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Reactions of Sulfamides with Thionyl Chloride and a Base

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On treatment of the N,N′-disubstituted sulfamides (III) bearing active hydrogens at α-carbons with thionyl chloride and triethylamine, sulfenimines (II) were obtained. These reactions were also applied to cephalosporins (XI and XIII).

Keywords——cephalosporin; sulfamide; sulfenimine; N-sulfinylamine; N-sulfonylamine; thionyl chloride

In the preceding paper,[2] we reported a new synthetic route to sulfenimines (II) starting from primary amines (I) bearing an activated hydrogen at the α-carbon by the reaction with thionyl chloride ($SOCl_2$) and a base. This report deals with another pathway to sulfenimines (II), which comprises the reaction of N,N′-disubstituted sulfamides (III) having active hydrogens at the α-carbon to nitrogen with thionyl chloride and a base.

In the reaction of primary amines with thionyl chloride the sulfinylamine (IV), the sulfenic acid (V) and the sulfoxide (VI) have been postulated as key intermediates.[2] Considering these intermediates and the reaction mechanisms it is very interesting that the N-chlorosulfinyl sulfamide (VII) derived from the sulfamide (III) and thionyl chloride would give either N-sulfinylamine (IV) (path a) or three membered intermediate (IX)[3] (path b) on

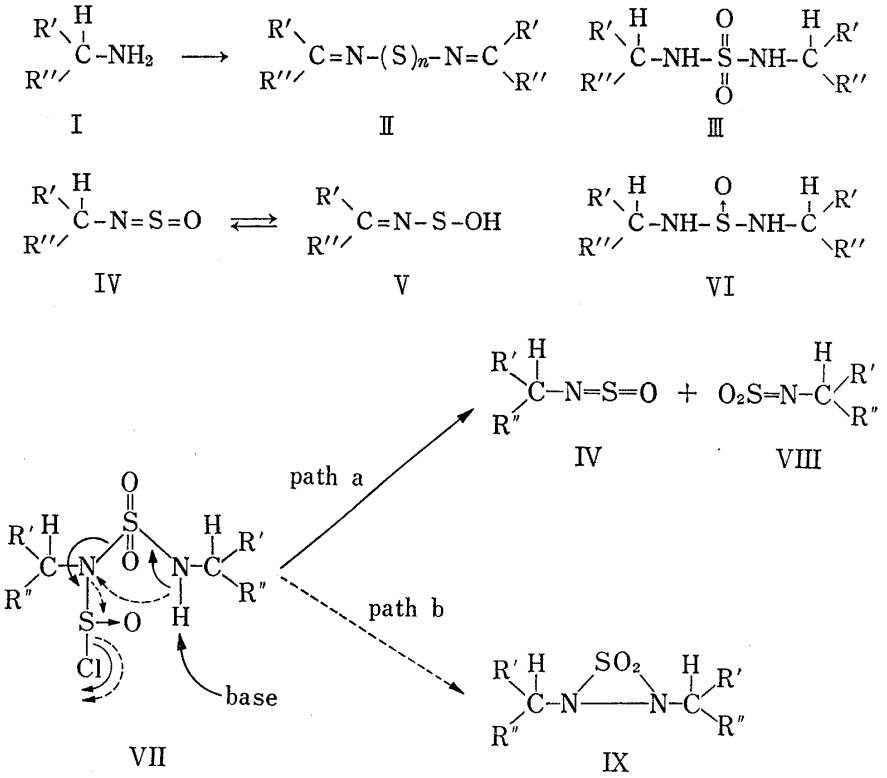

Chart 1

1) Location: *2–58, Hiromachi 1–chome, Shinagawa-ku, Tokyo, 140, Japan.*
2) T. Saito and T. Hiraoka, *Chem. Pharm. Bull.* (Tokyo), **25**, 784 (1977).
3) J.W. Timberlake, M.L. Hodges, and K. Betterton, *Synthesis*, **1972**, 632.

treatment with a base (Chart 1). Also our attention was focused on the fate of the N-sulfonylamine (VIII)[4] with active hydrogens at the α-position if that kind of species would be generated. According to literatures cleavage of N-SO_2 bond is achieved under relatively strong conditions[5] and a mild method is still being searched.[6] Thus, the path b might be more probable than the path a. This time we clarified that the latter path is actual case. Furthermore we examined whether this reaction could be applied to cephalosporins leading to 7-imino-compound or not.

The starting sulfamides (III) were prepared by similar procedure of known methods.[7] These results are summarized in Table I. The sulfamides of α-aminoacid esters and benzyl-

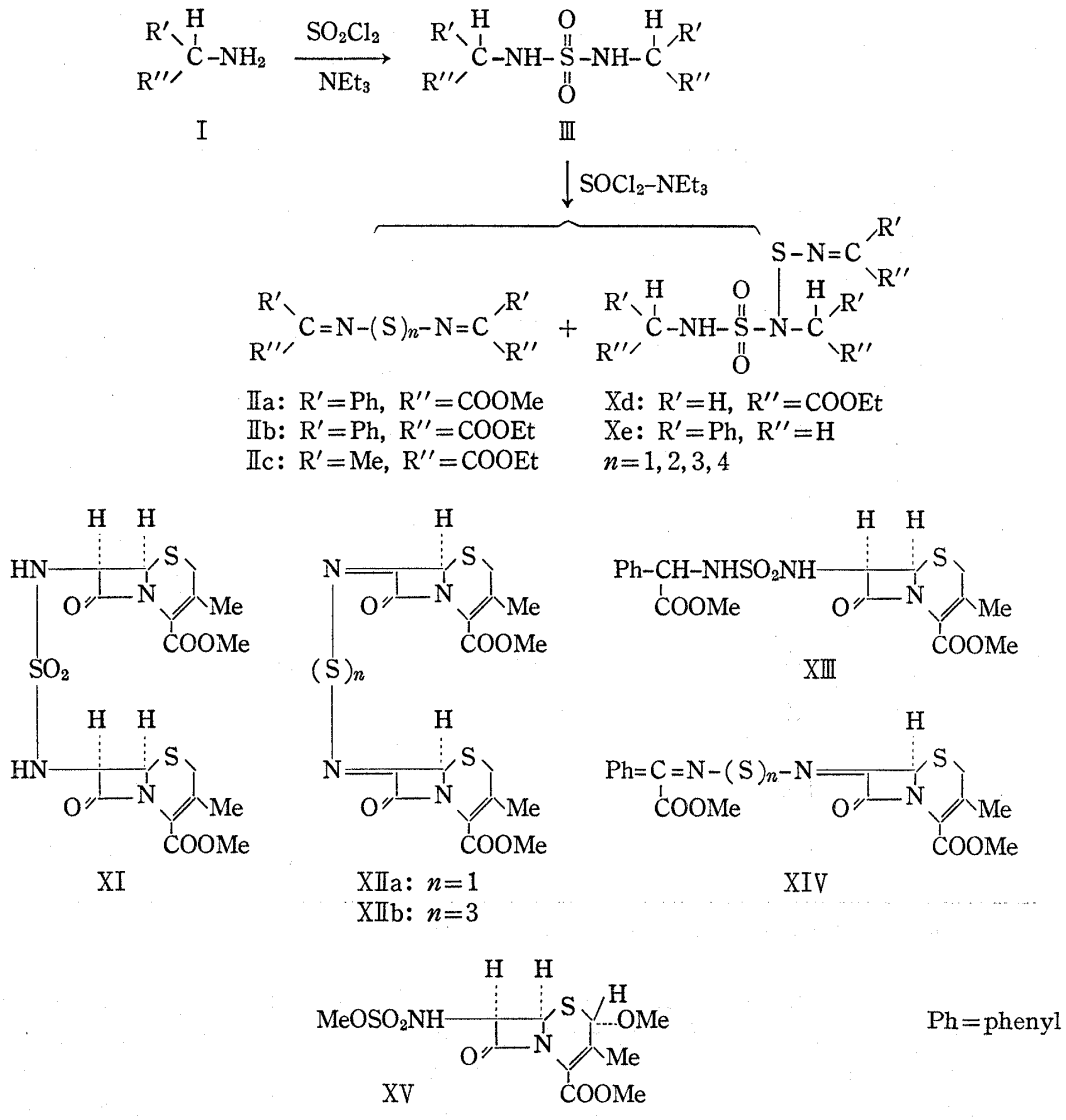

Chart 2

4) For the reactions of N-sulfonylamines having no active hydrogen at the α-position, see; *a*) G.M. Atkins, Jr. and E.M. Burgess, *J. Am. Chem. Soc.*, **89**, 2502 (1967); *b*) G.M. Atkins, Jr. and E.M. Burgess, *ibid.*, **90**, 4744 (1968); *c*) E.M. Burgess, H.R. Penton, Jr., E.A. Taylor, and W.M. Williams, *J. Org. Chem.*, **38**, 26 (1973); *d*) E.M. Burgess and W.M. Williams, *J. Org. Chem.*, **38**, 1249 (1973).

5) *a*) S. Searles and S. Nukina, *Chem. Rev.*, **59**, 1077 (1955); *b*) F.L. Scott, J.A. Barry, and W.J. Spillane, *J. Chem. Soc. Perkin I*, **1972**, 2666; *c*) W.J. Spillane, *Int. J. Sulfur Chem.*, **8**, 469 (1973) and references cited therein.

6) For example, see J.B. Hendrickson and R. Bergeron, *Tetrahedron Letters*, **1970**, 345.

7) *a*) E.W. Parnell, *J. Chem. Soc.*, **1960**, 4366; *b*) ref. 4*a*); *c*) D.L. Forster, T.L. Gilchrist, and C.W. Rees, *J. Chem. Soc.* (*C*), **1971**, 993, and references cited therein.

amine (IIIa—e) were prepared from the corresponding amines (Ia—e) by the reactions with sulfuryl chloride (SO_2Cl_2) and triethylamine (NEt_3) in dichloromethane (CH_2Cl_2) at −78° without difficulty. In the case of methyl 7β-amino-3-methyl-3-cephem-4-carboxylate (If) such conditions were not enough to complete the reaction and the yield of XI was low (15—20%) with recovery of the starting material. The reaction conditions of this case were not optimized. Using excess reagents (SO_2Cl_2, NEt_3) and quenching with methanol (MeOH) gave the unexpected product (XV) which would be derived from a 2-substituted intermediate by subsequent alcoholysis.[8] The unsymmetrical sulfamide (XIII) was also prepared, however, yields varied depending upon the order of the addition of two kinds of the amines (see Table I).

Table I. Preparation of Sulfamides (III, XI, XIII)

Run	Amine (mmole)	Amine (eq)	SO_2Cl_2 (eq)	NEt_3 (eq)	Temp. (°C)	Time (hr)	Sulfamide Compd.	Sulfamide Yield (%)
1	D(−)-Ia 10	1.0[1]*	0.6[2]*	1.5[3]*	−78	2.0	IIIa	68
2	D(−)-Ib 10	1.0[1]*	0.6[2]*	1.5[3]*	−78	2.0	IIIb	82
3	DL-Ic·HCl 50	1.0[1]*	0.6[3]*	1.1[2]* 1.4[4]*	−78	0.5		
					r.t.	0.5	IIIc	43
4	Ib·HCl 200	1.0[1]*	0.6[3]*	1.1[2]* 1.4[4]*	−78	0.5		
					r.t.	1.0	IIId	18
5	Ie 50	1.0[1]*	0.6[2]*	1.4[3]*	−78	0.5	IIIe	64
6	If 5	1.0[1]*	0.6[2]*	1.2[3]*	−78	1.0	XI (If	20 34)
7	If 4	1.0[1]*	1.0[3]*	2.5[2]*	−78	0.5		
	Ia 5	1.25[4]*			−78	0.5	XI	36
					r.t.	1.0	XIII	7
8	Ia 3	1.5[1]*	1.5[2]*	3.2[3]*	−78	0.5		
	If 2	1.0[4]*			−78	0.5	XI	28
					r.t.	1.0	XIII	43

The number bearing an asterisk shows the order of adding reagents.

Treatment of the sulfamide (IIIa) with thionyl chloride and triethylamine at 0—5° for 1 hour gave bis-N-(1-methoxycarbonylbenzylidene)amino-sulfide (IIa-S_1) and methyl phenylglyoxylate (XVIIIa) in 44% and 11% yield, respectively. Analogous result was obtained in the case of the ethylester (IIIb) under slightly different conditions. The reaction of the sulfamide (IIIc) with thionyl chloride and triethylamine afforded bis-N-(1-ethoxycarbonylethylidene)amino-disulfide (IIc-S_2) and N-(1-ethoxycarbonylethyl)-N-(1′-ethoxycarbonylethylidene)aminothio-N′-(1″-ethoxycarbonylethyl)-sulfamide (Xc) in 18% and 11% yield, respectively. Monosulfide (n=1) of IIc was not detected in an appreciable amount in striking contrast to the rection of IIIa—b. Structural determination of Xc was based on its nuclear magnetic resonance (NMR) and mass (MS) spectra together with elemental analysis. In the case of the sulfamide (IIId) derived from ethyl glycinate hydrochloride (Id-HCl), bis-N-(ethoxycarbonylmethylidene)amino-sulfide (IId-S_1), the corresponding disulfide (IId-S_2),

8) D.O. Spry, *Tetrahedron Letters*, **1972**, 3717.

trisulfide (IId-S_3), tetrasulfide (IId-S_4) and the thiosulfamide (Xd) were obtained in relatively low yields. Analogously N,N′-dibenzylsulfamide (IIIe) produced bis-N-(benzylidene)amino-sulfide (IIe-S_1), its disulfide (IIe-S_2) and tetrasulfide (IIe-S_4).

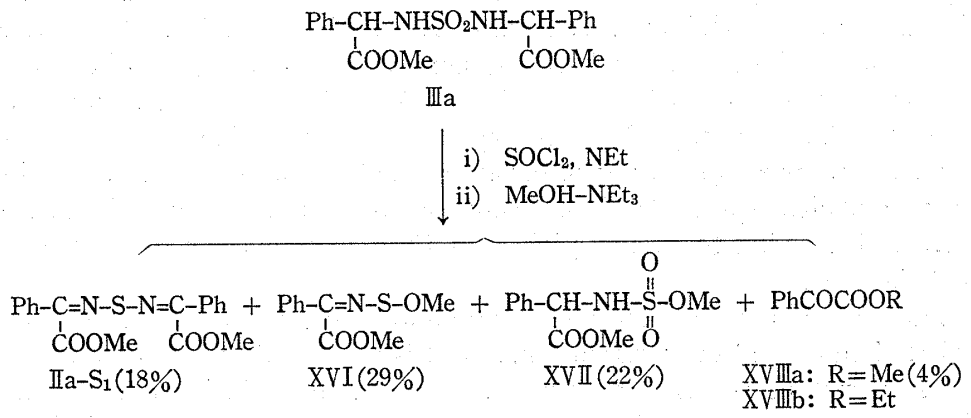

Chart 3

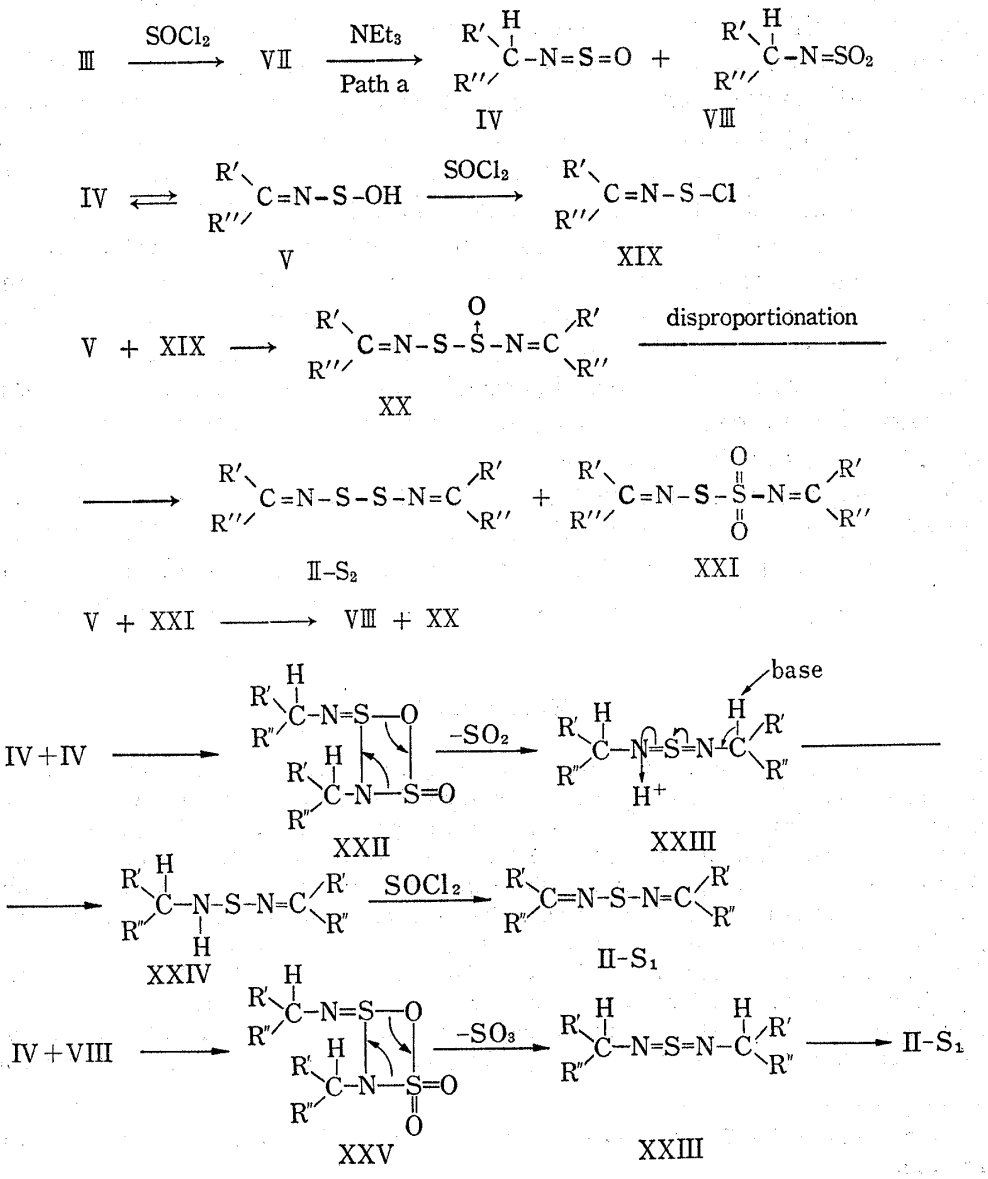

Chart 4

These reactions were applied to a cephalosporin derivative in order to obtain a 7-imino-cephalosporin which is an important precursor of 7-methoxy-cephalosporins with enhanced biological activity.[9] Treatment of the cephalosporin sulfamide (XI) with thionyl chloride and triethylamine at 0—5° for 1 hour afforded bis-N-(3-methyl-4-methoxycarbonyl-3-cephem-7-ylidene)amino-sulfide (XIIa) and its trisulfide (XIIb)[2] in low yields. In the case of unsymmetrical sulfamide (XIII), N-(3-methyl-4-methoxycarbonyl-3-cephem-7-ylidene)amino, N'-(1'-methoxycarbonylbenzylidene)amino-sulfide (XIV) and its di (or tri) sulfide were obtained together with IIa-S_1 and methyl phenylglyoxylate (XVIIIa). The sulfide could not be purely seperated with respects to number of sulfur atom due to their similar *Rf* values in chromatography. For an efficient synthesis of 7-imino-cephalosporin derivative this sulfamide reaction is not so attractive owing to its low yield, but the reaction seems to be valuable as a new N-SO_2 bond cleavage.

It is noteworthy that the reaction of sulfamide with thionyl chloride does not occur without triethylamine and only starting material is recovered quantitatively. For clarification of mechanisms the reaction mixture of IIIa, thionyl chloride and triethylamine was quenched with methanol at −78° to give monosulfide (IIa-S_1) (18%), methyl N-(1-methoxycarbonylbenzylidene)amino-sulfenate (XVI) (29%), methyl N-(1-methoxycarbonylbenzyl)-sulfamate (XVII) (22%) and methyl phenylglyoxylate (XVIIIa) (4%) (Chart 3). In this reaction only monosulfide was produced ,whereas the reaction of phenylglycine ester with thionyl chloride and triethylamine yielded the corresponding mono, di and trisulfide.[2] Furthermore N,N'-diphenylsulfamide bearing no active hydrogen at the α-carbon also reacted with thionyl chloride by adding triethylamine to give N-sulfinylaniline. From these results the mechanisms of the reaction of the sulfamides with thionyl chloride and triethylamine would be considered as follows (Chart 4). The sulfamide (III) gives the intermediate (VII), which would cleave to N-sulfinylamine (IV) and N-sulfonylamine (VIII). The fate of the former (IV) has been described in the preceding paper to afford disulfide (II-S_2) and thiolsulfonate (XXI).[2] There is a possibility that the sulfenic acid (V) would react with thiolsulfonate (XXI) to afford VIII and XX. From the experiments of the sulfamides (IIIa—b) which are shown in Chart 3 a dimerization mechanism ($\pi 2_s + \pi 2_a$ reaction) should be considered for explaining the products distribution (predominace of S_1-product) as in the case of Taguchi, *et al.*[10] Thus cycloaddition of the N-sulfinylamine (IV) might yield the adduct (XXII) which loses sulfur dioxide to furnish XXIII and finally to give II-S_1. A cross dimerization of IV and VIII would afford XXV which also leads to XXIII by elimination of sulfur trioxide. On the formation of trisulfide and tetrasulfide no clear-cut explanation is available at the present time, however, some disproportionation mechanism might be operative.

Experimental

All melting points were measured on a micro hot stage apparatus and are uncorrected. Infrared (IR) spectra were recorded on a JASCO A-2 spectrometer, ultraviolet (UV) spectra on a Cary 14 CM-50 (Serial 1258) and mass (MS) spectra on a JEOL JMS-01SG mass spectrometer. NMR spectra were taken on a Varian T-60 or a Hitachi-Perkin Elmer R-24, 60 MHz, spectrometer using tetramethylsilane as an internal standard. The abbreviations are as follows: s(singlet), d(doublet), t(triplet), m(multiplet) and b(broad). Usually absolute solvents were used for reactions. Thin-layer chromatography (TLC) was performed 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). Solvents were removed with a rotary flash evaporator under reduced pressure at room temperature.

Sulfamides (III)——N,N'-Bis(1-methoxycarbonylbenzyl)sulfamide (IIIa), N,N'-bis(1-ethoxycarbonylbenzyl)sulfamide (IIIb), N,N'-bis(1-ethoxycarbonylethyl)sulfamide (IIIc), N,N'-(1-ethoxycarbonylmethyl)-

9) For synthetic methods for 7-methoxy-cephalosporins and their biological importance see references cited in ref. 2).

10) T. Taguchi, S. Morita, and Y. Kawazoe, *Chem. Pharm. Bull.* (Tokyo), 23, 2654 (1975).

sulfamide (IIId) and N,N′-dibenzylsulfamide (IIIe) were prepared from the corresponding amines (or their hydrochlorides) (1 eq), SO_2Cl_2 (0.6 eq) and NEt_3 (1.2—1.5 eq) in CH_2Cl_2 at −78° by the similar method to that of Parnell. In the case of amine hydrochloride initial neutralization of HCl with NEt_3 (1 eq) was carried out. Reaction conditions and the results are given in Table I, physical data of the sulfamides (IIIa—e) in Table II.

Table II. Physical Data of Sulfamides (IIIa—e)

Compd.	mp (°C) (Recryst. Solvent)	IR[a] Nujol, cm^{-1} (or Film)	UV[b] $\lambda_{max}^{CH_3CN}$ nm (ε)	Formula	Analysis (%) Calcd. (Found) C	H	N	S	MS[c]
IIIa[e]	152—153 (AcOEt–*n*-hexane)	3310, 1740, 1615, 1600	247(233) 252(307) 258(394) 264(315)	$C_{18}H_{20}O_6N_2S$	55.09 (54.77)	5.14 (5.27)	7.14 (6.97)	8.17 (8.48)	392 (M^+)
IIIb[e]	96— 98 (AcOEt–*n*-hexane)	3280, 1730, 1615, 1600	252(339) 258(431) 264(344)	$C_{20}H_{24}O_6N_2S$	57.13 (57.18)	5.75 (5.58)	6.66 (6.58)	7.62 (7.82)	420 (M^+)
IIIc[e]	colorless oil	(3310, 1740)	210(232)	$C_{10}H_{20}O_6N_2S$	40.53 (40.44)	6.80 (6.92)	9.45 (9.50)	10.82 (10.69)	296 (M^+)
IIId	53— 54 (*n*-Hexane)	3250, 1740		$C_8H_{16}O_6N_2S$	35.82 (35.93)	6.01 (5.95)	10.44 (10.41)	11.95 (12.08)	268 (M^+)
IIIe	179—180 (AcOEt)	3300, 1610	247(212) 252(300) 258(379) 267(176)	$C_{14}H_{16}O_2N_2S$	60.85 (60.82)	5.84 (5.74)	10.14 (10.14)	11.60 (11.78)	276 (M^+)

Compd.	Solvent	NMR(δ-value)
IIIa[e]	$CDCl_3$	*e*) mixture of two isomers; major isomer: minor isomer=7:1 (major isomer): 3.68 (6H, s), 5.03(2H, d, J=8Hz), 5.69(2H, d, J=8 Hz), 7.29(10H, s). (Minor isomer): 3.58(6H, s), 5.01(2H, d, J=8 Hz), 5.66(2H, d, J=8Hz), 7.37(10H, s)
IIIb[e]	$CDCl_3$	*e*) mixture of two isomers; major isomer: minor isomer=2: 1 (major isomer): 1.11(6H, t, J=7Hz), 4.02(4H, q, J=7Hz), 4.96(2H, d, J=8Hz), 5.64(2H, d, J=8Hz), 7.28(10H, s). (Minor isomer): 1.17(6H, t, J=7Hz), 4.14(4H, q, J=7Hz), 4.97(2H, d, J=8Hz), 5.64 (2H, d, J=8Hz), 7.22(10H, s)
IIIc[e]	$CDCl_3$	(1: 1-mixture of two isomers): 1.27(6H, t, J=7Hz; δ of two isomers is identical), 1.37 and 1.41(6H, two species of d, J=8Hz), 3.75—4.45(6H, m), 5.37(2H, d, J=8Hz; identical δ-value for isomers)
IIId	$CDCl_3$	1.27(6H, t, J=7Hz), 3.85(4H, d, J=6Hz), 4.20(4H, q, J=7Hz), 5.30 (2H, t, J=6Hz)
IIIe	DMF-d_7	4.15(4H, d, J=7Hz), 7.15(2H, d, J=7Hz), 7.16—7.53(10H, m)

a) run on a JASCO A-2
b) run on a Cary 14 CM-50
c) run on a JEOL JMS-01SG
d) run on a Varian T-60 spectrometer
e) mixture of two isomers

N,N′-Bis(3-methyl-4-methoxycarbonyl-3-cephem-7β-yl)sulfamide (XI)——To a stirred solution of methyl 7β-amino-3-methyl-3-cephem-4-carboxylate (If) (1.14 g) in CH_2Cl_2 (20 ml) were added dropwise a solution of SO_2Cl_2 (405 mg) in CH_2Cl_2 (2 ml) and a solution of NEt_3 (610 mg) in CH_2Cl_2 (3 ml) successively under cooling at −78°. After the reaction mixture was kept at −78° for 1 hr, warmed to −10°. Absolute MeOH (20 ml) was dropwise added to the mixture to quench excess SO_2Cl_2. The reaction mixture was evaporated under diminished pressure. Tetrahydrofuran (THF) was added to the residue to filter off precipitates of NEt_3·HCl. The filtrate was concentrated and purified by preparative TLC (silica gel plates, benzene–AcOEt =1: 1) to give XI (260 mg, 20%) together with the starting amine (If) (388 mg, 34%). Recrystallization of XI from acetone–*n*-hexane afforded white granules. mp 120—121°. *Anal.* Calcd. for $C_{18}H_{22}O_8N_4S_3$: C, 41.69; H, 4.28; N, 10.80; S, 18.55. Found: C, 41.27; H, 4.35; N, 10.42; S, 18.28. Mass Spectrum *m/e*: 518 (M^+). IR ν_{max}^{Nujol} cm^{-1}: 3240, 1780, 1725, 1640. NMR (CD_3COCD_3) δ ppm: 2.08 (6H, s), 3.34 and 3.62 (4H, AB-q, J=18 Hz), 3.77 (6H, s), 5.10 (2H, d, J=4 Hz), 5.33 (2H, dd, J=8 Hz, J=4 Hz), 7.34 (2H, d, J=8 Hz).

N-(3-Methyl-4-methoxycarbonyl-3-cephem-7β-yl)-N′-(1′-methoxycarbonylbenzyl)sulfamide (XIII)——A) A solution of NEt_3 (1.01 g) in CH_2Cl_2 (5 ml) and a solution of SO_2Cl_2 (540 mg) in CH_2Cl_2 (5 ml) were added successively to a stirred solution of amine (If) (913 mg) in CH_2Cl_2 (10 ml) under cooling at −78°. After the reaction mixture was allowed to stand for 30 min at the same temperature, methyl phenylglycinate (Ia) (826 mg) was added and stirring was continued for further 30 min at −78°. Then the mixture was warmed to room temperature and aged for additional 1 hr at room temperature. The solution was poured into a mixture of AcOEt and water. The organic layer was washed successively with 5% HCl, sat. $NaHCO_3$ aq. and water, and dried over $MgSO_4$. After evaporation of the solvents, the residue was purified by silica gel TLC (benzene: AcOEt=1: 1) to give XI (373 mg, 36%) and XIII (120 mg, 7%).

B) To a stirred solution of methyl phenylglycinate (Ia) (500 mg) in CH_2Cl_2 (10 ml) were dropwise added a solution of SO_2Cl_2 (410 mg) in CH_2Cl_2 (3 ml) and a solution of NEt_3 (650 mg) in CH_2Cl_2 (5 ml) under cooling at −78°. After aging the reaction mixture for 30 min at −78°, If (456 mg) in CH_2Cl_2 (5 ml) was added dropwise and stirring was continued at −78° for 30 min. Then the reaction mixture was warmed to room temperature, and allowed to stand at that temperature for additional 1 hr. After evaporation of solvents, THF was added to filter off $NEt_3 \cdot HCl$. The filtrate was evaporated again and the obtained residue was purified by silica gel TLC (benzene: AcOEt=2: 1). Symmetrical sulfamides (IIIa), (XI) and unsymmetrical sulfamide (XIII) were obtained in 37% (222 mg), 28% (145 mg) and 43% (390 mg) yield, respectively. Physical data of XIII are as follows: white foam. *Anal.* Calcd. for $C_{18}H_{21}O_7N_3S_2$: C, 47.46; H, 4.65; N, 9.23; S, 14.08. Found: C, 47.47; H, 4.44; N, 9.37; S, 14.15. Mass Spectrum *m/e*: 455 (M^+). UV $\lambda_{max}^{CH_3CN}$ nm (ε): 256 (5290). IR ν_{max}^{Nujol} cm^{-1}: 3280, 1775, 1740, 1725, 1640. NMR ($CDCl_3$) δ ppm: 2.13 (3H, s), 3.17 and 3.40 (2H, AB-q, J=18 Hz), 3.73 (3H, s), 3.77 (3H, s), 4.65—5.35 (3H, m), 5.5—6.3 (2H, b), 7.2—7.6 (5H, m).

Methyl 7β-Methoxysulfonamido-2α-methoxy-3-methyl-3-cephem-4-carboxylate (XV)——To a stirred solution of amine (If) (456 mg) in CH_2Cl_2 (5 ml) were added a solution of NEt_3 (670 mg) in CH_2Cl_2 (3 ml) and a solution of SO_2Cl_2 (445 mg) in CH_2Cl_2 (2 ml) under cooling at −78°. After 2 hr at −78°, a solution of NEt_3 (335 mg) in MeOH (2 ml) was added, and stirring was continued for further 30 min at −78°. The reaction mixture was evaporated under reduced pressure, then THF was added to the residue to remove $NEt_3 \cdot HCl$ by filtration. The filtrate was evaporated *in vacuo* and the residue was purified by preparative TLC (silica gel, benzene: AcOEt=2: 1) to afford XV as foam. The foam was dissolved in small amount of $CHCl_3$, white powder of XV was obtained by adding *n*-hexane to the solution and removing solvents by decantation (210 mg, 30%). *Anal.* Calcd. for $C_{11}H_{16}O_7N_2S_2$: C, 37.49; H, 4.58; N, 7.95; S, 18.20. Found: C, 37.40; H, 4.52; N, 8.01; S, 18.10. Mass Spectrum *m/e*: 352 (M^+). UV $\lambda_{max}^{CH_3CN}$ nm (ε): 218 (3870), 265 (9360). IR ν_{max}^{Nujol} cm^{-1}: 3270, 1785, 1725, 1645. NMR (CD_3COCD_3) δ ppm: 2.09 (3H, s), 3.48 (3H, s), 3.80 (3H, s), 3.92 (3H, s), 5.09 (1H, s), 5.13 (1H, d, J=4.8 Hz), 5.38 (1H, dd, J=10 Hz, J=4.8 Hz), 7.95 (1H, d, J=10 Hz).

Bis-N-(1-methoxycarbonylbenzylidene)amino-sulfide (IIa-S_1)——To a stirred solution of sulfamide (IIIa) (785 mg) and $SOCl_2$ (480 mg) in CH_2Cl_2 (12 ml) was dropwise added a solution of NEt_3 (810 mg) in CH_2Cl_2 (3 ml) under ice-cooling (0—5°). After the reaction mixture was kept at 0—5° for 1 hr, the solvent was evaporated and to the residue was added dry THF to filter off precipitates of $NEt_3 \cdot HCl$. The filtrate was evaporated and the resulting residue was purified by silica gel TLC (benzene: AcOEt=20: 1). Sulfide (IIa-S_1) (316 mg, 44%) was obtained after recrystallization from AcOEt as yellow needles together with methyl phenylglyoxylate (XVIIIa) (70 mg, 11%) as a colorless oil. Physical data of products are as follows. IIa-S_1: mp 167—168°. *Anal.* Calcd. for $C_{18}H_{16}O_4N_2S$: C, 60.66; H, 4.53; N, 7.86; S, 9.00. Found: C, 60.61; H, 4.56; N, 7.87; S, 9.05. Mass Spectrum *m/e*: 356 (M^+). UV $\lambda_{max}^{CH_3CN}$ nm (ε): 231 (14800), 360 (21240). IR ν_{max}^{Nujol} cm^{-1}: 1705, 1585, 1570. NMR ($CDCl_3$) δ ppm: 3.86 (6H, s), 7.2—7.8 (10H, m). XVIIIa: Mass Spectrum *m/e*: 164 (M^+). IR ν_{max}^{Liquid} cm^{-1}: 1740, 1695, 1600, 1580. NMR ($CDCl_3$) δ ppm: 3.90 (3H, s), 7.2—8.1 (10H, m).

Bis-N-(1-ethoxycarbonylbenzylidene)amino-sulfide (IIb-S_1)——Monosulfide (IIb-S_1) (86 mg, 22%) and ethyl phenylglyoxylate (XVIIIb) (85 mg, 24%) were similarly obtained from the reaction of sulfamide (IIIb) (420 mg) with $SOCl_2$ (250 mg) and NEt_3 (500 mg). Physical data of these products were completely identical with those of the authentic samples described in the preceding paper.[2]

Bis-N-(1-ethoxycarbonylethylidene)amino-disulfide (IIc-S_2) and N-(1-Ethoxycarbonylethyl)-N-(1′-ethoxycarbonylethylidene)aminothio-N′-(1″-ethoxycarbonylethyl)-sulfamide (Xc)——To a stirred solution of sulfamide (IIIc) (1.335 g) in CH_2Cl_2 (10 ml) was added a solution of $SOCl_2$ (1.08 g) in CH_2Cl_2 (5 ml) under ice-cooling, followed by the addition of a solution of NEt_3 (1.85 g) in CH_2Cl_2 (5 ml). After keeping the reaction mixture for 1 hr at 0—5°, work-up was carried out according to the procedure for preparation of IIa-S_1, and purified by silica gel chromatography (benzene: AcOEt=5: 1) to yield IIc-S_2 (241 mg, 18%) as orange oil and Xc (150 mg, 11%) as yellow oil. IIc-S_2: *Anal.* Calcd. for $C_{10}H_{16}O_4N_2S_2$: C, 41.08; H, 5.52; N, 9.58; S, 21.93. Found: C, 41.00; H, 5.15; N, 9.55; S, 21.52. Mass Spectrum *m/e*: 292 (M^+). UV $\lambda_{max}^{CH_3CN}$ nm (ε): 266 (13970). IR ν_{max}^{Liquid} cm^{-1}: 1720, 1595. NMR ($CDCl_3$) δ ppm: 1.33 (6H, t, J=7 Hz), 2.29 (6H, s), 4.31 (4H, q, J=7 Hz). Xc: *Anal.* Calcd. for $C_{15}H_{27}O_8N_3S_2$: C, 40.81; H, 6.16; N, 9.52; S, 14.52. Found: C, 41.36; H, 5.93; N, 9.38; S, 14.10. Mass Spectrum *m/e*: 441 (M^+). UV $\lambda_{max}^{CH_3CN}$ nm (ε): 279 (6370). IR ν_{max}^{Liquid} cm^{-1}: 3290, 1740, 1625, 1590. NMR ($CDCl_3$) δ ppm: 1.27 (6H, t, J=7 Hz), 1.33 (3H, t, J=7 Hz), 1.54 (3H,

d, J=6 Hz), 1.57 (3H, d, J=6 Hz), 2.18 (3H, s), 3.9—4.5 (7H, m), 4.81 (1H, q, J=6 Hz), 5.63 (1H, d, J=6 Hz).

Reaction of Sulfamide (IIId) with $SOCl_2$ and NEt_3——A solution of NEt_3 (1.82 g) in CH_2Cl_2 (5 ml) was added to a slurry of sulfamide (IIId) (1.03 g) and $SOCl_2$ (1.00 g) in CH_2Cl_2 (35 ml) with vigorous stirring at 0—5°. After stirring for 1 hr at 0—5°, the reaction mixture was treated as before and separated by silica gel chromatography (benzene: AcOEt=9: 1) to yield a mixture (50 mg, as yellow oil) of IId-S_1 (40 mole %, estimated by NMR analysis) and IId-S_2 (60 mole %), a mixture (64 mg, as yellow oil) of IId-S_3 (75 mole %, estimated by NMR analysis) and IId-S_4 (25 mole %) and Xd (75 mg, 7% yield, as pale yellow oil). Xd: *Anal.* Calcd. for $C_{12}H_{21}O_8N_3S_2$: C, 36.08; H, 5.30; N, 10.52; S, 16.05. Found: C, 35.49; H, 5.37; N, 10.43; S, 15.90. Mass Spectrum m/e: 399 (M^+). IR ν_{max}^{Liquid} cm^{-1}: 3320, 1750, 1600. NMR ($CDCl_3$) δ ppm: 1.15—1.50 (9H, m), 3.75—4.60 (10H, m), 5.60 (1H, b), 7.57 (1H, s).

Reaction of Sulfamide (IIIe) with $SOCl_2$ and NEt_3——To a slurry of IIe (830 mg) in CH_2Cl_2 (50 mg) were added dropwise a solution of $SOCl_2$ (715 mg) in CH_2Cl_2 (5 ml) and a solution of NEt_3 (1.4 g) in CH_2Cl_2 (5 ml) with vigorous stirring under ice-cooling. After the reaction mixture was kept at 0—5° for 1 hr, it was treated with similar procedure described above. Purification by preparative TLC (silica gel, benzene-*n*-hexane= 1: 2) afforded IIe-S_1 (12 mg, 1.6%), IIe-S_2 (43 mg, 5.2%) and IIe-S_4 (67 mg, 6.6%). IIe-S_1: yellow oil. Mass Spectrum m/e: 240 (M^+). IR $\nu_{max}^{CH_2Cl_2}$ cm^{-1}: 1630, 1600. NMR ($CDCl_3$) δ ppm: 7.2—8.0 (10H, m), 8.67 (2H, s). IIe-S_2: yellow powder. mp 93—95°. *Anal.* Calcd. for $C_{14}H_{12}N_2S_2$: C, 61.73; H, 4.44; N, 10.28; S, 23.54. Found: C, 61.35; H, 4.26; N, 9.75; S, 24.58. Mass Spectrum m/e: 272 (M^+). UV $\lambda_{max}^{CH_3CN}$ nm (ε): 217 (25030), 302 (25840). IR ν_{max}^{Nujol} cm^{-1}: 1610, 1570. NMR ($CDCl_3$) δ ppm: 7.2—7.9 (10H, m), 8.15 (2H, s). IIe-S_4: yellow crystal (*n*-hexane). mp 97—99°. *Anal.* Calcd. for $C_{14}H_{12}N_2S_4$: C, 49.97; H, 3.59; N, 8.32; S, 38.11. Found: C, 49.79; H, 3.40; N, 8.16; S, 37.81. Mass Spectrum m/e: 336 (M^+). UV $\lambda_{max}^{CH_3CN}$ nm (ε): 254 (14870), 304 (23000). IR ν_{max}^{Nujol} cm^{-1}: 1610, 1580. NMR ($CDCl_3$) δ ppm: 6.8—7.6 (10H, m), 7.96 (2H, s).

Bis-N-(3-methyl-4-methoxycarbonyl-3-cephem-7-ylidene)aminosulfide (XIIa) and Bis-N-(3-methyl-4-methoxycarbonyl-3-cephem-7-ylidene)amino-trisulfide (XIIb)——To a stirred solution of cephalosporin (XI) (520 mg) in CH_2Cl_2 (15 ml) were added dropwise a solution of $SOCl_2$ (260 mg) in CH_2Cl_2 (2 ml) and a solution of NEt_3 (450 mg) in CH_2Cl_2 (3 ml) under ice-cooling. The reaction mixture was stirred for 1 hr at 0—5°, then the solvent was evaporated under reduced pressure. Dry THF was added and NEt_3·HCl was filtered off. The filtrate was concentrated and purified by silica gel TLC (benzene: AcOEt=4: 1) to afford XIIa (37 mg, 8%) and XIIb (44 mg, 8%). Physical data of these products were identical with those of authentic samples reported before.[2]

N-(3-Methyl-4-methoxycarbonyl-3-cephem-7-ylidene)amino, N'-(1'-methoxycarbonylbenzylidene)amino-sulfide (XIV)——Similarly, the reaction of the unsymmetrical sulfamide (XIII) (280 mg) with $SOCl_2$ (150 mg) and NEt_3 (250 mg) in CH_2Cl_2 (10 ml) for 1 hr at 0—5°, and purification by silica gel TLC (benzene: AcOEt= 5: 1) gave sulfenimine (IIa-S_1) (12 mg, 5%) and a mixture of two sulfenimines of cephalosporin (XIV) as yellow foam (14 mg) in addition to methyl phenylglyoxylate (XVIIIa) (8 mg, 16%).

Methyl N-(1-Methoxycarbonylbenzylidene)amino-sulfenate (XVI) and Methyl N-(1-Methoxycarbonylbenzyl)sulfamate (XVII)——To a stirred solution of sulfamide (IIIa) (400 mg) and $SOCl_2$ (300 mg) in CH_2Cl_2 (8 ml) was added dropwise a solution of NEt_3 (600 mg) in CH_2Cl_2 (2 ml) under ice-cooling. The reaction mixture was kept at 0—5° for 1 hr, and cooled to −78°. Then a solution of NEt_3 (600 mg) in MeOH (3 ml) was added to it, and the mixture was stirred at −78° for 15 min and gradually warmed to room temperature. The solution was poured into a mixture of AcOEt and sat. $NaHCO_3$ aq., and organic layer was washed with sat. NaCl aq. and dried over $MgSO_4$. After evaporation of solvents, the resulting residue was separated by silica gel TLC (benzene: AcOEt=20: 1) to afford IIa-S_1 (65 mg, 18%), XVI (133 mg, 29%), XVII (116 mg, 22%) and methyl phenylglyoxylate (XVIIIa) (14 mg, 4%). XVI: pale yellow crystal (from *n*-hexane). mp 52—53°. *Anal.* Calcd. for $C_{10}H_{11}O_3NS$: C, 53.34; H, 4.89; N, 6.22; S, 14.24. Found: C, 53.36; H, 4.90; N, 6.11; S, 14.28. Mass Spectrum m/e: 225 (M^+). UV $\lambda_{max}^{CH_3CN}$ nm (ε): 236 (10040), 339 (12320). IR ν_{max}^{Nujol} cm^{-1}: 1680, 1595, 1580. NMR ($CDCl_3$) δ ppm: 3.80 (3H, s), 3.88 (3H, s), 7.1—7.8 (5H, m). XVII: white powder (from *n*-hexane). mp 62—63°. *Anal.* Calcd. for $C_{10}H_{13}O_5NS$: C, 46.32; H, 5.05; N, 5.40; S, 12.37. Found: C, 46.80; H, 5.09; N, 5.33; S, 12.37. Mass Spectrum m/e: 259 (M^+). UV $\lambda_{max}^{CH_3CN}$ nm (ε): 252 (238), 257 (280), 264 (242), 267 (171), 323 (159). IR ν_{max}^{Nujol} cm^{-1}: 3270, 1725, 1600, 1585. NMR ($CDCl_3$) δ ppm: 3.57 (3H, s), 3.67 (3H, s), 5.04 (1H, d, J=8 Hz), 5.90 (1H, d, J=8 Hz), 7.25 (5H, s).