2-Isopropylthio-6-chloropurine (7d).—This was obtained as colorless plates, R_f 0.92 in D, mp 187°, in 59% yield from 2-isopropyl-6-hydroxypurine as described for the prepn of **7c**. *Anal.* ($C_8H_9ClN_4S$) C, H, N.

2-*n*-Propylthioadenosine (**2c**).—A finely powd mixt of **7c** (104 mg, 0.455 mmole) and **8** (230 mg, 0.455 mmole) was heated *in vacuo* at 140–160° for 20 min. The resulting colorless viscous melt (291 mg) was kept for 10 days in anhyd MeOH (15 ml) satd with NH_3 at 0°. MeOH was evapd, and the cream semisolid residue was extd with 5 ml of boiling hexane–$CHCl_3$ (1:1) and crystd from H_2O (20 ml) to give colorless crystals, which were recrystd from aq EtOH to give **2c** as hydrated plates (129 mg, 80%) of indefinite mp. The anal. sample was obtained by recrystn from H_2O, and dried *in vacuo* at 100° for 8 hr: mp 168°; $[\alpha]_{21.5D}$ − 26.2° (*c* 2.06, DMSO). *Anal.* ($C_{13}H_{19}N_5O_4S \cdot 0.5H_2O$) C, H, N.

2-Isopropylthioadenosine (2d).—A powd mixt of **7d** (2.26 g, 10 mmoles) and **8** (5.04 g, 10 mmoles) was fused *in vacuo* at 140–150° for 35 min, and the product was worked up as described for the reaction of **7b** with **8** to give the blocked nucleoside **9d** as a pale yellow foam (6.95 g). This (1.0 g, 1.5 mmoles) was kept for 9 days at room temp in anhyd CH_3OH (30 ml) satd with NH_3. MeOH was evapd, and the residue was extd with boiling $CHCl_3$ (50 ml) and crystd from H_2O yielding 34.0 mg (66%) of **2d**. Recrystn from EtOH gave the anal. sample: mp 188–189°; $[\alpha]_{21.5D}$ 24.6° (*c* 0.50, DMSO). ($C_{13}H_{19}N_5O_4S$) C, H, N.

2-Alkylthioadenosines from 2-Chloroadenosine.—Finely divided Na (0.35 g, 15 mg-atoms) was added gradually with stirring to 20 ml of Et, *n*-Pr, or *i*-Pr mercaptan at room temp. When reaction was complete (30–60 min), DMF (20 ml) was added, and the mixt was heated at 80–90° to give a clear soln. 1[21] (302 mg, 1 mmole) was added, and the soln was heated at 80–90° for 4–7 hr during which time NaCl sepd. The reaction mixt was cooled, neutralized with HCl, evapd to dryness *in vacuo*, and dried *in vacuo* over P_2O_5. The residue was extd with three 100-ml portions of abs EtOH or (for 2-*n*-propylthioadenosine) *i*-PrOH, and the alcoholic extracts were filtered and evapd to give in each case a colorless glass which crystd from H_2O to give almost quant yields of 2-ethylthio-, 2-*n*-propylthio-, and 2-isopropylthioadenosines (**2b**–d). Paper chromatog of the products in solvents A, B, C, and D with markers of 1 and the appropriate 2-alkylthioadenosine showed no contamination with **1**. The prepns were scaled up tenfold without difficulty.

For the synthesis of **2a** from 1, NaSMe was prepd by the gradual addn of Na (1.5 g, 67 mg-atoms) to MeSH (20 g) cooled in a solid CO_2–MeOH bath. The reaction mixt was then kept at room temp while MeSH refluxed from a condenser through which passed MeOH cooled with solid CO_2. The coating of NaSMe which formed on the particles of Na was dissolved by the addition of several 1- to 2-ml portions of DMF. After 1.5 hr Na had completely reacted. DMF (80 ml) was added, and the soln was heated at 80° to evap excess MeSH. 1 (2.0 g, 6.6 mmoles) was added, and the prepn was continued as described in the general procedure yielding 2.0 g of pure cryst **2a** which was shown by paper chromatog in solvents A, B, and C to be uncontaminated by 1.

(21) J. A. Montgomery and K. Hewson, *J. Heterocycl. Chem.*, **1**, 213 (1964).

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Chemistry of Cephalosporin Antibiotics. 23. 2-Methyl- and 2-Methylenecephalosporins

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Cephalosporin sulfoxide esters **4** react with CH_2O under Mannich conditions to give 2-methylene derivatives **6**. Reduction of the exocyclic double bond yields a mixture of isomeric 2-Me compounds (**7**, **8**, and **9**). The double bond, when treated with Br_2, gives dibromide **16a**; with disiamylborane, gives exclusively the 2α-methyl derivative **8** and the corresponding sulfide 11; and with SH compounds, gives 1:1 adducts (**15**). Reduction of the sulfoxides to the sulfides and removal of the ester-protecting group R^3 give 2-substituted cephalosporanic acids which have antibiotic activity.

We have recently investigated the preparation and properties of cephalosporin sulfoxide esters **4** (Scheme I).[1] As part of that program, we were interested in new structural modifications of the cephem molecule and sought to use the doubly activated CH_2 group at C-2 in condensation reactions with CO compounds. Both 3-methyl- and 3-acetoxymethylcephem derivatives were investigated.

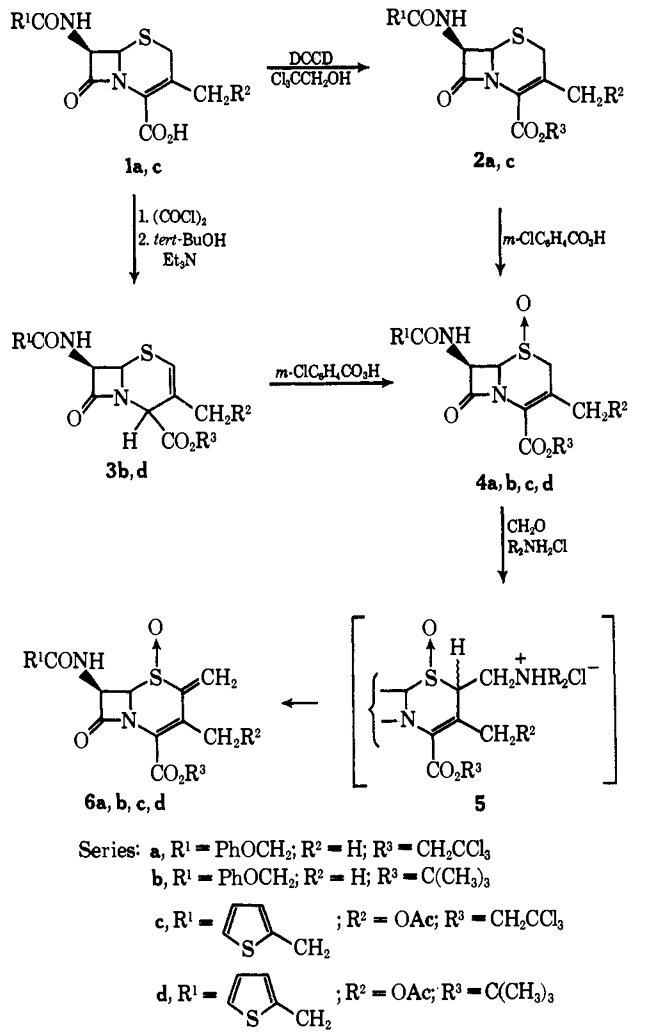
Upon treatment of sulfoxide ester **4a** (prepared from **1a** *via* **2a** as outlined in Scheme I[1]) with aq CH_2O and a variety of primary and secondary amine salts under Mannich conditions, a single new crystalline product, 2-methylene sulfoxide **6a**, formed in high yield. The sulfoxide **4a** and *N*,*N*-dimethylformaldimmonium trifluoroacetate[2] under anhyd conditions gave the same 2-methylene sulfoxide **6a**. Evidently the primary Mannich reaction product **5a** is unstable under the reaction conditions and loses the amino group. The amine salt functions only as a catalyst in the condensation. Acidic and basic catalysts, other than primary and secondary amines and their salts, are ineffective. From this evidence we concluded that the condensation is truly a Mannich type. Similarly, the sulfoxide **4c** gave the 2-methylene sulfoxide **6c**.

Surprisingly, the nature of the ester-protecting group R^3 affected the ease of the reaction. Relatively mild conditions (refluxing in *tert*-BuOH–CH_2Cl_2) were used for the cephalosporin sulfoxides **4a** and **4c** which were protected with the electron-withdrawing trichloroethyl group, but more severe conditions (refluxing in DMF–dioxane) were necessary when the electron-donating *tert*-Bu esters **4b** and **4d** were used. The ease of deuterium exchange at the 2 position of various sulfoxide esters (4) paralleled the ease of the Mannich reaction.

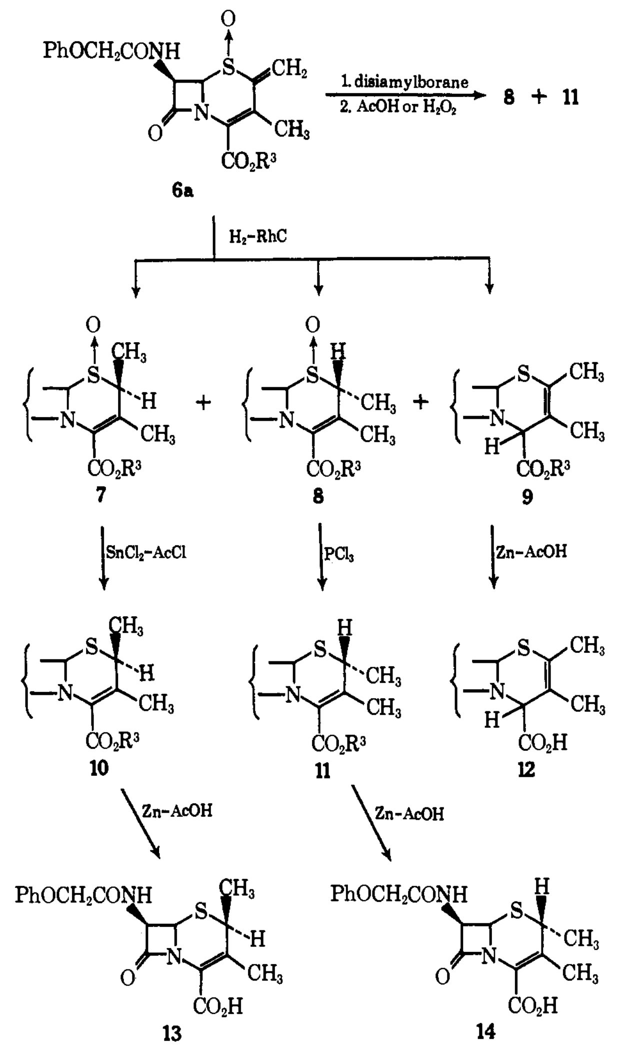
(1) G. V. Kaiser, R. D. G. Cooper, R. E. Koehler, C. F. Murphy, J. A. Webber, I. G. Wright, and E. M. Van Heyningen, *J. Org. Chem.*, **35**, 2430 (1970).

(2) A. Ahond, A. Cave, C. Kan-Fan, H. P. Husson, J. de Rostolan, and P. Potier, *J. Amer. Chem. Soc.*, **90**, 5622 (1968).

SCHEME I



SCHEME II



$R^3 = CH_2CCl_3$

Others have also observed D exchange at the 2 position of cephalosporin sulfoxides.[3]

Addition Reactions of 2-Methylene Sulfoxide 6a. (a) **Catalytic Hydrogenations.**—A variety of reagents were added to the unsaturated system of **6a**. Addition of H_2 over Pd or Rh catalysts gave a mixture of 3 products (**7**, **8**, **9**, Scheme II). The 2β-methyl and 2α-methyl sulfoxides (**7** and **8**) were separated by fractional crystallization. The major product was assigned the β stereochemistry on the basis of the expected preferential attack of the catalyst on the unhindered α side of the molecule. The observation of long-range coupling ($J = 1.5$ Hz) between the axial protons at C-2 (δ 3.27, m, $J = 8$, 1.5 Hz) and C-6 (δ 4.71, *q*, $J = 5$, 1.5 Hz) across the backside of the (*S*)-sulfoxide in the nmr spectrum of the major isomer **7** confirmed this conclusion.[4] The corresponding protons in the spectrum of minor isomer **8** showed no long-range coupling (C-2 proton, δ 3.60, q, $J = 7.5$ Hz; C-6 proton, δ 4.55, d, $J = 5$ Hz). There was no long-range coupling in the corresponding sulfides **10** and **11**.[4]

The conditions used to carry out the Mannich reaction or to exchange the C-2 protons in sulfoxides **4** converted each of the 2-methyl sulfoxide isomers **7** and **8** into an equilibrium mixture containing 83% of **8** and 17% of **7**. From inspection of Dreiding models, this isomerization likely involves conversion from conformation A, in which the 2β-methyl group is pseudo-equatorial and the (*S*)-sulfoxide oxygen[1] is axial, to B in which both the 2α-methyl group and the (*S*)-sulfoxide oxygen are equatorial. The existence of **8** in conformation B is supported by the absence of a nuclear Overhauser effect between the 2α-methyl group and the proton at C-6.[5] An NOE would be expected if the 2α-methyl group were axial.[6]

The third product of the hydrogenation of **6a** was the 2-methyl Δ^2-sulfide **9**. It was an annoying side product; occasionally it was the major product. No way was found to inhibit its formation. Although **9** was never obtained in crystalline form, its structure was clear from spectral characteristics.[7,8]

(b) **Addition of Thiols.**—A variety of thiols (R^4-SH) reacted with the 2-methylene sulfoxides **6**, forming

(3) M. L. Sassiver and R. G. Shepherd, *Tetrahedron Lett.*, 3993 (1969).

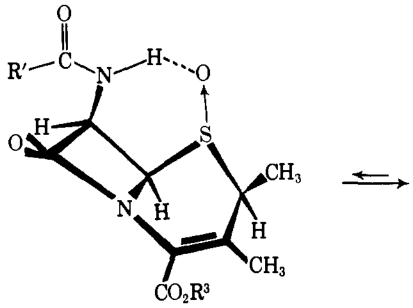
(4) R. D. G. Cooper, P. V. DeMarco, C. F. Murphy, and L. A. Spangle, *J. Chem. Soc. C*, 340 (1970).

(5) We thank Dr. P. V. DeMarco for this determination.

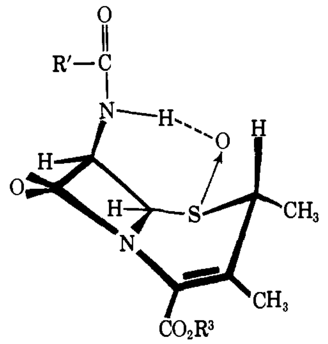
(6) R. D. G. Cooper, P. V. DeMarco, J. C. Cheng, and N. D. Jones, *J. Amer. Chem. Soc.*, **91**, 1408 (1969).

(7) J. D. Cocker, S. Eardly, G. I. Gregory, M. E. Hall, and A. G. Long, *J. Chem. Soc. C*, 1142 (1966).

(8) Unpublished work in these laboratories; see also ref 1, 4, 9, and G. F. H. Green, J. E. Page, and S. E. Staniforth, *J. Chem. Soc.*, 1595 (1965).



A
7



B
8

1:1 adducts **15** (Scheme III). The chemistry of these compounds is the subject of another paper.[9]

(c) **Addition of Other Reagents.**—Br_2 added rapidly to 2-methylene sulfoxide **6a** to give a single product (**16a**) (Scheme III), characterized by elemental analysis and nmr spectrum. The C-6 proton (δ 5.43, d, J = 5 Hz) was shifted downfield 0.72 ppm from the position of the C-6 proton in **7**, suggesting that the Br on the ring is α axial.[10]

Amines, alcohols, and water did not add to **6a** under any conditions which did not destroy the β-lactam ring.

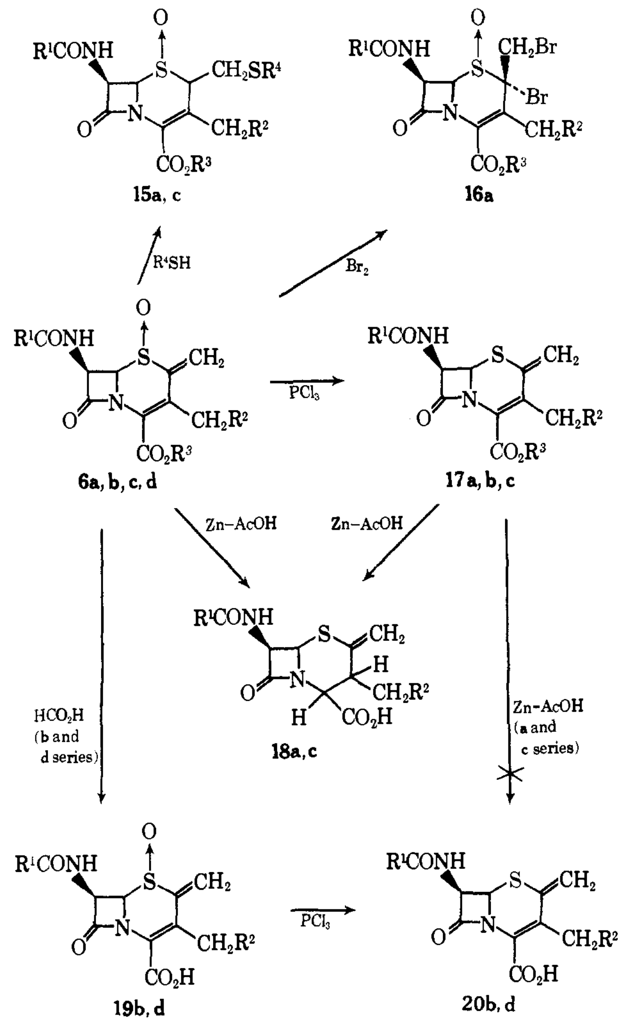
As an alternative method of introducing an O function, the hydroboration of **6a** was attempted. Reaction of **6a** with disiamylborane, followed by either oxidative or protonolytic work-up,[11] gave only 2 identifiable products, the same in each case, 2α-methyl sulfoxide (**8**) and 2α-methyl sulfide (**11**) (Scheme II).

This reaction, coupled with catalytic hydrogenation and isomerization, provided selective routes to each of 2 series of 2-methylcephalosporins. A quantitative separation of the 2 isomeric series was achieved and is described in the next section.

Reduction of Sulfoxides.—Cephalosporin sulfoxides generally have a much lower level of biological activity than the corresponding sulfides. Consequently, the reduction of the 2-methylene (**6a** and **6c**) and 2-methyl (**7** and **8**) sulfoxides to the sulfides is necessary for the synthesis of biologically active compounds. A versatile set of reagents has been developed for sulfoxide reductions under mild conditions.[1]

(a) **2-Methylene Series.**—The 2-methylene sulfoxide **6a** was reduced to **17a** (Scheme III) in 65% yield

SCHEME III



Series **a**, **b**, **c**, d have the same significance as in Scheme I.

in 1 hr by a mixture of $SnCl_2$ and AcCl in CH_2Cl_2–MeCN at $-40°$.[1] The increased intensity of the long wavelength uv band (λ_{max} 307 nm, ϵ 8100) due to the changed electronic character of the S, the absence of the characteristic SO band at 1040 cm^{-1}, and the characteristic changes in the chemical shifts of protons in the vicinity of the S atom in the nmr spectrum[8] supported the assigned structure. The compound **6c** was reduced under similar conditions and the product **17c** was characterized spectrally. Interestingly, **17a** underwent none of the conjugate addition reactions characteristic of **6a**.

(b) **2-Me Series.**—Under the conditions given above, **7** was reduced to **10** (Scheme II), but **8** was inert under the same conditions. This difference in reactivity allowed a quantitative "chemical separation" of the isomers since the polarity difference between sulfoxides and sulfides allows separation by simple chromatography.

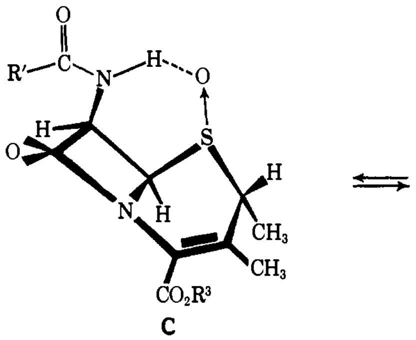
Reduction of **8** to **11** (Scheme II) was then easily accomplished, using PCl_3 in DMF at 25° for 20 min.[1] The difference in the ease of reduction of the 2 sulfoxides may reflect the greater steric hindrance to attack on the S of the (S)-sulfoxide[1] in the 2α-Me series. In conformation C of the 2α-methyl sulfoxide **8** the axial C-2 Me provides hindrance to the back of the axial

(9) G. V. Kaiser, C. W. Ashbrook, T. Goodson, I. G. Wright, and E. M. Van Heyningen, *J. Med. Chem.*, **14**, 426 (1971).

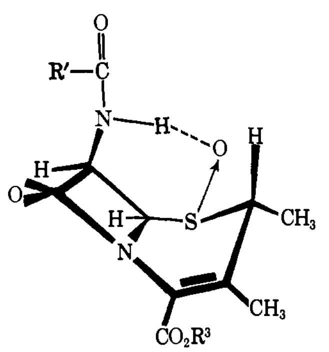
(10) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, p 187; a value is given of −0.63 ppm for the shift due to 1,3-diaxial H-Cl interaction.

(11) H. C. Brown, "Hydroboration," W. A. Benjamin, Inc., New York, N. Y., 1962, pp 62, 69.

sulfoxide; in conformation D of **8** the back of the equatorial sulfoxide is shielded by the ring.



C
8



D
8

Trichloroethyl Ester Cleavages.—The final step in converting 2-methylene- and 2-methylcephalosporin esters to biologically active forms was the removal of the trichloroethyl ester protecting group.[12] The 3 isomeric 2-methylcephalosporin esters (**9**, **10**, and **11**) were treated with Zn dust in AcOH to furnish the corresponding crystalline cephalosporanic acids **12**, **13**, and **14** (Scheme II).

The 2-methylene sulfide **17a** also gave a crystalline acid upon treatment with Zn dust and AcOH, but the structure of the product was shown by the spectral changes to be **18a** (Scheme III). The low uv absorption (λ_{max} 267 nm, ϵ 1500) indicated destruction of the conjugated system. In the nmr the vinyl protons of the 2-CH_2 remained (δ 5.37 and 5.47, d, J = 2 Hz), but the 3-proton C-3 Me group signal appeared at δ 1.29 (d, J = 7 Hz). Two additional 1-proton signals due to the C-3 H (δ 2.97, m, J = 7 Hz) and C-4 H (δ 5.39, d, J = 7 Hz) were present. Several other chemical reducing agents gave the same result. Even **6a** gave only **18a** under reductive cleavage conditions. Cleavage of **6c** and **17c** also failed. The poorly characterized product appeared to be **18c**.

Alternate Approach to 2-Methylenecephalosporanic Acids.—To avoid the necessity for reductive conditions when removing the ester-protecting group, the corresponding *tert*-Bu esters were prepared as outlined in Scheme I (**b** and **d** series). The esterification reaction (**1** → **3**) probably occurs *via* the cephalosporin ketene and results in Δ^2-cephalosporin esters **3b** and **3d**;[13] but the double bond shifts back to the Δ^3 position upon oxidation to the sulfoxide.[1]

(12) R. B. Woodward, *Science*, **153**, 487 (1966); *Angew. Chem.*, **78**, 557 (1966). 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); F. Eckstein, *Chem. Ber.*, **100**, 2228 (1967).

(13) C. F. Murphy and R. E. Koehler, *J. Org. Chem.*, **35**, 2429 (1970).

The 2-methylene sulfoxide **6b** (Scheme III) was reduced to **17b** in good yield. Treatment of **17b** with HCO_2H or F_3CCO_2H resulted in complete destruction of the compound.

The 2-methylene sulfoxides **6b** and **6d** (Scheme III), however, were cleaved to acids **19b** and **19d** in nearly quant yield by HCO_2H (25°, 2 hr). Reduction of sulfoxide acids **19** to sulfide acids **20** was accomplished in low yield with PCl_3 and DMF under carefully controlled conditions. The 2-methylenecephalosporanic acids **20** were isolated as crystalline Na salts.

The antibiotic activities of the new cephalosporanic acids were evaluated against several strains of benzylpenicillin-resistant *Staphylococcus aureus* and a variety of Gram-negative organisms by a standard gradient plate technique (Table I). The 2-methylene-3,4-dihydro compounds **18** and 2-methyl-Δ^2 compound **12** showed no activity in these screens.

TABLE I
In Vitro ACTIVITY OF 2-METHYL- AND 2-METHYLENECEPHALOSPORINS AGAINST GRAM-POSITIVE AND GRAM-NEGATIVE ORGANISMS[a]

	Gram-positive[b]		Gram-negative[c]		
Compd	V-32	V-84	N-10	X-26	X-68
13 (2β-Me-**1a**)	12.8/>20	10.4/>20	>50	>50	>50
14 (2α-Me-**1a**)	15.0/>20	12.2/>20	>50	>50	>50
20b (2-CH_2-**1a**)	0.6/1.0	0.5/1.0	>50	18.8	>50
1a (ref compd)	1.2/1.0	0.7/1.0	>50	40.0	>50
20d (2-CH_2-**1c**)	2.1/>20	1.8/>20	29.0	23.6	7.6
1c (ref compd)	0.6/1.0	0.5/1.0	19.5	4.8	4.4

[a] Test by gradient plate procedure, MIC's in μg/ml. [b] Benzylpenicillin-resistant strains of *Staphylococcus aureus*, MIC's in absence/presence of human serum. [c] N-10 = *Escherichia coli;* X-26 = *Klebsiella pneumoniae;* X-68 = *Aerobacter aerogenes.*

Experimental Section[14,15]

2,2,2-Trichloroethyl 3-Methyl-2-methylene-7-phenoxyacetamido-3-cephem-4-carboxylate 1-Oxide (6a) (A).—To a soln of **4a**[1] (15.0 g, 30.3 mmoles) in hot CH_2Cl_2 (50 ml) was added CH_2O (3.0 g, 37% aq soln, 37 mmoles), $Me_2NH\cdot HCl$ (2.46 g, 30.2 mmoles), and *tert*-BuOH (500 ml). The mixt was refluxed gently for 24 hr, until tlc anal. (C_6H_6–EtOAc, 1:1) showed complete disappearance of starting material (R_f 0.27) and appearance of a new, less polar spot (R_f 0.45). The soln was then concd to *ca.* 300 ml. On cooling, **6a** sepd as fine, light yellow needles (13.0 g, mp 173–174° dec). Concn of the mother liquors yielded a small second crop, 1.6 g (total yield 95%). Generally, this material was sufficiently pure to use in subsequent reactions. Recrystn of **6a** from CH_2Cl_2–*tert*-BuOH raised the mp to 177–178° dec: uv max (EtOH) 267 nm (ϵ 7250), 313 (3950); nmr ($CDCl_3$) δ 2.31 (3 H, s), 4.57 (2 H, s), 4.71 (1 H, d, J = 5 Hz), 4.88 (1 H, d, J = 12 Hz), 5.06 (1 H, d, J = 12 Hz), 6.12 (1 H, d, J = 1 Hz), 6.16 (1 H, d/d, J = 5 Hz, J = 10 Hz), 6.26 (1 H, d, J = 1 Hz).[15] *Anal.* ($C_{19}H_{17}Cl_3N_2O_6S$) C, H, Cl, N, S.

Under similar conditions 2,2,2-trichloroethyl 3-acetoxymethyl-2-methylene-7-(2′-thienylacetamido)-3-cephem-4-carboxylate 1-oxide (**6c**) was obtained from **4c** in 81% yield; mp 171–173°

(14) Melting points were determined in open capillaries in a Mel-Temp apparatus. Ir spectra were determined with a Perkin-Elmer Model 21 in $CHCl_3$ soln or Nujol mull as specified. Uv spectra were obtained with a Cary 15. Nmr spectra were recorded using Varian A60, HA60, and HA100 spectrometers; chemical shifts are reported in δ units. Elemental anal. were determined by the microanalytical group of the Lilly Research Laboratories. Where anal. are indicated only by symbols of the elements, anal. results obtained for those elements were within ±0.4% of the calcd values. Tlc employed Merck silica gel F_{254} plates, and spots were visualized by uv and with I_2. C_6H_6–EtOAc (7:3) was used for sulfide esters; C_6H_6–EtOAc (1:1) for sulfoxide esters; and 8% 0.1 *M* pH 5 NaOAc buffer in MEK for acids.

(15) Complete ir, uv, and nmr spectra were obtained for every compound. Where the given spectral data are incomplete, some has been omitted for the sake of brevity. In the nmr data, signals due to the amide NH and aromatic ring protons generally have not been included.

dec: uv max (EtOH) 272 nm (ϵ 5900), 308 (5900); nmr ($CDCl_3$) δ 2.03 (3 H, s), 3.87 (2 H, s), 4.67 (1 H, d, J = 5 Hz), 4.73 (1 H, d, J = 12.5 Hz), 4.86 (1 H, d, J = 12 Hz), 5.06 (1 H, d, J = 12 Hz), 5.59 (1 H, d, J = 12.5 Hz), 6.11 (1 H, d/d, J = 5 Hz, J = 10 Hz), 6.12 (1 H, d, J = 1 Hz), 6.41 (1 H, d, J = 1 Hz).[15] *Anal.* ($C_{19}H_{17}Cl_3N_2O_7S_2$) C, H, Cl, N, S.

The HCl salts of $MeNH_2$, $EtNH_2$, Et_2NH, piperidine, and pyrrolidine worked as well as $Me_2NH \cdot HCl$ as catalysts in the condensation. The corresponding free amines also worked but gave highly colored, difficult to purify products. NH_4Cl, $Me_3N \cdot HCl$, and $Et_3N \cdot HBr$ were much less satisfactory. Pyridine, pyridine·HCl, BF_3 etherate, p-TsOH, and K_2CO_3 did not work.

(**B**).—When **4a**[1] (750 mg, 1.5 mmoles) was heated under reflux for 25 hr in CH_2Cl_2 (10 ml) with $Me_2{}^+N{=}CH_2 \cdot CF_3CO_2^-$ [2 mmoles, prepd from $(CF_3CO)_2O$ (0.28 ml, 2 mmoles) and freshly sublimed $(CH_3)_3N \rightarrow O$ (150 mg, 2 mmoles)[2]]; **6a** (320 mg, mp 173–175° dec) was obtained.

Catalytic Hydrogenation of 6a.—**6a** (1.0 g, 1.97 mmoles), suspended in EtOAc (20 ml) and AcOH (2 ml), was added to a suspension of 5% Rh/C (1.0 g) in EtOAc (10 ml) satd with H_2 in an atm pressure hydrogenation apparatus. In 60 min 44.0 cm^3 of H_2 was absorbed (90% of theory). The catalyst was then sepd by filtration, and the soln was evapd to dryness *in vacuo*. Tlc (C_6H_6–EtOAc, 1:1) showed a new, more polar spot (R_f 0.39) and a less polar spot (R_f 0.69). Crystn from CH_2Cl_2–*tert*-BuOH gave the polar material as a mixt of two isomers (750 mg, 75%, mp 171–176° dec). Several recrystns from CH_2Cl_2–EtOAc gave the pure major isomer 2,2,2-trichloroethyl 2β,3-dimethyl-7-phenoxyacetamido-3-cephem-4-carboxylate 1-oxide (**7**); mp 177–179° dec; uv max (EtOH) 268 nm (ϵ 8800); nmr ($CDCl_3$) δ 1.73 (3 H, d, J = 8 Hz), 2.16 (3 H, s), 3.27 (1 H, m, J = 8 Hz, J = 1.5 Hz), 4.61 (2 H, s), 4.71 (1 H, d/d, J = 5 Hz, J = 1.5 Hz), 4.89 (1 H, d, J = 12 Hz), 5.05 (1 H, d, J = 12 Hz), 6.17 (1 H, d/d, J = 5 Hz, J = 10 Hz).[15] *Anal.* ($C_{19}H_{19}Cl_3N_2O_6S$) C, H, Cl, N, S.

The minor isomer 2,2,2-trichloroethyl 2α,3-dimethyl-7-phenoxyacetamido-3-cephem-4-carboxylate 1-oxide (**8**) (mp 186–188° dec) was isolated by exhaustive fractional crystn: uv max (EtOH) 267 nm (ϵ 9300); nmr ($CDCl_3$) δ 1.32 (3 H, d, J = 7.5 Hz), 2.26 (3 H, s), 3.60 (1 H, q, J = 7.5 Hz), 4.55 (1 H, d, J = 5 Hz), 4.59 (2 H, s), 4.90 (1 H, d, J = 12 Hz), 5.02 (1 H, d, J = 12 Hz), 6.21 (1 H, d/d, J = 5 Hz, J = 11 Hz).[15] *Anal.* ($C_{19}H_{19}Cl_3N_2O_6S$) C, H, Cl, N, S.

The less polar material (R_f 0.69) formed in the reduction remained in the mother liquors. It was isolated by chromatography and characterized as 2,2,2-trichloroethyl 2,3-dimethyl-7-phenoxyacetamido-2-cephem-4-carboxylate (**9**) by its spectral properties: uv max (EtOH) 267 nm (ϵ 4500); ir ($CHCl_3$) 1785, 1750, 1695 cm^{-1}; nmr ($CDCl_3$) δ 1.90 (6 H, s), 4.56 (2 H, s), 4.76 (1 H, d, J = 12 Hz), 4.88 (1 H, d, J = 12 Hz), 4.93 (1 H, s), 5.39 (1 H, d, J = 4 Hz), 5.72 (1 H, d/d, J = 4 Hz, J = 9 Hz).[15]

Addition of Br_2 to 6a.—To a stirred soln of **6a** (1.0 g, 1.97 mmoles) in CH_2Cl_2 (100 ml) under N_2 was added a soln of Br_2 (0.2 ml, 3.6 mmoles) in CH_2Cl_2 (40 ml) over a 15-min period. After standing 3 hr at 25°, the reaction mixt was washed with $Na_2S_2O_3$ soln (2 × 100 ml), then with H_2O (1 × 100 ml), dried ($MgSO_4$), filtered, and evapd to dryness *in vacuo*. The crude, pale orange solid (1.34 g) was recrystd from EtOAc to give the dibromide **16a** (mp 123–125° dec): ir ($CHCl_3$) 1810, 1745, 1695, 1600, 1055 cm^{-1}; nmr ($CDCl_3$) δ 2.20 (3 H, s), 4.11 (2 H, s), 4.60 (2 H, s), 4.95 (2 H, s), 5.43 (1 H, d, J = 5 Hz), 6.22 (1 H, d/d, J = 5 Hz, J = 10 Hz).[15] *Anal.* ($C_{19}H_{17}Br_2Cl_3N_2O_6S$) C, H, N, S, O, halogen.

Reaction of 6a with Disiamylborane.[11]—To a soln of **6a** (5.0 g, 9.185 mmoles) in dry THF (150 ml) under N_2 was added, with stirring at room temp, a 1 M soln of disiamylborane (10 ml, 10 mmoles). The reaction was followed by tlc. After 12 min and 70 min, further portions (5 ml) of disiamylborane soln were added, with little visible effect. After 90 min, NaOAc (2.4 g) and H_2O_2 (5 ml, 30% soln) were added, and the mixt was stirred for 2.25 hr longer. The products were isolated by dilg the reaction mixt with satd NaCl soln and extg with CH_2Cl_2. The crude mixt (3.81 g) was chromatographed on silica gel (300 g) using a C_6H_6–EtOAc gradient (6 l.). The first compd eluted (900 mg) was identified as 2,2,2-trichloroethyl 2α,3-dimethyl-7-phenoxyacetamido-3-cephem-4-carboxylate (**11**): uv max (EtOH) 267 nm (ϵ 8100); nmr ($CDCl_3$) δ 1.57 (3 H, d, J = 7.5 Hz), 2.20 (3 H, s), 3.46 (1 H, q, J = 7.5 Hz), 4.55 (2 H, s), 4.83 (1 H, d, J = 12 Hz), 4.99 (1 H, d, J = 12 Hz), 5.13 (1 H, d, J = 5 Hz), 5.95 (1 H, d/d, J = 5 Hz, J = 9 Hz).[15]

The second compd (1.2 g) was **8**, identical in all respects with the product obtained previously from the catalytic hydrogenation.

Equilibration of 7 and 8.—Samples (100 mg) of pure **7** and **8** were heated in DMF (0.8 ml) and dioxane (3 ml) with $Me_2NH \cdot HCl$ (15 mg) for 3 hr. The recovered samples (80 mg) were essentially identical mixts of 83% **8** and 17% **7** as detd from the 100-MHz nmr spectra.

Reduction of Sulfoxide Esters (6a, 6c, 7, 8) to Sulfide Esters (17a, 17c, 10, 11). (**a**) **2,2,2-Trichloroethyl 3-Methyl-2-methylene-7-phenoxyacetamido-3-cephem-4-carboxylate (17a).**—**6a** (20.0 g, 39.5 mmoles), was dissolved in CH_2Cl_2 (200 ml) and MeCN (200 ml) and cooled to −40° in a Dry Ice–MeCN bath. Finely powdered anhyd $SnCl_2$ (10 g, 52.8 mmoles) was added with stirring, followed by AcCl (10 ml). After 15 min and 45 min, further portions of $SnCl_2$ (5 g) and AcCl (5 ml) were added. After 70 min, when tlc anal. showed reaction to be complete, MeOH (50 ml) was added to the cold reaction mixt; this was poured into ice H_2O and extd with CH_2Cl_2. The CH_2Cl_2 ext was washed with ice-cold $NaHCO_3$ soln and with H_2O, dried ($MgSO_4$), filtered, and evapd to dryness *in vacuo*. The cryst product **17a** was recrystd from Me_2CO (12.61 g, 65% yield): uv max (EtOH) 307 nm (ϵ 8100); nmr ($CDCl_3$) δ 2.30 (3 H, s), 4.56 (2 H, s), 4.82 (1 H, d, J = 12 Hz), 5.04 (1 H, d, J = 12 Hz), 5.17 (1 H, d, J = 5 Hz), 5.68 (1 H, s), 5.91 (1 H, s), 5.92 (1 H, d/d, J = 5 Hz, J = 9 Hz).[15] *Anal.* ($C_{19}H_{17}Cl_3N_2O_5S$) C, H, Cl, N, S.

(**b**) **2,2,2-Trichloroethyl 3-Acetoxymethyl-7-(2′-thienylacetamido)-3-cephem-4-carboxylate (17c).**—Under conditions similar to those above, **6c** was reduced in poor yield to a crude, noncrystalline product, identified as **17c** by spectral comparisons.

(**c**) **2,2,2-Trichloroethyl 2β,3-Dimethyl-7-phenoxyacetamido-3-cephem-4-carboxylate (10).**—When a mixt of **7** and **8** (2.67 g, 5.24 mmoles) was reduced with $SnCl_2$ and AcCl by the above procedure, only partial reduction occurred according to tlc anal. Column chromatography on silica gel (300 g) using a C_6H_6–EtOAc gradient (8 l.) sepd from pure unchanged **8** (1.02 g) 1.1 g of **10**: nmr ($CDCl_3$) δ 1.45 (3 H, d, J = 7.5 Hz), 2.09 (3 H, s), 3.66 (1 H, q, J = 7.5 Hz), 4.57 (2 H, s), 4.82 (1 H, d, J = 12 Hz), 4.95 (1 H, d, J = 12 Hz), 5.16 (1 H, d, J = 5 Hz), 5.80 (1 H, d/d, J = 5 Hz, J = 9 Hz).[15]

(**d**) **2,2,2-Trichloroethyl 2α,3-Dimethyl-7-phenoxyacetamido-3-cephem-4-carboxylate (11).**—**8** (760 mg, 1.49 mmoles) was dissolved in DMF (4 ml) and cooled in an ice bath. PCl_3 (0.8 ml) was added; the mixt was stirred at room temp for 20 min and then poured into ice-cold 10% NaCl soln (100 ml). The solid product was filtered, washed with H_2O, then dissolved in EtOAc, dried ($MgSO_4$), filtered, and evapd to dryness *in vacuo*. The product, 11 (650 mg), was identical in all respects with the compd obtained from the disiamylborane reaction.

Cleavage of Trichloroethyl Esters.[12] **2β,3-Dimethyl-7-phenoxyacetamido-3-cephem-4-carboxylic Acid (13).**—**10** (3.85 g, 7.79 mmoles) was dissolved in 90% HCO_2H (140 ml) at room temp, and Zn dust (14 g) was added with stirring. Tlc anal. showed no further change after 10 min. The reaction mixt was filtered, and the residual Zn was washed with CH_2Cl_2. The filtrate was evapd to dryness *in vacuo;* the acidic fraction of the solid residue was isolated by shaking it between cold dil $NaHCO_3$ soln and EtOAc. The aq layer was sepd, acidified to pH 2 with dil HCl, and extd with EtOAc. The acidic fraction (2.07 g, 73.5%) was recrystd several times from Me_2CO–CH_2CN, yielding pure **13** (1.03 g): mp 151–153°; uv max (EtOH) 268 nm (ϵ 6700); nmr ($CDCl_3$) δ 1.42 (3 H, d, J = 7 Hz), 2.19 (3 H, s), 3.61 (1 H, q, J = 7 Hz), 4.61 (2 H, s), 5.16 (1 H, d, J = 5 Hz), 5.75 (1 H, d/d, J = 5 Hz, J = 10 Hz), 10.22 (1 H, s).[15] *Anal.* ($C_{17}H_{18}N_2O_5S$) C, H, N, S.

2,3-Dimethyl-7-phenoxyacetamido-2-cephem-4-carboxylic Acid (12).—**9** (1.57 g, 3.18 mmoles) was dissolved in 90% AcOH (60 ml) and treated with Zn dust (6.0 g) at room temp for 1.5 hr. The acidic product was isolated as described above to give **12**: mp 184–185°; uv max (EtOH) 266 nm (ϵ 2200); nmr ($CDCl_3$ plus 0.05 ml of DMSO-d_6) δ 1.90 (6 H, s), 4.58 (2 H, s), 4.66 (1 H, s), 5.33 (1 H, d, J = 4 Hz), 5.60 (1 H, d/d, J = 4 Hz, J = 8.5 Hz), 10.1 (1 H, broad).[15] *Anal.* ($C_{17}H_{18}N_2O_5S$) C, H, N, S.

2α,3-Dimethyl-7-phenoxyacetamido-3-cephem-4-carboxylic Acid (14).—11 (4.23 g, 8.56 mmoles) was dissolved in DMF (80 ml) and cooled in ice. AcOH (16 ml) and Zn dust (4 g) were added, and the mixture was stirred in the ice bath for 1.5 hr. It was filtered through Super-Cel and washed with large vols of H_2O and EtOAc. The EtOAc phase of the filtrate was sepd and washed well with H_2O, then evapd to dryness *in vacuo*. The acidic fraction was sepd and isolated as described earlier to give crude **14** (2.46 g, 78%) which was crystd from EtOAc: mp 201–203° dec; uv max (EtOH) 260 nm (ϵ 8700); nmr (DMSO-d_6) δ 1.48 (3 H, d, J = 7 Hz), 2.05 (3 H, s), 3.63 (1 H, q, J = 7 Hz), 4.62 (2 H, s), 5.18 (1 H, d, J = 4.5 Hz), 5.72 (1 H, d/d, J = 4.5 Hz, J = 8.5 Hz), 13.2 (1 H, broad).[15] *Anal.* ($C_{17}H_{18}N_2O_5S$) C, H, N, S.

3-Methyl-2-methylene-7-phenoxyacetamidocepham-4-carboxylic Acid (18a).—Treatment of **17a** (1.45 g, 2.95 mmoles) in 90% AcOH (60 ml) with Zn dust (5 g) by any of the above procedures gave an acidic product (1.06 g, 99%) which crystd from Me_2CO–CH_3CN (mp 155–156° dec). It was identified as **18a** by the following data: ir (mull), 1750, 1720, 1690 cm^{-1}; uv max (EtOH) 267 nm (ϵ 1500); nmr ($CDCl_3$ plus DMSO-d_6) δ 1.29 (3 H, d, J = 7 Hz), 2.97 (1 H, m, J = 7 Hz), 4.55 (2 H, s), 4.61 (1 H, d, J = 4 Hz), 5.37 (1 H, d, J = 2 Hz), 5.39 (1 H, d, J = 7 Hz), 5.47 (1 H, d, J = 2 Hz), 5.60 (1 H, d/d, J = 4 Hz, J = 9 Hz), 11.54 (1 H, broad).[15] *Anal.* ($C_{17}H_{18}N_2O_5S$) C, H, N, S.

18a was also obtained directly from **6a** by reduction with Zn in 90% HCO_2H.

3-Acetoxymethyl-2-methylene-7-(2′-thienylacetamido)cepham-4-carboxylic Acid (18c).—Under the conditions given above, **6c** and **17a** gave the analogous dihydro product **18c** according to spectral comparisons.

Alternate Route to 2-Methylenecephalosporins. ***tert*-Butyl 3-Methyl-2-methylene-7-phenoxyacetamido-3-cephem-4-carboxylate 1-Oxide (6b).**—**4b**[1] (13.4 g, 31.9 mmoles), $Me_2NH \cdot HCl$ (2.55 g, 31.3 mmoles), and CH_2O (3.5 g, 37% aq soln, 43.2 mmoles) were dissolved in DMF (50 ml) and dioxane (200 ml) and heated under reflux with stirring for 3.5 hr. Dioxane was then removed *in vacuo*, and the residue was poured into ice-cold 10% NaCl soln (800 ml). The ppt was sepd, washed, dissolved in CH_2Cl_2, extd twice with H_2O, dried ($MgSO_4$), filtered, and evapd to dryness *in vacuo*. Crude **6b** (11.0 g) crystd from C_6H_6 as a solvate (10.3 g, 64%): mp 170–172° dec; uv max (EtOH) 311 nm (ϵ 6700); nmr ($CDCl_3$) δ 1.55 (9 H, s), 2.20 (3 H, s), 4.54 (2 H, s), 4.60 (1 H, d, J = 5 Hz), 5.98 (1 H, s), 6.08 (1 H, d/d, J = 5 Hz, J = 10 Hz), 6.10 (1 H, s), 7.38 (6 H, s) (C_6H_6).[15] *Anal.* ($C_{21}H_{24}N_2O_6S$) C, H, N, S.

***tert*-Butyl 3-Methyl-2-methylene-7-phenoxyacetamido-3-cephem-4-carboxylate (17b).**—**6b** (1.0 g, 2.34 mmoles) was dissolved in DMF (18 ml) and cooled to −20° in ice–MeOH. PCl_3 (1.0 ml, 11.4 mmoles) was added from a syringe; the reaction mixt was stirred vigorously for 30 sec, then poured into ice-cold NaCl soln. The ppt was filtered, washed with H_2O, dissolved in CH_2Cl_2, extd with cold dil NaCl, dried ($MgSO_4$), filtered, and evapd to dryness *in vacuo*, giving **17b** as a yellow foam (600 mg): uv max (EtOH) 307 nm (ϵ 9600); nmr ($CDCl_3$) δ 1.56 (9 H, s), 2.20 (3 H, s), 4.55 (2 H, s), 5.10 (1 H, d, J = 5 Hz), 5.57 (1 H, s), 5.80 (1 H, s), 5.87 (1 H, d/d, J = 5 Hz, J = 8 Hz).[15]

Cleavage of *tert*-Bu Esters 17b and 6b.—**17b** (70 mg) was dissolved in 98–100% HCO_2H in an nmr tube; the spectrum was run immediately and again after 0.5 and 2 hr. Rapid destruction of the molecule was apparent from the spectra.

6b was converted cleanly into 3-methyl-2-methylene-7-phenoxyacetamido-3-cephem-4-carboxylic acid 1-oxide (**19b**) under the same conditions. On a preparative scale, **6b** (2.0 g, 4.63 mmoles) was allowed to stand in 98–100% HCO_2H (25 ml) for 1.5 hr at room temp; the solvent was removed *in vacuo*, and the solid residue was recrystd from EtOAc to give **19b** (1.48 g, 85%): mp 209–210° dec; uv max (EtOH) 309 nm (ϵ 8500); nmr (DMSO-d_6) δ 2.16 (3 H, s), 4.69 (2 H, s), 5.10 (1 H, d, J = 5 Hz), 6.10 (1 H, d/d, J = 5 Hz, J = 10 Hz), 6.19 (1 H, s), 6.36 (1 H, s).[15] *Anal.* ($C_{17}H_{16}N_2O_6S$) C, H, N, S.

The corresponding cephalothin derivative, 3-acetoxymethyl-2-methylene-7-(2-thienylacetamido-3-cephem-4-carboxylic acid 1-oxide (**19d**), was prepd as follows. (a) ***tert*-Butyl 3-acetoxymethyl-7-(2′-thienylacetamido)-2-cephem-4-carboxylate (3d)** was prepd by an improvement of Murphy's procedure.[13] Cephalothin (**1c**) (23.7 g, 60 mmoles) was suspended in a mixt of CH_2Cl_2 (300 ml), PhMe (300 ml), and DMF (1.5 ml) under N_2 in an ice bath at 0°. A soln of $(COCl)_2$ (8.7 ml, 102 mmoles) in C_6H_6 (25 ml) was added with stirring over 10 min. With the temp at 6° all starting material had dissolved 15 min after addn was complete. The soln was light yellow. The temp was lowered to 0°; in 10 min the soln was orange, and a new ppt began to form. The reaction mixt was concd to ~ 100 ml on a rotary evaporator; the H_2O bath temp was kept at 0° until CH_2Cl_2 was removed and was then allowed to rise to 10°. The orange slurry of cephalothin acid chloride was dissolved in 300 ml of CH_2Cl_2, transferred to a dropping funnel, and added slowly (over 1.5 hr) to a well-stirred, ice-cold mixt of CH_2Cl_2 (500 ml), *tert*-BuOH (100 ml), and Et_3N (16 ml). When addn was complete, the soln was concd *in vacuo* at 0° for 30 min, then dild with EtOAc (500 ml) and extd with ice-cold 10% NaCl soln (2 × 500 ml), ice-cold 2 *N* HCl (2 × 500 ml), and ice-cold 5% $NaHCO_3$ soln (2 × 500 ml), the aq exts being back-washed with EtOAc (2 × 400 ml). The combined EtOAc layers were dried ($MgSO_4$), treated with charcoal, filtered, and concd *in vacuo* to give **3d** (21.48 g, 79%): mp 175–177° dec; nmr ($CDCl_3$) δ 1.47 (9 H, s), 2.04 (3 H, s), 3.84 (2 H, s), 4.55 (1 H, d, J = 12.5 Hz), 4.71 (1 H, d, J = 12.5 Hz), 4.88 (1 H, d, J = 1.5 Hz), 5.26 (1 H, d, J = 4 Hz), 5.61 (1 H, d/d, J = 4 Hz, J = 8 Hz), 6.37 (1 H, d, J = 1.5 Hz).[15] *Anal.* ($C_{20}H_{24}N_2O_6S_2$) C, H, N, S.

(b) ***tert*-Butyl 3-acetoxymethyl-7-(2′-thienylacetamido)-3-cephem-4-carboxylate 1-oxide (4d)** was prepd by a modification of a published general procedure.[1] To **3d** (14.29 g, 31.6 mmoles) dissolved in CH_2Cl_2 (100 ml) and *i*-PrOH (100 ml) at 0° was added a soln of 85% *m*-$ClC_6H_4CO_3H$ (6.48 g, 31.6 mmoles) in CH_2Cl_2 (25 ml) and *i*-PrOH (25 ml). Tlc anal. indicated reaction to be complete after 10 min. After 40 min, the reaction mixt was dild with CH_2Cl_2 and extd with ice-cold 5% $NaHCO_3$ soln (3 × 500 ml). The aq exts were washed with CH_2Cl_2 (2 × 100 ml); the combined CH_2Cl_2 solns were dried ($MgSO_4$), filtered, and evapd to dryness *in vacuo*, giving **4d** as a yellow glue which formed intractable jelly-like solvates with most common solvents and was, therefore, identified spectrally and used directly in the next reaction: nmr ($CDCl_3$) δ 1.55 (9 H, s), 2.06 (3 H, s), 3.24 (1 H, d/d, J = 18 Hz, J = 1 Hz), 3.73 (1 H, d, J = 18 Hz), 3.85 (2 H, s), 4.49 (1 H, d/d, J = 5 Hz, J = 1 Hz), 4.69 (1 H, d, J = 14 Hz), 5.29 (1 H, d, J = 14 Hz), 6.00 (1 H, d/d, J = 5 Hz, J = 10 Hz).[15]

(c) ***tert*-Butyl 3-Acetoxymethyl-2-methylene-7-(2′-thienylacetamido)-3-cephem-4-carboxylate 1-Oxide (6d).**—**4d** (31.6 mmoles) was taken up in DMF (50 ml), dild with dioxane (150 ml) contg CH_2O (3.65 ml, 37% aq soln, 45 mmoles) and $(CH_3)_2NH \cdot HCl$ (2.50 g, 30.7 mmoles), and heated at reflux under N_2 with stirring for 3 hr. The soln was concd to ~50 ml *in vacuo*, dild with CH_2Cl_2 (200 ml), and extd with ice-cold dil NaCl soln (6 × 350 ml), the aq exts being washed with CH_2Cl_2 (3 × 100 ml). The combined CH_2Cl_2 solns were dried ($MgSO_4$), treated with charcoal, filtered, and evapd to dryness *in vacuo*, giving again an intractable glue which was purified by chromatography on silica gel, using a 0–10% MeOH in CH_2Cl_2 gradient. **6d** was characterized spectrally: uv max (EtOH) 306 nm (ϵ 6900); nmr ($CDCl_3$) δ 1.56 (9 H, s), 2.02 (3 H, s), 3.83 (2 H, s), 4.58 (1 H, d, J = 5 Hz), 4.67 (1 H, d, J = 12.5 Hz), 5.5 (1 H, d, J = 12.5 Hz), 6.01 (1 H, s), 6.03 (1 H, d/d, J = 5 Hz, J = 10 Hz), 6.31 (1 H, s).[15]

(d) **3-Acetoxymethyl-2-methylene-7-(2′-thienylacetamido)-3-cephem-4-carboxylic Acid 1-Oxide (19d).**—**6d** (9.7 g, 20.2 mmoles) was stirred at room temp under N_2 for 2 hr 50 min in 98–100% HCO_2H (70 ml). The solvent was removed *in vacuo;* the residue was taken up in MeOH–CH_2Cl_2 and extd with ice-cold $NaHCO_3$ soln (3 × 150 ml). The aq layers were washed with CH_2Cl_2 (400 ml), then acidified to pH 1.5 with dil HCl. The gelatinous ppt was filtered and taken up in Me_2CO. The soln was dried (Na_2SO_4), filtered, and evapd to dryness *in vacuo*, giving **19d** (4.5 g, 53%): uv max (MeOH) 301 nm (ϵ 5500) nmr (DMSO-d_6) δ 2.01 (3 H, s), 3.90 (2 H, s), 4.78 (1 H, d, J = 12.5 Hz), 5.08 (1 H, d, J = 5 Hz), 5.40 (1 H, d, J = 12.5 Hz), 5.92 (1 H, d/d, J = 5 Hz, J = 8.5 Hz), 6.16 (1 H, d, J = 1.5 Hz), 6.33 (1 H, d, J = 1.5 Hz).[15]

Reduction of Sulfoxide Acids 19b and 19d. (a) **3-Methyl-2-methylene-7-phenoxyacetamido-3-cephem-4-carboxylic Acid 20b).**—**19b** (580 mg, 1.55 mmoles) was reduced with PCl_3 (1.08 ml, 12.4 mmoles) in DMF (12 ml) at −18° (30 sec) as described for **6b**; but the reaction mixt was worked up by pouring into an ice-cold soln of $(NH_4)_2HPO_4$ (5.0 g, 37.2 mmoles) in H_2O (100 ml), adjusting the final pH to 2.5 with dil HCl, and extg the product into EtOAc. The acidic fraction was isolated by extg the EtOAc with ice-cold $NaHCO_3$ soln, acidifying to pH 2, and extg with EtOAc. The acidic fraction (190 mg) in dioxane was treated with NaOAc (45 mg) in MeOH to give the cryst Na salt (140 mg) of **20b**: ir (mull) 1760, 1670, 1615, 1515 cm^{-1}; uv max (MeOH) 300 nm (ϵ 11,350), nmr (DMSO-d_6) δ 2.01 (3 H, s), 4.64 (2 H, s), 5.10 (1 H, d, J = 5 Hz), 5.22 (1 H, s), 5.49 (1 H, s), 5.55 (1 H, d/d, J = 5 Hz, J = 9 Hz).[15]

(b) **3-Acetoxymethyl-2-methylene-7-(2′-thienylacetamido)-3-**

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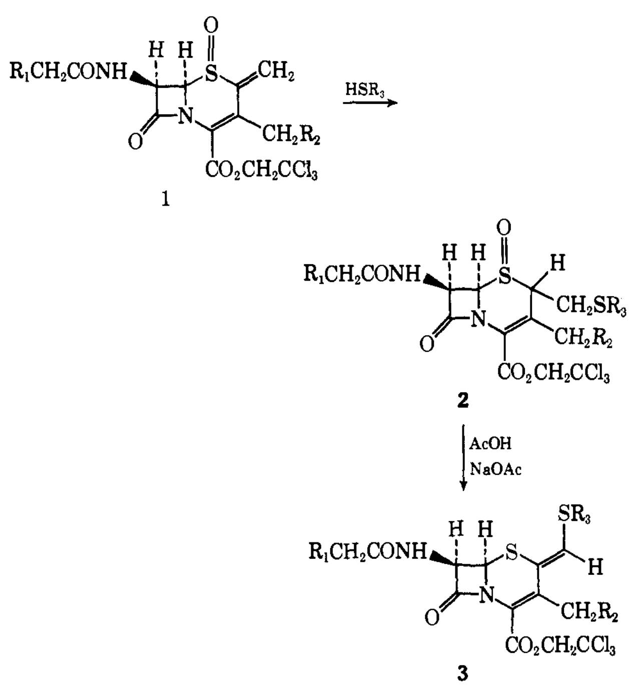
2-Methylenecephalosporin sulfoxide trichloroethyl esters, **1**, were treated with a variety of thiols to give the corresponding 2-thiomethyl adducts **2**. These compounds are stable, but lose the elements of H_2O in HOAc–NaOAc to give 2-thiomethylene esters **3**. Deesterification and sulfoxide reduction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

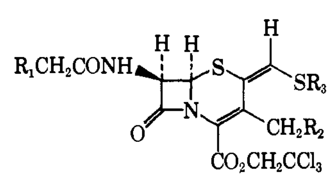


1 2 3

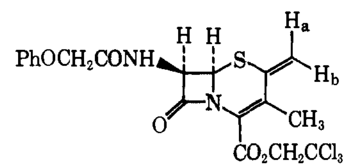
The isolated dehydration products (**3**) were not mixtures of cis and trans isomers but were single compounds in each case. In two cases we used nuclear Overhauser effects (NOE)[2] to determine the configuration of the isolated product. If the compound were isomer **3** (R_2 = H), the nmr signal intensity 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

(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).