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Synthesis of Oxapenam Derivatives by Silver Induced Cyclization

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The chloro-β-lactam derivatives (VII and XIIIa,b,c) were prepared from the readily available 4-acetoxy-2-azetidinone (III) in four steps. Silver triflate treatment of these chloro β-lactam derivatives in the presence of NaH gave the oxapenam derivatives (VIII and XIVa,b,c) in 3.5—11.6% yield after careful chromatography separation. Preliminary biological activities of natural and synthesized oxapenam derivatives are listed.

Keywords——β-lactam derivative; oxapenam derivative; silver induced cyclization; azetidinone; carbanion formation

In 1976 Beecham group chemists and T.J. King reported the isolation and structure determination of clavulanic acid (Ia).[2] Clavulanic acid has the so-called oxapenam skeleton and is a potent irreversible inhibitor of various β-lactamases. This interesting pharmacological property and novel fused β-lactam ring system were of great interest to those of us concerned with the synthetic study of β-lactam antibiotics. The present report describes a study directed towards the synthesis of the oxapenam skeleton utilizing the readily available 4-acetoxy-2-azetidinone (III).[3]

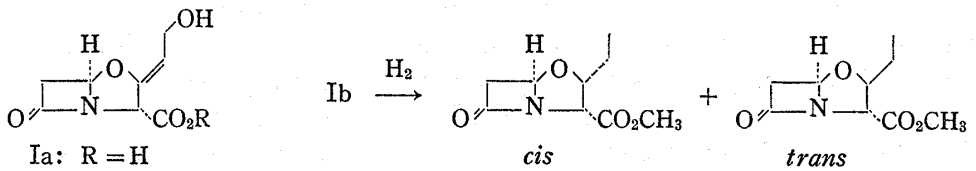


Chart 1

To form the oxapenam skeleton, we chose a Ag^+-induced cyclization (intramolecular Koenigs-Knorr reaction) originally developed by Merck chemists,[4] which served as the key step in our synthesis of clavulanic acid analogues. Our starting material was the known 4-acetoxy-2-azetidinone (III)(Chart 2). Compound III was converted into the crystalline methylthio analogue (IV), mp 63—64° by treating with sodium methylmercaptide in ethanol. The structure of IV was fully assigned by nuclear magnetic resonance (NMR) decoupling experiments. The geminal coupling constant of the methylene group at the C-3 position was 16 Hz. The C-3αH was coupled with the C-4H with a coupling constant of 5.0 Hz, and the C-3βH was coupled with the C-4H with a coupling constant of 2.7 Hz. Both the α-H and β-H were further coupled with the proton of the NH group with coupling constants of 1.2 and 1.8 Hz, respectively. On the other hand, the C-4H appeared as a pair of doublets (d.d.) at δ 4.8 (J=5 and 2.7 Hz) and, interestingly, no coupling was observed with the proton from the NH group. Condensation of IV with methyl bromoacetate was tried with NaH in dimethylformamide (DMF) and tetrahydrofuran (THF) (1: 1 v/v) at temperatures between −70° and 0° to give V, but the yield was variable depending on the reaction conditions.

1) Location: *1-2-58, Hiromachi, Shinagawa-ku, Tokyo 140, Japan.*
2) T.T. Howarth, A.G. Brown, and T.J. King, *Chem. Commun.*, **1976**, 266.
3) K. Klauß, D. Grimm, and G. Prossel, *Ann.*, **1974**, 539.
4) L.D. Cama and B.G. Christensen, *J. Am. Chem. Soc.*, **96**, 7582 (1974).

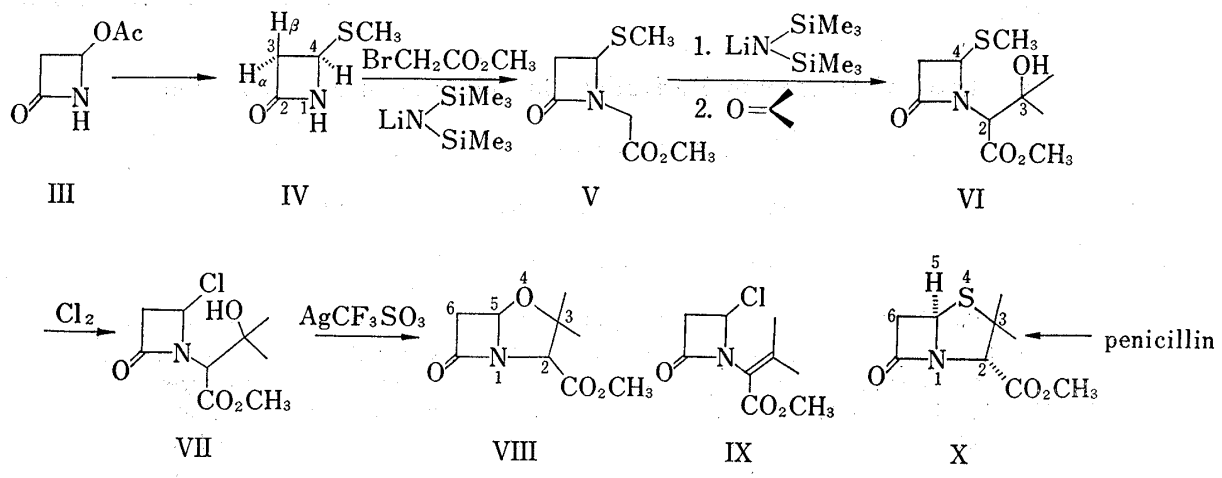
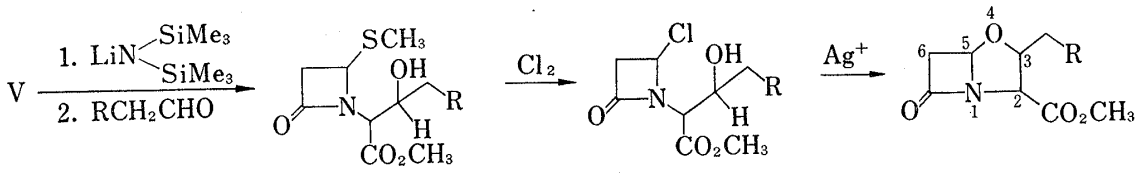


Chart 2

Occasionally, uncharacterised by-products were detected on thin-layer chromatography (TLC) analysis. To improve results, lithium disilazane was used as base in THF at −78°, which afforded a cleaner reaction, yielding the desired product (V) in 75.2% yield. Compound V showed an infrared (IR) absorption hand at 1770 cm^{-1} (β-lactam), and in the NMR the newly introduced $-C\underline{H}_2CO_2Me$ group appeared as a well-defined AB quartet (J= 18 Hz) at 3.74 and 4.24 ppm. As a suitable compound for the cyclization, we first tried to obtain the carbinol VI. For this purpose carbanion formation at $NC\underline{H}_2CO_2Me$ of V was attempted, and successfully achieved by means of lithium disilazane at −78° in THF.[5] The carbanion thus generated attacked the acetone molecule to give the desired carbinol VI in 83.6% yield.[6] Compound VI has two asymmetric centers at position 2 and 4′, and TLC showed clearly two spots as expected. The NMR showed the dimethyl group at 1.2—1.5 ppm and $NC\underline{H}CO_2$ at 3.95 as a singlet. Furthermore the characteristic signal of C-4′H appeared as a d.d. at 4.72 (1/4 H) and 4.90 (3/4 H), and from the area of these signals the ratio of the diastereoisomers was shown to be 3: 1. In an effort to introduce a Cl-substituent at C-4′ of the β-lactam ring system, without resorting to trimethylsilyl protection of the hydroxy group, an attempt was made to directly exchange the SCH_3 group with a Cl group. Thus, without separating the diastereoisomers we treated compound VI with Cl_2 gas in carbon tetrachloride to successfully yield the expected Cl-derivative (VII). Compound VII was rather unstable, however. The NMR showed the signal from the $SC\underline{H}_3$ group of VI (δ 2.2) to have disappeared and the characteristic downfield shift of C-4′H from 4.72 and 4.90 (in VI) to 5.68 and 5.85 (in VII) was observed. This type of the downfield shift is general observed in compounds having SCH_3 groups changed to Cl groups. The next step was the key cyclization step. First we tried to treat VII with only silver triflate ($AgCF_3SO_3$) in THF; However, no trace of the cyclized compound (VIII) could be detected on TLC or NMR. Because of the instability of the Cl derivative (VII) towards acid we used triethylamine to exclude the strong acid (CF_3SO_3H) generated from silver reagent in this important cyclization step. The unstable Cl derivative (VII) was dissolved in THF and one equivalent amount of triethylamine was added to the solution. The addition of $AgCF_3SO_3$ then gave the expected oxapenam derivative VIII in 9.19% yield after careful column chromatography separation [Method A]. During this cyclization study we found that it was necessary to use freshly prepared Cl_2 gas

5) R.F. Borch, *Tetrahedron Lett.*, **1972**, 3761.
6) This type of carbinol formation reaction was first done by Drs. S. Oida and A. Yoshida of these laboratories using methyl 2-(4′-phenylthio-2′-oxo-azetidinyl)acetate. We are very grateful for their kind presentation of the procedure and useful discussion throughout this work.

in CCl_4 solution, otherwise the dehydrated product IX (NMR ($CDCl_3$) δ: 2.01 and 2.28 (6H, s.), 3.27 (1H, d.d., J=15.5 and 2 Hz, C-3βH), 3.62 (1H, d.d., J=15.5 and 4 Hz, C-3αH), 3.77 (3H, s.), 5.90 (1H, d.d., J=4 and 2 Hz, C-4 H)) was obtained. Furthermore in order to suppress this undesirable side reaction and increase the yield of the oxapenam derivative without resorting to the complex procedures involved in method A, we took advantage of NaH to facilitate the cyclization at 0° [Method B]. The structure of VIII was confirmed by physicochemical data. The CO maximum absorption of the β-lactam group appeared at 1790 cm^{-1} in the IR. The NMR spectrum is very similar to that of the sulfur analogue (X) derived from penicillin.[7] However a very characteristic difference is the signal patterns of the C-5H and the C-6 CH_2 between VIII and X. Compound VIII showed a C-5H signal at 5.47 ppm as a d.d. (J=3 and 0.5 Hz), and the C-6 βH at 3.32 as a d.d. (J=17 and 0.5 Hz), and the C-6 αH at 2.93 as a d.d. (J=17 and 3 Hz). On the other hand compound X showed a C-5H signal at 5.31 as a d.d. (J=4 and 1.5 Hz), the C-6 αH at 3.58 as a d.d. (J=16 and 1.5 Hz) and C-6βH at 3.05 as a d.d. (J=16 and 4 Hz). Furthermore, from the chemical shift of the C-2H (δ 4.27), the relative configuration of the C-2H and C-5H was thought to be *trans* (more stable) to each other as in the natural penicillin derivative (δ 4.49).[8]



XI a, b, c XII a, b, c XIII a, b, c XIV a, b, c

a : R=CH_3, b : R=$OCH_2C_6H_5$, C : R=$CH_2OCH_2C_6H_5$

Chart 3

Next we applied this synthetic method to the other type of oxapenam derivatives (XIVa, b, c)(Chart 3). By an analogous method the carbinol derivatives (XIIa, b, c) were synthesised from an appropriate aldehyde (XIa, b, c) *via* the carbanion intermediate (Chart 3). Each of the carbinols (XIIa, b, c) showed a mixture of four isomers on TLC analysis, as was expected. Without separation of the mixture, the carbinols (XIIa, b, c) were further treated with freshly prepared Cl_2 in CCl_4, and the resulting unstable products (Cl-derivatives) were treated successively with NaH and $AgCF_3SO_3$ in THF at 0°. After careful column chromatographic separation each product (XIVa, b, c) was obtained in 3.5—9% yield from XII. The precise NMR study showed clearly that every cyclized product (XIVa, b, c) was a mixture of the two diastereomeric isomers. In the case of XIVa the ratio of the isomers was 1: 2. An attempt to separate the isomers was unsuccessful. However the precise comparison of the NMR of the product (XIVa) and the dihydrodeoxy derivative (II) derived from natural methyl clavulanate (Ib) revealed that these two were identical. Interestingly, the dihydrodeoxy derivative (II) was also a mixture of *cis* and *trans* forms (1: 2)[9](Chart 1). The C-5H proton signals in both II and XIVa appeared at δ 5.38 (2/3 H, d.d., J=3 and 0.5 Hz, *trans*) and 5.58 (1/3 H, d.d., J=3 and 1 Hz, *cis*). In the case of XIVb only the *trans* isomer was isolated (see experimental part), and after debenzylation of XIVb over Pd-black purification on the silica gel TLC gave the bicyclo-[4.2.1] derivative XVI (69.9% from XIVb)[10](Chart 4). This result gave additional support for the *trans* relationship between C-5H and C-3 CH_2OH

7) J.P. Clayton, *J. Chem. Soc.*, **1969**, 2123.
8) R.G. Alexander and R. Southgate, *Chem. Commun.*, **1977**, 405.
9) A. Terahara, M. Nakajima, Y. Itoh, Y. Fukazawa, and M. Arai, Private Communication.
10) Analogous reaction was reported in the cephalosporin series: G.E. Gutowski, C.M. Daniels, and R.D.G. Cooper, *Tetrahedron Lett.*, **1971**, 3429.

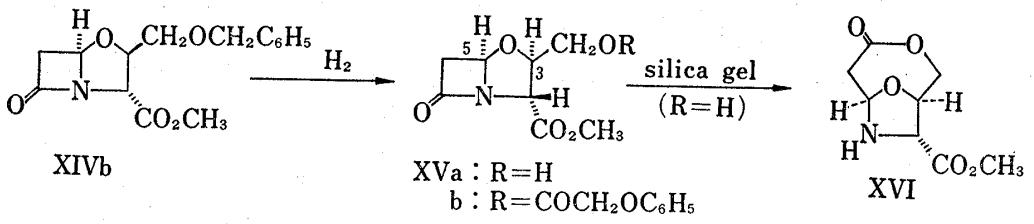


Chart 4

and was coincident with the previous observation reported by Oida *et al.*[11] The above mentioned results show that in an oxapenam ring system synthesized *via* silver induced cyclization the ring closure occurred to give the more stable compound, *i.e.* C-2Hand C-5H are oriented *trans* to each other, and at the mechanistic level the formation of the two isomers may be attributed to the difference in ease with which the cyclization occurs among the four isomers in the Cl derivative (XIII).

The preliminary results of the antimicrobial activity and the β-lactamase inhibitor activity of some of the natural and synthesized oxapenam derivatives are listed in the Table I and II.

Table I. Antimicrobial Activity (Paper disc-plate method)/disc

	I 1000 μg	VIII 2000 μg	10% horse serum added 2000 μg	XIVa 2000 μg	10% horse serum added 2000 μg
Staphylococcus aureus FDA 209P JC-1	21.6 mm	9.5 mm	13.3 mm	12.8 mm	23.8 mm
Klebsiella pneumoniae PCI 602	17.2	——	——	12.6	25.4
Pseudomonas aeruginosa SANK 73860	27.5	——	——	0	0
Bacillus subtilis PCI 219	24.1	12.6	12.6	13.2	14.1

Table II. β-Lactamase Inhibitor Activity of *Escherichia coli* 609

Clavulanic acid (Ia)			Ib	VIII	XIVa
0.1	g/ml	48.3%	2.1%	6.2%	5.2%
10	g/ml	95.4%	9.6%	13.5%	11.0%

Experimental

General——All melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer Model 137 spectrometer. NMR spectra were taken using a Hitachi R-24 spectrometer (60 MHz) and the chemical shifts were expressed in ppm unit using tetramethylsilane (TMS) as the internal standard; s., singlet; d., doublet; t., triplet; q., quartet; d.d., pair of doublets; m., multiplet. Mass spectra (MS) were measured on a JEOL: 01SG mass spectrometer. (Preparative) TLC were carried out on Merck TLC-plates silica gel F_{254} Pre-coated, layer thickness: (2 mm) 0.25 mm and spots were visualized by ultraviolet-irradiation or by spraying with vanadic acid–sulfuric acid or molybdatophosphoric acid followed by heating or exposing with iodine. Columns for ordinary chromatography were prepared with Silica Gel, for Chromatography, 60—80 mesh (KANTO Chemical Co., INC).

4-Methylthio-2-azetidinone (IV)——To a solution of 12 g of 4-acetoxy-2-azetidinone (III) in 100 ml of ethanol was added 43.2 ml of 2.16 N ethanolic CH_3SNa solution under ice cooling and the whole mixture was stirred for 2 hours. Ethyl acetate was added and the solution was washed with small amount of aq. NaCl solution and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave 9.7 g of the title compound as crystals. Yield 90%, Rf=0.5 (benzene: AcOEt=2: 1). mp 64—66° (recrystallized from

11) S. Oida, A. Yoshida, and E. Ohki, *Chem. Pharm. Bull.* (Tokyo), **26**, 448 (1978).

$CHCl_3$–isopropyl ether). IR ν_{max}^{Nujol} 3300, 3775, 1780, 1730 cm^{-1}. NMR ($CDCl_3$) δ: 2.15 ($SC\underline{H}_3$, s.), 2.97 (1H, d.d.d., $J=16$, 2.7 and 1.2 Hz), 3.38 (1H, d.d.d., $J=16$, 5 and 1.8 Hz), 4.80 (1H, d.d., $J=5$ and 2.7 Hz), 7.1—7.5 (1H, N$\underline{H}$, m.). *Anal.* Calcd. for C_4H_7NOS: C, 41.00; H, 6.03; N, 11.96; S, 27.36. Found: C, 40.96; H, 5.93; N, 11.84, S, 27.40.

4-Methylthio-N-methoxycarbonylmethyl-2-azetidinone (V)——To a solution of 8.9 ml of hexamethyldisilazane in 80 ml of ab. ether was added 32.4 ml of *n*-BuLi solution (1.62 mmol in *n*-hexane solution) at 0° and the mixture was refluxed gently for one hour, and then the solution was cooled to −78°. 100 ml of dry THF and 5.8 g of 4-methyltio-2-azetidinone (II) in 50 ml THF solution were added successively. Stirring was continued for one hour at −78° and then 11.5 ml of methyl bromoacetate was added and stirring was continued further thirty minutes at the same temperature. The temperature was gradually raised to 0° during 1.5 hours and ethyl acetate was added. The solution was washed with aq. NaCl solution twice and dried over $MgSO_4$. After removal of the solvent the crude product were separated on silica-gel column chromatograph, and from the elution part of benzene: ethyl acetate=10: 1—5: 1 7.1 g of the title compound was obtained as oil. Rf=0.65 (benzene: ethyl acetate=2: 1), yield 75.2%. IR $\nu_{max}^{liq.}$ 1770, 1742, 1220 cm^{-1}. NMR ($CDCl_3$) δ: 2.04 ($SC\underline{H}_3$, s.), 3.05 (1H, d.d., $J=16$ and 2.8 Hz), 3.37 (1H, d.d., $J=16$ and 5 Hz), 3.74 and 4.24 (2H, AB type q., $J=18$ Hz), 3.76 ($OC\underline{H}_3$, s.), 4.94 (1H, d.d., $J=5$ and 2.8 Hz). *Anal.* Calcd. for $C_7H_{11}NO_3S$: C, 44.43; H, 5.86; N, 7.41; S, 16.94. Found: C, 44.56; H, 5.95; N, 7.32; S, 16.96.

Methyl 3-Hydroxy-2-(4′-methylthio-2′-azetidinyl)isovalerate (VI)——To a solution of 7.75 ml hexamethyldisilazane in 80 ml dry ether was added 27.2 ml *n*-BuLi solution (1.62 mmol/ml in *n*-hexane) with ice-cooling in argon atmosphere. After gentle refluxing for one hour the mixture was cooled to −78° and 100 ml of THF was added to dissolve the lithium hexamethyldisilazanate formed. To the solution was added 7.57 g of azetidinone derivative (V) in 50 ml THF solution. After one hour stirring at −78° 9.0 ml of acetone was added and the whole mixture was stirred for additional one hour at the same temperature. The reaction temperature was rised to −60° and then cooled to −78° again. Acetic acid (2.6 ml), ethyl acetate and water were added successively at the same temperature. The aqueous layer was extracted twice with ethyl acetate and the organic layer was washed with water, aq. sat. $NaHCO_3$ and aq. sat. NaCl successively. After drying over $MgSO_4$ the solvent was evaporated under reduced pressure. The residual oil was purified on silica gel column chromatograph (benzene: ethyl acetate=2: 1) to give 8.27 g of the title compound. Yield 83.6%. IR $\nu_{max}^{CHCl_3}$ 3400 (OH), 1765 (β-lactam), 1745 (ester). NMR ($CDCl_3$), δ: 1.2—1.5 (6H, $C(C\underline{H}_3)_2$), 2.0—2.3 (3H, $SC\underline{H}_3$), 3.17 (1H, d.d., $J=15$ and 3.5 Hz, 3′β-H), 3.40 (1H, d.d., $J=15$ and 5 Hz, 3′α-H), 3.83 (3H, s, $CO_2C\underline{H}_3$), 3.95 (1H, s), 4.0—4.4 (1H, br, s., O$\underline{H}$), 4.72 (1/4H) and 4.90 (3/4H) (each, d.d., $J=5$ and 3.5 Hz, 4′-H). By the same procedure the other β-lactam derivatives (XIVa,b,c) were prepared using propyl aldehyde (XIa), 2-benzyloxyacetaldehyde (XIb), and 2-benzyloxy propylaldehyde (XIc) respectively.

Methyl 3-Hydroxy-2-(4′-methylthio-2′-oxo-azetidinyl)valerate (XIIa)——Yield 79%. NMR ($CDCl_3$), δ: 0.97 (3H, d, $J=7$), 1.4—1.8 (2H, m, $C\underline{H}_2CH_3$), 2.0—2.2 (3H, $SC\underline{H}_3$), 3.10 (1H, d.d., $J=16$ and 2.5 Hz, 3′β-H), 3.35 (1/2H) and 3.38 (1/2H), (each d.d., $J=16$ and 5 Hz, 3′-α-H), 3.77 (3H, s., $CO_2C\underline{H}_3$), 3.8—4.2 (3H, m, –C$\underline{H}$–C$\underline{H}$–O$\underline{H}$), 4.58—4.75 (1/2H) and 4.80—4.98 (1/2H) (4′-H).

Methyl 4-Benzyloxy-3-hydroxy-2-(4′-methylthio-2′-oxo-azetidinyl)butyrate (XIIb)——Purification on column chromatography was not enough, however the contaminated 2-benzyloxy acetaldehyde was successfully removed under reduced pressure (0.05 mmHg) at 85°. Yield 55.76%. NMR ($CDCl_3$) δ: 1.9—2.2 (3H, SCH_3), 2.70—3.12 (1H, d.d., $J=15$ and 3 Hz, 3′β-H), 3.17—3.53 (1H, d.d., $J=15$ and 3 Hz, 3′α-H), 3.4—3.8 (2H, –C$\underline{H}_2$–O), 3.70 (3H, s., $CO_2C\underline{H}_3$), 4.0—4.7 (3H), 4.55 (2H, s., $C\underline{H}_2C_6H_5$), 4.63—4.95 (1H, d.d., $J=5$ and 3 Hz, 4′-H), 7.33 (5H, s, C_6H_5).

Methyl 3-Hydroxy-4-benzyloxy-2-(4′-methylthio-2′-oxo-azetidinyl)valerate (XIIc)——Yield 90%. NMR ($CDCl_3$) δ: 1.9—2.1 (5H, $SC\underline{H}_3$ and CH_2), 3.0—3.4 (2H), 3.5—4.45 (5H), 3.77 ($CO_2C\underline{H}_3$), 4.51 (–$OC\underline{H}_2$), 4.2—5.0 (1H), 7.3—7.6 ($C_6\underline{H}_5$).

Methyl 2-(4′-Chloro-2′-oxo-azetidinyl)-3-hydroxy-isovalerate (VII)——To a solution of 502.8 mg of methyl 3-hydroxy-2-(4′-methylthio-2′-oxo-azetidinyl)-iso-valerate (VI) in 30 ml of carbon tetrachloride was added 5 ml of Cl_2–CCl_4 solution (28 g Cl_2 in 300 ml CCl_4) under ice-cooling. Stirring was continued for 15 min at r.t. The excess Cl_2 and carbon tetrachloride were evaporated under reduced pressure (5 mmHg) and to the residue was added 20 ml of benzene and the solvent was removed also under reduced pressure. This azeotropic procedure was repeated three times more to give 500.3 mg transparent methyl 2-(4′-chloro-2′-oxo-azetidinyl)-3-hydroxy-iso-valerate (VII). IR $\nu_{max}^{CHCl_3}$ 3450 (OH), 1770 (β-lactam), 1740 cm^{-1} (ester). NMR ($CDCl_3$) δ: 1.2—1.5 (6H, $C(C\underline{H}_3)_2$), 3.23 (1/3H) and 3.28 (2/3H) (each, d.d., $J=16$ and 2 Hz, 3′β-H), 3.60 (1H, d.d., $J=16$ and $J=4.5$ Hz, 3′α-H), 3.78 (3H, s., $CO_2C\underline{H}_3$), 3.90 (1/3H) and 4.02 (2/3H) (each, br. s., C$\underline{H}$-CO_2), 4.0—4.4 (1H, O$\underline{H}$), 5.68 (2/3H) and 5.85 (1/3) (each, d.d., $J=4.5$ and 4.2, 4′-H). By the same procedure the following chloro-β-lactam derivatives (XIIIa—c) were prepared.

Methyl 2-(4′-Chloro-2′-oxo-azetidinyl)-3-hydroxy-valerate (XIIIa)——Oily, NMR ($CDCl_3$) δ: 1.00 (3H, d, $J=7$ Hz), 1.3—1.9 (2H, m, $C\underline{H}_2CH_3$), 3.00—3.37 (1H, $J=16$ Hz, 3′β-H), 3.45—3.87 (1H, $J=16$ Hz, 3′α-H), 3.7—4.3 (3H, m), 3.78 (3H, s., $CO_2C\underline{H}_3$), 5.50—5.65 and 5.75—5.92 (1H, 4′-H).

2-Benzyloxypropionaldehyde (XIb)——To a solution of 40 g of benzyl alcohol and 0.2 ml of 50% aq. NaOH was added 11.2 g of acrolein at −2—10° during 40 min. Stirring was continued further 10 min at −5°, and then at 0° a mixture of 0.5 ml of acetic acid and 0.056 ml of conc. phosphoric acid were added. The

whole mixture was distilled directly at 7 mmHg. After distillation of benzyl alcohol 9 g of the crude title compound was obtained at 120—130°/7 mmHg. Redistillation gave 7 g of the title compound as transparent oil. bp 128°/7 mm. IR $\nu_{max}^{liq.}$ 2720, 1719 cm^{-1}. NMR ($CDCl_3$) δ: 2.54 (1H, d.t., J=6 and 2 Hz), 3.74 (2H, t, J=6 Hz), 4.49 (2H, s.), 9.82 (1H, t, J=2 Hz).

Methyl 4-Benzyloxy-3-hydroxy-2-(4′-chloro-2′-oxo-azetidinyl)butyrate (XIIIb)——Oiry, NMR ($CDCl_3$) δ: 2.98—3.32 (1H, 3′β-H), 3.37—3.80 (1H, 3′α-H), 3.6—3.8 (2H, m, C-C$\underline{H}_2$–O), 3.70 (3H, s, $CO_2C\underline{H}_3$), 4.0—4.7 (3H, m), 4.57 (2H, s., $OC\underline{H}_2C_6H_5$), 5.55—5.67 (1/2H) and 5.75—5.87 (1/2H) (each, 4′-H), 7.35 (5H, s., $C_6\underline{H}_5$).

Methyl2-(4′-Chloro-2′-oxo-azetidinyl)-3-hydroxy-5-benzyloxyvalerate (XIIIc)——Oily, NMR ($CDCl_3$) δ: 1.7—2.1 (2H, m), 2.8—3.7 (3H), 3.66 ($CO_2C\underline{H}_3$, 3H, s.), 3.9—44. (2H), 4.44 (2H, s., $OC\underline{H}_2C_6H_5$), 5.40—5.57 and 5.58—5.80 (1H, 4′-H, ratio 1:1).

General procedure for the formation of the oxapenam-derivatives (VIII and XIVa,b,c) from the chloro-β-lactams (VII and XIIIa,b,c).

Representative Example

Methyl 3,3-Dimethyl-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptan-2-carboxylate (VIII)——[Method A: Et_3N Method]: To a solution of 937 mg of silver trifluoromethanesulfonate in 10 ml of THF was added dropwise a solution of 0.2 ml of triethylamine in 5 ml THF at −78° to prepare silver trifluoromethanesulfonate–triethylamine solution. This solution was added by syringe to the solution of 428.7 mg of Cl β-lactam (VII) in 20 ml THF at 0°. Precipitation of AgCl was observed immediately. After vigorous stirring for 30 min benzene and NaCl saturated phosphate buffer (pH 6.86) were added successively with vigorous stirring. The reaction mixture was filtered and the aqueous layer was extracted with benzene. The combined benzene extract was washed with saturated NaCl solution well and dried over $MgSO_4$. Evaporation of the solvent *in vacuo* gave residue, which was carefully separated on silica gel column chromatography (benzene: ethyl acetate=5:1) to afford 32.3 mg (9.19%) of the desired methyl 3,3-dimethyl-7-oxo-4-oxa-1-azabicyclo[3.2.0]-heptane-2-carboxylate (VIII).

[Method B: NaH Method]: To a solution of Cl β-lactam (VII) which was prepared from 505.5 mg of SCH_3 β-lactam (VI) in 25 ml THF was added 70.7 mg of 50% NaH directly at 0°. After stirring for 5 min a solution of 637 mg silver trifluoromethane sulfonate in 5 ml THF was added dropwise to precipitate AgCl immediately. After vigorous stirring for 20 min benzene and NaCl saturated phosphate buffer (pH 6.86) were added successively with vigorous stirring. The reaction mixture was filtered and the aqueous layer was extracted with benzene. The combined benzene extract was washed with saturated NaCl solution well and dried over $MgSO_4$. Evaporation of the solvent *in vacuo* gave residue, which was carefully separated on silica gel column chromatography (benzene: ethyl acetate=5:1) to afford 47.4 mg (11.6%) of the desired title compound (VIII). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1790 (β-lactam), 1750 (ester). NMR ($CDCl_3$) δ: 1.30 and 1.55 (6H, s., $C(C\underline{H}_3)_2$) 2.93 (1H, d.d., J=17 and 0.5 Hz, 6β-H), 3.32 (1H, d.d., J=17 and 3 Hz, 6α-H), 3.77 (3H, s., $CO_2C\underline{H}_3$), 4.27 (1H, s., $C\underline{H}CO_2$), 5.47 (1H, d.d., J=3 and 0.5 Hz, 5-H). MS *m/e*: 199 (M^+). *Anal.* Calcd. for $C_9H_{13}NO_4$: C, 54.26; H, 6.58; N, 7.03. Found: C, 54.38; H, 6.65; N, 6.78.

By the method B the following oxa-penam derivatives (XIVa,b,c) were prepared similarly from the corresponding Cl β-lactam derivatives (XIIIa,b,c).

Methyl 3-Ethyl-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptan-2-carboxylate (XIVa)——Yield 9.11%, oily. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1790 (β-lactam), 1745 (ester). NMR ($CDCl_3$) δ: 1.02 (3H, d, J=7 Hz), 1.42—2.0 (2H, m, –C$\underline{H}_2$-CH_3), 2.92 (1H, d.d., J=16.5 and 0.5 Hz, 6β-H), 3.30 (2/3H) and 3.35 (1/3H) (each, d.d., J=16.5 and 3 Hz, 6α-H), 3.75 (1/3H) and 3.77 (2/3H) (3H, s., $CO_2C\underline{H}_3$), 4.1—4.8 (2H, m), 5.38 (2/3H) and 5.58 (1/3H) (each, d.d., J=3 and 0.5 Hz, 5-H). MS *m/e*: 199 (M^+). *Anal.* Calcd. for $C_9H_{13}NO_4$: C, 54.26, H, 6.58; N, 7.03. Found: C, 53.82, H, 6.80; N, 6.66.

Methyl 3-Benzyloxymethyl-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptan-2-carboxylate (XIVb)——Yield 8.37%, oily. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1790 (β-lactam), 1750 (ester). NMR ($CDCl_3$) δ: 2.95 (1H, d, J=16 Hz, 6β-H), 3.28 (1H, d.d., J=16 and 3 Hz, 6α-H), 3.6—3.8 (2H, C–C$\underline{H}_2$–O), 3.74 (3H, s., $CO_2C\underline{H}_3$), 4.4—4.6 (2H, m), 4.57 (2H, s., O–C$\underline{H}_2C_6H_5$), 5.36 (1H, d., J=3 Hz, 5-H), 7.32 (5H, s, $C_6\underline{H}_5$). MS *m/e*: 291 (M^+).

Methyl 2-(2-Benzyloxy)ethyl-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptan-2-carboxylate (XIVc)——Yield 3.2 %. NMR ($CDCl_3$) δ: 1.5—2.25 (2H), 2.86 (1H, br.d., J=16 Hz), 3.15—3.5 (1H), 3.62 (t, J=6 Hz), 3.72 (–$OC\underline{H}_3$), 4.2—4.75 (2H), 4.50 and 4.52 (–$OC\underline{H}_2C_6H_5$), 5.32 (1/2H, J=2.7 Hz), 5.54 (1/2H, J=4.5 and 1 Hz).

Methyl 2-Hydroxymethyl-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptan-2-carboxylate (XVa) and Its Phenoxy-acetate (XVb)——To the solution of 163.6 mg of above obtained benzyl ester (XIVb) in 50 ml of ethanol–ethyl acetate (1:1) was added 4 ml volume of Raney-nickel (NDT-90 from KAWAKEN fine chemicals), and the mixture was stirred for 4 hr at r.t. After removal of the Raney-nickel the solvent was removed *in vacuo* and to the residue was added 20 ml of the same solvent and freshly prepared Pd-black (2 ml volume) successively. The hydrogenolysis was performed in the Parr apparatus at 40 lb/in^2 for 5 hr, and then the same amount of Pd-black was added and the mixture was further stirred for 16 hr. The catalysts were filtered and the filtrate was condensed *in vacuo* to give the oily title compound. NMR ($CDCl_3$) δ: 3.08 (1H, d, J=16.5 Hz, 6β-H), 3.30 (1H, d.d., J=16.5 and 3 Hz, 6α-H), 3.5—4.8 (5H, m), 3.77 (3H, s., $CO_2C\underline{H}_3$), 5.45 (1H, d., J=3 Hz, 5-H).

Phenoxyacetate (XVb)——Above obtained carbinol (XVa) was dissolved in 10 ml of methylene chloride, and to the solution was added 66 mg of dicyclohexylcarbodiimide (DCC) and 44 mg of phenoxyacetic acid

under ice-cooling. After stirring for 5 hours under ice-cooling 177 mg of DCC and 132 mg of phenoxyacetic acid were added and the whole mixture was stirred for 16 hr. To the reaction mixture was added 0.1 ml of pyridine and the whole mixture was stirred for 3 hr. The insoluble part was filtered and the filtrate was condensed *in vacuo*. The crude product was purified on the silica gel column chromatography (benzene: ethyl acetate =5: 1) to afford 57.5 mg of the phenoxyacetate (XVb). Yield 33.9% from XVa. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1800 (β-lactam), 1760 (ester). NMR ($CDCl_3$) δ: 2.97 (1H, d., J=16.5 Hz, 6β-H), 3.33 (1H, d.d., J= 16.5 and 3 Hz, 6α-H), 3.80 (3H, s., $CO_2C\underline{H}_3$) 4.4—4.9 (3H, m), 4.70 (2H, s., $C\underline{H}_2OC_6H_5$), 5.47 (1H, d., J=3 Hz, 5-H), 6.9—7.5 (5H, m, $C_6\underline{H}_5$). MS *m/e*: 335 (M^+).

Methyl 3,9-Dioxa-4-oxo-7-azabicyclo[4.2.1]nonan-8-carboxylate (XVI)——After hydrogenolysis the crude carbinol (XVa) was subjected to the silica gel preparative TLC (benzene: ethyl acetate=2: 1) to give crystalline title compound in 69.9% from the benzyloxy derivative (XIVb). mp 155—156° (recrystallized from ethyl acetate and *n*-hexane). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1760 (CO). NMR (CD_3CN) δ: 2.88 (1H, d.d., J=12 and 1.5 Hz, 5β-H), 2.92 (1H, d., J=12 Hz, 5α-H), 3.3—3.7 (1H, br. s., N$\underline{H}$), 3.75 (3H, s., $CO_2C\underline{H}_3$), 4.0 (1H, d, J=4 Hz, 8-H), 4.37 (1H, d.d., J=13 and 4 Hz, 2β-H), 4.42 (1H, d., J=13 Hz, 2α-H), 4.78 (1H, d.d., J=3 and 1.5 Hz, 6-H), 5.28 (1H, d.d., J=4 and 3 Hz, 1-H). *Anal.* Calcd. for $C_8H_{11}NO_5$: C, 47.76; H, 5.51; N, 6.96. Found: C, 47.56; H, 5.49; N, 6.62.

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