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Studies on Heterocyclic Compounds. IX.[1] Synthesis and Antiallergic Activity of Furo[2,3-*b*][1,8]naphthyridine-3,4(2*H*,9*H*)-diones and 4*H*-Furo[2,3-*d*']pyrido[1,2-*a*]-pyrimidine-3,4(2*H*)-diones

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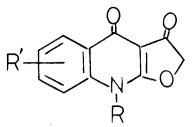
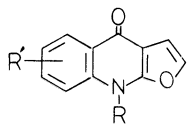
A series of furo[2,3-*b*][1,8]naphthyridine-3,4(2*H*,9*H*)-dione and 4*H*-furo[2,3-*d*]pyrido[1,2-*a*]pyrimidine-3,4(2*H*)-dione derivatives were synthesized and evaluated for antiallergic activity by rat passive cutaneous anaphylaxis (PCA) screening. Most of these compounds were found to be orally active. Among them, 9-ethyl-7-methylfuro[2,3-*b*][1,8]naphthyridine-3,4(2*H*,9*H*)-dione was the most promising, and was selected for further modifications.

Keywords——antiallergic activity; furo[2,3-*b*][1,8]naphthyridine-3,4(2*H*,9*H*)-dione; 4*H*-furo-[2,3-*d*]pyrido[1,2-*a*]pyrimidine-3,4(2*H*)-dione; thermal cyclization; rat-PCA method

In a previous paper[1] of this series, we reported the antiallergic activity of a novel series of *N*-alkylfuro[2,3-*b*]quinoline-3,4(2*H*,9*H*)-diones of type I, that were developed on the basis of our studies on furo[2,3-*b*]quinolin-4(9*H*)-one alkaloids (type II).[2]



I



II

As part of this program, we also investigated some analogs, furo[2,3-*b*][1,8]naphthyridine-3,4(2*H*,9*H*)-diones (III) and 4*H*-furo[2,3-*d*]pyrido[1,2-*a*]pyrimidine-3,4(2*H*)-diones (IV), which constitute a new class of antiallergic compounds as assessed by their ability to inhibit the IgE-mediated passive cutaneous anaphylaxis (PCA) reaction in the rat. This paper will describe the synthesis and the antiallergic activities of these compounds.

Chemistry

9-Alkyl-7-methylfuro[2,3-*b*][1,8]naphthyridine-3,4(2*H*,9*H*)-diones (III)

The synthetic pathway to compound III is shown in Chart 1. Ethyl 2-ethoxy-4-oxo-4,5-dihydrofuran-3-carboxylate (VI)[2a] was condensed with 2-amino-6-methylpyridine (Va) to give ethyl 2-(6-methyl-2-pyridylamino)-4-oxo-4,5-dihydrofuran-3-carboxylate (VIIa). Thermal cyclization of VIIa in boiling diphenylether afforded 7-methylfuro[2,3-*b*][1,8]naphthyridine-3,4(2*H*,9*H*)-dione (IIIa) in 85% yield. The proton nuclear magnetic resonance (^{1}H-

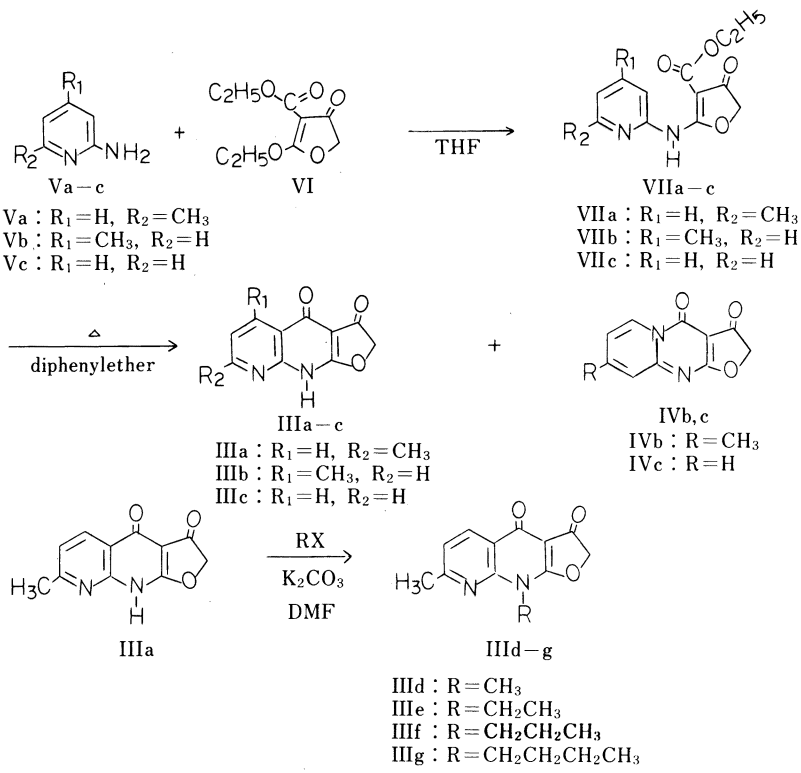


Chart 1

NMR) spectrum of IIIa exhibited a single-proton signal at δ 7.70 (J=8.0 Hz) which was coupled only with the proton at δ 9.13 (J=8.0 Hz). The spectral data supported the pyridine ring substitution pattern in structure IIIa. Compound IIIa was treated with a variety of alkyl halides (or dialkyl sulfates) in the presence of potassium carbonate in dimethylformamide (DMF) to give the corresponding N-alkyl derivatives (IIId—g).

4*H*-Furo[2,3-*d*]pyrido[1,2-*a*]pyrimidine-3,4(2*H*)-diones (IVa, b)

As shown in Chart 1, 2-amino-4-methyl pyridine (Vb) was condensed with compound VI to give ethyl 2-(4-methyl-2-pyridylamino)-4-oxo-4,5-dihydrofuran-2-carboxylate (VIIb). When compound VIIb was treated with boiling diphenylether, two products were isolated. The elemental analysis and mass spectra of both products were consistent with a molecular formula of $C_{11}H_8N_2O_3$, indicating that they are isomers. The major product (71%) displayed no N–H absorption band in its infrared (IR) spectrum. Its ^{1}H-NMR spectrum exhibited a single-proton signal at δ 7.65 (d, J=7.0 Hz) which was coupled to a proton at δ 9.28 (d, J=7.0 Hz) and a one-proton singlet appeared at δ 7.95. These observations suggested that this major product was derived from cyclization at the ring nitrogen atom of VIIb and its structure is therefore assigned as 4*H*-8-methylfuro[2,3-*d*]pyrido[1,2-*a*]pyrimidine-3,4(2*H*)-dione (IVb).

The minor product (3%) exhibited a ultraviolet (UV) spectrum with $\lambda_{max}^{CHCl_3}$ at 272, 365 and 382 nm (log ε=3.43, 3.01 and 3.15, respectively), which is very similar to that of IIIa. This product also displayed an N–H absorption band at 3010 cm^{-1} in its IR spectrum. These results suggest that the minor isomer was derived from cyclization at the 3 position of the pyridine ring and its structure is therefore assigned as 5-methylfuro[2,3-*b*][1,8]naphthyridine-3,4(2*H*,9*H*)-dione (IIIb). The structure of IIIb is further supported by its ^{1}H-NMR spectrum, which exhibited absorptions of two protons on the pyridine ring at δ 6.88 (1H, d, J=7.0 Hz)

and 8.15 (d, 1H, $J=7.0$ Hz).

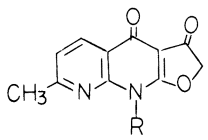
By analogy, the syntheses of 4*H*-furo[2,3-*d*]pyrido[1,2-*a*]pyrimidine-3,4(2*H*)-dione (IVc) and furo[2,3-*b*][1,8]naphthyridine-3,4(2*H*,9*H*)-dione (IIIc) were accomplished by subjecting 2-aminopyridines (VIIc) to condensation and cyclization as shown in Chart 1.

From the above studies, we found that the orientation of thermal cyclization of compound VII is apparently influenced by the steric effects of substituents on the pyridine ring.

Biological Results and Discussion

The compounds were tested for ability to inhibit rat PCA at the oral dosage of 80 mg/kg: PCA[3,4] was caused by intravenous injection of the antigen together with a 0.5% Evan's blue solution into male Wistar rats 48 h after an intradermal injection of mouse antiserum to egg albumin, and 30 min later the blueing area was measured. As shown in Table I, compound IIIa was found to have a significant inhibitory activity, about a half as potent as that of theophylline. Then, derivatives of compound IIIa having a lower alkyl group at the 9 position

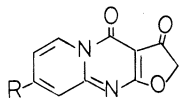
TABLE I. Antiallergic Activity of 9-Alkyl-7-methylfuro[2,3-*b*][1,8]-naphthyridine-3,4(2*H*,9*H*)-diones



Compd.	R	Rat PCA inhibition %[a,b] (80 mg/kg, *p.o.*)
IIIa	H	45.6[c]
IIId	$-CH_3$	46.6[c]
IIIe	$-CH_2CH_3$	53.4[c]
IIIf	$-CH_2CH_2CH_3$	44.3[c]
IIIg	$-CH_2CH_2CH_2CH_3$	23.0
Theophylline		67.2[c]

a) Test compounds were administered orally to the rats 1 h before antigen challenge. The antiallergic activity of the compounds was expressed as percent inhibition of the PCA reaction as compared with the control. Statistical significance was assessed by using Student's *t*-test.[3,4] *b*) The figure represents the mean from 3—8 rats. *c*) $p<0.01$ significantly different from each control group.

TABLE II. Antiallergic Activity of 4*H*-8-Alkylfuro[2,3-*d*]pyrido[1,2-*a*]-pyrimidine-3,4(2*H*)-diones (IVb, c)



Compd.	R	Rat PCA inhibition %[a] (80 mg/kg, *p.o.*)
IVc	H	35.2[b]
IVb	$-CH_3$	35.1
Theophylline		67.2[b]

a) See Table I. *b*) $p<0.01$ significantly different from each control group.

were prepared and tested. The potency order was ethyl > methyl, propyl, H > butyl at R, and compound IIIe with an ethyl group was the most active (Table I).

On the other hand, in the series of 4*H*-8-alkyl furo[2,3-*d*]pyrido[1,2-*a*]pyrimidine-3,4(2*H*)-diones, compounds IVc and IVb showed significant but somewhat weaker activity than that of a series of furo[2,3-*b*][1,8]naphthyridine-3,4(2*H*,9*H*)-diones (Table II).

Several classes of antiallergic agents are utilized for the treatment of asthma. They are disodium cromoglycate and tranilast as inhibitors of mediator release from mast cells, theophylline as a phosphodiesterase inhibitor and adenosine receptor antagonist, beta-adrenergic drugs as beta-adrenoceptor agonists, antihistamines as histamine H_1 antagonists and glucocorticoids. However, compound IIIe has a novel chemical structure, being dissimilar to these agents. Thus, compound IIIe may be expected to have a unique mode of antiallergic action.

Experimental

All melting points are uncorrected. IR spectra were recorded on a Shimadzu IR-400 spectrometer in KBr. NMR spectra were taken at 90 MHz on a JEOL FX-90Q spectrometer with tetramethylsilane (TMS) as an internal reference in $CDCl_3$ or CF_3COOD, or dimethyl sulfoxide (DMSO)-d_6. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. Mass spectra (MS) were measured with a HP5995 GC-MS instrument. The UV spectra were recorded on a Shimadzu UV-210A. Elemental analyses were performed by Chung Shan Institute of Science Technology (R.O.C.).

Ethyl 2-(6-Methyl-2-pyridylamino)-4-oxo-4,5-dihydrofuran-3-carboxylate (VIIa)——Sodium hydride (21 g, 80%, 0.7 mol), previously washed with dry *n*-hexane, was suspended in dry tetrahydrofuran (THF) (125 ml) and this suspension was added slowly, with shaking, over 20 min to a solution of diethyl malonate (115 ml, 0.075 mol) in dry THF (250 ml). The reaction mixture was refluxed on a water bath for 2 min, then cooled to 10—12 °C, and chloroacetyl chloride (31.8 ml, 0.4 mol) in dry THF (170 ml) was added dropwise over 1 h. The solution was kept at this temperature for 1 h, and at 40—50 °C for another 1 h, then cooled to 10—12 °C. 2-Amino-6-methylpyridine (Va) (40.5 g, 0.38 mol) in dry THF (200 ml) was then added dropwise over 1 h. The reaction mixture was left at room temperature overnight, heated under reflux for 1 h, then cooled and poured into iced H_2O. The precipitated solid was extracted with $CHCl_3$, and the extract was washed with H_2O and dried ($MgSO_4$). The solvent was partially evaporated and the concentrated residue was refrigerated for 3 d. The precipitate was collected and recrystallized from EtOH to afford compound VIIa (53.7 g, 54%), mp 147—149 °C. IR (KBr) cm^{-1}: 3200 (NH), 1695 (C=O), 1652 (C=O). NMR ($CDCl_3$) δ ppm: 1.35 (3H, t, J=7.0 Hz, $-OCH_2CH_3$), 2.44 (3H, s, 6′-CH_3), 4.30 (2H, q, J=7.0 Hz, $-OCH_2-CH_3$), 4.60 (2H, s, $-O-CH_2-CO-$), 6.82—7.70 (3H, m, 3′-H, 4′-H, 5′-H), 10.35 (1H, br, N-H). MS *m/z*: 262 (M^+). *Anal.* Calcd for $C_{13}H_{14}N_2O_4$: C, 59.53; H, 5.38; N, 10.68. Found C, 59.18; H, 5.01; N, 10.89.

7-Methylfuro[2,3-*b*][1,8]naphthyridine-3,4(2*H*,9*H*)-dione (IIIa)——Compound VIIa (2 g, 7.6 mmol) as a fine powder was added with stirring in one portion to diphenyl ether (20 ml) maintained at 240 °C. The temperature was then raised to 256 °C and kept there for 5 min. The mixture was cooled to room temperature and diluted with a large volume of *n*-hexane to precipitate a solid that was collected, washed with hot *n*-hexane and purified by chromatography on a silica gel (150 g) column. Elution with $CHCl_3$–EtOH (98 : 2) yielded compound IIIa as a light yellow solid (1.38 g, 85%), mp 260—262 °C. IR (KBr) cm^{-1}: 3010 (NH), 1710 (C=O), 1645 (C=O). NMR (CF_3COOD) δ ppm: 2.97 (3H, s, 7-CH_3), 5.06 (2H, s, $-OCH_2-CO-$), 7.70 (1H, d, J=8.0 Hz, 6-H), 9.13 (1H, d, J=8.0 Hz, 5-H). UV $\lambda_{max}^{CHCl_3}$ nm: 272, 367, 384 ($\log\varepsilon$=3.44, 3.12, 3.10). MS *m/z*: 216 (M^+). *Anal.* Calcd for $C_{11}H_8N_2O_3$: C, 66.11; H, 3.73; N, 12.96. Found: C, 65.91; H, 3.50; N, 12.79.

7,9-Dimethylfuro[2,3-*b*][1,8]naphthyridine-3,4(2*H*,9*H*)-dione (IIId)——Compound IIIa (2.0 g, 9.3 mmol) was suspended in EtOH (50 ml) and the suspension was warmed to 40 °C, then anhydrous K_2CO_3 (15 g, 0.12 mol) was added. Dimethyl sulfate (13 ml, 0.1 mol) was then added dropwise over 1 h. The reaction mixture was evaporated *in vacuo*. Iced H_2O was added to the residue, and the precipitate was collected by filtration, washed with H_2O and dissolved in $CHCl_3$. The $CHCl_3$ solution was dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography on silica gel (150 g). Elution with $CHCl_3$–EtOH (98 : 2) yielded compound IIId (1.66 g, 78%), mp 279—282 °C. IR (KBr) cm^{-1}: 1705 (C=O), 1635 (C=O). NMR ($CDCl_3$) δ ppm: 2.60 (3H, s, 7-CH_3), 3.83 (3H, s, N-CH_3), 4.73 (2H, s, $-O-CH_2-CO-$), 7.17 (1H, d, J=8.0 Hz, 6-H), 8.50 (1H, d, J=8.0 Hz, 5-H). MS *m/z*: 230 (M^+). *Anal.* Calcd for $C_{12}H_{10}N_2O_3$: C, 62.60; H, 4.38; N, 12.17. Found: C, 62.88; H, 4.12; N, 12.40.

9-Ethyl-7-methylfuro[2,3-*b*][1,8]naphthyridine-3,4(2*H*,9*H*)-dione (IIIe)——Compound IIIa (2.0 g, 9.3 mmol) was reacted with diethyl sulfate (13 ml, 0.1 mol) as described for the preparation of IIId to afford IIIe, 1.8 g (80%), mp 252—254 °C. IR (KBr) cm^{-1}: 1705 (C=O), 1635 (C=O). NMR ($CDCl_3$) δ ppm: 1.40 (3H, t, J=7.0 Hz, N-CH_2-CH_3), 2.65 (3H, s, 7-CH_3), 4.50 (2H, q, J=7.0 Hz, N-CH_2-CH_3), 4.76 (2H, s, $-OCH_2-CO-$), 7.23 (1H, d, J=8.0 Hz, 6-H), 8.52 (1H, d, J=8.0 Hz, 5-H). MS *m/z*: 244 (M^+). *Anal.* Calcd for $C_{13}H_{12}N_2O_3$: C, 63.92; H, 4.95;

N, 11.47. Found: C, 63.59; H, 4.54; N, 11.31.

7-Methyl-9-propylfuro[2,3-*b*][1,8]naphthyridine-3,4(2*H*,9*H*)-dione (IIIf)——Compound IIIa (2.0 g, 9.3 mmol) was reacted with propyl iodide (15 ml, 0.15 mol) as described for the preparation of IIId to afford IIIf (1.86 g, 78%), mp 218—220 °C. IR (KBr) cm^{-1}: 1705 (C=O), 1635 (C=O). NMR ($CDCl_3$) δ ppm: 1.00 (3H, t, J=7.0 Hz, >N–CH_2–CH_2–$\underline{CH_3}$), 1.55—2.33 (2H, m, N–CH_2–$\underline{CH_2}$–CH_3), 2.61 (3H, s, 7-CH_3), 4.43 (2H, t, J=7.0 Hz, N–$\underline{CH_2}$–CH_2–CH_3), 4.75 (2H, s, –O–CH_2–CO–), 7.16 (1H, d, J=8.0 Hz, 6-H), 8.50 (1H, d, J=8.0 Hz, 5-H). MS *m/z*: 258 (M^+). *Anal.* Calcd for $C_{14}H_{14}N_2O_3$: C, 65.10; H, 5.46; N, 10.85. Found: C, 65.35; H, 5.37; N, 10.61.

9-Butyl-7-methylfuro[2,3-*b*][1,8]naphthyridine-3,4(2*H*,9*H*)-dione (IIIg)——Compound IIIa (2.0 g, 9.3 mmol) was reacted with butyl iodide (15 ml, 0.13 mol) as described for the preparation of IIId to afford IIIg (1.96 g, 78%), mp. 173—174 °C. IR (KBr) cm^{-1}: 1705, (C=O), 1635 (C=O). NMR ($CDCl_3$) δ ppm: 1.00 (3H, t, J=7.0 Hz, >N–$CH_2CH_2CH_2\underline{CH_3}$), 1.67—2.00 (4H, m, N–$CH_2\underline{CH_2}\underline{CH_2}CH_3$), 2.60 (3H, s, 7-$CH_3$), 4.50 (2H, t, J=7.0 Hz, N–CH_2–), 4.80 (2H, s, –O–CH_2–CO–), 7.11 (1H, d, J=8.0 Hz, 6-H), 8.53 (1H, d, J=8.0 Hz, 5-H). MS *m/z*: 272 (M^+). *Anal.* Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.38; H, 5.72; N, 10.00.

Ethyl 2-(4-Methyl-2-pyridylamino)-4-oxo-4,5-dihydrofuran-3-carboxylate (VIIb)——2-Amino-6-methylpyridine (Vb) (40.5 g, 0.38 mol) was treated as described for the preparation of VIIa to afford VIIb (58 g, 71%), mp 152—154 °C. IR (KBr) cm^{-1}: 3200 (NH), 1695 (C=O), 1655 (C=O). NMR ($CDCl_3$) δ ppm: 1.03 (3H, t, J=7.0 Hz, –O–CH_2–$\underline{CH_3}$), 2.35 (3H, s, 4′-CH_3), 4.33 (2H, q, J=7.0 Hz, –O–$\underline{CH_2}$–CH_3), 4.70 (2H, s, –O–CH_2–CO–), 6.88 (1H, d, J=5.0 Hz, 5′-H), 7.33 (1H, s, 3′-H), 8.17 (1H, d, J=5.0 Hz, 6′-H), 10.45 (1H, br, NH–). MS *m/z*: 262 (M^+). *Anal.* Calcd for $C_{13}H_{14}N_2O_4$: C, 59.53; H, 5.38; N, 10.68. Found: C, 59.21; H, 5.13; N, 10.79.

Ethyl 2-(2-Pyridylamino)-4-oxo-4,5-dihydrofuran-3-carboxylate (VIIc)——2-Aminopyridine (Vc) (35 g, 0.38 mol) was treated as described for the preparation of VIIa to afford VIIc (58 g, 62%), mp 162—164 °C. IR (KBr) cm^{-1}: 3200 (N–H), 1700 (C=O), 1650 (C=O). NMR ($CDCl_3$) δ ppm: 1.03 (3H, t, J=7.0 Hz, –O–$CH_2\underline{CH_3}$), 4.33 (2H, q, J=7.0 Hz, –O–$\underline{CH_2}$–CH_3), 4.70 (2H, s, –O–CH_2–CO–), 6.90—8.50 (4H, m, 3′-H, 4′-H, 5′-H, 6′-H), 10.55 (1H, br, N–H). MS *m/z*: 248 (M^+). *Anal.* Calcd for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.29. Found: C, 57.90; H, 4.95; N, 11.04.

5-Methylfuro[2,3-*b*][1,8]naphthyridine-3,4(2*H*,9*H*)-dione (IIIb) and 4*H*-8-Methylfuro[2,3-*d*]pyrido[1,2-*a*]pyrimidine-3,4(2*H*)-dione (IVb)——Compound VIIb (2.0 g, 7.6 mmol) was treated as described for the preparation of IIIa to afford IIIb (0.06 g, 2.5%), mp 250—252 °C. IR (KBr) cm^{-1}: 3010 (NH), 1710 (C=O), 1645 (C=O). NMR (CF_3COOD) δ ppm: 2.96 (3H, s, 5-CH_3), 5.04 (2H, s, –OCH_2–CO–), 7.70 (1H, d, J=5.0 Hz, 6H), 8.50 (1H, d, J=5.0 Hz, 7-H). MS *m/z*: 216 (M^+). UV $\lambda_{max}^{CHCl_3}$ nm: 272, 365, 382 ($\log\varepsilon$=3.43, 3.01, 3.15). *Anal.* Calcd for $C_{11}H_8N_2O_3$: C, 61.11; H, 3.73; N, 12.96. Found: C, 61.01; H, 3.85; N, 12.70. IVb (1.6 g, 71%), mp 268—270 °C. IR (KBr) 1750 (C=O), 1675 (C=O). NMR (CF_3COOD) δ ppm: 2.83 (3H, s, 7-CH_3), 5.28 (2H, s, –O–CH_2–CO–), 7.65 (1H, d, J=7.0 Hz, 7-H), 7.95 (1H, s, 9-H), 9.28 (1H, d, J=7.0 Hz, 6-H). UV $\lambda_{max}^{CHCl_3}$ nm: 268, 350, 365 ($\log\varepsilon$=4.50, 4.20, 4.12). MS *m/z*: 216 (M^+). *Anal.* Calcd for $C_{11}H_8N_2O_3$: C, 61.11; H, 3.73; N, 12.96. Found: C, 61.35; H, 3.98; N, 12.74.

Furo[2,3-*b*][1,8]naphthyridine-3,4(2*H*,9*H*)-dione (IIIc) and 4*H*-Furo[2,3-*d*]pyrido[1,2-*a*]pyrimidine-3,4(2*H*)-dione (IVc)——Compound VIIc (2.0 g, 8 mmol) was treated as described for the preparation of IIIa to afford IIIc (0.05 g, 3%), mp 261—263 °C. IR (KBr) cm^{-1}: 3008 (NH), 1700 (C=O), 1645 (C=O). NMR (CF_3COOD) δ ppm: 5.05 (2H, s, –OCH_2–CO–), 7.70—8.50 (2H, m, 6-H, 7-H), 9.17 (1H, d, J=8.0 Hz, 5-H). MS *m/z*: 202 (M^+). UV $\lambda_{max}^{CHCl_3}$ nm: 370, 365, 380 ($\log\varepsilon$=3.02, 3.10, 3.15). *Anal.* Calcd for $C_{10}H_6N_2O_3$: C, 59.41; H, 2.99; N, 13.86. Found: C, 59.00; H, 2.70; N, 13.59. IVc (1.2 g, 71%): mp 281—282 °C. IR (KBr) cm^{-1}: 1750 (C=O), 1665 (C=O). NMR (CF_3COOD) δ ppm: 5.10 (2H, s, –OCH_2–CO–), 7.76—8.80 (4H, m, 6-H, 7-H, 8-H, 9-H). MS *m/z*: 202 (M^+). UV $\lambda_{max}^{CHCl_3}$ nm: 268, 349, 365 ($\log\varepsilon$=4.23, 4.11, 3.65). *Anal.* Calcd for $C_{10}H_6N_2O_3$: C, 59.41; H, 2.99; N, 13.86. Found: C, 59.26; H, 2.69; N, 13.98.

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References and Notes

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