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Synthesis of Oxapenam Derivatives[1]

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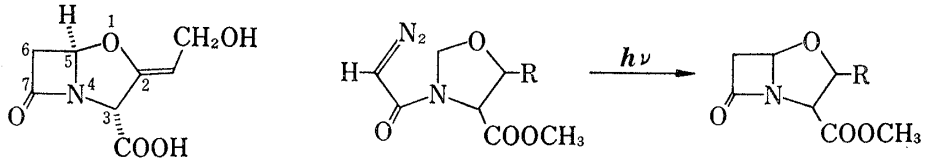
Photolysis of N-diazoacetyloxazolidine compounds, **7c** and **8c**, afforded oxapenams, **9** and **10**, respectively. The physical data of **9** and **10** along with their behavior on thin-layer chromatograms were consistent with that of the samples derived from clavulanic acid (**1**), a β-lactamase inhibitor, confirming their structures. Further, a methylene oxapenam **18** was obtained from an oxapenam **17** having a phenylseleno group by selenoxide elimination reaction.

Keywords——clavulanic acid; β-lactamase inhibitor; oxapenam synthesis; methylene oxapenam; photolysis of oxazolidine diazoacetamide; α-amino-β-hydroxy ester

Clavulanic acid (**1**), a fermentation product of *Streptomyces clavuligerus*[3] and *S. jumonjinensis*,[4] is a β-lactamase inhibitor which acts as a synergist for penicillins and cephalosporins, increasing their activity against resistant strains of bacteria such as *Escherichia coli*, *Klebsiella aerogenes*, and *Staphylococcus aureus*. Adding to its interesting biological activity, **1** is structurally unique in that it is the naturally occurring first member of penicillin analogs containing oxygen instead of sulfur. This paper deals with chemical synthesis of some side chain varients of clavulanic acid (**1**) amenable to biological tests.



1 **2** **3**

Chart 1

In the outset of this study, the oxapenam skeleton as represented by **1** was judged too unstable for attempting ring formation reactions or subsequent chemical manipulations requiring severe conditions; therefore, our synthetic approach was planned to initially synthesize a N-diazoacetyloxazolidine **2** having all structural requirements for an objective oxapenam and to convert **2** into a fused β-lactam **3** by photolysis according to Golding, *et al.*[5] Synthesis of oxapenams having an ethyl side chain (**3**, R=C_2H_5) was carried out in the following way.

Lithiation of N-benzylidene glycine methyl ester[6] (**4**) with *n*-butyllithium in tetrahydrofuran (THF) followed by treatment with propionaldehyde at −78° and acid hydrolysis of the

1) Presented at the 36th Spring Meeting of the Chemical Society of Japan, April 1977, Osaka.
2) Location: *Hiromachi, Shinagawa-ku, Tokyo.*
3) T.T. Howarth and A.G. Brown, *J.C.S. Chem. Commun.*, **1976**, 266; A.G. Brown, D. Butterworth, M. Cole, G. Hanscomb, J.D. Hood, C. Reading, and N. Rolinson, *J. Antibiotics*, **29**, 668 (1976). Also see related patent application.
4) M. Arai, Y. Itoh, R. Enokita, T. Haneishi, M. Nakahara, H. Yoshikawa, and Y. Takiguchi, *J. Antibiotics*, Submitted.
5) B.T. Golding and D.R. Hall, *J. Chem. Soc. Perkin* I, **1975**, 1517.
6) The ester **4** was obtained by mixing glycine methyl ester and benzaldehyde in benzene according to O. Gerngross and A. Olcay (*Chem. Ber.*, **96**, 2550 (1963)).

resulting 2-phenyloxazolidine **5a** gave a diastereomeric mixture of serine homolog esters **6** in 77% overall yield.[7] Treatment of the ester **6** with paraformaldehyde in benzene gave an oxazolidine **5b** whose thin-layer chromatogram revealed two spots, indicating a 1:1 cis, *trans*-isomeric mixture. Acetylation of **5b** was carried out and the resulting acetamides were separated by silica gel chromatography and each component characterized.

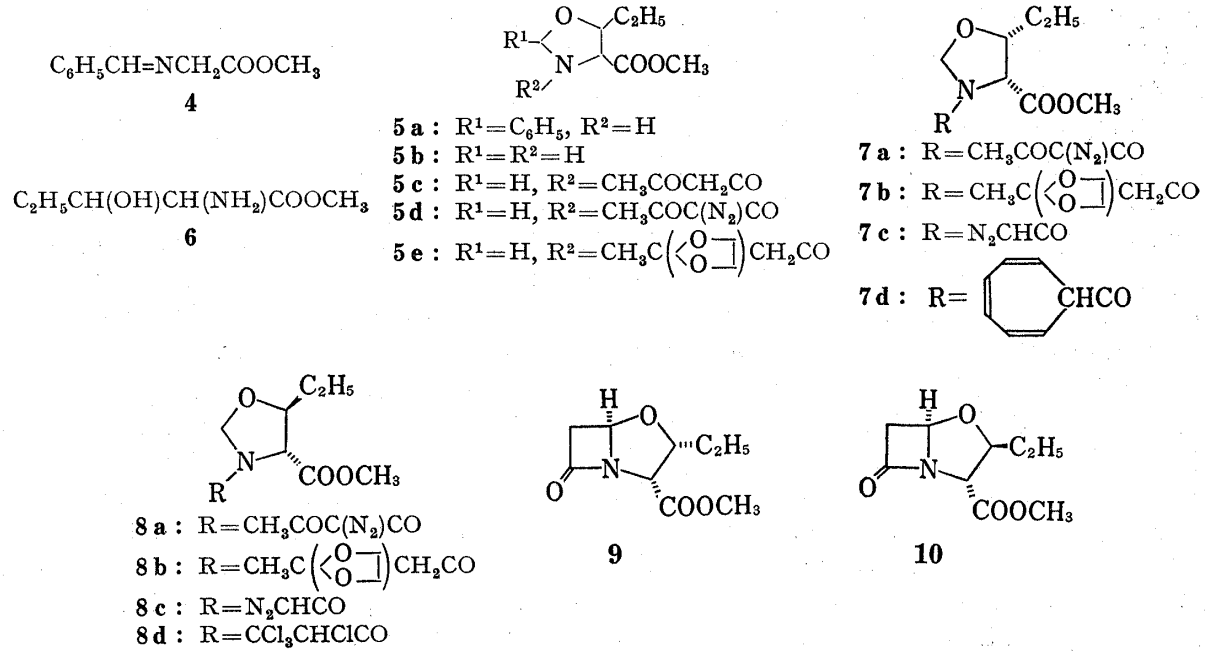


Chart 2

Reaction of the isomeric mixture **5b** with diketene gave an acetoamide mixture **5c** in 70% yield. Diazo transfer reaction[8] to **5c** with *p*-toluenesulfonyl azide in the presence of triethylamine gave a 1:1 mixture of isomeric diazoketones **5d** in 57% yield, from which each component, **7a** and **8a**, was separated by silica gel chromatography. These *cis*,*trans* structures were determined as follows. Ketalization of the acetoacetamide mixture **5c** with ethylene glycol gave a mixture **5e** which was converted into one isomer **8b** by warming in methanol containing a trace amount of sodium methoxide. This fact indicated an isomerization of the *cis* isomer **7b** in the mixture into the thermodynamically more stable *trans* isomer **8b**. Deketalization of **8b** thus obtained and subsequent diazotransfer reaction afforded a *trans* diazoacetoacetamide **8a** which was identified with one of the afore-mentioned samples prepared by separation of the diazoacetoacetamide mixture **5d**.

Desacetylation of the *cis* and *trans* diazoacetoacetamides, **7a** and **8a**, was effected by treatment with a trace amount of sodium methoxide and methanol in THF at low temperature, giving the corresponding diazoacetamides, **7c** and **8c**. Photolysis of **7c** and **8c** was carried out in benzene and carbon tetrachloride, respectively. Purification of each reaction mixture by preparative thin-layer chromatography yielded the objective *cis* and *trans* ethyl oxapenams, **9** and **10**. The yield of the photolysis was 2—3% in both cases. Moreover, N-(2,4,6-cycloheptatrienecarbonyl)oxazolidine **7d** in photolysis of **7c** in benzene and N-(2,3,3,3-tetrachloropropionyl)oxazolidine **8d** in photolysis of **8c** in carbon tetrachloride were obtained as by-products. These compounds may have come about by reaction of a carbene intermediate with the solvent.

7) This serine homolog synthesis is based on a personal communication of Dr. T. Miyadera of our Laboratories.
8) M. Regitz, *Synthesis*, **1972**, 351.

Both of the ethyl oxapenams, **9** and **10**, exhibited infrared absorption due to the β-lactam at 1795 cm^{-1} and also characteristic ABX-pattern nuclear magnetic resonance absorption (NMR) due to the three protons on the β-lactam ring, indicating that the insertion reaction occurred at the C-2 position of the oxazolidine ring. Further, all physical data of these synthesized oxapenams are consistent with those of the corresponding samples obtained by hydrogenation of clavulanic acid methyl ester.[9] This fact indicated that the presence of an ester substituent in the diazoacetamides **7c** and **8c** directed the carbene insertion into the least hindered C-H bond[10] and generated the β-lactam heterocyclic system with the same 3,5-stereochemical relationship as clavulanic acid (**1**).

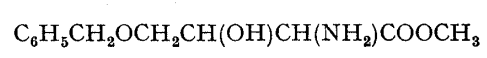
Next, our efforts were directed towards the introduction of an exocyclic double bond in the oxapenam skeleton. After several attempts directed along this line proved fruitless, an effective method for the formation of an enol ether like clavulanic acid was found in the facile syn elimination reaction of a selenoxide function, $-\dot{C}H-\dot{C}-Se(O)R\rightarrow-\dot{C}=\dot{C}-$, which can be performed under mild and neutral conditions. First, applying this synthetic method, an oxazolidine compound having an exocyclic methylene group was synthesized in the following way as a model experiment for the objective synthesis of oxapenam analogs.

Lithiation of N-benzylidene glycine methyl ester (**4**) with lithium diisopropylamide and successive treatment with benzyloxyacetaldehyde[11] gave an 2-phenyloxazolidine like **5a** whose acid hydrolysis resulted in a 50% yield of an α-amino-β-hydroxy ester mixture **11**. Treatment of **11** with paraformaldehyde followed by acetylation gave an N-acetyloxazolidine mixture (75% yield) whose chromatographic separation afforded a *trans* component **12a** along with the *cis* isomer **13a**. **12a** was converted into a phenyl selenide **12b** by a sequence of reactions: debenzylation by hydrogenation over palladium-charcoal, mesylation of the resulting alcohol **12c**, and treatment of the mesylate **12d** with phenylselenium anion which was generated from diphenyl diselenide and sodium borohydride in methanol.[12] Treatment of the phenyl selenide **12b** thus obtained with 30% hydrogen peroxide in the presence of anhydrous magnesium sulfate in THF followed by heating at 70° resulted in a 64% yield of an exocyclic methylene oxazolidine compound **14**.

Based on this result, preparation of an oxapenam compound starting from the α-amino-β-hydroxy ester **11** was carried out as follows. Treatment of **11** with paraformaldehyde and successive acylation with 2-methyl-1,3-dioxolane-2-acetic acid[13] in the presence of dicyclohexylcarbodiimide gave an 82% yield of an oxazolidine mixture whose chromatographic separation provided a *cis* **13b** and a *trans* component **15a**. Refluxing the *cis,trans* mixture in methanol containing sodium methoxide gave the *trans* component **15a**. Deblocking of the benzyl group in **13b** and **15a** was carried out by hydrogenation over palladium-charcoal; and the *cis* **13b** was converted into a lactone **16** and the *trans* **15a** into a hydroxy ester **15b**, respectively, in good yields. Mesylation of **15b** followed by analogous treatment with sodium phenylselenide gave a 73% yield of a phenyl selenide **15c**. Deprotection of the ketal function in **15c** with acid and subsequent diazo transfer reaction to the formed acetoacetamide **15d** gave a diazoacetoacetamide **15e** in 85% overall yield. Treatment of **15e** with sodium methoxide afforded a diazoacetamide **15f** in 75% yield. Analogous photolysis of **15f** in benzene resulted in a 1.3% yield of an oxapenam **17** whose infrared spectrum exhibited a β-lactam absorption at 1792 cm^{-1}. Oxidative elimination reaction of the selenide function in **17** was performed to give a 50% yield of the objective oxapenam **18** having an exocyclic methylene group. The oxapenam **18** also showed a β-lactam infrared absorption at 1800 cm^{-1} and also

9) A. Terahara, M. Nakajima, Y. Itoh, Y. Fukazawa, and M. Arai, *J. Antibiotics*, submitted.
10) *Cf.* D.M. Brunwin, G. Lowe, and J. Parker, *J. Chem. Soc.* (*C*), **1971**, 3756.
11) M. Rotbart, *Compt. Rend.*, **197**, 1225 (1933).
12) K.B. Sharpless and R.F. Lauer, *J. Am. Chem. Soc.*, **95**, 2697 (1973).
13) U. Schmidt and M. Schwochau, *Chem. Ber.*, **97**, 1649 (1964).

ABX-pattern NMR absorptions at 3.06, 3.45 and 5.65 ppm due to the three protons on the β-lactam ring. The biological activity of these oxapenams as β-lactamase inhibitors will be announced in a forthcoming paper.



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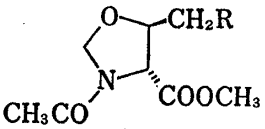
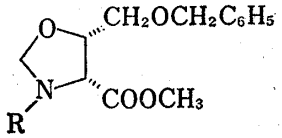
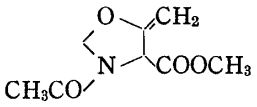


12a: R=$C_6H_5CH_2O$
12b: R=C_6H_5Se
12c: R=OH
12d: R=CH_3SO_2O



13a: R=CH_3CO
13b: R=$CH_3C(<^{O}_{O}\square)CH_2CO$



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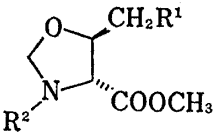
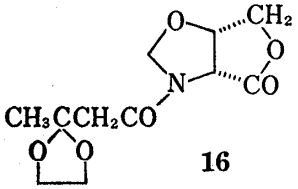


15a: $R^1=C_6H_5CH_2O$, $R^2=CH_3C(<^{O}_{O}\square)CH_2CO$
15b: R^1=OH, $R^2=CH_3C(<^{O}_{O}\square)CH_2CO$
15c: $R^1=C_6H_5Se$, $R^2=CH_3C(<^{O}_{O}\square)CH_2CO$
15d: $R^1=C_6H_5Se$, $R^2=CH_3COCH_2CO$
15e: $R^1=C_6H_5Se$, $R^2=CH_3COC(N_2)CO$
15f: $R^1=C_6H_5Se$, $R^2=N_2CHCO$



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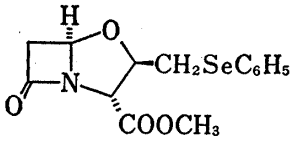

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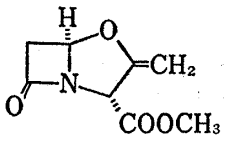

18

Chart 3

Experimental

Melting points are not corrected. Infrared spectra (IR) were recorded on a JASCO A-2 spectrometer, NMR spectra on a Hitachi Perkin-Elmer R-24 spectrometer, 60 MHz, or a Varian HA-100 spectrometer, 100 MHz, and mass spectra (MS) on a JEOL-01SG mass spectrometer. Assignable NMR signals of methyl 3-acyl-4-oxazolidinecarboxylates are shown in Table I. Thin–layer chromatography (TLC) was performed on TLC-plates, Silica gel F_{254} precoated, layer thickness 0.25 mm (E. Merck) and spots were visualized by UV-irradiation or by spraying with vanadic acid-surfuric acid followed by heating or with iodine. Columns for ordinary chromatography were prepared with Wakogel C-200 (WAKO Pure Chemical Industries, Ltd.) and plates for preparative TLC were provided with Silica gel $60F_{254}$ (E. Merck). The amount of silica gel used and the developing solvents are shown in parenthesis. Solvents were removed by a rotary flash evaporator at diminished pressure and usually at 15—35°. The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

Methyl 2-Amino-3-hydroxypentanoate (6)——To a stirred solution of 13.5 g of N-benzylidene glycine methyl ester[6] (4) in 180 ml of THF was added dropwise 37 ml of a 15% *n*-butyllithium hexane solution (E. Merck) at −78° under N_2 atmosphere. The mixture was stirred for 10 min and, after gradually adding 4.5 g of propionaldehyde at −78°, was further stirred for 45 min at the same temperature. Then, 4.5 g of acetic acid was added with cooling and the mixture was diluted with 10 ml of water and further with 200 ml of AcOEt. After vigorous shaking, the organic layer was collected, dried, and evaporated *in vacuo* to dryness, leaving 18.9 g of a crude 2-phenyloxazolidine **5a** as a syrup. Without purification, **5a** was dissolved in 90 ml of 50% aqueous THF and 7 ml of conc. HCl was added with ice-cooling and stirring. After further stirring for 10 min at 0°, the mixture was washed twice with $CHCl_3$ and was made alkaline by addition of $NaHCO_3$ (solid). Then, after washing with benzene, the mixture was saturated with NaCl and extracted with AcOEt about 15 times. The combined extracts were dried and evaporated *in vacuo* to give 8.59 g (77%) of a crude

6 which revealed two spots (1: 1) on a TLC plate (MeOH–$CHCl_3$, 1: 20, v/v). The crude **6** thus obtained was transferred to the next reaction without further purification. IR $\nu_{max}^{liq.}$ cm^{-1}: 3380 (br), 1735. NMR ($CDCl_3$, 60 MHz) δ: 0.97 (3H, t, J=6.5 Hz, $-CH_2\underline{CH_3}$), 3.74 (3H, s, $-COOCH_3$).

Methyl 5-Ethyl-4-oxazolidinecarboxylate (5b) and Its Acetamides——A mixture of 930 mg of the crude **6** obtained above, 200 mg of paraformaldehyde and 25 ml of benzene was refluxed for 1.5 hr. Filtration to remove the remaining paraformaldehyde and evaporation *in vacuo* left 948 mg (94%) of a crude **5b** which was transferred to the next reaction without purification. NMR ($CDCl_3$, 60 MHz) δ: 0.99 (3H, t, J=7 Hz, $-CH_2\underline{CH_3}$), 3.70 and 3.74 (3H, s and s, $-COOCH_3$).

Acetylation of 500 mg of the crude **5b** with acetic anhydride and triethylamine in CH_2Cl_2 in the usual manner gave an acetamide mixture which was chromatographed (20 g, benzene–AcOEt, 3: 1, v/v). Thus, 209 mg of the isomer A as a fast-mobile component, successively 151 mg of the isomeric (1: 1) mixture and 213 mg of the isomer B as a slow-mobile component were obtained as syrup. Total yield was 91%. IR $\nu_{max}^{liq.}$ cm^{-1} for A: 1750, 1662; for B: 1745, 1660. *Anal.* Calcd. for $C_9H_{15}NO_4$: C, 53.72; H, 7.51; N, 6.96. Found: for A: C, 53.65; H, 7.77; N, 6.97; for B: C, 53.48; H, 7.75; N, 7.15.

Methyl 5-Ethyl-3-(3-oxobutyryl)-4-oxazolidinecarboxylate (5c)——To an ice-cold and stirred solution of 948 mg of the crude mixture **5b** in 10 ml of CH_2Cl_2 was added 0.53 g of diketene in one portion. The mixture was stirred for 45 min at 0° and further for 15 min at room temperature. After evaporation of the solvent *in vacuo*, the residue was chromatographed (40 g, benzene–AcOEt, 4: 1, v/v) to give 771 mg (50%) of a *cis*, *trans* mixture of **5c** as a syrup. IR $\nu_{max}^{liq.}$ cm^{-1}: 1745, 1655. *Anal.* Calcd. for $C_{11}H_{17}NO_5$: C, 54.31; H, 7.04; N, 5.76. Found: C, 54.14; H, 7.35; N, 6.12.

Methyl 3-(2-Diazo-3-oxobutyryl)-5α-ethyl- (7a) and -5β-Ethyl-4α-oxazolidinecarboxylate (8a)——(i) To an ice-cold solution of 559 mg of the isomeric mixture of **5c** and 600 mg of triethylamine in 6 ml of CH_2Cl_2 was added 500 mg of *p*-toluenesulfonyl azide[14] with stirring and then allowed to stand for 5 hr at room temperature. The product obtained by evaporation of the solvent was chromatographed (15 g, benzene–AcOEt, 10: 1, v/v) to give 158 mg of the *trans* isomer **8a** as early chromatographic fractions, 104 mg of the isomeric mixture as intermediate fractions and 107 mg of the *cis* isomer **7a** as later fractions. Total yield was 60%. IR $\nu_{max}^{liq.}$ cm^{-1} for **7a**: 2120, 1745, 1660; for **8a**: 2120, 1750, 1660. MS *m/e*: for **7a** and **8a**: 210 (M^+-CH_3CO), 158 ($M^+-CH_3COCN_2$) (M^+, Calcd for $C_{11}H_{15}N_3O_5$).

(ii) A mixture of 116 mg of **5c** (isomeric mixture), 300 mg of ethylene glycol, 2 ml of benzene and 10 mg of *p*-toluenesulfonic acid was refluxed for 1.5 hr. Work-up of the resulting mixture in the usual manner and preparative TLC of the product (benzene–AcOEt, 1: 1, v/v) gave 90 mg (66%) of a ketal mixture **5e**. IR $\nu_{max}^{liq.}$ cm^{-1}: 1750, 1655.

A mixture of 80 mg of **5e** thus obtained and 0.8 ml of 1% $NaOCH_3$ methanolic solution was kept at 50° for 45 min under N_2 atmosphere. Monitoring reaction progress by TLC showed that a spot corresponding to the *cis* isomer **7b** gradually disappeared. Evaporation of the solvent and preparative TLC of the product (benzene–AcOEt, 1: 1, v/v) gave 50 mg (62%) of the *trans* isomer **8b** as a syrup. A stirred mixture of 50 mg of **8b** thus obtained, 0.5 ml of acetone, and 0.5 ml of 2 N HCl was kept at 50° for 45 min. Work-up of the resultant mixture in the usual manner gave 38 mg of a *trans* acetoacetamide which, without purification, was converted into 22 mg of **8a** by treating with 46 mg of *p*-toluenesulfonyl azide and 20 mg of triethylamine for 3 hr as described above.

Methyl 3-Diazoacetyl-5α-ethyl- (7c) and -5β-Ethyl-4α-oxazolidinecarboxylate (8c)——To a stirred solution of 395 mg of the *trans* isomer **8c** in 5 ml of THF was added 0.3 ml of 1 N $NaOCH_3$ methanolic solution at −78° and the mixture was stirred for 2 hr at the same temperature. After 50 mg of triethylamine and successively 30 mg of acetic acid were added with cooling, the mixture was diluted with $CHCl_3$ and washed with water. The organic layer was dried and evaporated *in vacuo* to give 340 mg of a red syrup. Purification by preparative TLC (benzene–AcOEt, 2: 1, v/v) gave 284 mg (84%) of **8c** as a yellow syrup.

On the other hand, 210 mg of the *cis* isomer **7a** was dissolved in a mixture of 1 ml of water and 2 ml of acetonitrile and, after cooling to 0°, 1 ml of 1 N NaOH was added with stirring. The mixture was allowed to stand for 10 min at 0° and extracted with CH_2Cl_2. The extract was dried and evaporated *in vacuo* and the residue was analogously purified by preparative TLC, giving 104 mg (59%) of **7c** as a yellow syrup. IR $\nu_{max}^{liq.}$ cm^{-1} for **7c**: 2120, 1742, 1620; for **8c**: 2120, 1748, 1620. MS *m/e* for **7c** and **8c**: 227 (M^+, $C_9H_{13}N_3O_4$), 199 (M^+-N_2), 168 (M^+-CH_3OCO), 158 (M^+-N_2CHCO).

Methyl 3α-Ethyl- (9) and 3β-Ethyl-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2α-carboxylate (10)——Using a high-pressure Hanovia mercury lamp (450 W) with a pyrex filter, a solution of 100 mg of **7c** in 100 ml of benzene was irradiated at 0° for 45 min with aggitation by bubbling dry N_2. The solvent was evaporated *in vacuo* and the residue was purified by preparative TLC (hexane–acetone, 3: 1, v/v), giving 2 mg of **9**, along with 15 mg of the starting material **7c** and 4 mg of an oxazolidine compound **7d** as syrup.

Analogous irradiation of 210 mg of **8c** in 10 ml of carbon tetrachloride at 0° for 40 min gave 2 mg of **10** as a syrup, along with 42 mg of **8c** and 23 mg of an oxazolidine compound **8d** as fine needles (from hexane–benzene), mp 103—110°. Physical data of these products are as follows. IR $\nu_{max}^{CHCl_3}$ cm^{-1} for **9**: 1795, 1745;

14) M. Regitz, J. Hocker, and A. Liedhegener, "Org. Syn.," Coll. Vol. 5, 1973, p. 179.

for **10**: 1795, 1745; for **7d**, 1746, 1660; ν_{max}^{Nujol} cm^{-1} for **8d**: 1748, 1668. NMR ($CDCl_3$, 100 MHz) δ: for **9**: 1.04 (3H, t, J=7 Hz, $-CH_2\underline{CH_3}$), 1.54 (2H, m, $-\underline{CH_2}CH_3$), 3.10 (1H, dd, J=17, 1.5 Hz, $-\underline{CH_A}H_B-CO\underline{N}-$), 3.54 (1H, dd, J=17, 3 Hz, $-CH_A\underline{H_B}-CO\underline{N}-$), 3.74 (3H, s, $-COOCH_3$), 4.63 (1H, d, J=6.5 Hz, $-\underline{N}-\underline{CH}-COO-$), 4.29 (1H, q, J=7 Hz, $-O-\underline{CH}-C_2H_5$), 5.51 (1H, dd, J=3, 1.5 Hz, $-\underline{N}-\underline{CH}-O-$); for **10**: 1.01 (3H, t, J=7 Hz, $-CH_2\underline{CH_3}$), 1.79 (2H, m, $-\underline{CH_2}CH_3$), 3.08 (1H, d, J=17 Hz, $-\underline{CH_A}H_B-CO\underline{N}-$), 3.51 (1H, dd, J=17, 3 Hz, $-CH_A\underline{H_B}-CO\underline{N}-$), 3.77 (3H, s, $-COOCH_3$), 4.14 (1H, d, J=6.5 Hz, $-\underline{N}-\underline{CH}-COO-$), 4.32 (1H, q, J=7 Hz, $-O-\underline{CH}-C_2H_5$), 5.31 (1H, br. d, J=3 Hz, $-\underline{N}-\underline{CH}-O-$). MS *m/e*: for **9** and **10**: 171 (M^+–CO), 98 (ethyloxazolium ion) (M^+, Calcd. for $C_9H_{13}NO_4$); for **7d**: 277 (M^+, $C_{15}H_{19}NO_4$), 218 (M^+—$COOCH_3$), 91 ($C_7H_7^+$). *Anal.* Calcd. for $C_{10}H_{13}Cl_4NO_4$: C, 34.02; H, 3.71; N, 3.97; Cl, 40.17. Found for **8d**: C, 35.06; H, 3.41; N, 3.77; Cl, 39.76.

Methyl 2-Amino-4-benzyloxy-3-hydroxybutanoate (11)——To an ice-cold solution of 11.39 g of diisopropylamine in 400 ml of THF was added dropwise 70.5 ml of a 15% *n*-butyllithium hexane solution with stirring under N_2 atmosphere. Then, after cooling at −78°, 19.97 g of N-benzylidene glycine methyl ester (**4**) was added over a 10 min period at the same temperature. After stirring for 30 min, 20.08 g of benzyloxyacetaldehyde[11] was added at −78° and the mixture was further stirred for 50 min at the same temperature. Then, 15.36 g of acetic acid was added with cooling and the mixture was diluted with 800 ml of AcOEt, washed twice with 40 ml of brine, dried and evaporated *in vacuo*, leaving 41.1 g of a 2-phenyloxazolidine derivative as a syrup.

The crude product (41.1 g) was dissolved in 270 ml of 33% aqueous THF and 17 ml of conc. HCl was added with cooling. After standing for 15 min at room temperature, the mixture was washed with 20 ml of $CHCl_3$ three times, then made basic by addition of 18.4 g of $NaHCO_3$ (solid) and extracted with $CHCl_3$ three times. The combined extracts were dried and evaporated *in vacuo* to dryness, giving 17.75 g of a syrup which was purified by chromatography (140 g, MeOH–$CHCl_3$, 1: 20, v/v) to give 13.6 g (50%) of **11** as a syrup. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 1735. NMR ($CDCl_3$, 60 MHz) δ: 3.60 and 3.66 (3H, s and s, *ca.* 5: 4, $-COOCH_3$), 4.45 and 4.50 (2H, s and s, *ca.* 5: 4, $-O\underline{CH_2}C_6\underline{H_5}$), 7.24 (5H, s, $-C_6\underline{H_5}$). *Anal.* Calcd. for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.09; H, 7.26; N, 5.82. MS *m/e*: 239 (M^+, $C_{12}H_{17}NO_4$).

Methyl 3-Acetyl-5β-benzyloxymethyl-4α-oxazolidinecarboxylate (12a)——A mixture of 2.19 g of **11**, 258 mg of paraformaldehyde, and 60 ml of benzene was refluxed for 2 hr in an apparatus having a phase-separating head. After cooling, the solvent was evaporated *in vacuo* and the residue was dissolved in 20 ml of pyridine. To the stirred mixture was added 2 ml of acetic anhydride at −50° under N_2 atmosphere. After stirring for 2 hr with cooling and further for 30 min at room temperature, the mixture was worked-up in the usual manner and the product was chromatographed (14 g, benzene–AcOEt, 8: 1—3: 1, v/v), giving 692 mg of the *trans* isomer **12a** and 464 mg of the *cis* isomer **13a** and 795 mg of an isomeric mixture. Total yield was 1.95 g (73%).

Methyl 3-Acetyl-5β-(phenylseleno)methyl-4α-oxazolidinecarboxylate (12b)——Hydrogenation of 2.53 g of **12a** was carried out in 45 ml of MeOH over 400 mg of 10% Pd-C under 31 atm. at 70° for 15 hr. After filtration, the solvent was evaporated *in vacuo* and the residue was chromatographed (20 g, benzene–AcOEt, 1: 1; $CHCl_3$–MeOH, 30: 1, v/v), giving 1.57 g (90%) of **12c**.

To an ice-cold solution of 1.21 g of **12c** in 20 ml of CH_2Cl_2 was added 0.90 g of mesyl chloride and 1.0 g of triethylamine with stirring and the mixture was stirred for 20 min, then was partitioned between 4 ml of 2 N HCl and $CHCl_3$. The organic layer was collected and worked-up in the usual manner and the product was chromatographed (15 g, $CHCl_3$–MeOH, 50: 1, v/v) to give 1.25 g (75%) of **12d** as a syrup.

To a solution of sodium phenylselenide prepared by adding 99 mg of sodium borohydride to a solution of 342 mg of diphenyl diselenide in 15 ml of MeOH was added a solution of 617 mg of **12d** in 2 ml of MeOH with stirring under N_2 atmosphere. After refluxing for 2.5 hr, the solvent was evaporated *in vacuo* and the residue was dissolved in a 1: 1 mixture of water and $CHCl_3$. The $CHCl_3$ layer was separated and the aqueous layer was extracted twice with $CHCl_3$. The combined extracts and washings were washed with brine, dried and evaporated *in vacuo*. The residue (690 mg) was chromatographed (17 g, benzene–AcOEt, 2: 1, v/v), giving 527 mg (70%) of **12b**. MS *m/e*: 357 and 355 (M^+, $C_{14}H_{17}NO_4Se$).

Methyl 3-Acetyl-5-methylene-4-oxazolidinecarboxylate (14)——To an ice-cold mixture of 308 mg of **12b**, 0.9 g of anhydrous $MgSO_4$, and 6 ml of THF was added dropwise 122 mg (1.2 equiv.) of 30% H_2O_2 and the mixture was stirred for 4 hr at room temperature. The mixture was diluted with $CHCl_3$, washed with brine, dried, and evaporated *in vacuo*. The residue was chromatographed (6 g, $CHCl_3$–MeOH, 20: 1, v/v) to give 324 mg (98%) of a selenoxide.

A solution of 210 mg of the selenoxide in 4 ml of dioxane was kept at 70° for 80 min with stirring. Evaporation of the solvent *in vacuo* and chromatography of the residue (6 g, benzene–AcOEt, 3: 1, v/v) gave 69 mg (64%) of **14** as a syrup. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1753, 1662, 1500. MS *m/e*: 185 (M^+, $C_8H_{11}NO_4$).

Methyl 5α-Benzyloxymethyl- (13b) and 5β-Benzyloxymethyl-3-(3-ethylenedioxybutyryl)-4α-oxazolidinecarboxylate (15a)——A mixture of 3.25 g of **11**, 408 mg of paraformaldehyde, and 90 ml of benzene was refluxed for 2 hr, using a water-separator. The mixture was worked-up as described above and the resulting oxazolidine was dissolved in 90 ml of CH_2Cl_2. To the cooled solution was added a solution of 2.19 g (1.1 equiv.) of 2-methyl-1,3-dioxolane-2-acetic acid[13] in 12 ml of CH_2Cl_2 and, after stirring for 5 min, a solution of 3.09 g (1.1 equiv.) of dicyclohexylcarbodiimide in 40 ml of CH_2Cl_2 was added. The mixture was stirred at room temperature overnight, then filtered, and evaporated *in vacuo* and the residue was extracted with

benzene several times. The combined extracts were evaporated to give 6.60 g of a syrup which was chromatographed (100 g, benzene–AcOEt, 6: 1, v/v), giving 1.856 g (36%) of **15a** as early chromatographic fractions, 0.805 g (16%) of a *cis*, *trans* mixture as intermediate fractions, and 0.537 g (30%) of **13b** as later fractions. IR $\nu_{max}^{CHCl_3}$ cm^{-1} for **13b**: 1743, 1650; for **15a**: 1750, 1658. MS *m/e*: for **13b** and **15a**: 379 (M$^+$, $C_{19}H_{25}NO_7$).

To a solution of 116 mg of **13b** in 1 ml of MeOH was added 1 ml of 1.6% $NaOCH_3$ methanolic solution and the mixture was refluxed for 1.5 hr. The solvent was evaporated and the residue was dissolved in water and washed with AcOEt, then, after being acidified with 2 N HCl, was saturated with NaCl (solid) and extracted with $CHCl_3$. The combined extracts were washed with brine, dried and evaporated *in vacuo*, leaving 84 mg of a syrup, which was dissolved in THF and treated with ethereal diazomethane in the usual manner. The product obtained by work-up as usual was purified by preparative TLC (benzene–AcOEt, 3: 2, v/v) to give 75 mg (66%) of **15a**.

Methyl 3-(3-Ethylenedioxybutyryl)-5β-hydroxymethyl-4α-oxazolidinecarboxylate (15b)——Hydrogenation of 2.00 g of **15a** was carried out in 40 ml of MeOH over 300 mg of 10% Pd–C under 30 atm. at 70° overnight. After filtration, the solvent was evaporated *in vacuo* and the residue was chromatographed (10 g, benzene–AcOEt, 3: 1, v/v; $CHCl_3$–AcOEt, 1: 20, v/v), giving 1.44 g (94%) of **15b** as a syrup. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3460, 1750, 1646. MS *m/e*: 289 (M$^+$, $C_{12}H_{19}NO_7$).

3-(3-Ethylendioxybutyryl)-1,6-dioxa-3-azabicyclo[3.3.0]octan-5-one (16)——As described above, 111 mg of **14a** was hydrogenated in 35 ml of MeOH over 20 mg of 10% Pd–C under 50 atm. at 50° for 6 hr and the product was chromatographed (3 g, $CHCl_3$–acetone, 10: 1, v/v) to give 58 mg (77%) of **16** as a syrup. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1790, 1660. MS *m/e*: 257 (M$^+$, $C_{11}H_{15}NO_6$).

Methyl 3-(3-Ethylenedioxybutyryl)-5β-(phenylseleno)methyl-4α-oxazolidinecarboxylate (15c)——To a solution of 1.44 g of **15b** in 30 ml of CH_2Cl_2 was added portionwise a solution of 857 mg (1.5 equiv.) of mesyl chloride in 1 ml of CH_2Cl_2 and 752 mg (1.5 equiv.) of triethylamine in 1 ml of CH_2Cl_2 with cooling and stirring and the mixture was stirred for 20 min. After work-up in the usual manner, 1.82 g of a mesylate of **15b** was obtained as a syrup. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1753, 1657, 1178. MS *m/e*: 367 (M$^+$, $C_{13}H_{21}NO_9S$).

To a solution of sodium phenylselenide prepared by adding 194 mg of sodium borohydride to a solution of 727 mg of diphenyl diselenide in 28 ml of MeOH was added a solution of 1.56 g of the mesylate of **15b** in 6 ml of MeOH under N_2 atmosphere. Then, the mixture was refluxed for 2.5 hr. Work-up as described earlier and purification of the product by chromatography (15 g, benzene–AcOEt, 6: 1, v/v) gave 1.33 g (73%) of **15c** as a syrup. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1750, 1665, 1578. MS *m/e*: 429 and 427 (M$^+$, $C_{18}H_{23}NO_6Se$).

Methyl 3-(2-Diazo-3-oxobutyryl)-5β-(phenylseleno)methyl-4α-oxazolidinecarboxylate (15e)——A stirred mixture of 1.327 g of **15c**, 13 ml of acetone, and 13 ml of 2 N HCl was kept at 50° for 45 min, then the cooled mixture was saturated with NaCl (solid) and worked-up as described earlier. The product was chromatographed (13 g, benzene–AcOEt, 10: 1—3: 1, v/v) to give 1.084 g (91%) of **15d**. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1750, 1657, 1637, 1592, 1578. MS *m/e*: 384 and 382 (M$^+$−1, $C_{16}H_{18}NO_5Se$).

To a stirred solution of 619 mg of **15d** in 12 ml of CH_3CN was added a solution of 476 mg of *p*-toluenesulfonyl azide in 0.5 ml of CH_3CN at room temperature. The mixture was allowed to stand for 3.5 hr and worked-up as described before. The product was purified by chromatography (7 g, benzene–AcOEt, 14: 1, v/v), giving 590 mg (93%) of **15e** which was recrystallized from ether–hexane to yield prisms, mp 91.5—92°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2120, 1752, 1660, 1578. *Anal.* Calcd. for $C_{16}H_{17}N_3O_5Se$: C, 46.84; H, 4.18; N, 10.24. Found: C, 46.91; H, 4.10; N, 10.12.

Methyl 3-Diazoacetyl-5β-(phenylseleno)methyl-4α-oxazolidinecarboxylate (15f)——To a solution of 348 mg of **15e** in 6 ml of THF was added 0.24 ml of 1.4 N $NaOCH_3$ methanolic solution at −78° with stirring. The mixture was stirred for 1 hr, then, after 31 mg of acetic acid was added, was diluted with AcOEt, washed with aq. $NaHCO_3$ and successively with brine, dried, and evaporated *in vacuo*. The residue (312 mg) was chromatographed (4.5 g, AcOEt–benzene, 10: 1, v/v) and 236 mg (75%) of **15f** was obtained as a syrup. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2120, 1752, 1620, 1577. MS *m/e*: 269 and 267 (M$^+$, $C_{14}H_{15}N_3O_4Se$).

Methyl 3-(Phenylseleno)methyl-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylate (17)——As described before, 600 mg of **15f** was irradiated in 80 ml of benzene with ice-cooling and stirring for 1.5 hr. The solvent was evaporated and the residue was chromatographed by preparative TLC (benzene–AcOEt, 6: 1, v/v). The product thus obtained was further purified by preparative TLC (hexane–acetone, 2: 1, v/v). Thus, 7.30 mg (1.3%) of **17** was obtained as a syrup. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1792, 1750. NMR ($CDCl_3$, 100 MHz) δ: 2.85 (1H, d, J=16.5 Hz, –C$\underline{H}_A$H$_B$–CO–), 3.14 (1H, dd, J=13, 6 Hz, –C$\underline{H}_A$H$_B$–Se–), 3.29 (1H, dd, J=16.5, 2.5 Hz, –CH$_A$$\underline{H}_B$–CO–), 3.35 (1H, dd, J=13, 6 Hz, –CH$_A$$\underline{H}_B$–Se–), 3.72 (3H, s, –COOCH$_3$), 4.44 (1H, d, J=6 Hz, –N–C$\underline{H}$–COO–), 4.63 (1H, q, J=6 Hz, –O–C$\underline{H}$–CH$_2$–), 5.32 (1H, s, J=2.5 Hz, –N–C$\underline{H}$–O–). MS *m/e*: 341 and 339 (M$^+$, $C_{14}H_{15}NO_4Se$).

Methyl 3-Methylene-7-oxo-4-oxa-1-azabicyclo[3.2.0]heptane-2-carboxylate (18)——To an ice-cold mixture of 9.30 mg of **17**, 23 mg of anhydrous $MgSO_4$, and 0.7 ml of THF was added a solution of 3.1 mg of 30% H_2O_2 in 0.1 ml of THF and the mixture was stirred for 6 hr at room temperature. Then, the mixture was diluted with $CHCl_3$, washed with brine, dried and evaporated *in vacuo*. The residue was dissolved in 0.7 ml of dioxane and kept at 75° for 2 hr. Then, the solvent was evaporated and the residue was chromatographed (3 g, benzene) to give 2.6 mg (50%) of **18** as a syrup. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1800, 1750, 1683, 1658, 1600. NMR

($CDCl_3$, 100 MHz) δ: 3.06 (1H, d, J=17 Hz, $-CH_AH_B-CO-$), 3.45 (1H, dd, J=17, 2 Hz, $-CH_AH_B-CO-$), 3.79 (3H, s, $-COOCH_3$), 4.29 (1H, dd, J=3, 2 Hz, $=CH_AH_B$), 4.58 (1H, dd, J=3, 2 Hz, $=CH_AH_B$), 5.05 (1H, t, J=2 Hz, $-\underset{|}{N}-\underset{|}{C}H-COO-$), 5.65 (1H, d, J=2 Hz, $-\underset{|}{N}-\underset{|}{C}H-O-$). MS m/e: 183 (M^+, $C_8H_9NO_4$).

TABLE I. NMR Data of Methyl 3-Acyl-4-oxazolidinecarboxylates (60 MHz, $CDCl_3$)

Compound	2H	4H	5H	6H	$-COOCH_3$	R^1	R^2
Acetyl **5b** A	4.93, 5.06 ABq[a] (3.5) 4.81, 5.28 ABq (5)	—	—	—	3.70 s[a] 3.74 s	1.99 s[a], 1.93 s (A)	0.96 t (7) (B)
Acetyl **5b** B	4.94, 5.19 ABq[a] (3.5) 4.94, 5.25 ABq (3.5)	4.54 d[a] (6) 4.39 d (6)	—	—	3.71 s[a] 3.77 s	2.02 s[a], 1.97 s (A)	1.05 t (7) (B)
5c	4.7—5.4m	—	—	—	3.73 s	2.27 s[a], 1.92 s (C)	1.00 t (7) (B)
7a	4.95, 5.05 ABq (4)	4.47 d (7)	4.01 q (7)	1.51m	3.65 s	2.25 s (CH_3COCN_2-)	0.98 t (7) (B)
7c	4.86, 5.11 ABq (3)	4.40 d (7)	4.08 q (7)	1.58m	3.74 s	4.68 s (N_2CHCO-)	1.04 t (7) (B)
7d	4.87, 5.19 ABq (3)	4.63 d (7)	4.19m	—	3.76 s	5.5m, 6.3m, 6.7m (2H each, cycloheptatatriene)	1.06 t (7) (B)
8a	4.93, 5.01 ABq (5)	4.37 d (7)	3.98 q (7)	1.78m	3.71 s	2.32 s (CH_3COCN_2-)	1.03 t (7) (B)
8b	5.05, 5.28 ABq[a] (4.5) 4.95, 5.36 ABq (5)	—	—	1.76m	3.76 s	1.43 s (D); 2.60 s[a], 2.66 s (E); 3.97 s (F)	1.02 t (7) (B)
8c	4.82, 5.02 ABq (3)	4.0—4.5m		1.72m	3.79 s	4.73 s (N_2CHCO-)	1.03 t (7) (B)
8d	5.11, 5.34 ABq (4)	—	—	—	3.78 s	4.76 s[a], 4.83 s (CCl_3CHCl-)	1.03 t (7) (B)
12a	5.06, 5.16 ABq[a] (4) 4.95, 5.32 ABq (3)	—	—	3.75 d (7.5)	3.74 s[a] 3.70 s	2.00 s (A)	4.59 s (G)
12b	5.02, 5.13 ABq[a] (4) 4.95, 5.42 ABq (5)	—	—	3.16 d (6)	3.72 s[a] 3.75 s	2.02 s[a], 1.88 s (A)	—
12c[b]	5.00, 5.20 ABq[a] (4) 4.81, 5.35 ABq (5)	4.1—4.6m		—	3.75 s[a] 3.80 s	2.04 s[a], 2.00 s (A)	
12d	5.00, 5.21 ABq[a] (4) 4.82, 5.33 ABq (5)	4.2—4.6m		—	3.78 br s	1.98 s (A)	3.08 s (CH_3SO_2O-)
13a	5.01, 5.24 ABq[a] (3) 5.09, 5.28 ABq (3)	—	—	—	3.66 s	2.01 s (A)	4.55 s (G)
13b	5.0—5.5m	4.4—4.8m		3.7m	3.98 s	1.44 s (D); 2.62 br s (E); 3.67 s (F)	4.58 s (G)
14	5.31 s[a] 5.17, 5.49 ABq (5)	5.05 br s	—	4.27 dd (3, 2) 4.46 dd (3, 2)	3.73 br s	2.00 br s (A)	—
15a	5.08, 5.32 ABq[a] (4.5) 4.98, 5.41 ABq (6)	4.2—4.6m		3.7m	3.93 s	1.43 s (D); 2.63 br s (E); 3.72 br s (F)	4.59 s (G)
15b	4.98, 5.24 ABq[a] (4.5) 4.91, 5.42 ABq (5)	4.45 d (6)	4.0—4.4m	3.7m	3.87 s	1.40 s (D); 2.63 br s (E); 3.67 s (F)	—
Mesylate of **15b**	5.12, 5.42 ABq (4.5)	—	—	—	3.83 s	1.41 s (D); 2.72 s (E); 4.00 s (F)	3.12 s (CH_3SO_2O-)
15c	4.9—5.4m	4.54 d (6)	4.29 q (6)	3.15 d (6)	3.69 s[a] 3.73 s	1.40 s (D); 2.61 s[a], 2.53 s (E); 3.91 s (F)	—
15d	5.06, 5.18 ABq[a] (3.5) 5.02, 5.38 ABq (5.5)	—	—	3.22 d (5)	3.78 s	2.29 s[a], 1.90 s (C); 3.47 s[a], 3.40 s (CH_3COCH_2-)	—
15e	4.98, 5.14 ABq (5)	4.72 d (6)	4.36 q (6)	3.21 d[a] (6) 3.24 d (6)	3.75 s	2.32 s (C)	—
15f	4.90, 5.16 ABq (3.5)	4.3—4.5m		3.13 d (6)	3.77 s	4.78 s (N_2CHCO-)	—
16[c]	5.21, 5.30 ABq (4.5)	5.51 d (5.5)	5.01 dt (5.5, 2.5)	4.52 d (2.5)	—	1.63 s (D); 3.03, 3.25 ABq (14) (E); 3.96 br s (E)	—

a) Signals for a major rotamer. These compounds exist as two rotamers by hindered rotation of N-acyl group. Relative ratio of rotamers ranges from 1:4 to 1:1.

b) Measured in $CDCl_3$ containing D_2O.

c) Measured in d_5-pyridine at 90°. Assignable function is as follows: A, CH_3CO-; B, CH_3CH_2-; C, CH_3COCH_2-; D, $CH_3C(\langle O- \rangle)CH_2-$; E, $CH_3C(\langle O- \rangle)CH_2-$; F, $\langle OCH_3 \rangle$; G, $C_6H_5CH_2O-$.