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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-

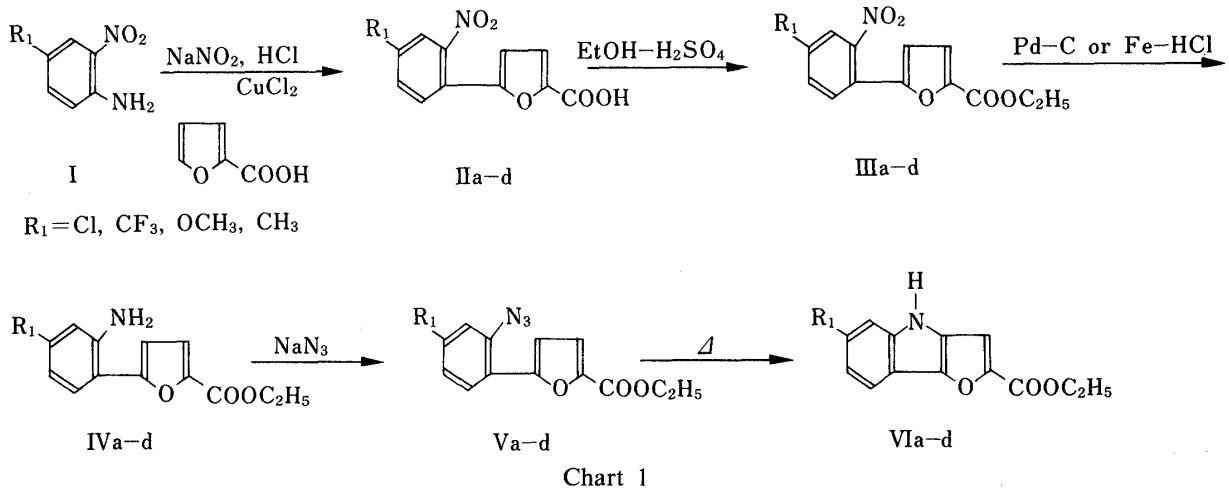


Chart 1

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

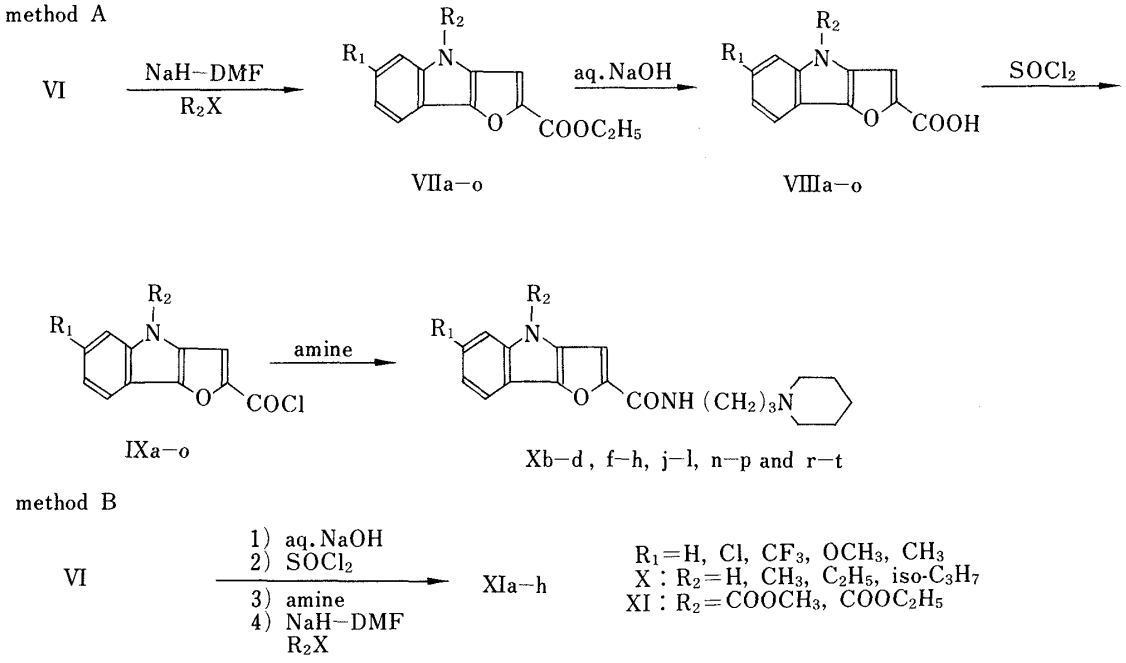


Chart 2

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.

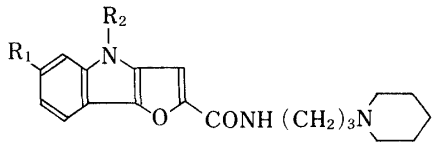
Acetic Acid Writhing

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.

TABLE I.



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	$C_{19}H_{23}N_3O_2$	32.5[f]	18.2
Xb	H	CH_3	148—150	P–B	A	$C_{20}H_{25}N_3O_2$	60.3[g]	19.2
Xc	H	C_2H_5	127—129	P–B	A	$C_{21}H_{27}N_3O_2$	30.4	23.5
Xd	H	iso-C_3H_7	131—132	H–B	A	$C_{22}H_{29}N_3O_2$	24.0	18.5
Xe	Cl	H	232—233	B	B	$C_{19}H_{22}ClN_3O_2$	32.8[f]	17.1
Xf	Cl	CH_3	154—156	P–B	A	$C_{20}H_{24}ClN_3O_2$	91.6[h]	30.3[f]
Xg	Cl	C_2H_5	137—138	H–A	A	$C_{21}H_{26}ClN_3O_2$	74.6[h]	34.0[f]
Xh	Cl	iso-C_3H_7	141—142	P–B	A	$C_{22}H_{28}ClN_3O_2$	83.7[h]	13.1
Xi	CF_3	H	198—199	B	B	$C_{20}H_{22}F_3N_3O_2$	10.4	0.0
Xj	CF_3	CH_3	155—156	H–A	A	$C_{21}H_{24}F_3N_3O_2$	88.9[h]	44.6[g]
Xk	CF_3	C_2H_5	124—126	H–A	A	$C_{22}H_{26}F_3N_3O_2$	82.6[h]	30.0[f]
Xl	CF_3	iso-C_3H_7	128—129	H–A	A	$C_{23}H_{28}F_3N_3O_2$	81.4[h]	51.4[g]
Xm	OCH_3	H	179—181	T	B	$C_{20}H_{25}N_3O_3$	N.T.	N.T.
Xn	OCH_3	CH_3	155—157	A	A	$C_{21}H_{27}N_3O_3$	77.8[h]	74.4[h]
Xo	OCH_3	C_2H_5	120—121	A	A	$C_{22}H_{29}N_3O_3$	72.0[h]	71.7[h]
Xp	OCH_3	iso-C_3H_7	168—170	A	A	$C_{23}H_{31}N_3O_3$	75.7[h]	63.2[g]
Xq	CH_3	H	194—199	T	B	$C_{20}H_{25}N_3O_2$	N.T.	N.T.
Xr	CH_3	CH_3	138—139	H–A	A	$C_{21}H_{27}N_3O_2$	66.9[g]	69.1[h]
Xs	CH_3	C_2H_5	133—134	A	A	$C_{22}H_{29}N_3O_2$	79.0[h]	38.9[f]
Xt	CH_3	iso-C_3H_7	143—145	A	A	$C_{23}H_{31}N_3O_2$	66.7[g]	54.4[g]
XIa	Cl	$COOCH_3$	146—148	A	B	$C_{21}H_{24}ClN_3O_4$	73.8[h]	23.5
XIb	Cl	$COOC_2H_5$	114—115	H–A	B	$C_{22}H_{26}ClN_3O_4$	39.5[f]	−1.5
XIc	CF_3	$COOCH_3$	146—148	A	B	$C_{22}H_{24}F_3N_3O_4$	47.8[g]	−1.8
XId	CF_3	$COOC_2H_5$	153—154	A	B	$C_{23}H_{26}F_3N_3O_4$	56.6[g]	5.5
XIe	OCH_3	$COOCH_3$	116—118	H–A	B	$C_{22}H_{27}N_3O_5$	59.7[g]	46.5[f]
XIf	OCH_3	$COOC_2H_5$	129—131	A	B	$C_{23}H_{29}N_3O_5$	38.9[g]	30.4[f]
XIg	CH_3	$COOCH_3$	112—114	H–E	B	$C_{22}H_{27}N_3O_4$	40.9[f]	37.2[f]
XIh	CH_3	$COOC_2H_5$	115—117	H–A	B	$C_{23}H_{29}N_3O_4$	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 ±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, CF_3, OCH_3 or CH_3 group as R_1 tends to increase these activities. The activity levels were, in general, more potent with an alkyl group as R_2 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

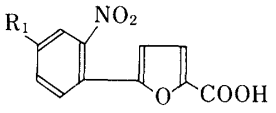
Melting points were determined on a Mitamura Rikken micro melting point apparatus and are uncorrected. Infrared (IR) spectra were taken on a Jasco DS-301 spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded on a Hitachi-Perkin-Elmer R-20 spectrometer. Chemical shifts are given in ppm 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 $NaNO_2$ (50 g) in H_2O (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), $CuCl_2$ (30 g) and H_2O (300 ml) at 50—55 °C. The resulting product was filtered off, then washed with H_2O and benzene to give crystals (84.3 g, 44.9%). Recrystallization from EtOH gave prisms, mp 182—184 °C. IR ν_{max}^{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 $C_{12}H_9NO_6$: 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. H_2SO_4 (30 ml) and EtOH (700 ml) was refluxed for 7 h, then concentrated, and poured into ice-H_2O. The resulting product was filtered off (73 g, 78.5%) and recrystallization from EtOH gave needles, mp 106—108 °C. IR ν_{max}^{KBr} cm^{-1}: 1713, 1540. MS *m/e*: 291 (M^+). NMR ($CDCl_3$) 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 $C_{14}H_{13}NO_6$:

TABLE II.



No.	R_1	Yield (%)	mp (°C)	Recrystn. solvent[a)]	Formula[c)]
IIa	Cl	60	216—218	T	$C_{11}H_6ClNO_5$
IIb	CF_3	58	182—184	T	$C_{12}H_6F_3NO_5$
IId	CH_3	58	193—194	T	$C_{12}H_9NO_5$

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

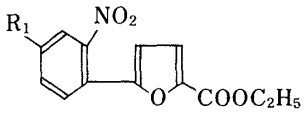
C, 57.73; H, 4.49; N, 4.80. Found: C, 57.60; H, 4.50; N, 4.61.

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 CH_2Cl_2. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated to give crystals (8.3 g, 92%). Recrystallization from EtOH gave needles, mp 124—125 °C. IR ν_{max}^{KBr} cm^{-1}: 3400, 1690. MS *m/e*: 265 (M^+). NMR ($CDCl_3$) 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 $C_{13}H_{12}ClNO_3$: 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-H_2O. The resulting product was filtered off (54.3 g, 84.1%), and recrystallization from EtOH gave needles, mp 95—96 °C. IR ν_{max}^{KBr} cm^{-1}: 3480, 1703. MS *m/e*: 261 (M^+). NMR ($CDCl_3$) 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

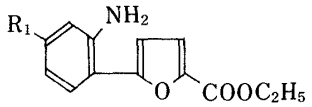
TABLE III.



No.	R_1	Yield (%)	mp (°C)	Recrystn. solvent[a]	Formula[c]
IIIa	Cl	98	120—122	T	$C_{13}H_{10}ClNO_5$
IIIb	CF_3	89	82—83	T	$C_{14}H_{10}F_3NO_5$
IIId	CH_3	83	59—60	T	$C_{14}H_{13}NO_5$

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

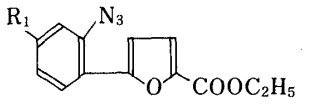
TABLE IV.



No.	R_1	Yield (%)	mp (°C)	Recrystn. solvent[a]	Formula[c]
IVb	CF_3	83	157—159	T	$C_{14}H_{12}F_3NO_3$
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	$C_{13}H_{10}ClN_3O_3$
Vb	CF_3	90	101—103	P	$C_{14}H_{10}F_3N_3O_3$
Vd	CH_3	71	74—75	T	$C_{14}H_{13}N_3O_3$

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.

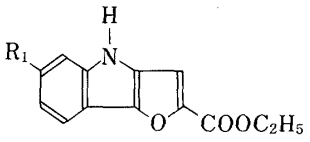
Compounds IVb and d were prepared in the same manner.

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-4*H*-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,

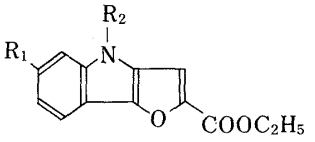
TABLE VI.



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	$C_{14}H_{10}F_3NO_3$
VId	CH_3	77	166—167	B	$C_{14}H_{13}NO_3$

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

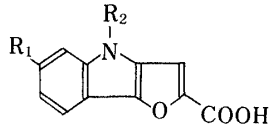
TABLE VII.



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_2H_5	75	88—90	T	$C_{15}H_{15}NO_3$
VIIc	H	iso-C_3H_7	66	143—145	T	$C_{16}H_{17}NO_3$
VIId	Cl	CH_3	89	120—122	B	$C_{14}H_{12}ClNO_3$
VIIe	Cl	C_2H_5	77	79—81	P	$C_{15}H_{14}ClNO_3$
VIIf	Cl	iso-C_3H_7	59	124—126	P	$C_{16}H_{16}ClNO_3$
VIIg	CF_3	CH_3	78	159—161	B	$C_{15}H_{12}F_3NO_3$
VIIh	CF_3	C_2H_5	87	123—125	B	$C_{16}H_{14}F_3NO_3$
VIIi	CF_3	iso-C_3H_7	54	168—171	P	$C_{17}H_{16}F_3NO_3$
VIIk	OCH_3	C_2H_5	79	108—109	H–A	$C_{16}H_{17}NO_4$
VIIl	OCH_3	iso-C_3H_7	69	113—114	H	$C_{17}H_{19}NO_4$
VIIm	CH_3	CH_3	95	148—149	H–A	$C_{15}H_{15}NO_3$
VIIn	CH_3	C_2H_5	94	86—87	H	$C_{16}H_{17}NO_3$
VIIo	CH_3	iso-C_3H_7	76	87—88	H	$C_{17}H_{19}NO_3$

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

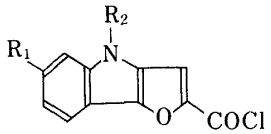
TABLE VIII.



No.	R_1	R_2	Yield (%)	mp (°C)	Recrystn. solvent[a]	Formula[c]
VIIIa	H	CH_3	51	202—204	M	$C_{12}H_9NO_3$
VIIIb	H	C_2H_5	60	184—186	M	$C_{13}H_{11}NO_3$
VIIIc	H	iso-C_3H_7	68	234—236	T	$C_{14}H_{13}NO_3$
VIIId	Cl	CH_3	91	220—224	M	$C_{12}H_8ClNO_3$
VIIIe	Cl	C_2H_5	88	233—235	T	$C_{13}H_{10}ClNO_3$
VIIIf	Cl	iso-C_3H_7	73	238—241	T	$C_{14}H_{12}ClNO_3$
VIIIg	CF_3	CH_3	88	214—216	M	$C_{13}H_8F_3NO_3$
VIIIh	CF_3	C_2H_5	78	240—243	T	$C_{14}H_{10}F_3NO_3$
VIIIi	CF_3	iso-C_3H_7	52	234—236	T	$C_{15}H_{12}F_3NO_3$
VIIIk	OCH_3	C_2H_5	90	184—187	A	$C_{14}H_{13}NO_4$
VIIIl	OCH_3	iso-C_3H_7	90	192—195	A	$C_{15}H_{15}NO_4$
VIIIm	CH_3	CH_3	88	213—216	H–A	$C_{13}H_{11}NO_3$
VIIIn	CH_3	C_2H_5	96	209—212	H–A	$C_{14}H_{13}NO_3$
VIIIo	CH_3	iso-C_3H_7	84	213—217	H–A	$C_{15}H_{15}NO_3$
VIIIp	Cl	H	92	280—283	M	$C_{11}H_6ClNO_3$
VIIIq	CF_3	H	90	270—274	M	$C_{12}H_6F_3NO_3$
VIIIr	OCH_3	H	88	215—216	T	$C_{12}H_9NO_4$
VIIIs	CH_3	H	86	240—241	T	$C_{12}H_9NO_3$

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

TABLE IX.



No.	R_1	R_2	Yield (%)	mp (°C)	Recrystn. solvent[a]	Formula[c]
IXa	H	CH_3	89	139—142	B	$C_{12}H_8ClNO_2$
IXb	H	C_2H_5	53	120—123	B	$C_{13}H_{10}ClNO_2$
IXc	H	iso-C_3H_7	69	162—165	B	$C_{14}H_{12}ClNO_2$
IXd	Cl	CH_3	81	170—173	B	$C_{12}H_7Cl_2NO_2$
IXe	Cl	C_2H_5	73	124—126	B–P	$C_{13}H_9Cl_2NO_2$
IXf	Cl	iso-C_3H_7	64	186—189	B	$C_{14}H_{11}Cl_2NO_2$
IXg	CF_3	CH_3	71	152—155	B	$C_{13}H_7ClF_3NO_2$
IXh	CF_3	C_2H_5	76	135—138	B–P	$C_{14}H_9ClF_3NO_2$
IXi	CF_3	iso-C_3H_7	70	160—162	P	$C_{15}H_{10}ClF_3NO_2$
IXk	OCH_3	C_2H_5	88	161—163	H–A	$C_{14}H_{12}ClNO_3$
IXl	OCH_3	iso-C_3H_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_2H_5	89	111—112	H–A	$C_{14}H_{12}ClNO_2$
IXo	CH_3	iso-C_3H_7	88	173—176	H–A	$C_{15}H_{14}ClNO_3$
IXp	Cl	H	76	221—222	B	$C_{11}H_5Cl_2NO_2$
IXq	CF_3	H	87	228—229	B	$C_{12}H_5ClF_3NO_2$
IXr	OCH_3	H	76	176—180	B	$C_{12}H_8ClNO_3$
IXs	CH_3	H	82	168—172	B	$C_{12}H_8ClNO_2$

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.

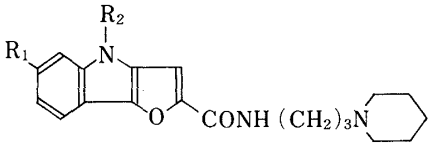
Compounds VIa, b and d were prepared in the same manner.

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 ν_{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.

TABLE X.



No.	Yield (%)	IR ν_{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 ν_{max}^{KBr} 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=$CDCl_3$, 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 ν_{max}^{KBr} cm^{-1}: 1655. MS *m/e*: 245 (M^+). NMR (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 $C_{13}H_{11}NO_4$: 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 ν_{max}^{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 $C_{13}H_{10}ClNO_3$: 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 bezene (80 ml), then the mixture was stirred for 1 h at room temperarure, 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 ν_{max}^{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 $C_{21}H_{27}N_3O_3$: 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 ν_{max}^{KBr} cm^{-1}: 1755, 1667. MS *m/e*: 413 (M^+). NMR (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 $C_{22}H_{27}N_3O_5$: 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

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