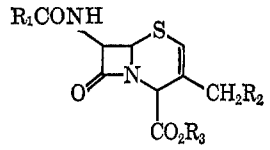
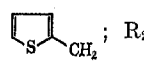
TABLE I



Compd[a]	Registry no.	Empirical formula	Mp, °C	% yield	Reaction conditions	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1	24647-38-9	$C_{20}H_{24}N_2O_5S$	78–80	87	A	59.20	5.98	6.93	59.20	6.08	6.63
2	24144-88-5	$C_{24}H_{24}N_2O_6S$	112–114	90	B	61.52	5.16	5.97	61.95	5.33	6.12
3	24647-40-3	$C_{21}H_{22}N_2O_5S$	92–93	85	A	60.86	5.35	6.76	61.02	5.59	7.00
4	24647-41-4	$C_{21}H_{24}N_2O_5S$	83–85	46	A	60.56	5.81	6.73	60.34	6.01	6.91
5	24647-42-5	$C_{24}H_{22}N_2O_6S$	145–146	77	B	61.80	4.75	6.01	62.06	4.97	6.14
6	24647-43-6	$C_{23}H_{21}N_3O_7S$	130	60	B	57.25	4.18	8.70	57.10	4.47	8.45
7	24647-44-7	$C_{29}H_{26}N_2O_5S$	110	45	B	67.69	5.09	5.45	67.82	5.18	5.59
8	24647-45-8	$C_{20}H_{24}N_2O_4S$	130–131	45	B	61.84	6.23	7.21	61.59	6.23	7.04
9	24647-46-9	$C_{20}H_{24}N_2O_6S_2$	178	33	A	53.09	5.35	6.19	53.08	5.33	6.11

[a] **1**, R_1 = $PhOCH_2$; R_2 = H; R_3 = $C(CH_3)_3$. **2**, R_1 = $PhOCH_2$; R_2 = H; R_3 = $-CH_2-C_6H_4-OCH_3$. **3**, R_1 = $PhOCH_2$; R_2 = H; R_3 = $-C(C{\equiv}CH)(CH_3)_2$. **4**, R_1 = $PhOCH_2$; R_2 = H; R_3 = $-C(CH{=}CH_2)(CH_3)_2$. **5**, R_1 = $PhOCH_2$; R_2 = H; R_3 = $CH_2C(=O)Ph$. **6**, R_1 = $PhOCH_2$; R_2 = H; R_3 = $CH_2-C_6H_4-NO_2$. **7**, R_1 = $PhOCH_2$; R_2 = H; R_3 = $-CH(Ph)_2$. **8**, R_1 = $PhCH_2$; R_2 = H; R_3 = $C(CH_3)_3$. **9**, R_1 =  ; R_2 = OAc; R_3 = $C(CH_3)_3$.

Model 21 in a KBr disk. The ultraviolet spectra were measured in methanol solution. The nmr spectra were recorded with Varian Models A-60 and HA-60 spectrometers at 60 MHz in 5–10% deuteriochloroform solution with tetramethylsilane as an internal standard. Elemental analyses were determined by our microanalytical laboratory.

3-Methyl-7-phenoxyacetamido-3-cephem-4-carbonyl Chloride.—A suspension of 0.353 g (1.02 mmol) of 3-methyl-7-phenoxyacetamido-3-cephem-4-carboxylic acid in 40 ml of C_6H_6 was cooled in ice and stirred while 0.256 g (2 mmol) of oxalyl chloride and 1 drop of DMF were added. The reaction mixture was stirred at about (7–10°) for 45 min, and then the solvents were removed under reduced pressure. An nmr spectrum of the acid chloride showed the absence of any 2-cephem isomer.

The acid chloride (~200 mg) was dissolved in 10 ml of MeOH and stirred at 25° for 30 min. The solvent was removed, and the residue was redissolved in C_6H_6. The C_6H_6 solution was washed with H_2O, 3% HCl, and 10% $NaHCO_3$. The solution was dried over Na_2SO_4 and evaporated to dryness to give 0.160 g of methyl 3-methyl-7-phenoxyacetamido-3-cephem-4-carboxylate. The ester was crystallized from EtOAc and was found to be identical with authentic material[1] by tlc, mp 135–137°, mmp 135–138°.

The acid chloride as prepared above was used in the following preparations. These preparations are presented as typical examples for the esterification of tertiary and primary alcohols, respectively. The esters listed in Table I are prepared analogously.

A. *t*-Butyl 3-Methyl-7-(phenoxyacetamido)-3-cephem-4-carboxylate.—A solution of 0.10 mol of the acid chloride (using proportions given above) in 1.0 l. of CH_2Cl_2 was added dropwise over a 3-hr period to a stirred solution of 92.5 g (1.25 mol) of *t*-butyl alcohol (freshly distilled from $KMnO_4$ and dried over molecular sieves) and 19.3 g (0.175 mol) of triethylamine (freshly distilled from phenyl isocyanate and dried over KOH pellets) in 650 ml of CH_2Cl_2 maintained under anhydrous conditions at ice bath temperature. The CH_2Cl_2 solution was washed with about 500 ml of H_2O and 100 ml of 3% HCl and evaporated to dryness. The residue was suspended in EtOAc, washed with 5% $NaHCO_3$ and H_2O, and then treated with 20 g of activated charcoal. The suspension was filtered and evaporated to dryness. The *t*-butyl ester crystallized from ether to give a total yield of 37.5 g (75%) of needles, mp 78–80°. From the neutral and basic washes was recovered 7.0 g of a mixture of Δ^2 and Δ^3 acids.

The nmr spectrum of the Δ^2 ester [δ ($CDCl_3$) C-2 H at 5.92, C-4 H at 4.66, $-OC(CH_3)_3$ at 1.50 ppm] was consistent with the proposed structure.

B. *p*-Methoxybenzyl 3-Methyl-7-(phenoxyacetamide)-2-cephem-4-carboxylate.—A solution of 2 mmol of the acid chloride in 20 ml of alcohol-free $CHCl_2$ was added dropwise over a 1-hr period to a stirred solution of 0.300 g (2.2 mmol) of *p*-methoxybenzyl alcohol and 0.300 g of triethylamine maintained at −50 to −75°. The solution was washed with H_2O and then 3% HCl and evaporated to dryness. The residue was suspended in EtOAc, washed with 5% $NaHCO_3$, dried over Na_2SO_4, and evaporated to dryness. The residue was crystallized from CCl_4 as needles, mp 108–110°. The nmr spectrum (C-2 H at 5.90, C-4 H at 4.80 ppm) was identical with that of authentic material.[2]

Chemistry of Cephalosporin Antibiotics. XIX. Transformation of Δ^2-Cephem to Δ^3-Cephem by Oxidation–Reduction at Sulfur

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A recent report from our laboratory details the final steps by which a penicillin can be converted into a cephalosporin.[1] A vital sequence in this synthesis is the conversion of a Δ^2-cephem ester (**1**) to a Δ^3-cephem ester (**3**) *via* the sulfoxide **2**. This process utilizes the concept that β,γ-unsaturated sulfoxides are thermodynamically more stable than the corresponding α,β-unsaturated sulfoxides.[2]

By contrast, an equilibrium mixture of cephem isomers before oxidation contains largely the unnatural

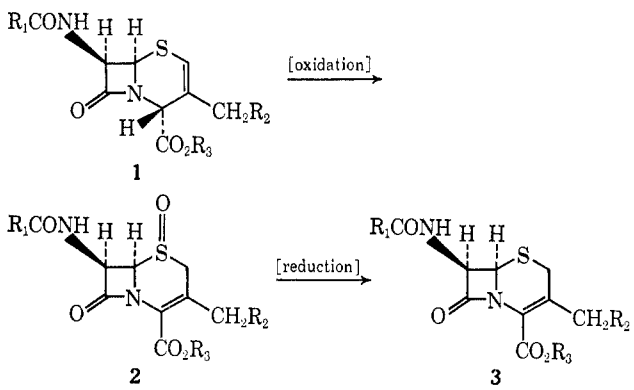
(1) J. A. Webber, E. M. Van Heyningen, and R. T. Vasileff, *J. Amer. Chem. Soc.*, **91**, 5674 (1969).

(2) D. E. O'Connor and W. I. Lyness, *ibid.*, **86**, 3840 (1964).

TABLE I
EXAMPLES OF CEPHEM SULFOXIDE FORMATION

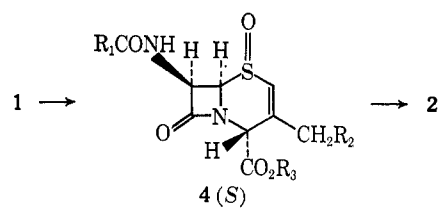
R_1	R_2	R_3	Starting sulfide isomer	Product sulfoxide isomer	Yield, %	Reaction conditions
$PhOCH_2$	H	*t*-Bu	Δ^2	Δ^2 (*R*)	0.8	A
$PhOCH_2$	H	*t*-Bu		Δ^2 (*S*)	93	A
$PhOCH_2$	H	*t*-Bu	Δ^2	Δ^3	100	A + isomerization
$PhOCH_2$	H	*t*-Bu	Δ^2	Δ^3	77	B
$PhOCH_2$	H	*t*-Bu	Δ^2	Δ^3	94	C
$C_4H_3SCH_2$ (2-thenyl)	OAc	CH_2CCl_3	Δ^3	Δ^3	62	A
$PhOCH_2$	OAc	$CH_2C_6H_4OCH_3$-*p*	$\Delta^2 + \Delta^3$	Δ^3	75	A
$PhOCH_2$	H	$-C(CH_3)_2CH{=}CH_2$	Δ^2	Δ^3	88	A
$PhOCH_2$	H	$CH_2C_6H_4NO_2$-*p*	Δ^2	Δ^3	90	A
$PhOCH_2$	H	CH_2CCl_3	Δ^3	Δ^3 (*R*)	0.5	D
				Δ^3 (*S*)	38	D
$PhOCH_2$	OH	*t*-Bu	Δ^2	Δ^3	77	A

Δ^2 isomer.[3] Woodward, *et al.*,[4] report *K* (normal/iso) = 1/3 for the trichloroethyl ester of cephalothin[5] (**3**, R_1 = 2-thienylmethyl, R_2 = OAc, R_3 = H), and the desired Δ^3-cephem isomer must be isolated by elution chromatography. Since a Δ^2-cephem ester is a key intermediate in both the Woodward, *et al.*, cephalosporin synthesis, and that reported by Webber, *et al.*,[1] from our laboratory, the need for a facile, efficient method to achieve the $\Delta^2 \rightarrow \Delta^3$ transformation is clear.



Although a report indicates that Δ^2-cephem esters are resistant to mild oxidizing agents,[6] we have found that a large number of percarboxylic acids transform Δ^2-cephem esters into the corresponding Δ^3-cephem sulfoxides. Strong percarboxylic acids (*m*-chloroperbenzoic acid) gave high yields of sulfoxides (70–90%), providing temperature and solvent were maintained to minimize sulfone formation. Periodic acid gave satisfactory yields of sulfoxides in organic solutions, but weaker oxidizing agents, such as hydrogen peroxide and peracetic acid, required longer reaction times and gave lower yields. To prevent acidic decomposition of the cephalosporin nucleus, trifluoroperacetic and performic acids were used in a diluting solvent such as CH_2Cl_2. The addition of a hydroxylic solvent such as *i*-PrOH reduced the rate of sulfone formation. Some of the sulfoxides were not obtained in crystalline form, even though their nmr spectra indicated a high degree of purity. The oxidations are applicable to a variety of cephem compounds: Δ^2, Δ^3, or $\Delta^2 + \Delta^3$ mixtures. Representative examples are listed in Table I.

The initial products from the oxidation of Δ^2-cephem sulfides were the (*R*)- and (*S*)-Δ^2-sulfoxides. When these isomers were dissolved in a hydroxylic solvent, the Δ^3-cephem isomers were obtained. Oxidation in hydroxylic solvents gave the (*R*)- and (*S*)-Δ^3-cephem sulfoxides directly. The major product (**4** and **2**) in both double-bond isomers has been shown by comprehensive nmr studies to be the (*S*)-sulfoxide.[7] Difficulty in reducing Δ^3-cephem sulfoxides to Δ^3-cephem sulfides by a wide variety of conventional reducing agents[6] has prevented employment of this isomerization procedure in the past. The resistance of Δ^3-cephem sulfoxides to reduction is probably due to electronic factors since no obvious steric inhibition of the reducing agent is present. Both the β-lactam nitrogen and the α,β-unsaturated carboxyl function exert an electron-withdrawing effect which strengthens the sulfur–oxygen bond relative to that in a normal aliphatic sulfoxide.



We discovered that many common reducing agents are effective in the reduction of Δ^3-cephem sulfoxides if the sulfoxide is first activated by a reactive acid halide. For example, $Na_2S_2O_4$ did not reduce cephalosporin sulfoxides,[6] but when AcCl was added, reduction proceeded smoothly.

Several types of reducing agents were effective in the presence of a reactive acid halide: anionic reducing agents such as $S_2O_4^{2-}$ and I^- ions; cationic agents such as Sn^{2+}, Fe^{2+}, and Cu^+ ions; and trivalent phosphorus compounds, including phosphines and phosphites. These reagents reduced both cephalosporanic acid sulfoxides and their esters.

(3) Δ^2-Cephalosporanic acids are inactive as antibiotics.

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

(5) A parenteral antibiotic having low toxicity, penicillinase resistance, and excellent activity against Gram-positive and Gram-negative bacteria marketed as KEFLIN (sodium cephalothin, Lilly) by Eli Lilly and Co.

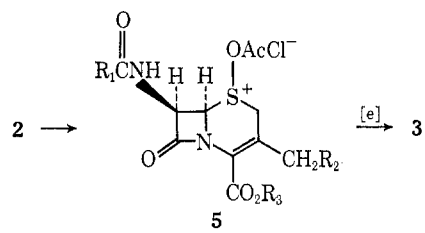
(6) J. D. Cocker, S. Eardley, G. I. Gregory, M. E. Hall, and A. G. Long, *J. Chem. Soc. C*, 1142 (1966).

(7) R. D. G. Cooper, P. V. DeMarco, C. F. Murphy, and L. A. Spangle, *ibid.*, in press.

The reductions proceeded smoothly in a wide variety of solvents such as DMF, THF, CH_2Cl_2, and CH_3CN. Even solvents in which the reactants are only partially soluble proved satisfactory.

Catalytic hydrogenation of Δ^3-cephem sulfoxides yielded only traces of reduced material even when large amounts of hydrogenation catalysts were employed. Inclusion of AcCl, however, effected the reduction in moderate yield.

We suggest that the "activating agent" reacts with the sulfoxide oxygen to form the sulfoxonium salt (**5**) which is much more reactive toward the reducing agent than the sulfoxide itself. Such activation of sulfoxides is apparent from the work of Jonsson[8] which showed that methyl *p*-tolyl sulfoxide racemizes rapidly at room temperature in Ac_2O containing 0.2 molar equiv of AcCl. Allenmark[9] has used I^-–AcCl–AcOH in a quantitative determination of dialkyl sulfoxides in AcOH, but added AcCl permits rapid determination.



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Several reagents such as PCl_3, PBr_3, $SiHCl_3$, and chloromethylene dimethyliminium chloride accomplished the reduction without external activation. These compounds all have acid halide character. The trihalophosphines reduce by donating the electron pair on phosphorous, while the success of the silanes and iminium halides probably involves hydride transfer subsequent to activation.

Experimental Section

Melting points were determined on a Mel-temp or Kofler melting point apparatus. Infrared spectra were determined with Perkin-Elmer Model 21. Thin layer chromatographic results were obtained on silica gel G, F254 plates. The nmr spectra were recorded with Varian Models A-60 and HA-60 spectrometers at 60 MHz in 5–10% deuteriochloroform solution with tetramethylsilane as an internal standard. Elemental analyses were determined by our microanalytical laboratory.

2,2,2-Trichloroethyl 3-Methyl-7-phenoxyacetamido-3-cephem-4-carboxylate.—To a stirred solution of 500 ml of CH_2Cl_2 containing 17.4 g (0.05 mol) of 3-methyl-7-phenoxyacetamido-3-cephem-4-carboxylic acid, 7.9 g (0.1 mol) of pyridine, and 14.9 g (0.1 mol) of 2,2,2-trichloroethanol was added dicyclohexylcarbodiimide (10.0 g, 0.05 mol). The reaction mixture was stirred at 25° for 90 min; then the dicyclohexylurea was removed by filtration. The organic solution was washed successively with cold 0.1 *N* HCl, saturated $NaHCO_3$, and H_2O, dried over $MgSO_4$, and evaporated *in vacuo*. The ester (9.5 g, 40%) was crystallized from ether: mp 114–116°; nmr ($CDCl_3$) δ 2.20 (3 H, s), 3.26, 3.46 (2 H, q, J = 18 Hz), 4.55 (2 H, s), 4.80, 4.95 (2 H, q, J = 12 Hz), 5.03 (1 H, d, J = 5 Hz), 5.85 (1 H, q, J = 4, 9 Hz), 6.8–7.4 (5 H, m), 7.6 (1 H, d, J = 9 Hz), showed pure Δ^3-cephem ester.

Anal. Calcd for $C_{18}H_{17}Cl_3N_2O_5S$: C, 45.06; H, 3.57; Cl, 22.17; N, 5.84. Found: C, 44.92; H, 3.86; Cl, 22.11; N, 5.89.

In a manner similar to that described above 2,2,2-trichloroethyl 3-acetoxymethyl-7-(2-thienylacetamido)-3-cephem-4-carboxylate was prepared in 62% yield. The ester crystallized from *i*-PrOH as needles: mp 120–122°;[10] uv (EtOH) 236 mμ (ϵ 11,900), 262 (7200); ir ($CHCl_3$) 1795, 1750, and 1690 cm^{-1}; nmr ($CDCl_3$) δ 2.07 (3 H, s), 3.39, 3.56 (2 H, q, J = 18 Hz), 3.83 (2 H, s), 4.75, 4.98 (2 H, q, J = 12 Hz), 4.85, 5.13, (2 H, q, J = 14 Hz), 4.99 (1 H, d, J = 5 Hz), 5.86 (1 H, q, J = 5, 9 Hz), 6.85–7.35 (4 H, m).

Anal. Calcd for $C_{18}H_{17}Cl_3N_2O_6S_2$: C, 40.95; H, 3.27; Cl, 12.14; N, 5.30; S, 20.15. Found: C, 41.19; H, 3.45; Cl, 12.23; N, 5.50; S, 19.91.

Representative Oxidation Reactions. A. *t*-Butyl 3-Methyl-7-phenoxyacetamido-2-cephem-4-carboxylate 1-Oxide.—To a stirred, cooled (in ice) solution of *t*-butyl 3-methyl-7-phenoxyacetamido-2-cephem-4-carboxylate (12.2 g, 0.03 mol) in CH_2Cl_2 (500 ml) over a 2-hr period was added a solution of 85% *m*-chloroperbenzoic acid (5.66 g, 0.028 mol) in CH_2Cl_2 (500 mol). The reaction mixture was washed successively with 10% $NaHCO_3$ and H_2O and then evaporated to give 12.0 g (93%) of a gummy product. The sulfoxide crystallized as prisms upon standing, mp 127–128°. The nmr spectrum of this compound showed it to be a Δ^2-cephem (*S*)-sulfoxide: ($CDCl_3$) δ 1.48 (9 H, d), 2.02 (3 H, s), 4.43 (2 H, s), 4.75 (1 H, d, J = 4 Hz), 4.95 (1 H, s), 6.15 (1 H, q, J = 4, 10 Hz), 6.70 (1 H, s), 6.8–7.5 (5 H, m), and 8.35 (1 H, d, J = 10 Hz).

Anal. Calcd for $C_{20}H_{24}N_2O_6S$: C, 57.13; H, 5.75; N, 6.66. Found: C, 57.16; H, 5.85; N, 6.59.

From the ether wash of the crystals above was obtained 0.110 g (0.8%) of another crystalline product, mp 160–161°. The nmr spectrum and elemental analysis of this compound also showed it to be a Δ^2 (*R*)-sulfoxide: ($CDCl_3$) δ 1.49 (9 H, s), 1.97 (3 H, s), 4.49 (2 H, s), 4.61 (1 H, s), 4.74 (1 H, d, J = 4 Hz), 5.55 (1 H, q, J = 4, 8 Hz), 6.17 (1 H, s), 6.8–7.5 (5 H, m), and 8.15 (1 H, d, J = 8 Hz).

Anal. Found: C, 57.30; H, 5.89; N, 6.71.

Both Δ^2-cephem sulfoxides, when dissolved in a hydroxylic solvent, were converted to the same Δ^3-cephem isomer produced by the performic acid oxidation cited below.

A. *p*-Methoxybenzyl 3-Acetoxymethyl-7-phenoxyacetamido-3-cephem-4-carboxylate 1-Oxide.—A mixture of Δ^2 and Δ^3 (1:3) isomers of *p*-methoxybenzyl 3-acetoxymethyl-7-phenoxyacetamidocephem-4-carboxylate (0.125 g) was dissolved in $CHCl_3$ (4 ml), cooled in ice, and stirred while 85% *m*-chloroperbenzoic acid (0.04 g) in $CHCl_3$ (2 ml) was added dropwise. After 4 hr the reaction mixture was washed with saturated $NaHCO_3$ and saturated NaCl. The organic solution was dried over $MgSO_4$, filtered, and evaporated *in vacuo* to give 0.127 g of product. This crystallized from CH_3OH to give 0.095 g (75% yield) of isomerically pure Δ^3-cephem sulfoxide: mp 161–163°; nmr (DMSO-d_6) δ 2.0 (3 H, s), 3.75 (3 H, s), 3.60, 4.05 (2 H, q, J = 16 Hz), 4.7 (2 H, s), 4.68, 5.10 (2 H, q, J = 12 Hz), 5.25 (2 H, s), 6.0 (1 H, d, J = 4 Hz), 6.10 (1 H, q, J = 4, 10 Hz), 6.8–7.5 (5 H, m), and 8.20 (1 H, d, J = 10 Hz).

Anal. Calcd for $C_{26}H_{26}N_2O_6S$: C, 57.55; H, 4.83; N, 5.16. Found: C, 57.88; H, 5.14; N, 5.06.

B. *t*-Butyl 3-Methyl-7-phenoxyacetamido-3-cephem-4-carboxylate 1-Oxide (Performic Acid as Oxidant).—A cooled (in ice) solution of 0.400 g of *t*-butyl 3-methyl-7-phenoxyacetamido-2-cephem-4-carboxylate in 20 ml of CH_2Cl_2 was stirred while 5 ml of AcOH containing 0.2 ml of 30% H_2O_2 was added dropwise. When the addition was complete, the reaction mixture was washed with H_2O and then with saturated $NaHCO_3$. The organic solution was dried over Na_2SO_4 and evaporated to dryness to give 0.32 g (77% yield) of the sulfoxide: nmr ($CDCl_3$) δ 1.51 (9 H, s), 2.10 (3 H, s), 3.23, 3.58 (2 H, q, J = 19 Hz), 4.5 (3 H, s + d, J = 4 Hz), 6.0 (1 H, q, J = 10 Hz), 6.8–7.4 (5 H, m), and 7.9 (1 H, d, J = 10 Hz).

C. *t*-Butyl 3-Methyl-7-phenoxyacetamido-3-cephem-4-carboxylate 1-Oxide (Periodic Acid as Oxidant).—A solution of 0.200 g of *t*-butyl 3-methyl-7-phenoxyacetamido-2-cephem-4-carboxylate in 20 ml of Et_2O was stirred at 25° and titrated with a solution of periodic acid in Et_2O. No starting material was evident by tlc. The reaction mixture was washed successively with water and 10% $NaHCO_3$ and dried over Na_2SO_4. Evaporation of solvent gave 0.196 g of crude product which was then equilibrated ($\Delta^2 \rightarrow \Delta^3$) in CH_3OH. Nmr of the equilibrated sulfoxide was identical with that of the Δ^3-cephem sulfoxide produced above.

D. 2,2,2-Trichloroethyl 3-Methyl-7-phenoxyacetamido-3-cephem-4-carboxylate 1-Oxide.—2,2,2-Trichloroethyl 3-methyl-7-phenoxyacetamido-3-cephem 4-carboxylate (1.61 g, 3.4 mmol) in glacial AcOH (10 ml) was cooled to the freezing point, and a

(8) E. Jonsson, *Tetrahedron Lett.*, 3675 (1967).
(9) S. Allenmark, *Acta Chem. Scand.*, **20**, 910 (1966).
(10) Reference 4, mp 120–123°.

solution of 30% H_2O_2 (0.76 g, 6.7 mmol) in glacial AcOH (5 ml) was added. The reaction mixture was stirred overnight, and the solvent was removed *in vacuo*. The residue was dissolved in CH_2Cl_2 and washed twice with H_2O and once with 5% $NaHCO_3$, dried over Na_2SO_4, filtered, and evaporated to dryness to give 1.50 g of a yellow foam. Tlc showed the presence of three components, none of which was starting material. The crude product was chromatographed over silica gel (60 g) using a linear 100% benzene → 100% EtOAc gradient. The fractions were pooled according to purity as determined by tlc. The major component (0.900 g) was crystallized from acetone–ether yielding 0.620 g (38%) of (*S*)-sulfoxide: mp 176–178° dec; uv_{max} (EtOH) 216 mμ (ε 3000), 264 (sh), 268 (9350), 273 (sh); ir ($CHCl_3$) 1790, 1730, 1680, and 1040 cm^{-1}; nmr (DMSO-d_6) δ 2.13 (3 H, s), 3.74, 3.96 (2 H, t, J = 19 Hz), 4.70 (2 H, s), 5.04 (1 H, d, J = 5 Hz), 5.05, 5.17 (2 H, t, J = 12 Hz), 6.04 (1 H, q, J = 5, 10 Hz), 6.8–7.5 (5 H, m), 8.18 (1 H, d, J = 10 Hz).

Anal. Calcd for $C_{18}H_{17}Cl_3N_2O_6S$: C, 43.61; H, 3.46; Cl, 21.46; N, 5.81; S, 6.47. Found: C, 44.23; H, 4.02; Cl, 21.63; N, 5.65; S, 6.55.

A second component crystallized from acetone to give the (*R*)-sulfoxide (0.090 g, 0.5%) as prisms: mp 186–187°; uv_{max} (EtOH) quartet 217, 263 (sh), 267, and 274 (sh) mμ; ir ($CHCl_3$) 1780, 1730, 1630, and 1040 cm^{-1}; nmr (DMSO-d_6) δ 2.19 (3 H, d), 3.75, 4.19 (2 H, q, J = 16.5 Hz), 4.63 (2 H, s), 4.78 (1 H, d, J = 5 Hz), 5.08 (2 H, s), 5.65 (1 H, q, J = 5, 8 Hz), 6.8–7.5 (5 H, m), 9.32 (1 H, d, J = 8 Hz).

Anal. Found: C, 43.66; H, 3.66; Cl, 21.39; N, 5.70; S, 6.38.

Reducing Agent without External Activation. Phosphorus Trichloride.—(*S*)-2,2,2-Trichloroethyl 3-methyl-7-phenoxyacetamido-3-cephem-4-carboxylate 1-oxide (2.00 g, 4.03 mmol) was dissolved in CH_2Cl_2 (100 ml) containing PCl_3 (3.2 g, 22 mmol). The solution was heated under reflux for 2.5 hr. After cooling to room temperature, the reaction was neutralized with a saturated solution of aqueous $NaHCO_3$, washed with H_2O, and dried over $MgSO_4$. Removal of solvent *in vacuo* yielded 1.65 g (85%) of reduced material, which crystallized from hot *i*-PrOH, mp 115–117°. The nmr, ir, and uv spectra and elemental analysis of the product were identical with those of an authentic sample of 2,2,2-trichloroethyl 3-methyl-7-phenoxyacetamido-3-cephem-4-carboxylate.

Cationic Reducing Agent. Stannous Chloride.—(*S*)-2,2,2-Trichloroethyl 3-acetoxymethyl-7-(2-thienylacetamido)-3-cephem-4-carboxylate 1-oxide (2.0 g, 3.7 mmol) was dissolved in CH_3CN (15 ml) and DMF (6 ml) and stirred at 0°. Stannous chloride (624 mg, 4.04 mmol) and AcCl (1.2 g, 1.54 mmol) were added. This mixture was stirred at 0° for 1 hr and then at room temperature for an additional hour. The CH_3CN was removed *in vacuo;* the residue was poured into H_2O and extracted into EtOAc. The organic solution was washed with 3% HCl solution, 5% $NaHCO_3$ solution, and then with H_2O. After drying over Na_2SO_4, the solvent was removed to give 1.9 g (98%) of product which crystallized from hot *i*-PrOH, mp 120–122°, and was identical in all respects with authentic 2,2,2-trichloroethyl 3-acetoxymethyl-7-(2-thienylacetamido)-3-cephem-4-carboxylate.

Registry No.—2,2,2-Trichloroethyl 3-methyl-7-phenoxyacetamido-3-cephem-4-carboxylate, 24647-47-0; 2,2,2-trichloroethyl 3-acetoxymethyl-7-(2-thienylacetamido)-3-cephem-4-carboxylate, 5317-29-3; *t*-butyl 3-methyl-7-phenoxyacetamido-2-cephem-4-carboxylate 1-oxide (*S*), 24647-49-2; *t*-butyl 3-methyl-7-phenoxyacetamido-2-cephem-4-carboxylate 1-oxide (*R*), 24647-50-5; *p*-methoxybenzyl 3-acetoxymethyl-7-phenoxyacetamido-3-cephem-4-carboxylate 1-oxide, 24670-41-5; *t*-butyl 3-methyl-7-phenoxyacetamido-3-cephem-4-carboxylate 1-oxide, 24647-51-6; 2,2,2-trichloroethyl 3-methyl-7-phenoxyacetamido-3-cephem-4-carboxylate 1-oxide (*S*), 24689-52-9; 2,2,2-trichloroethyl 3-methyl-7-phenoxyacetamido-3-cephem-4-carboxylate 1-oxide (*R*), 24689-53-0.

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A Novel Diaryl Ether, LL-V125α, from a Fungus of the Order Sphaeropsidales

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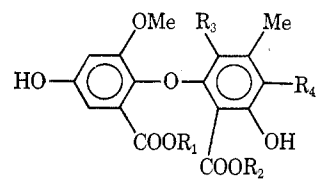
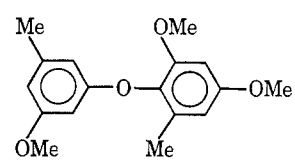
Diaryl ethers have been isolated from plants[1] and sea sponges.[2] To our knowledge the only microbial metabolite of this type isolated so far is asterric acid, I.[3] The closely related compounds, erdin hydrate, II, and geodin hydrate, III, have been obtained by chemical conversion of natural products[4] and the elaboration of III by mutants of *Aspergillus terreus* has been demonstrated.[5] Diphenyl ethers have been obtained as



I, $R_1 = CH_3$; $R_2 = R_3 = R_4 = H$
II, $R_1 = R_2 = R_3 = R_4 = H$
III, $R_1 = CH_3$; $R_2 = H$; $R_3 = R_4 = Cl$

breakdown products from *Lichen depsidones*[6,7] and, in particular, one such compound was characterized as the trimethyl ether of alectol, IV. We have isolated



IV

the novel metabolite, 5′-methoxy-5,6′-oxydi-*m*-cresol (V), from a fungus of the order Sphaeropsidales (Lederle culture V125). By *in vitro* testing V had weak antifungal activity.

Compound V has the formula $C_{15}H_{16}O_4$ (*m/e* 260). The nmr spectrum of V in $CDCl_3$ shows sharp, three-proton singlets at δ 2.05 and 2.20 (2 CH_3, aromatic) and 3.75 (OCH_3, aromatic), two broad one-proton exchangeable singlets at 5.20 and 4.57 (2 H, phenolic),

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