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Ring Transformation of 2-Furylcarbamates to 5-Hydroxy-3-pyrrolin-2-ones

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N-Ethoxycarbonyl- and *N*-benzyloxycarbonyl-5-hydroxy-5-methoxyalkylpyrrolinones (**6a**—**c**) and (**7a**—**c**) together with minor products **8**—**10** were obtained from the photooxidation or autoxidation of corresponding 2-furylcarbamates (**4a**—**c**) and (**5a**—**c**). The catalytic hydrogenation of **6a**—**c** afforded saturated γ-ketoamides (**11a**—**c**), while that of **7a**—**c** led to the formation of 5-hydroxypyrrolidones (**12a**—**c**).

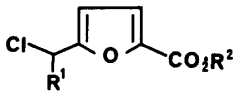
Keywords——2-furylcarbamate; 5-hydroxy-3-pyrrolin-2-one; γ-ketoamide; photooxidation; autoxidation; ring transformation; Baeyer-Villiger rearrangement; catalytic hydrogenation

Introduction

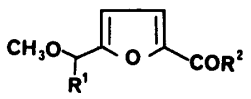
We have reported the ring transformation of various 2-furylcarbamates to 5-hydroxy-3-pyrrolin-2-ones by autoxidation or photooxidation.[1] In this reaction, we postulated that the transient furan endoperoxide was initially formed by the reaction of molecular oxygen with the electron-rich 2-aminofurans. Recently Feringa and Butselaar[2] reported that methoxymethyl substituted furan seems to be essential for intramolecular Baeyer-Villiger rearrangement of the endoperoxide. Their report prompted us to investigate the photooxidation or autoxidation of methoxyalkyl substituted 2-furylcarbamates (**4a**—**c**) and (**5a**—**c**).

Results and Discussion

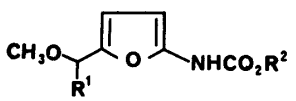
Ethyl and benzyl *N*-(5-methoxyalkyl-2-furyl)carbamates (**4a**—**c**) and (**5a**—**c**) were obtained by successive treatments of 5-methoxyalkyl-2-furoic acids (**2a**—**c**; prepared from **1a**—**c**[3,4] by treatment with sodium methoxide[5] followed by hydrolysis with sodium hydroxide) with ethyl chloroformate, sodium azide, and ethanol or benzyl alcohol, respectively.



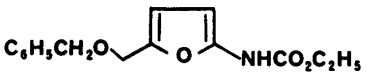
1a : R^1=H, R^2=CH_3
1b : R^1=CH_3, R^2=C_2H_5
1c : R^1=R^2=C_2H_5



2a : R^1=H, R^2=OH **3a** : R^1=H, R^2=N_3
2b : R^1=CH_3, R^2=OH **3b** : R^1=CH_3, R^2=N_3
2c : R^1=C_2H_5, R^2=OH **3c** : R^1=C_2H_5, R^2=N_3



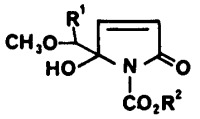
4a : R^1=H, R^2=C_2H_5 **5a** : R^1=H, R^2=$CH_2C_6H_5$
4b : R^1=CH_3, R^2=C_2H_5 **5b** : R^1=CH_3, R^2=$CH_2C_6H_5$
4c : R^1=R^2=C_2H_5 **5c** : R^1=C_2H_5, R^2=$CH_2C_6H_5$



4d

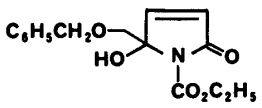
Chart 1

Irradiation of ethyl *N*-(5-methoxymethyl-2-furyl)carbamate (**4a**) in benzene with a 400 W high-pressure mercury lamp gave the 5-hydroxy-5-methoxymethylpyrrolinone (**6a**) as the main product, together with the 5-hydroxy-5-ethoxypyrrolinone (**8a**), the *cis*-γ-ketoamide (**9a**), and the *trans*-γ-ketoamide (**10a**). The structures of **6a** and **8a** were confirmed by comparison of the infrared (IR) and proton nuclear magnetic resonance (^{1}H-NMR) spectra with those of authentic 5-hydroxypyrrolinones,[1] and **10a** was identified by direct comparison with an authentic sample.[1b] The structure of **9a** was supported by the presence of *cis*-coupled olefinic proton signals at δ 6.69 (J=12 Hz) and 6.16 (J=12 Hz) in the ^{1}H-NMR spectrum, and the formation of the saturated γ-ketoamide (**11e**) on catalytic hydrogenation. Compound **6a** was also formed by the photooxidation of **4a** in ethanol or methanol along with **8a** and **9a** or **8b** and **9b**. The yields of the photooxidation products of **4a** are indicated in Table I. The mechanism of these reactions is considered to be as follows. The formation of **6a** as a major product seems to be due to spontaneous cyclization of the *cis*-γ-ketoamide B derived from decomposition of an endoperoxide A.[6] Thus, the major pathway did not involve the intermediate C formed by intramolecular Baeyer-Villiger rearrangement of A, and the greater yield of **6a** in protic solvents than in an aprotic solvent showed that the ring closure was accelerated by protonation from the solvent to the γ-carbonyl moiety in B. In the case of the reaction in protic solvents, the absence of the *trans*-γ-ketoamide **10a** as a product seems to be due to the inhibition of radical cleavage of the ether bond in the intermediate B in ethanol or methanol. The formation of **6d** (32%) and **10a** (5%) from ethyl *N*-(5-benzyloxymethyl-2-furyl)carbamate (**4d**) by irradiation in benzene also supports the mechanism described above. Furthermore, **9a** and **9b** were obtained as minor products, probably *via* addition of alcohols to radical D formed through a type I process from B, or by solvolysis of the rearrangement intermediate C, and these compounds cyclized to afford **8a**. The formation of **8a** and **9a** in the case of the reaction in benzene is considered to arise from decomposition of the carbamoyl moiety. The 5-hydroxypyrrolinones (**6a** and **7a**) were also formed by autoxidation of **4a** and **5a**, respectively, in benzene solution.

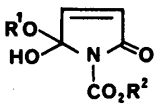


6a : R^1=H, R^2=C_2H_5
6b : R^1=CH_3, R^2=C_2H_5
6c : R^1=R^2=C_2H_5

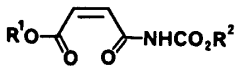
7a : R^1=H, R^2=$CH_2C_6H_5$
7b : R^1=CH_3, R^2=$CH_2C_6H_5$
7c : R^1=C_2H_5, R^2=$CH_2C_6H_5$



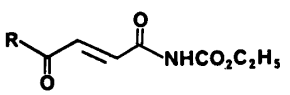
6d



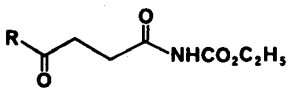
8a : R^1=R^2=C_2H_5
8b : R^1=CH_3, R^2=C_2H_5
8c : R^1=R^2=$CH_2C_6H_5$
8d : R^1=CH_3, R^2=$CH_2C_6H_5$



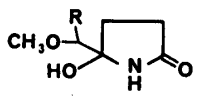
9a : R^1=R^2=C_2H_5
9b : R^1=CH_3, R^2=C_2H_5
9c : R^1=H, R^2=C_2H_5
9d : R^1=R^2=$CH_2C_6H_5$



10a : R=CH_3
10b : R=CH_3OCHCH_3



11a : R=CH_3OCH_2
11b : R=CH_3CHCH_3
11c : R=$CH_3OCHCH_2CH_3$
11d : R=$C_6H_5CH_2OCH_2$
11e : R=C_2H_5O



12a : R=H
12b : R=CH_3
12c : R=C_2H_5

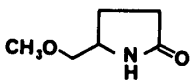


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Chart 2

TABLE I. The Yields of Products Obtained by Photooxidation of **4a**

Solvent	Yield (%)					
	6a	**8a**	**8b**	**9a**	**9b**	**10a**
Benzene	31.2	1.7	—	3.9	—	2.0
Ethanol	48.8	6.4	—	1.9	—	—
Methanol	46.1	—	8.4	—	1.5	—

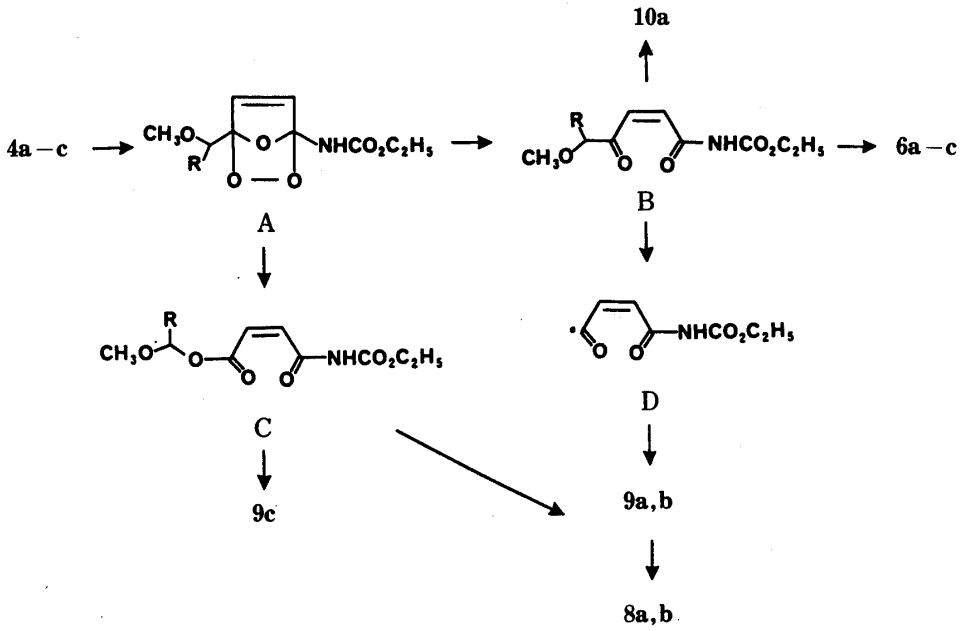

Chart 3

Photooxidation of ethyl *N*-[5-(1-methoxyethyl)-2-furyl]carbamate (**4b**) in benzene solution proceeded in the same way as in the case of **4a** to give the 5-hydroxy-5-(1-methoxyethyl)pyrrolinone (**6b**) (35%) and the *cis*-γ-carboxyamide (**9c**) (23.4%) together with **8a** and the *trans*-γ-ketoamide (**10b**). The similar reaction of **4b** in ethanol resulted in the formation of **6b** (24.8%), **9c** (10.3%), **8a** (5.4%), and **9a** (2.3%). The formation of **9c** seems to be permitted only when the substituent at the 5 position is tertiary, as in **4b** or **4c**. Thus, irradiation of **4c** in ethanol afforded the 5-hydroxy-5-(1-methoxypropyl)pyrrolinone (**6c**) (16.1%), **8a** (5.2%), and **9c** (10.9%). Although the mechanism of the formation of **9c** is not obvious, it may proceed *via* the cleavage of intermediate C. The 5-hydroxypyrrolinones **6b** and **6c** were mixtures of diastereoisomers as judged from the ^{1}H-NMR spectra (see Experimental), but separation was not attempted. Furthermore, irradiation of benzyl *N*-[5-(1-methoxyethyl)-2-furyl]carbamate (**5b**) or autoxidation of benzyl *N*-[5-(1-methoxypropyl)-2-furyl]carbamate (**5c**) in benzene gave **7b**, **8c**, and **9d**, or **7c** and **8d**, respectively.

On the basis of our results, we conclude that the endoperoxide intermediate A of these 2-furylcarbamates (**4**) and (**5**) does not undergo intramolecular Baeyer-Villiger rearrangement, although it is possible that decomposition of A to give the minor products **9a—c** might be due to such rearrangement.

Next, we examined the catalytic hydrogenation of **6a** over Pd–C in ethyl acetate to give the ring-opened saturated γ-ketoamide (**11a**) in 82% yield. Other γ-ketoamides (**11b—d**) were obtained by the same treatment of **6b—d**. On the other hand, hydrogenolysis of **7a** in the manner described above gave the 5-hydroxypyrrolidone (**12a**) and the pyrrolidone (**13**). Only

the 5-hydroxypyrrolidones (**12b** and **12c**) were formed from **7b** and **7c**.

Therefore, the hydrogenolysis of the *N*-carbobenzyloxy group is considered to be faster than the ring opening reaction.

Experimental

IR spectra were recorded on a Jasco IR A-1 spectrometer in $CHCl_3$ unless otherwise stated. The ^1H- and ^{13}C-NMR spectra were taken on JEOL PS-100 and/or JEOL FX-100 spectrometers in $CDCl_3$ unless otherwise stated. Chemical shifts are given in ppm (δ) with tetramethylsilane as an internal standard. Abbreviations used: s, singlet; d, doublet; t, triplet; q, quartet; qn, quintet; m, multiplet; br, broad. Mass spectra (MS) were recorded on a Hitachi M-52 spectrometer operating at an ionization potential of 70 eV. Column chromatography was performed with Kieselgel 60 (70—230 mesh, Merck). Preparative layer chromatography (PLC) was carried out on plates (20 × 20 cm, 0.75 mm in thickness) coated with Kieselgel PF_{254} (Merck). Irradiation was carried out with a 400 W high-pressure mercury lamp, Riko UVL-400P, with a Pyrex filter.

Ethyl 5-(1-Chloropropyl)-2-furoate (1c)——A mixture of ethyl 2-furoate (70 g, 0.5 mol) and anhyd. $ZnCl_2$ (16 g, 0.12 mol) in $CHCl_3$ (150 ml) was cooled to −5—0 °C with continuous stirring, and propionaldehyde (58 g, 1 mol) was added at a rate such that the temperature of the mixture did not rise above 5 °C. After the addition, a rapid stream of hydrogen chloride was passed through the mixture at 5—10 °C for 2 h, and the whole was left to stand overnight. The reaction mixture was poured into ice water, the $CHCl_3$ layer was separated, and the aqueous layer was extracted with $CHCl_3$. The combined $CHCl_3$ solution was washed with water and dried over $MgSO_4$. After removal of the solvent, the residue was vacuum-distilled to give **1c** (27.1 g, 25%) as a yellow oil, bp 113—115 °C at 3 mmHg. IR ν_{max} (neat) cm^{-1}: 1710. ^1H-NMR δ: 7.06 (1H, d, J=3.5 Hz), 6.38 (1H, d, J=3.5 Hz), 4.83 (1H, t), 4.30 (2H, q), 2.17 (2H, qn), 1.36 (3H, t), 1.04 (3H, t). *Anal.* Calcd for $C_{10}H_{13}ClO_3$: C, 55.43; H, 4.65. Found: C, 55.19; H, 4.44.

5-Methoxymethyl-2-furoic Acid (2a)——A solution of **1a**[3] (10 g, 0.057 mol) and NaOMe (3.1 g, 0.057 mol) in MeOH (100 ml) was boiled for 7 h. The reaction mixture was concentrated, then poured into water and extracted with ether. After removal of the solvent, the residue was vacuum-distilled to give methyl 5-methoxymethyl-2-furoate (7 g, 72%) as a colorless oil, bp 85—86 °C at 3 mmHg. IR ν_{max} cm^{-1}: 1720. ^1H-NMR δ: 7.14 (1H, d, J=3.5 Hz), 6.46 (1H, d, J=3.5 Hz), 4.45 (2H, s), 3.89 (3H, s), 3.39 (3H, s). Next, a mixture of the ester (5 g, 0.03 mol) and 10% NaOH (25 ml) in tetrahydrofuran (THF) (25 ml) was stirred for 5 h at room temperature. The mixture was poured into water and acidified with conc. HCl. The resulting product was filtered off and purified by recrystallization from $CHCl_3$ to give **2a** (3.9 g, 85%) as colorless needles, mp 63—65 °C. IR ν_{max} cm^{-1}: 3010, 2920, 1690. ^1H-NMR δ: 9.99 (1H, s, OH), 7.24 (1H, d, J=3.5 Hz), 6.48 (1H, d, J=3.5 Hz), 4.49 (2H, s), 3.41 (3H, s). *Anal.* Calcd for $C_7H_8O_4$: C, 53.84; H, 5.16. Found: C, 53.77; H, 5.05. **2b** and **2c** were prepared similarly from **1b**[4] and **1c**, respectively. The products were purified by silica gel column chromatography with benzene.

5-(1-Methoxyethyl)-2-furoic Acid (2b)——Methyl 5-(1-methoxyethyl)-2-furoate: A colorless oil (45%). IR ν_{max} cm^{-1}: 1715. ^1H-NMR δ: 7.18 (1H, d, J=3.5 Hz), 6.42 (1H, d, J=3.5 Hz), 4.44 (1H, q), 3.90 (3H, s), 3.33 (3H, s), 1.52 (3H, d). **2b**: Colorless needles (92%), mp 52—54 °C. IR ν_{max} cm^{-1}: 2960, 2900, 1675. ^1H-NMR δ: 9.69 (1H, s, OH), 7.27 (1H, d, J=3.5 Hz), 6.43 (1H, d, J=3.5 Hz), 4.46 (1H, q), 3.35 (3H, s), 1.54 (3H, d). *Anal.* Calcd for $C_8H_{10}O_4$: C, 56.46; H, 5.92. Found: C, 56.39; H, 5.75.

5-(1-Methoxypropyl)-2-furoic Acid (2c)——Methyl 5-(1-methoxypropyl)-2-furoate: A colorless oil (40%). IR ν_{max} cm^{-1}: 1715. ^1H-NMR δ: 7.12 (1H, d, J=3.5 Hz), 6.34 (1H, d, J=3.5 Hz), 4.15 (1H, t), 3.85 (3H, s), 3.28 (3H, s), 1.86 (2H, qn), 0.92 (3H, t). **2c**: A colorless oil (90%). IR ν_{max} cm^{-1}: 2960, 2900, 1675. ^1H-NMR δ: 8.45 (1H, br s, OH), 7.24 (1H, d, J=3.5 Hz), 6.41 (1H, d, J=3.5 Hz), 4.20 (1H, t), 3.33 (3H, s), 1.90 (2H, qn), 0.94 (3H, t). *Anal.* Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.52; H, 6.47.

Ethyl *N*-(5-Methoxymethyl-2-furyl)carbamate (4a)——A solution of ethyl chloroformate (0.75 g, 0.0069 mol) in THF (5 ml) was added to a solution of **2a** (1 g, 0.0064 mol) and triethylamine (0.7 g, 0.0069 mol) in THF (10 ml) at 0—10 °C with stirring. After half an hour, a solution of NaN_3 (1 g) in H_2O (15 ml) was added, and the whole was stirred for 1 h at room temperature. The reaction mixture was poured into ice water and extracted with ether. The organic layer was dried over $MgSO_4$ and the ether was removed to give 5-methoxymethyl-2-furoyl azide (**3a**), (0.8 g, 69%) as a colorless oil. IR ν_{max} cm^{-1}: 2135, 1680. Next, a solution of the azide (0.7 g, 0.0039 mol) and ethyl alcohol (5 ml) in benzene (30 ml) was stirred under reflux for 30 h. Removal of the benzene by evaporation and washing of the residue with petroleum ether gave **4a** (0.6 g, 78%) as a colorless oil. IR ν_{max} cm^{-1}: 3403, 1720. ^1H-NMR δ: 7.36 (1H, br s, NH), 6.31 (1H, d, J=3.5 Hz), 6.04 (1H, d, J=3.5 Hz), 4.31 (2H, s), 4.24 (2H, q), 3.34 (3H, s), 1.29 (3H, t). MS *m/z*: 199 (M^+), 168, 126, 124, 122, 96 (base), 95, 68, 66. **4b—d** and **5a—c** were similarly prepared in 55—70% yields.

Ethyl *N*-[5-(1-Methoxyethyl)-2-furyl]carbamate (4b)——**3b**: A colorless oil. IR ν_{max} cm^{-1}: 2135, 1680. **4b**: A colorless oil. IR ν_{max} cm^{-1}: 3410, 1720. ^1H-NMR δ: 7.13 (1H, br s, NH), 6.26 (1H, d, J=3.5 Hz), 6.05 (1H, d, J=3.5 Hz), 4.30 (1H, q), 4.25 (2H, q), 3.28 (3H, s), 1.48 (3H, d), 1.30 (3H, t).

Ethyl *N*-[5-(1-Methoxypropyl)-2-furyl]carbamate (4c)——**3c**: A colorless oil. IR ν_{max} cm^{-1}: 2135, 1680. **4c**: A colorless oil. IR ν_{max} cm^{-1}: 3410, 1720. ^1H-NMR δ: 7.29 (1H, br s, NH), 6.19 (1H, d, J=3.5 Hz), 5.99 (1H, d,

J=3.5 Hz), 4.19 (2H, q), 3.83 (1H, t), 3.21 (3H, s), 1.81 (2H, qn), 1.28 (3H, t), 0.89 (3H, t).

Benzyl *N*-(5-Methoxymethyl-2-furyl)carbamate (5a)——**5a**: A colorless oil. IR ν_{max} cm^{-1}: 3403, 1725. ^{1}H-NMR δ: 7.45 (1H, br s, NH), 7.36 (5H, s), 6.27 (1H, d, J=3.5 Hz), 6.04 (1H, d, J=3.5 Hz), 5.18 (2H, s), 4.28 (2H, s), 3.28 (3H, s). MS m/z: 261 (M^+), 230, 186, 153, 126, 91 (base).

Benzyl *N*-[5-(1-Methoxyethyl)-2-furyl]carbamate (5b)——**5b**: A colorless oil. IR ν_{max} cm^{-1}: 3405, 1720. ^{1}H-NMR δ: 7.45 (1H, br s, NH), 7.36 (5H, s), 6.21 (1H, d, J=3.5 Hz), 6.03 (1H, d, J=3.5 Hz), 5.18 (2H, s), 4.26 (1H, q), 3.22 (3H, s), 1.46 (3H, d). MS m/z: 275 (M^+), 244, 200, 140, 108, 91 (base).

Benzyl *N*-[5-(1-Methoxypropyl)-2-furyl]carbamate (5c)——**5c**: A colorless oil. IR ν_{max} cm^{-1}: 3400, 1720. ^{1}H-NMR δ: 7.37 (5H, s), 7.13 (1H, br s, NH), 6.22 (1H, d, J=3.5 Hz), 6.03 (1H, d, J=3.5 Hz), 5.18 (2H, s), 3.95 (1H, t), 3.22 (3H, s), 1.84 (2H, qn), 0.84 (3H, t).

Ethyl *N*-(5-Benzyloxymethyl-2-furyl)carbamate (4d)——5-Benzyloxymethyl-2-furoic acid (prepared from **1a**) was treated with sodium benzyloxide, and the product was hydrolyzed with 5% NaOH to give colorless needles, mp 97—99 °C. IR ν_{max} cm^{-1}: 2990, 2840, 1675. ^{1}H-NMR δ: 10.09 (1H, s, OH), 7.36 (5H, s), 7.26 (1H, d, J=3.5 Hz), 6.48 (1H, d, J=3.5 Hz), 4.60 (2H, s), 4.56 (2H, s). *Anal.* Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 67.10; H, 5.10. Further treatment of this product in the same manner as described for **4a** gave an azide: A colorless oil. IR ν_{max} cm^{-1}: 2130, 1675. **4d**: Colorless needles, mp 68—71 °C. IR ν_{max} cm^{-1}: 3405, 1725. ^{1}H-NMR δ: 7.38 (5H, s), 7.03 (1H, br s, NH), 6.31 (1H, d, J=3.5 Hz), 6.07 (1H, d, J=3.5 Hz), 4.54 (2H, s), 4.42 (2H, s), 4.24 (2H, q), 1.29 (3H, t). MS m/z: 275 (M^+), 169, 168, 124, 97, 91 (base).

Photooxidation of 4a in Benzene——A solution of **4a** (0.5 g, 0.0025 mol) in benzene (200 ml) was irradiated in the presence of oxygen at room temperature for 1 h. After removal of the solvent, the residue was purified by PLC with $CHCl_3$–ether (2 : 1) to give **8a** (1.7%), (*Z*)-**9a** (3.9%), (*E*)-**10a** (2%), and **6a** (31.2%). **8a**: A colorless oil. IR ν_{max} cm^{-1}: 3420, 1800, 1772, 1722. ^{1}H-NMR δ: 7.50 (1H, d, J=6 Hz), 6.24 (1H, d, J=6 Hz), 5.90 (1H, br s, OH), 4.13 (2H, q), 3.62 (2H, q), 1.24 (3H, t), 1.22 (3H, t). MS m/z: 216 (M^++H), 170, 142, 127, 114, 99 (base), 98, 82, 80. *Anal.* Calcd for $C_9H_{13}NO_5$: C, 50.23; H, 6.09; N, 6.51. Found: C, 50.15; H, 5.89; N, 6.31. **9a**: A colorless oil. IR ν_{max} cm^{-1}: 3385, 1750, 1700. ^{1}H-NMR δ: 9.00 (1H, br s, NH), 6.69 (1H, d, J=12 Hz), 6.16 (1H, d, J=12 Hz), 4.23 (4H, q), 1.30 (6H, t). MS m/z: 216 (M^++H), 215 (M^+), 170, 142, 127, 114, 99 (base), 98, 82, 80. *Anal.* Calcd for $C_9H_{13}NO_5$: C, 50.23; H, 6.09; N, 6.51. Found: C, 49.97; H, 5.89; N, 6.33. **10a**: Colorless needles, mp 97—99 °C. IR ν_{max} cm^{-1}: 3360, 1738, 1667. ^{1}H-NMR δ: 8.09 (1H, br s, NH), 7.72 (1H, d, J=16 Hz), 7.12 (1H, d, J=16 Hz), 4.30 (2H, q), 2.41 (3H, s), 1.36 (3H, t). MS m/z: 186 (M^++H), 185 (M^+), 170, 156, 142, 114, 98, 97, 80. *Anal.* Calcd for $C_8H_{11}NO_4$: C, 51.88; H, 5.99; N, 7.56. Found: C, 51.59; H, 5.67; N, 7.41. **6a**: A colorless oil. IR ν_{max} cm^{-1}: 3500, 1775, 1741, 1692. ^{1}H-NMR δ: 7.14 (1H, d, J=6 Hz), 6.16 (1H, d, J=6 Hz), 4.75 (1H, br s, OH), 4.37 (2H, q), 3.94 (2H, s), 3.36 (3H, s), 1.40 (3H, t). MS m/z: 216 (M^++H), 198, 170, 142, 124, 98 (base), 80. *Anal.* Calcd for $C_9H_{13}NO_5$: C, 50.23; H, 6.09; N, 6.51. Found: C, 50.15; H, 5.89; N, 6.35.

***N*, 3-Bis(ethoxycarbonyl)propionamide (11e)**——A solution of **9a** (0.1 g, 0.0005 mol) in AcOEt (10 ml) containing 5% Pd–C (20 mg) was hydrogenated at room temperature. The reaction mixture was filtered and the filtrate was evaporated to give **11e** (87 mg, 86%) as colorless needles, mp 57—59 °C. IR ν_{max} cm^{-1}: 3390, 1780, 1750, 1705. ^{1}H-NMR δ: 8.08 (1H, br s, NH), 4.30 (4H, q), 3.15 (2H, m), 2.70 (2H, m), 1.36 (6H, t). MS m/z: 218 (M^++H), 217 (M^+), 172, 144, 129, 116, 101 (base), 90, 82. *Anal.* Calcd for $C_9H_{15}NO_5$: C, 49.76; H, 6.96; N, 6.45. Found: C, 49.54; H, 6.69; N, 6.31.

Photooxidation of 4a in Ethanol——A solution of **4a** (0.5 g, 0.0025 mol) in ethanol (200 ml) was irradiated in the presence of oxygen at room temperature for 1 h. After removal of the solvent, the residue was purified by PLC with $CHCl_3$–ether (2 : 1) to give **8a** (6.4%), **9a** (1.9%), and **6a** (48.8%). These compounds were shown to be identical with authentic samples by IR and ^{1}H-NMR spectral comparisons.

Photooxidation of 4a in Methanol——A solution of **4a** (0.5 g, 0.0025 mol) in methanol (200 ml) was irradiated in the presence of oxygen at room temperature for 1 h. After removal of the solvent, the residue was purified by PLC with $CHCl_3$–ether (2 : 1) to give **8b** (8.4%), (*Z*)-**9b** (1.5%), and **6a** (46.1%). **8b**: A colorless oil. IR ν_{max} cm^{-1}: 3420, 1800, 1778, 1725. ^{1}H-NMR δ: 7.46 (1H, d, J=6 Hz), 6.20 (1H, d, J=6 Hz), 6.09 (1H, br s, OH), 4.11 (2H, q), 3.36 (3H, s), 1.25 (3H, t). MS m/z: 202 (M^++H), 170, 142, 128, 113, 98 (base), 82, 80. *Anal.* Calcd for $C_8H_{11}NO_5$: C, 47.76; H, 5.51; N, 6.96. Found: C, 47.56; H, 5.35; N, 6.79. **9b**: A colorless oil. IR ν_{max} cm^{-1}: 3380, 1795, 1748, 1715. ^{1}H-NMR δ: 8.63 (1H, br s, NH), 6.63 (1H, d, J=12 Hz), 6.11 (1H, d, J=12 Hz), 4.19 (2H, q), 3.74 (3H, s), 1.28 (3H, t). MS m/z: 202 (M^++H), 201 (M^+), 170, 142, 124, 113, 98 (base), 82, 80. *Anal.* Calcd for $C_8H_{11}NO_5$: C, 47.76; H, 5.51; N, 6.96. Found: C, 47.66; H, 5.35; N, 6.66. **6a** was shown to be identical with an authentic sample by IR and ^{1}H-NMR spectral comparisons.

Photooxidation of 4d in Benzene——**4d** (0.5 g, 0.0018 mol) was irradiated by a method similar to that described for **4a**. The separation of products was carried out by the same procedure to give **6d** (170 mg, 32%) and **10a** (17 mg, 5%). **6d**: A colorless oil. IR ν_{max} cm^{-1}: 3490, 1778, 1743, 1695. ^{1}H-NMR δ: 7.32 (5H, s), 7.12 (1H, d, J=6 Hz), 6.16 (1H, d, J=6 Hz), 4.53 (2H, s), 4.33 (2H, q), 3.89 (2H, s), 1.35 (3H, t). MS m/z: 292 (M^++H), 291 (M^+), 273, 185, 170, 142, 124, 105, 91. *Anal.* Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.71; H, 5.59; N, 4.71. **10a** was shown to be identical with an authentic sample by IR and ^{1}H-NMR spectral comparisons.

Autoxidation of 4a——A solution of **4a** in benzene (20 ml) was stirred under oxygen at room temperature in

daylight for 7 d. After removal of the solvent, the residue was purified by PLC with $CHCl_3$–ether (2 : 1) to give **6a** (25.6%), which was identified by comparison with an authentic sample.

Autoxidation of 5a——A solution of **5a** (0.5 g, 0.0019 mol) in benzene (20 ml) was stirred in the presence of oxygen at room temperature for 7 d. After removal of the solvent, the residue was purified by PLC with $CHCl_3$–ether (2 : 1) to give **7a** (27%) as a colorless oil. IR ν_{max} cm^{-1}: 3480, 1770, 1740, 1690. ^{1}H-NMR δ: 7.39 (5H, m), 7.11 (1H, d, J=6 Hz), 6.14 (1H, d, J=6 Hz), 5.35 (2H, s), 4.56 (1H, br s, OH), 3.80 (2H, s), 3.28 (3H, s). MS m/z: 278 (M^++H), 277 (M^+), 232, 188, 171, 153, 139, 110, 91 (base). *Anal.* Calcd for $C_{14}H_{15}NO_5$: C, 60.64; H, 5.45; N, 5.05. Found: C, 60.55; H, 5.33; N, 4.75.

Photooxidation of 4b in Benzene——**4b** (0.5 g, 0.0023 mol) was irradiated by a method similar to that described for **4a**. The separation of products was carried out by the same procedure to give **8a** (4.3%), (*E*)-**10b** (3.1%), **6b** (35%), and (*Z*)-**9c** (23.4%). **10b**: A colorless oil. IR ν_{max} cm^{-1}: 3395, 1780, 1755, 1685. ^{1}H-NMR δ: 7.97 (1H, br s, NH), 7.78 (1H, d, J=16 Hz), 7.44 (1H, d, J=16 Hz), 4.26 (2H, q), 3.96 (1H, q), 3.37 (3H, s), 1.36 (3H, d), 1.32 (3H, t). MS m/z: 230 (M^++H), 171 (base), 141, 98, 82. *Anal.* Calcd for $C_{10}H_{15}NO_5$: C, 52.39; H, 6.60; N, 6.11. Found: C, 52.11; H, 6.44; N, 5.87. **6b**: A colorless oil. IR ν_{max} cm^{-1}: 3500, 1770, 1740, 1690. ^{1}H-NMR δ: 7.22 and 7.10 (1H, each d, J=6 Hz), 6.20 (1H, d, J=6 Hz), 4.66 and 4.50 (1H, each br s, OH), 4.38 (2H, q), 4.19 and 4.06 (1H, each q), 3.52 and 3.29 (1H, each s), 1.40 (3H, t), 1.33 (3H, d), 0.97 (3H, d). MS m/z: 230 (M^++H), 212, 171, 153, 143, 123, 99 (base), 80. *Anal.* Calcd for $C_{10}H_{15}NO_5$: C, 52.39; H, 6.60; N, 6.11. Found: C, 52.33; H, 6.44; N, 5.87. **9c**: A colorless oil. IR ν_{max} (neat) cm^{-1}: 3440, 3240, 2965, 1750, 1695. ^{1}H-NMR δ (acetone-d_6): 9.88 (1H, br s, OH), 7.55 (1H, br s, NH), 6.77 (1H, d, J=12 Hz), 6.19 (1H, d, J=12 Hz), 4.16 (2H, q), 1.29 (3H, t). MS m/z: 188 (M^++H), 187 (M^+), 142, 114, 99 (base). *Anal.* Calcd for $C_7H_9NO_5$: C, 44.92; H, 4.85; N, 7.48. Found: C, 44.71; H, 4.61; N, 7.19. **8a** was shown to be identical with an authentic sample.

Photooxidation of 4b in Ethanol——**4b** was irradiated by a method similar to that described for **4a**. The separation of products was carried out by the same procedure to give **8a** (5.4%), **9a** (2.3%), **6b** (24.8%), and **9c** (10.3%), which were identified by comparison with authentic samples.

Photooxidation of 5b in Benzene——**5b** was irradiated by a method similar to that described for **4a**. The separation of products was carried out by the same procedure to give **8c** (4.8%), (*Z*)-**9d** (3%), and **7b** (29.4%). **8c**: A colorless oil. IR ν_{max} cm^{-1}: 3395, 1790, 1765, 1715. ^{1}H-NMR δ: 7.50 (1H, d, J=6 Hz), 7.32 (10H, s), 6.17 (1H, d, J=6 Hz), 6.17 (1H, br s, OH), 5.05 (2H, s), 4.59 (2H, 2 d, J=12 Hz). MS m/z: 340 (M^++H), 233, 142, 125, 107, 98, 91 (base), 82. *Anal.* Calcd for $C_{19}H_{17}NO_5$: C, 67.25; H, 5.05; N, 4.13. Found: C, 67.11; H, 4.87; N, 3.91. **9d**: A colorless oil. IR ν_{max} cm^{-1}: 3375, 1750, 1710. ^{1}H-NMR δ: 8.52 (1h, br s, NH), 7.34 (5H, s), 7.32 (5H, s), 6.66 (1H, d, J=12 Hz), 6.14 (1H, d, J=12 Hz), 5.16 (2H, s), 5.14 (2H, s). MS m/z: 340 (M^++H), 233, 142, 125, 107, 91 (base). *Anal.* Calcd for $C_{19}H_{17}NO_5$: C, 67.25; H, 5.05; N, 4.13. Found: C, 66.99; H, 4.85; N, 3.83. **7b**: A colorless oil. IR ν_{max} cm^{-1}: 3500, 1775, 1743, 1697. ^{1}H-NMR δ: 7.30 (5H, m), 7.13 and 7.00 (1H, each d, J=6 Hz), 6.12 (1H, d, J=6 Hz), 5.32 and 5.29 (2H, each s), 5.04 and 4.61 (1H, each br s, OH), 4.14 and 3.99 (1H, each q), 3.41 and 3.12 (3H, each s), 1.28 and 0.91 (3H, each d). MS m/z: 292 (M^++H), 291 (M^+), 233, 189, 167, 153, 142, 91 (base). *Anal.* Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.61; H, 5.59; N, 4.51.

Photooxidation of 4c in Ethanol——**4c** was irradiated by a method similar to that described for **4a**. The separation of products was carried out by the same procedure to give **8a** (5.2%), **9a** (2.5%), **6c** (16.1%), and **9c** (10.7%). **6c**: A colorless oil. IR ν_{max} cm^{-1}: 3500, 1770, 1738, 1690. ^{1}H-NMR δ: 7.19 and 7.01 (1H, each d, J=6 Hz), 6.17 and 6.13 (1H, each d, J=6 Hz), 4.63 and 4.56 (1H, each d, br s, OH), 4.38 and 4.36 (2H, each q), 3.82 (1H, m), 3.61 and 3.35 (3H, each s), 1.95 and 1.24 (2H, each m), 1.40 (3H, t), 1.05 and 0.98 (3H, each t). MS m/z: 244 (M^++H), 226, 171 (base), 143, 124, 99, 98, 82, 80. *Anal.* Calcd for $C_{11}H_{17}NO_5$: C, 54.31; H, 7.04; N, 5.76. Found: C, 54.11; H, 6.84; N, 5.51. **8a**, **9a**, and **9c** were shown to be identical with authentic samples.

Autoxidation of 5c in Benzene——A solution of **5c** (0.5 g, 0.0017 mol) in benzene (20 ml) was stirred under oxygen at room temperature in daylight for 7 d. After removal of the solvent, the residue was purified by PLC with $CHCl_3$–ether (2 : 1) to give **8d** (4.9%) and **7c** (14.1%). **8d**: A colorless oil. IR ν_{max} cm^{-1}: 3420, 1800, 1777, 1725. ^{1}H-NMR δ: 7.48 (1H, d, J=6 Hz), 7.36 (5H, s), 6.22 (1H, d, J=6 Hz), 6.07 (1H, br s, OH), 5.10 (2H, s), 3.36 (3H, s). ^{13}C-NMR δ_C: 167.7 (s), 152.8 (s), 149.9 (d), 135.2 (s), 128.3 (2 d), 128.1 (d), 127.9 (2 d), 123.5 (d), 109.3 (s), 67.2 (t), 51.0 (q). MS m/z: 264 (M^++H), 231, 209, 157, 129, 114, 113, 91 (base). *Anal.* Calcd for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.98; N, 5.32. Found: C, 59.05; H, 4.69; N, 5.15. **7c**: A colorless oil. IR ν_{max} cm^{-1}: 3480, 1765, 1740, 1690. ^{1}H-NMR δ: 7.32 (5H, m), 7.19 and 7.00 (1H, each d, J=6 Hz), 6.16 and 6.13 (1H, each d, J=6 Hz), 5.35 and 5.32 (2H, each s), 3.76 (1H, m), 3.60 and 3.24 (3H, each s), 1.96 and 1.28 (2H, each m), 1.07 and 0.97 (3H, each t). *Anal.* Calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.69; H, 5.97; N, 4.37.

Catalytic Hydrogenation of 6a—d——A solution of **6a** (0.1 g, 0.0005 mol) in AcOEt (10 ml) containing 5% Pd–C (20 mg) was hydrogenated at room temperature. The reaction mixture was filtered and the filtrate was evaporated to give **11a** (85%) as colorless needles, mp 36—38 °C. IR ν_{max} cm^{-1}: 3380, 1775, 1750, 1695. ^{1}H-NMR δ: 8.01 (1H, br s, NH), 4.24 (2H, q), 4.10 (2H, s), 3.44 (3H, s), 3.07 (2H, m), 2.76 (2H, m), 1.31 (3H, t). ^{13}C-NMR δ_C: 207.5 (s), 173.6 (s), 152.0 (s), 77.5 (t), 62.1 (t), 59.2 (q), 32.6 (t), 30.1 (t), 14.2 (q). *Anal.* Calcd for $C_9H_{15}NO_5$: C, 49.76; H, 6.96; N, 6.45. Found: C, 49.50; H, 6.79; N, 6.10. **6b—d** and **7a—c** were also hydrogenated in the same way. **11b** (83%): Colorless needles, mp 63—65 °C. IR ν_{max} cm^{-1}: 3400, 1782, 1755, 1710. ^{1}H-NMR δ: 8.25 (1H, br s, NH), 4.20 (2H, q), 3.80

(1H, q), 3.38 (3H, s), 3.03 (2H, m), 2.84 (2H, m), 1.33 (3H, d), 1.30 (3H, t). MS *m/z*: 232 ($M^+ + H$), 172 (base), 145, 143, 131, 111, 100. *Anal.* Calcd for $C_{10}H_{17}NO_5$: C, 51.94; H, 7.41; N, 6.06. Found: C, 51.69; H, 7.33; N, 5.87. **11c** (87%): Colorless needles, mp 47—49 °C. IR ν_{max} cm^{-1}: 3390, 1780, 1750, 1700. ^{1}H-NMR δ: 7.90 (1H, br s, NH), 4.18 (2H, q), 3.56 (1H, t), 3.36 (3H, s), 3.01 (2H, m), 2.80 (2H, m), 1.70 (2H, qn), 1.29 (3H, t), 0.93 (3H, t). MS *m/z*: 246 ($M^+ + H$), 172 (base), 157, 145, 115, 100, 82. *Anal.* Calcd for $C_{11}H_{19}NO_5$: C, 53.86; H, 7.81; N, 5.71. Found: C, 53.59; H, 7.56; N, 5.48. **11d** (85%): Colorless needles, mp 60—62 °C. IR ν_{max} cm^{-1}: 3390, 1780, 1750, 1700. ^{1}H-NMR δ: 7.69 (1H, br s, NH), 7.29 (5H, s), 4.56 (2H, s), 4.17 (2H, q), 4.10 (2H, s), 3.03 (2H, m), 2.77 (2H, m), 1.28 (3H, t). MS *m/z*: 294 ($M^+ + H$), 293 (M^+), 187, 172, 169, 144, 128, 100, 91 (base). *Anal.* Calcd for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.35; H, 6.40; N, 4.51.

Catalytic Hydrogenation of 7a—c——12a: A colorless oil (67%). IR ν_{max} cm^{-1}: 3530, 3400, 1690. ^{1}H-NMR δ: 7.44 (1H, br s, NH), 5.10 (1H, br s, OH), 3.45 (2H, s), 3.43 (3H, s), 2.78—2.00 (4H, m). ^{13}C-NMR δ_C: 178.6 (s), 88.1 (s), 77.4 (t), 59.4 (q), 31.6 (t), 29.8 (t). MS *m/z*: 146 ($M^+ + H$), 128, 127, 112, 100 (base), 97, 82, 72. *Anal.* Calcd for $C_6H_{11}NO_3$: C, 49.64; H, 7.64; N, 9.65. Found: C, 49.38; H, 7.39; N, 9.41. **13**: A colorless oil (18%). IR ν_{max} cm^{-1}: 3410, 1680. ^{1}H-NMR δ: 6.24 (1H, br s, NH), 3.85 (1H, m), 3.36 (3H, s), 3.48—3.13 (2H, m), 2.42—1.63 (4H, m). ^{13}C-NMR δ_C: 178.4 (s), 76.3 (t), 59.1 (q), 53.8 (d), 29.8 (t), 23.2 (t). MS *m/z*: 130 ($M^+ + H$), 129 (M^+), 98, 84 (base). *Anal.* Calcd for $C_6H_{11}NO_2$: C, 55.79; H, 8.58; N, 10.85. Found: C, 55.61; H, 8.59; N, 10.71. **12b** (83%): Colorless needles, mp 77—79 °C. IR ν_{max} cm^{-1}: 3420, 3395, 1685. ^{1}H-NMR δ: 7.34 (1H, br s, NH), 4.62 and 4.34 (1H, each br s, OH), 3.39 (3H, s), 3.29 (1H, m), 2.85—1.93 (4H, m), 1.32 and 1.20 (3H, each d). MS *m/z*: 160 ($M^+ + H$), 142, 100, 82, 72. *Anal.* Calcd for $C_7H_{13}NO_3$: C, 52.81; H, 8.23; N, 8.80. Found: C, 52.61; H, 7.99; N, 8.53. **12c** (85%): Colorless needles, mp 87—89 °C. IR ν_{max} cm^{-1}: 3520, 3395, 1680. ^{1}H-NMR δ: 7.52 (1H. br s, NH), 4.84 and 4.58 (1H, each br s, OH), 3.53 and 3.50 (3H, each s), 3.14 (1H, m), 2.92—1.94 (4H, m), 1.65 (2H, m), 1.26 (3H, t). MS *m/z*: 174 ($M^+ + H$), 173 (M^+), 156, 127, 112, 100, 82, 73, 72. *Anal.* Calcd for $C_8H_{13}NO_3$: C, 55.47; H, 8.73; N, 8.09. Found: C, 55.19; H, 8.51; N, 7.85.

References and Notes

1) *a*) K. Yakushijin, M. Kozuka, T. Morishita, and H. Furukawa, *Chem. Pharm. Bull.*, **29**, 2420 (1981); *b*) K. Yakushijin, R. Suzuki, R. Hattori, and H. Furukawa, *Heterocycles*, **16**, 1157 (1981) and references cited therein.
2) B. L. Feringa and R. J. Butselaar, *Tetrahedron Lett.*, **22**, 1447 (1981).
3) A. L. Mndzhoian and M. T. Grigorian, *Proc. Acad. Sci. Armenian SSR*, **17**, 101 (1953).
4) A. L. Mndzhoian and A. A. Aroian, *Proc. Acad. Sci. Armenian SSR*, **25**, 267 (1957).
5) Treatment of **1b** and **1c** with sodium methoxide resulted in transformation of the ester group (see Experimental).
6) The chemical behavior of furan endoperoxides has been reported by Adam *et al.*: W. Adam and A. Rodriguez, *J. Am. Chem. Soc.*, **102**, 404 (1980).