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SYNTHESIS OF OXAPENEM DERIVATIVES BY NOVEL REDUCTIVE CYCLIZATION

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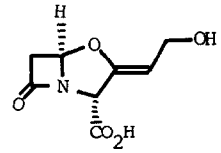
Abstract —— Several 6-ethyl-substituted 1-oxapenem derivatives were synthesized by the application of the established method. Furthermore novel and effective synthesis of oxapenems via reductive cyclization of 2-chloro-2-(4-chloro-3-ethyl-2-oxo-1-azetidinyl)acetoacetates (10) using sodium thiolates is reported.

Recent works have disclosed a number of new natural and synthetic β-lactams with structural features and biological properties distinct from penicillins and cephalosporins[1]. Among them, the strained bicyclic compounds having an oxygen atom in the ring system showed important pharmacological activities, for example, clavulanic acid (1)[2] is a potent inhibitor against many β-lactamases while moxalactam (6059-S)[3] (2) is a broad spectral antibacterial agent. Although 1-oxapenem (clavem) derivatives have been synthesized by several groups[4-6], its chemical stability and biological activity are known a little. The more stable character of the 6-substituted carbapenems comparing with the corresponding unsubstituted ones, which was experienced during our synthetic study, and the expectation of the potent antibacterial activity due to the 7-oxo-1-aza[3.2.0]hept-2-ene system[7] have promoted us the preparation of the 6-alkylated oxapenems (3). Here we wish to report a synthesis of some derivatives and an facile construction of the ring system using

novel reductive cyclization.



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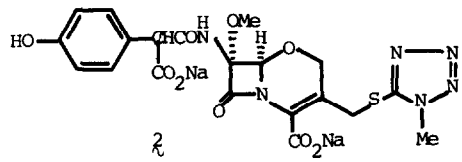

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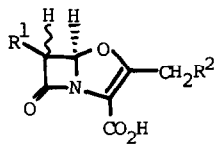


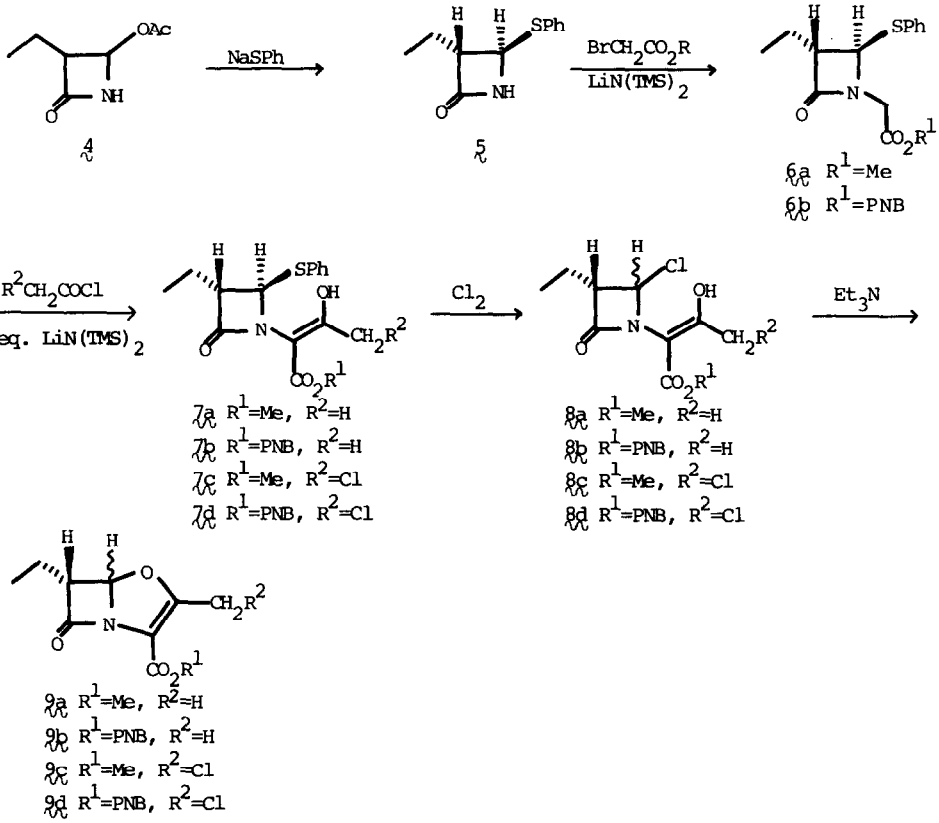
3

A convenient starting material was 4-acetoxy-3-ethylazetidin-2-one (4)[8], which was easily available from but-1-enyl acetate and chlorosulfonyl isocyanate. Treatment of 4 with sodium phenylthiolate according to the Clauss' procedure[9] afforded the trans-substituted azetidinone (5), which was alkylated with methyl or p-nitrobenzyl(PNB) bromoacetate using lithium hexamethyldisilazide. By the application of the Beacham's method[4], these esters (6a and 6b) were converted to clavems. Namely the above methyl ester (6a) was acetylated by the action of acetyl chloride in the presence of two equivalent moles of lithium hexamethyldisilazide in tetrahydrofuran at - 78°C to give in high yield the enol (7a) which showed the enol hydroxyl group at 11.6 ppm in the NMR spectrum ($CDCl_3$). Chlorinolysis of the enol (7a) using one equivalent mole of chlorine at - 78°C yielded the corresponding chloride (8a) as a rather unstable material.

When the crude chloride (8a) was treated with triethylamine, an incorporation of benzenesulfenyl group was indicated from the spectral data of the product. Therefore the chloride (8a) was purified by chromatography using Bio-Beads S-X3 eluting with benzene to remove benzenesulfenyl chloride formed by the chlorinolysis. It was revealed from the NMR spectrum that the chloride (8a) was composed of trans- and cis-isomers in a ratio of 2 : 1 which were inseparable. The hydrogen at C_4 position of trans-isomer was observed at 5.34 ppm as doublet with J = 1.8 Hz, whereas that of cis-one at 5.76 ppm as doublet with J = 4 Hz. Reaction of the chloride (8a) with triethylamine at 0°C for 10 min, followed by purification using medium pressure chromatography on silica gel produced, in 84 % yield from the sulfide (7a), the oxapenem (9a) as a mixture of inseparable two stereoisomers in a ratio of 1 : 1. The angular hydrogen at the C_5 position of trans-

compound was resonated at 5.58 ppm as doublet with J = 1 Hz, while that of cis-one at 5.87 ppm as doublet with J = 3 Hz, in the NMR spectroscopy. The oxapenem obtained was sufficiently stable under ordinary conditions. The corresponding p-nitrobenzyl ester (9b) was synthesized by the same reaction sequence.

It was expected from the structure-activity relationships of cephalosporins that existence of a leaving group on the C_2-methyl group would enhance the antibacterial activity. Thus the 2-chloromethyloxapenems (9c and 9d) were synthesized form 6a and 6b by the similar procedure in comparable yields. However the 2-chloromethyloxapenems were very labile and decomposed after standing for 24 h at room temperature.



4

5

6a R^1=Me
6b R^1=PNB

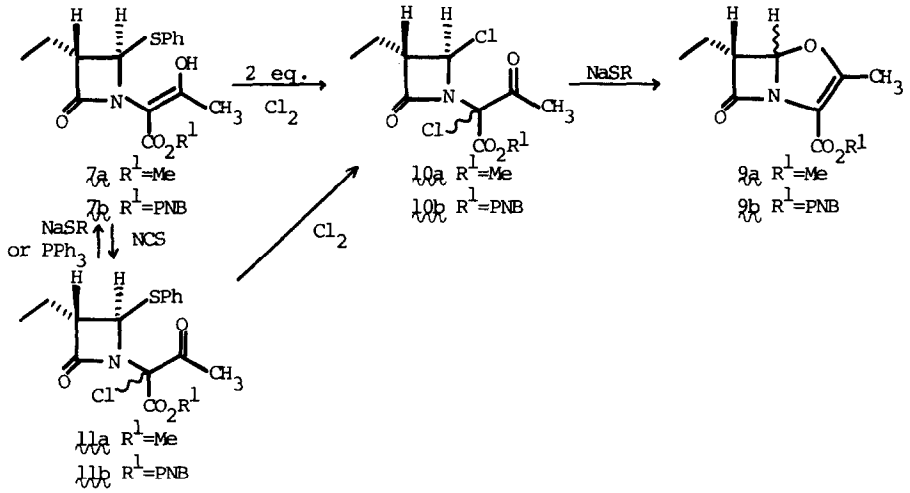
7a R^1=Me, R^2=H
7b R^1=PNB, R^2=H
7c R^1=Me, R^2=Cl
7d R^1=PNB, R^2=Cl

8a R^1=Me, R^2=H
8b R^1=PNB, R^2=H
8c R^1=Me, R^2=Cl
8d R^1=PNB, R^2=Cl

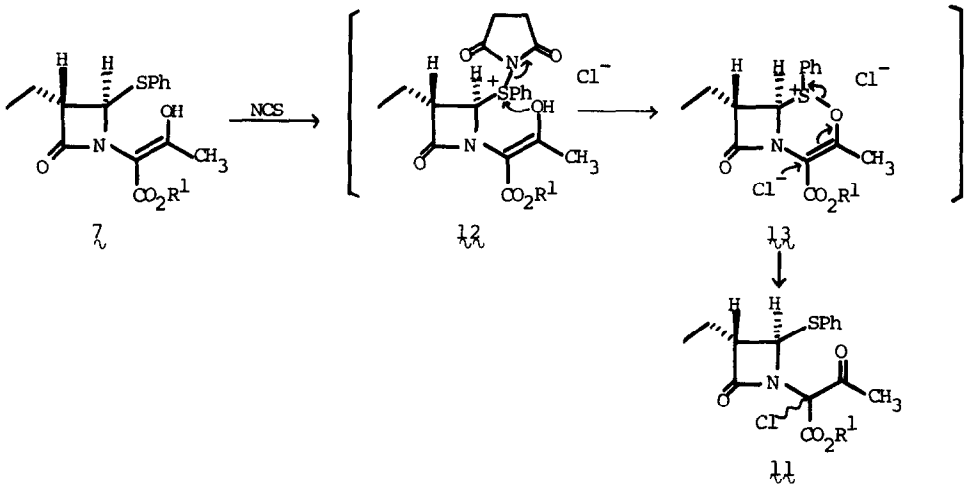
9a R^1=Me, R^2=H
9b R^1=PNB, R^2=H
9c R^1=Me, R^2=Cl
9d R^1=PNB, R^2=Cl

In the case of the above chlorinolysis, if the reaction was carried out using excess of chlorine and without care protecting from light, further chlorination occurred at the acetoacetate moiety. Namely treatment of 7a or 7b with two equivalent moles of chlorine gave the dichloride (10a or 10b) as a mixture of trans- and cis-isomers in a ratio of 2 : 1 in 86.5 % or 79.9 % yield, respectively. These isomers were separable by medium pressure silica gel

chromatography. The molecular formulae were determined by accurate mass spectrometry and the structures were assigned on the basis of IR and NMR spectroscopy, the latter of which suggested no existence of epimers due to the chiral center on the acetyl-α-chloroacetate part. Furthermore the structural assignment was confirmed by the ^{13}C-NMR spectroscopy of the trans-isomer of 10a which showed one quaternary carbon at the α-position at 96.1 and two tertiary carbons on β-lactam ring at 70.4 and 64.3 ppm.



The dichloride (10a and 10b) were alternatively synthesized in the different ratio of the stereoisomers as follows. Reaction of 7a with one equivalent mole of N-chlorosuccinimide in methylene chloride for 30 min at -20°C formed in 94.7 % yield the chlorosulfide (11a), which has trans-azetidinone



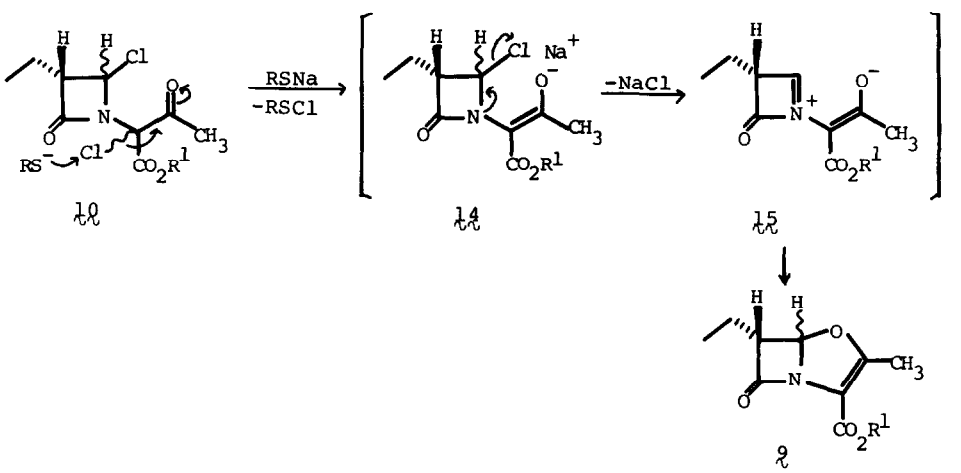
structure and is composed of two epimers (1 : 1) due to the chiral center on the α position. The ease and selective chlorination at the α-position of the acetoacetate function is accounted by the formation of the complex (12)[10] followed by cyclization to 13 and chlorination to 11.

Chlorinolysis of the above mixture (11a) using chlorine at - 78°C furnished the dichloride (10a) in 95.3 % yield as a mixture of trans- and cis-azetidinones in a ratio of 1 : 5. The trans- and cis-isomers were separated from each other by silica gel chromatography but each product is constituted by two epimers due to the α-asymmetric center.

The cyclization of the dichloride (10a) to the oxapenem (9a) was achieved in satisfactory yield by the action of thiolates; e.g. sodium phenylthiolate or sodium N-methyltetrazolylthiolate. In order to consume benzenesulfenyl chloride formed by the reaction, two equivalent moles of thiolates were used. Thus oxapenem (9a) was obtained in 94 % yield by the treatment of 10a with sodium phenylthiolate in dimethylformamide for 15 min at 0°C.

The mixture of dichlorides (10a) composed of stereoisomers in different ratio produced the same stereoisomeric mixture of oxapenems (9a) (1 : 1) in similar yields under the same reaction conditions. The above transformations were also carried out for the corresponding p-nitrobenzyl esters.

When the foregoing chloro-sulfide (11a) was treated with sodium thiolates or triphenylphosphin[11], the dechlorinated enol (7a) was gained. Therefore the above cyclization would be explained by the following reductive mechanism involving the formation of the enolate anion (14) followed by ring construc-



tion via the zwitter ion (15) yielding the stereoisomeric mixture of 9.

Application of the above novel cyclization for the synthesis of oxapenem derivatives and formation of other ring systems is in progress.

EXPERIMENTAL

UV spectra were measured with a Hitachi 124 spectrophotometer, IR spectra with a Hitachi 260-10 spectrophotometer, and NMR spectra with JEOL-PMX-60 and JEOL-PS-100 spectrometers. Ordinary mass spectra were obtained with a Hitachi M-52 G while FD and accurate mass spectra were taken with a JEOL-JMS-01SG-2 spectrometer.

trans-3-Ethyl-4-phenylthioazetidin-2-one (5). — To a stirred solution of NaOH (746 mg) and thiophenol (2.73 g) in a mixture of water (10 ml) and MeOH (20 ml) was added a solution of 4-acetoxy-3-ethylazetidin-2-one (4)[8] (3 g) in MeOH (5 ml) at ambient temparature, and the resulting mixture was stirred for 15 min. After evaporation of the solvent, the resulting residue was chromatographed on silica gel using benzene-AcOEt (7 : 1 v/v) as eluant to give 3.88 g (98.1 %) of the trans-azetidinone (5) as a colorless syrup : IR $\nu_{max.}$ ($CHCl_3$) 1765 cm^{-1} (C=O); NMR δ ($CDCl_3$) 1.01 (3H, t, J = 7 Hz, CH_2-Me), 1.77 (2H, q, J = 7 Hz, -CH_2-Me), 2.99 (1H, dt, J = 2 and 7 Hz, C_3-H), 4.62 (1H, d, J = 2 Hz, C_4-H), 6.81 (1H, br s, NH), 7.05 ∿ 7.47 (5H, br s, Ph), MS m/e 207 (M^+); m/e 207.0741 (M^+) [Calcd for $C_{11}H_{13}NOS$ (M^+), m/e 207.0718]. (Anal. Calcd for $C_{11}H_{13}NOS \cdot 0.1\ H_2O$: C, 63.18; H, 6.42; N, 6.76. Found: C, 62.83; H, 6.26; N, 6.57).

trans-3-Ethyl-1-methoxycarbonylmethyl-4-phenylthioazetidin-2-one (6a). — To a stirred solution of lithium hexamethyldisilazide [prepared from hexamethyldisilazane (2.2 ml) and 15 % w/w ^nBuLi in n-hexane (7.5 ml)] in dry THF (10 ml) was added a solution of the above azetidinone (5) (2 g) in dry THF (3 ml) at - 78°C under a current of nitrogen. After stirring for 0.2 h at - 78°C, methyl bromoacetate (1.3 ml) was added, and the resulting mixture was stirred for 1 h at - 78°C and then for 1 h at room temparature. The mixture was treated with water and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The resulting residue was purified by silica gel column chromatography using benzene-AcOEt (95 : 5 v/v) as eluant to give 2.39 g (88.7 %) of the methyl ester (6a) as a colorless syrup : IR $\nu_{max.}$ ($CHCl_3$) 1750

cm^{-1} (C=O); NMR δ ($CDCl_3$) 1.07 (3H, t, J = 7 Hz, CH_2-Me), 1.8 (2H, q, J = 7 Hz, CH_2-Me), 3.0 (1H, dt, J = 2.2 and 7 Hz, C_3-H), 3.63 (3H, s, OMe), 3.60 and 4.24 (each 1H, each d, each J = 18 Hz, N-CH_2-), 4.88 (1H, d, J = 2.2 Hz, C_4-H), 7.14 ∿ 7.57 (5H, br s, Ph); MS m/e 279 (M^+). (Anal. Calcd for $C_{14}H_{17}NO_3S$: C, 60.19; H, 6.13; N, 5.01. Found: C, 60.27; H, 6.18; N, 4.92).

trans-3-Ethyl-1-p-nitrobenzyloxycarbonylmethyl-4-phenylthioazetidin-2-one (6b). —— To a stirred solution of lithium hexamethyldisilazide [prepared from hexamethyldisilazane (1.1 ml) and 15 % w/w ^{n}BuLi in n-hexane (3.25 ml)] in dry THF (10 ml) was added a solution of the above azetidinone (5) (1 g) in dry THF (3 ml) at - 78°C under a current of nitrogen. After stirring for 0.2 h at - 78°C, a solution of p-nitrobenzyl bromoacetate (1.5 g) in dry THF (3 ml) was added. The same work-up and purification procedures as above afforded 1.47 g (76 %) of the p-nitrobenzyl ester (6b) as a colorless syrup: IR $\nu_{max.}$ ($CHCl_3$) 1750 (C=O), 1510 and 1350 cm^{-1} (NO_2); NMR δ ($CDCl_3$) 1.02 (3H, t, J = 7 Hz, CH_2-Me), 1.82 (2H, q, J = 7 Hz, -CH_2-Me), 3.07 (1H, dt, J = 2.2 and 7 Hz, C_3-H), 3.74 and 4.35 (each 1H, each d, each J = 18 Hz, N-CH_2-), 4.83 (1H, d, J = 2.2 Hz, C_4-H), 5.18 (2H, s, OCH_2Ar), 7.13 ∿ 7.46 (5H, br s, Ph), 7.43 and 8.16 (each 2H, each d, each J = 8 Hz, 4 × Ar-H); MS m/e 400 (M^+).

Methyl 2-[trans-(3-Ethyl-2-oxo-4-phenylthio-1-azetidinyl)]-3-hydroxycrotonate (7a). —— To a stirred solution of lithium hexamethyldisilazide [prepared from hexamethyldisilazane (1.07 ml) and 15 % w/w ^{n}BuLi in n-hexane (2.04 ml)] in dry THF (10 ml) was added a solution of the above methyl ester (6a) (425 mg) in dry THF (3 ml) at - 78°C under a current of nitrogen. After stirring for 0.2 h at - 78°C, acetyl chloride (119.6 mg) was added, and the resulting mixture was further stirred for 0.6 h at - 78°C. The mixture was treated with water (containing 60 mg of AcOH) and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The resulting yellowish residue was purified by silica gel column chromatography using benzene-AcOEt (4 : 1 v/v) as eluant to give 389 mg (79.6 %) of (7a) as a colorless gum: IR $\nu_{max.}$ ($CHCl_3$) 1750 cm^{-1} (C=O); NMR δ ($CDCl_3$) 0.98 (3H, t, J = 7 Hz, CH_2-Me), 1.79 (2H, q, J = 7 Hz, -CH_2-Me), 2.06 (3H, s, C_3-Me), 3.09 (1H, dt, J = 2.4 and 7 Hz, C_3'-H), 3.54 (3H, s, OMe), 4.89 (1H, d, J = 2.4 Hz, C_4'-H), 7.07 ∿ 7.5 (5H, br s, Ph), 11.6

(1H, br s, OH); MS m/e 321 (M^+); m/e 321.1030 [Calcd for $C_{16}H_{19}NO_4S$ (M^+), m/e 321.0990]. (Anal. Calcd for $C_{16}H_{19}NO_4S$: C, 59.79; H, 5.96; N, 4.36. Found: C, 59.55; H, 6.03; N, 4.40).

p-Nitrobenzyl 2-[trans-(3-Ethyl-2-oxo-4-phenylthio-1-azetidinyl)]-3-hydroxycrotonate (7b). — To a stirred solution of lithium hexamethyldisilazide [prepared from hexamethyldisilazane (0.45 ml) and 15 % w/w ^{n}BuLi in n-hexane (1.36 ml)] in dry THF (10 ml) was added a solution of the above p-nitrobenzyl ester (6b) (425 ml) in dry THF (3 ml) at - 78°C under a current of nitrogen. After stirring for 0.1 h at - 78°C, acetyl chloride (83.41 mg) was added under the above conditions. The same work-up and purification procedures as in the case of the above methyl ester (7a) gave 366 mg (77.9 %) of the p-nitrobenzyl ester (7b) as a colorless gum: IR $\nu_{max.}$ ($CHCl_3$) 1755 (C=O), 1510 and 1350 cm^{-1} (NO_2); NMR δ 0.97 (3H, t, J = 7 Hz, CH_2-Me), 1.77 (2H, q, J = 7 Hz, CH_2-Me), 2.17 (3H, s, C_3-Me), 3.2 (1H, dt, J = 2 and 7 Hz, C_3'-H), 4.87 (1H, d, J = 2 Hz, C_4'-H), 5.18 (2H, s, OCH_2Ar), 7.2~7.52 (5H, br s, Ph), 7.39 and 8.19 (each 2H, each d, each J = 8 Hz, 4 × ArH), 12.13 (1H, br s, OH); MS m/e 442 (M^+); m/e 442.1179 (M^+) [Calcd for $C_{22}H_{22}N_2O_6S$ (M^+), m/e 442.1154]. (Anal. Calcd for $C_{22}H_{22}N_2O_6S$ $0.5H_2O$: C, 58.52; H, 5.14; N, 6.21. Found: C, 58.50; H, 4.96; N, 6.06).

Methyl 4-Chloro-2-[trans-(3-ethyl-2-oxo-4-phenylthio-1-azetidinyl)]-3-hydroxycrotonate (7c). — To a stirred solution of hexamethyldisilazide [prepared form hexamethyldisilazane (1.08 ml) and 15 % w/w ^{n}BuLi in n-hexane (3.22 ml)] in dry THF (10 ml) was added a solution of the above methyl ester (6a) (684 mg) in dry THF (5 ml) at - 78°C under a current of nitrogen. After stirring for 0.1 h at - 78°C, chloroacetyl chloride (0.21 ml) was added, and the reaction mixture was stirred for 0.5 h at - 78°C. The same work-up and purification procedures as in the case of the above methyl ester (7a) gave 630 mg (79.6 %) of the chloride (7c) as a colorless gum: IR $\nu_{max.}$ ($CHCl_3$) 1760 cm^{-1} (C=O); NMR δ ($CDCl_3$) 1.11 (3H, t, J = 7 Hz, CH_2-Me), 1.89 (2H, q, J = 7 Hz, CH_2-Me), 3.23 (1H, dt, J = 2.8 and 7 Hz, C_3'-H), 3.77 (3H, s, OMe), 4.28 (2H, s, CH_2-Cl), 5.02 (1H, d, J = 2.8 Hz, C_4'-H), 7.2 ∿ 7.54 (5H, br s, Ph), 12.2 (1H, br s, OH); MS m/e 357 (M^+ + 2), 355 (M^+); m/e 357.0661 (M^+ + 2) [Calcd for $C_{16}H_{18}NO_4S(^{37}Cl)$ (M^+ + 2), m/e 357.0610], m/e 355.0647 (M^+) [Calcd for $C_{16}H_{18}NO_4S(^{35}Cl)$ (M^+), m/e 355.0645]. (Anal. Calcd for $C_{16}H_{18}NO_4SCl$: C, 54.00; H, 51.0; N, 3.94. Found: C, 54.19; H, 5.18; N, 3.92).

p-Nitrobenzyl 4-Chloro-2-[trans-(3-ethyl-2-oxo-4-phenylthio-1-azetidinyl)]-3-hydroxycrotonate (7d). —— To a stirred solution of lithium hexamethyldisilazide [prepared from hexamethyldisilazane (0.45 ml) and 15 % w/w ^{n}BuLi in n-hexane (1.33 ml)] in dry THF (10 ml) was added a solution of p-nitrobenzyl ester (6b) (407 mg) in dry THF (5 ml) at - 78°C under a current of nitrogen. After stirring for 0.1 h at - 78°C, chloroacetyl chloride (115 mg) was added, and the resulting mixture was stirred for 0.5 h at - 78°C, The same work-up and purification procedures as above gave 331 mg (69.5 %) of (7d) as a yellowish gum: IR $\nu_{max.}$ ($CHCl_3$) 1760 (C=O), 1345 cm^{-1}(NO_2); NMR δ ($CDCl_3$) 0.98 (3H, t, J = 7 Hz, CH_2-Me), 1.71 (2H, q, J = 7 Hz, -CH_2-Me), 3.17 (1H, dt, J = 2.6 and 7 Hz, C_3'-H), 4.19 (2H, s, -CH_2Cl), 4.83 (1H, d, J = 2.6 Hz, C_4'-H), 5.13 (2H, s, OCH_2Ar), 7.21 (5H, br s, Ph), 7.4 and 8.09 (each 2H, each d, each J = 8 Hz, 4 × Ar-H), 11.93 (1H, br s, OH); MS m/e 367 (M^+ - 109). (Anal. Calcd for $C_{22}H_{21}N_2O_6SCl\cdot 0.5H_2O$: C, 54.37; H, 4.56; N, 5.77; S, 6.60; Cl, 7.30. Found: C, 54.70; H, 4.96; N, 5.33; S, 6.95; Cl, 7.25).

Methyl 2-Chloro-2-[trans-(3-ethyl-2-oxo-4-phenylthio-1-azetidinyl)] acetoacetate (11a). —— A mixture of the methyl ester (7a) (576 mg) and N-chlorosuccinimide (250 mg) in dry CH_2Cl_2 (20 ml) was stirred at - 20°C for 0.5 h under a current of nitrogen. After filtration of the reaction mixture, the filtrate was evaporated under reduced pressure. The resulting residue was chromatographed on silica gel using benzene-AcOEt (95 : 5 v/v) as eluant to give 603 mg (94.7 %) of the mixture of inseparable two stereoisomers (1 : 1) of the trans-azetidinones (11a) as a colorless gum: IR $\nu_{max.}$ ($CHCl_3$) 1782 cm^{-1} (C=O); NMR δ ($CDCl_3$) 0.93 (3H, t, J = 7 Hz, CH_2-Me), 1.78 (2H, m, -CH_2-Me), 2.40 and 2.48 (each 3/2H, each s, C_3-Me), 3.04 (1H, dt, J = 2.6 and 7 Hz, C_3'-H), 3.75 and 3.88 (each 3/2H, each s, OMe), 5.08 and 5.13 (each 1/2H, each d, each J = 2.6 Hz, C_4'-H), 7.22 ∿ 7.78 (5H, br s, Ph); MS m/e 357 (M^+ + 2), 355 (M^+); m/e 357.0624 (M^+ + 2) [Calcd for $C_{16}H_{18}NO_4(^{37}Cl)S$ (M^+ + 2), m/e 357.0616], m/e 355.0630 (M^+) [Calcd for $C_{16}H_{18}NO_4(^{35}Cl)S$ (M^+), m/e 355.0643]. (Anal. Calcd for $C_{16}H_{18}NO_4SCl$: N, 3.94. Found: N, 3.52).

p-Nitrobenzyl 2-Chloro-2-[trans-(3-ethyl-2-oxo-4-phenylthio-1-azetidinyl)]-acetoacetate (11b). —— A mixture of the p-nitrobenzyl ester (7b) (142 mg) and N-chlorosuccinimide (45 mg) in dry CH_2Cl_2 (10 ml) was stirred for 0.5

h at - 20°C under a current of nitrogen. The same work-up and purification as above afforded 142 mg (93 %) of the inseparable two stereoisomeric mixture (1 : 1) of (11b) as a colorless gum: IR $\nu_{max.}$ ($CHCl_3$) 1775 (C=O), 1348 cm^{-1} (NO_2); NMR δ ($CDCl_3$) 0.98 (3H, t, J = 7 Hz, CH_2-Me), 1.77 (2H, q, J = 7 Hz, -CH_2-Me), 2.40 and 2.50 (each 3/2H, each s, C_3-Me), 3.06 (1H, dt, J = 2.8 and 7 Hz, C_3'-H), 5.07 (1H, d, J = 2.8 Hz, C_4'-H), 5.24 and 5.35 (each 1H, each s, OCH_2Ar), 7.08 ~ 7.64 (5H, br s, Ph), 7.47 and 8.2 (each 2H, each d, each J = 8 Hz, 4 × Ar-H), MS m/e 478 (M^+ + 2), 476 (M^+); m/e 478.0795 (M^+ + 2) [Calcd for $C_{22}H_{21}N_2O_6(^{37}Cl)S$ (M^+ +2), m/e 478.0780], m/e 476.0776 (M^+) [Calcd for $C_{22}H_{21}N_2O_6(^{35}Cl)S$ (M^+), m/e 476.0807]. (Anal. Calcd for $C_{22}H_{21}N_2O_6 \cdot SCl$: C, 55.40; H, 4.44; N, 5.87. Found: C, 55.16; H, 4.46; N, 5.73).

Methyl 2-Chloro-2-(4-chloro-3-ethyl-2-oxo-1-azetidinyl) acetoacetate (10a). —— [A]. To a stirred solution of the methyl ester (7a) (50 mg) in dry CH_2Cl_2 (5 ml) was added Cl_2 (23 mg) in dry CCl_4 (0.5 ml) at - 78°C under a current of nitrogen, and the resulting mixture was stirred for 10 min. After evaporation of the solvent, the resulting residue was purified by rapid chromatography on Kieselgel-60 (Art 9385) using benzene-AcOEt (97 : 3 v/v) as eluant to give 25.3 mg (57.7 %) of the azetidinone (10a-trans) as a colorless gum: IR $\nu_{max.}$ ($CHCl_3$) 1798 and 1770 cm^{-1} (C=O); NMR δ ($CDCl_3$) 1.08 (3H, t, J = 7 Hz, CH_2-Me), 1.83 (2H, q, J = 7 Hz, -CH_2-Me), 2.50 (3H, s, C_3-Me), 3.36 (1H, dt, J = 2.2 and 7 Hz, C_3'-H), 3.86 (3H, s, OMe) 5.7 (1H, d, J = 2.2 Hz, C_4'-H); ^{13}C-NMR δ ($CDCl_3$) 10.7 (-CH_2-CH_3), 20.4 (-CH_2-CH_3), 25.6 ($COCH_3$), 54.4 (OCH_3), 64.3 (C_3'), 70.4 (C_4'), 96.1 (C_2); MS m/e 286 (M^+ + 5), 284 (M^+ + 3), 282 (M^+ + 1); m/e 286.0224 (M^+ + 5) [Calcd for $C_{10}H_{14}NO_4(^{37}Cl)_2$ (M^+ + 5), m/e 286.0239], m/e 284.0255 (M^+ + 3) [Calcd for $C_{10}H_{14}NO_4(^{35}Cl) \cdot (^{37}Cl)$ (M^+ + 3), me/ 284.0270], m/e 282.0276 (M^+ + 1) [Calcd for $C_{10}H_{14}NO_4 \cdot (^{35}Cl)_2$ (M^+ + 1), m/e 282.0298]. (Anal. Calcd for $C_{10}H_{13}NO_4Cl_2$: C, 42.57; H, 4.64; N, 4.97; Cl, 25.13. Found: C, 42.78; H, 4.56; N, 4.90; Cl, 24.63). Further elution gave 12.7 mg (28.8 %) of the azetidinone (10a-cis) as a colorless gum: IR $\nu_{max.}$ ($CHCl_3$) 1798 and 1770 cm^{-1} (C=O); NMR δ ($CDCl_3$) 1.08 (3H, t, J = 7 Hz, CH_2-Me), 1.83 (2H, q, J = 7 Hz, -CH_2-Me), 2.50 (3H, s, C_3-Me), 3.48 (1H, dt, J = 5 and 7 Hz, C_3'-H), 3.86 (3H, s, OMe), 6.15 (1H, d, J = 5 Hz, C_4'-H); MS m/e 286 (M^+ + 5), 284 (M^+ + 3), 282 (M^+ + 1).

[B]. To a stirred solution of the methyl 2-chloroacetoacetate (11a) (200 mg) in dry CH_2Cl_2 (15 ml) was added a

solution of Cl_2 (40 mg) in dry CCl_4 (0.5 ml) at - 78°C under a current of nitrogen, and the reaction mixture was stirred for 10 min. The same work-up and purification procedures as above gave 25.2 mg (15.9 %) of the inseparable two stereoisomeric mixture (1 : 1) of the trans-azetidinone (10a) as a colorless gum, whose spectral data and TLC were identical with those of the above azetidinone (10a-trans) except the signal due to the C_3-methyl : 2.41 and 2.50 (each 3/2H, each s, C_3-Me) in the NMR spectrum ($CDCl_3$). Further elution gave 126 mg (79.6 %) of the inseparable two stereoisomers (1 : 1) of the cis-azetidinone (10a) as a colorless gum, whose spectral data and TLC were identical with those of the above azetidinone (10a-cis) except : δ 2.41 and 2.50 (each 3/2H, each s, C_3-Me), 6.11 and 6.15 (each 1/2H, each d, each J = 5 Hz, C_4'-H) in the NMR spectrum ($CDCl_3$).

p-Nitrobenzyl 2-Chloro-2-(4-chloro-3-ethyl-2-oxo-1-azetidinyl)acetoacetate (10b). — [A]. To a stirred solution of the p-nitrobenzyl ester (7b) (50 mg) in dry CH_2Cl_2 (5 ml) was added a solution of Cl_2 (17 mg) under the same conditions as previous. The same work-up and purification procedures as in the case of (10a) gave 20 mg (53.3 %) of the azetidinone (10b-trans) as a colorless gum : IR $\nu_{max.}$ ($CHCl_3$) 1795 (C=O), 1345 cm^{-1} (NO_2); NMR δ ($CDCl_3$) 1.06 (3H, t, J = 7 Hz, CH_2-Me), 1.84 (2H, q, J = 7 Hz, -CH_2-Me), 2.50 (3H, s, C_3-Me), 3.39 (1H, dt, J = 1.8 and 7 Hz, C_3'-H), 5.32 (2H, s, OCH_2Ar), 5.70 (1H, d, J = 1.8 Hz, C_4'-H), 7.49 and 8.21 (each 2H, each d, each J = 8 Hz, 4 × Ar-H); MS m/e 406 (M^+ + 4), 404 (M^+ + 2), 402 (M^+); m/e 403.0468 (M^+ + 1) [Calcd for $C_{16}H_{17}N_2O_6(^{35}Cl)_2$ (M^+ + 1), m/e 403.0463]. (Anal. Calcd for $C_{16}H_{16}N_2O_6Cl_2$: C, 47.66; H, 4.00; N, 6.95; Cl, 17.59. Found: C, 48.00; H, 3.76; N, 6.55; Cl, 17.27). Further elution gave 10 mg (26.6 %) of the azetidinone (10b-cis) as a colorless gum : IR $\nu_{max.}$ ($CHCl_3$) 1795 (C=O), 1343 cm^{-1} (NO_2); NMR δ ($CDCl_3$) 1.06 (3H, t, J = 7 Hz, CH_2-Me), 1.84 (2H, q, J = 7 Hz, -CH_2-Me), 2.50 (3H, s, C_3-Me), 3.50 (1H, dt, J = 4.8 and 7 Hz, C_3'-H), 5.32 (2H, s, OCH_2Ar), 6.10 (1H, d, J = 4.8 Hz, C_4'-H), 7.49 and 8.21 (each 2H, each d, each J = 8 Hz, 4 × Ar-H); MS m/e 406 (M^+ + 4), 404 (M^+ + 2), 402 (M^+).

[B]. To a stirred solution of p-nitrobenzyl 2-chloroacetoacetate (11b) (112 mg) in dry CH_2Cl_2 (10 ml) was added a solution of Cl_2 (16.7 mg) in dry CCl_4 (0.3 ml) at - 78°C under a current of nitrogen, and the resulting mixture was stirred for 10 min. The same work-up and purification procedures as in the case of (10a) gave 14.3 mg (15.1 %) of the inseparable two stereoisomers of

the trans-azetidinones (10b) as a colorless gum, whose spectral data and TLC were identical with those of the above (10b-trans) prepared from method [A] except signals : δ 2.44 and 2.50 (each 3/2H, each s, C_3-Me) in the NMR spectrum ($CDCl_3$). Further elution gave 71.4 mg (75.4 %) of the inseparable two stereoisomers of the azetidinones (10b-cis) as a colorless gum, whose spectral data and TLC behaviors were identical with those of the above azetidinone (10b-cis) prepared from the method [A] except signals : δ 2.44 and 2.50 (each 3/2H, each s, C_3-Me), in the NMR spectrum ($CDCl_3$).

Methyl 6-Ethyl-2-methyl-1-oxapen-2-em-3-carboxylate (9a). —— [A]. To a stirred solution of the above enol methyl ester (7a) (400 mg) in dry CH_2Cl_2 (30 ml) was added a solution of Cl_2 (88.75 mg) in dry CCl_4 (0.5 ml) at - 78°C under a current of nitrogen in the dark. After stirring for 5 min, the solvent was removed under reduced pressure in the dark. The resulting residue was chromatographed on Bio-Beads S-X3 (Bio-Road Laboratories) using benzene to afford 304 mg (98.5 %) of two stereoisomeric mixture (cis : trans = 1 : 2) of the chlorides (8a) as a colorless gum : IR $\nu_{max.}$ ($CHCl_3$) 1778 cm^{-1} (C=O); NMR δ (CCl_4) 1.08 (3H, t, J = 7 Hz, CH_2-Me), 1.83 (2H, q, J = 7 Hz, -CH_2-Me), 2.13 (3H, s, C_3-Me), 3.29 (1H, m, C_3'-H), 3.77 (3H, s, OMe), 5.34 [2/3H, d, J = 1.8 Hz, C_4'-H (trans)], 5.76 [1/3H, d, J = 4 Hz, C_4'-H (cis)], 12.27 (1H, br s, OH).

To a stirred solution of the above chloride (8a) (304 mg) in dry THF (10 ml) was added a solution of dry Et_3N (127 mg) in dry THF (2 ml) at 0°C under a current of nitrogen, and the reaction mixture was stirred for 10 min. After filtration of the resulting mixture, the filtrate was evaporated under reduced pressure. The brownish residue was purified by rapid chromatography on Kieselgel-60 (Art 9385) using benzene-AcOEt (97 : 3 v/v) as eluant to afford 220 mg [84 %, from (7a)] of the mixture of two stereoisomers (9a) (cis : trans = 1 : 1) as a colorless gum : $\lambda_{max.}$ (EtOH) 262 nm (ε 5000); IR $\nu_{max.}$ ($CHCl_3$) 1802 cm^{-1} (C=O); NMR δ ($CDCl_3$) 1.06 and 1.09 (each 3/2H, each t, each J = 7 Hz, CH_2-Me), 1.82 and 1.88 (each 1H, each q, each J = 7 Hz, -CH_2-Me), 2.26 and 2.29 (each 3/2H, each s, C_2-Me), 3.56 [1/2H, dt, J = 1 and 7 Hz, C_6-H (trans)], 3.79 [1/2, dt, J = 3 and 7 Hz, C_6-H (cis)], 3.8 (3H, s, OMe), 5.58 [1/2H, d, J = 1 Hz, C_5-H (trans)], 5.87 [1/2H, d, J = 3 Hz, C_5-H (cis)]; MS m/e 211 (M^+), 142 (M^+ - 69); m/e 211.0837 (M^+) [Calcd for $C_{10}H_{13}NO_4$ (M^+), m/e 211.0843]. (Anal. Calcd for $C_{10}H_{13}NO_4 \cdot H_2O$: C, 52.39; H, 6.60; N, 6.11.

Found: C, 52.45; H, 6.56; N, 5.74).

[B]. A mixture of the dichloride (10a) (15 mg) [prepared by the method either [A] or [B]] and sodium phenylthiolate (15 mg) in dry DMF (3 ml) was stirred for 15 min at 0°C under a current of nitrogen. The resulting mixture was diluted with benzene (30 ml). The organic layer was washed with 0.5 N phosphate buffer solution (pH = 7) (30 ml × 2), dried over Na_2SO_4 and evaporated. The resulting residue was purified as above to give 10.5 mg (94 %) of the oxapenem methyl ester (8a) as a mixture of two stereoisomers in the ratio of 1 : 1, whose spectral data and TLC behaviors were completely identical with those of the above sample prepared by the method [A].

p-Nitrobenzyl 6-Ethyl-2-methyl-1-oxapen-2-em-3-carboxylate (9b). —— [A]. To a stirred solution of the p-nitrobenzyl ester (7b) (50 ml) in dry CH_2Cl_2 (5 ml) was added a solution of Cl_2 (8.1 mg) in dry CCl_4 (0.2 ml) under the same conditions as above. The same work-up and purification procedures as above gave 41 mg (98.4 %) of the chloride (8b)(cis : trans = 1 : 2) as a colorless gum: IR $\nu_{max.}$ ($CHCl_3$) 1778 (C=O), 1520 and 1350 cm^{-1} (NO_2); NMR δ ($CDCl_3$) 1.04 (3H, t, J = 7 Hz, CH_2-Me), 1.68 (2H, m, -CH_2-Me), 2.2 (3H, s, C_3-Me), 3.37 (2/3H, dt, J = 1.5 and 7 Hz, C_3'-H (trans)], 3.39 [1/3H, dt, J = 4 and 7 Hz, C_3'-H (cis)], 5.39 [2/3H, d, J = 1.5 Hz, C_4'-H (trans)], 5.73 [1/3H, d, J = 4 Hz, C_4'-H (cis)], 7.53 and 8.26 (each 2H, each d, each J = 8 Hz, 4 × Ar-H), 12.13 (1H, br s, OH).

To a stirred solution of the above chloride (8b) (41 mg) in dry THF (5 ml) was added a solution of dry Et_3N (11.5 mg) in dry THF (2 ml) at 0°C under a current of nitrogen, and the reaction mixture was stirred for 10 min. The same work-up and purification procedures as previously gave 30 mg (79.9 %) of the oxapenem (9b) as a colorless gum, which was a mixture of inseparable two stereoisomers (cis : trans = 1 : 1): IR $\nu_{max.}$ ($CHCl_3$) 1800 and 1710 (C=O), 1355 cm^{-1} (NO_2); NMR δ ($CDCl_3$) 1.1 and 1.15 (each 3/2, each t, each J = 7 Hz, CH_2-Me), 1.82 and 1.88 (each 1H, each q, each J = 7 Hz, -CH_2-Me), 2.31 and 2.35 (each 3/2H, each s, C_2-Me), 3.58 [1/2H, dt, J = 1 and 7 Hz, C_6-H (trans)], 3.80 [1/2H, dt, J = 3 and 7 Hz, C_6-H (cis)], 5.23 and 5.57 (each 1H, each d, each J = 15 Hz, OCH_2Ar), 5.60 [1/2H, d, J = 1 Hz, C_5-H (trans)], 5.89 [1/2H, d, J = 3 Hz, C_5-H (cis)], 7.53 and 8.26 (each 2H, each d, each J = 8 Hz, 4 × Ar-H]; MS m/e 332 (M^+), 263 (M^+ - 69); m/e 332.1009 (M^+) [Calcd for $C_{16}H_{16}N_2O_6$ (M^+), m/e 332.1009]; (Anal. Calcd for $C_{16}H_{16}N_2O_6$: N, 8.43. Found: N, 8.48).

[B]. A mixture of the dichloride (10b) (9.5 mg) [prepared by the method either [A] or [B]] and sodium phenylthiolate (6.8 mg) in dry DMF (3 ml) was stirred for 15 min at 0°C under a current of nitrogen. The same work-up and purification procedures as above gave 6.7 mg (86 %) of the oxapenem (8b) as a mixture of two stereoisomers (cis : trans = 1 : 1), whose spectral data and TLC behaviors were completely identical with those of the above sample prepared by the method [A].

Methyl 2-Chloromethyl-6-ethyl-1-oxapen-2-em-3-carboxylate (9c). — To a stirred solution of the methyl ester (7c) (120 mg) in dry CH_2Cl_2 (10 ml) was added a solution of Cl_2 (10.4 mg) in dry CCl_4 (0.5 ml) under the above condition. The same work-up and purification procedures as previous afforded 94 mg (98.7 %) of the mixture of two stereoisomers (8c) (cis : trans = 1 : 1) as a colorless gum : IR $\nu_{max.}$ 1782 cm^{-1} (C=O); NMR δ ($CDCl_3$) 1.1 and 1.12 (each 3/2H, each t, each J = 7 Hz, CH_2-Me), 1.84 and 1.90 (each 1H, each q, each J = 7 Hz, CH_2-Me), 3.40 [1/2H, dt, J = 2.2 and 7 Hz, C_3'-H (trans)], 3.43 [1/2H, dt, J = 4.4 and 7 Hz, C_3'-H (cis)], 3.8 (3H, s, OMe), 4.17 and 4.20 (each 1H, each s, $-CH_2$-Cl), 5.43 [1/2H, d, J = 2.2 Hz, C_4'-H (trans)], 5.81 [1/2H, d, J = 4.4 Hz, C_4'-H (cis)], 12.28 (1H, br s, OH).

To a stirred solution of the above dichloride (8c) (94 mg) in dry THF (10 ml) was added a solution of dry Et_3N (34 mg) in dry THF (2 ml) under the same conditions as previous. The same work-up and purification procedures as above gave 63 mg (76 %) of the mixture of two stereoisomers (9c) (cis : trans = 1 : 1) as a colorless gum : IR $\nu_{max.}$ ($CHCl_3$) 1803 cm^{-1} (C=O); NMR δ ($CDCl_3$) 1.02 and 1.07 (each 3/2H, each t, each J = 7 Hz, CH_2-Me), 1.78 and 1.83 (each 1H, each q, each J = 7 Hz, CH_2-Me), 3.24 [1/2H, dt, J = 1 and 7 Hz, C_6-H (trans)], 3.44 [1/2H, dt, J = 3 and 7 Hz, C_6-H (cis)], 3.73 (3H, s, OMe), 4.23, 4.66, 4.31 and 4.69 (each 1/2H, each d, each J = 12.2 Hz, $-CH_2$-Cl), 5.60 [1/2H, d, J = 1 Hz, C_5-H (trans)], 5.82 [1/2H, d, J = 3 Hz, C_5-H (cis)]; MS(FD) m/e 247 (M^+ + 2), 245 (M^+).

P-Nitrobenzyl 2-Chloromethyl-6-ethyl-1-oxapen-2-em-3-carboxylate (9d). — To a stirred solution of the p-nitrobenzyl ester (7b) (111 mg) in dry CH_2Cl_2 (10 ml) was added a solution of Cl_2 (16.5 mg) in dry CCl_4 (0.2 ml) as previous. The same work-up and purification procedures as above gave 90.6 mg (96.5 %) of the mixture of two stereoisomers (8d) (cis : trans = 1 : 1) as a colorless gum : IR $\nu_{max.}$ ($CHCl_3$) 1782 (C=O), 1345 cm^{-1} (NO_2); NMR δ

($CDCl_3$) 1.13 (3H, t, J = 7 Hz, CH_2-Me), 1.74 (2H, m, -CH_2-Me), 3.39 (1H, m, C_3'-H) 4.56 (2H, s, -CH_2Cl), 5.31 (2H, s, OCH_2Ar), 5.37 [1/2H, d, J = 1.5 Hz, C_4'-H (trans)], 5.74 [1/2H, d, J = 4 Hz, C_4'-H (cis)], 7.46 and 8.15 (each 2H, each d, each J = 8 Hz, 4 × Ar-H), 12.1 (1H, br s, OH).

To a stirred solution of the above dichloride (8d) (90.6 mg) in dry THF (10 ml) was added a solution of dry Et_3N (23.6 mg) in dry THF (1 ml) under the same conditions as previous. The same work-up and purification procedures as above gave 53 mg (62.3 %) of the inseparable two stereoisomers (cis : trans = 1 : 1) of the oxapenem (9d) as a yellowish gum : IR $\nu_{max.}$ ($CHCl_3$) 1805 (C=O), 1345 cm^{-1} (NO_2); NMR δ ($CDCl_3$) 1.02 (3H, t, J = 7 Hz, CH_2-Me), 1.82 (2H, m, -CH_2-Me), 4.41 and 4.71, 4.45 and 4.73 (each 1/2H, each d, each J = 13 Hz, -CH_2-Cl), 5.75 [1/2H, d, J = 1 Hz, C_5-H (cis)], 7.58 and 8.20 (each 2H, each d, each J = 8 Hz, 4 × Ar-H).

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REFERENCES AND NOTES

1 R. D. G. Cooper, in 'Topics in Antibiotic Chemistry' vol. 3, ed. P. G. Sammes, Ellis Horwood Ltd., Chichester, England, 1980, pp. 39 - 199.

2 Isolation: T. T. Howarth, A. G. Brown, and T. J. King, J. Chem. Soc. Chem. Commun. 1976, 266. Synthesis: P. H. Bentley, P. D. Berry, G. Brooks, M. L. Gilpin, E. Hunt, and I. I. Zomaya, J. Chem. Soc. Chem. Commun. 1977, 748.

3 (a) M. Narisada, T. Yoshida, H. Onoue, M. Ohtani, T. Okada, T. Tsuji, I. Kikkawa, N. Haga, H. Satoh, H. Itani, and W. Nagata, J. Med. Chem. 22, 757 (1979); Y. Hamashima, H. Matsumura, S. Matsuura, W. Nagata, M. Narisada, and T. Yoshida, in 'Recent Advances in the Chemistry of β-Lactam Antibiotics' ed. G. I. Gregory, The Royal Society of Chemistry, London, 1981, pp. 57 - 79.

4 (a) A. J. Eglington, J. Chem. Soc. Chem. Commun. 1977, 720. (b) P. H. Bentley, G. Brooks, M. L. Gilpin, and E. Hunt, ibid. 1977, 905. (c) G. Brooks, T. T. Howarth, and E. Hunt, ibid. 1981, 642.

5 P. C. Cherry, G. I. Gregory, C. E. Newall, P. Ward, and N. S. Watson, J. Chem. Soc. Chem. Commum. 1978, 467; P. C. Cherry, C. Newall, and N. S. Watson, ibid. 1978, 469.

6 G. Johnson, B. C. Ross, and M. A. Yeomans, in 'Recent Advances in the Chemistry of β-Lactam Antibiotics', ed. G. I. Gregory, The Royal Society of Chemistry, London, 1981, pp. 170 - 174.

7 M. Lang, K. Prasad, W. Holick, J. Gosteli, I. Ernest, and R. B. Woodward, J. Am. Chem. Soc. 101, 6296 (1979); H. R. Pfaendler, J. Gosteli, R. B. Woodward, and G. Rihs, J. Am. Chem. Soc. 103, 4526 (1981).

8 T. Kametani, T. Honda, A. Nakayama, Y. Sakai, T. Mochizuki, and K. Fukumoto, J. Chem. Soc. Perkin Trans 1 1981, 2228.

9 K. Clauss, D. Grimm, and G. Prossel, Annalen 1974, 539.

10 E. J. Corey and C. U. Kim, J. Am. Chem. Soc. 94, 7586 (1972).

11 H. Hoffmann and H. J. Diehr, Angew. Chem. Internat. Ed. 3, 145 (1964).