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A Synthesis of Cephamycins from Cephalosporins and Related Reactions[1)]

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The sulfinamides **3** were transformed to sulfenimines **4** by treatment with thionyl chloride and a weak base such as quinoline (or triethylamine). The sulfenimines **4** were methoxylated with lithium methoxide to give 7α-methoxysulfenamides **5**, which were directly acylated with an acyl chloride to furnish cephamycin derivatives **6**. There was a major difference between the acylation of 7α-methoxysulfenamides **5** and that of the 7α-H derivatives **7**. Reduction of the imines **4a** with metal hydrides gave 7β-sulfenamino-cephalosporins **12** together with a small amount of the 7α-isomers **13**. The synthetic sequence **4a**→**12**→**14** provides a useful method for the isomerization of 7α-aminocephalosporins **17** to the corresponding 7β-isomers **18**.

Keywords——cephamycin; cephalosporin; sulfinamide; sulfenimine; methoxylation; oxidation; reduction

In the preceding paper[3)] a synthesis of 7α-methoxy-7β-acylamidocephalosporins through 7-sulfenimino derivatives was reported. In view of the growing importance of 7α-methoxy-cephalosporins (cephamycins) in the field of antibiotics, a more efficient method for methoxylation at the seven position of cephalosporins is desirable, even though several methods have been developed.[4)] In this paper we describe another route to 7α-methoxycephalosporins starting from 7β-sulfinamide-cephalosporins.

Though the chemistry of a sulfoxide adjacent to carbon atoms has been extensively investigated[5)] in connection with Pummerer-type reactions, the corresponding sulfinamides have been studied very little,[6)] probably due to the unstable nature of sulfinic acids[7)] which are the most suitable starting materials for sulfinamides. For example, aliphatic sulfinic acids are unstable and readily disproportionate to thiolsulfonates and sulfonic acids.[7)] On the other hand, aromatic sulfinic acids seem to be sufficiently stable for utilization in synthesis. Thus we sought to develop a new synthetic route to 7-methoxylated cephalosporins using aromatic sulfinyl chlorides to form the sulfinamides.

Treatment of *tert*-butyl 7β-amino-3-cephem-4-carboxylate (**2**) with *o*-nitrobenzenesulfinyl chloride gave the sulfinamide **3a**. *p*-Nitrobenzenesulfinamide **3b**, benzhydryl 3-acetoxymethyl-7β-*o*-nitrobenzenesulfinamido-3-cephem-4-carboxylate (**3c**), and 3-{[(1-methyl-1H-tetrazol-5-yl)thio]methyl}-7β-*o*-nitrobenzenesulfinamido-3-cephem-4-carboxylic acid (**3d**) were similarly prepared. The sulfinamides **3a**—**d** were mixtures of diastereomers due to chirality at the sulfinyl sulfur, but these diastereomers were smoothly converted into a single sulfenimine **4a**—**d** in the next reaction (*vide infra*). Treatment of the sulfinamide **3a** with thionyl chloride

1) A part of this work has been published in T. Kobayashi, K. Iino, and T. Hiraoka, *J. Am. Chem. Soc.*, **99**, 5505 (1977) as a preliminary communication.
2) Location: *1-2-58, Hiromachi, Shinagawa-ku, Tokyo, 140, Japan.*
3) T. Kobayashi and T. Hiraoka, *Chem. Pharm. Bull.* (Tokyo), **27**, 2718 (1979).
4) see T. Hiraoka, Y. Sugimura, T. Saito, and T. Kobayashi, *Heterocycles*, **8**, 719 (1977) and references cited therein.
5) S. Oae, "Organic Chemistry of Sulfur," Plenum Press, New York, 1977, p. 406.
6) M. Quaedyling, "Methoden der Organischen Chemie," Bd. IX, Houben-Weyl, Stuttgart, 1955, p. 297. therein.
7) S. Oae, "Organic Chemistry of Sulfur," Plenum Press, New York, 1977, p. 613.

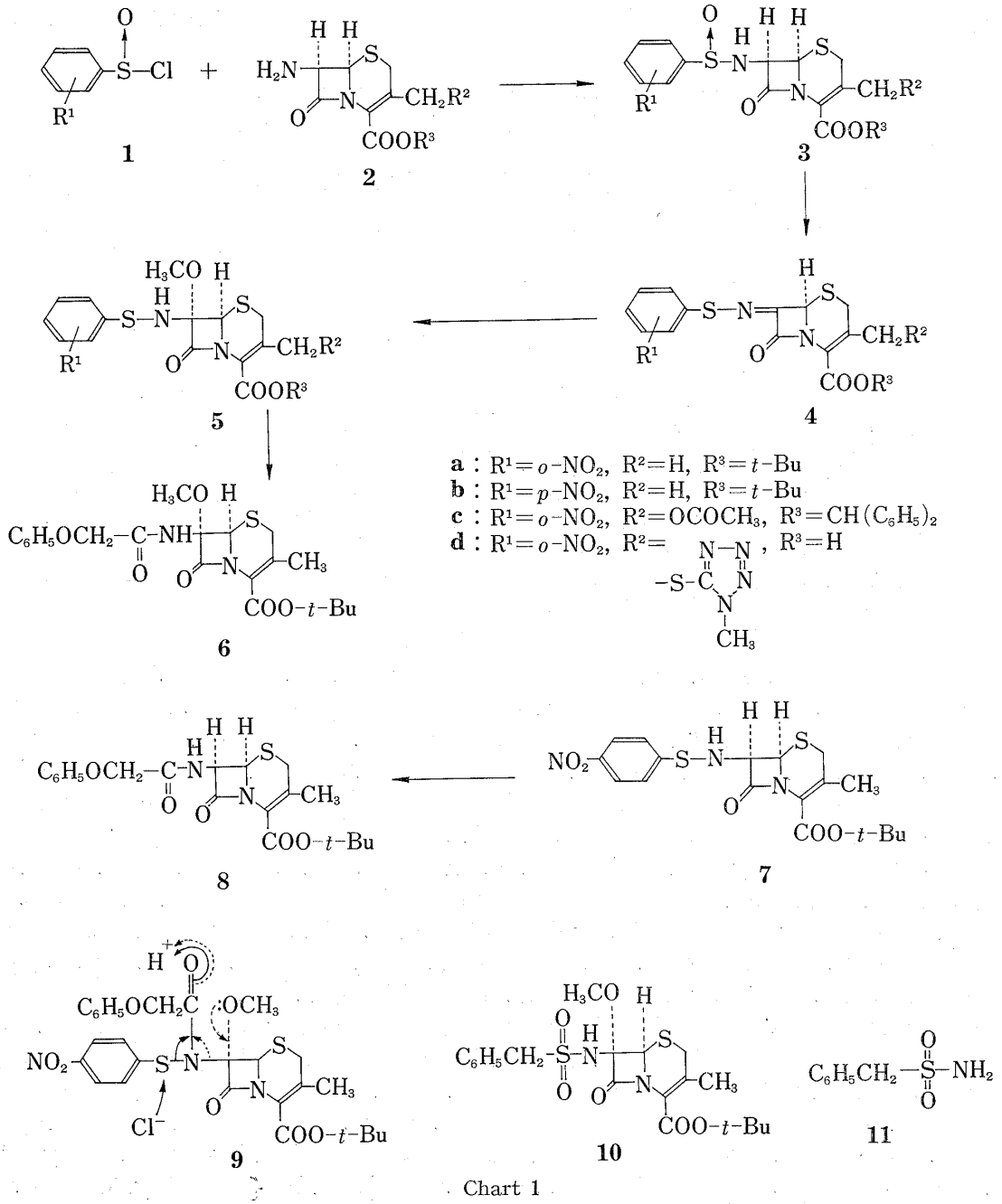

Chart 1

in the presence of quinoline gave the desired sulfenimine **4a** in 53.6% yield. To our knowledge, this is the first example of a Pummerer-type reaction of a sulfinamide. Curiously, the reaction of **3a** with trifluoroacetic anhydride and triethylamine or with acetyl chloride and quinoline afforded a mixture of the desired sulfenimine **4a** and the reduction product, *tert*-butyl 3-methyl-7β-*o*-nitrobenzenesulfenamido-3-cephem-4-carboxylate (**12**). Reduction of a sulfoxide with an acylating reagent in the presence of an alkali metal iodide is well known,[8] but in our case reduction occurred with a combination of an acylating reagent and an organic base. The mechanism of this reduction is not clear, but it was not further investigated in the present work. Analogously, the sulfinamides **3b**, **c** were converted into the sulfinimines **4b**, **c** by treatment with thionyl chloride and quinoline (or triethylamine). Methoxylation

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

of the imines **4a**—**c** was achieved by reaction with lithium methoxide in methanol as described in the preceding paper[3] to give the 7α-methoxy-7β-sulfenamides **5a**—**c** in good yields. In the case of the free carboxylic acid **3d**, the carboxylic group was protected as the trimethylsilyl ester, using trimethylsilyl chloride and triethylamine in chloroform. The resulting sulfinamide trimethylsilyl ester was treated with thionyl chloride and quinoline at −40° to afford the sulfenimino trimethylsilyl ester **4d** (R^3=$SiMe_3$), which was reacted with lithium methoxide in methanol without isolation to furnish 7α-methoxysulfenamide **5d** in 19.5% overall yield from **3d**.

We next investigated direct acylation of the sulfenamides **5**, since the process of conversion of **5** to an unstable 7α-methoxy-7β-amino derivative and subsequent acylation is likely to be less efficient than direct acylation of **5** in a single step. A model experiment using *tert*-butyl 3-methyl-7β-*p*-nitrobenzenesulfenamido-3-cephem-4-carboxylate **7** was encouraging. Namely, treatment of **7** with phenoxyacetyl chloride in the absence of a base afforded the acylated product **8** in 96.3% yield. This reaction was applied to the 7α-methoxy-7β-*p*-nitrobenzenesulfenamide **5b**, using the same reaction conditions, to give the acyl-derivative **6** in only 5.1% yield. This acylation reaction was repeated many times under various conditions, but the yield could not be improved. The reason for this may be steric crowding and instability of the intermediate 7α-methoxy-N-benzenesulfenyl-N-acylaminocephalosporin **9** in the presence of hydrochloric acid liberated in the reaction. In the postulated intermediate shown in formula **9**, chloride ion would attack the sulfur atom with protonation of the carbonyl adjacent to the nitrogen to produce the desired amide **6** (shown by solid arrows), while protonation of the carbonyl oxygen with the assistance of lone pair electrons of the methoxy oxygen would cleave the 7β-nitrogen group to afford a decomposed product (shown by dotted arrows). A similar decomposition was observed in the case of the 7β-methoxysulfonamide **10**,[9] which gradually decomposed during chromatography on silica gel or alumina with the liberation of benzylsulfonamide **11**; no cephalosporin compound was isolated.

We next considered reduction of the sulfenimines **4**, since this kind of reduction might be useful for the epimerization of 7α-aminocephalosporins **17** to the 7β-isomers **18** (Chart 2). Such epimerization is necessary in the total synthesis of cephalosporins or penicillins obtained by (2+2) cycloaddition as *trans* isomers at the 6, 7 (5, 6)-position.[10] Christensen *et al.* have carried out this transformation at the seven position of cephalosporins by proton abstraction from the corresponding Schiff base with a strong base.[12] However, the procedure is not efficient unless repeated several times, since protonation of the anion at the seven position gives a mixture of 7α- and 7β-isomers. If the reduction of sulfenimines **4** could be done stereospecifically, isomerization of the 7α-amino derivative **17** to the β-isomer **18** might be useful to complete a total synthesis of cephalosporins. We found that treatment of **4a** with lithium tri-*tert*-butoxyaluminum hydride in tetrahydrofuran at 0° for 2 hr gave the 7β-sulfenamide **12** (50.4%) together with a fair amount of the α-isomer **13** (27.7%) and the starting material (12.7%). This disappointing result led us to investigate other reduction reagents and reaction conditions. Thus, reduction of **4a** with sodium borohydride in a mixture of THF and DMSO at 0° for 10 min produced the desired 7β-sulfenamide **12** (52.0%) in addition to some 7α-isomer **13** (5.6%). Other reduction conditions were also examined and the results

9) *tert*-Butyl 7β-benzylsulfonylamino-7α-methoxy-3-methyl-3-cephem-4-carboxylate (**10**) was prepared by the *tert*-butyl hypochlorite method[11] starting from *tert*-butyl 7β-benzylsulfonylamino-3-methyl-3-cephem-4-carboxylate. The NMR spectrum of the crude compound **10** showed peaks consistent with the structure **10**.

10) *a*) A.K. Bose, G. Spiegelman, and M.S. Manhas, *J. Am. Chem. Soc.*, **90**, 4506 (1968); *b*) R.W. Ratcliffe and B.G. Christensen, *Tetrahedron Lett.*, **1973**, 4645, 4649, 4653.

11) *a*) J.E. Baldwin, F.J. Urban, R.D.G. Cooper, and F.L. Jose, *J. Am. Chem. Soc*, **95**, 2401 (1973); *b*) G.A. Koopel and R.E. Koehler, *ibid.*, **95**, 2403 (1973).

12) R.A. Firestone, N.S. Maciejewicz, R.W. Ratcliffe, and B.G. Christensen, *J. Org. Chem.*, **39**, 437 (1974).

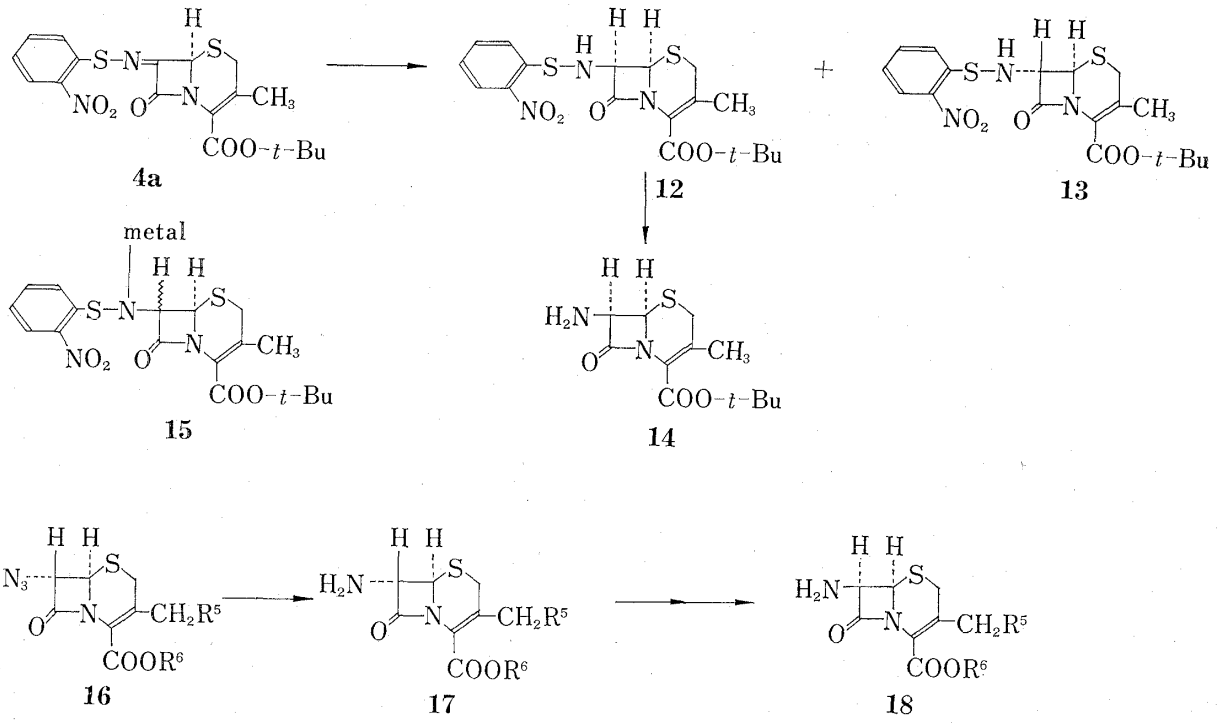

Chart 2

are summarized in Table I. It should be noted that the product ratio α/β given in Table I does not indicate the exact ratio of attack of the reagent from the α and β sides, since equilibration between α- and β-isomers is probable after reduction is completed, judging from the larger α/β ratios at longer reaction times. Namely, before quenching the reaction, the nitrogen of the reduction product is bonded by the metal species as depicted in formula **15**, and this kind of compound without hydrogen at the nitrogen atom is known to equilibrate easily between 7α- and 7β-isomers on treatment with a base.[13]

Penicillin reduction of methyl 6β-*o*-nitrobenzenesulfenimino-penicillanate (**19**)[3] with sodium borohydride gave only 7β-sulfenamide **20**. The 7α-isomer was not detected by thin-

Table I. Reduction of **4a**

Reagent	Conditions	*cis* (**12**)	*trans* (**13**)	(**4a**)	α (**13**)/β (**12**)
$LiAl(OBu^t)_3$	THF −78°, 2 hr	32.7%	10.1%	41.0%	0.309
$LiAl(OBu^t)_3$	THF −78°, 10 min 0°, 2 hr	50.4%	27.7%	12.7%	0.550
$NaBH_4$	THF–DMSO 0°, 10 min	52.0%	5.6%	Trace	0.108

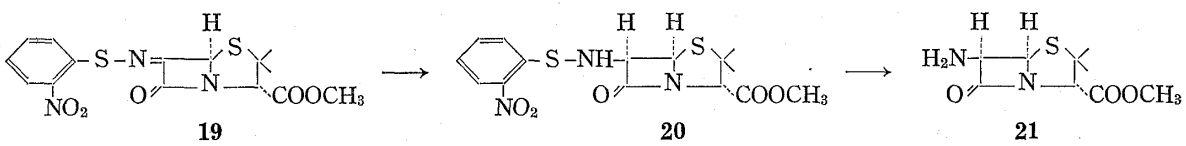

Chart 3

13) S. Wolfe and W.S. Lee, *J. Chem. Soc., Chem. Commun.*, **1968**, 242.

layer chromatography, in striking contrast to the case with the cephalosporin series. The sulfur-nitrogen bond of the amide **12** or **20** was cleaved by treatment with potassium iodide in methanol–acetic acid at 0° to afford the desired amine **14** or **21**.

The isomerization method at the seven position of cephalosporins described above (**17**→**18**) was successfully applied by Miyadera *et al.*[14] in our laboratories for a total synthesis of 3-trifluoromethylcephalosporin, in which they used diborane as a reducing reagent with very satisfactory results.

In conclusion, a novel conversion of cephalosporins to cephamycins using sulfinamides has been established, together with a method for the isomerization of 7α-aminocephalosporins to the 7β-amino isomer.

Experimental[15]

***tert*-Butyl 3-Methyl-7β-*o*-nitrobenzenesulfinamido-3-cephem-4-carboxylate (3a)**——*o*-Nitrobenzenesulfinyl chloride (590 mg, 2.8 mmol) in dry THF (3 ml) was added to a stirred solution of *tert*-butyl 7β-amino-3-methyl-3-cephem-4-carboxylate (540 mg, 2.0 mmol) and triethylamine (253 mg, 2.5 mmol) in dry THF (7 ml) at 0°. The resulting suspension was further stirred at 0° for 2 hr. The solution was diluted with EtOAc, then washed with water, $NaHCO_3$ solution and saturated NaCl solution. After drying over Na_2SO_4 the solvents were evaporated off under reduced pressure to afford an oil. This crude product was purified by chromatography on silica gel to give *o*-nitrobenzenesulfinamide **3a** (739 mg, 84.2%). The sulfinamide **3a** was a mixture of diastereoisomers due to the sulfinyl group in the 7β-side chain, and was used without further separation in the next reaction. **3a**: NMR ($CDCl_3$) δ=1.45 and 1.48 (9H, two kinds of s), 2.02 and 2.05 (3H, two kinds of s), 3.06 and 3.25; 3.17 and 3.43 (2H, two kinds of ABq, J=18 Hz), 4.33 (2/3H, d, J=4.5 Hz), 4.82—5.03 (2/3H, m), 5.27 (2/3H, dd, J=4.5 and 9 Hz), 5.60 (1H, bd, J=9 Hz), 7.58—8.43 (4H, m).

***tert*-Butyl 3-Methyl-7-*o*-nitrobenzenesulfenimino-3-cephem-4-carboxylate (4a)**——Quinoline (93 mg, 0.72 mmol) was added to a cold solution of *o*-nitrobenzenesulfinamide **3a** (70 mg, 0.16 mmol) in dry $CHCl_3$ (2.5 ml) and dry THF (1 ml), followed by addition of thionyl chloride (29 mg, 0.24 mmol) in dry $CHCl_3$ (0.2 ml). The mixture was stirred at −30° for 1 hr and at 0° for 1 hr. Further quinoline (93 mg, 0.72 mmol) in dry $CHCl_3$ (0.4 ml) and thionyl chloride (29 mg, 0.24 mmol) in dry $CHCl_3$ (0.2 ml) were added to this mixture and the reaction was continued overnight at 0°. The mixture was diluted with EtOAc, washed with aqueous $NaHCO_3$ and water, then dried over $MgSO_4$. The solvents were removed *in vacuo* to give a solid, which was purified by silica gel chromatography (solvent: benzene–EtOAc 10: 1) to furnish *o*-nitrobenzenesulfenimine **4a** (36 mg, 53.6%). **4a**: mp 183—184° (isopropyl ether–$CHCl_3$); IR ν_{max}^{Nujol} (cm^{-1}): 1780; NMR ($CDCl_3$) δ: 1.60 (9H, s), 2.16 (3H, s), 3.27 and 3.58 (2H, ABq, J=19 Hz), 5.47 (1H, s), 7.33—8.62 (4H, m).

***tert*-Butyl 3-Methyl-7β-*p*-nitrobenzenesulfinamido-3-cephem-4-carboxylate (3b)**——A solution of *p*-nitrobenzenesulfinyl chloride (4.11 g, 20 mmol) in dry THF (25 ml) was added to a solution of *tert*-butyl 7β-amino-3-cephem-4-carboxylate (4.5 g, 16.6 mmol) and triethylamine (2.79 ml, 20.0 mmol) in dry THF (90 ml) at 0°. The resulting suspension was stirred for 2 hr at 0° then at room temperature for 3 hr. The mixture was then diluted with EtOAc, washed with water, and dried over $MgSO_4$. The solvents were removed *in vacuo* and the residue was purified by chromatography on silica gel (solvent: benzene–EtOAc 2: 1) to give *p*-nitrobenzenesulfinamide **3b** (6.9 g, 95.2%). The sulfinamide **3b** was a mixture of diastereoisomers due to the sulfinyl group in the 7β-side chain, and was used without further separation in the next step. **3b**: NMR ($CDCl_3$) δ: 1.43 (9H, s), 2.02 (3H, s), 3.06 and 3.37; 3.15 and 3.45 (2H, two kinds of ABq, J=18 Hz), 4.52 (1H, d, J=5 Hz), 4.78 and 5.06 (1H, two kinds of dd, J=5 and 9 Hz), 6.25 (1H, d, J=9 Hz), 7.77—8.48 (4H, m).

***tert*-Butyl 3-Methyl-7-*p*-nitrobenzenesulfenimino-3-cephem-4-carboxylate (4b)**——Triethylamine (0.20 ml, 1.43 mmol) and thionyl chloride (0.10 ml, 1.38 mmol) were added to a solution of *p*-nitrobenzenesulfinamide **3b** (200 mg, 0.455 mmol) in dry CH_2Cl_2 (5 ml) at −78° under vigorous stirring. The solution was maintained at −78° for 1.5 hr, then methylene chloride was added. The mixture was washed with saturated $NaHCO_3$ solution and water, dried over $MgSO_4$, and evaporated down *in vacuo*. The resulting solid was

14) *a*) T. Hashimoto, T. Watanabe, Y. Kawano, T. Tanaka, and T. Miyadera, *Heterocycles*, **11**, 207 (1978); *b*) T. Watanabe, Y. Kawano, T. Tanaka, T. Hashimoto, and T. Miyadera, *Chem. Pharm. Bull.* (Tokyo), accepted.

15) All melting points are uncorrected. IR spectra were recorded on a JASCO A-2 spectrometer. NMR spectra were measured on Hitachi R-24 spectrometer using tetramethylsilane as an internal standard. The abbreviations in the NMR spectra are as follows: s, singlet; bs, broad singlet; d, doublet; dd, doublet of doublets; q, quartet; m, multiplet.

chromatographed on silica gel using benzene–EtOAc (10: 1) to yield *p*-nitrobenzenesulfenimine **4b** (77 mg, 44%). **4b**: mp 169—170° (isopropyl ether–EtOAc); IR ν_{max}^{Nujol} (cm^{-1}): 1790; NMR ($CDCl_3$) δ: 1.58 (9H, s), 2.15 (3H, s), 3.23 and 3.57 (2H, ABq, J=18 Hz), 5.37 (1H, s), 7.55—8.40 (4H, m).

Benzhydryl 3-Acetoxymethyl-7β-*o*-nitrobenzenesulfinamido-3-cephem-4-carboxylate (3c)——A solution of 7β-amino-3-methyl-3-cephem-4-carboxylic acid (3.41 g, 12.5 mmol) and triethylamine (7.0 ml, 50 mmol) in dry CH_2Cl_2 (50 ml) was stirred and cooled to 0°. *o*-Nitrobenzenesulfinyl chloride (3.85 g, 18.7 mmol) in dry CH_2Cl_2 (25 ml) was added and the mixture was stirred overnight at room temperature. Cold phosphate buffer solution (pH 7.8, 100 ml) was added to the mixture and stirred well. The solid precipitate was removed by filtration, then the aqueous layer was separated, washed with a small amount of CH_2Cl_2, and adjusted to pH 2.6 (15% HCl). Repeated extraction with EtOAc gave combined extracts, which were dried (Na_2SO_4) and evaporated down to a yellow foam. This foam was dissolved in EtOAc (300 ml). A small amount of insoluble substance was filtered off, and the filtrate was again evaporated down to give a foam (3.35 g). This was taken up in THF (25 ml), an excess of diphenyldiazomethane in THF (15 ml) was added, and the solution was left overnight at room temperature. After removal of the solvent, the residue was triturated with *n*-hexane and the resulting solid was purified by chromatography using silica gel (solvent: benzene–EtOAc 4: 1) to give *o*-nitrobenzenesulfinamide **3c** (1.17 g, 15.3%). The sulfinamide **3c** was a mixture of diastereoisomers due to the sulfinyl group in the 7β-side chain, and was used without further separation. **3c**: NMR ($CDCl_3$) δ: 1.92 (3H, s), 3.27 (6/5H, bs), 3.30 and 3.53 (4/5H, ABq, J=18 Hz), 4.32 (4/5H, d, J=4.5 Hz), 4.25—5.52 (21/5H, m), 6.95 (1H, s), 7.17—8.48 (14H, m).

Benzhydryl 3-Acetoxymethyl-7-*o*-nitrobenzenesulfenimino-3-cephem-4-carboxylate (4c)——Quinoline (233 mg, 1.8 mmol) in dry $CHCl_3$ (0.5 ml) was added to a solution of *o*-nitrobenzenesulfinamide **3c** (122 mg, 0.2 mmol) in dry $CHCl_3$ (3 ml), followed by the addition of thionyl chloride (72 mg, 0.6 mmol) in $CHCl_3$ (1 ml) under ice-water cooling. The mixture was stirred at 0° for 1.5 hr. The solution was treated with EtOAc–aqueous $NaHCO_3$ solution, and the organic layer was washed twice with water. After drying over Na_2SO_4 the solvents were evaporated off *in vacuo* to afford a residue. Purification by chromatography on silica gel using benzene–EtOAc (4: 1) gave *o*-nitrobenzenesulfenimine **4c** (18.5 mg, 15.6%) and benzhydryl 3-acetoxymethyl-7-*o*-nitrobenzenesulfenimino-2-cephem-4-carboxylate (18.5 mg, 15.6%). **4c**: mp 134—135° (*n*-hexane–EtOAc); IR ν_{max}^{Nujol} (cm^{-1}): 1780; NMR ($CDCl_3$) δ: 2.01 (3H, s), 3.39 and 3.65 (2H, ABq, J=19 Hz), 4.85 and 5.08 (2H, ABq, J=14 Hz), 5.47 (1H, s), 7.08 (1H, s), 7.25—8.60 (14H, m).

3-{[(1-Methyl-1H-tetrazol-5-yl)thio]methyl}-7β-*o*-nitrobenzenesulfinamido-3-cephem-4-carboxylic Acid (3d)——Trimethylchlorosilane (0.5 ml, 3.9 mmol) was added to a cold solution of 7β-amino-3-{[(1-methyl-1H-tetrazol-5-yl)thio]methyl}-3-cephem-4-carboxylic acid (986 mg, 3 mmol) and triethylamine (0.5 ml, 3.6 mmol) in CH_2Cl_2 (15 ml), and the mixture was stirred for 1 hr at room temperature. After cooling the solution to −40°, dimethylaniline (0.57 ml, 4.5 mmol) was added, followed by the addition of *o*-nitrobenzenesulfinyl chloride (920 mg, 4.5 mmol) in dry CH_2Cl_2 (5 ml) with vigorous stirring. The mixture was stirred for 30 min at −40° then for 2 hr at 0°. A cold phosphate buffer solution (pH 7.8, 50 ml) was added to the mixture and well stirred. The aqueous layer was separated and adjusted to pH 2.7 (15% HCl). Repeated extraction with EtOAc gave combined extracts, which were washed with NaCl solution, dried ($MgSO_4$) and evaporated down to give a solid. The solid was triturated with ether to give *o*-nitrobenzenesulfinamide **3d** (531 mg, 35.0%). This *o*-nitrobenzenesulfinamide **3d** was a mixture of two diastereoisomers due to the 7β-sulfinyl group. The structures of the two isomers were confirmed by conversion to the corresponding benzhydryl esters, which were chromatographed on silica gel using benzene–EtOAc (1: 1) to give a more polar isomer (Rf=0.53) and a less polar isomer (Rf=0.61). Rf=0.53 compound: IR ν_{max}^{Nujol} (cm^{-1}): 1790; NMR (DMF-d_7) δ: 3.80 (2H, s), 3.95 (3H, s), 4.31 and 4.42 (2H, ABq, J=14 Hz), 5.13—5.50 (2H, m), 6.95 (1H, s), 7.25—8.51 (14H, m). Rf=0.61 compound: IR ν_{max}^{Nujol} (cm^{-1}): 1785; NMR (DMF-d_7) δ: 3.66 (2H, s), 3.92 (3H, s), 4.25 and 4.41 (2H, ABq, J=14 Hz), 4.53 (1H, d, J=4.5 Hz), 5.50 (1H, dd, J=4.5 and 9 Hz), 6.98 (1H, s), 7.25—8.50 (14H, m).

Benzhydryl 7α-Methoxy-3-{[(1-methyl-1H-tetrazol-5-yl)thio]methyl}-7β-*o*-nitrobenzenesulfenamino-3-cephem-4-carboxylate (5d)——Trimethylchlorosilane (52 mg, 0.48 mmol) was added to a stirred suspension of *o*-nitrobenzenesulfinamide **3d** (200 mg, 0.4 mmol) (a mixture of two isomers) and triethylamine (44.4 mg, 0.44 mmol) in dry $CHCl_3$ (5 ml) and the mixture was stirred for 30 min at room temperature. The solution was cooled to −40°, then quinoline (310 mg, 2.4 mmol) in dry $CHCl_3$ (1 ml) was added, followed by the addition of thionyl chloride (119 mg, 1.0 mmol) with vigorous stirring. The mixture was stirred for 2 hr at −30°. The solution was then cooled to −78° and lithium methoxide (prepared from 36 mg (5.2 mmol) of lithium) in dry MeOH (2 ml) was added. After reaction for 2 hr at −78°, glacial AcOH was added. Cold phosphate buffer solution (pH 7.8) was added to the mixture and stirred well. The aqueous phase was separated and acidified to pH 3.0 with 15% HCl. The aqueous layer was saturated with NaCl and extracted twice with EtOAc. The combined extracts were washed with saturated NaCl and dried over $MgSO_4$. Excess diphenyldiazomethane (194 mg, 1 mmol) was added and the solution was allowed to stand at room temperature overnight. After removal of the solvent, the residue was purified by silica gel preparative TLC (solvent: benzene–EtOAc 4: 1) to give 7α-methoxy-*o*-nitrobenzenesulfenamide **5d** (58 mg, 19.5%). **5d**: IR ν_{max}^{Nujol} (cm^{-1}): 1785; NMR ($CDCl_3$) δ: 3.50 (3H, s), 3.60 (2H, s), 3.76 (3H, s), 4.20 and 4.46 (2H, ABq, J=14 Hz), 4.40 (1H, s), 4.92 (1H, s), 6.90 (1H, s), 7.05—8.36 (14H, m).

***tert*-Butyl 3-Methyl-7β-phenoxyacetoamido-3-cephem-4-carboxylate (8)**——A stirred solution of *tert*-butyl 3-methyl-7β-*p*-nitrobenzenesulfenamido-3-cephem-4-carboxylate **7** (102 mg, 0.24 mmol) in dry methylene chloride (10 ml) was cooled to 0°, and phenoxyacetyl chloride (0.12 ml, 0.72 mmol) was added with vigorous stirring. The mixture was stirred for 1.5 hr at room temperature. Removal of the solvent *in vacuo* left a residue, which was purified by preparative chromatography on silica gel to give 7β-phenoxyacetoamide **8** (93.8 mg, 96.3%) using benzene–EtOAc (5: 1). **8**: oil; IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 1780; NMR ($CDCl_3$) δ: 1.53 (9H, s), 2.10 (3H, s), 3.15 and 3.50 (2H, ABq, J=19 Hz), 4.57 (2H, s), 5.01 (1H, d, J=4.5 Hz), 5.85 (1H, dd, J=4.5 and 10 Hz), 6.83—7.80 (6H, m).

***tert*-Butyl 7α-Methoxy-3-methyl-7β-phenoxyacetoamido-3-cephem-4-carboxylate (6)**——Phenoxyacetyl chloride (0.10 ml, 0.6 mmol) was added to a solution of 7α-methoxy-*p*-nitrobenzenesulfenamide **5b** (101 mg, 0.22 mmol) in dry acetonitrile (5 ml) at 0°, and the mixture was stirred for 30 min at 0°. After dilution with EtOAc, the solution was washed with saturated $NaHCO_3$ solution and saturated NaCl solution. Concentration of the dried solution (over $MgSO_4$) *in vacuo* left a residue, which was subjected to preparative TLC on silica gel (benzene–EtOAc 5: 1) to give 7α-methoxy-7β-phenoxyacetoamide **6** (4.8 mg, 5.1%). **6**: oil; IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 1780; NMR ($CDCl_3$) δ: 1.53 (9H, s), 2.12 (3H, s), 3.08 and 3.33 (2H, ABq, J=18 Hz), 3.55 (3H, s), 4.60 (2H, s), 5.07 (1H, s), 6.80—7.53 (5H, m).

***tert*-Butyl 3-Methyl-7β-*o*-nitrobenzenesulfenamido-3-cephem-4-carboxylate (12)**——(a) Reduction with Lithium Tri-*tert*-butoxyaluminum Hydride at −10°: Lithium tri-*tert*-butoxyaluminum hydride (205 mg, 0.81 mmol) in dry THF (2 ml) was added to a solution of *o*-nitrobenzenesulfenimine **4a** (98.8 mg, 0.23 mmol) in dry THF (4 ml) at −78° with vigorous stirring. The solution was stirred at −78° for 10 min, then the reaction was continued at −10° for 1 hr. The mixture was diluted with $CHCl_3$, and phosphate buffer (pH 4.01) was added. The precipitate was removed by filtration, and the organic layer was separated and washed with water. The solution was dried over $MgSO_4$ and concentrated *in vacuo* to give a residue, which was purified by preparative TLC using benzene–EtOAc (10: 1) to afford *o*-nitrobenzenesulfenimine **4a** (Rf=0.78, 40.8 mg, 41.0%), 7β-*o*-nitrobenzenesulfenamide **12** (Rf=0.62, 32.5 mg, 32.7%), and 7α-*o*-nitrobenzenesulfenamide **13** (Rf=0.45, 10.0 mg, 10.1%). 7β-*o*-Nitrobenzenesulfenamide **12**: mp 171—172° (isopropyl ether–$CHCl_3$); IR ν_{max}^{Nujol} (cm^{-1}): 1775; NMR ($CDCl_3$) δ: 1.50 (9H, s), 2.08 (3H, s), 3.22 and 3.60 (2H, ABq, J=18 Hz), 3.67 (1H, d, J=9 Hz), 4.73 (1H, dd, J=9 and 5 Hz), 4.99 (1H, d, J=5 Hz), 7.17—8.37 (4H, m). 7α-*o*-Nitrobenzenesulfenamide **13**: yellow oil; IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 1780; NMR ($CDCl_3$) δ: 1.45 (9H, s), 2.01 (3H, s), 3.15 and 3.43 (2H, s, J=18 Hz), 3.73 (1H, d, J=7 Hz), 4.38 (1H, dd, J=7 and 2 Hz), 4.68 (1H, d, J=2 Hz), 7.12—8.35 (4H, m).

(b) Reduction with Lithium Tri-*tert*-butoxyaluminum Hydride at 0°: Lithium tri-*tert*-butoxyaluminum hydride (327 mg, 1.29 mmol) in dry THF (4 ml) was added to a solution of *o*-nitrobenzenesulfenimine **4a** (101 mg, 0.24 mmol) in dry THF (4 ml) at −78°. The solution was stirred at −78° for 10 min and then at 0° for 2 hr. The mixture was then diluted with $CHCl_3$, followed immediately by the addition of phosphate buffer solution (pH 4.01) with vigorous stirring. The organic layer was separated, washed with water, and dried over $MgSO_4$. Removal of organic solvents and preparative TLC of the residue on silica gel (solvent benzene–EtOAc 10: 1) gave *o*-nitrobenzenesulfinimine **4a** (Rf=0.78, 12.8 mg, 12.7%), 7β-*o*-nitrobenzenesulfenamide **12** (Rf=0.62, 51.0 mg, 50.4%), and 7α-*o*-nitrobenzenesulfenamide **13** (Rf=0.45, 28.0 mg, 26.7%).

(c) Reduction with Sodium Borohydride: A solution of sodium borohydride (110 mg, 2.9 mmol) in dry DMSO (4 ml) and dry THF (4 ml) was added to a solution of *o*-nitrobenzenesulfenimine **4a** (284 mg, 0.67 mmol) in dry THF (28 ml) and dry DMSO (4 ml) at 0° over a period of 10 min. The mixture was stirred at 0° for 10 min and quenched with AcOH (1.2 ml). The solution was diluted with EtOAc and washed successively with water, $NaHCO_3$ solution, and saturated NaCl solution. After drying over Na_2SO_4, the solvent was evaporated off *in vacuo* to give a yellow oil (crude product: 300 mg). Preparative TLC of the crude product (solvent: benzene–EtOAc 10: 1) gave 7β-*o*-nitrobenzenesulfenamide **12** (Rf=0.62, 148 mg, 52.0%) and 7α-*o*-nitrobenzenesulfenamide **13** (Rf=0.45, 15.9 mg, 5.6%).

***tert*-Butyl 7β-Amino-3-methyl-3-cephem-4-carboxylate (14)**——The reduction of *o*-nitrobenzenesulfenimine **4a** (284 mg, 0.67 mmol) with sodium borohydride was repeated as described above. The resulting crude 7β-*o*-nitrobenzenesulfenamide **12** (300 mg) was dissolved in CH_2Cl_2 (4.5 ml), and a solution of potassium iodide (1.18 g, 7.1 mmol) in a mixture of MeOH (15 ml) and AcOH (2.2 ml) was added under ice-water cooling, followed by the addition of 1 M $Na_2S_2O_3$ solution (1.5 ml). The reaction mixture, containing precipitates, was stirred at room temperature for 2 hr. Ethyl acetate and $NaHCO_3$ solution were added to the mixture, and the organic layer was separated. The organic phase was washed with $NaHCO_3$ solution and saturated NaCl solution, dried over Na_2SO_4 and evaporated down to furnish a yellow solid (231 mg). This crude product was dissolved in a small amount of EtOAc (insoluble material was filtered off) and applied to a preparative TLC plate, developed with benzene–EtOAc (1: 1). The usual work-up gave 7β-amino-cephalosporin **14** (90 mg, 49.4% from **4a**). **14**: amorphous solid; IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 1780; NMR ($CDCl_3$) δ: 1.48 (9H, s), 2.02 (3H, s), 2.05 (2H, bs), 3.15 and 3.53 (2H, ABq, J=18 Hz), 4.72 (1H, d, J=5 Hz), 4.90 (1H, d, J=5 Hz).

Methyl 6β-*o*-Nitrobenzenesulfenamido-penicillanate (20)——Sodium borohydride (167 mg, 4.4 mmol) in dry THF (6 ml) and dry DMSO (6 ml) was added to a solution of methyl 6-*o*-nitrobenzenesulfenimino-penicillanate **19**[3] (380 mg, 1.0 mmol) in dry THF (32 ml) and dry DMSO (6 ml) at 0° with vigorous stirring.

The mixture was stirred at 0° for 15 min, then the solution was quenched with AcOH (1.8 ml), diluted with EtOAc, and washed successively with water, $NaHCO_3$ solution, and saturated NaCl solution. The organic solution was dried over $MgSO_4$ and evaporated down *in vacuo* to afford a residue, which was purified by preparative TLC (solvent: benzene–EtOAc 5:1) to give 6β-*o*-nitrobenzenesulfenamide **20** (200 mg, 52.2%). **20**: yellow oil; IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 1790; NMR ($CDCl_3$) δ: 1.54 (3H, s), 1.70 (3H, s), 3.70 (1H, d, J=10 Hz), 3.80 (1H, s), 4.51 (1H, s), 4.67 (1H, dd, J=4.5 and 10 Hz), 5.67 (1H, d, J=4.5 Hz), 7.22—8.48 (4H, m).

Methyl 6β-Amino-penicillanate (21)——6β-*o*-Nitrobenzenesulfenamide **20** (298 mg, 0.78 mmol) in CH_2Cl_2 (4.5 ml) was added to a solution of potassium iodide (1.20 g, 7.2 mmol) in a mixture of MeOH (15 ml) and AcOH (2.2 ml) at 0°, followed by the addition of 1 M $Na_2S_2O_3$ solution (1.5 ml). The mixture was stirred for 2 hr at room temperature. EtOAc and $NaHCO_3$ solution were added to the mixture and the organic phase was washed with saturated $NaHCO_3$ solution then saturated NaCl solution. The organic solution was dried over $MgSO_4$ and concentrated *in vacuo* to give a crude substance, which was purified by silica gel chromatography using benzene–EtOAc (1:4) to furnish 6β-amino-penicillin **21** (59.7 mg, 33.4%). **21**: oil; IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 1780; NMR ($CDCl_3$) δ: 1.48 (3H, s), 1.64 (3H, s), 2.15 (2H, bs), 3.78 (3H, s), 4.41 (1H, s), 4.56 (1H, d, J=5 Hz), 5.55 (1H, d, J=5 Hz).

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