.

We have found that esters of 2-methylenecephalosporin sulfoxides[1] (**1**) react rapidly with thiols at room temp to form 1:1 adducts (**2**) in high yields. The addition is general in that a variety of alkyl, aryl, alkaryl, and heterocyclic thiols add to the 2-exomethylene function.

Although the adducts are generally stable, they lose the elements of H_2O in the presence of AcOH to give 2-thiomethylenecephalosporin esters **3**. The unsaturated esters can be prepared directly by dissolving molar equiv of thiol and 2-methylene sulfoxide (**1**) in AcOH containing approximately a molar equiv of NaOAc.



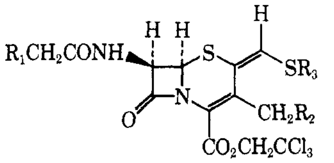
3

The isolated dehydration products (**3**) were not mixtures of cis and trans isomers but were single compounds in each case. In two cases we used nuclear Overhauser effects (NOE)[2] to determine the configuration of the isolated product. If the compound were isomer **3** (R_2 = H), the nmr signal intensity for the vinyl proton should increase when the 3-Me is irradiated, due to the proximity of the two groups. However, if the compound were isomer **4** (R_2 = H), no such signal intensity increase for the vinyl proton would be expected. We determined the NOE's for the cases listed in Table I. Both examples of 2-thiomethylene compounds exhibit large increases in vinyl proton intensity. This strongly suggests that the compounds we isolated are substituted as in **3**—not as in **4**.

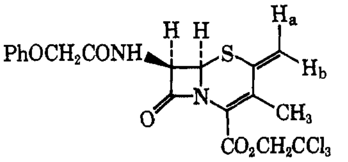
TABLE I

NUCLEAR OVERHAUSER EFFECT RESULTS

Compd	Signal increase for vinyl proton
3h (R_1 = PhO; R_2 = H; R_3 = pyrimidinyl)	+29%
3k (R_1 = PhO; R_2 = H; R_3 = *N*-methyltetrazolyl	+31%
5	H_a, 0%; H_b, 8%



4



5

The NOE determination on the 2-CH_2 compound[1] (**5**) was instructive. Irradiation of the 3-Me group did not affect the H_a signal, but the H_b signal intensity increased 8%. The increase in signal intensity of H_b

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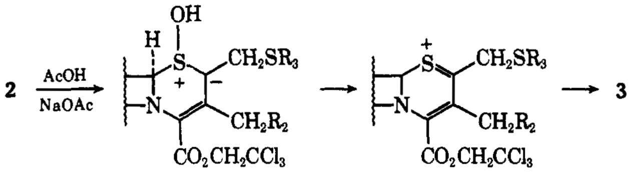
[1] I. G. Wright, C. W. Ashbrook, T. Goodson, G. V. Kaiser, and E. M. Van Heyningen, *J. Med. Chem.*, **14**, 420 (1971).

(2) (a) We are grateful to Dr. P. V. DeMarco and Mr. L. A. Spangle of The Lilly Research Laboratories for the NOE measurements and helpful discussions concerning their interpretation. (b) F. A. L. Anet and A. J. R. Bourn, *J. Amer. Chem. Soc.*, **87**, 5250 (1965). (c) R. A. Bell and J. K. Saunders, *Can. J. Chem.*, **46**, 3421 (1968).

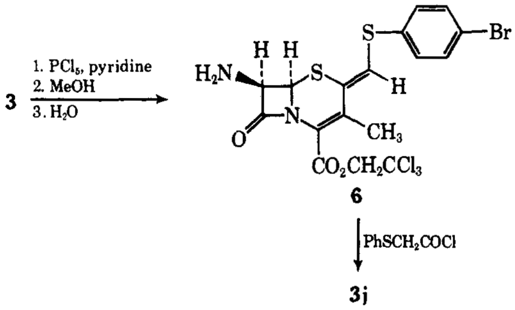
is smaller than that seen in the case of the 2-thiomethylene compounds **3** because H_a provides a much more effective relaxation pathway than the protons on the 3-Me group.

The dehydration reaction, **2** → **3**, resembles the Pummerer reaction which involves the reduction of a sulfonium S with oxidation of the α-C.[3] However, this dehydration did not proceed smoothly under the normal conditions for a Pummerer reaction—Ac_2O in refluxing benzene. We suggest that the reaction proceeds according to Scheme I. The 2-thiomethyl sulfoxide (**2**) in AcOH–NaOAc gives an ylide intermediate, which undergoes acid-catalyzed elimination of OH. The resulting S-stabilized carbonium ion loses a proton to yield **3**.

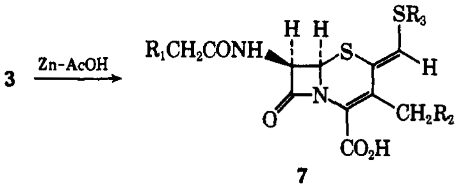
SCHEME I



The 7-acyl side chain can be removed from **3** to yield the 2-thiomethylene amino ester.[4] The amino esters can then be reacylated with other groups to generate new cephalosporin esters. For example, **3a** (R_1 = PhO; R_2 = H; R_3 = 4-BrC_6H_4) was cleaved to the amino ester **6**, which was treated with phenylmercaptoacetyl chloride to give **3j** (R_1 = PhS; R_2 = H; R_3 = 4-BrC_6H_4).

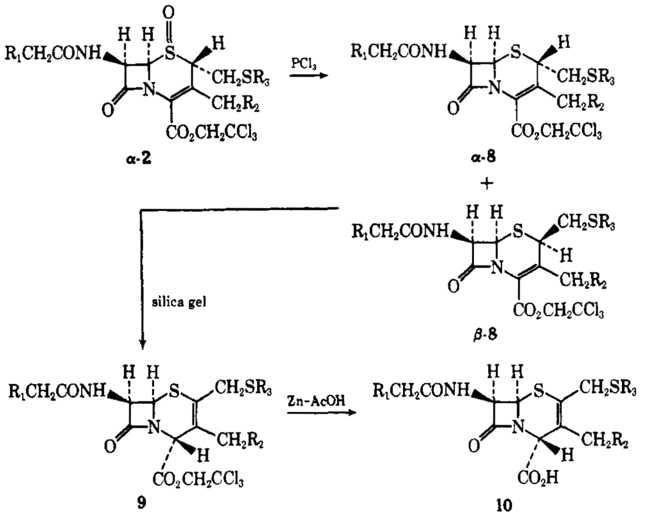


The 2-thiomethylenecephalosporin trichloroethyl esters **3** were converted into the corresponding cephalosporanic acids **7** with Zn dust and AcOH.[5]



7

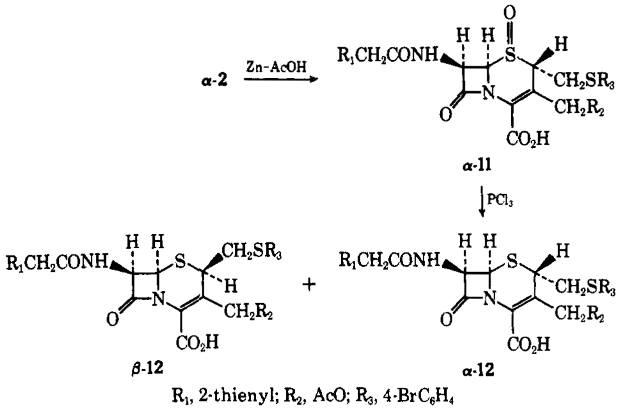
The 2-thiomethylcephalosporin sulfoxide esters (**2**) are frequently mixtures of C-2 epimers if the reactions are run at room temp. However, when the reagent thiol is added at −80° only one epimer is obtained; to this we have assigned the α configuration by analogy with the corresponding 2-Me compounds.[1] Treatment of α-**2** (R_1 = 2-thienyl; R_2 = AcO; R_3 = 4-BrC_6H_4) with a variety of sulfoxide reducing reagents[6] (PCl_3; $SnCl_2$–AcCl; KI–AcCl) resulted in a mixture of sulfide epimers, α- and β-**8** (R_1 = 2-thienyl; R_2 = AcO; R_3 = 4-BrC_6H_4). We were unable to separate these; silica gel chromatography converted the mixture into the Δ^2 isomer **9** (R_1 = 2-thienyl; R_2 = AcO; R_3 = 4-BrC_6H_4).



R_1, 2-thienyl; R_2, AcO; R_3, 4-BrC_6H_4

Ester cleavage of **9** with Zn dust and AcOH gave the Δ^2-cephalosporanic acid **10** (R_1 = 2-thienyl; R_2 = AcO; R_3 = 4-BrC_6H_4), which was inactive.

Using an alternate route, the sulfoxide α-**2** (R_1 = 2-thienyl; R_2 = AcO; R_3 = 4-BrC_6H_4) was first de-esterified with Zn and AcOH. The result was a single acid epimer, α-**11** (R_1 = 2-thienyl; R_2 = AcO; R_3 = 4-BrC_6H_4). However, when this sulfoxide acid was subjected to the reduction conditions, an epimeric mixture of antimicrobials α- and β-**12** (R_1 = 2-thienyl; R_2 = AcO; R_3 = 4-BrC_6H_4) was obtained.



R_1, 2-thienyl; R_2, AcO; R_3, 4-BrC_6H_4

The new cephalosporins were all active against penicillin-resistant *Staphylococcus aureus* (Table II), but no significant Gram-negative activity was noted. Serum binding is a severe problem with these compounds. When the *in vitro* Gram-positive tests are done in the presence of 25% human serum, the activities are greatly reduced (MIC values >50 μg/ml).

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(3) C. R. Johnson and W. G. Phillips, *J. Amer. Chem. Soc.*, **91**, 682 (1969).

(4) R. R. Chauvette, P. A. Pennington, C. W. Ryan, R. D. G. Cooper, F. L. Jose, I. G. Wright, E. M. Van Heyningen, and G. W. Huffman, *J. Org. Chem.*, in press.

(5) R. B. Woodward, K. Heusler, J. Gosteli, P. Naegeli, W. Oppolzer, R. Ramage, S. Ranganathan, and H. Vorbrüggen *J. Amer. Chem. Soc.*, **88**, 852 (1966).

(6) G. V. Kaiser, R. D. G. Cooper, R. E. Koehler, C. F. Murphy, J. A. Webber, I. G. Wright, and E. M. Van Heyningen, *J. Org. Chem.*, **35**, 2430 (1970).

TABLE II

In Vitro ACTIVITY OF 2-THIOMETHYL- AND 2-THIOMETHYLENECEPHALOSPORINS AGAINST PENICILLIN G RESISTANT *S. aureus*[a,b]

Compd	R_1	R_2	R_3	V_{30}	V_{32}	V_{84}
7a	PhO	H	4-BrC_6H_4	12.4	10.4	10.1
7b	PhO	H	Ph	8.2	12.8	8.8
7c	PhO	H	$PhCH_2$	8.7	9.9	8.6
7d	2-Thienyl	AcO	$PhCH_2$	1.0	1.0	1.2
7e	2-Thienyl	AcO	4-ClC_6H_4	0.4	0.5	0.5
7f	PhO	H	CH_3	7.7	9.1	9.2
7g	PhO	H	CH_3CH_2	4.8	5.9	1.4
7h	PhO	H	Pyrimidinyl	5.2	8.7	8.6
7i	PhO	H	3-$CH_3OCOC_6H_4$	1.9	7.7	7.4
7j	PhS	H	4-BrC_6H_4	2.8	3.1	5.8
α and β-12	2-Thienyl	AcO	4-BrC_6H_4	0.6	0.6	0.6

[a] Test by gradient plate procedure, MIC in μg/ml. [b] We thank Dr. John Ott and his associates of the Lilly Research Laboratories for determining these values.

Experimental Section[7]

The following are specific representative procedures used to prep the compounds in this study.

2,2,2-Trichloroethyl 2-(4-Bromophenyl)thiomethyl-3-methyl-7-phenoxyacetamido-3-cephem-4-carboxylate 1-Oxide (2, R_1 = PhO; R_2 = H; R_3 = 4-BrC_6H_4).—2,2,2-Trichloroethyl 3-methyl-2-methylene-7-phenoxyacetamido-3-cephem-4-carboxylate 1-oxide[1] (507 mg, 1.0 mmole) and 4-bromothiophenol (189 mg, 1.0 mmole) were dissolved in 100 ml of CH_2Cl_2. The soln was stirred for 2 hr at room temp and then evapd to dryness *in vacuo*. The crude solid material was recrystd from hot *i*-PrOH to give 605 mg (87%) of the 1:1 adduct: mp 148–149°; ir ($CHCl_3$) 3350, 1790, 1730, 1700 cm^{-1}; uv max (EtOH) 253 mμ (ε 15,000), 313 (4000); nmr ($CDCl_3$) δ 2.12 (s, 3 H), 2.80 (d/d, 1 H, J = 9 Hz, J = 15 Hz), 3.30 (d/d, 1 H, J = 4.5 Hz, J = 15 Hz), 3.71 (d/d, 1 H, J = 4.5 Hz, J = 9 Hz), 4.58 (s, 2 H), 4.72 (d, 1 H, J = 5 Hz), 4.86 (d, 1 H, J = 12 Hz), 5.01 (d, 1 H, J = 12 Hz), 6.33 (d/d, 1 H, J = 5 Hz, J = 10 Hz), 6.9–7.7 (m, 9 H), 7.89 (d, 1 H, J = 10 Hz). *Anal.* ($C_{25}H_{22}BrCl_3N_2O_6S_2$) C, H, Br, Cl, N, S.

2,2,2-Trichloroethyl 2-(4-Bromophenyl)thiomethylene-3-methyl-7-phenoxyacetamido-3-cephem-4-carboxylate (3a, R_1 = PhO; R_2 = H; R_3 = 4-BrC_6H_4).—2,2,2-Trichloroethyl 2-(4-bromophenyl)thiomethyl-3-methyl-7-phenoxyacetamido-3-cephem-4-carboxylate 1-oxide (3.34 g, 4.80 mmoles) was dissolved in 150 ml of AcOH. NaOAc (500 mg, 6.1 mmoles) was added, and the resulting soln was stirred for 74 hr at room temp. The AcOH was removed *in vacuo*, and the residue was taken up in 150 ml of EtOAc. The org layer was thoroughly washed with H_2O and dried ($MgSO_4$). Removal of the solvent yielded 3.20 g (93%) of crude product, which was purified by column chromatography (Florisil support eluting with 20% EtOAc, 80% CH_2Cl_2). The chromatographed material (60% recovery) was recrystd from hot *i*-PrOH: mp 158–160°; ir ($CHCl_3$) 3400, 3000, 1785, 1745, 1695 cm^{-1}; uv max (EtOH) 272 mμ (ε 5000), 363 (10,000); nmr ($CDCl_3$) δ 2.32 (s, 3 H), 4.58 (s, 2 H), 4.77 (d, 1 H, J = 13 Hz), 5.07 (d, 1 H, J = 13 Hz), 5.18 (d, 1 H, J = 4 Hz), 5.96 (d/d, 1 H, J = 4 Hz, J = 10 Hz), 6.8–7.7 (m, 11 H). *Anal.* ($C_{25}H_{20}BrCl_3N_2O_5S_2$) C, H, Br, Cl, N, S.

2,2,2-Trichloroethyl 2-Ethylthiomethylene-3-methyl-7-phenoxyacetamido-3-cephem-4-carboxylate (3g, R_1 = PhO; R_2 = H; R_3 = Et).—2,2,2-Trichloroethyl 2-methylene-3-methyl-7-phenoxyacetamido-3-cephem-4-carboxylate 1-oxide (5.0 g, 9.8 mmoles) was dissolved in 75 ml of AcOH and 30 ml of ethanethiol. The soln was stirred overnight at 45° and then evapd to dryness *in vacuo*. The residue was taken up in hot *i*-PrOH and allowed to cryst. The crude product was recrystd from *i*-PrOH to give 1.9 g (37%) of pure product: mp 155–156°.[7] *Anal.* ($C_{21}H_{21}Cl_3N_2O_5S_2$) C, H, Cl, N, S.

2,2,2-Trichloroethyl 2-(1-Methyl-1*H*-tetrazol-5-yl)thiomethylene-3-methyl-7-phenoxyacetamido-3-cephem-4-carboxylate (3k, R_1 = PhO; R_2 = H; R_3 = *N*-Methyltetrazolyl).—1 (R_1 = PhO; R_2 = H) was treated with 1-methyl-5-thiotetrazole in AcOH–NaOAc as above to give the product: mp 198–200°; ir ($CHCl_3$) 3300, 1790, 1740, 1695 cm^{-1}; uv max (EtOH) 342 mμ (ε 21,000); nmr ($CDCl_3$) δ 2.41 (s, 3 H), 4.00 (s, 3 H), 4.60 (s, 2 H), 4.80 (d, 1 H, J = 12 Hz), 5.05 (d, 1 H, J = 12 Hz), 5.26 (d, 1 H, J = 4 Hz), 5.99 (d/d, 1 H, J = 4 Hz, J = 8 Hz), 6.9–7.6 (m, 6 H), 7.73 (s, 1 H). *Anal.* ($C_{21}H_{19}Cl_3N_6O_5S_2$) C, H, Cl, N, S.

2,2,2-Trichloroethyl 2-(2-Pyrimidinyl)thiomethylene-3-methyl-7-phenoxyacetamido-3-cephem-4-carboxylate (3h, R_1 = PhO; R_2 = H; R_3 = Pyrimidinyl).—1 (R_1 = PhO; R_2 = H) was treated with 2-mercaptopyrimidine in AcOH–NaOAc to give the desired product as a viscous oil: ir (KBr) 3400, 1770, 1720, 1680 cm^{-1}; uv max (EtOH) 270 mμ (ε 8000), 352 (19,000); nmr ($CDCl_3$) δ 2.50 (s, 3 H), 4.63 (s, 2 H), 4.86 (d, 1 H, J = 12 Hz), 5.06 (d, 1 H, J = 12 Hz), 5.24 (d, 1 H, J = 5 Hz), 6.00 (d/d, 1 H, J = 5 Hz, J = 9 Hz), 6.9–7.6 (m, 7 H), 8.30 (s, 1 H), 8.62 (d, 2 H, J = 5 Hz), 9.03 (d, 1 H, J = 9 Hz).

2,2,2-Trichloroethyl 7-Amino-2-(4-bromophenyl)thiomethylene-3-methyl-3-cephem-4-carboxylate, Tosylate Salt (6).—2,2,2-Trichloroethyl 2-(4-bromophenyl)thiomethylene-3-methyl-7-phenoxyacetamido-3-cephem-4-carboxylate (3.12 g, 4.6 mmoles) was dissolved in 150 ml of C_6H_6 containing pyridine (540 mg, 6.8 mmoles). The soln was placed in a H_2O bath at 65°, and PCl_5 (1.40 g, 6.8 mmoles) was added. The mixt was stirred under N_2 for 2.5 hr at 65°. After cooling to room temp, the flask contents were evapd to dryness *in vacuo*. Anhyd MeOH (250 ml) was added, and the soln was stirred at room temp overnight.

The MeOH was removed *in vacuo*, and the residue was dissolved with 50 ml of H_2O and 50 ml of THF and stirred for 15 min at room temp. The THF was removed *in vacuo*. EtOAc (100 ml) was added to the residue, and the pH of the resulting slurry was adjusted to 6.5. The org layer was washed with H_2O and dried ($MgSO_4$). *p*-TsOH·H_2O (875 mg, 4.6 mmoles), dissolved in 25 ml of EtOAc, was added to the soln; and 2.10 g (66%) of the amine salt pptd: mp 179–182°.[7]

2,2,2-Trichloroethyl 2-(4-Bromophenyl)thiomethylene-3-methyl-7-phenylmercaptoacetamido-3-cephem-4-carboxylate (3j, R_1 = PhS; R_2 = H; R_3 = 4-BrC_6H_4).—2,2,2-Trichloroethyl 2-(4-bromophenyl)thiomethylene-3-methyl-7-amino-3-cephem-4-carboxylate, tosylate salt (2.10 g, 2.94 mmoles) was suspended in a slurry of 50 ml of EtOAc and 50 ml of H_2O. The pH was adjusted to 7, liberating the free amine. The EtOAc layer was washed with H_2O and dried ($MgSO_4$). Removal of solvent *in vacuo* gave the amine as a yellow oil.

The oil was dissolved in 50 ml of dry Me_2CO. Then urea (354 mg, 5.88 mmoles) was added. The resulting suspension was stirred at room temp while phenylmercaptoacetyl chloride (546 mg, 2.94 mmoles) in 25 ml of dry Me_2CO was added dropwise over a period of 15 min. Stirring was contd for an addl 30 min. By this time all the urea had dissolved. The Me_2CO was removed *in vacuo;* the residue was dissolved in EtOAc and washed with 5% aq HCl, satd aq $NaHCO_3$, and then with H_2O. After drying ($MgSO_4$), the EtOAc soln was evapd to dryness to give the product (1.90 g, 93%) as a viscous oil which readily crystd from hot *i*-PrOH: mp 131–132°.[7] *Anal.* ($C_{25}H_{20}BrCl_3N_2O_4S_3$) C, H, N, S.

2-(4-Bromophenyl)thiomethylene-3-methyl-7-phenoxyacetamido-3-cephem-4-carboxylic Acid (7a, R_1 = PhO; R_2 = H; R_3 = 4-BrC_6H_4).—2,2,2-Trichloroethyl 2-(4-bromophenylthiomethylene)-3-methyl-7-phenoxyacetamido-3-cephem-4-carboxylate (950 mg, 1.40 mmoles) was dissolved in 15 ml of DMF. AcOH (3.0 ml) was added, and the soln was cooled to 0°. Zn dust (975 mg, 15.0 mmoles) was added, and the resulting mixt was stirred in an ice–H_2O bath for 1.5 hr. The Zn was filtered, and the soln was poured into a slurry of 100 ml of EtOAc and 100 ml of H_2O. The org layer was sepd and washed twice with 100-ml portions of H_2O. It was then stirred with 100 ml of H_2O, and the pH was adjusted to 8. The aq layer was sepd and combined with 100 ml of EtOAc, and the pH was adjusted to 3. The EtOAc layer was sepd, washed with H_2O, and dried ($MgSO_4$). Removal of the solvent *in vacuo* yielded 570 mg (74%) of the acid, which was recrystd from hot *i*-PrOH: mp 196–197°; ir (mull) 3240, 1780, 1725, 1665 cm^{-1}; uv max (EtOH) 272 mμ (ε 8000), 344 (21,000); nmr ($CDCl_3$ plus DMSO-d_6) δ 2.27 (s, 3 H), 4.58 (s, 2 H), 5.13 (d, 1 H, J = 4.5 Hz), 5.93 (d/d, 1 H, J = 4.5 Hz, J = 9 Hz), 6.9–7.7 (m, 12 H). *Anal.* ($C_{23}H_{19}BrN_2O_5S_2$) C, H, Br, N, S.

3-Methyl-2-phenylthiomethylene-7-phenoxyacetamido-3-

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(7) Melting points are uncorrected. Nmr spectra were recorded for all of the compounds on a Varian HA-100 spectrometer, but only spectra necessary for structure identification were included in the manuscript. The same policy was used for ir and uv spectra. Elemental analyses were determined by the microanalytical group of the Lilly Research Laboratories. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4%.

cephem-4-carboxylic acid (7b, R_1 = PhO; R_2 = H; R_3 = Ph) had mp 177–178°.[7] *Anal.* ($C_{23}H_{20}N_2O_5S_2$) C, H, N, S.

2-Benzylthiomethylene-3-methyl-7-phenoxyacetamido-3-cephem-4-carboxylic acid (7c, R_1 = PhO; R_2 = H; R_3 = $PhCH_2$) had mp 180–182°.[7]

3-Acetoxymethyl-2-benzylthiomethylene-7-(2-thienyl)acetamido-3-cephem-4-carboxylic acid (7d, R_1 = 2-thienyl; R_2 = OAc; R_3 = $PhCH_2$) had mp 144–145°.[7] *Anal.* ($C_{24}H_{22}N_2O_6S_3$) C, H, N, S.

3-Acetoxymethyl-2-(4-chlorophenyl)thiomethylene-7-(2-thienyl)acetamido-3-cephem-4-carboxylic acid (7c, R_1 = 2-thienyl; R_2 = OAc; R_3 = 4-ClC_6H_4) had mp 220–222°.[7] *Anal.* ($C_{23}H_{19}ClN_2O_6S_3$) C, H, Cl, N, S.

2-Methylthiomethylene-3-methyl-7-phenoxyacetamido-3-cephem-4-carboxylic acid (7f, R_1 = PhO; R_2 = H; R_3 = CH_3) had mp 198–199°.[7] *Anal.* ($C_{18}H_{18}N_2O_5S_2$) C, H, N, S.

2-Ethylthiomethylene-3-methyl-7-phenoxyacetamido-3-cephem-4-carboxylic acid (7g, R_1 = PhO; R_2 = H; R_3 = Et) had mp 186–187°.[7] *Anal.* ($C_{19}H_{20}N_2O_5S_2$) C, H, N, S.

3-Methyl-2-pyrimidinylthiomethylene-7-phenoxyacetamido-3-cephem-4-carboxylic acid (7h, R_1 = PhO; R_2 = H; R_3 = 2-pyrimidinyl) had mp 237–238°.[7] *Anal.* ($C_{21}H_{18}N_4O_5S_2$) C, H, N, S.

2-(3-Carbomethoxyphenyl)thiomethylene-3-methyl-7-phenoxyacetamido-3-cephem-4-carboxylic acid (7i, R_1 = PhO; R_2 = H; R_3 = 3-$CH_3OCOC_6H_4$) had mp 206–208°.[7] *Anal.* ($C_{25}H_{22}N_2O_7S_2$) C, H, N, S.

2-(4-Bromophenyl)thiomethylene-3-methyl-7-phenylmercaptoacetamido-3-cephem-4-carboxylic acid (7j, R_1 = PhS; R_2 = H; R_3 = 4-BrC_6H_4) had mp 203–205°.[7] *Anal* ($C_{23}H_{19}BrN_2O_4S_3$) C, H, N.

2,2,2-Trichloroethyl 3-Acetoxymethyl-α-2-(4-bromophenyl)thiomethyl-7-(2-thienyl)acetamido-3-cephem-4-carboxylate 1-Oxide (α-2, R_1 = 2-Thienyl; R_2 = AcO; R_3 = 4-BrC_6H_4).—1 (R_1 = 2-thienyl; R_2 = AcO) (10.0 g, 18.0 mmoles) was dissolved in 500 ml of CH_2Cl_2 and cooled to −80°. 4-Bromophenylmercaptan (3.4 g, 18.0 mmoles) in 100 ml of CH_2Cl_2 was added dropwise over a period of 30 min. Stirring was contd for 1 hr while the temp was gradually raised to −15°. Then the soln was concd *in vacuo* and crystd from hot *i*-PrOH to give 11.2 g (83%) of a single epimer: mp 150–151°; ir ($CHCl_3$) 3290, 1800, 1735, 1682 cm^{-1}; uv max (EtOH) 234 mμ (ϵ 18,000), 274 (11,000), 318 (3000); nmr ($CDCl_3$) δ 1.97 (s, 3 H), 2.73 (d/d, 1 H, J = 15 Hz, J = 9.5 Hz), 3.43 (d/d, 1 H, J = 15 Hz, J = 4.5 Hz), 3.85 (s, 2 H), 3.99 (d/d, 1 H, J = 9.5 Hz, J = 4.5 Hz), 4.69 (d, 1 H, J = 5 Hz), 4.76 (d, 1 H, J = 14 Hz), 4.82 (d, 1 H, J = 11.5 Hz), 5.03 (d, 1 H, J = 11.5 Hz), 5.10 (d, 1 H, J = 14 Hz), 6.19 (d/d, 1 H, J = 5 Hz, J = 9 Hz), 6.8–7.6 (m, 8 H). *Anal.* ($C_{25}H_{22}BrCl_3N_2O_7S_3$) C, H, N, S.

2,2,2-Trichloroethyl 3-Acetoxymethyl-2-(4-bromophenyl)thiomethyl-7-(2-thienyl)acetamido-2-cephem-4-carboxylate (9, R_1 = 2-Thienyl; R_2 = AcO; R_3 = 4-BrC_6H_4).—*α*-**2** (R_1 = 2-thienyl; R_2 = AcO; R_3 = 4-BrC_6H_4) (8.0 g, 10.1 mmoles) was added to a chilled soln of 25 ml of DMF (−20°). Then 2 ml of PCl_3 was added, and the soln was allowed to warm to −10°. At this time, 3 more ml of PCl_3 was added and stirred until the soln warmed to +5°. Then it was poured into 300 ml of ice-cold satd NaCl soln and extd 5 times with 80 ml of CH_2Cl_2. The combined exts were washed with H_2O, dried ($MgSO_4$), and evapd *in vacuo* to give 5.3 g (68%) of reduced material, α- and β-**8**, as a glass. Tlc using silica gel plates and C_6H_6–EtOAc (2:1) as an eluent showed two spots which were almost superimposible. The nmr of the glass confirmed the presence of two reduced materials in a 7:2 ratio. Elution chromatography of α- and β-**8**, using silica gel and C_6H_6–EtOAc, gave a new, faster running material **9** (R_f 0.85 in 7:3 C_6H_6–EtOAc) which crystd from *i*-PrOH: mp 149–150°; uv max (EtOH) 233 mμ (ϵ 16,000), 256 (9000); ir ($CHCl_3$) 3280, 1780, 1740, 1680 cm^{-1}; nmr ($CDCl_3$ plus DMSO-d_6) δ 2.01 (s, 3 H), 3.58 (d, 1 H, J = 14 Hz), 3.82 (s, 2 H), 4.01 (d, 1 H, J = 14 Hz), 4.45 (d, 1 H, J = 13 Hz), 4.77 (d, 1 H, J = 13 Hz), 4.82 (s, 2 H), 5.24 (s, 1 H), 5.30 (d, 1 H, J = 4 Hz), 5.55 (d/d, 1 H, J = 4 Hz, J = 9 Hz), 6.9–7.6 (m, 8 H). *Anal.* ($C_{25}H_{22}BrCl_3N_2O_6S_3$) C, H, N, O, S.

3-Acetoxymethyl-2-(4-bromophenyl)thiomethyl-7-(2-thienyl)acetamido-2-cephem-4-carboxylic Acid (10, R_1 = 2-Thienyl; R_2 = AcO; R_3 = 4-BrC_6H_4).—9 (R_1 = 2-thienyl; R_2 = AcO; R_3 = 4-BrC_6H_4) was deesterified using Zn–AcOH in the same fashion used with **3** to give the Δ^2-cephalosporanic acid which crystd from a soln of C_6H_6–petr ether: mp 156–157°; ir (mull) 3300, 1760, 1720, 1670 cm^{-1}; uv max (EtOH) 232 mμ (ϵ 25,000), 254 (10,000); nmr ($CDCl_3$ plus DMSO-d_6) δ 2.00 (s, 3 H), 3.52 (d, 1 H, J = 14 Hz), 3.84 (s, 2 H), 3.97 (d, 1 H, J = 14 Hz), 4.37 (d, 1 H, J = 13 Hz), 4.66 (d, 1 H, J = 13 Hz), 5.01 (s, 1 H), 5.34 (d, 1 H, J = 4 Hz), 5.55 (d/d, 1 H, J = 4 Hz, J = 8 Hz), 6.9–7.6 (m, 7 H), 7.94 (d, 1 H, J = 8 Hz). *Anal.* ($C_{23}H_{21}BrN_2O_6S_3$) C, H, N.

A bioautograph (*Bacillus subtilis*) showed that this 2-cephem derivative was not active at the level at which **7** were quite active.

3-Acetoxymethyl-2-(4-bromophenyl)thiomethyl-7-(2-thienyl)acetamido-3-cephem-4-carboxylic Acid 1-Oxide (*α*-11, R_1 = 2-Thienyl; R_2 = AcO; R_3 = 4-BrC_6H_4).—*α*-**2** (R_1 = 2-thienyl; R_2 = AcO; R_3 = 4-BrC_6H_4) was deesterified in the same manner used for **3** to give the sulfoxide acid, which crystd from EtOAc: mp 185–186°.[7] *Anal.* ($C_{23}H_{21}BrN_2O_7S_3$) C, H, Br, N, S.

A bioautograph (*B. subtilis*) showed that this sulfoxide derivative was not active at the level at which compounds α- and β-**12** were quite active.

3-Acetoxymethyl-2-(4-bromophenyl)thiomethyl-7-(2-thienyl)acetamido-3-cephem-4-carboxylic Acid (α- and β-12, R_1 = 2-Thienyl; R_2 = AcO; R_3 = 4-BrC_6H_4).—*α*-**11** (R_1 = 2-thienyl; R_2 = AcO; R_3 = 4-BrC_6H_4) (2.0 g, 3.26 mmoles) was dissolved in 25 ml of DMF cooled to −50°. PCl_3 (3 ml) was added, and the soln was allowed to warm to 0° over a period of 35 min. The reaction soln was poured into 250 ml of ice-cold satd NaCl soln which was extd 4 times with 150 ml of CH_2Cl_2. The org layer was extd into a satd $NaHCO_3$ soln, and the acidic material obtained was back extracted into fresh CH_2Cl_2 by adjusting the pH of the aq soln to 2 with 5% HCl. The org layer was washed with H_2O, dried ($MgSO_4$), and evapd *in vacuo* to give 500 mg (25%) of an oil which crystd from C_6H_6–petr ether: mp 153–155°; ir (mull) 3250, 1785, 1730, 1670 cm^{-1}; uv max (EtOH) 233 mμ (ϵ 19,000), 264 (15,000). *Anal.* ($C_{23}H_{21}BrN_2O_6S_3$) C, H, Br, N, S.

Although tlc (using silica gel plates and 4:1 $CHCl_3$–AcOH as eluent) showed a single spot (R_f 0.6), the bioautograph (*B. subtilis*) established the presence of two antimicrobials. Nmr confirmed the presence of two compounds: all of the bands in the sulfoxide were present in the reduced material with the expected shifts, but they were present in sets of two.