Synthesis of 2-, 4-, and 7-Methylthio-Substituted Cephalosporins[1]

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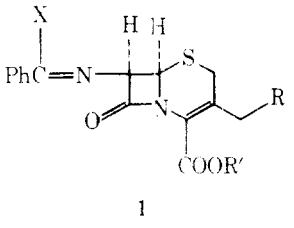
Methylthiolation of various 7-substituted cephalosporins in the presence of lithium amide bases proceeded stereospecifically (7-imino ether, 7-[(triphenylmethyl)amino], or 7-phthalimido) or stereoselectively (7-amido) to give 4β-(methylthio) derivatives. Methylthiolation of 7-imino, 7-imino chloride, or 7-imino ether cephalosporins using KO-*t*-Bu afforded 7α substitution or 7α and 4β, 7α substitution depending upon substituents at C-3, C-4, and C-7. Methylthiolation of 7-(tritylamino)- and 7-phthalimidocephalosporins using KO-*t*-Bu proceeded stereospecifically to give 4β-(methylthio)cephems, although epimerization at C-7 accompanied thiolation in the case of phthalimido. Methylthiolation of 7-amidocephalosporin *S*-sulfoxides proceeded regiospecifically to give 2α substitution which was sometimes accompanied by 2,2-disubstitution. These various 2-, 4-, and 7-methylthiolated cephems were converted to corresponding 7-amidocephalosporanic acid derivatives. Attempted removal of ester protecting groups from 4-(methylthio)-Δ^2-cephems using CF_3COOH gave allylically rearranged products, 2α-(methylthio)cephalosporanic acids.

We previously reported the regiospecific methylthiolation of Schiff bases **1a** and **1b** that afforded the 7α-(methylthio)cephalosporins **2a** and **2b,** respectively, which served as intermediates to various 7-(methylthio)- and 7-methoxycephalosporanic acids.[2] We now report details of regiospecific methylthiolations of the cephem nucleus that have led to 2-, 4-, and 7-methylthio-substituted cephems which we have used to prepare 2-, 4-, and 7-methoxycephalosporin intermediates,[2] 2-, 4-, and 7-(methylthio)cephalosporanic acids, and mercury mercaptide azetidinone intermediates.[3]

7-Methylthiolation of the Cephem Nucleus. Methylthiolation of Schiff bases **1a** and **1b** with 1 equiv each of KO-*t*-Bu and methylmethanethiol sulfonate ($MsSCH_3$) afforded exclusively the 7α-methylthiolation products **2a** and **2b,** respectively, as already described.[2,4] Methylthiolation of imino ether **1c** under identical conditions provided the 7α-methylthiolated product **2c,** although in low yield (13%), and starting material.[5] On the other hand, similar treatment of the 3′-acetoxy derivative **1d** afforded both the 7α- and 4β, 7α-disubstituted products **2d** (14%) and **3d** (6%), respectively, in addition to starting material.[5] Finally, methylthiolation of imino chloride **1f,** using the same conditions, smoothly gave the 7α-substituted product **2f** (60%) in addition to starting material.[5,14] Thus, methylthiolation of cephems with Schiff base, imino chloride, or imino ether moieties at C-7 always resulted in substitution at C-7, although concomitant 4,7-disubstitution occurred depending upon the substituents at C-3.



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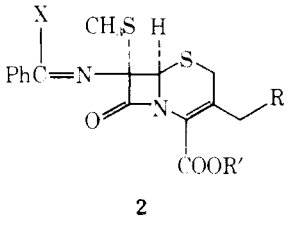

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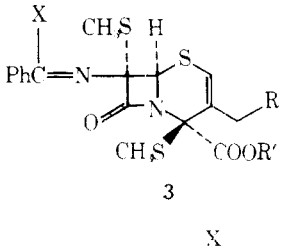

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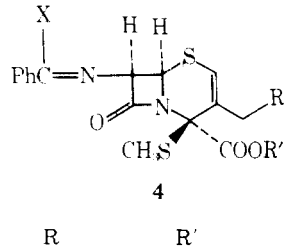
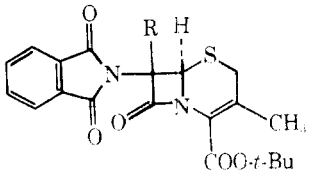
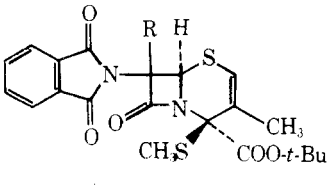


4

	X	R	R′
a	H	H	*t*-Bu
b	H	OAc	*t*-Bu
c	OCH_3	H	*t*-Bu
d	OCH_3	OAc	*t*-Bu
e	OCH_3	H	TCE[a]
f	Cl	H	*t*-Bu



5a, R = α-H
b, R = β-H

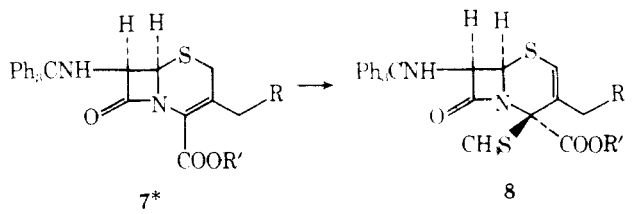


6a, R = α-H
b, R = β-H

[a] TCE = CH_2CCl_3

4-Methylthiolation of the Cephem Nucleus. In contrast to methylthiolations of imino ethers with 1 equiv of KO-*t*-Bu, which always resulted in 7α-methylthiolated products, methylthiolation of imino ethers **1d,e** with 1 equiv of lithium *N*-cyclohexylisopropylamide (LCIA) and $MsSCH_3$ gave exclusively the 4β-substituted products **4d,e** in yields of 35 and 53%, respectively. Methylthiolation of the 7β-phthalimido derivative **5a** with KO-*t*-Bu also proceeded regiospecifically providing a separable mixture containing **6a** (30%) and recovered **5a** (39%), and their respective C-7 epimers, **6b** (9%) and **5b** (6%), due to accompanying epimerization at C-7. When (triphenylmethyl)lithium was used as base, epimerization was reduced and yields were increased, giving **6a** (58%), **5a** (15%), **6b** (12%), and **5b** (2%).[7,8] Additionally, methylthiolation of the 7α-(methylthio) Schiff base **2b**[2] with KO-*t*-Bu afforded the 4β,7α-bis(methylthio) Schiff base **3b** in 90% yield.

A more facile synthesis of 4β-methylthiocephems, that avoids epimerization at C-7, was provided by methylthiolation of 7β-[(triphenylmethyl)amino] derivatives **7**.[9] Methylthiolation of **7a,b** with LCIA and $MsSCH_3$ proceeded regiospecifically and stereospecifically to give the 4β-(methylthio) derivatives **8a,b** in 90 and 62%, respectively.



7*

8

a, R = H; R′ = TCE
b, R = OAc; R′ = *t*-Bu
*7a = Δ^3-Δ^2 cephem mixture

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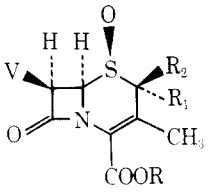
Table I. Proton Resonance Shifts (Δ_{SO}) Induced by Sulfoxide Bond[a]



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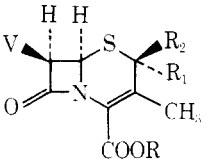
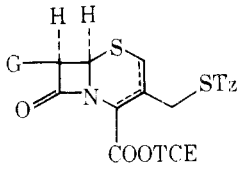


25

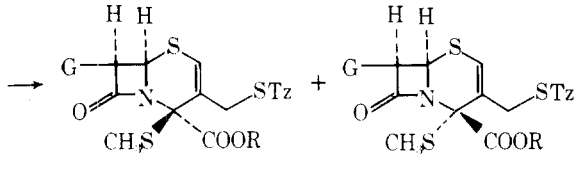
	R	R_1	R_2	R_1 (α)	R_2 (β)	H_6	H_7
a	CH_3	SCH_3	H	+0.11 (SCH_3)	−0.12 (H)	+0.41	−0.21
b[12b]	TCE	CH_3	H	+0.25 (CH_3)	−0.14 (H)	+0.58	−0.26
c[12b]	TCE	H	CH_3	+0.39 (H)	−0.33 (CH_3)	+0.45	−0.37

[a] $\Delta_{SO} = \delta_{(S)} - \delta_{(S-O)}$ ($DCCl_3$).

Finally, methylthiolation of the 7β-amidocephem **9** with LCIA and $MsSCH_3$ gave, in 22% yield, a mixture of 4α and 4β epimers **10** and **11**, respectively. Similar results were obtained with KO-*t*-Bu as base. The identification of **10** and **11** as 4-substituted derivatives was facilitated by spectral comparisons with 2-substituted cephems **16e** and **12**, which were obtained by methylthiolation of cephem sulfoxides as outlined in the following section. The major epimer **10** was isolated as a pure substance, whereas the minor epimer **11** was obtained as a mixture (1:1) of **10** and **11**. The assignment of stereochemistry to these methylthiolation products is discussed below.

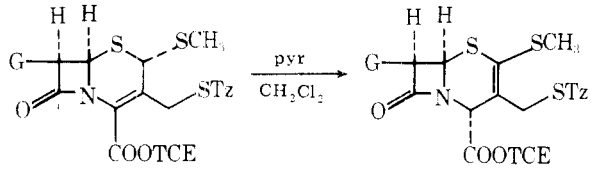


9

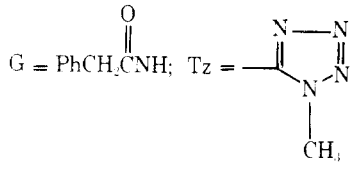


10 11

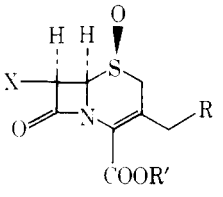
a, R = TCE
b, R = H
c, R = K



16e 12



2-Methylthiolation of the Cephem Nucleus. Regiospecific substitution at C-2 was easily accomplished via electrophilic substitution of *S*-sulfoxide derivatives. Thus, methylthiolation of **13a** with KO-*t*-Bu and $MsSCH_3$ gave a mixture of 2α-(methylthio) sulfoxide **14a** (44%) and 2,2-bis(methylthio) sulfoxide **15a** (26%).[7,10] In some cases, single products were obtained in high yield as in the case of **13d**, wherein methylthiolation (KO-*t*-Bu–$MsSCH_3$) gave only the 2α-substituted derivative **14d** (90%). The C-2 substituted sulfoxides were readily reduced (PBr_3–DMF) to the corresponding sulfides. These results parallel those of Yoshida et al. for similar sulfoxides.[11]



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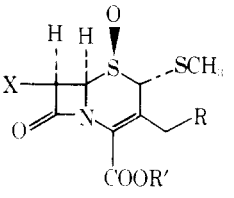

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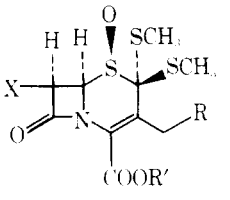

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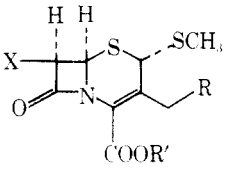

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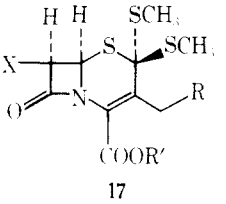
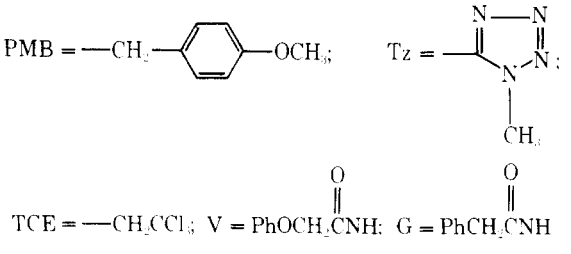


17

	X	R	R′
a	V	H	CH_3
b	V	H	PMB
c	G	OAc	PMB
d	G	STz	Ph_2CH
e	G	STz	TCE

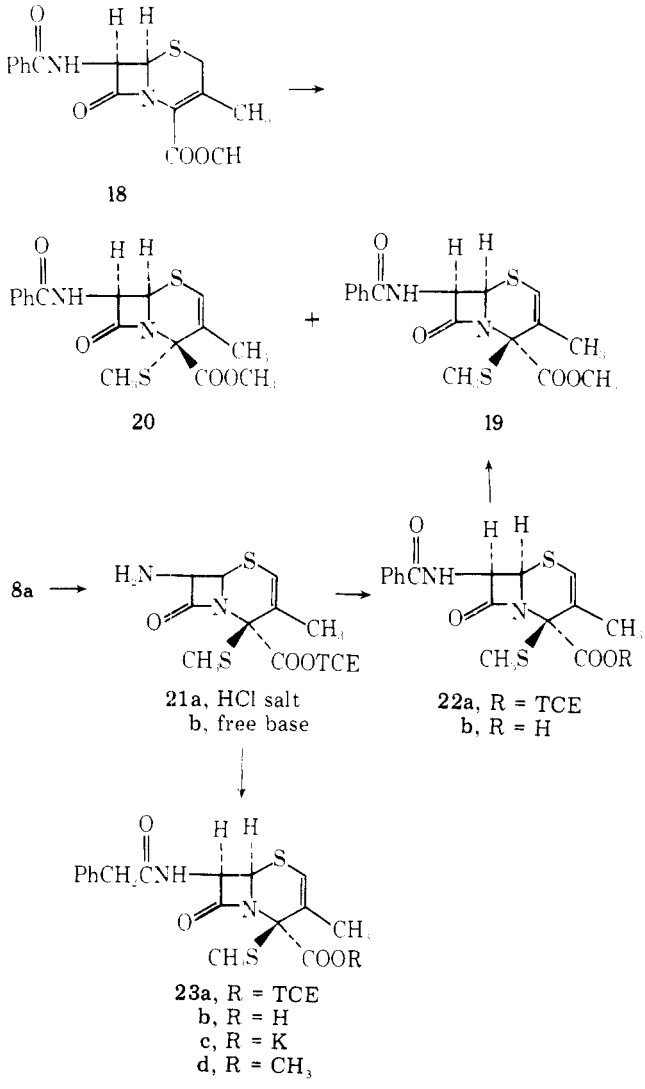


Stereochemistry at C-4. Yoshida and co-workers have assigned structures **19** and **20** to the 4-substituted epimers derived from methylthiolation of the 7-(acylamino)cephalosporin **18**.[11] We have correlated the single 4-methylthio epimer, obtained via 7-imino ether or 7-[(triphenylmethyl)-amino] derivatives, with the major epimer **19** prepared by Yoshida et al. Thus, amine hydrochloride **21a**, obtained by methylthiolation of 7-[(triphenylmethyl)amino]cephem **7a**

Table II. Proton Resonance Chemical Shifts and Benzene Induced Chemical Shifts of 24a and 25a

compd	solvent	H_7	H_6	H_2	SCH_3	CH_3	OCH_3
25a	$CDCl_3$	5.98	5.34	4.34	2.25	2.22	3.84
25a	C_6D_6	5.76	5.00	3.68	1.70	2.11	3.52
Δ_S = ASIS ($\delta_{CDCl_3-C_6D_6}$)		+0.22	+0.34	+0.66	+0.55	+0.11	+0.32
24a	$CDCl_3$	6.19	4.93	4.22	2.36	2.30	3.89
24a	C_6D_6	6.04	4.09	3.47	1.40	2.00	3.48
$\Delta_{S\rightarrow O}$ = ASIS ($\delta_{CDCl_3-C_6D_6}$)		+0.15	+0.84	+0.75	+0.96	+0.30	+0.41
Net ASIS ($\Delta_{S\rightarrow O} - \Delta_S$)		−0.07	+0.50	+0.09	+0.41	+0.19	+0.09

and subsequent hydrolysis, was converted via **22a** and **22b** to **19**, which was found to be identical with an authentic sample prepared as described by Yoshida et al. Additionally, the 7-(phenylacetamido) derivative **23a**, obtained by acylation of **21a**, was found to be identical with the derivative obtained by phenylacetylation of the 4-(methylthio)imino ether **4e**. We have also performed europium shift reagent studies on **23d**, the 7-(phenylacetamido) derivative of **19**, and our findings[3a] completely parallel those reported by Yoshida et al. for **19**.



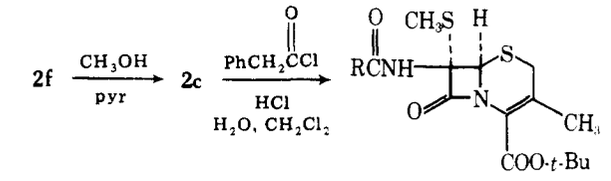
Therefore, methylthiolation of various 7-substituted deacetoxycephalosporins, in the presence of lithium bases, proceeded either stereospecifically (7-imino ether, 7-[(triphenylmethyl)amino], or 7-phthalimido) or stereoselectively (7-amido) to give 4β-(methylthio) derivatives. By analogy with these results, and on the basis of ^1H NMR considerations, we have assigned 4β-stereochemistry to the single 4-(methylthio) epimers obtained via 7-imino ether or 7-[(triphenylmethyl)-amino]cephems having an acetoxymethyl group at the 3 position. Similarly, we have tentatively assigned 4β-stereochemistry (structure **10**) to the *major* methylthio epimer obtained from the 7-amido-3-[(*N'*-methyltetrazolylthio)-methyl]cephem derivative **9**.

Stereochemistry at C-2. We have assigned 2α-(methylthio) stereochemistry to sulfoxides **14** and sulfides **16** on the basis of ^1H NMR studies.[7,12] The shielding of methylthio and C-6 protons and deshielding of C-2 and C-7 protons for the process sulfoxide → sulfide (**24a** → **25a**, Table I)[13] are similar to perturbation shifts (Δ_{SO}) observed for the 2α-sulfoxide–2α-sulfide pair **24b** → **25b** and, therefore, consistent with a 2α-(methylthio) assignment in **24a**. Net ASIS values for sulfoxide **24a** obtained in $DCCl_3$ and $DCCl_3$–benzene-d_6 are given in Table II. Upfield shifts for the methylthio and C-6 protons and a downfield shift for the C-7 proton are again consistent with assignment of α-(methylthio) configuration at C-2 in **24a**.

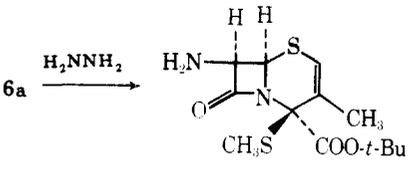
Conversion to 2-, 4-, and 7-(Methylthio)-7-amidocephalosporanic Acids. The Schiff bases and imino ethers of structure **2** could all be acylated directly (acid chloride, H_2O, CH_2Cl_2) to afford 7-(acylamino)-7α-methylthiolated cephems.[2,5] Imino chlorides of structure **2** could be converted to the same amides after conversion to imino ethers (pyridine–CH_3OH) and acylation. In the case of imino ethers, competing hydrolysis to 7β-benzamido compounds occurred. For example, acylation of **2c** with phenylacetyl chloride provided **26a** (23%) and **26b** (26%). Similarly, the 4β-(methylthio)imino ethers **4** could be acylated directly in 40–60% yield; however, these products were also accompanied by the 7β-benzamido analogue, for example **23a** (51%) and **22a** (27%) from **4e**. 7β-Phthalimido-(**6a**) or 7-[(triphenylmethyl)-amino]-4β-(methylthio)cephems (**8a**) are converted via the parent 7β-amino-4β-(methylthio)cephem (**21a** or **27**) to acylated derivatives in the usual manner.

The ester protecting groups of the 4β-(methylthio)cephems could be removed under basic conditions only. Treatment of 4β-(methylthio)trichloroethyl esters with 1 equiv of NaOH in aqueous dioxane gave the acids in high yield. When the *tert*-butyl ester **28** was treated with CF_3COOH–anisole, the 2α-(methylthio)cephem **29**, resulting from deesterification and allylic rearrangement, was isolated. This acid was found to be identical with material prepared by 2α-methylthiolation of the sulfoxide **13b**, deesterification to **30**, and reduction.[7] Acid-labile protecting groups (benzhydryl, *p*-methoxybenzyl, *tert*-butyl) were removed from 2α-(methylthio)cephems using combinations of CF_3COOH–anisole and solvents such as CH_2Cl_2 or benzene.

Biological Activity. The free acids or salts of selected 2α- and 4β-(methylthio)cephems were evaluated in vitro against a variety of bacteria. Some of the 2α-(methylthio)cephems



26a, R = $PhCH_2$–
b, R = Ph–



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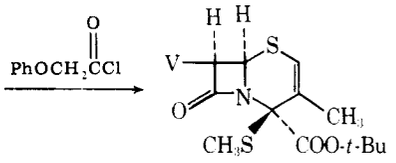

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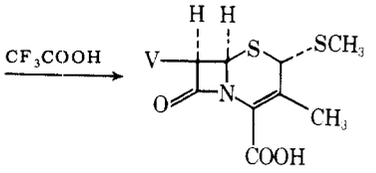

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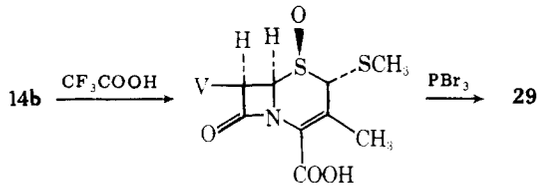

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were as active or slightly more active than the parent unsubstituted molecules against gram-positive bacteria; the same compounds were much less active than the parent molecule against gram-negative bacteria. The 4-(methylthio)cephems were less active than the corresponding 2-(methylthio) Δ^3-compounds.

Experimental Section

The ^1H NMR spectra were obtained on Varian nuclear magnetic resonance spectrometers (Models T-60 and XL-100-15), and the infrared spectra were recorded on Perkin-Elmer spectrometers (Models 257 and 621). Mass spectra were obtained from an AEI-M S-902 mass spectrometer. Melting points are not corrected.

General Preparation of Imino Ethers Used for Methylthiolations. A mixture of the 7-aminocephem ester (0.10 mol), trimethyl orthobenzoate (0.10 mol), and *p*-toluenesulfonic acid monohydrate (50 mg) in dry benzene (450 mL) was refluxed under N_2 for 5 h during which time 300 mL of benzene was removed by distillation and fresh benzene was added to maintain the volume of the mixture at 400 mL. The mixture was washed sequentially with dilute aqueous $NaHCO_3$ (pH 7.6), dilute HCl (pH 2), and water, dried (Na_2SO_4), and evaporated in vacuo to a residue, which was crystallized to give the desired imino ether cephem.

***tert*-Butyl 7β-[(methoxyphenylmethylene)amino]-3-methyl-Δ³-cephem-4-carboxylate (1c):** 91% from *tert*-butyl 7-aminodeacetoxycephalosporanate; mp 105–106 °C (acetone–hexane); ^1H NMR ($DCCl_3$) δ 3.87 (3 H, s, OCH_3), 4.88 (1 H, d, J = 5 Hz, C-6), 5.17 (1 H, d, J = 5 Hz, C-7); IR ($CHCl_3$) 1780, 1720, 1655 cm^{-1}. Anal. Calcd for $C_{20}H_{24}N_2O_4S$: C, 61.84; H, 6.23; N, 7.21; S, 8.24. Found: C, 61.73; H, 6.38; N, 7.03; S, 7.99.

***tert*-Butyl 7β-[(methoxyphenylmethylene)amino]-3-[(acetyloxy)methyl]-Δ³-cephem-4-carboxylate (1d):** 53% from *tert*-butyl 7-aminocephalosporanate; mp 143–144 °C (acetone–hexane); ^1H NMR ($DCCl_3$) δ 3.90 (3 H, s, OCH_3), 4.95 (1 H, d, J = 4 Hz, C-6), 5.23 (1 H, d, J = 4 Hz, C-7); I R ($CHCl_3$) 1780, 1740 (sh), 1725, 1650 cm^{-1}. Anal. Calcd for $C_{22}H_{26}N_2O_6S$: C, 59.18; H, 5.87; N, 6.28. Found: C, 59.18; H, 5.91; N, 6.13.

2,2,2-Trichloroethyl 7β-[(methoxyphenylmethylene)amino]-3-methyl-Δ³-cephem-4-carboxylate (1e): 74% from 2,2,2-trichloroethyl 7-aminodeacetoxycephalosporanate; mp 133–135.5 °C (Et_2O); ^1H NMR ($DCCl_3$) δ 3.90 (3 H, s, OCH_3), 4.97 (1 H, d, J = 5 Hz, C-6), 5.22 (1 H, d, J = 5 Hz, C-7); IR ($CHCl_3$) 1780, 1738, 1650 cm^{-1}. Anal. Calcd for $C_{18}H_{17}N_2O_4SCl_3$: C, 46.62; H, 3.70; N, 6.04; Cl, 22.93. Found: C, 46.60; H, 3.63; N, 5.94; Cl, 23.20.

***tert*-Butyl 7β-[(Chlorophenylmethylene)amino]-3-methyl-Δ³-cephem-4-carboxylate (1f).** To a stirred solution of 5.03 g (13.5 mmol) of *tert*-butyl 7β-benzamidodeacetoxycephalosporanate and 2.43 mL (11.2 mmol) of *N,N*-diethylaniline in 50 mL of dry CH_2Cl_2 at −30 °C under N_2 was added 4.07 g (19.6 mmol) of PCl_5. After stirring for 1.5 h, the mixture was poured into ice–pH 6.6 buffer, and the CH_2Cl_2 layer was dried (Na_2SO_4) and evaporated to a residue, which was taken up in benzene. The benzene solution was washed with H_2O, dried (Na_2SO_4), decolorized with Norite, and evaporated to a yellow oil, which crystallized (hexane–Et_2O–CH_2Cl_2) to give 3.50 g (66%) of **1f**: mp 127–128 °C dec; ^1H NMR ($DCCl_3$) δ 5.12 (1 H, d, J = 5 Hz, C-6), 5.75 (1 H, d, J = 5 Hz, C-7); IR ($CHCl_3$) 1785, 1720, 1650 cm^{-1}. Anal. Calcd for $C_{19}H_{21}N_2O_3SCl$: C, 58.09; H, 5.39; N, 7.13. Found: C, 57.94; H, 5.32; N, 7.01.

General Preparation of [*N*-(Triphenylmethyl)amino]cephems for Methylthiolation. A mixture of the 7-aminocephem ester (0.040 mol), triphenylmethyl chloride (0.040 mol), and Et_3N or *N,N*-diisopropylethylamine (0.040 mol) in dry CH_2Cl_2 (150 mL) was stirred at 25 °C under N_2 for 4 h and then washed with water, dried (Na_2SO_4), and evaporated in vacuo to a residue which was chromatographed on silica gel to give the desired product as a foam.

2,2,2-Trichloroethyl 7β-[(triphenylmethyl)amino]deacetoxycephalosporanate (7a) (Δ²–Δ³ isomer mixture): 83% from 2,2,2-trichloroethyl 7-aminodeacetoxycephalosporanate using Et_3N; ^1H NMR ($DCCl_3$) δ 1.87 (br s, Δ^2 C-3 CH_3), 2.18 (s, Δ^3 C-3 CH_3), 2.8–3.4 (m, Δ^3 C-2 and NH), 4.2–5.2 [complex: 4.88 (q, J = 12 Hz, Δ^3 CH_2CCl_3); 4.7 (br s, Δ^2 CH_2CCl_3, C-7 and C-6)], 5.80 (br s, Δ^2 C-2), 7.1–7.7 (aromatics).

***tert*-Butyl 7β-[(triphenylmethyl)amino]cephalosporanate (7b):** 72% from *tert*-butyl 7-aminocephalosporanate using *N,N*-diisopropylethylamine; ^1H NMR ($DCCl_3$) δ 3.08, 3.42 (2 H, q, J = 18 Hz, C-2), 4.25 (1 H, d, J = 5 Hz, C-6), 4.67 (1 H, m, C-7), 4.70, 5.02 (2 H, q, J = 14 Hz, C-3 CH_2); IR ($CHCl_3$) 1785, 1740, 1725 cm^{-1}.

Δ²–Δ³ Cephem Isomer Mixture 9. A mixture of 7.6 g (17 mmol) of 3-[(1-methyl-1*H*-tetrazol-5-yl)thiomethyl]-7β-(phenylacetamido)-Δ³-cephem-4-carboxylic acid, 2.06 mL (25.6 mmol) of pyridine, 1.66 mL (17 mmol) of 2,2,2-trichloroethanol, and 3.86 g (18.7 mmol) of *N,N'*-dicyclohexylcarbodiimide in 80 mL of dry dimethoxyethane was stirred at 25 °C for 18 h. The crystalline urea was removed by filtration, and the filtrate was evaporated to a residue, which was taken up in EtOAc, and washed successively with H_2O, dilute HCl, H_2O, dilute $NaHCO_3$, and H_2O. The EtOAc layer was dried (Na_2SO_4) and evaporated to a residue, which was purified by chromatography on silica gel using $CHCl_3$ to give 3.12 g (32%) of Δ²–Δ³ isomers **9** as a foam: ^1H NMR ($DCCl_3$) Δ^2 isomer δ 3.92 (3 H, s, NCH_3), 4.07, 4.38 (2 H, q, J = 14 Hz, C-3 CH_2), 5.27 (1 H, d, J = 4.5 Hz, C-6), 5.33 (1 H, br s, C-4), 5.55, 5.70 (1 H, q, J = 4.5, 8 Hz, C-7), 6.57 (1 H, br s, C-2); Δ^3 isomer δ 3.75 (2 H, br s, C-2), 3.92 (3 H, s, NCH_3), 4.27, 4.62 (2 H, q, J = 14 Hz, C-3 CH_2), 5.03 (1 H, d, J = 4.5 Hz, C-6), 5.83, 5.98 (1 H, q, J = 4.5, 8.5 Hz, C-7).

General Procedure for Preparation of Sulfoxides. A solution of *m*-chloroperbenzoic acid (8 mmol) in 40 mL of dry CH_2Cl_2 was added dropwise over 10 min to a stirred solution of 8 mmol of the cephem sulfide in 100 mL of CH_2Cl_2 under N_2. The reaction was complete after stirring at room temperature for 1–2 h. The mixture was washed with dilute aqueous $NaHCO_3$ solution and then saturated NaCl solution, dried (Na_2SO_4), and evaporated to a residue, which was purified by chromatography to give the desired product.

Sulfoxide 13d: 72% as a foam from diphenylmethyl 7β-(phenylacetamido)-3-[(1-methyl-1*H*-tetrazol-5-yl)thiomethyl]-Δ³-cephem-4-carboxylate after dry column chromatography on silica gel using EtOAc–$CHCl_3$ (8:1); ^1H NMR ($DCCl_3$) δ 3.37 (1 H, q, J = 2, 19 Hz, C-2α), 4.03 (1 H, d, J = 19 Hz, C-2β), 3.58 (2 H, s, $ArCH_2$–), 3.73 (3 H, s, NCH_3), 4.07, 4.45 (2 H, q, J = 14 Hz, C-3 CH_2), 4.38 (1 H, q, J = 2, 5 Hz, C-6), 6.02 (1 H, q, J = 5, 9 Hz, C-7).

Sulfoxide 13e: 72% from **9** after preparative TLC on silica gel using

EtOAc–$CHCl_3$ (2:1); mp 169–170 °C (acetone–hexane); ^1H NMR ($DCCl_3$) δ 3.51 (1 H, q, J = 2, 19 Hz, C-2α), 4.15 (1 H, d, J = 19 Hz, C-2β), 4.20, 4.70 (2 H, q, J = 14 Hz C-3 CH_2), 4.85, 5.15 (2 H, q, J = 12 Hz, CH_2CCl_3), 4.57 (1 H, q, J = 2, 5 Hz, C-6), 6.10 (1 H, q, J = 4, 9 Hz, C-7); IR ($CHCl_3$) 1810, 1742, 1690 cm^{-1}. Anal. Calcd for $C_{20}H_{19}N_6O_5S_2Cl_3$: C, 40.45; H, 3.23; N, 14.16. Found: C, 40.69; H, 2.93; N, 14.04.

7β-Phthalimido-Δ³-cephem 5a. To a solution of *tert*-butyl 7-aminodeacetoxycephalosporanate (11.3 g, 42 mmol) in 300 mL of dry CH_2Cl_2 was added phthalic anhydride (6.20 g, 42 mmol) followed by triethylamine (3.82 g, 38.2 mmol). After stirring under N_2 for 2 h, acetic anhydride (107 g, 105 mmol) was added, and the mixture was stirred for 16 h. The mixture was then diluted with $CHCl_3$ and washed sequentially with dilute HCl, H_2O, dilute $NaHCO_3$ solution, and saturated NaCl solution. After drying and evaporating to a crystalline mass, treatment with CH_3OH gave 12.72 g (76%) of **5a:** mp 197–199 °C dec; ^1H NMR ($DCCl_3$) δ 2.27 (1 H, s, C-3 CH_3), 3.05, 3.65 (2 H, q, J = 16 Hz, C-2), 5.12 (1 H, d, J = 5 Hz, C-6), 5.77 (1 H, d, J = 5 Hz, C-7). Recrystallization from EtOH gave an analytical sample of **5a,** mp 205–205.5 °C dec. Anal. Calcd for $C_{20}H_{20}N_2O_5S$: C, 59.99; H, 5.03; N, 7.00; S, 8.00. Found: C, 59.75; H, 5.09; N, 6.98; S, 7.85.

General Procedure for Methylthiolation of Schiff Bases, Imino Ethers, imino Chlorides, and Phthalimides using Potassium *tert*-Butoxide. Potassium *tert*-butoxide (1 equiv) was added to a stirred solution of 1 equiv of the Schiff base, imino ether, imino chloride, or phthalimide and 1 equiv of methylmethanethiol sulfonate in dry dimethoxyethane (DME) (10 mL/mmol of Schiff base) under N_2 at the stated temperature. The mixture was stirred for the indicated time and poured into $CHCl_3$ or EtOAc–pH 6.6 buffer–ice. The organic layer was washed with saturated NaCl solution, dried (Na_2SO_4), and evaporated to a residue, which was purified by chromatography on silica gel as indicated.

7α-(Methylthio) imino ether 2c from 1c: −50 °C; 30 min; TLC, benzene–EtOAc (19:1). **2c** (13%): ^1H NMR ($DCCl_3$) δ 2.08 (3 H, s, C-3 CH_3), 2.23 (3 H, s, SCH_3), 3.83 (3 H, s, OCH_3), 5.00 (1 H, s, C-6); IR ($CHCl_3$) 1780, 1720, 1650 cm^{-1}; mass spectrum *m/e* 434 (M^+), 377 (M − *t*-Bu), 238 (Ph − $C(OCH_3)$=N—$C(SCH_3)$=CHS^+).

7α-(Methylthio) imino ether 2d and 4β,7α-bis(methylthio) imino ether 3d from 1d: −50 °C; 30 min; TLC, benzene–EtOAc (19:1). **2d** (14%): ^1H NMR ($DCCl_3$) δ 2.25 (3 H, s, SCH_3), 3.87 (3 H, s, OCH_3), 4.77, 5.13 (2 H, q, J = 13 Hz, C-3 CH_2), 5.00 (1 H, s, C-6); IR ($CHCl_3$) 1785, 1730 (br), 1645 cm^{-1}; mass spectrum *m/e* 492 (M^+), 477, 464, 445, 435, 417, 238, 178 (base). **3d** (6%): ^1H NMR ($CDCl_3$) δ 2.00, 2.07, 2.32 (three 3 H singlets, 2 SCH_3 and 1 OAc), 3.83 (3 H, s, OCH_3), 5.28 (1 H, s, C-6), 6.77 (1 H, br s, C-2); IR ($CHCl_3$) 1778, 1738, 1650 cm^{-1}; mass spectrum *m/e* 538 (M^+).

7α-(Methylthio)imino chloride 2f from 1f: −70 °C; 30 min; no chromatography. **2f** (60%): ^1H NMR ($CDCl_3$) δ 2.13 (3 H, s, C-3 CH_3), 2.48 (3 H, s, SCH_3), 5.20 (1 H, s, C-6); IR ($CHCl_3$) 1780, 1720, 1640 cm^{-1}; mass spectrum *m/e* 438 and 440 (M^+), 381 (M − *t*-Bu), 242, 225, 207, 197, 196, 182, 57 (base).

4β,7α-Bis(methylthio) Schiff base 3b from 7α-(methylthio) Schiff base 2b:[2] −5 °C, 50 min. **3b** (90%) as a foam: mp 159–161 °C (Et_2O–CH_2Cl_2); ^1H NMR ($DCCl_3$) δ 2.00, 2.05, 2.30 (three 3 H singlets, OAc, 2SCH_3), 5.35 (1 H, s, C-6), 6.82 (1 H, s, C-2); IR ($CHCl_3$) 1775, 1735, 1625 cm^{-1}. Anal. Calcd for $C_{23}H_{28}N_2O_5S_3$: C, 54.31; H, 5.55; N, 5.51. Found: C, 54.08; H, 5.55; N, 5.34.

4β-(Methylthio)-7β-phthalimidocephem 6a, 4β-(methylthio)-7α-phthalimidocephem 6b, and 7α-phthalimidocephem 5b from 5a: 25 °C; 1 h; TLC, benzene–EtOAc (19:1). **6a** (30%): ^1H NMR ($DCCl_3$) δ 2.00 (3 H, br s, C-3), 2.30 (3 H, s, SCH_3), 5.40 (1 H, d, J = 4.5 Hz, C-6), 5.63 (1 H, d, J = 4.5 Hz, C-7), 6.33 (1 H, d, J = 1 Hz, C-2); IR ($CHCl_3$) 1790, 1775, 1740, 1730 cm^{-1}; mass spectrum *m/e* 446 (M^+), 57 (base); mp 169–170 °C dec (Et_2O). Anal. Calcd for $C_{21}H_{22}N_2O_5S_2$: C, 56.48; H, 4.97; N, 6.27; S, 14.36. Found: C, 56.74; H, 4.97; N, 6.50; S, 14.26. **6b** (9%): ^1H NMR ($DCCl_3$) δ 2.00 (3 H, d, J = 1.5 Hz, C-3), 2.03 (3 H, s, SCH_3), 5.38 (1 H, d, J = 2 Hz, C-6), 5.67 (1 H, d, J = 2 Hz, C-7), 6.33 (1 H, d, J = 1.5 Hz, C-2); IR ($CHCl_3$) 1785, 1775, 1740 (sh), 1725 cm^{-1}; mass spectrum *m/e* 446 (M^+). **5b** (6%): ^1H NMR ($DCCl_3$) δ 2.12 (3 H, s, C-3), 5.06 (1 H, d, J = 2.5 Hz, C-6), 5.62 (1 H, d, J = 2.5 Hz, C-7); IR ($CHCl_3$) 1790, 1775, 1740 (sh), 1725 cm^{-1}; mp 189 °C (EtOAc–hexane). Anal. Calcd for $C_{20}H_{20}N_2O_5S$: C, 59.99; H, 5.03; N, 7.00. Found: C, 59.84; H, 4.55; N, 6.71. **5a** (39%).

4β-(Methylthio)-7β-phthalimidocephem 6a, 4β-(Methylthio)-7α-phthalimidocephem 6b, and 7α-Phthalimidocephem 5b from 5a Using (Triphenylmethyl)lithium as Base. Ester **5a** (5 mmol) in 50 mL of dry dimethoxyethane was added to a red solution of (triphenylmethyl)lithium in 20 mL of dry dimethoxyethane (from 5 mmol of triphenylmethane and 7.5 mmol of *n*-butyllithium in hexane) under argon at 25 °C. After stirring for 2 min, methylmethanethiol sulfonate (5 mmol) in 20 mL of dimethoxyethane was added, and the mixture was stirred for 1 h at 25 °C and then poured into cold pH 6.6 buffer–$CHCl_3$. The $CHCl_3$ extract was washed with H_2O and then saturated NaCl solution, dried (Na_2SO_4), and evaporated to a residue. Trituration with hexane removed triphenylmethane, and the remaining residue was crystallized from Et_2O to give 679 mg of **6a.** Preparative TLC on silica gel using benzene–EtOAc (19:1) provided an additional 557 mg of **6a** (55% total yield), **6b** (258 mg, 12%), **5b** (45 mg, 2%), and **5a** (300 mg, 15%).

General Procedure from Methylthiolation of 7-Imino Ether and 7-(Tritylamino) Cephems Using Lithium Cyclohexylisopropylamide. A solution of lithium cyclohexylisopropylamide was prepared by adding 1 equiv of *n*-butyllithium in hexane to *N*-cyclohexylisopropylamine (1 equiv) in dry dimethoxyethane (3 mL/mmol) at −60 °C under N_2. After stirring for several minutes, 1 equiv of cephem in dry dimethylformamide (3 mL/mmol) was added rapidly. After 2 min, methylmethanethiol sulfonate (1 equiv in dimethoxyethane) was added, and the mixture was stirred for the time and at the temperature given. The mixture was poured into benzene, $CHCl_3$, or EtOAc–pH 6.6 buffer–ice, and the organic layer was washed with water, dried (Na_2SO_4), and evaporated to a residue, which was purified by chromatography on silica gel as indicated.

4β-(Methylthio) imino ether 4d from 1d: −55 °C; 50 min; TLC, $CHCl_3$. **4d** (35%): ^1H NMR ($DCCl_3$) δ 2.07 (3 H, s, OAc), 2.12 (3 H, s, SCH_3), 5.02 (1 H, d, J = 5 Hz, C-6), 5.22 (1 H, d, J = 5 Hz, C-7), 6.95 (1 H, s, C-2); IR ($CHCl_3$) 1770, 1735, 1650 cm^{-1}; mass spectrum *m/e* 492 (M^+), 445 (M − SCH_3), 417 (M − SCH_3 − CO), 391 (M − COO-t-Bu), 105 (base).

4β-(Methylthio) imino ether 4e from 1e: −55 °C; 50 min; dry column silica gel, hexane–EtOAc (17:3). **4e** (53%): ^1H NMR ($DCCl_3$) δ 2.00 (3 H, d, J = 0.5 Hz, C-3), 2.17 (3 H, s, SCH_3), 3.90 (3 H, s, OCH_3), 4.98 (1 H, d, J = 5 Hz, C-6), 5.28 (1 H, d, J = 5 Hz, C-7), 6.55 (1 H, d, J = 0.5 Hz, C-2).

4β-(Methylthio)-7β-(tritylamino)cephem 8a from 7a: −10 °C, 1 h. **8a** (90%): ^1H NMR ($DCCl_3$) δ 1.93 (3 H, d, J = 0.5 Hz, C-3), 2.10 (3 H, s, SCH_3), 4.50 (2 H, br s, C-6, C-7), 6.15 (1 H, d, J = 0.5 Hz, C-2); IR ($CHCl_3$) 1775, 1760 (sh) cm^{-1}.

4β-(Methylthio)-7β-(tritylamino)cephem 8b from 7b: −10 °C, 1 h; dry column silica gel ($CHCl_3$). **8b** (62%): ^1H NMR ($DCCl_3$) δ 2.02 (3 H, s, OAc), 2.08 (3 H, s, SCH_3), 4.48 (1 H, d, J = 4 Hz, C-6), 4.92 (1 H, q, J = 4, 9 Hz, C-7), 6.57 (1 H, br s, C-2); IR ($CHCl_3$) 1772, 1738 cm^{-1}; mass spectrum *m/e* 616 (M^+), 317, 299, 243 (base).

4β-(Methylthio)-7β-aminocephem Hydrochloride 21a and Free Base 21b. A mixture of crude **8a** (12.0 g) and 3.0 mL of concentrated HCl in 180 mL of acetone was stirred at 25 °C for 3 h under N_2. After removal of solvents, the resulting residue was treated with acetone–Et_2O to give 6.46 g (80%) of **21a** as a powder. When a sample of **8a,** purified by preparative TLC on silica gel using $CHCl_3$–hexane (3:1), was treated similarly, **21a** was obtained as a powder: mp 128 °C dec; ^1H NMR (Me_2SO-d_6) δ 1.93 (3 H, d, J = 1 Hz, C-3), 2.05 (3 H, s, SCH_3), 4.88 (1 H, d, J = 4.5 Hz, C-6), 5.27 (1 H, d, J = 4.5 Hz, C-7), 6.67 (1 H, d, J = 1 Hz, C-2); IR ($CHCl_3$) 1790, 1760 cm^{-1}. Anal. Calcd for $C_{11}H_{14}N_2O_3S_2Cl_4$: C, 30.86; H, 3.30; N, 6.56, S, 14.95. Found: C, 31.01; H, 3.25; N, 6.75; S, 14.75.

Treatment of crude **21a** with $CHCl_3$–aqueous $NaHCO_3$ gave the free base **21b:** ^1H NMR ($DCCl_3$) δ 2.00 (3 H, d, J = 0.5 Hz, C-3), 2.07 (3 H, s, SCH_3), 4.48 (1 H, d, J = 5 Hz, C-6), 5.28 (1 H, d, J = 5 Hz, C-7), 6.40 (1 H, d, J = 0.5 Hz, C-2); IR ($CHCl_3$) 1770 (br) cm^{-1}; mass spectrum 390 (M^+), 74 (base).

4β-(Methylthio)-7β-(phenylacetamido)cephem 23a from Hydrochloride 21a. To a stirred mixture of 6.42 g (15 mmol) of **21a** in 100 mL of dry CH_2Cl_2 at 0 °C under N_2 was added 4.3 mL (31.6 mmol) of triethylamine followed by 2.39 mL (18.1 mmol) of phenylacetyl chloride. After stirring at 25 °C for 1.5 h, the mixture was washed twice with H_2O, H_2O at pH 7.6, and saturated aqueous NaCl to give, after drying (Na_2SO_4) and evaporation, 7.42 g (97%) of **23a** as a residue: ^1H NMR ($DCCl_3$) δ 1.98 (3 H, d, J = 1.5 Hz, C-3), 2.03 (3 H; s, SCH_3), 5.30 (1 H, d, J = 4.5 Hz, C-6), 5.49 (1 H, q, J = 4, 8 Hz, C-7), 6.33 (1 H, d, J = 1.5 Hz, C-2); IR ($CHCl_3$) 1782, ~1762 (sh), 1680 cm^{-1}; mass spectrum *m/e* 508 (M^+), 91 (base).

4β-(Methylthio)-7β-benzamidocephem 22a from Hydrochloride 21a. Treatment of **21a** with benzoyl chloride instead of phenylacetyl chloride, as described above, gave **22a** (50%) after preparative TLC on silica gel using $CHCl_3$–EtOAc (9:1): ^1H NMR ($DCCl_3$) δ 2.05 (3 H, d, J = 0.5 Hz, C-3 CH_3), 2.17 (3 H, s, SCH_3), 4.92 (2 H, J = 12 Hz, $-CH_2CCl_3$), 5.48 (1 H, d, J = 4 Hz, C-6), 5.72 (1 H, q, J = 4, 8 Hz, C-7), 6.43 (1 H, d, J = 0.5 Hz, C-2); IR ($CHCl_3$) 1770, 1760 (sh), 1670 cm^{-1}.

4β-(Methylthio)-7β-(phenylacetamido)cephem 23a and 4β-(Methylthio)-7β-benzamidocephem 22a from Imino Ether 4e.

A mixture of 510 mg (1 mmol) of **4e**, 137 μL (1 mmol) of phenylacetyl chloride, and 18 μL (1 mmol) of H_2O in 5 mL of CH_2Cl_2 was stirred at 25 °C under N_2 for 1 h. The mixture was diluted with CH_2Cl_2, washed with dilute $NaHCO_3$ solution (pH 7.5) and then H_2O, dried (Na_2SO_4), and evaporated to a residue. Preparative TLC on silica gel using hexane–EtOAc (1:1) provided 260 mg (51%) of **23a** and 135 mg (27%) of **22a**. **22a** was identical by comparisons (^1H NMR, IR, TLC) with **22a** obtained via **8a** and **21**.

General Procedure for Deesterification of Trichloroethyl 4-(Methylthio)-Δ^2-cephem-4-carboxylates. A mixture of 0.5 mmol of trichloroethyl ester, 5 mL of dioxane, and 0.5 mmol of aqueous 0.1 N NaOH solution was stirred at 25 °C for 1 h under N_2 and then evaporated in vacuo to a residue, which was taken up in H_2O and washed repeatedly with EtOAc. The aqueous layer, after layering with fresh EtOAc, was adjusted to pH 2 and extracted repeatedly with EtOAc. The acidic EtOAc extract was dried (Na_2SO_4) and evaporated to give the desired acid as a residue.

4β-(Methylthio)-7β-(phenylacetamido)cephem acid 23b: 97% from **23a**; ^1H NMR ($DCCl_3$) δ 1.97 (3 H, s, J = 0.5 Hz, C-3), 2.07 (3 H, s, SCH_3), 5.25 (1 H, d, J = 4 Hz, C-6), 5.45 (1 H, q, J = 4, 7 Hz, C-7), 6.27 (1 H, d, J = 0.5 Hz, C-2); IR ($CHCl_3$) 1775, 1742, 1680 cm^{-1}; mass spectrum of bis(trimethylsilyl) derivative m/e 522 (M^+), 91 (base).

4β-(Methylthio)-7β-(phenylacetamido)cephem potassium salt 23c: 73% from **23b** using potassium 2-ethylhexanoate; mp 192–194 °C dec; ^1H NMR (D_2O–CD_3OD) δ 1.86 (3 H, d, J = 0.5 Hz, C-3), 1.91 (3 H, s, SCH_3), 5.25 (1 H, d, J = 4 Hz, C-6), 5.37 (1 H, d, J = 4 Hz, C-7), 6.34 (1 H, d, J = 0.5 Hz, C-2); IR (KBr) 1750, 1660, 1620 cm^{-1}. Anal. Calcd for $C_{17}H_{17}N_2O_4S_2K$: C, 49.03; H, 4.12; N, 6.73; S, 15.37. Found: C, 48.89; H, 4.38; N, 6.53; S, 15.10.

4β-(Methylthio)-7β-(phenylacetamido)cephem methyl ester 23d: 100% from **23b** using CH_3OH–Et_2O–CH_2N_2; ^1H NMR ($DCCl_3$) δ 1.92 (3 H, d, J = 1.5 Hz, C-3), 1.97 (3 H, s, SCH_3), 3.80 (3 H, s, OCH_3), 5.20 (1 H, d, J = 5 Hz, C-6), 5.42 (1 H, q, J = 5, 8 Hz, C-7), 6.25 (1 H, d, J = 1.5 Hz, C-2); IR ($CHCl_3$) 1780, 1746, 1680 cm^{-1}.

4β-(Methylthio)-7β-benzamidocephem acid 22b: 83% from **22a**; ^1H NMR ($DCCl_3$–D_3COD) δ 2.00 (3 H, d, J = 0.5 Hz, C-3), 2.10 (3 H, s, SCH_3), 5.43 (1 H, d, J = 4 Hz, C-6), 5.62 (1 H, d, J = 4 Hz, C-7), 6.40 (1 H, d, J = 0.5 Hz, C-2); IR ($CHCl_3$) 1770, 1730, 1670 cm^{-1}.

4β-(Methylthio)-7β-benzamidocephem methyl ester 19: 100% from **22b** using CH_3OH–Et_2O–CH_2N_2; ^1H NMR ($DCCl_3$) δ 1.97 (3 H, d, J = 0.5 Hz, C-3), 2.08 (3 H, s, SCH_3), 3.85 (3 H, s, OCH_3), 5.35 (1 H, d, J = 4 Hz, C-6), 5.67 (1 H, q, J = 4, 8 Hz, C-7), 6.30 (1 H, d, J = 0.5 Hz, C-2); IR ($CHCl_3$) 1770, 1738, 1670 cm^{-1}; IR (Nujol) 1768, 1730, 1645 cm^{-1}; mass spectrum m/e 378 (M^+), 331 ($M - SCH_3$), 319 ($M - COOCH_3$), 105 (base). Comparison (^1H NMR, IR, TLC) of this sample with **19**, prepared by the method of Yoshida et al.,[11] showed the samples to be identical.

Conversion of 7β-Phthalimido-4β-(methylthio)cephem 6a to 7β-Amino-4β-(methylthio)cephem 27. A mixture of 90 mg (0.20 mmol) of **6a**, 0.4 mL of 0.5 M $H_2NNH_2 \cdot H_2O$ in dioxane, and 6 mL of dry dioxane was stirred at 25 ° C for 4 h under argon and then evaporated in vacuo to dryness. A mixture of 0.2 mL of 1 N HCl in 6 mL of H_2O–dimethoxyethane (1:1) was added, and the mixture was stirred for 1 h, concentrated, and redissolved in EtOAc–H_2O at pH 2. After extracting, the aqueous layer was covered with EtOAc and adjusted to pH 7.7. Repeated extraction gave, after drying (Na_2SO_4) and evaporation, 30 mg (71%) of **27** as a residue: ^1H NMR ($DCCl_3$) δ 2.00 (3 H, br s, C-3), 2.30 (3 H, s, SCH_3), 5.40 (1 H, d, J = 4.5 Hz, C-6), 5.63 (1 H, d, J = 4.5 Hz, C-7), 6.33 (1 H, d, J = 1 Hz, C-2).

7β-(Phenoxyacetamido)-4β-(methylthio)cephem 28 from 27. Acylation of **27** with equivalent amounts of phenoxyacetyl chloride and triethylamine in CH_2Cl_2 according to the procedure for acylation of **21a** provided **28** (50%) as a residue: ^1H NMR ($DCCl_3$) δ 1.50 (9 H, s, t-Bu), 2.00, 2.05 (two 3 H singlets, SCH_3, CH_3), 5.30 (1 H, d, J = 4 Hz, C-6), 5.60 (1 H, q, J = 4, 8 Hz, C-7), 6.28 (1 H, d, J = 0.5 Hz, C-2).

7β-(Phenoxyacetamido)-2α-(methylthio)cephem Acid 29 from 28. Treatment of **28** according to the general procedure for removal of p-methoxybenzyl and benzhydryl ester protecting groups but using neat CF_3COOH at 10 °C for 0.5 h provided **29** (66%) as a residue. This sample was identical by ^1H NMR and IR comparisons with **29** obtained by reduction of 2α-(methylthio)cephem sulfoxide **30**.

General Procedure for Methylthiolation of Sulfoxides. Potassium *tert*-butoxide (1 equiv) was added to a stirred solution of the sulfoxide **13** (1 equiv) under N_2 or argon in the solvent(s) (10 mL/1 mmol) given and at the temperature indicated. After 2–5 min, methylmethanethiol sulfonate (1 equiv) was added, and the mixture was stirred for the time and at the temperature given, and then diluted with CH_2Cl_2 ($CHCl_3$ or EtOAc) and H_2O. The organic layer was washed with H_2O, dried, and evaporated in vacuo to a residue, which was purified by chromatography on silica as indicated.

2α-(Methylthio)-7β-(phenoxyacetamido)cephem sulfoxide 14a and 2,2-bis(methylthio)-7β-(phenoxyacetamido)cephem sulfoxide 15a: dimethoxyethane, anion formation at 25 °C, thiolation initially at −23 °C, and warming to 25 °C over 1 h; preparative TLC on silica gel using $CHCl_3$–EtOAc (3:1). **14a** (44%): mp 165–166 °C ($CHCl_3$–Et_2O); ^1H NMR (Table II, **24a**). Anal. Calcd for $C_{18}H_{20}N_2O_6S_2$: C, 51.19; H, 4.30; N, 6.63; S, 15.11. Found: C, 51.15; H, 5.02; N, 6.57; S, 15.26. **15a** (26%): mp 112–113.5 °C (Et_2O); ^1H NMR ($DCCl_3$) δ 2.32, 2.37 (9 H, 2 s, CH_3, $2SCH_3$), 3.90 (3 H, s, OCH_3), 5.21 (1 H, d, J = 5 Hz, C-6), 6.15 (1 H, q, J = 5, 11 Hz, C-7); IR ($CHCl_3$) 1805, 1735, 1695 cm^{-1}. Anal. Calcd for $C_{19}H_{22}N_2O_6S_3$: C, 48.49; H, 4.71; N, 5.95; S, 20.44. Found: C, 48.39; H, 4.47; N, 5.72; S, 20.44.

2α-(Methylthio)-7β-(phenoxyacetamido)cephem sulfoxide 14b and 2,2-bis(methylthio)-7β-(phenoxyacetamido)cephem sulfoxide 15b: same conditions as for preparation of **14a**. **14b** (38%): mp 128–129 °C dec ($CHCl_3$–EtOAc); ^1H NMR ($DCCl_3$) δ 2.27, 2.32 (two 3 H singlets, CH_3, SCH_3), 3.78 (3 H, s, OCH_3), 4.20 (1 H, s, C-2), 4.87 (1 H, d, J = 5 Hz, C-6), 6.12 (1 H, q, J = 5, 10 Hz, C-7); IR ($CHCl_3$) 1800, 1730, 1690 cm^{-1}. Anal. Calcd for $C_{25}H_{26}N_2O_7S_2$: C, 56.59; H, 4.94; N, 5.28. Found: C, 56.64; H, 4.87; N, 5.11. **15b** (20%) as a residue: ^1H NMR ($DCCl_3$) δ 2.30, 2.37 (9 H, 2 s, CH_3, $2SCH_3$), 3.82 (3 H, s, OCH_3), 5.17 (1 H, d, J = 5 Hz, C-6), 6.10 (1 H, q, J = 5, 10 Hz, C-7); IR ($CHCl_3$) 1800, 1730, 1690 cm^{-1}.

2α-(Methylthio)-7β-(phenylacetamido)cephem sulfoxide 14c: dimethoxyethane–DMF, −20 °C then warming to 25 °C, 1.5 h, dry silica gel column (EtOAc). **14c** (65%) as a residue: ^1H NMR ($DCCl_3$) δ 2.02 (3 H, s, SCH_3), 4.52 (1 H, br s, C-2), 4.84 (1 H, d, J = 5 Hz, C-6), 6.10 (1 H, q, J = 5, 8 Hz, C-7).

2α-(Methylthio)-7β-(phenylacetamido)cephem sulfoxide 14d: dimethoxyethane–DMF (2:1), 0 °C, 1.75 h, dry column on silica gel using EtOAc–hexane. **14d** (90%) as a foam: ^1H NMR ($DCCl_3$) δ 2.53 (3 H, s, SCH_3), 4.87 (1 H, d, J = 5 Hz, C-6), 5.03 (1 H, d, J = 0.5 Hz, C-2), 6.20 (1 H, m, J = 0.5, 5, 8 Hz, C-7).

2α-(Methylthio)-7β-(phenylacetamido)cephem sulfoxide 14e: dimethoxyethane–DMF (2:1), 0 °C, 1.75 h, preparative TLC on silica gel using EtOAc–$CHCl_3$ (2:1). **14e** (55%) as a residue: ^1H NMR ($DCCl_3$) δ 2.58 (3 H, s, SCH_3), 4.92 (1 H, d, J = 5 Hz, C-6), 5.08 (1 H, d, J = 1 Hz, C-2), 6.22 (1 H, m, J = 1, 5, 9 Hz, C-7); IR ($CHCl_3$) 1810, 1742, 1690 cm^{-1}.

General Procedure for Reduction of Sulfoxides. Phosphorous tribromide (7 equiv) was added to a solution of sulfoxide **14** (1 equiv) in dry DMF (10 mL/mmol) under N_2 at −20 to −35 °C. The cooling bath was removed, and the mixture was stirred for 5–10 min and poured into excess aqueous K_2HPO_4–EtOAc. The EtOAc layer was washed with H_2O, dried (Na_2SO_4), and evaporated in vacuo to give the sulfide.

2α-(Methylthio)-7β-(phenoxyacetamido)cephem 16a: 77%, mp 128.5–130 °C (CH_2Cl_2–Et_2O–hexane); ^1H NMR (Table II, **25a**); IR ($CHCl_3$) 1790, 1735, 1695 cm^{-1}. Anal. Calcd for $C_{18}H_{20}N_2O_6S_2$: C, 52.92; H, 4.94; N, 6.86; S, 15.70. Found: C, 52.63; H, 4.86; N, 6.60; S, 15.95.

2α-(Methylthio)-7β-(phenylacetamido)cephem 16d: 80% as a residue; ^1H NMR ($DCCl_3$) δ 2.03 (3 H, s, SCH_3), 3.78 (3 H, s, NCH_3), 5.30 (1 H, d, J = 5 Hz, C-6), 5.27 (1 H, d, J = 0.5 Hz, C-2), 6.03 (1 H, m, J = 0.5, 5, 8 Hz, C-7); IR ($CHCl_3$) 1794, 1720, 1685 cm^{-1}.

2α-(Methylthio)-7β-(phenylacetamido)cephem 16e: 85% as an oil; ^1H NMR ($DCCl_3$) δ 2.42 (3 H, s, SCH_3), 3.90 (3 H, s, NCH_3), 4.30, 4.70 (2 H, q, J = 14 Hz, C-3), 4.77, 5.08 (2 H, q, J = 12 Hz, CH_2CCl_3), 5.32 (1 H, d, J = 0.5 Hz, C-2), 5.37 (1 H, d, J = 4.5 Hz, C-6), 6.02 (1 H, m, J = 0.5, 4.5, 8 Hz, C-7); IR ($CHCl_3$) 1795, 1740, 1690 cm^{-1}; mass spectrum m/e 622 (M^+), 507 ($M - SC_2H_3N_4$), 116 (base).

2-(Methylthio)-7β-(phenylacetamido)-Δ^2-cephem 12 from Isomerization of 16e. Ester **16e** (57 mg) was stirred with 5 drops of pyridine in 2 mL of $CHCl_3$ for 4 days at room temperature. The $CHCl_3$ and pyridine were removed in vacuo, and the residue was purified by preparative TLC on silica gel using $CHCl_3$–EtOAc (9:1) to give 6 mg of recovered **16e** and 14 mg (25%) of **12** as a residue: ^1H NMR ($DCCl_3$) δ 2.26 (3 H, s, SCH_3), 4.00 (3 H, s, NCH_3), 3.97, 5.08 (2 H, q, J = 14 Hz, C-3), 4.75, 4.90 (2 H, q, J = 12 Hz, CH_2CCl_3), 5.37 (1 H, d, J = 4 Hz, C-6), 5.54 (1 H, q, J = 4, 8 Hz, C-7), 5.60 (1 H, s, C-4); IR ($CHCl_3$) 1790, 1765 (sh), 1685 cm^{-1}; mass spectrum m/e 622 (M^+), 507 ($M - SC_2H_3N_4$), 506, 116, 91.

4β-(Methylthio)cephem 10a and 4α-(Methylthio)cephem 11a from Methylthiolation of 7β-(Phenylacetamido)cephem 9. To a stirred solution of N-isopropylcyclohexylamine (0.76 mL, 4.14 mmol) in dry dimethoxyethane (15 mL) at −70 °C under N_2 was added 1.73 mL of 2.4 M n-butyllithium in hexane. After stirring for 5 min, Δ^2–Δ^3 cephem mixture **9** (1.60 g, 2.76 mmol) in dry DMF (6 mL) was added rapidly, and the mixture was stirred for 2 min. A solution

of methylmethanethiol sulfonate (0.52 g, 4.14 mmol) in dimethoxyethane (2 mL) was added, and the mixture was stirred at −65 °C for 20 min and poured into EtOAc–pH 6.6 buffer–ice. The pH was adjusted to 2 (1 N HCl), and the EtOAc layer was washed with H_2O, dried (Na_2SO_4), and evaporated to a residue (1.28 g). Preparative TLC on silica gel using $CHCl_3$–EtOAc–hexane (1:1:1) provided 209 mg of starting material and 378 mg (22%) of a mixture of **10a** and **11a** in the ratio (4:1) as determined by ^1H NMR spectroscopy. Repeated preparative TLC gave a sample of **10a** as a residue: ^1H NMR ($DCCl_3$) δ 2.11 (3 H, s, SCH_3), 3.90 (3 H, s, NCH_3), 4.40 (2 H, br s, C-3), 4.87 (2 H, s, CH_2CCl_3), 5.27 (1 H, d, J = 4 Hz, C-6), 5.46 (1 H, q, J = 4, 7 Hz, C-7), 7.20 (1 H, s, C-2); IR ($CHCl_3$) 1785, 1764, 1685 cm^{-1}; mass spectrum m/e 622 (M^+), 575 (M − SCH_3), 507 (M − $SC_2H_3N_4$), 116, 91. A mixture (1:1) of **10a** and **11a** was isolated as a residue having IR ($CHCl_3$) 1785, 1764, 1685 cm^{-1}. Examination of the ^1H NMR spectrum of this mixture and the ^1H NMR spectrum of the **10a** isolated indicated that **11a** had: ^1H NMR ($DCCl_3$) δ 2.25 (3 H, s, SCH_3), 3.90 (3 H, s, NCH_3), 4.05, 4.40 (2 H, q, J = 14 Hz, C-3), 4.58, 4.90 (2 H, q, J = 12 Hz, CH_2CCl_3), 5.15 (1 H, d, J = 4.5 Hz, C-6), 5.75 (1 H, q, J = 4.5, 8.5 Hz, C-7), 7.17 (1 H, s, C-2).

4β-(Methylthio)cephem Acid 10b and 4α-(Methylthio)cephem Acid 11b. Treatment of 205 mg (0.33 mmol) of the mixture (4:1) of **10b** and **11b**, respectively, according to the general procedure for deesterification of trichloroethyl esters, provided a mixture of acids as a residue (131 mg), which was purified by preparative TLC on silica gel using acetone–AcOH (16:1). Elution of the band with $R_f \sim 0.6$, evaporation of solvents, and workup with EtOAc–H_2O at pH 7 and then pH 2 provided 74 mg of **10b:** ^1H NMR ($DCCl_3$–CD_3OD) δ 2.08 (3 H, s, SCH_3), 3.93 (3 H, s, NCH_3), 4.40 (2 H, br s, C-3), 5.23 (1 H, d, J = 4.5 Hz C-6), 5.43 (1 H, d, J = 4.5 Hz, C-7), 7.03 (1 H, s, C-2); IR ($CHCl_3$) 1780, 1738, 1682 cm^{-1}. Similar treatment of the band with $R_f \sim 0.7$ gave 4 mg of a mixture (1:1) of **10b** and **11b.** Isomer **11b** had: ^1H NMR ($DCCl_3$–CD_3OD) δ 2.22 (3 H, s, SCH_3), 3.97 (3 H, s, NCH_3), 4.28 (2 H, br s, C-3), 5.13 (1 H, d, J = 4 Hz, C-6), 5.57 (1 H, d, J = 4 Hz, C-7), 7.03 (1 H, s, C-2).

4β-(Methylthio)cephem Potassium Salt 10c. Treatment of acid **10b** with potassium 2-ethylhexanoate provided the potassium salt **10c:** 84%; mp 137–139 °C dec; ^1H NMR (D_2O) δ 2.00 (3 H, s, SCH_3), 3.97 (3 H, s, NCH_3), 4.42 (2 H, br s, C-3), 5.37 (2 H, br s, C-6, C-7), 6.87 (1 H, s, C-2); IR (KBr) 1745, 1670 (sh), 1620 cm^{-1}. Anal. Calcd for $C_{19}H_{19}N_6O_4S_3K$: C, 40.00; H, 3.61; N, 15.84. Found: C, 42.76; H, 3.74; N, 15.30.

General Procedure for Removal of *p*-Methoxybenzyl or Benzhydryl Ester Protecting Groups. Trifluoroacetic acid (2 mL) was added to a solution of 1 mmol of ester and 0.5 mL of anisole in 14 mL of solvent (benzene or CH_2Cl_2) at 0 °C under N_2. After stirring for 1 h, the reaction was usually complete, and the solvents were removed in vacuo. Benzene was added and evaporated in vacuo to complete removal of CF_3COOH. The residue was taken up in EtOAc–dilute aqueous $NaHCO_3$ (pH 7.5), and the aqueous layer was washed with EtOAc two times. The aqueous layer was covered with fresh EtOAc, and the pH was adjusted to 2. The acidic EtOAc extract was dried (Na_2SO_4) and evaporated in vacuo to give the desired free acid.

2α-(Methylthio)cephem sulfoxide acid 14b (R′ = H): benzene–anisole–CF_3COOH, 50 min from **14b** (99%); mp 153–154 °C ($CHCl_3$–EtOAc); ^1H NMR ($DCCl_3$) δ 2.33, 2.38 (6 H, 2 s, CH_3, SCH_3), 4.48 (1 H, s, C-2), 5.03 (1 H, d, J = 5 Hz, C-6), 6.23 (1 H, q, J = 5, 10 Hz, C-7); IR ($CHCl_3$) 1800, 1720 (sh), 1690 cm^{-1}. Anal. Calcd for $C_{17}H_{18}N_2O_6S_2$: C, 49.74; H, 4.42; N, 6.83. Found: C, 49.92; H, 4.46; N, 7.09.

2α-Methylthiocephem sulfoxide acid 14c (R′ = H): CF_3COOH–anisole from **14c, 14c** (R′ = H) (65%): mp 175–176 °C dec (EtOAc–hexane); ^1H NMR Me_2SO-d_6 δ 2.08 (3 H, s, OAc), 2.35 (3 H, s, SCH_3), 4.90 (1 H, s, C-2), 5.02 (1 H, d, J = 4.5 Hz, C-6), 5.95 (1 H, q, J = 4.5, 8 Hz, C-7); IR (KBr) 1790, 1730, 1722, 1665 cm^{-1}. Anal. Calcd for $C_{19}H_{20}N_2O_7S_2$: C, 50.44; H, 4.42; N, 6.19; S, 14.16. Found: C, 50.37; H, 4.67; N, 6.04; S, 13.88.

2α-(Methylthio)cephem Sulfide Acid 16b (R′ = H). Treatment of sulfoxide acid **14b** (R′ = H) according to the general procedure for reduction with PBr_3 in DMF provided, after workup with EtOAc at pH 7.5 and then at pH 2. **16b** (R′ = H) (40%): mp 163–165 °C dec (trituration, Et_2O–hexane); ^1H NMR ($DCCl_3$) δ 2.28 (6 H, s, CH_3, SCH_3), 4.37 (1 H, s, C-2), 5.40 (1 H, d, J = 5 Hz, C-6), 6.02 (1 H, q, J = 5, 9 Hz, C-7); IR ($CHCl_3$) 1785, 1732, 1695 cm^{-1}; mass spectrum of trimethylsilyl ester m/e 466 (M^+).

2α-(Methylthio)cephem acid 16d (R′ = H): CF_3COOH–anisole; 20 min from **16d;** preparative TLC on silica gel using acetone–AcOH (16:1), followed by extraction (R_f 0.7), evaporation of solvents, and workup with EtOAc–H_2O at pH 7.5 and pH 2. **16d** (R′ = H) (17%): ^1H NMR ($DCCl_3$–D_3COD) δ 2.37 (3 H, s, SCH_3), 3.97 (3 H, s, NCH_3), 5.17 (1 H, d, J = 0.5 Hz, C-2), 5.33 (1 H, d, J = 5 Hz, C-6), 5.97 (1 H, br d, J = 0.5, 5 Hz, C-7).

2α-(Methylthio)cephem acid potassium salt 16d (R′ = K): 74% from **16d** (R′ = H) using potassium 2-ethylhexanoate; mp 139–141 °C dec; ^1H NMR (D_2O) δ 2.20 (3 H, s, SCH_3), 3.97 (3 H, s, NCH_3), 4.85 (1 H, br s, C-2), 5.35 (1 H, d, J = 4.5 Hz, C-6), 5.75 (1 H, d, J = 4.5 Hz, C-7); IR (KBr) 1755, 1660, 1600 cm^{-1}. Anal. Calcd for $C_{19}H_{19}N_6O_4S_3K·H_2O$: C, 41.60; H, 3.86; N, 15.32. Found: C: 41.94; H, 4.13; N, 15.17.

Conversion of 7α-(Methylthio)imino Chloride 2f to 2c. A mixture of 2.40 g (5.46 mmol) of **2f,** 1.6 mL of pyridine, and 30 mL of CH_3OH was stirred at 25 °C under N_2 for 3 h and then poured into benzene–pH 6.6 buffer. The benzene layer was washed with H_2O, dried (Na_2SO_4), and evaporated to a residue. Purification by preparative TLC on silica gel using benzene–EtOAc (19:1) gave 351 mg (14%) of **2c** as a residue, which was identical by ^1H NMR and TLC comparisons with **2c** prepared by methylthiolation of imino ether **1c.**

7β-(Phenylacetamido)-7-(methylthio)cephem 26a and 7β-Benzamido-7-(methylthio)cephem 26b from Acylation of 2c with Phenylacetyl Chloride. A mixture of imino ether **2c** (87 mg, 0.20 mmol), phenylacetyl chloride (31 mg, 0.20 mmol), and 200 μL of 1 N HCl in 3 mL of CH_2Cl_2 was stirred at 25 °C under N_2 for 16 h. After diluting with CH_2Cl_2–H_2O, the CH_2Cl_2 layer was washed with dilute $NaHCO_3$ and then H_2O, dried (Na_2SO_4), and evaporated to a residue. Preparative TLC on silica gel using benzene–EtOAc (19:1) gave 18 mg (23%) of **26a,** which was identical by ^1H NMR, IR, and TLC comparisons with an authentic sample, and 20 mg (26%) of 7α-(methylthio)-7β-benzamidocephem **26b:** ^1H NMR ($DCCl_3$) δ 1.55 (9 H, s, *t*-Bu), 2.17 (3 H, s, C-3 CH_3), 2.43 (3 H, s, SCH_3), 3.33 (2 H, br s, C-2), 5.10 (1 H, s, C-6), 7.00 (1 H, br, NH), and 7.4–8.0 (5 H, m, aromatics); IR ($CHCl_3$) 1790, 1720, 1675 cm^{-1}.

Registry No.—**1c,** 56043-89-1; **1d,** 56043-90-4; **1e,** 64207-74-5; **1f,** 56043-87-9; **2b,** 37787-02-3; **2c,** 56043-93-7; **2d,** 56043-94-8; **2f,** 56043-91-5; **3b,** 68474-70-4; **3d,** 68474-71-5; **4d,** 68538-91-0; **4e,** 68538-92-1; **5a,** 55151-51-4; **5b,** 68474-72-6; **6a,** 66428-79-3; **6b,** 68510-35-0; **7a** (Δ^2 isomer), 63853-70-3; **7a** (Δ^2 isomer), 63853-71-4; **7b,** 63853-66-7; **8a,** 66428-77-1; **8b,** 66428-78-2; **9** (Δ^2 isomer), 68474-73-7; **9** (Δ^3 isomer), 68474-74-8; **10a,** 68474-75-9; **10b,** 68474-76-0; **10c,** 68474-77-1; **11a,** 68474-78-2; **11b,** 68474-79-3; **12,** 68474-80-6; **13d,** 68474-81-7; **13e,** 68474-82-8; **14b,** 68538-93-2; **14b** (R′ = H), 68510-36-1; **14c,** 68524-90-3; **14c** (R′ = H), 68539-54-8; **14d,** 68510-85-0; **14e,** 68510-86-1; **15a,** 68474-83-9; **15b,** 68510-87-2; **16d,** 68510-88-3; **16d** (R′ = H), 68474-84-0; **16d** (R′ = K), 68474-85-1; **16e,** 68474-86-2; **19,** 58491-73-9; **21a,** 68510-37-2; **21b,** 68510-38-3; **22a,** 68474-87-3; **22b,** 68474-88-4; **23a,** 66428-74-8; **23b,** 68510-39-4; **23c,** 68510-90-7; **23d,** 66428-75-9; **24,** 68510-33-8; **25,** 68510-34-9; **26a,** 37786-95-1; **26b,** 56043-92-6; **27,** 68510-40-7; **28,** 68538-94-3; **29,** 68510-41-8; *tert*-butyl 7-aminodeacetoxycephalosporanate, 33610-06-9; *tert*-butyl 7-aminocephalosporanate, 6187-87-7; 2,2,2-trichloroethyl 7-aminodeacetoxycephalosporanate, 28180-82-7; *tert*-butyl 7β-benzamidodeacetoxycephalosporanate, 56043-86-8; 3-[(1-methyl-1*H*-tetrazol-5-yl)thiomethyl]-7β-(phenylacetamido)-Δ³-cephem-4-carboxylic acid, 47653-82-7; diphenylmethyl 7β-(phenylacetamido)-3-[(1-methyl-1*H*-tetrazol-5-yl)thiomethyl]-Δ³-cephem-4-carboxylate, 67366-01-2; trimethyl orthobenzoate, 707-07-3; 2,2,2-trichloroethanol, 115-20-8; phthalic anhydride, 85-44-9; methylmethanethiol sulfonate, 2949-92-0; phenylacetyl chloride, 103-80-0; benzoyl chloride, 98-88-4; phenoxyacetyl chloride, 701-99-5.

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Reaction of Guanidines with α-Diketones. Syntheses of 4,5-Disubstituted-2-aminoimidazoles and 2,6-Unsymmetrically Substituted Imidazo[4,5-*d*]imidazoles[1]

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2-Amino-4,5-diaryl-4-hydroxy-4*H*-imidazoles were obtained by the reaction of substituted benzils with guanidine in methanol at room temperature. Catalytic hydrogenation of the 4-hydroxy-4*H*-imidazoles produced 2-amino-4,5-diarylimidazoles in excellent yields. In the case of 1-phenyl-1,2-propanedione and butane-2,3-dione, the intermediate 4-hydroxy-4*H*-imidazoles could not be isolated and the reaction mixtures were hydrogenated directly to yield the corresponding 2-aminoimidazoles. 1,1-Dimethylguanidine and benzils also produced the corresponding 4*H*-imidazoles in excellent yields. These compounds were quantitatively converted to 2-(dimethylamino)-5,5-diarylimidazolin-4-ones by heating. 1-Amidino-3,5-dimethylpyrazole did not give the corresponding 4*H*-imidazoles, but produced the 2,6-unsymmetrically substituted imidazo[4,5-*d*]imidazoles. Probable mechanisms for the formation of these products are discussed.

It is well known that the base-catalyzed reaction of benzil with guanidine produces 2-amino-5,5-diphenylimidazolin-4-one and 2,6-diamino-4,8-diphenylimidazo[4,5-*d*]imidazole,[2-5] while that with 1,1-disubstituted guanidines gives only 2-(disubstituted amino)-5,5-diphenylimidazolin-4-ones.[6] However, our previous results[7,8] suggested the possibility of also obtaining 4-hydroxy-4*H*-imidazoles or 4,5-dihydroxyimidazolines in this condensation reaction. In this paper, we report the successful syntheses of 4-hydroxy-4*H*-imidazoles by the reaction of α-diketones with guanidine and 1,1-dimethylguanidine, a new route to 2-amino-4,5-disubstituted imidazoles, and the reaction of 1-amidino-3,5-dimethylpyrazole with α-diketones to form unsymmetrical imidazo[4,5-*d*]imidazoles.

Results and Discussion

Reaction of α-Diketones with Guanidine. Lempert-Sréter et al.[5] have reported that benzil (**1a**) and guanidine (**2**) gave 2,6-diamino-4,8-diphenylimidazo[4,5-*d*]imidazole (**3**) with a small amount of 2-amino-5,5-diphenylimidazolin-4-one (**4**) when the reaction was carried out in methanol at room temperature either in the presence or absence of a small amount of alkali.

When we substituted dioxane for methanol in this reaction, colorless needles, mp 212 °C, were obtained. IR, NMR, MS and elemental analysis of this product were inconsistent with the desired 2-amino-4*H*-imidazole or 4,5-dihydroxyimidazoline. Since recrystallization from methanol and ether gave imidazo[4,5-*d*]imidazole **3** and its NMR spectrum showed a signal assignable to the *O*-methylene protons of dioxane, this material was identified as **3** containing one molecule of dioxane as the solvent of crystallization. The yield of **3** was 74% based on **2**. When 2 equiv of **2** were used, the yield of **3** was reduced to 31% and, furthermore, **4** was obtained in 53% yield. This result can be explained by the report of Lempert-Sréter et al.[5] that higher alkali concentration increased the yield of **4** compared to that of **3**. However, by stirring a suspension of **1a** and **2** in a smaller amount of methanol than that reported by Lempert-Sréter et al. at room temperature, we succeeded in isolating the desired 2-amino-4,5-diphenyl-4-hydroxy-4*H*-imidazole (**5a**) in 85% yield.

When 4-hydroxy-4*H*-imidazole **5a** was refluxed in methanol in the presence of NaOH, imidazolin-4-one **4** was obtained in 92% yield. Treatment of **5a** with concentrated HCl in an attempt to prepare the HCl salt gave the unstable 2-amino-4,5-dihydroxy-4,5-diphenylimidazoline (**6**) hydrochloride by addition of water to the 1,5 C=N bond. In another attempt to obtain **5a**·HCl, treatment of **5a** with methanol containing a slight excess of HCl yielded 2-amino-4,5-dimethoxy-4,5-diphenylimidazoline (**7**) hydrochloride. The only other reported examples of this type of compound are 4,5-dimethoxyimidazolin-2-ones, which were obtained by photosensitized oxidation of imidazoles in methanol.[9]

It is interesting to note that although **5a** decomposed to unidentified products when dissolved in untreated THF, imidazo[4,5-*d*]imidazole **3** precipitated in 72% yield when **5a** was dissolved in sodium-dried and distilled THF at room temperature.

Hydrogenation of 4*H*-imidazole **5a** in methanol with palladium on charcoal gave 2-amino-4,5-diphenylimidazole (**8a**) in 84% yield, and the nitrate salt in 90% yield after acidification with nitric acid. Thus, we attempted to apply this syn-

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