

Phosphorus in Organic Synthesis. XII.^{1a)} Amino Acids and Peptides.
XXII.^{1b)} Reaction of Penicillin Sulfoxides with Diethyl
Phosphorocyanidate (DEPC)²⁾

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Reaction of penicillin sulfoxides with diethyl phosphorocyanidate (DEPC) was investigated. Treatment of benzylpenicillin (*S*)-sulfoxide methyl ester (**4a**) with a slight excess of DEPC in *N,N*-dimethylacetamide gave the 3-cephem (**5a**), the 2-cephem (**6a**), and the 3-methylenecepham (**7a**) in 22, 4, and 4% yields, respectively. Increase of the quantity of DEPC to a three or five fold excess increased the yield of the 3-cephem (**5a**). Phenoxymethylpenicillin (*S*)-sulfoxide methyl ester (**4b**) also afforded the 3-cephem (**5b**) and the 3-methylenecepham (**7b**) under analogous reaction conditions as above, while phthalimidopenicillin (*R*)-sulfoxide methyl ester (**8**) furnished the 3-cephem (**9**) and the isothiazolones (**10** and **11**).

Recent publications from our laboratories have revealed that the reaction of diethyl phosphorocyanidate (DEPC) with carboxylic acids in the presence of triethylamine showed the transient formation of acyl cyanides¹⁾ and DEPC, in combination with triethylamine, is a convenient reagent for condensing carboxylic acids with suitable nucleophiles such as amines,^{1,4)} thiols,⁵⁾ and alcohols.¹⁾

Further research into the synthetic applications of DEPC has led us to investigate the reaction of DEPC with sulfenic acids. Sulfenic acids are, in general, labile chemical species and have only been known as transient intermediates. It is now well proved⁶⁾ that labile sulfenic acids

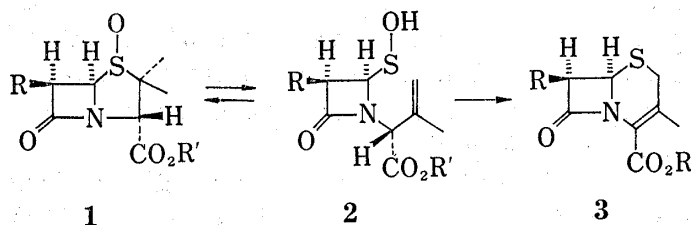


Chart 1

(**2**) are produced by the thermal treatment of penicillin sulfoxides (**1**),⁷⁾ and the reaction of **2** with acidic reagents, e.g., acetic anhydride, sulfonic acids, sulfuric acid, or phosphoric acid, gives desacetoxycephalosporins (**3**) as shown in Chart 1. As DEPC appeared to become a substitute for these acidic reagents, investigations were made on the interaction of DEPC with penicillin sulfoxides (**1**) or, correctly, sulfenic acids (**2**).

- 1) a) Part XI: T. Shioiri, Y. Yokoyama, Y. Kasai, and S. Yamada, *Tetrahedron*, **32**, 2211 (1976); b) Part XXI: *Idem*, *ibid.*, **32**, 2211 (1976).
- 2) Presented in part at the 94th Annual Meeting of Pharmaceutical Society of Japan, Sendai, April 1974, Abstracts of Papers, I, p. 119, II, p. 68.
- 3) Location: 7-3-1, Hongo, Bunkyo-ku, Tokyo, 113, Japan.
- 4) S. Yamada, Y. Kasai, and T. Shioiri, *Tetrahedron Letters*, **1973**, 1595.
- 5) S. Yamada, Y. Yokoyama, and T. Shioiri, *J. Org. Chem.*, **39**, 3302 (1974).
- 6) See reviews: a) D.H.R. Barton, *Pure and Applied Chem.*, **33**, 1 (1973); b) R.D.G. Cooper, L.D. Hatfield, and D.O. Spry, *Accounts. Chem. Res.*, **6**, 32 (1973); c) R.D.G. Cooper and D.O. Spry, "Cephalosporins and Penicillins. Chemistry and Biology," ed. by E.H. Flynn, Academic Press, New York and London, 1972, Chapter 5.
- 7) After our work had been completed, the sulfenic acids (**2**) (*R*=phthalimido, *R'*=*p*-nitrobenzyl or methyl) were isolated and well identified; T.S. Chou, J.R. Burgdorf, A.L. Ellis, S.R. Lammert, and S.P. Kulolja, *J. Am. Chem. Soc.*, **96**, 1609 (1974).

Thus benzylpenicillin (S)-sulfoxide methyl ester (**4a**) was treated with a slight excess of DEPC in N,N-dimethylacetamide at 120° for 0.5 hr. Three components were obtained after a silica gel column chromatography. The first fraction to be eluted, the major product, was identified as the 3-cephem derivative (**5a**) by comparisons of physical data with known ones.⁸⁾

The second product to be eluted showed the same elemental composition, C₁₇H₁₈O₄N₂S, as that of **5a**. The infrared (IR) spectrum exhibited the presence of the β -lactam group at 1775 cm⁻¹ as well as the ester (1743 cm⁻¹) and the secondary amide (3265 and 1660 cm⁻¹) groups. The nuclear magnetic resonance (NMR) spectrum contained, in addition to signals that can be clearly assigned to the phenylacetamido side chain, the ester methyl, and the β -lactam ring protons, peaks at δ 1.82 (C₃-methyl), 4.67 and 5.87 (each 1H, singlet). The latter two signals can be ascribed to the C₄- β -proton and the olefinic proton at C₂, respectively. These data allow the structural assignment for the second product as the 2-cephem derivative (**6a**).⁹⁾

The third product, which showed the same elemental composition as **5a** and **6a**, was assigned the 3-methylenecepham (**7a**) on the basis of physical data. The main peaks on its IR spectrum was quite similar to those of **5a** and **6a**, confirming the presence of the β -lactam, the ester, and the secondary amide functions. The NMR spectrum also affirmed the presence of the β -lactam ring, the ester methyl, and the phenylacetamido side chain. The peaks of AB pattern at δ 3.10 and 3.58 can be ascribed to the C₂ protons, while the C₄- β -proton and the C₃-methylene protons can be assigned at δ 5.10 and 5.15.¹⁰⁾ The yields of **5a**, **6a**, and **7a** were 22, 4, and 4%, respectively.

The formation of **6a** and **7a** may be worthy of comment for two reasons: (i) to our knowledge, there will be no report on the definite isolation of 2-cephem and 3-methylenecepham derivatives by the ring expansion of penicillin sulfoxides;¹¹⁾ (ii) 2-cephem¹²⁾ and 3-methylenecepham compounds may be used as starting materials for 3-functionalized 3-cephems which are clinically useful. Recently appeared several reports concerning the preparation¹³⁾ of 3-methylenecephams and their utilization¹⁴⁾ as the starting materials for the synthesis of modified cephalosporins.

Repetition of the ring expansion reaction of **4a** using a five-fold excess of DEPC increased the yields of cephalosporin derivatives (**5a**, **6a**, and **7a**) to 34.5, 6, and 6%, respectively, whereas the lower temperature (100°) and the longer reaction time (2 hr) resulted in 26.5% yield of **5a**.

When phenoxymethylpenicillin (S)-sulfoxide methyl ester (**4b**) was treated with a five-fold excess of DEPC in N,N-dimethylacetamide at 120° for 0.5 hr, the 3-cephem (**5b**) and the 3-methylenecepham (**7b**) were obtained in 38 and 4% yields, respectively, but the 2-cephem

8) D.H.R. Barton, F. Comer, D.G.T. Greig, P.G. Sammes, C.M. Cooper, G. Hewitt, and W.G.E. Underwood, *J. Chem. Soc. (C)*, **1971**, 3540.

9) a) R.B. Morin, B.G. Jackson, R.A. Mueller, E.R. Lavagnino, W.B. Scanlon, and S.L. Andrews, *J. Am. Chem. Soc.*, **91**, 1401 (1969); b) See also ref. 6c) p. 698, Fig. 28.

10) Resemblance of this NMR spectrum with that of **7b** also confirmed the structure of **7a**.

11) R.B. Morin and B.G. Jackson, U.S. Patent 3275626 (1966), have briefly mentioned the possibility of the formation of 2-cephems and 3-methylenecephams during the ring expansion reaction but given no experimental detail.

12) Ref. 6c) Chapter 4.

13) a) M. Ochiai, O. Aki, A. Morimoto, T. Okada, K. Shinozaki, and Y. Asahi, *Tetrahedron Letters*, **1972**, 2341; *idem*, *J. Chem. Soc. Perkin I*, **1974**, 258; b) M. Ochiai, O. Aki, A. Morimoto, T. Okada, and T. Kaneko, *Tetrahedron Letters*, **1972**, 2345; c) M. Ochiai, O. Aki, A. Morimoto, and T. Okada, *ibid.*, **1972**, 3241; d) M. Ochiai, E. Mizuta, O. Aki, A. Morimoto, and T. Okada, *ibid.*, **1972**, 3245; e) M. Ochiai, O. Aki, A. Morimoto, T. Okada, and H. Shimadzu, *J. Chem. Soc. Chem. Comm.*, **1972**, 800; M. Ochiai, O. Aki, A. Morimoto, T. Okada, and K. Morita, *Tetrahedron*, **31**, 115 (1975); f) R.R. Chauvette and P.A. Pennington, *J. Org. Chem.*, **38**, 2994 (1973); g) D.O. Spry, *Tetrahedron Letters*, **1973**, 165.

14) a) R.R. Chauvette and P.A. Pennington, *J. Am. Chem. Soc.*, **96**, 4986 (1974); *idem*, *J. Med. Chem.*, **18**, 403 (1975); b) R. Scartazzini and H. Bickel, *Helv. Chim. Acta*, **57**, 1919 (1974).

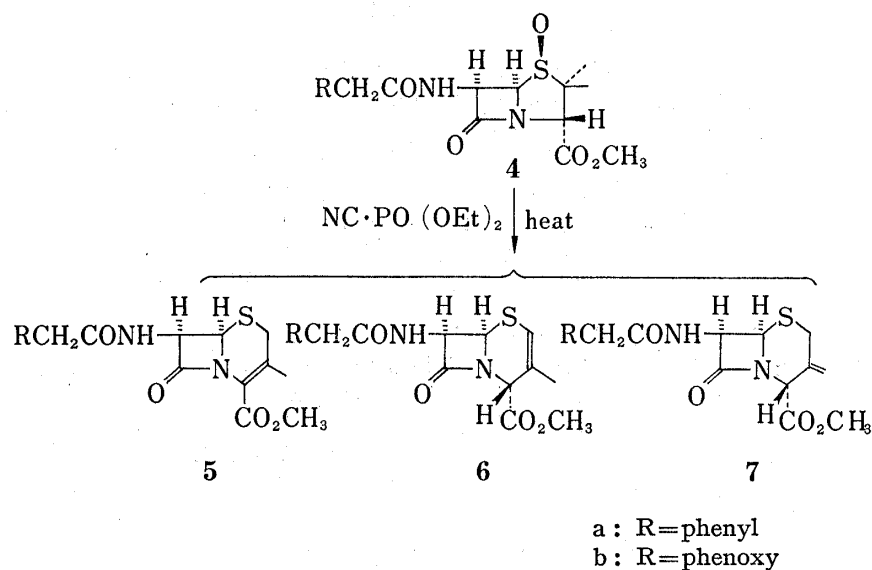


Chart 2

derivative (**6b**) could not be isolated. The structures of **5b^{9a)}** and **7b^{13c)}** were amply confirmed by comparisons of physical data with known ones. Reaction at 100° for 2 hr using a three-fold excess of DEPC afforded the similar results.

Finally, phthaloylpenicillin (*R*)-sulfoxide methyl ester (**8**) was allowed to react with a five-fold excess of DEPC in N,N-dimethylacetamide. Heating at 120° for 0.5 hr gave the 3-cephem derivative (**9**) in 28% yield as well as the isothiazolone derivative (**10**) in 35% yield, while the reaction at 100° for 2 hr afforded the 3-cephem derivative (**9**) in 29.5% yield and the isothiazolone (**10**) in 13% yield. In the latter case, the isomerized isothiazolone (**11**) were also isolated. Formation of isothiazolones such as **10** and **11** during the thermal decomposition of penicillin sulfoxides is well documented.^{6c,7,8,9a)}

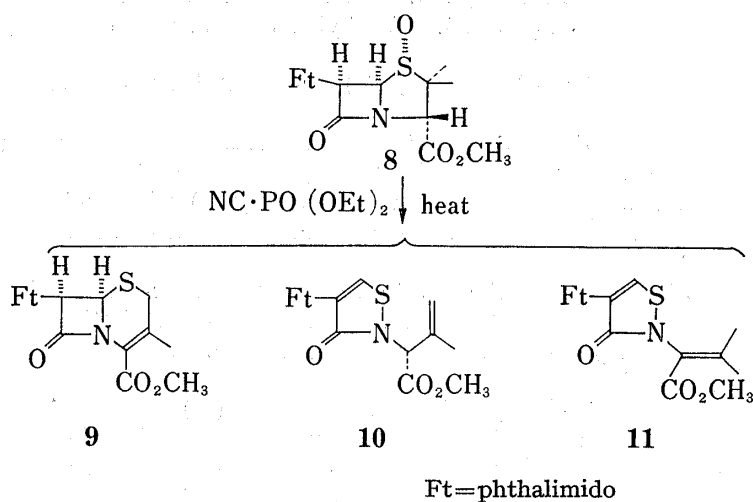


Chart 3

In comparison with the known ring expansion reaction of the penicillin sulfoxides,^{6,11)} one of the most interesting feature of the above results with DEPC will be the formation of 3-methylenecepham derivatives (**7a** and **7b**) in the case of **4a** and **4b**, though each yield should be much improved.

Experimental

Unless otherwise stated, melting points were measured on a hot stage apparatus and uncorrected; IR spectra were measured either in nujol mulls (for crystals) or in liquid films (for oils); NMR spectra (60 MHz) were measured in deuteriochloroform, and chemical shifts (δ) are given in ppm relative to internal tetramethylsilane. After the reaction, the reaction mixture was diluted with a mixture of methylene chloride and benzene (1:10, 250 ml), and successively washed with 0.5% aqueous hydrochloric acid (100 ml $\times$ 6), 5% aqueous sodium bicarbonate (100 ml $\times$ 2), water (100 ml $\times$ 1), and saturated aqueous sodium chloride (100 ml $\times$ 2). Drying over sodium sulfate followed by evaporation gave a neutral residue, which was subjected to silica gel (Wakogel C-200) column chromatography. DEPC was prepared according to our previous reports.^{1,4)}

Reaction of Benzylpenicillin (S)-Sulfoxide Methyl Ester (4a) with DEPC—(i) With a Slight Excess of DEPC at 120° for 0.5 hr: A mixture of benzylpenicillin (S)-sulfoxide methyl ester⁸⁾ (4a) (1.092 g, 3 mmol) and DEPC (0.587 g, 3.2 mmol) in N,N-dimethylacetamide (20 ml) was stirred at 120° (internal temperature) for 0.5 hr. After work-up as in the general direction, the neutral residue was fractionated by silica gel (100 g) column chromatography with a mixture of benzene and ethyl acetate (6:1). The first fraction to be eluted was the 3-cephem (5a) (236 mg, 22%) as colorless needles (ethyl acetate–diethyl ether), mp 189–192° (lit.⁸⁾ 187–188°), $[\alpha]_D^{25} + 86.7^\circ$ ($c=1$, chloroform) (lit.⁸⁾ $[\alpha]_D^{25} + 86.5^\circ$ ($c=1$, chloroform)), IR $\nu_{\max}$ cm⁻¹: 3270, 1775, 1738, 1655, 1543, 690. NMR 2.07 (3H, singlet, C₃–CH₃), 3.05 and 3.46 (2H, AB pattern, $J=16$ Hz, C₂–H₂), 3.54 (2H, singlet, CH₂CO), 3.72 (3H, singlet, CO₂CH₃), 3.85 (1H, doublet, $J=5$ Hz, C₆–H), 5.63 (1H, doublet of doublet, $J_1=5$ Hz, $J_2=9$ Hz, C₇–H), 6.55 (1H, doublet, $J_2=9$ Hz, NH), 7.20 (5H, singlet, C₆H₅).

The second fraction to be eluted was the 2-cephem (6a) (45 mg, 4%) as colorless crystals (chloroform–diethyl ether–*n*-hexane), mp 153–155°. IR $\nu_{\max}$ cm⁻¹: 3265, 1775, 1743, 1660, 1533, 720. NMR 1.82 (3H, singlet, C₃–CH₃), 3.61 (2H, singlet, CH₂), 3.76 (3H, singlet, CO₂CH₃), 4.67 (1H, singlet, C₄–H), 5.18 (1H, doublet, $J_1=4.5$ Hz, C₆–H), 5.60 (1H, doublet of doublet, $J_1=4.5$ Hz, and $J_2=9$ Hz, C₇–H), 5.87 (1H, singlet, C₂–H), 6.56 (1H, doublet, $J_2=9$ Hz, NH), 7.25 (5H, singlet, C₆H₅). Anal. Calcd. for C₁₇H₁₈O₄N₂S: C, 58.95; H, 5.24; N, 8.09. Found: C, 59.24; H, 5.21; N, 8.21.

The third fraction to be eluted was the 3-methylenecepham (7a) (43 mg, 4%) as colorless crystals (chloroform–diethyl ether–*n*-hexane), mp 108–109°. IR $\nu_{\max}$ cm⁻¹: 3360, 1778, 1748, 1660, 1525, 730, 695. NMR 3.10 and 3.58 (2H, AB pattern, $J=14$ Hz, C₂–H₂), 3.54 (1H, singlet, CH₂CO), 3.70 (3H, singlet, CO₂CH₃), 5.10 (1H, singlet, C₄–H), 5.15 (2H, singlet, C₈–CH₂), 5.31 (1H, doublet, $J_1=4.5$ Hz, C₆–H), 5.57 (1H, doublet of doublet, $J_1=4.5$ Hz, $J_2=9$ Hz, C₇–H), 6.70 (1H, doublet, $J_2=9$ Hz, NH), 7.25 (5H, singlet, C₆H₅). Anal. Calcd. for C₁₇H₁₈O₄N₂S: C, 58.95; H, 5.24; N, 8.09. Found: C, 59.09; H, 5.26; N, 8.20.

(ii) With a Five-fold Excess of DEPC at 120° for 0.5 hr: A mixture of 4a (1.82 g, 5 mmol) and DEPC (4.075 g, 25 mmol) in N,N-dimethylacetamide (30 ml) was stirred at 120° for 0.5 hr, and worked up as above to give a neutral residue. Trituration with a mixture of chloroform, ethyl acetate, and benzene afforded colorless crystals of 5a (230 mg). The filtrate was fractionated by silica gel (160 g) column chromatography with a mixture of benzene and ethyl acetate (5:1). The first fraction was recrystallized from a mixture of chloroform and diethyl ether to give 5a (367 mg). Total yield of 5a was 597 mg (34.5%). From the filtrate was obtained 6a (100 mg, 6%).

The second fraction to be eluted was 7a (100 mg, 6%). Further elution of the column afforded the starting material 4a (250 mg, 14%).

(iii) With a Five-fold Excess of DEPC at 100° for 2 hr: A stirred mixture of 4a (1.092 g, 3 mmol) and DEPC (2.445 g, 15 mmol) in N,N-dimethylacetamide (20 ml) was heated at 100° for 2 hr, and worked up as above. The neutral residue was chromatographed over silica gel (30 g) using a mixture of benzene and ethyl acetate (3:1). The first fraction to be eluted was recrystallized from a mixture of chloroform and diethyl ether to furnish 5a (140 mg).

The second fraction to be eluted and the filtrate from the above recrystallization were combined, and again chromatographed over silica gel (40 g) with a mixture of benzene and ethyl acetate (4:1). The first fraction was 5a (135 mg), the total yield of which was 275 mg (26.5%). Further elution of the column afforded the starting 4a (330 mg, 20%).

Reaction of Phenoxymethylpenicillin (S)-Sulfoxide Methyl Ester (4b) with DEPC—(i) With a Five-fold Excess of DEPC at 120° for 0.5 hr: A mixture of phenoxymethylpenicillin (S)-sulfoxide methyl ester^{9a)} (4b) (0.761 g, 2 mmol) and DEPC (1.63 g, 10 mmol) in N,N-dimethylacetamide (15 ml) was stirred at 120° for 0.5 hr. Work-up as usual gave a neutral residue, which was fractionated over silica gel (100 g) with a mixture of benzene and ethyl acetate (5:1). The first fraction to be eluted was the 3-cephem (5b) (277 mg, 38%) as colorless crystals (methanol), mp 142.5–143° (lit.^{9a)} 141–142°), $[\alpha]_D^{25} + 91.2^\circ$ ($c=1$, dioxane) (lit.^{9a)} $[\alpha]_D + 94^\circ$). IR $\nu_{\max}$ cm⁻¹: 3270, 1780, 1740, 1675, 1550, 1505, 1225, 750, 685. NMR 2.12 (3H, singlet, C₃–CH₃), 3.09 and 3.51 (2H, AB pattern, $J=17$ Hz, C₂–H₂), 3.80 (3H, singlet, CO₂CH₃), 4.51 (2H, singlet, CH₂CO), 4.94 (1H, doublet, $J_1=5$ Hz, C₆–H), 5.75 (1H, doublet of doublet, $J_1=5$ Hz, $J_2=10$ Hz, C₇–H), 6.8–7.6 (6H, multiplet, NH and C₆H₅).

The second fraction to be eluted was the 3-methylenecepham (7b) (30 mg, 4%) as colorless crystals (chloroform–methanol), mp 153–155° (lit.^{13c)} 145–147°). IR $\nu_{\max}$ cm⁻¹: 3335, 1780, 1743, 1675, 1530, 1500, 1250,

1240, 1230, 753. NMR 3.20 and 3.70 (2H, AB pattern, $J=13$ Hz, C_2-H_2), 3.75 (3H, singlet, CO_2CH_3), 4.50 (2H, singlet, CH_2CO), 5.10 (1H, singlet, C_4-H), 5.21 (2H, singlet, C_8-CH_2), 5.40 (1H, doublet, $J_1=5$ Hz, C_6-H), 5.70 (1H, doublet of doublet, $J_1=5$ Hz, $J_2=9$ Hz, C_7-H), 6.8—7.5 (6H, multiplet, NH and C_6H_6). *Anal.* Calcd. for $C_{17}H_{18}O_5N_2S$: C, 56.35; H, 5.01; N, 7.73. Found: C, 56.42; H, 5.07; N, 7.61.

The third fraction to be eluted was the starting **4b** (95 mg, 12.5%).

(ii) With a Three-fold Excess of DEPC at 100° for 2 hr: The ester (**4b**) (1.902 g, 5 mmol) was stirred with DEPC (2.445 g, 15 mmol) in *N,N*-dimethylacetamide (20 ml) at 100° for 2 hr. The mixture was treated as usual to give a neutral residue, which was fractionated over silica gel (120 g) with a mixture of benzene and ethyl acetate (5:1). The first fraction to be eluted was presumably methyl 3-methyl-2-(3-oxo-4-phenoxyacetamido-4^{isothiazolin-2-yl}) but-2-enoate (46 mg, 2.5%) as an oil (lit.^{9a}) mp $143-145^\circ$, IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3380, 1760, 1700, 1660, 1540, 1500. NMR 1.80 (3H, broad singlet, $C-CH_3$), 3.77 (3H, singlet, CO_2CH_3), 4.60 (2H, singlet, CH_2CO), 5.10 and 5.25 (2H, each broad singlet, $CH_2=C$), 5.60 (1H, singlet, $CHCO_2CH_3$), 6.8—7.4 (5H, multiplet, C_6H_5), 8.60 (1H, singlet, C_5-H of isothiazolone), 8.83 (1H, broad singlet, NH).

The second fraction to be eluted was **5b** (670 mg, 37%), and the third fraction was **7b** (70 mg, 3.9%). Further elution of the column furnished the starting material (**4b**) (400 mg, 21%).

Reaction of Phthalimidopenicillin (R)-Sulfoxide Methyl Ester (8) with DEPC—(i) With a Five-fold Excess of DEPC at 120° for 0.5 hr: A stirred mixture of phthalimidopenicillin (*R*)-sulfoxide methyl ester (**8**)¹⁵ (752 mg, 2 mmol) and DEPC (1.63 g, 10 mmol) in *N,N*-dimethylacetamide (20 ml) was heated at 120° for 0.5 hr, and worked up as usual. The neutral residue was chromatographed over silica gel (70 g) with a mixture of benzene and ethyl acetate (8:1). The first fraction to be eluted was the 3-cephem (**9**) (199 mg, 28%) which was identical with **9** prepared from 7-amino-3-methyl-3-cephem-4-carboxylic acid as below.

The second fraction to be eluted was the isothiazolone (**10**) (250 mg, 35%) as colorless crystals (chloroform-methyl ethyl ketone-cyclohexane), mp $205-218^\circ$ (decomp.). IR ν_{max} cm^{-1} : 1758, 1728, 1670, 708. NMR 1.83 (3H, singlet, $C-CH_3$), 3.77 (3H, singlet, CO_2CH_3), 5.08 and 5.22 (2H, each singlet, $C=CH_2$), 5.68 (1H, singlet, $CHCO_2CH_3$), 7.8 (4H, multiplet, C_6H_4), 8.30 (1H, singlet, C_5-H of isothiazolone). *Anal.* Calcd. for $C_{17}H_{14}O_5N_2S$: C, 56.98; H, 3.94; N, 7.82. Found: C, 56.74; H, 3.86; N, 7.71.

(ii) With a Five-fold Excess of DEPC at 100° for 2 hr: A mixture of **8** (752 mg, 2 mmol) and DEPC (1.63 g, 10 mmol) in *N,N*-dimethylacetamide (20 ml) was stirred at 100° for 2 hr, and treated as usual. Column chromatography over silica gel (80 g) with a mixture of benzene and ethyl acetate (6:1) gave the 3-cephem (**9**) (211 mg, 29.5%) and the isothiazolone (**10**) (90 mg, 13%) as the first and the second fractions, respectively.

The third fraction to be eluted was the isothiazolone (**11**) (30 mg, 4%) as colorless crystals, mp $220-236^\circ$ (decomp.), (lit.⁷) $>230^\circ$ (decomp.). IR ν_{max} cm^{-1} : 1735, 1665, 1640, 705. NMR 1.92 and 2.37 (6H, each singlet, $2 \times C-CH_3$), 3.68 (3H, singlet, CO_2CH_3), 7.8 (4H, multiplet, C_6H_4), 8.26 (1H, singlet, C_5-H of isothiazolone). *Anal.* Calcd. for $C_{17}H_{14}O_5N_2S$: C, 56.98; H, 3.94; N, 7.82. Found: C, 56.89; H, 3.83; N, 7.69.

Preparation of Methyl 3-Methyl-7-phthalimido-3-cephem-4-carboxylate^{16,17}—To a stirred mixture of 7-amino-3-methyl-3-cephem-4-carboxylic acid (4.29 g, 20 mmol) and sodium carbonate (2.12 g, 20 mmol) in water (80 ml) was added *N*-carbethoxyphthalimide (4.38 g, 20 mmol). The mixture was stirred at room temperature for 4 hr, and washed with methylene chloride. A fresh portion of methylene chloride was added to the aqueous phase, which was acidified with 1 *N* hydrochloric acid and the extraction was completed with additional portions of methylene chloride. The combined organic layers were washed with water and saturated aqueous sodium chloride, dried over sodium sulfate, and evaporated. Recrystallization of the residue from a mixture of acetone, methylene chloride, and diethyl ether afforded 3-methyl-7-phthalimido-3-cephem-4-carboxylic acid as colorless crystals, mp $190-210^\circ$ (decomp.), IR ν_{max} cm^{-1} : 1795, 1730, 1707, 720.

The acid (0.13 g) was dissolved in dioxane (100 ml) and the solution was stirred with ethereal diazomethane (10 ml, prepared from 1 g of *N*-nitrosomethylurea)¹⁸ at 0° for 10 min, and then at room temperature for 30 min. Evaporation followed by recrystallizations from a mixture of ethyl acetate and *n*-hexane gave methyl 3-methyl-7-phthalimido-3-cephem-4-carboxylate (**9**) as colorless needles, mp $169-170.5^\circ$ (lit.¹⁶⁷⁻¹⁶⁸,^{17a}) $176-177^\circ$,^{7,19} $187-188^\circ$ ^{17b,20}). IR ν_{max} cm^{-1} : 1790, 1775, 1735, 705; $\nu_{max}^{CHCl_3}$ cm^{-1} : 1790, 1735. NMR 2.40 (3H, singlet, C_3-CH_3), 3.05 and 3.85 (2H, AB pattern, $J=16$ Hz, C_2-H_2), 3.90 (3H, singlet, CO_2CH_3), 5.18 (1H, doublet, $J=4.5$ Hz, C_6-H), 5.79 (1H, doublet, $J=4.5$ Hz, C_7-H), 7.85 (4H, multiplet, C_6H_4).

Acknowledgement We wish to thank Dr. M. Kuramoto of Toyo Jozo, Co., Ltd. for gifts of penicillin and cephalosporin derivatives.

15) R.D.G. Cooper, P.V. Demarco, and D.O. Spry, *J. Am. Chem. Soc.*, **91**, 1528 (1969).

16) Cf. J.C. Sheehan and K.R. Henery-Logan, *J. Am. Chem. Soc.*, **84**, 2983 (1962).

17) a) S. Kukolja and S.R. Lammert, *J. Am. Chem. Soc.*, **94**, 7169 (1972). b) S. Kukolja and S.R. Lammert, *Angew. Chem. internat. Edit.*, **12**, 67 (1973).

18) F. Arndt, "Organic Syntheses," Coll. Vol. II, ed. by A.H. Blatt, John Wiley and Sons, Inc., New York, 1943, p. 165, Note 3.

19) T.S. Chou, *Tetrahedron Letters*, **1974**, 725.

20) S. Kukolja, S.R. Lammert, M.R. Gleissner, and A.I. Ellis, *J. Am. Chem. Soc.*, **97**, 3129 (1975).