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Synthesis of 3-Carboxyceph-3-em Compounds and Reactions of Cephalosporin Thiolactones[1)]

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Starting from cephalosporin thiolactones (**1**), a sequence of reactions (bromination, hydrolysis, oxidation and opening of the dioxo thiophene ring) yielded 3-carboxyceph-3-ems (**10**). Several reactions of thiolactone derivatives are also described.

Keywords——3-carboxyceph-3-ems; cephalosporin thiolactones; bromination of cephalosporin thiolactones; hydrolysis; cleavage of dioxo cephalosporins; Amberlite XAD-2

An intensive synthetic effort has been made to prepare cephalosporins with improved properties.[3)] Much of the work has been concerned with chemical modifications at the C_7- and C_3-positions, resulting in clinically useful drugs. Recently, 3-carboxyceph-3-em derivatives have been synthesized from the corresponding 3-formylceph-2-em derivatives by Spry[4a)] and Peter *et al.*[4b)] Our interest in modification at the C_3-position has led to an improved synthesis of 3-carboxyceph-3-em derivatives using readily available cephalosporin thiolactones[5)] as a starting material.

This report deals with a convenient synthetic route to 3-carboxyceph-3-ems (**10**) starting from cephalosporin thiolactones (**1**), and describes several reactions of the thiolactone derivatives. The process for the production of **10** from **1** comprises a two-step oxidation at the $C_{3'}$-position followed by opening of the dioxo thiophene ring.

The first oxidation step involves the introduction of a bromine atom into the $C_{3'}$-position. Bromination of thiolactones (**1**) was tried by alternate addition of bromine and triethylamine in CH_2Cl_2, but the yields were variable, depending on the rate of addition of the reagents. However, it was found that treatment of **1** with phenyltrimethylammonium perbromide (PTAB)[6)] in tetrahydrofuran (THF) gave the bromides (**3**) in 73—83% yields. The crude product was expected to contain two epimers. Although the bromide appeared to give a single spot on thin-layer chromatography, the presence of two epimers (in a ratio of about 5 : 4) was obvious from the nuclear magnetic resonance (NMR) spectrum. The separation of each epimer by chromatography was difficult. The NMR spectrum of **3a** (a mixture of two epimers) showed signals (2H) due to C_2–H at 3.81, 4.03 ppm (major epimer, ABq, J=18 Hz) and 3.71, 3.96 ppm (minor epimer, ABq, J=18 Hz), together with singlets (1H) at 6.99 ppm (major epimer) and 6.88 ppm (minor epimer), and analogous results were obtain-

1) A part of this work was presented at the 36th Annual Meeting of the Chemical Society of Japan, Osaka, April 1977, and has also been described in Japan. Patent Provisional Publication, 52-5786 (1977).
2) Location: *Jusohonmachi 2-chome, Yodogawa-ku, Osaka 532, Japan.*
3) E.H. Flynn (ed.), "Cephalosporins and Penicillins," Academic Press, New York and London, 1972.
4) *a*) D.O. Spry, *Chem. Commun.*, **1974**, 1012; *b*) H. Peter, B. Müller, and H. Bickel, *Helv. Chim. Acta*, **58**, 2450 (1975).
5) *a*) Fr. Patent 1524242 [Roussel-Uclaf; *C.A.*, **71**, 81386 *w* (1969)]; *b*) Japan. Patent Provisional Publication, 51-32637 (1976); *c*) R.R. Clauvette and P.A. Pennington, *J. Org. Chem.*, **38**, 2994 (1973).
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ed for **3b**. Based on these data, the position of the bromine atom was proposed to be $C_{3'}$. Compounds **3** were also prepared by bromination of the enol acetates (**2**) followed by treatment of **4** with $TiCl_4$. In this method, the ratio of the epimers was the same (about 5: 4) as before.

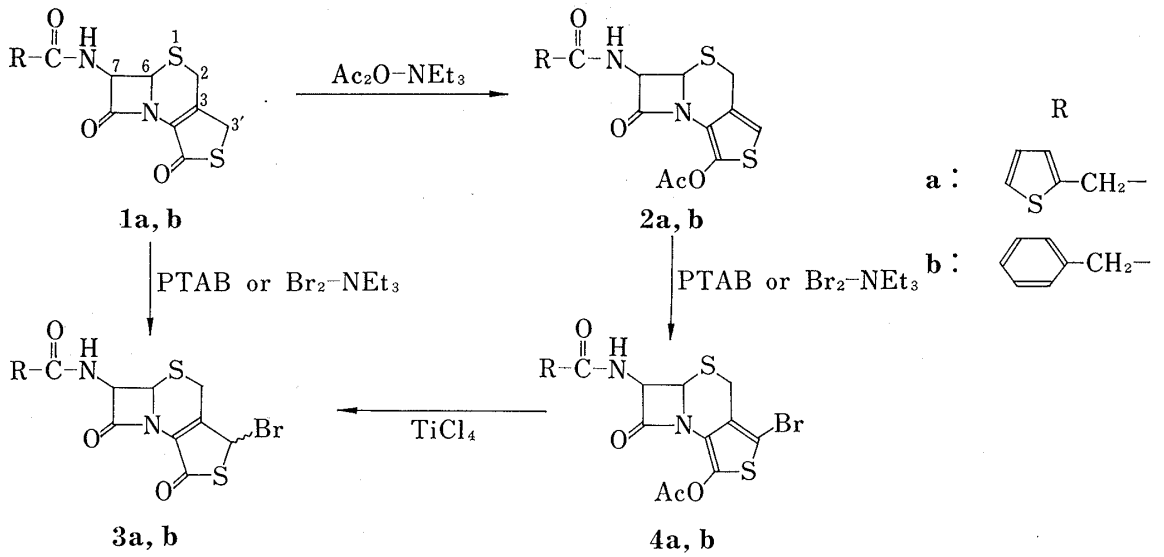

Chart 1

The bromides (**3**), each a mixture of two epimers, were then hydrolyzed in aqueous dimethyl sulfoxide (DMSO) to give the hydroxy compounds (**5**) in over 90% yields. Although these hydroxy compounds (**5**) seemed to be mixtures of epimers like the bromides (**3**), separation and characterization of the products were unsuccessful. On the other hand, methanolysis of the bromides (**3**) gave the methoxy compounds (**6**) as a mixture of epimers. The epimers of **6b** were successfully sepaated rfrom the mixture by silica gel chromatography, eluting with isopropyl ether–THF (3: 1). The first elution gave **6b—A** [colorless needles, mp 210—213° (dec.)], and the second elution gave **6b-B** [colorless needles, mp 191—193° (dec.)]. The NMR spectra of **6b-A** and **6b-B** showed the presence of a methoxyl group at 3.40 and 3.37 ppm and the $C_{3'}$–H at 6.52 and 6.56 ppm, respectively, and from those signals the ratio of the epimers (**6b-A**: **6b-B**) was calculated to be 4: 5. An attempt to separate the epimers of **6a** was unsuccessful, but precise NMR study clearly showed that the ratio of the epimers (**6a-A**: **6a-B**) was 4: 5. The circular dichroism (CD) curves of **6b-A** and **6b-B** showed three Cotton effects, two positive maxima at about 300 and 260 nm and a negative maximum at about 230 nm (Fig. 1). Interestingly, the entire shape of the CD curve of the epimer **6b-B** is quite similar to that of the thiolactone (**1b**).

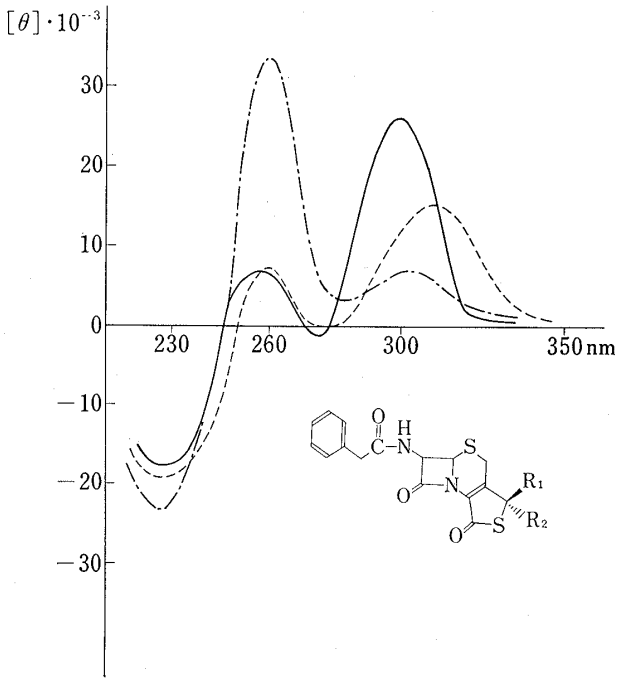

Fig. 1. CD Curves of the Thiolactone and Methoxy Derivatives in Methanol
———: thiolactone (R_1=R_2=H),
—·—·—: epimer A
------: epimer B (R_1 or R_2=OMe).

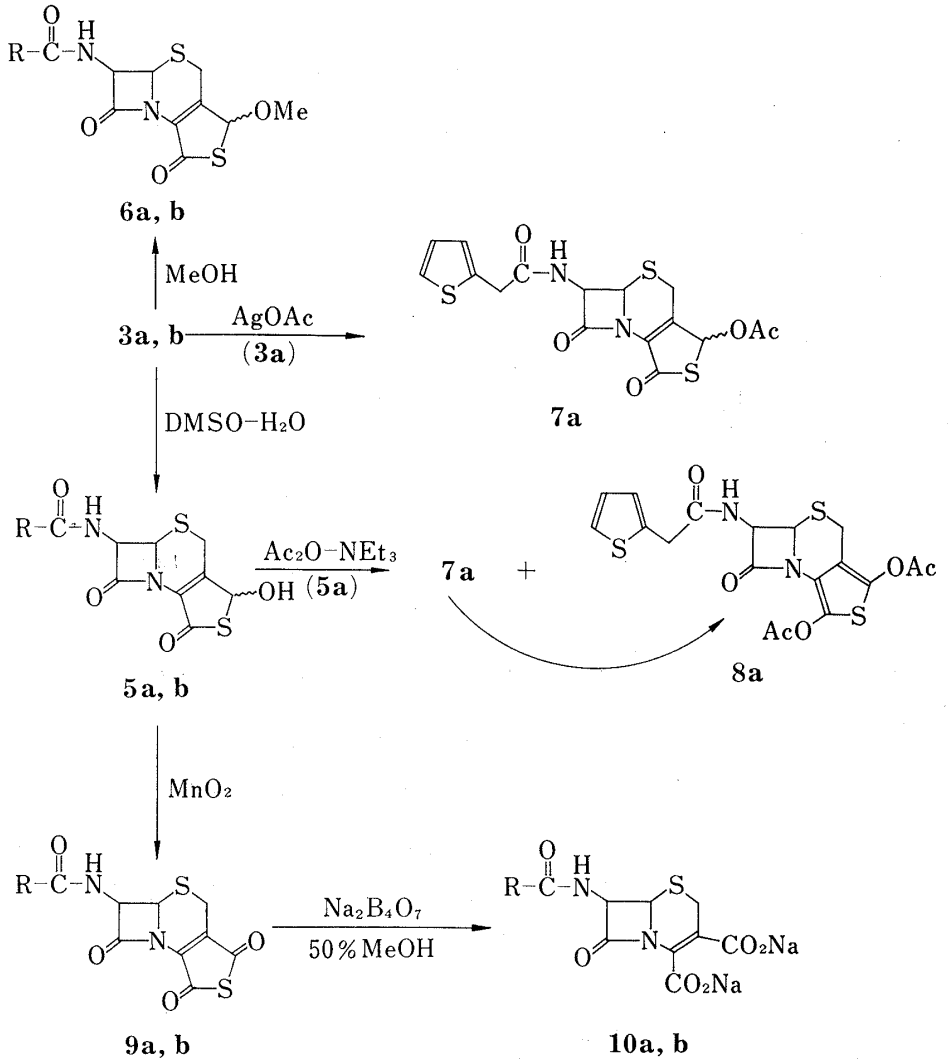

Chart 2

Consequently, it is assumed that the methoxyl group of **6b-B** (less hindered epimer) is in the α-configuration and that of **6b-A** is in the β-configuration.

Treatment of **3a** with silver acetate in acetic acid gave the acetoxy compound (**7a**, a 4:5 mixture of epimers), which was also obtained together with the diacetyl derivative **8a** by treatment of **5a** with acetic anhydride–triethylamine. The structures of **7a** and **8a** were easily established by NMR spectroscopy.

The second oxidation step involves conversion of the hydroxy compounds (**5**) to the dioxo compounds (**9**). Oxidation of **5** was performed with activated manganese dioxide (5 mol eq) in 1,2-dichloroethane at room temperature for 40 min. The hydroxy compounds (**5**) were oxidized to the dioxo compounds (**9**) in relatively low yields (35% for **9a** and 63% for **9b**). Compounds **9a** and **9b** showed infrared (IR) absorption bands at 1800 and 1802 cm^{-1} (β-lactam), respectively, which are higher than those of the usual cephalosporins. Therefore, the stability of the β-lactam ring in the dioxo compounds seemed to be reduced.

A successful ring opening of **9** was achieved with sodium tetraborate. Treatment of **9** with sodium tetraborate in 50% methanol gave 3-carboxyceph-3-ems (**10**), which were purified by column chromatography on Amberlite XAD-2 as the sodium salts. On the other hand, the dioxo compound (**9a**) was stirred in methanol for 8 hr to afford **11a** quantitatively, which gave a molecular peak at *m/e* 398 in the mass spectrum (MS) and showed an absorption band

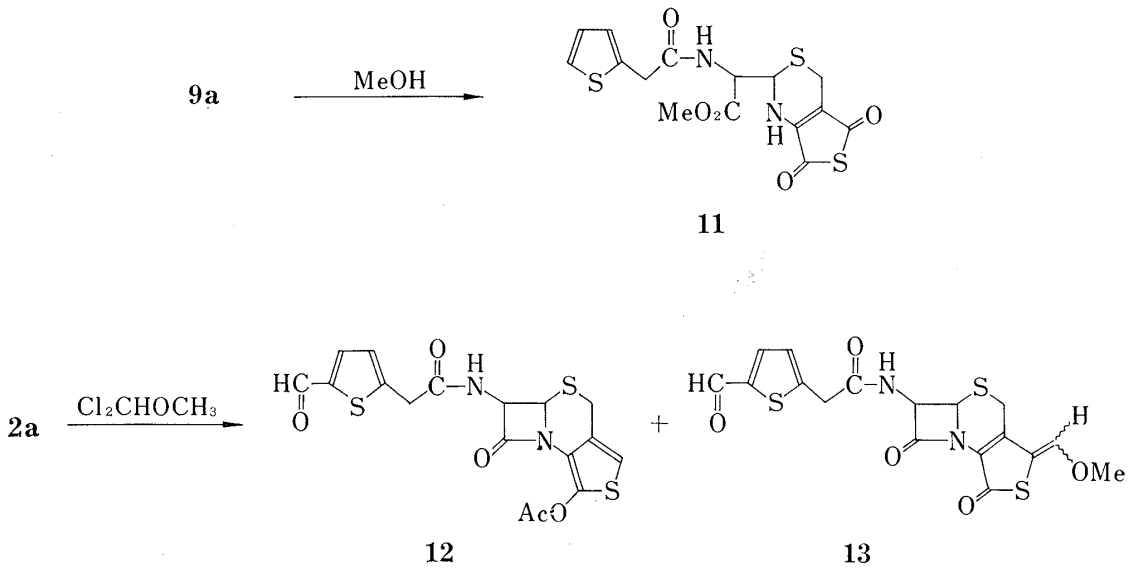

Chart 3

at 1735 cm^{-1} in the IR spectrum, indicating the presence of an ester group rather than a β-lactam ring.

Reaction of **2a** with dichloromethyl methyl ether and $TiCl_4$ in CH_2Cl_2 resulted in the formation of two products, **12** (38%) and **13** (46%). The structure of theses compounds were assigned by NMR spectroscopy.

The cephalosporin derivatives thus obtained were tested for antibacterial activities. The minimum inhibitory concentrations of **10a** were 3.13, 2.5 and 12.5 μg/ml against *Staphylococcus aureus*, *Klebsiella pneumoniae* and *Proteus vulgaris*, respectively.

Experimental

All melting points were taken with a Yanagimoto microscope hot stage and are uncorrected. The ultraviolet (UV), CD and IR spectra were taken with Perkin-Elmer 450, Jasco ORD/UV-5 and Hitachi EPI-S2 models, respectively. NMR spectra were recorded with Varian T-60 (60 MHz) and HR-100 (100 MHz) spectrophotometers using tetramethylsilane (TMS) as an internal (in DMSO-d_6) or external (in D_2O) standard. Abbreviations are as follows: s=singlet; br.s=broad singlet; d=doublet; dd=doublet of doublets; t=triplet; q=quartet. Mass spectra were measured with a Hitachi RMU-6D double focussing mass spectrometer. Column chromatography was carried out on Kiesel G (0.05—0.2 nm, Merck).

3-Bromomercaptomethyl-7-(2-thienylacetamido)ceph-3-em-4-carboxylic Acid Thiolactone (**3a**)——1) PTAB (4.65 g) was added in small portions to a solution of cephalosporin thiolactone (**1a**, 4.1 g) in dry THF (600 ml) under a nitrogen atmosphere and the mixture was stirred for 30 min. After removal of insoluble material by filtration, the filtrate was concentrated, and the residue was dissolved in AcOEt (300 ml). The solution was washed with water, dried (Na_2SO_4) and concentrated to yield **3a** as colorless flakes (4.7 g; about 5: 4 mixture of epimers), mp 138—143° (dec.). IR ν_{max}^{KBr} cm^{-1}: 1785 (β-lactam), 1700 (C=O), 1661 (CONH). NMR (DMSO-d_6, ppm) of the major product: 3.73 (2H, s, $-CH_2-$), 3.81 and 4.03 (2H, ABq, J=18 Hz, C_2–H), 5.13 (1H, d, J=5 Hz, C_6–H), 5.80 (1H, q, J=5 Hz and 8 Hz, C_7–H), 6.99 (1H, s, –CHBr), 9.14 (1H, d, J=8 Hz, NH). NMR (DMSO-d_6, ppm) of the minor product: 3.73 (2H, s, $-CH_2-$), 3.71 and 3.96 (2H, ABq, J=18 Hz, C_2–H), 5.12 (1H, d, J=5 Hz, C_6–H), 5.83 (1H, q, J=5 Hz and 8 Hz, C_7–H), 6.88 (1H, s, –CHBr), 9.17 (1H, d, J=8 Hz, NH).

2) A solution of cephalosporin thiolactone enol acetate (**2a**, mp 209—216°, 40 mg), which had been prepared by acetylation of **1a** with acetic anhydride–triethylamine, and PTAB (1.02 mol eq.) in THF (5 ml) was stirred for 1 hr at 0°. After removal of the solvent *in vacuo*, the residue was dissolved in AcOEt (50 ml). The solution was washed with dil. $NaHCO_3$ aq. solution and then dried (Na_2SO_4). After removal of the solvent, the residue was chromatographed on silica gel. Elution with benzene–acetone (9: 1) gave **4a** (31 mg) as colorless flakes, mp 193—197°. IR ν_{max}^{KBr} cm^{-1}: 1790 (β-lactam), 1772 (OAc), 1660 (CONH). NMR (DMSO-d_6, ppm): 2.27 (3H, s, Ac), 3.87 (2H, s, C_2–H), 5.23 (1H, d, J=5 Hz, C_6–H), 5.73 (1H, q, J=5 Hz and 8 Hz, C_7–H), 9.18 (1H, d, J=8 Hz, NH). A solution of **4a** (20 mg) in CH_2Cl_2 (5 ml) was treated with $TiCl_4$ (0.1 ml) at 0° with stirring for 15 min. After addition of water, the organic layer was separated, washed with water

and dried (Na_2SO_4). Removal of the solvent gave **3a** (8.3 mg), which gave IR and NMR spectra identical with those of the sample obtained in the above run.

3-Bromomercaptomethyl-7-phenylacetamidoceph-3-em-4-carboxylic Acid Thiolactone (3b)——1) Treatment of **1b** with PTAB in THF as described above gave **3b** as colorless needles (about 5:4 mixture of epimers), mp 166—167° (dec.). IR ν_{max}^{KBr} cm^{-1}: 1778 (β-lactam), 1712 (C=O), 1665 (CONH). NMR (DMSO-d_6, ppm) of the major product: 3.53 (2H, s, $-CH_2-$), 3.70 and 4.02 (2H, ABq, $J=18$ Hz, C_2–H), 5.10 (1H, d, $J=5$ Hz, C_6–H), 5.71 (1H, q, $J=5$ Hz and 8 Hz, C_7–H), 7.04 (1H, s, –CHBr), 9.05 (1H, d, $J=8$ Hz, NH). NMR (DMSO-d_6, ppm) of the minor product: 3.54 (2H, s, $-CH_2-$), 3.75 and 4.06 (2H, ABq, $J=18$ Hz, C_2–H), 5.00 (1H, d, $J=5$ Hz, C_6–H), 5.71 (1H q $J=5$ Hz and 8 Hz, C_7–H), 6.95 (1H, s, –CHBr), 9.11 (1H, d, $J=8$ Hz, NH).

2) Compound **4b** was prepared by the reaction of the corresponding cephalosporin thiolactone enol acetate (**2b**, mp 228—235° (dec.), colorless needles) with PTAB in THF as colorless needles, mp 214—216° (dec.). IR ν_{max}^{KBr} cm^{-1}: 1778 (β-lactam), 1765 (OAc), 1658 (CONH). NMR (DMSO-d_6, ppm): 2.26 (3H, s, Ac), 3.48 (2H, s, $-CH_2-$), 3.82 (2H, s, C_2–H), 5.18 (1H, d, $J=5$ Hz, C_6–H), 5.67 (1H, q, $J=5$ Hz and 8 Hz, C_7–H), 7.22 (5H, s, C_6H_5-), 9.06 (1H, d, $J=8$ Hz, NH).

3) Compound **3b** was also prepared in a similar manner.

3-Hydroxymercaptomethyl-7-(2-thienylacetamido)ceph-3-em-4-carboxylic Acid Thiolactone (5a)——A solution of **3a** (4 g) in DMSO (20 ml)–water (1 ml) was stirred for 4 hr at room temperature. The mixture was then poured into ice-water (400 ml) and the precipitate was collected, and washed with water. Recrystallization from AcOEt gave **5a** (3.5 g) as pale yellow crystals, mp 177—179° (about 4:5 mixture of epimers). IR ν_{max}^{KBr} cm^{-1}: 1782 (β-lactam), 1660 (CONH). NMR (DMSO-d_6, ppm): 3.73 (2H, s, C_2–H), 5.01 (1H, d, $J=5$ Hz, C_6–H), 5.75 (1H, q, $J=5$ Hz and 8 Hz, C_7–H), 6.28 and 6.43 (1H, each s, –CHOH), 7.20 and 7.45 (1H, each br. s, –CHOH, exchangeable on addition of D_2O), 9.09 (1H, d, $J=8$ Hz, NH).

3-Hydroxymercaptomethyl-7-phenylacetamidoceph-3-em-4-carboxylic Acid Thiolactone (5b)——The above procedure gave **5b** from **3b** as a roughly 1:1 mixture of epimers. IR ν_{max}^{KBr} cm^{-1}: 1780 (β- lactam), 1670 (CONH). NMR (DMSO-d_6, ppm): 3.51 (2H, s, C_2–H), 3.76 (2H, s, $-CH_2-$), 5.00 (1H, d, $J=5$ Hz, C_6–H), 5.76 (1H, q, $J=5$ Hz and 8 Hz, C_7–H), 6.28 (1H, s, –CHOH), 9.06 (1H, d, $J=8$ Hz, NH).

3-Methoxymercaptomethyl-7-(2-thienylacetamido)ceph-3-em-4-carboxylic Acid Thiolactone (6a)——A suspension of **3a** (75 mg) in methanol (30 ml) was stirred for 5 hr at room temperature. After removal of methanol *in vacuo*, the residue was dissolved in AcOEt. The solution was washed with watar and dried (Na_2SO_4). The solvent was removed and the residue was chromatographed on silica gel. Elution with benzene–acetone (3:1) gave **6a** (35 mg; about 4:5 mixture of epimers). IR ν_{max}^{KBr} cm^{-1}: 1780 (β-lactam), 1683 (CONH). NMR (DMSO-d_6, ppm) of the minor epimer: 3.35 (3H, s, OCH_3), 3.78 (2H, s, $-CH_2-$), 3.81 (2H, s, C_2–H), 5.11 (1H, d, $J=5$ Hz, C_6–H), 5.88 (1H, q, $J=5$ Hz and 9 Hz, C_7–H), 6.41 (1H, s, $-CHOCH_3$), 9.21 (1H, d, $J=9$ Hz, NH). NMR (DMSO-d_6, ppm) of the major epimer: 3.38 (3H, s, OCH_3), 3.78 (2H, s, $-CH_2-$), 3.82 (2H, s, C_2–H), 5.11 (1H, d, $J=5$ Hz, C_6–H), 5.80 (1H, q, $J=5$ Hz and 9 Hz, C_7–H), 6.52 (1H, s, $-CHOCH_3$), 9.15 (1H, d, $J=9$ Hz, NH).

3-Methoxymercaptomethyl-7-phenylacetamidoceph-3-em-4-carboxylic Acid Thiolactone (6b)——A suspension of **3b** (200 mg) in methanol (80 ml) was stirred at 50° for 10 min. After removal of methanol *in vacuo*, the residue was dissolved in CH_2Cl_2. The solution was washed with water and dried (Na_2SO_4). The solvent was removed and the residue was chromatographed on silica gel, eluting with isopropyl ether–THF (3:1). The first fraction gave **6b-A** as colorless prisms (78 mg) of mp 210—213° (dec.). IR ν_{max}^{KBr} cm^{-1}: 1779 (β-lactam) 1700 (C=O), 1658 (CONH). NMR (DMSO-d_6, ppm): 3.40 (3H, s, OCH_3), 3.55 (2H, br. s, C_2–H), 3.82 (2H, s, $-CH_2-$), 5.10 (1H, d, $J=5$ Hz, C_6–H), 5.80 (1H, q, $J=5$ Hz and 9 Hz, C_7–H), 6.52 (1H, s, $-CHOCH_3$), 7.29 (5H, s, C_6H_5-), 9.08 (1H, d, $J=9$ Hz, NH). $[\alpha]_D^{19}$ +112.3° ($c=0.0356$, methanol). The second fraction gave **6b-B** as colorless needles (88 mg) of mp 191—193° (dec.). IR ν_{max}^{KBr} cm^{-1}: 1780 (β-lactam), 1700 (C=O), 1655 (CONH). NMR (DMSO-d_6, ppm): 3.37 (3H, s, OCH_3), 3.54 (2H, br. s, C_2–H), 3.79 (2H, s, $-CH_2-$), 5.10 (1H, d, $J=5$ Hz, C_6–H), 5.84 (1H, q, $J=5$ Hz and 9 Hz, C_7–H), 6.56 (1H, s, $-CHOCH_3$), 7.29 (5H, s, C_6H_5-), 9.14 (1H, d, $J=9$ Hz, NH). $[\alpha]_D^{19}$ +190.8° ($c=0.0833$, methanol).

Acetylation of the Hydroxy Compound (5a)——A solution of **5a** (130 mg) in dry THF (5 ml) was treated with acetic anhydride (1 ml) and triethylamine (43 mg) at 0° with stirring, and the solution was stirred for a further 3 hr at room temperature. The reaction mixture was poured into ice-water and the mixture was extracted with AcOEt. The extract was washed with water, dried (Na_2SO_4) and evaporated down to afford a resinous material which was chromatographed on silica gel. Elution with benzene–acetone (8:1) gave the monoacetate **7a** (60 mg, in about 4:5 mixture of epimers). IR ν_{max}^{KBr} cm^{-1}: 1788 (β-lactam), 1748 (OAc), 1680 (CONH). NMR (DMSO-d_6, ppm) of the minor epimer: 2.14 (3H, s, Ac), 3.77 (2H, s, $-CH_2-$), 3.86 (2H, s, C_2–H), 5.13 (1H, d, $J=5$ Hz, C_6–H), 5.81 (1H, $J=5$ Hz and 9 Hz, C_7–H), 7.00 (1H, s, –CHOAc), 9.16 (1H, d, $J=9$ Hz, NH). NMR (DMSO-d_6, ppm) of the major epimer: 2.16 (3H, s, Ac), 3.77 (2H, s, $-CH_2-$), 3.82 (2H, s, C_2–H), 5.11 (1H, $J=5$ Hz, C_6–H), 5.83 (1H, q, $J=5$ Hz and 9 Hz, C_7–H), 6.83 (1H, s, –CHOAc), 9.17 (1H, d, $J=9$ Hz, NH). The monoacetate **7a** was also prepared by the reaction of the bromide **3a** with silver acetate in acetic acid. Compound **5a** (130 mg) was treated with triethylamine (86 mg) and acetic anhydride (2 ml) to give **7a** (13 mg) and the diacetate **8a** (95 mg). IR ν_{max}^{KBr} cm^{-1}: 1775 (β-lactam), 1660 (CONH). NMR (DMSO-d_6, ppm): 2.26 and 2.32 (each 3H, each s, Ac), 3.77 and 4.03 (2H, ABq, $J=16$ Hz,

C_2–H), 5.27 (1H, d, J=5 Hz, C_6–H), 5.72 (1H, q J=5 Hz and 8 Hz, C_7–H), 9.16 (1H, d, J=8 Hz, NH).

Oxidation of the Hydroxy Compound (5)——Active manganese dioxide (472 mg) was added to a solution of **5a** (400 mg) in 1,2-dichloroethane (450 ml) with stirring. After stirring for 40 min, the excess manganese dioxide was removed by filtration. The filtrate was washed with dil. HCl and then water, and dried (Na_2SO_4). The solvent was removed *in vacuo*, and the residue was chromatographed on silica gel. Elution of the column with benzene–acetone (3: 1—5: 1) gave **9a** (139 mg, 35%) as colorless flakes, mp 138—140°. IR ν_{max}^{KBr} cm^{-1}: 1800 (β-lactam), 1700 (shoulder), 1685, 1660 (C=O, CONH). NMR (DMSO-d_6, ppm): 3.72 and 3.99 (2H, ABq, J=18 Hz, C_2–H), 5.20 (1H, d, J=5 Hz, C_6–H), 5.95 (1H, q, J=5 Hz and 8 Hz, C_7–H), 9.21 (1H, d, J=8 Hz, NH). MS m/e: 366 (M^+).

A similar procedure gave **9b** from **5b** as colorless needles (63%), mp 135—137° (dec.). IR ν_{max}^{KBr} cm^{-1}: 1802 (β-lactam), 1692 (C=O), 1665 (CONH). NMR (DMSO-d_6, ppm): 3.69 and 3.95 (2H. ABq, J=18 Hz, C_2–H), 5.17 (1H, d, J=5 Hz, C_6–H), 5.91 (1H, q, J=5 Hz and 8 Hz, C_7–H), 9.14 (1H, d, J=8 Hz, NH).

Ring Opening of the Dioxo Compound (9)——A solution of the dioxo compound **9a** (100 mg) in 50% methanol (50 ml) was treated with sodium tetraborate (350 mg) in water (5 ml) at 0°, and the mixture was stirred for 2 hr at room temperature. After removal of insoluble material by filtration, the methanol was evaporated off *in vacuo* and the aq. solution was charged onto a column of Amberlite XAD-2. The column was eluted with water and then 5% methanol. The fraction containing the desired product was lyophilized to give disodium 7-(2-thienylacetamido)ceph-3-em-3,4-dicarboxylate (**10a**, 31.5 mg, 28%). IR ν_{max}^{KBr} cm^{-1}: 1775 (β-lactam), 1660 (CONH), 1605 (carboxylate). NMR (D_2O, ppm): 3.81 (2H, s, $-CH_2-$), 3.72 and 4.17 (2H, ABq, J=20 Hz, C_2–H), 5.25 (1H, d, J=5 Hz, C_6–H), 5.74 (1H, d, J=5 Hz, C_7–H). UV $\lambda_{max}^{H_2O}$ nm (ε): 237 (7260), 277 (4840).

A similar procedure gave disodium 7-phenylacetamidoceph-3-em-3,4-dicarboxylate (**10b**, 35%) from **9b**. IR ν_{max}^{KBr} cm^{-1}: 1775 (β-lactam), 1660 (CONH), 1608 (carboxylate). NMR (D_2O, ppm): 3.77 (3H, s, $-CH_2-$), 5.19 (1H, d, J=5 Hz, C_6–H), 5.70 (1H, d, J=5 Hz, C_7-H). UV $\lambda_{max}^{95\%EtOH}$ nm (ε): 236 (4900), 278 (6540).

A suspension of **9a** (40 mg) in methanol (10 ml) was stirred for 8 hr at room temperature. After removal of methanol, the residue was chromatographed on silica gel. Elution with benzene–acetone (4: 1) gave **11a** (31 mg) as a pale yellow oil. IR ν_{max}^{Neat} cm^{-1}: 1735 (CO_2CH_3), 1690 (shoulder), 1675, 1630. MS m/e (relative intensity): 398 (M^+, 6%), 257 (25%), 213 (51%), 186 (69%), 141 (17%) and 97 (base peak, 100%). NMR ($CDCl_3$, ppm): 3.51 (2H, s, $-CH_2-$),3.81 (2H, s, C_2–H), 4.87 (1H, dd, J=4 Hz and 4 Hz, C_6–H), 5.00 (1H, dd, J=4 Hz and 8 Hz, C_7–H), 6.73 (1H, d, J=8 Hz, NH), 7.08 (1H, d, J=4 Hz, NH).

Formylation of the Cephlosporin Thiolactone Enol Acetate (2a)——A solution of **2a** (400 mg) in CH_2Cl_2 (50 ml) was treated with dichloromethyl methyl ether (720 mg) followed by $TiCl_4$ (1.5 ml) at 0° with stirring, and the mixture was then stirred for 1 hr at room temperature. After treatment of the mixture with 10% HCl, the organic layer was separated, washed with dil. $NaHCO_3$ aq. solution and dried (Na_2SO_4). After removal of the solvent, the residue was chromatographed on silica gel. Elution with benzene–acetone (4: 1) gave **12** (65 mg) and **13** (110 mg). Compound **12**: colorless needles of mp 246—256°. IR ν_{max}^{KBr} cm^{-1}: 1792 (β-lactam), 1775 (OAc), 1670 (CONH). NMR (DMSO-d_6, ppm): 2.26 (3H, s, Ac), 3.88 (2H, s, $-CH_2-$), 3.98 (2H, s, C_2–H), 5.27 (1H, d, J=5 Hz, C_6–H), 5.70 (1H, q J=5 Hz and 8 Hz, C_7–H), 7.06 (1H, s, =C<u>H</u>–S–), 7.12 (1H, d, J=4 Hz), 7.83 (1H, d, J=4 Hz), 9.28 (1H, d, J=8 Hz, NH), 9.83 (1H, s, –C<u>H</u>O). Compound **13**: pale yellow amorphous material. IR ν_{max}^{KBr} cm^{-1}: 1785 (β-lactam), 1667 (CONH). NMR (DMSO-d_6, ppm): 3.84 (2H, s, $-CH_2-$), 3.90 (5H, s, C_2–H and OCH_3), 5.06 (1H, d, J=5.5 Hz, C_6–H), 5.78 (1H, q, J= 5.5 Hz and 8 Hz, C_7–H), 7.14 (1H, d, J=7 Hz), 7.33 (1H, s, $C_{3'}$=C<u>H</u>–), 7.83 (1H, d, J=4 Hz), 9.28 (1H, d, J=8 Hz, NH), 9.84 (1H, s, –C<u>H</u>O).

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