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Reactions of α-Amino Acid Derivatives with Thionyl Chloride. An Application to a Synthesis of 7α-Methoxycephalosporins

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Treatment of the α-amino acid ester (IV) and the 7-amino-cephalosporin (VIII) with thionyl chloride and triethylamine afforded the sulfenimines (V) and (IX), respectively. 7β-Amino-7α-methoxy-cephalosporin derivative (XVI) was obtained by methoxylation of the sulfenimine (IXb) with methanol in the presence of triethylamine.

Keywords——amino acid; 7-amino-cephalosporin; 7β-amino-7α-methoxy-cephalosporin; 7,7′-dimer of cephalosporin; 7-methoxylation of cephalosporin; sulfenimine; thionyl chloride

The recent discovery[2] of 7α-methoxycephalosporins produced by various species of *Streptomyces* has stimulated the chemical studies, especially on the methods for the introduction of a methoxy group at the 7-position of the 3-cephem system.[3] Furthermore, much attention has been focused on some of 7α-methoxy-cephalosporin derivatives which show enhanced activity against gram negative bacteria as compared to that of 7α-unsubstituted derivatives.[4]

Recently new methods for a synthesis of 7α-methoxycephem compounds have been disclosed by our group,[3l,m] and now we wish to report another new method for the methoxylation *via* sulfenimines. Our methodology comprises oxidation of a primary amine (I) to an isolable 7-imino-cephalosporins (II) which will be methoxylated to a compound (III) (Chart 1). In this case the substituent x should be easily removed after methoxylation, or x should be helpful for acylation of the methoxy derivative (III). With these in mind we came to a conclusion that sulfur is attractive for x.

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2) *a*) R. Nagarajan, L.D. Boeck, M. Gorman, R.L. Hamill, C.E. Higgens, M.M. Hoehn, W.M. Stark, and J.G. Whitney, *J. Am. Chem. Soc.*, 93, 2308 (1971); *b*) E.O. Stapley, M. Jackson, S. Hernandez, S.B. Zimmerman, S.A. Currie, S. Mochales, J.M. Mata, H.B. Woodruff, and D. Hendlin, *Antimicrobial Agents and Chemotheray*, 2, 122 (1972); *c*) T.W. Miller, R.T. Goegelman, R.G. Weston, I. Putter, and F.J. Wolf, *ibid.*, 2, 132 (1972).

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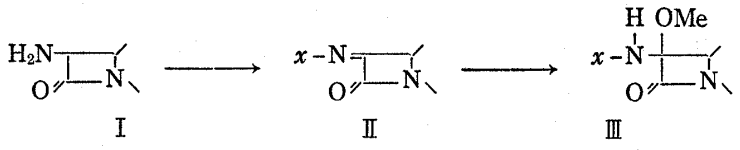
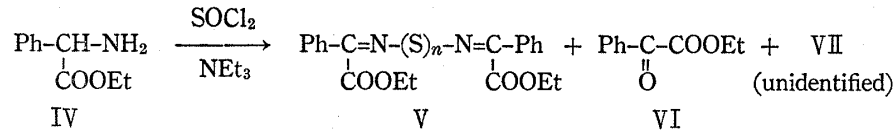


I II III

Chart 1

At first ethyl phenylglycinate (IV) was chosen as a model compound. Treatment of the ester (IV) with thionyl chloride ($SOCl_2$) in the presence of triethylamine (NEt_3) at −78° gave bis-N-(1-ethoxycarbonylbenzylidene)amino-sulfide (Va), bis-N-(1-ethoxycarbonylbenzylidene)amino-disulfide (Vb), bis-N-(1-ethoxycarbonylbenzylidene)amino-trisulfide (Vc), ethyl phenylglyoxylate (VI) and a small amount of unidentified substance (VII) ($C_{18}H_{16}O_3N_2$) (yields are summarized in Table I) after careful chromatographic separation.



a: $n=1$
b: $n=2$
c: $n=3$

Ph=phenyl

Chart 2

Table I. Reaction of Amines (IV and VIII) with Thionyl Chloride and Triethylamine in Dichloromethane

Run	Amine (eq) mmole*	$SOCl_2$ (eq)	NEt_3 (eq)	Temp. (°C)	Time (hr)	Compd. No.	Compd. Yield (%)
	IV					Va	3
1[a]	1.0	1.6	3.5	−78	2.0	Vb	13
	5.0*					Vc	15
						VI	37
						VII	4
	VIII					IXa—c	trace
2[a]	1.0	1.6	3.2	−78	1.5	Xa	3
	3.0*					XI	61
	VIII					IXa	1
3[a]	1.0	1.6	3.2	−20——30	1.0	IXb	2
	3.0*					IXc	1
						Xa	6
						XI	55
	VIII					IXa	7
4[b]	1.0	1.6	3.2	−20——30	1.0	IXb	4
	3.0*					IXc	7
						Xa	7
						XI	23

The order of the addition of reagents:
a) i) Amine-NEt_3/CH_2Cl_2, ii) $SOCl_2/CH_2Cl_2$.
b) i) $SOCl_2/CH_2Cl_2$, ii) Amine/CH_2Cl_2, iii) NEt_3/CH_2Cl_2.
* The reaction was carried out in this scale.

Analogous result was obtained except slight increase of formation of the unidentified substance (VII) when the reaction was carried out at 0—5°. Five compounds were obtained by these reactions, however, four of them should be useful for the next methoxylation reaction since ethyl phenylglyoxylate (VI) might be derived from the sulfenimines (Va, b, c) by simple hydrolysis during working-up or chromatography on silica gel. Actually

hydrolysis of the sulfenimine (Vc) with 10% hydrochloric acid in tetrahydrofuran (THF) afforded ethyl phenylglyoxylate (VI) almost quantitatively. These reactions suggest that the model experiments would be successfully applied to 7-amino-cephalosporins.

Treatment of methyl 7-amino-3-methyl-3-cephem-4-carboxylate (VIII) with thionyl chloride and triethylamine in dichloromethane (CH_2Cl_2) afforded sulfenimines (IXa), (IXb), (IXc), (Xa) and unexpected dimer (XI). The ratio of products varied depending on the reaction

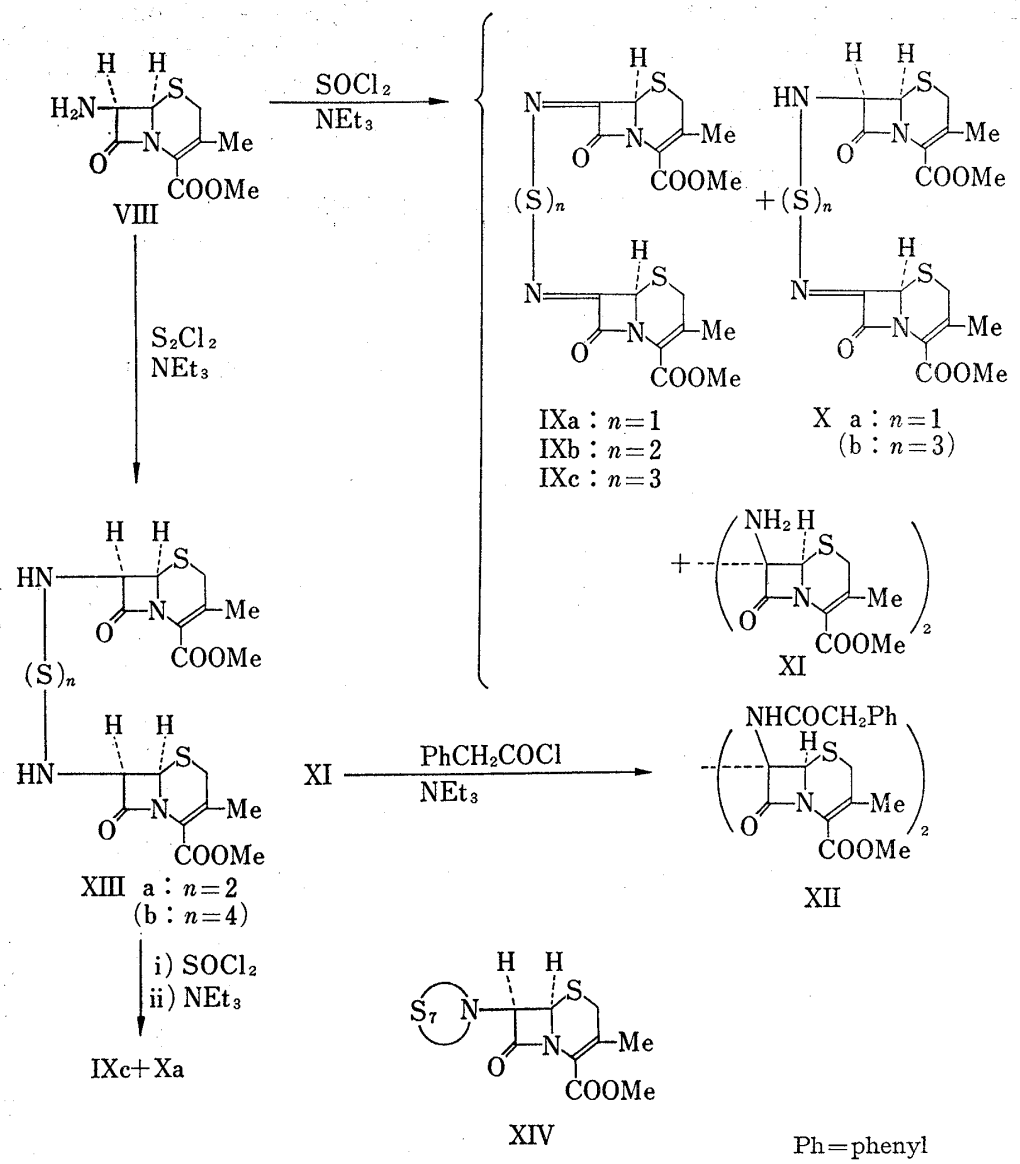


Chart 3

conditions. These results are summarized in Table I. The order of addition of thionyl chloride and triethylamine affected the yields of sulfenimines (IXa—c) and the dimer (Xl). Addition of thionyl chloride to a mixture of VIII and triethylamine favored the formation of the dimer (XI), whereas successive addition of the 7-amino-cephem (VIII) and triethylamine to a solution of thionyl chloride in dichloromethane increased the yields of sulfenimines (IX) as compared to those of the reverse addition. The structures of IXa, IXb, IXc and Xa were easily established by nuclear magnetic resonance (NMR) and mass (MS) spectra, and especially by elemental analyses with respect to the number of sulfur atom.

The structure of the dimer (XI) was confirmed by acylation with phenylacetyl chloride to give the dimeric amide (XII), which was identical with an authentic sample prepared by Yanagisawa, *et al.*[5] quite recently *via* another intermediate.

Another route to the sulfenimines (IXa, b, c) was also investigated in connection with clarification of reaction mechanisms. Treatment of VIII with sulfur monochloride (S_2Cl_2) (0.5 eq) in the presence of triethylamine (1 eq) in tetrahydrofuran at −78° afforded the sulfenamide (XIIIa) in 74% yield. This reaction was accompanied, under some reaction conditions, by many by-products, such as the sulfenimines (IXa, c), (Xb), the sulfenamide (XIIIb) and the cycloheptasulfurimide (XIV). Especially use of large excess reagents (1.5 eq S_2Cl_2 and 3 eq NEt_3) increased the formation of the cycloheptasulfurimide (XIV) up to 10%. Reaction of XIIIa with thionyl chloride and subsequent addition of triethylamine at −78° gave IXc and Xa in 22% and 14% yield, respectively.

Methoxylation of the sulfenimine (IXa) with methanol (MeOH) in the presence of triethylamine at room temperature produced the mono-methoxy-cephalosporin (XV) in 74% yield. Di-methoxylated product was not obtained even under forced reaction conditions, *i.e.* the longer reaction time and use of large excess triethylamine. On the other hand treatment of the sulfenimine (IXb) with methanol and triethylamine afforded methyl 7β-amino-7α-methoxy-3-methyl-3-cephem-4-carboxylate (XVI) in 27% yield. The mechanism of desulfurization or cleavage of S–N bond in this reaction is not clear although sulfenamides are known to be converted to the corresponding amines with various nucleophiles.[6] In the case of sulfenimine (IXc) different results were observed depending on the reaction conditions. Thus, keeping a solution of IXc in a mixture of methanol and dichloromethane (1:2) with 2,4,6-trimethylpyridine at room temperature for 5 hr gave the disulfide (IXb) in 38% yield together with the starting material (IXc) (25%). Treatment of IXc with 2,4,6-trimethyl-

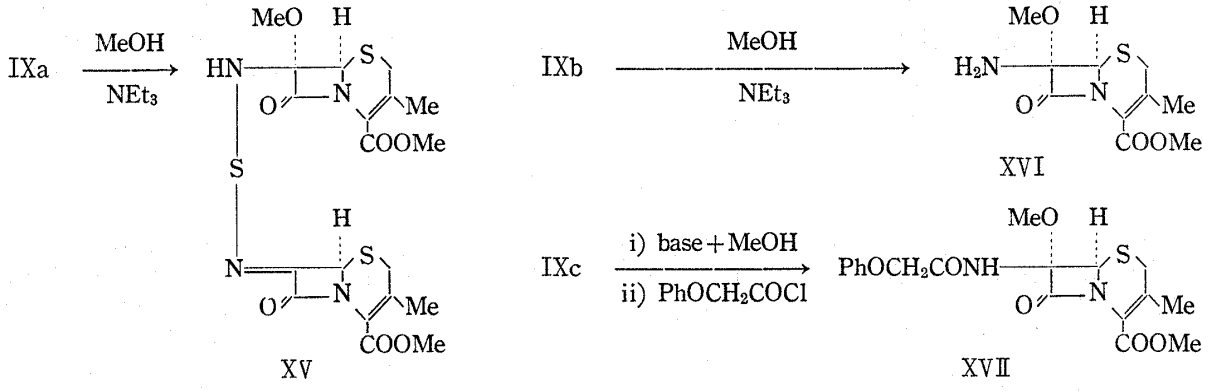


Chart 4

pyridine in large excess methanol for a few hours at room temperature, followed by methoxylation with methanol in the presence of triethylamine and acylation with phenoxyacetyl chloride afforded methyl 7α-methoxy-7β-phenoxyacetamido-3-methyl-3-cephem-4-carboxylate (XVII) in 16% yield, whereas XVII was obtained in 8% yield without pre-treatment with 2,4,6-trimethylpyridine. The main route leading to XVII from IXc would be 7β-amino-7α-methoxy compound (XVI) judging from the above reactions although isolation of the intermediates was not carried out since yields of intermediates are not so reliable owing to loss of the substances by partial decomposition during chromatography.

The reaction pathways of primary amines to sulfenimines should be briefly discussed (Chart 5). Treatment of the amine (XVIII) with thionyl chloride gives N-sulfinylamine

5) H. Yanagisawa and H. Nakao, *Tetrahedron Letters*, **1976**, 1811; for formation of 6,6′-penicillin dimer see R.A. Firestone, N. Schelechow, and B.G. Christensen, *Chem. Commun.*, **1972**, 1106.
6) E. Müller, Houben-Weyl, "Die Methoden der Organischen Chemie," 4 Aufl. Bd. XV ,1974, p. 210.

(XIX)[7] which would be equilibrated with XX due to an active hydrogen located at the α-position of the nitrogen atom. The sulfenic acid derivative (XX) might be transformed to

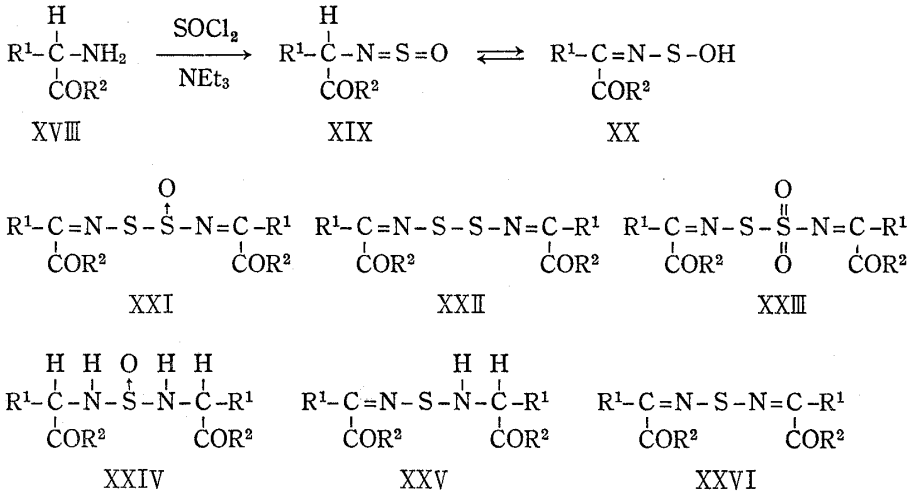


Chart 5

XXI, which is disproportionated into the disulfide (XXII) and thiolsulfonate (XXIII) according to a known sulfenic acid reaction.[8] The reaction of N-sulfinylamine (XIX) with the starting amine (XVIII) would give the sulfoxide (XXIV), which may be converted to XXV by the reaction with thionyl chloride.[9] The unsymmetrical sulfenimine (XXV) would be further transformed to the symmetrical sulfenimine (XXVI) with thionyl chloride by analogy with the reaction of XIII with thionyl chloride and triethylamine. The mechanism of formation of C–C–dimer (XI) is not clear at the present time, however, this dimerization might be, in part, related to formation of diethyl 1,2,5-thiadiazole-3,4-dicarboxylate from ethyl glycinate and N-sulfinylaniline reported by Taguchi, *et al.*[10] or formation of 7,7′-dimer of cephalosporin disclosed by Yanagisawa, *et al.*[5]

Experimental

All melting points are not corrected. Infrared (IR) spectra were recorded on a JASCO A-2 spectrometer, ultraviolet (UV) spectra on a Cary 14 CM-50 (Serial 1258) and MS spectra on a JEOL JMS-01SG mass spectrometer. NMR spectra were taken on a Hitachi-Perkin Elmer R-24, 60 MHz and Varian T-60 (or A-60D) spectrometer using tetramethylsilane as an internal standard. The abbreviations used are as follows: s(singlet), d(doublet), t(triplet), m(multiplet), and b(broad). All reactions were carried out with stirring under an atmosphere of dried argon or nitrogen and using absolute solvents to avoid moisture. Thin-layer chromatography (TLC) was peformed on TLC plates, Silica Gel F_{254} precoated, layer thickness 0.25 mm (E. Merck) and spots were visualized by UV-irradiation. Plates used for preparative TLC were Silica Gel $60F_{254}$ (E. Merck). Evaporations were carried out under reduced pressure with rotatory evaporator at room temperature.

Reactions of Amines (IV and VIII) with Thionyl Chloride——Procedure a): To a stirred solution of the amine (IV; 5 mmoles, VIII; 3 mmoles) and NEt_3 (about 3 eq to amine (IV) or (VIII)) in CH_2Cl_2 (15 ml) was dropwise added $SOCl_2$ (about 1.5 eq to amine (IV) or (VIII)) in CH_2Cl_2 (5 ml) at the temperature described in Table I. The reaction conditions are shown in Table I. After evaporation of the solvent and excess reagents, THF was added to the residue to filter off precipitates of triethylamine hydrochloride ($NEt_3 \cdot HCl$). The

7) For a review of N-sulfinyl compounds see G. Kreeze, A. Maschke, R. Albrecht, K. Bederke, H.P. Patzchke, H. Smalla, and A. Trede, *Angew. Chem. Intern. Ed. Engl.*, **1**, 89 (1962).
8) E. Müller, Houben-Weyl, "Die Methoden der Organishen Chemie," 4 Aufl. Bd. IX, 1955, p. 276.
9) This kind of reaction was verified in another system; T. Hiraoka and T. Kobayashi, manuscript in preparation.
10) T. Taguchi, S. Morita, and Y. Kawazoe, *Chem. Pharm. Bull.* (Tokyo), **23**, 2654 (1975). The reaction of VIII with N-sulfinylaniline in the presence of NEt_3 in CH_2Cl_2 at −78° gave XI in 80% yield, whereas the reaction was very slow without base.

filtrate was evaporated *in vacuo*. The residue was purified by silica gel preparative TLC using benzene–hexane (for amino acid derivatives) or benzene–AcOEt (for cephalosporins) as developing solvents.

Procedure b): The solution of amine (VIII) (3 mmoles) in CH_2Cl_2 (5 ml) was added dropwise to a solution of $SOCl_2$ (about 1.5 eq to VIII) in CH_2Cl_2 (10 ml) which was pre-cooled to the temperature shown in Table I. After a few minutes, a solution of NEt_3 (about 3 eq to VIII) in CH_2Cl_2 (5 ml) was dropwise added. The reaction mixture was kept under such conditions as shown in Table I and worked up as same as procedure a).

Yields of products obtained in these reactions are given in Table I, physical data and spectral data of those are as follows: bis-N-(1-ethoxycarbonylbenzylidene)amino-sulfide (Va), mp 118—119° (EtOAc–*n*-hexane). *Anal.* Calcd. for $C_{20}H_{20}O_4N_2S$: C, 62.48; H, 5.24; N, 7.29; S, 8.34. Found: C, 62.12; H, 5.06; N, 7.26; S, 8.68. Mass Spectrum *m/e*: 384 (M^+). UV $\lambda_{max}^{CH_3CN}$ nm (ε): 231 (14780), 360 (20210). IR ν_{max}^{Nujol} cm^{-1}: 1700, 1600, 1580. NMR ($CDCl_3$) δ ppm: 1.33 (6H, t, $J=7$ Hz), 4.35 (4H, q, $J=7$ Hz), 7.2—8.0 (10H, m), bis-N-(1-ethoxycarbonylbenzylidene)amino-disulfide (Vb), mp 65—66° ($CHCl_3$–*n*-hexane). *Anal.* Calcd. for $C_{20}H_{20}O_4N_2S_2$: C, 57.67; H, 4.84; N, 6.73; S, 15.40. Found: C, 57.67; H, 4.85; N, 6.55; S, 15.20. Mass Spectrum *m/e*: 416 (M^+). UV $\lambda_{max}^{CH_3CN}$ nm (ε): 302 (20090). IR ν_{max}^{Nujol} cm^{-1}: 1705, 1600, 1580. NMR ($CDCl_3$) δ ppm: 1.33 (6H, t, $J=7$ Hz), 4.38 (4H, q, $J=7$ Hz), 7.2—8.0 (10H, m), bis-N-(1-ethoxycarbonylbenzylidene)-amino-trisulfide (Vc), mp 102—103° ($CHCl_3$–*n*-hexane). *Anal.* Calcd. for $C_{20}H_{20}O_4N_2S_3$: C, 53.55; H, 4.49; N, 6.25; S, 21.44. Found: C, 53.21; H, 4.51; N, 6.22; S, 21.49. UV $\lambda_{max}^{CH_3CN}$ nm (ε): 316 (19000). IR ν_{max}^{Nujol} cm^{-1}: 1705, 1600, 1585. NMR ($CDCl_3$) δ ppm: 1.27 (6H, t, $J=7$ Hz), 4.27 (4H, q, $J=7$ Hz), 7.0—7.8 (10H, m), ethyl phenylglyoxylate (VI), transparent pale yellowish liquid. *Anal.* Calcd. for $C_{10}H_{10}O_3$: C, 67.41; H, 5.66. Found: C, 67.05; H, 5.60. Mass Spectrum *m/e*: 178 (M^+). IR ν_{max}^{Liquid} cm^{-1}: 1735, 1690, 1600, 1580. NMR ($CDCl_3$) δ ppm: 1.27 (3H, t, $J=7$ Hz), 4.30 (2H, q, $J=7$ Hz), 7.1—7.7 (3H, m), 7.8—8.1 (2H, m), unidentified substance (VII), mp 145—146° (white crystal from $CHCl_3$–*n*-hexane). *Anal.* Calcd. for $C_{18}H_{16}O_3N_2$: C, 70.12; H, 5.23; N, 9.09. Found: C, 69.65; H, 5.22; N, 9.04. Mass Spectrum *m/e*: 308 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 3150, 3075, 1740, 1715, 1600, 1570. NMR ($CDCl_3$) δ ppm: 1.17 (3H, t, $J=7$ Hz), 4.17 (2H, q, $J=7$ Hz), 6.9—7.8 (8H, m), 8.2—8.6 (2H, m), 9.37 (1H, b), bis-N-(3-methyl-4-methoxycarbonyl-3-cephem-7-ylidene)amino-sulfide (IXa), mp 174—175° (yellow crystal from AcOEt). *Anal.* Calcd. for $C_{18}H_{18}O_6N_4S_3$: C, 44.80; H, 3.76; N, 11.61; S, 19.93. Found: C, 44.75; H, 3.17; N, 11.50; S, 20.53. Mass Spectrum *m/e*: 482 (M^+). UV $\lambda_{max}^{CH_3CN}$ nm (ε): 248 (10740), 349 (16210). IR ν_{max}^{Nujol} cm^{-1}: 1770, 1755, 1730, 1675, 1635. NMR ($CDCl_3$) δ ppm: 2.17 (6H, s), 3.23 and 3.43 (4H, AB-q, $J=18$ Hz), 3.82 (6H, s), 5.39 (2H, s), bis-N-(3-methyl-4-methoxycarbonyl-3-cephem-7-ylidene)amino-disulfide (IXb), mp 64—65° (pale yellow powder from AcOEt–*n*-hexane). *Anal.* Calcd. for $C_{18}H_{18}O_6N_4S_4$: C, 42.01; H, 3.53; N, 10.89; S, 24.92. Found: C, 42.06; H, 3.17; N, 10.30; S, 24.62. UV $\lambda_{max}^{CH_3CN}$ nm (ε): 250 (14880), 280 (11210). IR ν_{max}^{Nujol} cm^{-1}: 1775, 1730, 1680, 1635. NMR ($CDCl_3$) δ ppm: 2.17 (6H, s), 3.25 and 3.47 (4H, AB-q, $J=18$ Hz), 3.84 (6H, s), 5.39 (2H, s), bis-N-(3-methyl-4-methoxycarbonyl-3-cephem-7-ylidene)amino-trisulfide (IXc), mp 174—175° (yellow crystal from AcOEt). *Anal.* Calcd. for $C_{18}H_{18}O_6N_4S_5$: C, 39.55; H, 3.32; N, 10.25; S, 29.33. Found: C, 39.64; H, 3.04; N, 9.79; S, 29.14. UV $\lambda_{max}^{CH_3CN}$ nm (ε): 301 (17140). IR ν_{max}^{Nujol} cm^{-1}: 1780, 1735, 1680, 1640. NMR ($CDCl_3$) δ ppm: 2.18 (6H, s), 3.23 and 3.47 (4H, AB-q, $J=18$ Hz), 3.83 (6H, s), 5.48 (2H, s), N-(3-methyl-4-methoxycarbonyl-3-cephem-7-yl) amino, N′-(3′-methyl-4′-methoxycarbonyl-3′-cephem-7′-ylidene)amino-sulfide (Xa), mp 117—119° (pale yellow powder from AcOEt–*n*-hexane). *Anal.* Calcd. for $C_{18}H_{20}O_6N_4S_3$: C, 44.62; H, 4.16; N, 11.56; S, 19.85. Found: C, 44.48; H, 4.22; N, 10.99; S, 19.78. UV $\lambda_{max}^{CH_3CN}$ nm (ε): 279 (12470). IR ν_{max}^{Nujol} cm^{-1}: 3330, 1780, 1730, 1670, 1640. NMR ($CDCl_3$) δ ppm: 2.16 (6H, s), 3.20 and 3.49 (2H, AB-q, $J=18$ Hz), 3.24 and 3.52 (2H, AB-q, $J=18$ Hz), 3.82 (3H, s), 3.86 (3H, s), 4.53 (1H, d, $J=9$ Hz), 4.8—5.2 (2H, m), 5.76 (1H, s), 7,7′-dimer (XI), mp 168—170° (pale yellowish powder from $CHCl_3$–*n*-hexane). *Anal.* Calcd. for $C_{18}H_{22}O_6N_4S_2$: C, 47.57; H, 4.88; N, 12.33; S, 14.11. Found: C, 47.43; H, 4.56; N, 11.88; S, 13.80. Mass Spectrum *m/e*: 454 (M^+). UV $\lambda_{max}^{CH_3CN}$ nm (ε): 271 (13530). IR ν_{max}^{Nujol} cm^{-1}: 3380, 3310, 1775, 1725, 1640. NMR ($CDCl_3$) δ ppm: 2.07 (6H, s), 2.20 (4H, b), 3.19 and 3.50 (4H, AB-q, $J=18$ Hz), 3.80 (6H, s), 5.16 (2H, s).

Ethyl Phenylglyoxylate (VI) from Vc——10% hydrochloric acid (HCl) solution (3 ml) was added to a solution of Vc (135 mg) in THF (3 ml) with stirring at room temperature. Exothermic reaction subsided within 10 minutes, and TLC showed ethyl phenylglyoxylate (VI) and sulfur with complete disappearance of the starting material. The reaction mixture was poured into a mixture of AcOEt and water. The organic layer was washed successively with water, sat. $NaHCO_3$ solution and sat. NaCl solution. After drying over $MgSO_4$ the solvents were evaporated under reduced pressure at room temperature. Purification of the residue by silica gel preparative TLC (benzene–*n*-hexane=20: 1) gave VI (86 mg, 80%) as a transparent pale yellowish liquid. Spectral data of the product were completely identical with those described above.

7,7′-Dimer of Methyl 7β-Phenylacetamido-3-methyl-3-cephem-4-carboxylate (XII)——To a stirred solution of XI (300 mg) in CH_2Cl_2 (10 ml) was dropwise added phenylacetyl chloride (200 mg) under ice-cooling, followed by addition of NEt_3 (150 mg). After the reaction mixture was stirred at room temperature for 1.5 hr, the solution was poured into a mixture of AcOEt and water. The organic layer was separated, washed successively with 5% HCl solution, sat. $NaHCO_3$ solution and water, and dried over $MgSO_4$. After evaporation of the solvents, the residue was purified by silica gel preparative TLC (benzene–AcOEt=1: 1) to afford XII (160 mg, 35% yield) as white powder. mp 96—98°. *Anal.* Calcd. for $C_{34}H_{34}O_8N_4S_2$: C, 59.12; H, 4.96; N, 8.11; S, 9.28. Found: C, 58.87; H, 5.14; N, 7.75; S, 9.09. Mass Spectrum *m/e*: 690 (M^+). IR ν_{max}^{Nujol} cm^{-1}:

3400, 3300, 1780, 1725, 1685, 1630, 1600. NMR ($CDCl_3$) δ ppm: 2.17 (6H, s), 2.80 and 3.03 (4H, AB-q, $J=18$ Hz), 3.50 (4H, s), 3.76 (6H, s), 5.53 (2H, s), 7.17 (2H, s), 7.23 (10H, s-like). Spectroscopy (MS, IR and NMR) of the product was identical with that of an authentic sample.[5,11]

Bis-N-(3-methyl-4-methoxycarbonyl-3-cephem-7β-yl)aminodisulfide (XIIIa)——S_2Cl_2 (150 mg) in CH_2Cl_2 (2 ml) was added to a solution of VIII (456 mg) in CH_2Cl_2 (5 ml) at $-78°$, followed by the addition of NEt_3 (250 mg) in CH_2Cl_2 (2 ml). The reaction mixture was stirred at $-78°$ for 1 hr. The solvent was removed under reduced pressure. To the residue was added THF and $NEt_3 \cdot HCl$ was filtered off. The filtrate was again evaporated and purified by silica gel TLC (benzene–AcOEt=5: 1). Further washing the residue with a small amount of cold AcOEt yielded XIIIa (387 mg, 74%) as colorless powder. mp 153—154°. *Anal.* Calcd. for $C_{18}H_{22}O_6N_4S_4$: C, 41.69; H, 4.28; N, 10.80; S, 24.73. Found: C, 42.19; H, 4.22; N, 10.37; S, 24.76. UV $\lambda_{max}^{CH_3CN}$ nm (ε): 266 (12370). IR ν_{max}^{Nujol} cm^{-1}: 3330, 1775, 1725, 1645. NMR ($CDCl_3$) δ ppm: 2.13 (6H, s), 3.27 and 3.56 (4H, AB-q, $J=18$ Hz), 3.83 (6H, s), 4.20 (2H, d, $J=10$ Hz), 4.8—5.1 (4H, m). In some cases this reaction was accompanied by many side products such as IXa, IXc, N-(3-methyl-4-methoxycarbonyl-3-cephem-7β-yl)amino, N′-(3′-methyl-4′-methoxycarbonyl-3′-cephem-7′-ylidene)amino-trisulfide (Xb), mp 142—143° (yellow powder from AcOEt). *Anal.* Calcd. for $C_{18}H_{20}O_6N_4S_5$: C, 39.40; H, 3.67; N, 10.21; S, 29.22. Found: C, 39.07; H, 3.93; N, 9.72; S, 28.80. UV $\lambda_{max}^{CH_3CN}$ nm (ε): 312 (10280). IR ν_{max}^{Nujol} cm^{-1}: 3310, 1780, 1770, 1735, 1670, 1640. NMR ($CDCl_3$) δ ppm: 2.14 (3H, s), 2.19 (3H, s), 3.24 and 3.46 (2H, AB-q, $J=18$ Hz), 3.26 and 3.54 (2H, AB-q, $J=18$ Hz), 3.83 (3H, s), 3.86 (3H, s), 4.30 (1H, d, $J=8$ Hz), 4.8—5.1 (2H, m), 5.41 (1H, s), bis-N-(3-methyl-4-methoxycarbonyl-3-cephem-7β-yl)amino-tetrasulfide (XIIIb), mp 95—96° (pale yellow powder from *n*-hexane–AcOEt). *Anal.* Calcd. for $C_{18}H_{22}O_6N_4S_6$: C, 37.10; H, 3.81; N, 9.61; S, 33.01. Found: C, 37.10; H, 4.09; N, 9.07; S, 32.46. IR ν_{max}^{Nujol} cm^{-1}: 3270, 1775, 1725, 1640. NMR ($CDCl_3$) δ ppm: 2.14 (6H, s), 3.25 and 3.41 (4H, AB-q, $J=18$ Hz), 3.79 (6H, s), 4.8—5.1 (4H, m), 5.48 (2H, d, $J=9$ Hz), and 7β-cycloheptasulfurimide (XIV).

3-Methyl-4-methoxycarbonyl-3-cephem-7β-cycloheptasulfurimide (XIV)——To a solution of VIII (456 mg) and NEt_3 (650 mg) in CH_2Cl_2 (10 ml) was added dropwise a solution of excess S_2Cl_2 (400 mg) in CH_2Cl_2 (2 ml) under cooling at $-78°$. The reaction mixture was stirred at $-78°$ for 1 hr and then poured into a mixture of AcOEt and sat. $NaHCO_3$ solution. The organic layer was washed twice with water, dried over $MgSO_4$ and evaporated. The residue was purified by silica gel preparative TLC (benzene–AcOEt=5: 1) and recrystallized from AcOEt to afford XIV (72 mg, 8%) as white powder. mp 104—106°. *Anal.* Calcd. for $C_9H_{10}O_3N_2S_8$: C, 23.99; H, 2.24; N, 6.22; S, 56.91. Found: C, 24.27; H, 2.15; N, 6.00; S, 57.09. IR ν_{max}^{Nujol} cm^{-1}: 1775, 1715, 1640. NMR ($CDCl_3$) δ ppm: 2.20 (3H, s), 3.38 and 3.48 (2H, AB-q, $J=18$ Hz), 3.85 (3H, s), 4.97 (1H, d, $J=4$ Hz), 5.19 (1H, d, $J=4$ Hz). Molecular weight was determined to be about 500.

IXc and Xa from XIIIa——To a stirred solution of XIIIa (520 mg) in CH_2Cl_2 (10 ml) was added a solution of $SOCl_2$ (150 mg) in CH_2Cl_2 (2 ml), followed by the addition of NEt_3 (250 mg) in CH_2Cl_2 (2 ml) at $-78°$ and stirring was continued for additional 1 hr. After evaporation of the solvent, dry THF was added to the residue and $NEt_3 \cdot HCl$ was filtered off. The filtrate was evaporated and the residue was purified by silica gel preparative TLC (benzene–AcOEt=5: 1) to give IXc (120 mg, 22%) and Xa (68 mg, 14%). These products were identical with those obtained by the reaction of VIII with $SOCl_2 \cdot NEt_3$.

IXb from the Trisulfide (IXc)——To a solution of IXc (200 mg) in CH_2Cl_2 (10 ml) and MeOH (5 ml) was added 2,4,6-trimethylpyridine (200 mg). The reaction mixture was kept at room temperature for 5 hr. The solution was evaporated under reduced pressure and the residue was purified by preparative TLC (silica gel, benzene–AcOEt=4: 1) to afford IXb (72 mg, 38% yield) together with recovered starting material (50 mg, 25%). These samples also showed identical physical and spectral data with those of authentic compounds described above.

N-(7α-Methoxy-3-methyl-4-methoxycarbonyl-3-cephem-7β-yl)amino, N′-(3′-Methyl-4′-methoxycarbonyl-3′-cephem-7′-ylidene)amino-sulfide (XV)——A mixture of IXa (200 mg), MeOH (1 ml) and NEt_3 (4 drops) in CH_2Cl_2 (3 ml) was allowed to stand at room temperature for 1 hr. After evaporation of the solvent, the residue was purified by silica gel TLC (benzene–AcOEt=4: 1) to afford XV (158 mg, 74%). Pale yellowish powder was obtained by precipitation of XV in AcOEt with *n*-hexane. mp 96—97°. *Anal.* Calcd. for $C_{19}H_{22}O_7N_4S_3$: C, 44.35; H, 4.31; N, 10.89; S, 18.69. Found: C, 44.44; H, 4.67; N, 10.36; S, 18.29. UV $\lambda_{max}^{CH_3CN}$ nm (ε): 247 (10940), 283 (11460). IR ν_{max}^{Nujol} cm^{-1}: 3320, 1775, 1740, 1730, 1670, 1635. NMR ($CDCl_3$) δ ppm: 2.13 (3H, s), 2.18 (3H, s), 3.17 and 3.46 (2H, AB-q, $J=18$ Hz), 3.21 (2H, s), 3.57 (3H, s), 3.81 (6H, s), 4.89 (1H, s), 5.28 (1H, s), 5.44 (1H, s).

Methyl 7β-Amino-7α-methoxy-3-methyl-3-cephem-4-carboxylate (XVI)——To a solution of IXb (200 mg) in CH_2Cl_2 (2 ml) and MeOH (2 ml) was added dropwise NEt_3 (8 drops), the mixture was allowed to stand at room temperature for 1 hr and worked up as in the case of preparation of XV to give 7α-methoxy compound (XVI) (54 mg, 27% yield) as pale brownish foam. *Anal.* Calcd. for $C_{10}H_{14}O_4N_2S$: C, 46.50; H, 5.46; S, 12.41. Found: C, 46.56; H, 5.49; S, 11.86. UV $\lambda_{max}^{CH_3CN}$ nm (ε): 240 (5400). IR $\nu_{max}^{CH_2Cl_2}$ cm^{-1}: 3425, 3350, 1775, 1725, 1640. NMR ($CDCl_3$) δ ppm: 2.1—2.3 (2H, b), 2.20 (3H, s), 3.20 (2H, s), 3.49 (3H, s), 3.82 (3H, s), 4.83 (1H, s).

11) We thank Dr. Yanagisawa for supplying the authentic sample.

Methyl 7α-Methoxy-3-methyl-7β-phenoxyacetamido-3-cephem-4-carboxylate (XVII) from IXc——a) To a stirred solution of IXc (200 mg) in a mixture of CH_2Cl_2 and MeOH (CH_2Cl_2–MeOH=2: 1, 20 ml) was added NEt_3 (300 mg) in CH_2Cl_2 (3 ml). The mixture was allowed to stand at room temperature for 1 hr and then the solvents were evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2 (10 ml) to which was added NEt_3 (150 mg) and phenoxyacetyl chloride (250 mg) successively under ice-cooling. After 1 hr, the reaction mixture was poured into a mixture of AcOEt and water. The organic layer was separated and washed successively with 5% HCl, sat. $NaHCO_3$ and sat. NaCl solution. After drying over $MgSO_4$ the solvent was evaporated, and the residue was chromatographed on silica gel (benzene–AcOEt=2: 1) to afford XVII (23 mg, 8%) as foam.

b) To a solution of IXc (220 mg) in CH_2Cl_2 (10 ml) and MeOH (5 ml) was added 2,4,6-trimethylpyridine (500 mg). The solution was kept at room temperature for 2 hr. Then NEt_3 (300 mg) was added to the resulting solution. After the reaction mixture was allowed to stand at room temperature for 1 hr, solvents were completely evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2 (10 ml), to which was added phenoxyacetyl chloride (275 mg) and NEt_3 (200 mg) under ice-cooling. Stirring was continued for 1 hr at 0—5°. The reaction mixture was worked up as described above to afford XVII in 16% yield (51 mg, pale yellow foam). *Anal.* Calcd. for $C_{18}H_{20}O_6N_2S$: C, 55.09; H, 5.14; N, 7.14; S, 8.17. Found: C, 55.03; H, 5.42; N, 6.61; S, 7.86. Mass Spectrum *m/e*: 392 (M^+). UV $\lambda_{max}^{CH_3CN}$ nm (ε): 218 (12110), 269 (6790), 275 (6210). IR $\nu_{max}^{CH_2Cl_2}$ cm^{-1}: 3420, 1780, 1730, 1710, 1640, 1600. NMR ($CDCl_3$) δ ppm: 2.18 (3H, s), 3.18 (2H, s), 3.56 (3H, s), 3.84 (3H, s), 4.60 (2H, s), 5.08 (1H, s), 6.8—7.6 (6H, m).