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Furo[3,2-*b*]indole Derivatives. I. Synthesis and Analgesic and Anti-inflammatory Activities of 4,6-Disubstituted-furo[3,2-*b*]indole-2-carboxamide Derivatives

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N-(3-Piperidinopropyl)-4,6-disubstituted-furo[3,2-*b*]indole-2-carboxamide derivatives were prepared and examined for analgesic and anti-inflammatory activities using the acetic acid writhing method in mice and the carrageenin edema method in rats. Some of the compounds were found to have potent analgesic and anti-inflammatory activities in the animal model.

Keywords—*N*-(3-piperidinopropyl)-4,6-disubstituted-furo[3,2-*b*]indole-2-carboxamide; *N*-(3-piperidinopropyl)-4-methyl-6-trifluoromethyl-furo[3,2-*b*]indole-2-carboxamide; Meerwein arylation; analgesic activity; anti-inflammatory activity

2,4-Disubstituted-furo[3,2-*b*]indole derivatives were first synthesized by Tanaka *et al.*^{1,2)} The structure of the furo[3,2-*b*]indole skeleton seemed to us to be particular interest in view of its possible relationship with biological activity. In the present investigation, various *N*-(3-piperidinopropyl)-4,6-disubstituted-furo[3,2-*b*]indole-2-carboxamides were synthesized and their analgesic and anti-inflammatory activities were evaluated.

Chemistry

The synthesis of 6-substituted-4*H*-furo[3,2-*b*]indole-2-carboxylates (VIa—d) was carried out using the same method as that reported for 4*H*-furo[3,2-*b*]indole-2-carboxylates.³⁾ The method of synthesis is summarized in Chart 1. Thus, Meerwein arylation of the 4-substituted-

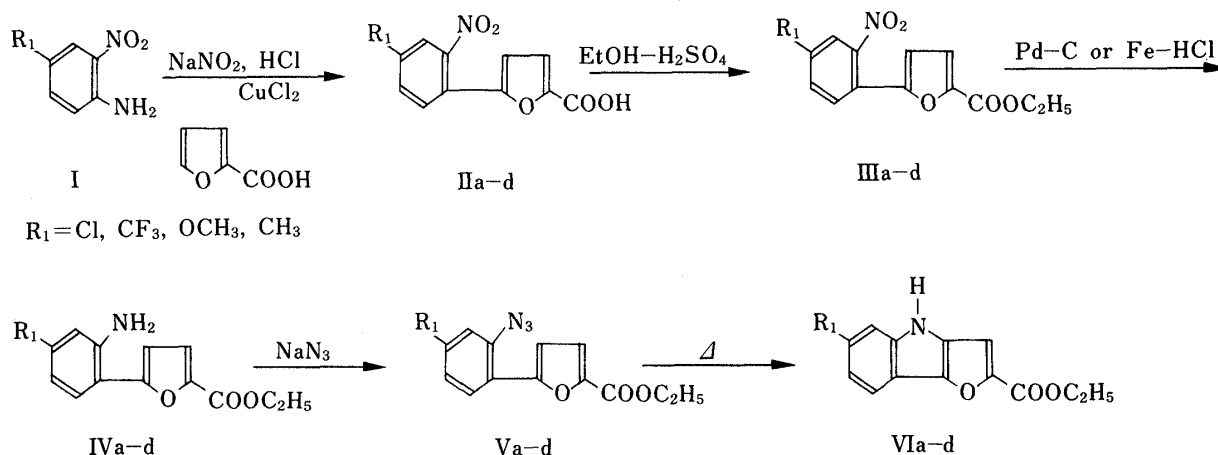


Chart 1

2-nitroanilines (I) with 2-furancarboxylic acid gave the corresponding 5-(4-substituted-2-nitrophenyl)-2-furancarboxylic acids (IIa—d). By esterification with EtOH and conc. H_2SO_4 , followed by catalytic reduction or Fe—HCl reduction of the nitro group, compounds IIa—d were led to IVa—d. The diazonium salts of IVa—d were allowed to react with NaN_3 to give Va—d. Compounds VIa—d were obtained by thermolysis of Va—d.

N-(3-Piperidinopropyl)-4,6-disubstituted-furo[3,2-*b*]indole-2-carboxamides (Xa—t, XIa—h) were prepared according to the route shown in Chart 2. Compounds VIa—d were

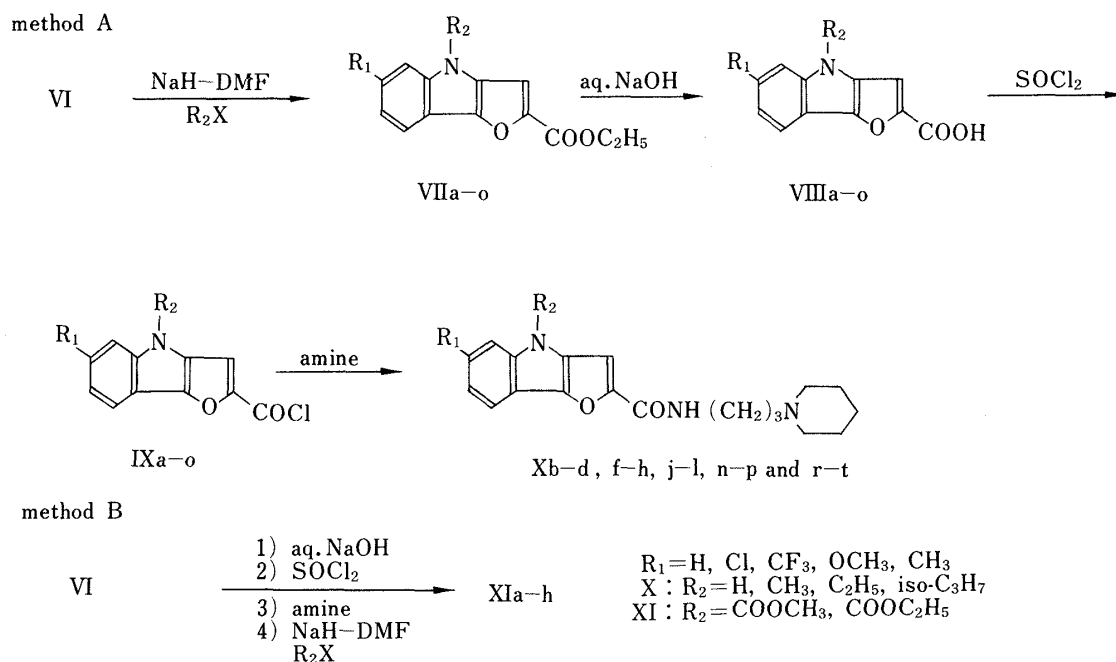


Chart 2

converted to the corresponding 4-alkyl derivatives (VIIa—o) by alkylation. Hydrolysis of VIIa—o with aq. NaOH gave the free acids (VIIIa—o). Chlorination of VIIIa—o with SOCl_2 gave the acid chlorides (IXa—o), which were treated with *N*-(3-aminopropyl)piperidine to give the corresponding carboxamide derivatives (Xb—d, f—h, j—l, n—p and r—t) (method A).

On the other hand, XIa—h were prepared by initial hydrolysis of VIa—d, followed by chlorination, treatment with an amine (Xa, e, i, m and q) and alkoxycarbonylation at the 4-position with alkylchloroformates (method B). Physical and analytical data for Xa—t and XIa—h are recorded in Table I.

Biological Methods

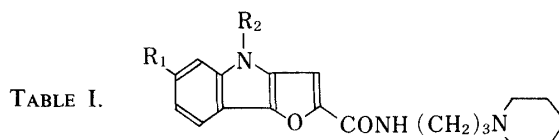
Analgesic activities of the compounds synthesized in this study were evaluated by the acetic acid writhing method in mice.⁴⁾ Anti-inflammatory activities were examined using the carrageenin edema method in rats.⁵⁾ The test compounds and positive controls were suspended in 5% gum arabic solution.

Acetic Acid Writhing

Groups of 10 male ddY mice weighing 19—23 g were used. The test compounds and positive controls were administered orally (100 mg/kg) 30 min before the intraperitoneal injection (10 ml/kg) of 0.7% acetic acid solution. The number of writhes by each mouse was counted during a period of 10 to 20 min after the acetic acid injection. The inhibitory percent was calculated by comparing the number of writhes with that in the untreated control group.

Carrageenin Edema

Groups of 6 male Wistar rats weighing 140—170 g were used. The test compounds and positive control drugs were administered orally (100 mg/kg) 30 min before the subplantar injection (0.1 ml/rat) of 1% carrageenin suspension into the left hind foot. The foot volume was measured 3 h after the carrageenin injection. The swelling percent was calculated as compared with the pre-drug volume and the inhibitory percent was calculated as compared with the swelling percent in the control group.



No.	R ₁	R ₂	mp (°C)	Recrystn. solvent ^{a)}	Method ^{b)}	Formula ^{c)}	Analgesic activity ^{d)}	Anti-infl. activity ^{e)}
Xa	H	H	198—199	A	B	C ₁₉ H ₂₃ N ₃ O ₂	32.5 ^{f)}	18.2
Xb	H	CH ₃	148—150	P-B	A	C ₂₀ H ₂₅ N ₃ O ₂	60.3 ^{g)}	19.2
Xc	H	C ₂ H ₅	127—129	P-B	A	C ₂₁ H ₂₇ N ₃ O ₂	30.4	23.5
Xd	H	iso-C ₃ H ₇	131—132	H-B	A	C ₂₂ H ₂₉ N ₃ O ₂	24.0	18.5
Xe	Cl	H	232—233	B	B	C ₁₉ H ₂₂ ClN ₃ O ₂	32.8 ^{f)}	17.1
Xf	Cl	CH ₃	154—156	P-B	A	C ₂₀ H ₂₄ ClN ₃ O ₂	91.6 ^{h)}	30.3 ^{f)}
Xg	Cl	C ₂ H ₅	137—138	H-A	A	C ₂₁ H ₂₆ ClN ₃ O ₂	74.6 ^{h)}	34.0 ^{f)}
Xh	Cl	iso-C ₃ H ₇	141—142	P-B	A	C ₂₂ H ₂₈ ClN ₃ O ₂	83.7 ^{h)}	13.1
Xi	CF ₃	H	198—199	B	B	C ₂₀ H ₂₂ F ₃ N ₃ O ₂	10.4	0.0
Xj	CF ₃	CH ₃	155—156	H-A	A	C ₂₁ H ₂₄ F ₃ N ₃ O ₂	88.9 ^{h)}	44.6 ^{g)}
Xk	CF ₃	C ₂ H ₅	124—126	H-A	A	C ₂₂ H ₂₆ F ₃ N ₃ O ₂	82.6 ^{h)}	30.0 ^{f)}
Xl	CF ₃	iso-C ₃ H ₇	128—129	H-A	A	C ₂₃ H ₂₈ F ₃ N ₃ O ₂	81.4 ^{h)}	51.4 ^{g)}
Xm	OCH ₃	H	179—181	T	B	C ₂₀ H ₂₅ N ₃ O ₃	N.T.	N.T.
Xn	OCH ₃	CH ₃	155—157	A	A	C ₂₁ H ₂₇ N ₃ O ₃	77.8 ^{h)}	74.4 ^{h)}
Xo	OCH ₃	C ₂ H ₅	120—121	A	A	C ₂₂ H ₂₉ N ₃ O ₃	72.0 ^{h)}	71.7 ^{h)}
Xp	OCH ₃	iso-C ₃ H ₇	168—170	A	A	C ₂₃ H ₃₁ N ₃ O ₃	75.7 ^{h)}	63.2 ^{g)}
Xq	CH ₃	H	194—199	T	B	C ₂₀ H ₂₅ N ₃ O ₂	N.T.	N.T.
Xr	CH ₃	CH ₃	138—139	H-A	A	C ₂₁ H ₂₇ N ₃ O ₂	66.9 ^{g)}	69.1 ^{h)}
Xs	CH ₃	C ₂ H ₅	133—134	A	A	C ₂₂ H ₂₉ N ₃ O ₂	79.0 ^{h)}	38.9 ^{f)}
Xt	CH ₃	iso-C ₃ H ₇	143—145	A	A	C ₂₃ H ₃₁ N ₃ O ₂	66.7 ^{g)}	54.4 ^{g)}
XIa	Cl	COOCH ₃	146—148	A	B	C ₂₁ H ₂₄ ClN ₃ O ₄	73.8 ^{h)}	23.5
XIb	Cl	COOC ₂ H ₅	114—115	H-A	B	C ₂₂ H ₂₆ ClN ₃ O ₄	39.5 ^{f)}	—1.5
XIc	CF ₃	COOCH ₃	146—148	A	B	C ₂₂ H ₂₄ F ₃ N ₃ O ₄	47.8 ^{g)}	—1.8
XId	CF ₃	COOC ₂ H ₅	153—154	A	B	C ₂₃ H ₂₆ F ₃ N ₃ O ₄	56.6 ^{g)}	5.5
XIe	OCH ₃	COOCH ₃	116—118	H-A	B	C ₂₂ H ₂₇ N ₃ O ₅	59.7 ^{g)}	46.5 ^{f)}
XIf	OCH ₃	COOC ₂ H ₅	129—131	A	B	C ₂₃ H ₂₉ N ₃ O ₅	38.9 ^{g)}	30.4 ^{f)}
XIg	CH ₃	COOCH ₃	112—114	H-E	B	C ₂₂ H ₂₇ N ₃ O ₄	40.9 ^{f)}	37.2 ^{f)}
XIh	CH ₃	COOC ₂ H ₅	115—117	H-A	B	C ₂₃ H ₂₉ N ₃ O ₄	48.0 ^{f)}	5.5
Aminopyrin							80.5 ^{h)}	55.3 ^{g)}
Tiaramide							75.0 ^{h)}	40.8 ^{g)}

a) A = acetone, B = benzene, E = ether, H = hexane, P = petroleum benzin, M = MeOH, T = EtOH.

b) See Chart 2.

c) All compounds were analyzed for C, H and N: analytical results obtained for these elements were within $\pm 0.4\%$ of calculated values.

d) % inhibition of acetic acid writhing.

e) % inhibition of carrageenin edema.

Statistically significant at f) $p < 0.05$, g) $p < 0.01$, h) $p < 0.001$.

N.T.: not tested.

Results and Discussion

The biological data for *N*-(3-piperidinopropyl)-4,6-disubstituted-furo[3,2-*b*]indole-2-carboxamides (Xa—t and XIa—h) are shown in Table I. The analgesic activities of compounds Xf—h, j—l, n—p, r—t and XIa were roughly equivalent to those of the positive controls (aminopyrine and tiaramide). The anti-inflammatory activities of compounds Xn, o and r were more potent than those of the positive controls, and those of compounds Xj, l, p, t and XIe were roughly equivalent to those of the positive controls.

These results indicate that compounds Xj, l, n—p, r and t show potent analgesic and anti-inflammatory activities, and it appears that the presence of a Cl, CF₃, OCH₃ or CH₃ group as R₁ tends to increase these activities. The activity levels were, in general, more potent with an alkyl group as R₂ than with an alkoxycarbonyl group. In mice, compounds Xk—l, n—p and r—t induced tremor and convulsion at an oral dose of 200 mg/kg, but the other compounds did not show these behavioral changes at the same dose. Therefore, among these compounds, *N*-(3-piperidinopropyl)-4-methyl-6-trifluoromethyl-furo[3,2-*b*]indole-2-carboxamide (Xj) seems to have a desirable combination of high activities and low toxicity. Further work on the synthesis and biological activities of this new class of furo[3,2-*b*]indole derivatives is in progress.

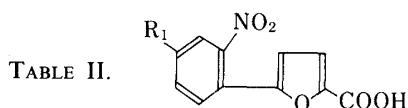
Experimental

Melting points were determined on a Mitamura Rikken micro melting point apparatus and are uncorrected. Infrared (IR) spectra were taken on a Jasco DS-301 spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded on a Hitachi-Perkin-Elmer R-20 spectrometer. Chemical shifts are given in ppm with tetramethylsilane as an internal standard and the following abbreviations are used: singlet (s), broad singlet (br s), doublet (d), double doublet (dd), quartet (q) and multiplet (m). Mass spectra (MS) were taken on a Shimadzu LKB 9000 spectrometer.

Compounds II: 5-(4-Methoxy-2-nitrophenyl)-2-furancarboxylic Acid (IIc)—A mixture of 4-methoxy-2-nitroaniline (120 g) and 6 N HCl (800 ml) was heated at 70 °C, then cooled in an ice bath. A solution of NaNO₂ (50 g) in H₂O (200 ml) was added dropwise to the cold solution below −5 °C. After the solution had been stirred at −5 °C for 1 h, it was added dropwise to a stirred mixture of 2-furancarboxylic acid (85 g), CuCl₂ (30 g) and H₂O (300 ml) at 50—55 °C. The resulting product was filtered off, then washed with H₂O and benzene to give crystals (84.3 g, 44.9%). Recrystallization from EtOH gave prisms, mp 182—184 °C. IR $\nu_{\max}^{\text{KBr}}$ cm^{−1}: 1675. MS *m/e*: 263 (M⁺). NMR (acetone-*d*₆) δ : 4.00 (3H, s), 6.79 (1H, d, *J*=4 Hz), 7.33 (1H, d, *J*=4 Hz), 7.40 (2H, m), 7.83 (1H, d, *J*=8 Hz). Anal. Calcd for C₁₂H₉NO₆: C, 54.76; H, 3.44; N, 5.32. Found: C, 54.92; H, 3.40; N, 5.15.

Compounds IIa, b and d were prepared in the same manner.

Compounds III: Ethyl 5-(4-Methoxy-2-nitrophenyl)-2-furancarboxylate (IIIc)—A mixture of IIc (84 g), conc. H₂SO₄ (30 ml) and EtOH (700 ml) was refluxed for 7 h, then concentrated, and poured into ice-H₂O. The resulting product was filtered off (73 g, 78.5%) and recrystallization from EtOH gave needles, mp 106—108 °C. IR $\nu_{\max}^{\text{KBr}}$ cm^{−1}: 1713, 1540. MS *m/e*: 291 (M⁺). NMR (CDCl₃) δ : 1.38 (3H, t, *J*=7 Hz), 3.90 (3H, s), 4.35 (2H, q, *J*=7 Hz), 6.57 (1H, d, *J*=4 Hz), 7.18 (1H, d, *J*=4 Hz), 7.20 (2H, m), 7.69 (1H, d, *J*=8 Hz). Anal. Calcd for C₁₄H₁₃NO₆:



No.	R ₁	Yield (%)	mp (°C)	Recrystn. solvent ^{a)}	Formula ^{a)}
IIa	Cl	60	216—218	T	C ₁₁ H ₆ ClNO ₅
IIb	CF ₃	58	182—184	T	C ₁₂ H ₆ F ₃ NO ₅
IIc	CH ₃	58	193—194	T	C ₁₂ H ₉ NO ₅

a, c) See the corresponding footnotes in Table I.

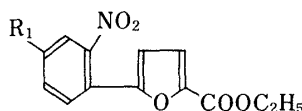
C, 57.73; H, 4.49; N, 4.80. Found: C, 57.60; H, 4.50; N, 4.61.

Compounds IIIa, b and d were prepared in the same manner.

Compounds IV: Ethyl 5-(2-Amino-4-chlorophenyl)-2-furancarboxylate (IVa)—A mixture of IIIa (10 g), 50% aq. EtOH (60 ml) and Fe powder (11 g) was stirred at 80 °C and a solution of conc. HCl and 50% aq. EtOH (7 ml) was added thereto. The mixture was refluxed for 2 h, made basic with aq. NaOH (pH 7–8) and filtered. The filtrate was concentrated and extracted with CH₂Cl₂. The extract was washed with H₂O, dried (MgSO₄) and concentrated to give crystals (8.3 g, 92%). Recrystallization from EtOH gave needles, mp 124–125 °C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3400, 1690. MS *m/e*: 265 (M⁺). NMR (CDCl₃) δ : 1.38 (3H, t, *J* = 7 Hz), 4.38 (2H, q, *J* = 7 Hz), 6.7 (3H, m), 7.3 (2H, m). *Anal.* Calcd for C₁₃H₁₂ClNO₃: C, 58.76; H, 4.55; N, 5.27. Found: C, 58.50; H, 4.54; N, 5.21.

Ethyl 5-(2-Amino-4-methoxyphenyl)-2-furancarboxylate (IVc)—A mixture of IIIc (72 g), 10% Pd-C (6 g) and AcOH (500 ml) was hydrogenated at room temperature and atmospheric pressure. The catalyst was filtered off and the filtrate was concentrated, then poured into ice-H₂O. The resulting product was filtered off (54.3 g, 84.1%), and recrystallization from EtOH gave needles, mp 95–96 °C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3480, 1703. MS *m/e*: 261 (M⁺). NMR (CDCl₃) δ : 1.39 (3H, t, *J* = 7 Hz), 3.74 (3H, s), 4.37 (2H, q, *J* = 7 Hz), 6.26 (1H, m), 6.35 (1H, dd, *J* = 8, 2 Hz), 6.52

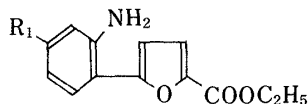
TABLE III.



No.	R ₁	Yield (%)	mp (°C)	Recrystn. solvent ^{a)}	Formula ^{c)}
IIIa	Cl	98	120–122	T	C ₁₃ H ₁₀ ClNO ₃
IIIb	CF ₃	89	82–83	T	C ₁₄ H ₁₀ F ₃ NO ₃
IIIc	CH ₃	83	59–60	T	C ₁₄ H ₁₃ NO ₃

a, c) See the corresponding footnotes in Table I.

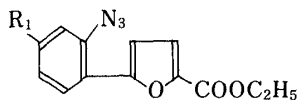
TABLE IV.



No.	R ₁	Yield (%)	mp (°C)	Recrystn. solvent ^{a)}	Formula ^{c)}
IVb	CF ₃	83	157–159	T	C ₁₄ H ₁₂ F ₃ NO ₃
IVd	CH ₃	89	65–66	T	C ₁₄ H ₁₅ NO ₃

a, c) See the corresponding footnotes in Table I.

TABLE V.



No.	R ₁	Yield (%)	mp (°C)	Recrystn. solvent ^{a)}	Formula ^{c)}
Va	Cl	83	79–81	P	C ₁₃ H ₁₀ ClN ₃ O ₃
Vb	CF ₃	90	101–103	P	C ₁₄ H ₁₀ F ₃ N ₃ O ₃
Vd	CH ₃	71	74–75	T	C ₁₄ H ₁₃ N ₃ O ₃

a, c) See the corresponding footnotes in Table I.

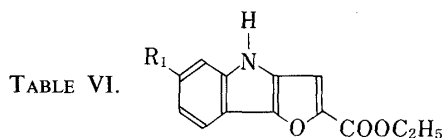
(1H, d, $J=4$ Hz), 7.23 (1H, d, $J=4$ Hz), 7.41 (1H, d, $J=8$ Hz). *Anal.* Calcd for $C_{14}H_{15}NO_4$: C, 64.35; H, 5.78; N, 5.36. Found: C, 64.30; H, 5.80; N, 5.10.

Compounds IVb and d were prepared in the same manner.

Compounds V: Ethyl 5-(2-Azide-4-methoxyphenyl)-2-furancarboxylate (Vc)—A mixture of IVc (54 g) and 6 *N* HCl (400 ml) was heated at 70 °C, then cooled in an ice bath. A solution of $NaNO_2$ (14 g) in H_2O (50 ml) was added dropwise to the cold solution below -5 °C. After the solution had been stirred at -5 °C for 1 h, a solution of NaN_3 (13.5 g) in H_2O (50 ml) was added thereto and the temperature was raised to room temperature. The resulting product was filtered off, and washed with H_2O and hexane to give crystals (50.4 g, 85.0%). Recrystallization from EtOH gave needles, mp 89–90 °C. IR ν_{max}^{KBr} cm^{-1} : 2100, 1733. MS m/e : 287 (M^+). NMR ($CDCl_3$) δ : 1.39 (3H, t, $J=7$ Hz), 3.87 (3H, s), 4.38 (2H, q, $J=7$ Hz), 6.8 (2H, m), 7.00 (1H, d, $J=4$ Hz), 7.23 (1H, d, $J=4$ Hz), 7.92 (1H, d, $J=8$ Hz). *Anal.* Calcd for $C_{14}H_{13}N_3O_4$: C, 58.53; H, 4.56; N, 22.27. Found: C, 58.23; H, 4.76; N, 22.50.

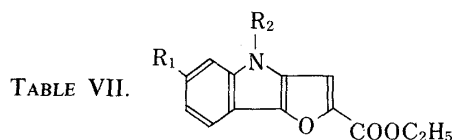
Compounds Va, b and d were prepared in the same manner.

Compounds VI: Ethyl 6-Methoxy-4H-furo[3,2-*b*]indole-2-carboxylate (VIc)—A mixture of Vc (50.4 g) and *o*-dichlorobenzene (300 ml) was stirred at 160–170 °C for 1 h. The resulting product was filtered off, and washed with hexane to give crystals (35 g, 77%). Recrystallization from benzene gave prisms, mp 178–179 °C. IR ν_{max}^{KBr} cm^{-1} : 3300, 1765. MS m/e : 259 (M^+). NMR ($DMSO-d_6$) δ : 1.39 (3H, t, $J=7$ Hz), 3.90 (3H, s), 4.38 (2H, q, $J=7$ Hz), 6.85 (1H, dd,



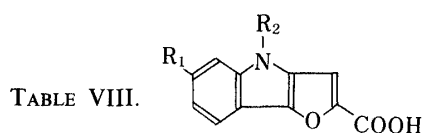
No.	R ₁	Yield (%)	mp (°C)	Recrystn. solvent ^{a)}	Formula ^{c)}
VIa	Cl	56	225–226	B	C ₁₃ H ₁₀ ClNO ₃
VIb	CF ₃	70	225–226	B	C ₁₄ H ₁₀ F ₃ NO ₃
VIc	CH ₃	77	166–167	B	C ₁₄ H ₁₃ NO ₃

a, c) See the corresponding footnotes in Table I.



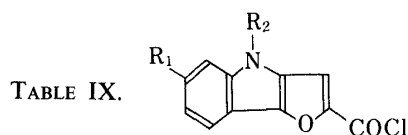
No.	R ₁	R ₂	Yield (%)	mp (°C)	Recrystn. solvent ^{a)}	Formula ^{c)}
VIIa	H	CH ₃	80	120–123	B	C ₁₄ H ₁₃ NO ₃
VIIb	H	C ₂ H ₅	75	88–90	T	C ₁₅ H ₁₅ NO ₃
VIIc	H	iso-C ₃ H ₇	66	143–145	T	C ₁₆ H ₁₇ NO ₃
VIIId	Cl	CH ₃	89	120–122	B	C ₁₄ H ₁₂ ClNO ₃
VIIe	Cl	C ₂ H ₅	77	79–81	P	C ₁₅ H ₁₄ ClNO ₃
VIIIf	Cl	iso-C ₃ H ₇	59	124–126	P	C ₁₆ H ₁₆ ClNO ₃
VIIg	CF ₃	CH ₃	78	159–161	B	C ₁₅ H ₁₂ F ₃ NO ₃
VIIh	CF ₃	C ₂ H ₅	87	123–125	B	C ₁₆ H ₁₄ F ₃ NO ₃
VIIi	CF ₃	iso-C ₃ H ₇	54	168–171	P	C ₁₇ H ₁₆ F ₃ NO ₃
VIIk	OCH ₃	C ₂ H ₅	79	108–109	H–A	C ₁₆ H ₁₇ NO ₄
VIIl	OCH ₃	iso-C ₃ H ₇	69	113–114	H	C ₁₇ H ₁₉ NO ₄
VIIIm	CH ₃	CH ₃	95	148–149	H–A	C ₁₅ H ₁₅ NO ₃
VIIIn	CH ₃	C ₂ H ₅	94	86–87	H	C ₁₆ H ₁₇ NO ₃
VIIIo	CH ₃	iso-C ₃ H ₇	76	87–88	H	C ₁₇ H ₁₉ NO ₃

a, c) See the corresponding footnotes in Table I.



No.	R ₁	R ₂	Yield (%)	mp (°C)	Recrystn. solvent ^{a)}	Formula ^{c)}
VIIIa	H	CH ₃	51	202—204	M	C ₁₂ H ₉ NO ₃
VIIIb	H	C ₂ H ₅	60	184—186	M	C ₁₃ H ₁₁ NO ₃
VIIIc	H	iso-C ₃ H ₇	68	234—236	T	C ₁₄ H ₁₃ NO ₃
VIIId	Cl	CH ₃	91	220—224	M	C ₁₂ H ₈ ClNO ₃
VIIIe	Cl	C ₂ H ₅	88	233—235	T	C ₁₃ H ₁₀ ClNO ₃
VIIIf	Cl	iso-C ₃ H ₇	73	238—241	T	C ₁₄ H ₁₂ ClNO ₃
VIIIg	CF ₃	CH ₃	88	214—216	M	C ₁₃ H ₈ F ₃ NO ₃
VIIIh	CF ₃	C ₂ H ₅	78	240—243	T	C ₁₄ H ₁₀ F ₃ NO ₃
VIIIi	CF ₃	iso-C ₃ H ₇	52	234—236	T	C ₁₅ H ₁₂ F ₃ NO ₃
VIIIk	OCH ₃	C ₂ H ₅	90	184—187	A	C ₁₄ H ₁₃ NO ₄
VIIIl	OCH ₃	iso-C ₃ H ₇	90	192—195	A	C ₁₅ H ₁₅ NO ₄
VIII m	CH ₃	CH ₃	88	213—216	H-A	C ₁₃ H ₁₁ NO ₃
VIII n	CH ₃	C ₂ H ₅	96	209—212	H-A	C ₁₄ H ₁₃ NO ₃
VIII o	CH ₃	iso-C ₃ H ₇	84	213—217	H-A	C ₁₅ H ₁₅ NO ₃
VIII p	Cl	H	92	280—283	M	C ₁₁ H ₆ ClNO ₃
VIII q	CF ₃	H	90	270—274	M	C ₁₂ H ₆ F ₃ NO ₃
VIII r	OCH ₃	H	88	215—216	T	C ₁₂ H ₉ NO ₄
VIII s	CH ₃	H	86	240—241	T	C ₁₂ H ₉ NO ₃

a, c) See the corresponding footnotes in Table I.



No.	R ₁	R ₂	Yield (%)	mp (°C)	Recrystn. solvent ^{a)}	Formula ^{c)}
IXa	H	CH ₃	89	139—142	B	C ₁₂ H ₈ ClNO ₂
IXb	H	C ₂ H ₅	53	120—123	B	C ₁₃ H ₁₀ ClNO ₂
IXc	H	iso-C ₃ H ₇	69	162—165	B	C ₁₄ H ₁₂ ClNO ₂
IXd	Cl	CH ₃	81	170—173	B	C ₁₂ H ₇ Cl ₂ NO ₂
IXe	Cl	C ₂ H ₅	73	124—126	B-P	C ₁₃ H ₉ Cl ₂ NO ₂
IXf	Cl	iso-C ₃ H ₇	64	186—189	B	C ₁₄ H ₁₁ Cl ₂ NO ₂
IXg	CF ₃	CH ₃	71	152—155	B	C ₁₃ H ₇ ClF ₃ NO ₂
IXh	CF ₃	C ₂ H ₅	76	135—138	B-P	C ₁₄ H ₉ ClF ₃ NO ₂
IXi	CF ₃	iso-C ₃ H ₇	70	160—162	P	C ₁₅ H ₁₀ ClF ₃ NO ₂
IXk	OCH ₃	C ₂ H ₅	88	161—163	H-A	C ₁₄ H ₁₂ ClNO ₃
IXl	OCH ₃	iso-C ₃ H ₇	89	173—176	H-A	C ₁₅ H ₁₄ ClNO ₃
IXm	CH ₃	CH ₃	82	126—127	H-A	C ₁₃ H ₁₀ ClNO ₂
IXn	CH ₃	C ₂ H ₅	89	111—112	H-A	C ₁₄ H ₁₂ ClNO ₂
IXo	CH ₃	iso-C ₃ H ₇	88	173—176	H-A	C ₁₅ H ₁₄ ClNO ₃
IXp	Cl	H	76	221—222	B	C ₁₁ H ₅ Cl ₂ NO ₂
IXq	CF ₃	H	87	228—229	B	C ₁₂ H ₅ ClF ₃ NO ₂
IXr	OCH ₃	H	76	176—180	B	C ₁₂ H ₈ ClNO ₃
IXs	CH ₃	H	82	168—172	B	C ₁₂ H ₈ ClNO ₂

a, c) See the corresponding footnotes in Table I.

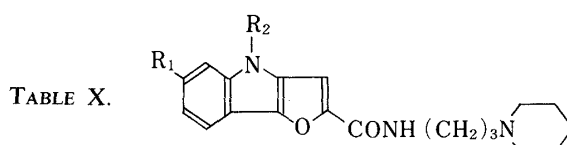
$J=8, 2$ Hz), 7.09 (1H, d, $J=2$ Hz), 7.67 (1H, s), 7.76 (1H, d, $J=8$ Hz). *Anal.* Calcd for $C_{14}H_{13}NO_4$: C, 64.85; H, 5.05; N, 5.40. Found: C, 64.80; H, 5.00; N, 5.39.

Compounds VIa, b and d were prepared in the same manner.

Compounds VII: Ethyl 6-Methoxy-4-methyl-furo[3,2-*b*]indole-2-carboxylate (VIIj)—A solution of VIc (3 g) in dimethylformamide (DMF) (20 ml) was added dropwise with stirring to a suspension of NaH (0.3 g) in DMF (10 ml), then the mixture was stirred for 1 h at room temperature. Methyl iodide (2 g) was added thereto and the whole was stirred for 2 h at room temperature, then concentrated, and poured into ice- H_2O . The resulting product was filtered off (2.7 g, 86.0%) and recrystallization from acetone gave needles, mp 114–115 °C. IR $\nu_{\max}^{KBr}$ cm^{-1} : 1690. MS m/e : 273 (M^+). NMR ($CDCl_3$) δ : 1.40 (3H, t, $J=7$ Hz), 3.67 (3H, s), 3.85 (3H, s), 4.38 (2H, q, $J=7$ Hz), 6.70 (1H, m), 6.80 (1H, dd, $J=8, 2$ Hz), 7.22 (1H, s), 7.65 (1H, d, $J=8$ Hz). *Anal.* Calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.12. Found: C, 65.84; H, 5.52; N, 5.00.

Compounds VIIa–i and k–o were prepared in the same manner.

Compounds VIII: 6-Methoxy-4-methyl-furo[3,2-*b*]indole-2-carboxylic Acid (VIIIj)—A mixture of VIIj (2.7 g), 10% aq. NaOH (50 ml) and EtOH (50 ml) was refluxed for 1 h, then diluted with H_2O and acidified with conc. HCl.



No.	Yield (%)	IR $\nu_{\max}^{KBr}$ cm^{-1}	MS m/e (M^+)	NMR	
				Solv. ^{a)}	Chemical shift (δ)
Xa	75	3200 1630	325	C	1.6 (2H, m), 1.8 (6H, m), 2.5 (6H, m), 3.6 (2H, m), 7.2 (2H, m), 7.29 (1H, s), 7.43 (1H, d, $J=8$ Hz), 7.64 (1H, d, $J=8$ Hz), 8.86 (1H, s), 9.17 (1H, br s)
Xb	78	1645	339	C	1.6 (2H, m), 1.8 (6H, m), 2.5 (6H, m), 3.6 (2H, m), 3.80 (3H, s), 7.2 (2H, m), 7.30 (1H, s), 7.35 (1H, m), 7.64 (1H, d, $J=8$ Hz), 9.10 (1H, br s)
Xc	69	1645	353	C	1.47 (3H, t, $J=7$ Hz), 1.6 (2H, m), 1.8 (6H, m), 2.5 (6H, m), 3.6 (2H, m), 4.22 (2H, q, $J=7$ Hz), 7.2 (2H, m), 7.32 (1H, s), 7.38 (1H, d, $J=8$ Hz), 9.10 (1H, br s)
Xd	70	1650	367	C	1.57 (6H, d, $J=7$ Hz), 1.6 (2H, m), 1.8 (6H, m), 2.7 (6H, m), 3.62 (2H, m), 4.78 (1H, m), 7.17 (1H, dd, $J=8, 2$ Hz), 7.30 (1H, dd, $J=8, 2$ Hz), 7.40 (1H, s), 7.43 (1H, d, $J=8$ Hz), 7.66 (1H, d, $J=8$ Hz), 9.17 (1H, br s)
Xe	81	3230 1635	359	D	1.5 (8H, m), 2.4 (6H, m), 3.4 (2H, m), 7.16 (1H, dd, $J=8, 2$ Hz), 7.38 (1H, s), 7.58 (1H, d, $J=2$ Hz), 7.66 (1H, d, $J=8$ Hz), 8.85 (1H, br s)
Xf	74	1641	373	C	1.7 (8H, m), 2.5 (6H, m), 3.6 (2H, m), 3.73 (3H, s), 7.10 (1H, dd, $J=8, 2$ Hz), 7.21 (1H, s), 7.30 (1H, d, $J=2$ Hz), 7.47 (1H, d, $J=8$ Hz), 9.01 (1H, br s)
Xg	67	1645	387	C	1.42 (3H, t, $J=7$ Hz), 1.6 (2H, m), 1.8 (6H, m), 2.4 (6H, m), 3.5 (2H, m), 4.06 (2H, q, $J=7$ Hz), 6.95 (1H, dd, $J=8, 2$ Hz), 7.14 (1H, s), 7.20 (1H, d, $J=2$ Hz), 7.36 (1H, d, $J=8$ Hz), 8.90 (1H, br s)
Xh	65	1640	401	C	1.57 (6H, d, $J=7$ Hz), 1.6 (2H, m), 1.9 (6H, m), 2.6 (6H, m), 3.6 (2H, m), 4.68 (1H, m), 7.13 (1H, dd, $J=8, 2$ Hz), 7.40 (1H, s), 7.42 (1H, d, $J=2$ Hz), 7.56 (1H, d, $J=8$ Hz), 8.94 (1H, br s)
Xi	80	3450 1640	393	D	1.6 (8H, m), 2.6 (6H, m), 3.4 (2H, m), 7.45 (1H, dd, $J=8, 2$ Hz), 7.53 (1H, s), 7.90 (1H, d, $J=8$ Hz), 8.05 (1H, s), 8.95 (1H, br s)
Xj	89	1655	407	D	1.6 (8H, m), 2.4 (6H, m), 3.4 (2H, m), 3.98 (3H, s), 7.50 (1H, d, $J=8$ Hz), 7.60 (1H, s), 7.85 (1H, d, $J=8$ Hz), 8.03 (1H, s), 9.02 (1H, br s)

TABLE X. (continued)

No.	Yield (%)	IR $\nu_{\text{max}}^{\text{KBr}} \text{ cm}^{-1}$	MS m/e (M^+)	NMR	
				Solv. ^{a)}	Chemical shift (δ)
Xk	66	1640	421	D	1.40 (3H, t, $J=7$ Hz), 1.8 (8H, m), 2.8 (6H, m), 3.4 (2H, m), 4.45 (2H, q, $J=7$ Hz), 7.46 (1H, d, $J=8$ Hz), 7.68 (1H, s), 7.89 (1H, d, $J=8$ Hz), 8.08 (1H, s), 8.94 (1H, br s)
Xl	67	1650	435	D	1.50 (6H, d, $J=7$ Hz), 1.6 (8H, m), 2.4 (6H, m), 3.4 (2H, m), 4.94 (1H, m), 7.19 (1H, dd, $J=8, 2$ Hz), 7.65 (1H, d, $J=8$ Hz), 7.83 (1H, d, $J=2$ Hz), 8.06 (1H, s), 8.86 (1H, br s)
Xm	67	3210 1625	355	D	1.6 (8H, m), 2.4 (6H, m), 3.3 (2H, m), 3.85 (3H, s), 6.83 (1H, dd, $J=8, 2$ Hz), 7.06 (1H, d, $J=2$ Hz), 7.35 (1H, s), 7.56 (1H, d, $J=8$ Hz), 8.00 (1H, br s)
Xo	89	1652	383	C	1.46 (3H, t, $J=7$ Hz), 1.7 (8H, m), 2.5 (6H, m), 3.6 (2H, m), 3.87 (3H, s), 4.50 (2H, q, $J=7$ Hz), 6.75 (1H, dd, $J=8, 2$ Hz), 6.82 (1H, d, $J=2$ Hz), 7.23 (1H, s), 7.47 (1H, d, $J=8$ Hz), 8.90 (1H, m)
Xp	79	1642	397	C	1.55 (6H, d, $J=7$ Hz), 1.7 (8H, m), 2.5 (6H, m), 3.6 (2H, m), 4.62 (1H, m), 6.76 (1H, dd, $J=8, 2$ Hz), 6.83 (1H, d, $J=2$ Hz), 7.31 (1H, s), 7.49 (1H, d, $J=8$ Hz), 8.80 (1H, br s)
Xq	63	3230 1630	339	D	1.6 (8H, m), 2.4 (6H, m), 2.44 (3H, s), 3.3 (2H, m), 6.95 (1H, dd, $J=8, 2$ Hz), 7.28 (1H, d, $J=2$ Hz), 7.29 (1H, s), 7.50 (1H, d, $J=8$ Hz), 8.76 (1H, br s)
Xr	80	1650	353	C	1.7 (8H, m), 2.50 (3H, s), 2.5 (6H, m), 3.5 (2H, m), 3.71 (3H, s), 6.94 (1H, dd, $J=8, 2$ Hz), 7.09 (1H, d, $J=2$ Hz), 7.20 (1H, s), 7.46 (1H, d, $J=8$ Hz), 8.90 (1H, br s)
Xs	75	1642	367	C	1.44 (3H, t, $J=7$ Hz), 1.7 (8H, m), 2.5 (6H, m), 3.5 (2H, m), 4.12 (2H, q, $J=7$ Hz), 6.94 (1H, dd, $J=8, 2$ Hz), 7.10 (1H, d, $J=2$ Hz), 7.23 (1H, s), 7.46 (1H, d, $J=8$ Hz), 8.90 (1H, br s)
Xt	69	1650	381	C	1.55 (6H, d, $J=7$ Hz), 1.7 (8H, m), 2.5 (6H, m), 3.55 (2H, m), 4.67 (1H, m), 6.91 (1H, dd, $J=8$ Hz), 7.12 (1H, d, $J=2$ Hz), 7.28 (1H, s), 7.45 (1H, d, $J=8$ Hz), 8.90 (1H, br s)
XIa	46	1763 1673	451	C	1.7 (8H, m), 2.6 (6H, m), 3.6 (2H, m), 4.10 (3H, s), 7.47 (1H, s), 7.6 (2H, m), 8.76 (1H, br s), 9.10 (1H, br s)
XIb	39	1750 1665	431	C	1.50 (3H, t, $J=7$ Hz), 1.7 (8H, m), 2.5 (6H, m), 3.6 (2H, m), 4.51 (2H, q, $J=7$ Hz), 7.35 (2H, m), 7.40 (1H, s), 8.35 (1H, s), 9.10 (1H, br s)
XIc	46	1763 1673	451	C	1.7 (8H, m), 2.6 (6H, m), 4.10 (3H, s), 7.47 (1H, s), 7.6 (2H, m), 8.76 (1H, s), 9.10 (1H, br s), 3.6 (2H, m)
XId	45	1750 1663	465	C	1.52 (3H, t, $J=7$ Hz), 1.6 (8H, m), 2.5 (6H, m), 3.6 (2H, m), 4.56 (2H, q, $J=7$ Hz), 7.50 (1H, s), 7.63 (2H, m), 8.73 (1H, s), 9.25 (1H, br s)
XIf	55	1743 1657	427	C	1.7 (8H, m), 2.5 (6H, m), 3.6 (2H, m), 3.90 (3H, s), 4.51 (2H, q, $J=7$ Hz), 6.93 (1H, dd, $J=8, 2$ Hz), 7.43 (1H, d, $J=8$ Hz), 7.41 (1H, s), 7.69 (1H, d, $J=2$ Hz), 8.99 (1H, br s), 1.50 (3H, t, $J=7$)
XIg	59	1750 1663	397	D	1.6 (8H, m), 2.4 (6H, m), 2.43 (3H, s), 3.4 (2H, m), 4.02 (3H, s), 7.09 (1H, dd, $J=8, 2$ Hz), 7.32 (1H, s), 7.40 (1H, d, $J=8$ Hz), 7.94 (1H, d, $J=2$ Hz), 8.77 (1H, br s)
XIh	50	1740 1658	411	D	1.44 (3H, t, $J=7$ Hz), 1.6 (8H, m), 2.4 (6H, m), 2.42 (3H, s), 3.4 (2H, m), 4.41 (2H, q, $J=7$ Hz), 7.03 (1H, dd, $J=8, 2$ Hz), 7.22 (1H, s), 7.36 (1H, d, $J=8$ Hz), 7.89 (1H, d, $J=8$ Hz), 7.89 (1H, d, $J=2$ Hz), 8.74 (1H, br s)

a) C = CDCl₃, D = DMSO-*d*₆.

The resulting product was filtered off (2.2 g, 90.0%) and recrystallization from acetone gave needles, mp 193–197 °C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1655. MS m/e : 245 (M^+). NMR ($\text{DMSO}-d_6$) δ : 3.77 (3H, s), 3.84 (3H, s), 6.76 (1H, dd, $J=8, 2$ Hz), 7.04 (1H, d, $J=2$ Hz), 7.52 (1H, s), 7.63 (1H, d, $J=8$ Hz). Anal. Calcd for $\text{C}_{13}\text{H}_{11}\text{NO}_4$: C, 63.67; H, 4.52; N, 5.71. Found: C, 63.97; H, 4.20; N, 5.85.

Compounds VIIIa–i and k–s were prepared in the same manner.

Compounds IX: 6-Methoxy-4-methyl-furo[3,2-*b*]indole-2-carbonylchloride (IXj)—A mixture of VIIIj (2.1 g), SOCl_2 (5 ml) and benzene (100 ml) was refluxed for 30 min, then concentrated *in vacuo*, and diluted with hexane. The resulting product was filtered off (2.0 g, 88%) and recrystallization from hexane–acetone gave needles, mp 173–176 °C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1730. MS m/e : 263 (M^+). NMR (CDCl_3) δ : 3.71 (3H, s), 3.90 (3H, s), 6.72 (1H, m), 6.81 (1H, dd, $J=8, 2$ Hz), 7.45 (1H, s), 7.66 (1H, d, $J=8$ Hz). Anal. Calcd for $\text{C}_{13}\text{H}_{10}\text{ClNO}_3$: C, 59.21; H, 3.82; N, 5.31. Found: C, 59.00; H, 3.85; N, 5.50.

Compounds IXa–i and k–s were prepared in the same manner.

Compound X: *N*-(3-Piperidinopropyl)-6-methoxy-4-methyl-furo[3,2-*b*]indole-2-carboxamide (Xn)—*N*-(3-Aminopropyl)piperidine (3 g) in benzene (10 ml) was added dropwise to a solution of IXj (2 g) in benzene (80 ml), then the mixture was stirred for 1 h at room temperature, concentrated, and poured into ice- H_2O . The resulting product was filtered off (2.3 g, 82.0%) and recrystallization from acetone gave needles, mp 155–157 °C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1648. MS m/e : 369 (M^+). NMR (CDCl_3) δ : 1.7 (8H, m), 2.5 (6H, m), 3.68 (3H, s), 3.5 (2H, m), 3.85 (3H, s), 6.70 (1H, s), 6.80 (1H, dd, $J=8, 2$ Hz), 7.18 (1H, s), 7.43 (1H, d, $J=8$ Hz), 8.90 (1H, br s). Anal. Calcd for $\text{C}_{21}\text{H}_{27}\text{N}_3\text{O}_3$: C, 68.26; H, 7.36; N, 11.37. Found: C, 68.24; H, 7.46; N, 11.47.

Compounds Xa–m and o–t were prepared in the same manner.

Compounds XI: *N*-(3-Piperidinopropyl)-6-methoxy-4-methoxycarbonyl-furo[3,2-*b*]indole-2-carboxamide (XIe)—A solution of Xm (3 g) in DMF (20 ml) was added dropwise with stirring to a solution of NaH (0.4 g) in DMF (10 ml), then the mixture was stirred for 1 h at room temperature. Methylchloroformate (1.8 g) was added thereto and the whole was stirred for 30 min at room temperature, poured into H_2O and extracted with CH_2Cl_2 . The extract was washed with H_2O , and dried (MgSO_4). The solvent was evaporated off to give crystals (1.2 g, 35.0%). Recrystallization from hexane–acetone gave prisms, mp 116–118 °C. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1755, 1667. MS m/e : 413 (M^+). NMR ($\text{DMSO}-d_6$) δ : 1.6 (8H, m), 2.4 (6H, m), 3.4 (2H, m), 3.80 (3H, s), 4.00 (3H, s), 6.90 (1H, dd, $J=8, 2$ Hz), 7.28 (1H, s), 7.40 (1H, d, $J=8$ Hz), 7.65 (1H, d, $J=2$ Hz), 8.73 (1H, br s). Anal. Calcd for $\text{C}_{22}\text{H}_{27}\text{N}_3\text{O}_5$: C, 63.90; H, 6.58; N, 10.16. Found: C, 63.91; H, 6.70; N, 10.25.

Compounds XIa–d and f–h were prepared in the same manner. Data for compounds Xa–t and XIa–h are listed in Table X.

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References and Notes

- 1) A. Tanaka, K. Yakushijin, and S. Yoshina, *J. Heterocycl. Chem.*, **14**, 975 (1977).
- 2) A. Tanaka, K. Yakushijin, and S. Yoshina, *J. Heterocycl. Chem.*, **15**, 123 (1978).
- 3) A. Tanaka, K. Yakushijin, and S. Yoshina, *J. Heterocycl. Chem.*, **16**, 785 (1979).
- 4) R. Koster, M. Anderson, and E. J. Dobber, *Fed. Proc.*, **18**, 412 (1958).
- 5) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, **111**, 544 (1962).