Tetrahedron Vol. 36, pp 2735–2740
© Pergamon Press Ltd., 1980. Printed in Great Britain

0040-4020/80/1001-2735/$02.00/0

CLEAVAGE AND SOME MODIFICATIONS OF THE 7-AMIDE GROUP OF THE CEPHAMYCINS

MASAO SHIOZAKI,* NOBORU ISHIDA, KIMIO IINO and TETSUO HIRAOKA
Central Research Laboratories, Sankyo Co. Ltd., Hiromachi 1-2-58, Shinagawa-ku, Tokyo, 140, Japan

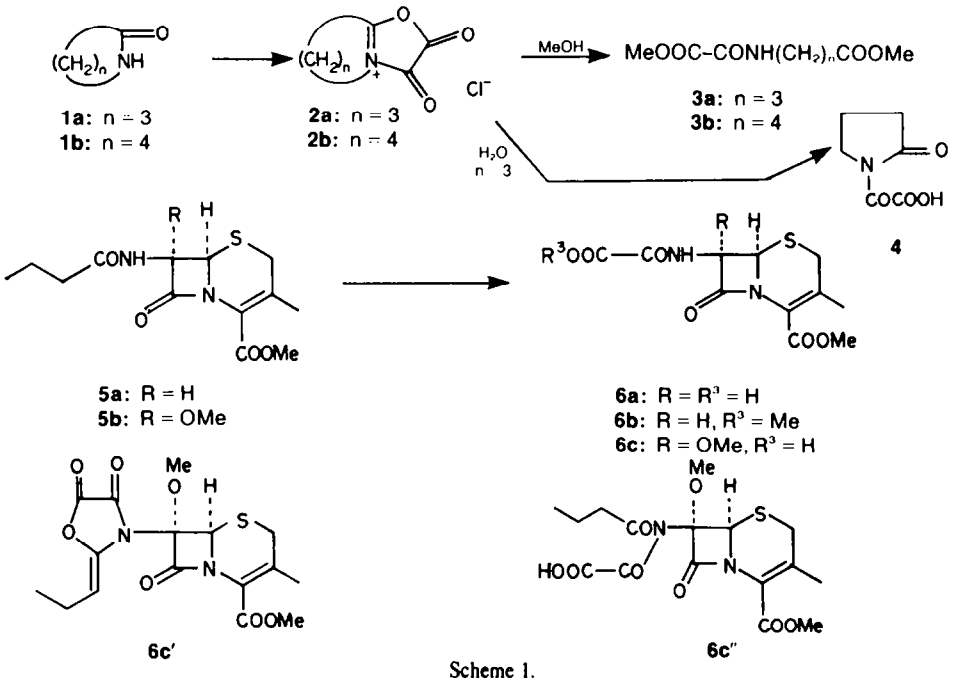
(*Received in Japan* 10 *January* 1980)

Abstract—The cleavage and some modifications of the 7-amide group of cephamycins are described. Cephamycin derivatives **16b, c** which were synthesized from the naturally occurring cephamycin C (**16a**) were converted to the corresponding oxamic acid derivatives **17a, e** respectively by the reaction with oxalyl chloride and successive treatment with water. The reaction of the oxamic acid **17a** with diphenylcarbodiimide gave 7-aminocephamycinoic acid (7-ACMA) benzhydryl ester (**21a**) which was further converted to cefoxitin (**21c**). These compounds **17a, b, c, d, e, f** thus obtained from cephamycin C appear to be favorable intermediates for the syntheses of cephamycin analogues such as cefmetazole (**28c**).

Naturally occurring cephalosporin C and cepamycin C (**16a**)[1] possessing an aminoadipoyl side chain at the C-7 position have been used as starting materials for many modified analogues exhibiting broad antibiotic activity. There is an excellent method which utilizes phosphorus pentachloride[2] for cleaving this aminoadipoyl side chain of cephalosporin C to give 7-aminocephalosporanic acid (7-ACA). However application of this method to the conversion of naturally occurring cephamycin C into the (7S) - 7 - amino - 7 - methoxy derivative (7-ACMA ester) is difficult for two reasons: first, the (7S) - 7 - amino - 7 - methoxy compound produced by the methanolysis of the intermediate imidoyl chloride undergoes epimerization via the imine,[3] and second, a strong phosphorus–nitrogen bond is formed by the reaction of phosphorus pentachloride with the 3-carbamoyloxy group of cephamycin C.[4] On the other hand, two good procedures for transforming the aminoadipoyl chain of cephamycin C into the thiopheneacetamide group via the N-diacyl compound were reported by Merck groups.[5] In this paper, we wish to report a new method for cleavage and modification of the 7-amide group of cephamycins (7-methoxycephalosporins).[6]

This procedure for cleavage of the aminoadipoyl side chain involves formation of oxamic acid with oxalyl chloride followed by treatment with diphenylcarbodiimide to give the free amine.

It is known that the reaction of N-monosubstituted amides (**7**, R^1=H, Cl, C_6H_5, etc.)[7] with oxalyl chloride produces 2 - methyleneoxazolidine - 4,5 - dione derivatives (**15**) via the intermediate **8** as shown in Scheme 2 (path B). Without activation of the methylene hydrogens adjacent to R^1 by electron withdrawal or the conjugative effect of R^1 leading to **15**, the iminium salt **8** might persist in the mixture and should react with two moles of water (alcohols) to cleave a carboxylic acid (esters) and an oxamic acid (esters). We first chose α-pyrrolidone (**1a**), α-piperiodne (**1b**), methyl (6R, 7R) - 7 - *n* - butylamido - 3 - methyl - 3 - cephem - 4 - carboxylate (**5a**) and its analogue **5b** as model compounds to check this hypothesis (Scheme 1). The reaction of **1a, b** with oxalyl chloride gave unstable iminium salts **2a, b** respectively,

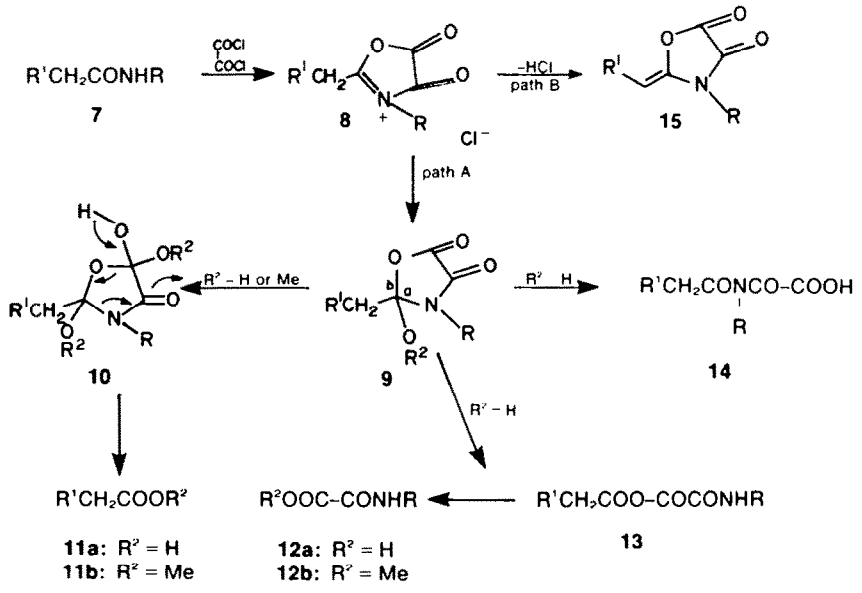


Scheme 1.

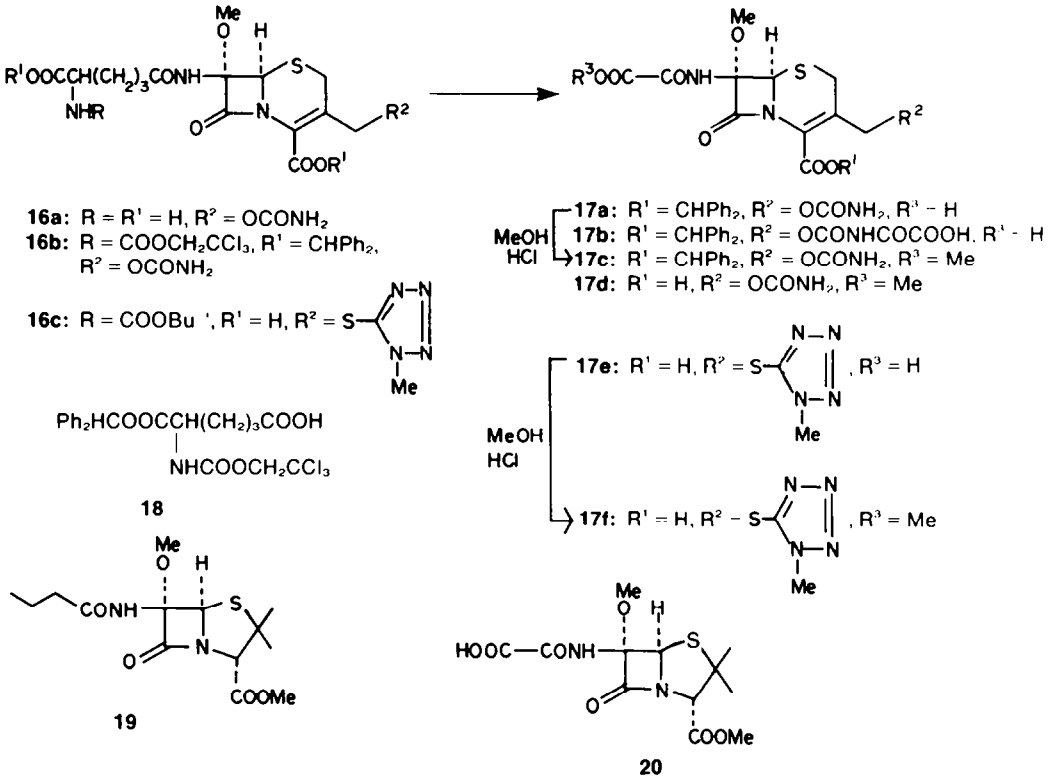
as white crystals which gradually changed to methyleneoxazolidine - 4,5 - dione derivatives by loss of hydrogen chloride at room temperature. Treatment of the salts **2a, b** with methanol yielded methyl oxamates **3a, b** respectively. On the other hand, quenching of **2a** with water–acetone (1:1) afforded α-pyrrolidone N-oxamic acid (**4**) as the major product. However, successive treatment of **5a** with oxalyl chloride and water–acetone produced the expected oxamic acid (**6a**), m.p. 187°, in good yield, and also methanol quenching gave **6b**. Under the former conditions, **5b** yielded **6c** as the major product, and **6c'** and **6c''** as minor products. By addition of sodium carbonate as a hydrogen chloride scavenger, the formation of the minor products was prevented. A probable mechanism is shown in Scheme 2. The final products (**11a, b** and **12a, b**) should be obtained from **8** via the intermediate **9** (path A). Three paths are possible for the quenching reaction of **9** with water: (i) the carbonyl group of the intermediate **9** may be attacked by water to give **10** affording **11a** and **12a** (bond **a** fission, giving **6a, c**), (ii) the oxazolone ring opening of **9** may give the acid anhydride **13** (bond **a** fission) which should hydrolyze to **11a** and **12a**, or (iii) the ring cleavage of **9** may occur at a different position furnishing the N-diacyl compound **14** (bond **b** fission, affording **4** and **6c''**). When the iminium salt **8** is unstable, it is easily converted to **15** (path B, **6c'**). Path A is dominant when the carbon adjacent to the methylene carbon of **7** has an sp^3 orbital, and bond **a** and **b** fissions compete with each other, but bond **a** fission may be more prefered than bond **b** fission in the presence of a hydrogen chloride scavenger such as sodium carbonate.

We applied these results to cleave the aminoadipoyl side chain of cephamycin C derivatives. (Scheme 3). The protected cephamycin C (**16b**) obtained by N-trichloroethoxycarbonylation and benzhydryl esterification of cephamycin C (**16a**) was treated with 6 equivalents each of oxalyl chloride and anhydrous sodium carbonate[8] as a hydrogen chloride scavenger, and then the reaction mixture was quenched with water. Separation by column chromatography on silica gel gave three products; oxamic acid (**17a**, 37% yield), dioxamic acid (**17b**, 34%), and α-aminoadipic acid derivative (**18**, 85%). Acid catalyzed hydrolysis of **17b** afforded **17a**. By the same treatment, the acid **16c**[9] was converted to oxamic acid **17e** in good yield. If the 7 - amino - 7 - methoxycephem compound is produced through a series of these reactions, C-7 position would be apt to epimerize, but such an intermediate is never produced during these reactions as known from the mechanism of this reaction. In fact, neither epimerization at the chiral centers nor double bond isomerization occurred under the conditions employed. This procedure was applicable to members of the penicillin series, and methyl (5R, 6S) - 6 - n - butylamido - 6 - methoxypenicillanate (**19**)[10] yielded the corresponding 6-oxamic acid (**20**). Formation of **17c** and **17f** by the route of methanolysis (**8**→**9**→**10**→**11b**) of type **9** compounds obtained from **16b, c** with oxalyl chloride is troublesome, because of contamination by the C-4 methyl ester of **17f** (this shows the presence of C-4 acid anhydride or acid chloride with oxalyl chloride), and of the formation of a fair amount of the methyl ester of **17b** at the C-3 side chain.

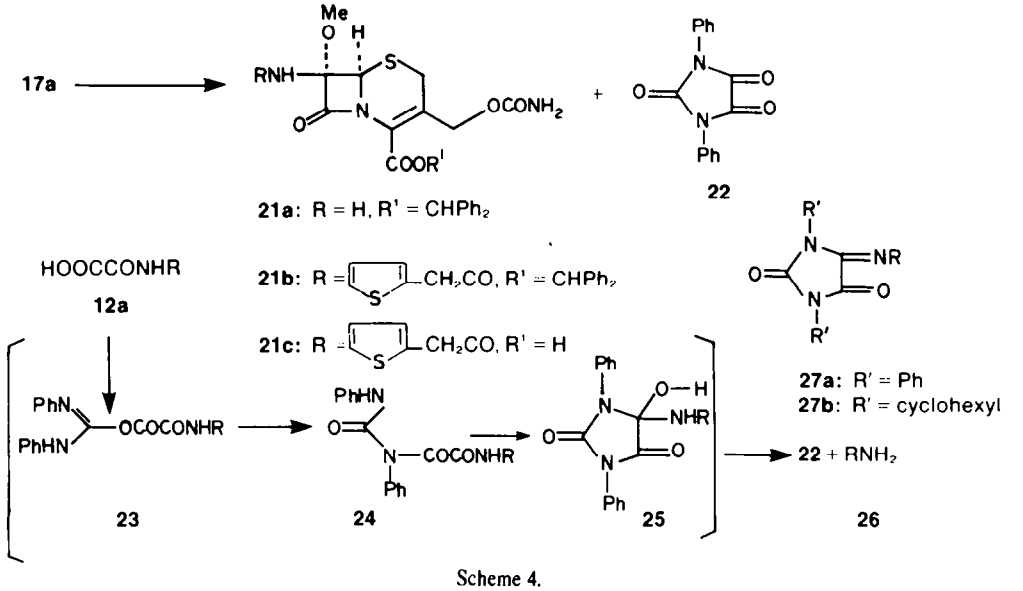
Usual oxamic acids undergo both acid and base catalyzed hydrolysis to give free amines. Actually the oxamic acid **6a** was hydrolyzed to the methyl ester of 7-aminodeacetoxycephalosporanic acid (7-ADCA) by reaction with dilute hydrochloric acid or saturated sodium bicarbonate solution at room temperature. However, it is difficult to change 7-oxamic acids of cephamycin to 7 - amino - 7 - methoxycephalosporins without side reactions such as epimerization at the chiral C-7 center, ketonization at the C-7 position, double bond isomerization, and ring cleavage of azetidinone under basic or acidic conditions. In order to avoid these undesirable side reactions, it is necessary to use milder conditions. We expected that carbodiimides would be useful for this purpose. However, the reaction of **6a** with dicyclohexylcarbodiimide was not fruitful.[6a] On the other hand, the treatment of **6a** with diphenylcarbodiimide produced 7-ADCA methyl ester and diphenylimidazolidinetrione (**22**).[6a] (Scheme 4). The 7-ACMA benzhydryl ester (**21a**) which is unstable in both acidic and basic conditions was obtained from the oxamic acid



Scheme 2.



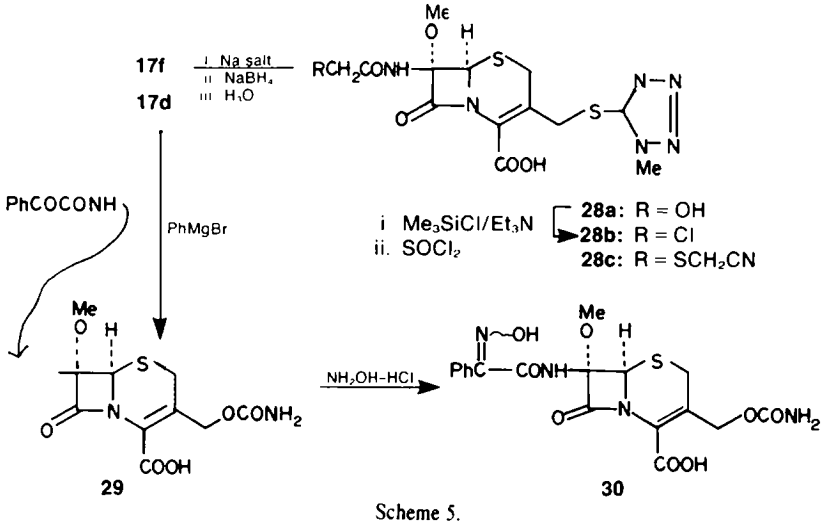
Scheme 3.



Scheme 4.

(17a) in 56% yield by the same procedure without epimerization at the C-7 position, because diphenylcarbodiimide and its adducts with oxamic acid (17a) are not acidic enough to form the 7-imino compound from 21a. One of the possible mechanisms is shown in Scheme 4. The oxamic acid 12a attacks the C=N double bond of diphenylcarbodiimide to give the adduct 23 which rearranges to 24. The N-acylurea (24) cyclizes to the hydroxyimidazolidinedione (25) which is further cleaved into two parts, the imidazolidinetrione (22) and the amine (26), instead of being converted to the dehydration product (27a). By use of dicyclohexylcarbodiimide, the dehydration becomes a main reaction to form the imine (27b).[6a] This series of reactions may proceed irreversibly to the formation of a primary amine and diphenylimidazolidine-2,4,5-trione.

Modification of compounds 17a, b, c, d, e, f which are very important intermediates for the preparation of many analogues of cephamycins was investigated. (Scheme 5). Reaction of the oxamic acid (17a) with diphenylcarbodiimide followed by treatment with diethylaniline/thienylacetylchloride gave cefoxitin benzhydryl ester (21b) which was converted to cefoxitin (21c) on treatment with trifluoroacetic acid in anisole. The diacid (17e) was regio-



Scheme 5.

specifically esterified to the corresponding mono-methyl ester (**17f**) on treatment with methanol in the presence of catalytic amounts of hydrochloric acid at room temperature for 18 hr, and analogously **17a** was also transformed to **17c**. The carbomethoxy group of oxamates such as **17c, d, f** activated by the neighbouring ketone group can react easily with various types of reagents. The oxamate **17f** was reduced to the alcohol (**28a**) with sodium borohydride after neutralization of the carboxylic part with sodium bicarbonate, and also **17d** was converted to the corresponding 7-hydroxyacetamide. The alcohol **28a** was transformed to the chloroacetamide **28b** by successive treatments with trimethylsilyl chloride and thionyl chloride, which could be further converted to cefmetazole (**28c**) by reaction with sodium cyanomethylmercaptide.[11] Grignard reaction of **17d**, obtained from the benzhydryl ester (**17c**), using phenyl magnesium bromide yielded the α-oxoamide (**29**). Also, **17d** reacted with ethyl or thiophene-2-magnesium bromide to give the corresponding α-oxoamides. Similarly the reaction of the acid **17f** or the ester of **17f** with Grignard reagents gave the corresponding α-oxoamides. The α-oxoamide (**29**) was converted to the oxime (**30**) as a single product without detection of the other isomer.

Thus the oxamic acids **17a, e** and the oxamic acid esters **17c, d, f** obtained from cephamycin C by a new method using oxalyl chloride, appear to be favorable intermediates for the syntheses of cephamycin analogues.

EXPERIMENTAL

All m.ps are uncorrected and were taken on a Yanagimoto m.p. apparatus. IR spectra were obtained on a Jasco IR A-2 spectrophotometer, ^{1}H NMR spectra on a Hitachi R-24, Varian A-60 or HA-100 using tetramethylsilane ($\delta = 0$) as an internal standard, and UV spectra on a Perkin–Elmer 137 spectrophotometer. MS spectra were determined on a JMS-01SG mass spectrometer.

Methyl 4-carbomethoxycarbonylamino - n - butylate (**3a**). To a stirred soln of α-pyrrolidone (8.51 g, 0.10 mol) in benzene, oxalyl chloride (10 ml, 0.126 mol) was added at room temp to precipitate a white salt (**2a**). After 1 hr, **2a** was collected by filtration in a dry box, and stirred with MeOH (20 ml) for 30 min at 20°. To this soln, EtOAc (200 ml) was added, and the organic layer washed with sat $NaHCO_3$ and sat NaCl, and dried over $MgSO_4$. Evaporation of EtOAc, and column chromatography of the residual oil on silica gel gave **3a** (8.52 g, 42% yield): IR ν_{max} (film) 3360, 2955, 1760 (shoulder), 1735, 1692 cm^{-1}; NMR ($CDCl_3$) δ 1.50–2.10 (2H, m), 2.10–2.50 (2H, m), 3.05–3.50 (2H, m), 3.53 (3H, s), 3.72 (3H, s), 7.90 (1H, s broad, NH); UV λ_{max} (EtOH) 223.5 nm ($\epsilon = 4280$); MS *m/e* 203 (M^+).

N - Carboxycarbonyl - α - pyrrolidone (**4**). The salt **2b** was quenched with H_2O–Me_2CO (1:1, 20 ml), and the mixture was extracted with EtOAc. The extract was washed with H_2O and dried over $MgSO_4$. Evaporation of the EtOAc gave crude crystals (6.66 g) which were recrystallized from Et_2O–pet. ether, m.p. 129–131°; IR ν_{max} (nujol) 3200–2400, 1752, 1710, 1693 cm^{-1}; NMR (DMF-d_7) δ 1.80–2.80 (4H, m), 3.72 (2H, t, J = 7 Hz), 13.23 (1H, s, COOH); UV ν_{max} (EtOH) 218.5 nm ($E^{1\%}_{1cm}$ = 606.1); MS *m/e* 157 (M^+). (Found: C, 46.03; H, 4.09; N, 9.05. $C_6H_7O_4N$ requires: C, 45.86; H, 4.49; N, 8.92%).

Methyl 5 - carbomethoxycarbonylamino - n - pentanoate (**3b**). The same treatment of **1b** as described above gave **3b** via the intermediate **2b**: IR ν_{max} (film) 3310, 2950, 1760 (shoulder), 1740, 1700 cm^{-1}; NMR ($CDCl_3$) δ 1.40–1.80 (2H, m), 2.05–2.50 (2H, m), 3.00–3.60 (2H, m), 3.59 (3H, s), 7.95 (1H, t, J = 6 Hz); UV ν_{max} (EtOH) 223 nm ($\epsilon = 4300$); MS *m/e* 217 (M^+).

Methyl (6R, 7R) *- 7 - carboxycarbonylamino - 3 - methyl - 3 - cephem - 4 - carboxylate* (**6a**). To a suspension of **5a** (5.30 g, 20 mmol) in benzene (100 ml), oxalyl chloride (3 ml) was added with stirring at 20°. After 1.5 hr, the mixture was cooled on an ice water bath, quenched with H_2O–Me_2CO (1:1, 20 ml), and stirred for 4 hr at room temp. The mixture was diluted with EtOAc, and extracted with sat $NaHCO_3$ to separate neutral material consisting mainly of **5a** (1.04 g). The aqueous layer was acidified with 10% HCl and extracted with EtOAc. The extract was then washed with sat NaCl and dried over $MgSO_4$. Evaporation of EtOAc gave **6a** (4.49 g); m.p. 186–187° (from EtOAc); IR ν_{max} (nujol) 3270, 1775, 1728, 1688, 1679, 1640 cm^{-1}; NMR (DMF-d_7) δ 1.98 (3H, s, C_3–CH_3), 3.42 (2H, s, SCH_2), 3.64 (3H, s, $COOCH_3$), 5.06 (1 H, d, J = 5 Hz, C_6–H), 5.59 (1 H, d,d, J = 5, 10 Hz, C_7–H), 9.18 (1H, d, J = 10 Hz, NH), 10.68 (1H, s broad, COOH); MS *m/e* 300 (M^+). (Found: C, 43.87; H, 4.03; N, 9.14; S, 10.73. $C_{11}H_{12}O_6N_2S$ requires: C, 44.00; H, 4.03; N, 9.33; S, 10.66%)

Methyl (6R, 7R) *- 7 - carbomethoxycarbonylamino - 3 - methyl - 3 - cephem - 4 - carboxylate* (**6b**). Compound **5a** was reacted with oxalyl chloride and the mixture quenched with MeOH at 20° for 20 hr. The mixture was diluted with EtOAc, washed with sat $NaHCO_3$ and sat NaCl, and dried over $MgSO_4$. Evaporation of EtOAc gave an oil which was purified by silica gel column chromatography to give **6b** (80%) as crystalline solid. An analytical sample was prepared by recrystallization from EtOAc-n-hexane: m.p. 130–131.5°; IR ν_{max} ($CHCl_3$) 3400 (w), 1783, 1718, 1640 (w) cm^{-1}; NMR ($CDCl_3$) δ 2.13 (3H, s, C_3–CH_3), 3.37 (2H, s broad, SCH_2), 3.79 (3H, s, $COOCH_3$), 3.87 (3H, s, $COOCH_3$), 5.02 (1 H, d, J = 5 Hz, C_6–H), 5.68 (1 H, d,d J = 5, 9 Hz, C_7–H), 8.15 (1H, d, J = 9 Hz, NH); MS *m/e* 314 (M^+). (Found: C, 45.85; H, 4.46; N, 8.78; S, 10.28. $C_{12}H_{14}O_6N_2S$ requires: C, 45.86; H, 4.49; N, 8.92; S, 10.18%)

Methyl (6R, 7S) *- 7 - carboxycarbonylamino - 7 - methoxy - 3 -*

methyl - 3 - *cephem* - 4 - *carboxylate* (**6c**). (a) To a soln of **5b** (3.28 g, 10 mmol) in dioxane (50 ml), Na_2CO_3 (1.60 g, 15 mmol) and oxalyl chloride (1.28 ml, 15 mmol) were added with stirring at 5°. After 12 hr of stirring at 20°, water (10 ml) was added gradually. The mixture was allowed to stand for 1 hr, acidified to pH 2.0 with 10% HCl, and extracted with EtOAc. The extract was washed with water and sat NaCl, dried over $MgSO_4$, and evaporated to give an oily mixture, which was separated by column chromatography on silica gel (65 g, 15% water impregnated; eluted with C_6H_6/EtOAc = 9/1) to produce 2.21 g (67%) of **6c** as a crystalline solid; m.p. 209° (dec); IR ν_{max} (KBr) 3400 (broad), 1775, 1720, 1630 cm^{-1}; NMR (DMF-d_7) δ 2.16 (3H, s, C_3–CH_3), 3.46 (2 H, s, SCH_2), 3.59 (3 H, s, C_7–OCH_3), 3.85 (3 H, s, $COOCH_3$), 5.18 (1H, s, C_6–H), 7.16 (1H, s, NH), 9.47 (1H, s, COOH); MS *m/e* 330 (M^+). (b) The same treatment of **5b** with oxalyl chloride in benzene at 20° for 2 hr without Na_2CO_3, gave **6c** (61%), **6c'** (28%); m.p. 157–158°; IR ν_{max} (KBr) 1820, 1785, 1752, 1718, 1700 cm^{-1}; NMR ($CDCl_3$) δ 1.07 (3H, t, J = 7.5 Hz), 2.29 (2H, d,t, J = 7.5, 7.5 Hz), 2.32 (3H, s, C_3–CH_3), 2.95 (1H, d, J = 16 Hz, C_2–H), 3.36 (1H, d, J = 16 Hz, C_2–H), 3.78 (3H, s, C_7–OCH_3), 3.89 (3 H, s, $COOCH_3$), 5.08 (1 H, s, C_6–H), 5.20 (1 H, t, J = 7.5 Hz); Ms *m/e* 382 (M^+); (Found: C, 50.23; H, 4.43; N, 7.25; S, 8.48. $C_{16}H_{18}O_7N_2S$ requires: C, 50.26; H, 4.75; N, 7.33; S, 8.37%), and **6c''** (3%); powder; IR ν_{max} (KBr) 3425 (broad), 1785, 1768, 1720, 1700 (shoulder), 1665 (w), 1625 (w) cm^{-1}; NMR ($CDCl_3$) δ 1.14 (3H, t, J = 7.5 Hz), 0.9–1.4 (2H, m), 2.21 (3H, s, C_3–CH_3), 2.27 (2H, t, J = 8 Hz), 3.14 (2H, s, SCH_2), 3.61 (3H, s, C_7–OCH_3), 3.88 (3 H, s, $COOCH_3$), 5.09 (1 H, s, C_6–H), 6.63 (1 H, s, COOH).

Diphenylmethyl (6R, 7S) - 7 - *carboxycarbonylamino* - 7 - *methoxy* - 3 - *carbamoyloxymethyl* - 3 - *cephem* - 4 - *carboxylate* (**17a**). Using the same method as for the formation of **6c**, **16b** (954 mg, 1.0 mmol) was reacted with 6.0 mmol each of oxalyl chloride and anhyd Na_2CO_3 in dry dioxane (5 ml), and quenched with H_2O. Column chromatography over 15% H_2O impregnated silica gel (20 g) with C_6H_6/EtOAc = 7/3 elution gave 430 mg of **18** as a crystalline solid which was partly recrystallized from C_6H_6–Et_2O for an analytical sample; m.p. 113–115°; IR ν_{max} (nujol) 3360, 3200–2500 (w), 1742, 1720, 1708 cm^{-1}; NMR ($CDCl_3$) δ 1.50–2.05 (4H, m), 2.05–2.45 (2H, m), 4.55 (1H, m broad), 4.67 (2H, s), 5.80 (1H, d, J = 8.5 Hz, NH), 6.89 (1H, s), 7.27 (10H, s), 9.30 (1H, s broad, COOH); MS *m/e* 501 (M^+, ^{35}Cl). Further elution gave 199 mg (37%) of **17a** as foam; IR ν_{max} (nujol) 3500, 3360, 3200–2400, 1780, 1720 cm^{-1}; NMR (DMF-d_7) δ 3.56 (2H, s, SCH_2), 4.89, 4.99 (2H, AB-q, J = 15 Hz, C_3–CH_2), 5.27 (1H, s, C_6–H), 6.62 (2H, s broad, $OCONH_2$), 6.98 (1H, s, $CHPh_2$), 7.2–7.8 (10 H, m, $C_6H_5 \times 2$), 9.68 (1 H, s, C_7–NHCO), and 205 mg (34%) of **17b** as foam; IR ν_{max} (nujol) 3500, 3300, 1780, 1720 cm^{-1}; NMR (DMF-d_7) δ 3.57 (5H, s, C_7–OCH_3 and SCH_2), 5.01, 5.14 (2H, AB-q, J = 15 Hz, C_3–CH_2), 5.22 (1H, s, C_6–H), 6.94 (1H, s, $CHPh_2$), 7.1–7.7 (10H, m, $C_6H_5 \times 2$), 9.55 (1H, s, C_7–NHCO), 10.25 (2H, s broad, COOH × 2), 11.30 (1H, s, OCONHCOCOOH).

Diphenylmethyl (6R, 7S) - 7 - *carboxycarbonylamino* - 7 - *methoxy* - 3 - *carbamoyloxymethyl* - 3 - *cephem* - 4 - *carboxylate* (**17a**) from **17b**. A soln of **17b** (307 mg) in acetone (5 ml)–H_2O (2.5 ml)–conc HCl (0.5 ml) was allowed to stand for 3 days at room temp. The soln was diluted with H_2O, and extracted with EtOAc. The extract was washed with sat NaCl, dried over $MgSO_4$ and evaporated to give 236 mg (87%) of **17a**.

Diphenylmethyl (6R, 7S) - 7 - *carbomethoxycarbonylamino* - 7 - *methoxy* - 3 - *carbamoyloxymethyl* - 3 - *cephem* - 4 - *carboxylate* (**17c**). (a) A soln of **17b** (307 mg) in MeOH (10 ml) and conc HCl (0.2 ml) was allowed to stand for 18 hr at room temp. The soln was neutralized with sat $NaHCO_3$ and extracted with EtOAc. The extract was washed with H_2O, dried over $MgSO_4$ and evaporated to give 233 mg (84%) of 17c: foam; IR ν_{max} (nujol) 3500 (w), 3375 (w), 1780, 1720 cm^{-1}; NMR ($CDCl_3$) δ 3.31 (2H, s, SCH_2), 3.55 (3H, s, C_7–OCH_3), 3.88 (3H, s, $COOCH_3$), 4.74 (2H, s broad, $OCONH_2$), 4.74, 5.15 (2H, AB-q, J = 15 Hz, C_3–CH_2O), 5.05 (1H, s, C_6–H), 6.88 (1H, s, $CHPh_2$), 7.29 (10H, m, $C_6H_5 \times 2$), 7.98 (1H, s, broad, C_7–NHCO). (b) The same procedure of **17a** gave **17c** (85%) as described above (a).

(6R, 7S) - 7 - *Carboxycarbonylamino* - 7 - *methoxy* - 3 - (1' - *methyl* - 1'*H* - *tetrazol* - 5' - *yl*)*thiomethyl* - 3 - *cephem* - 4 - *carboxylic acid* (**17e**). The same treatment of **16c** as described in the formation of **17a** from **16b** gave **17e** (72%): powder; IR ν_{max} (nujol) 3500–2500, 1775, 1710, 1630 (w) cm^{-1}; NMR (CD_3COCD_3) δ 3.60 (3H, s, C_7–OCH_3), 3.71 (2H, s broad, SCH_2), 4.02 (3H, s, N–CH_3), 4.37, 4.63 (2H, AB-q, J = 14 Hz, C_3–CH_2S-tetrazol), 5.17 (1H, s, C_6–H), 8.03 (2H, s broad, COOH × 2), 8.94 (1H, s broad, C_7–NHCO).

(6R, 7S) - 7 - *Carbomethoxycarbonylamino* - 7 - *methoxy* - 3 - (1' - *methyl* - 1'*H* - *tetrazol* - 5' - *yl*)*thiomethyl* - 3 - *cephem* - 4 - *carboxylic acid* (**17f**). A soln of **17e** (38 mg) in MeOH (2 ml) and 2 drops of conc HCl was allowed to stand for 18 hr at room temp, and diluted with EtOAc. The organic layer was washed with H_2O and sat NaCl, dried over $MgSO_4$ and evaporated to give 35 mg of **17f**; IR ν_{max} (nujol) 2400–3600, 1778, 1745, 1718, 1630 cm^{-1}; NMR (CD_3COCD_3) δ 3.54 (3H, s, C_7–OCH_3), 3.69 (2H, s broad, C_2–H), 3.86 (3H, s, $COOCH_3$), 4.00 (3H, s, N–CH_3), 4.32, 4.60 (2H, AB-q, J = 14 Hz, C_3–CH_2S-tetrazol), 5.12 (1H, s, C_6–H), 6.95 (1H, s broad, COOH or NH), 8.86 (1H, s broad, COOH or NH). (Found: C, 37.39; H, 3.94; N, 18.65; S, 14.08. $C_{14}H_{16}O_7N_6S_2$ requires: C, 37.84; H, 3.63; N, 18.91; S, 14.43%).

Methyl (3S, 5R, 6S) - 6 - *carboxycarbonylamino* - 6 - *methoxypenicillanate* (**20**). The same treatment of **19**, as described in the formation of **6c** from **5b**, gave **20** (18%) as a powder; IR ν_{max} ($CHCl_3$) 3400, 1780, 1750, 1720, 1610, 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.44 (3H, s, C_2–CH_3), 1.50 (3H, s, C_2–CH_3), 3.56 (3H, s, C_6–OCH_3), 3.80 (3H, s, $COOCH_3$), 4.52 (1H, s, C_3–H), 5.64 (1H, s, C_5–H), 8.60 (1H, s, NH).

Diphenylmethyl (6R, 7S) - 7 - *amino* - 7 - *methoxy* - 3 - *carbamoyloxymethyl* - 3 - *cephem* - 4 - *carboxylate* (**21a**), (7-*ACMA benzhydryl ester*). To a soln of **17a** (54 mg) in CH_2Cl_2 (2 ml), diphenylcarbodiimide (21.3 mg) was added at 0° with stirring. The mixture was stirred for 18 hr at 0° to complete the reaction. A small amount of ppt was filtered off, and washed with cold CH_2Cl_2. The filtrate was evaporated *in vacuo* at room temp to give an oily mixture which was separated on a preparative tlc plate (silica gel 60 F-254, Merck, thickness 0.25 mm) with EtOAc/C_6H_6 = 1/1 development to give 26 mg (56%) of **21a** as a powder; IR ν_{max} (KBr) 3400, 1775, 1730 cm^{-1}; NMR ($CDCl_3$) δ 2.35 (2H, s broad, C_7–NH_2), 3.32 (2H, s, C_2–H_2), 3.45 (3H, s, C_7–OCH_3), 4.76, 5.06 (2H, AB-q, J = 14 Hz, C_3–CH_2S-tetrazol), 4.82 (1H, s, C_6–H), 4.88 (2H, s broad, $OCONH_2$), 6.95 (1H, s, $CHPh_2$), 7.35 (10H, m, $C_6H_5 \times 2$); (Found: C, 59.21; H, 4.99; N, 9.36; S, 6.41. $C_{23}H_{23}O_6N_3S$ requires: C, 58.84; H, 4.94; N, 8.95; S, 6.82%): and 1,3 - diphenylimidazolidine - 2,4,5 - trione (**22**, 72%); m.p. 203°; IR ν_{max} (nujol) 1790 (w), 1741 cm^{-1}; MS *m/e* 266 (M^+).

Diphenylmethyl (6R, 7S) - 7 - (2' - *thienyl*)*acetamido* - 7 - *methoxy* - 3 - *carbamoyloxymethyl* - 3 - *cephem* - 4 - *carboxylate* (**21b**). (a) To a soln of the oxamic acid **17a** (217 mg, 0.4 mmol) in CH_2Cl_2 (8 ml), PhN=C=NPh (85 mg, 0.44 mmol) in CH_2CL_2 (4 ml) was added with stirring at 0°. The mixture was allowed to stand for 18 hr at 0°. N,N-Dimethylaniline (77 mg, 0.6 mmol) in CH_2Cl_2 (1 ml) and 2-thienylacetylchloride (80 mg, 0.5 mmol) in CH_2Cl_2 (1 ml) were added to this mixture in the given order. The resulting precipitate was filtered off and washed with EtOAc. The combined organic layer was washed with 2% HCl and sat $NaHCO_3$, dried over $MgSO_4$, and evaporated to give an oily mixture which was separated by preparative tlc (silica gel, C_6H_6/EtOAc = 1/1 development) to give 74 mg (31%) of **21b** as foam; IR ν_{max} (nujol) 3500–3200, 1780, 1725 cm^{-1}; NMR ($CDCl_3$) δ 3.30 (2H, s broad, C_2–H_2), 3.44 (3H, s, C_7–OCH_3), 3.78 (2H, s, $CHCONH$), 5.04 (1H, s, C_6–H), 4.75–5.30 (4H, m, C_4–CH_2OCONH_2), 6.8–7.6 (15H, m, thiophane-H_3, $C_6H_5 \times 2$, $CHPh_2$ and C_7–NHCO).

(b) N,N-Dimethylaniline (7.7 mg) in CH_2Cl (1 ml) and 2-thienylacetylchloride in CH_2Cl_2 (1 ml) were added to a soln of the amine **21a** (24 mg) in CH_2Cl_2 (1 ml) in the given order with stirring on an ice-water bath. After 15 hr at 0°, EtOAc was added to this mixture. The mixture was then washed with 2% HCl and sat $NaHCO_3$, dried over $MgSO_4$, and evaporated to give a crude product which was purified on a silica gel preparative tlc plate (C_6H_6/EtOAc = 1/1 development) to afford 18 mg (61%) of **21b**.

Cefoxitin (**21c**). To a soln of **21b** 594 mg, 1.0 mmol) in anisol (2 ml), CF_3COOH (2 ml) was added gradually with stirring at −30°. Stirring was continued at −20° for 20 min and at −10° for

another 20 min. EtOAc (60 ml) was added and the pH adjusted to 3.3 with sat $NaHCO_3$. The organic layer was separated to remove CF_3COONa, and extracted with 10% K_2HPO_4. The aqueous extract was adjusted to pH 2.0 with dil HCl and re-extracted with EtOAc. The extract was washed with H_2O and sat NaCl, dried over $MgSO_4$, and evaporated to give an oil which was precipitated from EtOAc/n-hexane = 3/1 to give 233 mg (56%) of **21c** as a powder: NMR (DMF-d_7) δ 3.34, 3.70 (2H, AB-q, J = 18 Hz, C_2–H_2), 3.48 (3H, s, C_7–OCH_3), 4.00 (2H, s, CH_2CONH), 4.80, 5.08 (2H, AB-q, J = 13 Hz, C_3–CH_2OCO), 5.19 (1H, s, C_6–H), 6.55 (2H, s broad, $OCONH_2$), 6.95–7.49 (3H, m, thiophene), 9.38 (1H, s, COOH). Data was identical in all respects with an authentic sample.

(6R, 7S) - 7 - *Hydroxyacetamido* - 7 - *methoxy* - 3 - (1' - *methyl* - 1'*H* - *tetrazol* - 5' - *yl*)*thiomethyl* - 3 - *cephem* - 4 - *carboxylic acid* (**28a**). Methyl oxamate **17f** (444 mg, 1.0 mmol) was dissolved in H_2O (10 ml) containing $NaHCO_3$ (100 mg). To this soln, MeOH (40 ml) was added at room temp, and $NaBH_4$ (50 mg) was added at −15° with stirring. After 5 min, the mixture was adjusted to pH 2.0 with dil HCl, and extracted with EtOAc. The extract was washed with sat NaCl, dried over $MgSO_4$, and evaporated to give 401 mg (95%) of **28a** as a powder: IR ν_{max} (nujol) 3220, 1775, 1705 cm^{-1}; NMR (CD_3COCD_3) δ 3.50 (3H, s, C_7–OCH_3), 3.70 (2H, s broad, C_2–H_2), 4.00 (3H, s, N–CH_3), 4.13 (2H, s, $COCH_2OH$), 4.31, 4.57 (2H, AB-q, J = 13 Hz, C_3–CH_2S-tetrazol), 5.13 (1H, s, C_6–H), 5.32 (2H, s broad, COOH and CH_2OH), 7.35 (1H, s broad, NH).

(6R, 7S) - 7 - *Chloroacetamido* - 7 - *methoxy* - 3 - (1' - *methyl* - 1'*H* - *tetrazol* - 5' - *yl*)*thiomethyl* - 3 - *cephem* - 4 - *carboxylic acid* (**28b**). To a soln of **28a** (42 mg, 0.1 mmol) in THF (2 ml), Et_3N (10 mg, 0.1 mmol) and Me_3SiCl (30 mg, 0.3 mmol) were added at room temp to form the trimethylsilyl ester of **28a**. To this mixture, K_2CO_3 (50 mg) and $SOCl_2$ (30 mg) were added with stirring at room temp. After 3 hr, the mixture was poured into H_2O, adjusted to pH 2.0 with dil HCl, and extracted with EtOAc. The extract was washed with H_2O and sat NaCl, dried over Na_2SO_4, and evaporated to give 42 mg (98%) of **28b** as a powder: IR ν_{max} ($CHCl_3$) 1778, 1730 cm^{-1}; NMR (CD_3COCD_3) δ 3.52 (3H, s, C_7–OCH_3), 3.70 (2H, s broad, C_2–H_2), 4.00 (3H, s, N–CH_3), 4.25 (2H, s, CH_2Cl), 4.33, 4.58 (2H, AB-q, J = 14 Hz, C_3–CH_2S-tetrazol), 5.11 (1H, s, C_6–H), 7.45 (1H, s broad, NH), 8.50 (1H, s broad, COOH).

(6R, 7S) - 7 - *Benzoylcarbonylamino* - 7 - *methoxy* - 3 - *carbamoyloxymethyl* - 3 - *cephem* - 4 - *carboxylic acid* (**29**). To a soln of **17d** (110 mg, 0.28 mmol) in THF (10 ml), PhMgBr (0.7 mmol) in THF (5 ml) was added with stirring at −78°. After 3 hr, AcOH (0.4 ml) in THF (2 ml) was added to this mixture to decompose excess PhMgBr. The reactant was diluted with EtOAc, washed with sat NaCl, dried over $MgSO_4$, and evaporated to give an oily mixture. This mixture was separated by column chromatography (silica gel, C_6H_6/EtOAc = 7/1 elution) to give 79 mg (65%) of **29** as a powder: NMR (CD_3COCD_3) δ 3.62 (5H, s broad, C_7–OCH_3 and C_2–H_2), 4.88 5.11 (2H, AB-q, J = 13 Hz, C_3–CH_2OCONH_2), 5.27 (1H, s, C_6–H), 6.10 (2H, s broad, $OCONH_2$), 7.4–8.5 (5H, m, C_6H_5), 9.10 (1H, s, C_7–NHCO).

(6R, 7S) - 7 - *Benzoyloximecarbonylamino* - 7 - *methoxy* - 3 - *carbamoyloxymethyl* - 3 - *cephem* - 4 - *carboxylic acid* (**30**). A mixture of **29** (75 mg) in EtOH (5 ml) and NH_2OH·HCl (45 mg) in H_2O (2 ml) was stirred at 0° for 18 hr. This mixture was then diluted with EtOAc, washed with H_2O and sat NaCl, dried over $MgSO_4$, and evaporated to give an oily mixture. This mixture was separated by column chromatography (silica gel, C_6H_6/EtOAc = 4/1 elution) to give 46 mg of **30** as foam: NMR (CD_3COCD_3) δ 3.40, 3.72 (2H, AB-q, J = 18 Hz, C_2–H_2), 3.67 (3H, s, C_7–OCH_3), 4.82, 5.07 (2H, AB-q, J = 13 Hz, C_3–CH_2OCO), 5.23 (1H, s, C_6–H), 6.02 (2H, s broad, $OCONH_2$), 7.3–8.1 (5H, m, C_6H_5), 8.90 (1H, s, C_7–NHCO). (Found: C, 47.64; H, 4.10; N, 11.90; S, 7.01. $C_{18}H_{18}O_8N_4S$ requires: C, 48.00; H, 4.03; N, 12.44; S, 7.11%).

REFERENCES

[1a] R. Nagarajan, L. D. Boeck, M. Gorman, R. L. Hamill, C. E. Higgins, M. M. Hoehm, W. M. Stark and J. G. Whitney, *J. Am. Chem. Soc.* **93**, 2308 (1971); [b] E. O. Stapley, M. Jackson, S. Helnandez, S. B. Zimmerman, S. A. Currie, S. Mochales, J. M. Mata, H. B. Woodruff and D. Hendlin, *Antimicrobial Agents and Chemotherapy* **2**, 112 (1972); [c] T. W. Miller, R. T. Goegelman, R. G. Weston, I. Putter and F. J. Wolf, *Ibid.* **2**, 132 (1972); [d] G. Albert-Schönberg, H. B. Arison and J. L. Smith, *Tetrahedron Letters* 2911 (1972); [e] H. Fukase, T. Hasegawa, K. Hatano, H. Iwasaki and M. Yoneda, *J. Antibiotics* **29**, 113 (1976).

[2] *Cephalosporins and Penicillins* (Edited by E. H. Flynn). Academic Press, New York (1972).

[3] W. H. W. Lunn, R. W. Burchfield, T. K. Elzey and E. V. Mason, *Tetrahedron Letters* 1307 (1974).

[4] S. Karady, L. M. Weinstock, F. E. Roberts, J. ten Broeke, R. F. Shuman, A. M. Hoinowski, S. H. Pines and M. Sletzinger, *Ibid.* 2401 (1976).

[5a] S. Karady, S. H. Pines, L. M. Weinstock, F. E. Roberts, G. S. Brenner, A. W. Hoinowski, T. Y. Cheng and M. Sletzinger, *J. Am. Chem. Soc.* **94**, 1410 (1972); [b] L. M. Weinstock, S. Karady, F. E. Roberts, A. M. Hoinowski, G. S. Brenner, T. B. K. Lee, W. C. Lumma and M. Sletzinger, *Tetrahedron Letters* 3979 (1975).

[6a] M. Shiozaki, N. Ishida, K. Iino and T. Hiraoka, *Tetrahedron Letters* 4059 (1977); [b] *Idem, J. Chem. Soc. Chem. Commun.* 517 (1978).

[7a] R. Stollé and M. Luther, *Chem. Ber.* **53**, 314 (1972); [b] J. C. Sheehan and E. J. Corey, *J. Am. Chem. Soc.* **47**, 360 (1952); [c] A. J. Speziale and L. R. Smith, *J. Org. Chem.* **28**, 1805 (1963); [d] J. C. Sheehan, *Pure Appl. Chem.* **6**, 297 (1963).

[8] The C-4 benzhydryl ester was cleaved partially to the corresponding acid, when Na_2CO_3 was not added.

[9] **16c** was prepared from cephamycin C as follows. The amine on the aminoadipoyl side chain of cephamycin C was protected as an urethane with iso-butyl chloroformate in H_2O–CH_3COCH_3 at pH 8.0–8.2, whose carbamoyloxy group was further converted to the thiotetrazole (**16c**) with 1 - methyl - 5 - mercaptotetrazol.

[10] **19** was prepared from methyl 6-n-butylamidopenicillanate by the methoxylation method using t-butylhypochlorite and $LiOCH_3$. [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. Koppel and R. E. Koehler, *Ibid.* **95**, 2403 (1973); [c] W. H. W. Lunn and E. V. Mason, *Tetrahedron Letters* 1311 (1974).

[11] T. Hiraoka, *Ann. Rep. Sankyo Res. Lab.* **31**, 4 (1979).