Synthesis of 4*H*-Furo[3,2-*b*]indole Derivatives. III (1). Preparation of 4*H*-Furo[3,2-*b*]indole-2-carboxylic Acid Derivatives

Akira Tanaka

Faculty of Pharmacy, Josai University, Sakatomachi, Irumagun, Saitama, Japan

Kenichi Yakushijin and Shigetaka Yoshina (the late)

Faculty of Pharmacy, Meijo University, Tenpakucho, Tenpakuku, Nagoya, Japan

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Methyl or ethyl 4*H*-furo[3,2-*b*]indole-2-carboxylates (Va,b) were prepared from deoxygenation of methyl or ethyl 5-(2-nitrophenyl)-2-furoates (IIIa,b) and thermolysis of methyl or ethyl 5-(2-azidophenyl)-2-furoates (VIIIa,b). 4*H*-Furo[3,2-*b*]indole-2-carboxylic acid amides (XIa-h) were obtained by the reaction of 4*H*-furo[3,2-*b*]indole-2-carboxyl chloride (X) with the appropriate amines.

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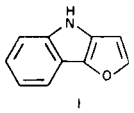
Recently, we have reported the synthesis of 4*H*-furo[3,2-*b*]indole (I) and some of its derivatives in order to study their possible biological activity (1). In this paper, the preparation of 4*H*-furo[3,2-*b*]indole-2-carboxylic acid derivatives is described.

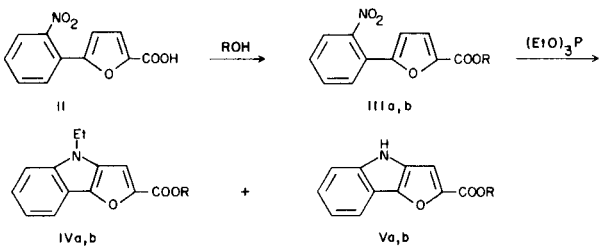


I

For the synthesis of this ring system, 5-(2-nitrophenyl)-2-furoic acid (II) served as the starting material (2). The ring closure was carried out by deoxygenation of the nitro group with triethyl phosphite (3) and thermolysis of the azido group (4). Thus, methyl or ethyl 5-(2-nitrophenyl)-2-furoates (IIIa,b) were initially prepared with esterification of II by the usual method. When IIIa and IIIb, respectively, were refluxed with triethyl phosphite for five hours in a nitrogen atmosphere, IIIa gave methyl 4-ethylfuro[3,2-*b*]-indole-2-carboxylate (IVa) and methyl 4*H*-furo[3,2-*b*]-indole-2-carboxylate (Va), and IIIb gave ethyl 4-ethyl-furo[3,2-*b*]indole-2-carboxylate (IVb) and ethyl 4*H*-furo[3,2-*b*]indole-2-carboxylate (Vb). The uv spectra of these compounds all showed a similar pattern (319, 254, 231 and 207 nm in ethanol); therefore, the ring systems appeared to be the same. The structures of IVa,b and Va,b were supported by spectral data and elemental analyses as shown in Experimental. Concerning the nmr spectra of these compounds, the signals for the ring protons were observed as a multiplet peak between δ 7.06 and 7.83; the pattern for these peaks all appeared to be like that for indole. Namely, the strong singlet peak in the multiplet was ascribed to the furan ring proton, and one proton of the distorted doublet at low field was assigned as the C_8-proton.

The mechanism for the formation of the *N*-ethyl compounds (IVa,b) appears to be the alkylation of Va,b with excess triethyl phosphite, according to the study of Sundberg and Cadogan (5). The preparation of IVa,b and Va,b was accomplished with triethyl phosphite. However, synthetic yields were below 25% because of the difficulty in removing triethyl phosphonate. Therefore, this synthetic procedure proved unsatisfactory.

Scheme I



Accordingly, methyl or ethyl 5-(2-azidophenyl)-2-furoates (VIIIa,b) were subsequently prepared in three steps from II, in order to improve the synthetic yields of Va,b. Thus, 5-(2-aminophenyl)-2-furoic acid (VI) was prepared from II *via* hydrogen sulfide in aqeous ammonia (1). Esterifications of VI gave alkyl 5-(2-aminophenyl)-2-furoates (VIIa,b); compounds VIIa,b were also obtained by catalytic reduction of the corresponding compounds IIIa,b. The diazonium salts of VIIa and VIIb were allowed to react with sodium azide to give VIIIa and VIIIb.

A comparison of the two preceding methods for the preparation of VIIa,b revealed that the latter was the better one with respect to yield. Compounds VIIIa and VIIIb eliminated a molecule of nitrogen to give Va and Vb, respectively, upon heating in *o*-dichlorobenzene. These compounds were identified with the compounds prepared above by mixed melting points and ir spectra. The latter of the two methods reported above gave the desired end products Va,b in 49 and 53% overall yield, respectively, from II. The eventual thermal ring closure of the azides VIIIa,b gave better yields than deoxygenation of the nitro compounds IIIa,b (24 and 20% yield, respectively).

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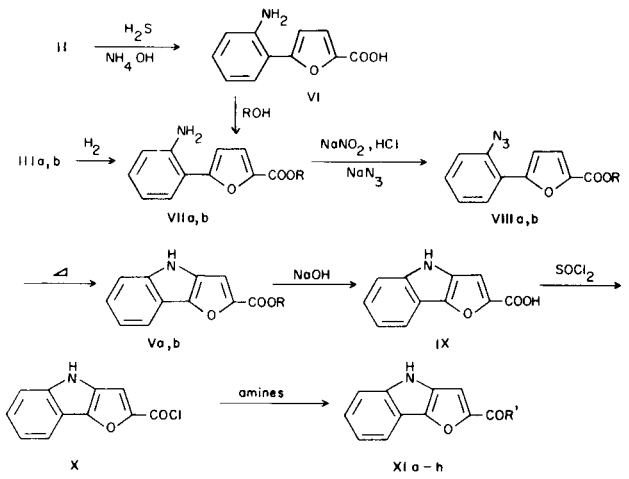
Scheme 2



IIIa, Va, VIIa, VIIIa; R=Me

IIIb, Vb, VIIb, VIIIb; R=Et

We have reported that 4*H*-furo[3,2-*b*]indole (I) was very unstable relative to acids, because it consists of the electron rich furan and indole rings fused together (1). It was believed that compounds IVa,b and Va,b would be more stable toward acidic media, since they contain the electron-withdrawing carboxyl group substituted on their ring systems. Accordingly, the behavior of IVa,b and Va,b toward mineral acids and bases was examined. Thus, the following experiments were performed: (A) hydrolysis in a catalytic amount of mineral acid; (B) hydrolysis in sodium hydroxide solution; and (C) ester exchange in acidic medium. Compounds Va,b reacted readily in all cases, but IVa,b were decomposed giving tarry products, under acidic condition (A and C); IVa,b gave only the free acid (IX) in experiment B. These results show that IVa,b are less stable than Va,b in acidic medium, owing to the electron-donating properties of the *N*-alkyl groups.

4*H*-Furo[3,2-*b*]indole-2-carboxylic acid (IX) was obtained from the hydrolysis of Va,b; chlorination of IX gave 4*H*-furo[3,2-*b*]indole-2-carboxoyl chloride (X). 4*H*-Furo-[3,2-*b*]indole-2-carboxylic acid amides (XIa-h) were prepared from the reaction of X with the corresponding amines as shown in Table I. An investigation into the pharmacological activity of the compounds which were synthesized in this study is currently in progress.

EXPERIMENTAL

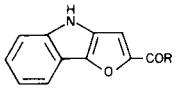
Melting points are uncorrected. Ir spectra were measured with a Jasco IRA-1 spectrometer and nmr spectra were recorded on a JEOL-PS-100 spectrometer using TMS as an internal standard. Mass spectra were taken with a Hitachi RMU-6 spectrophotometer.

Methyl 5-(2-Nitrophenyl)-2-furoate (IIIa).

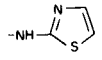
A solution of 23.3 g. (0.1 mole) of 5-(2-nitrophenyl)-2-furoic acid (II) in 400 ml. of methanol containing 40 g. of concentrated sulfuric acid was refluxed for 5 hours. The reaction mixture was poured into 2000 ml. of ice-water and filtered. Purification of the precipitate by recrystallization from ligroin gave 23.2 g. (94%) of IIIa as yellow prisms, m.p. 80-81°; ir (potassium bromide): ν 1723 cm^{-1} (C=O); nmr (deuteriochloroform): δ 7.61 (4H, m, benzene-H), 7.23 (1H, d, J = 3.7 Hz, furan C_3-H), 6.67 (1H, d, J = 3.7 Hz, furan C_4-H), 3.89 (3H, s, CH_3); ms: (m/e) 247 (M^+).

Table I

4*H*-Furo[3,2-*b*]indole-2-carboxylic Acid Amides (XIa-h)



XIa-h

Compound No.	R	Appearance	M.p. °C	Yield %	Recrystallization solvent	Empirical Formula	Calcd., %			Found, %		
							C	H	N	C	H	N
XIa	$-NH_2$	Yellow plates	223-224	69	acetone-water	$C_{11}H_8N_2O_2$	65.99	4.03	13.99	65.75	3.74	14.02
XIb	$-N(CH_3)_2$	Colorless needles	177-178	73	benzene	$C_{13}H_{12}N_2O_2$	68.41	5.30	12.27	68.70	5.16	12.27
XIc	$-N(C_2H_5)_2$	Colorless needles	184-185	70	methanol	$C_{15}H_{16}N_2O_2$	70.29	6.29	10.93	70.50	6.28	10.68
XId	$-NHCH_2CH_2OH$	Colorless scales	167-169	37	chloroform	$C_{13}H_{12}N_2O_4$	63.92	4.95	11.47	64.15	4.78	11.47
XIe	$-N(CH_2CH_2OH)_2$	Colorless prisms	240-241	46	ethanol	$C_{15}H_{16}N_2O_4$	62.49	5.59	9.42	62.59	5.34	9.70
XIf		Colorless scales	168-169	55	methanol	$C_{16}H_{16}N_2O_2$	71.62	6.01	10.44	71.82	6.04	10.22
XIg		Colorless needles	154-155	73	methanol	$C_{16}H_{14}N_2O_3$	66.65	5.22	10.37	66.69	5.11	10.08
XIh		Orange powders	306-308	74	acetone	$C_{14}H_9N_3O_2S$	59.36	3.20	14.84	59.30	2.92	14.55

Anal. Calcd. for $C_{12}H_9NO_5$: C, 58.30; H, 3.67; N, 5.67. Found: C, 58.51; H, 3.49; N, 5.92.

Ethyl 5-(2-Nitrophenyl)-2-furoate (IIIb).

Compound II was esterified with ethanol to give IIIb as yellow prisms, m.p. 79-80° (from ligroin), in 90% yield; ir (potassium bromide): ν 1720 cm^{-1} (C=O); nmr (deuteriochloroform): δ 7.62 (4H, m, benzene-H), 7.25 (1H, d, J = 3.6 Hz, furan C_3-H), 6.71 (1H, d, J = 3.6 Hz, furan C_4-H), 4.37 and 1.37 (5H, q and t, C_2H_5); ms: (m/e) 261 (M^+).

Anal. Calcd. for $C_{13}H_{11}NO_5$: C, 59.77; H, 4.24; N, 5.36. Found: C, 59.77; H, 4.05; N, 5.09.

Reaction of IIIa with Triethyl Phosphite.

A solution of 2.5 g. (0.01 mole) of IIIa in 20 ml. of triethyl phosphite was refluxed in an atmosphere of nitrogen for 7 hours. After evaporation of the excess triethyl phosphite *in vacuo*, a small amount of methanol and water was added to the solution and it was allowed to stand overnight. The resulting product was filtered and purified by recrystallization from methanol to give 0.23 g. (9%) of methyl 4-ethylfuro[3,2-*b*]indole-2-carboxylate (IVa) as yellow needles, m.p. 126-127°; ir (potassium bromide): ν 1705 cm^{-1} (C=O); nmr (deuteriochloroform): δ 7.80 (1H, m, C_8-H), 7.32 (1H, s, C_3-H), 7.20 (3H, m, C_{5-7}-H), 4.17 and 1.47 (5H, q and t, C_2H_5), 3.92 (3H, s, CH_3); ms: (m/e) 243 (M^+).

Anal. Calcd. for $C_{14}H_{13}NO_3$: C, 69.12; H 5.39; N, 5.76. Found: C, 68.95; H, 5.40; N, 5.86.

The filtrate was extracted with ether and dried over magnesium sulfate. Evaporation of the ether gave amorphous materials, which were purified by column chromatography on silica gel. Elution of benzene gave 0.3 g. (14%) of methyl 4*H*-furo[3,2-*b*]indole-2-carboxylate (Va) as pale yellow scales, m.p. 199-200°; ir (potassium bromide): ν 3270 (NH), 1685 cm^{-1} (C=O); nmr (deuteriochloroform): δ 7.90 (1H, br, NH), 7.78 (1H, m, C_8-H), 7.28 (1H, s, C_3-H), 7.25 (3H, m, C_{5-7}-H), 3.94 (3H, s, CH_3); ms: (m/e) 215 (M^+).

Anal. Calcd. for $C_{12}H_9NO_3$: C, 66.97; H, 4.22; N, 6.51. Found: C, 66.92; H, 4.13; N, 6.46.

Reaction of IIIb with Triethyl Phosphite.

A solution of 2.6 g. (0.01 mole) of IIIb in 20 ml. of triethyl phosphite was treated in a similar manner as described above. Ethyl 4-ethylfuro-[3,2-*b*]indole-2-carboxylate (IVb) was obtained as colorless neeldes, m.p. 89-90° (from ethanol, 0.22 g., 9% yield); ir (potassium bromide): ν 1705 cm^{-1} (C=O); nmr (deuteriochloroform): δ 7.78 (1H, m, C_8-H), 7.29 (1H, s, C_3-H), 7.19 (3H, m, C_{5-7}-H), 4.27 and 1.44 (10H, 2 x q and 2 x t, 2 x C_2H_5); ms: (m/e) 257 (M^+).

Anal. Calcd. for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 69.95; H, 5.76; N, 5.30.

Also, ethyl 4*H*-furo[3,2-*b*]indole-2-carboxylate (Vb) was obtained as colorless scales, m.p. 152-153° (from benzene, 0.3 g., 13% yield); ir (potassium bromide): ν 3290 (NH), 1685 cm^{-1} (C=O); nmr (deuteriochloroform): δ 8.07 (1H, br, NH), 7.78 (1H, m, C_8-H), 7.28 (1H, s, C_3-H), 7.26 (3H, m, C_{5-7}-H), 4.42 and 1.42 (5H, q and t, C_2H_5); ms: (m/e) 229 (M^+).

Anal. Calcd. for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11. Found: C, 68.32; H, 4.91; N, 6.05.

Methyl 5-(2-Aminophenyl)-2-furoate (VIIa).

a. Esterification of 5-(2-Aminophenyl)-2-furoic Acid (VI).

A solution of 20 g. (0.1 mole) of VI in 200 ml. of methanol containing 20 g. of concentrated sufluric acid was refluxed for 2 hours. The reaction mixture was poured into 2000 ml. of ice-water and extracted with ether after being neutralized with sodium carbonate. The ether solution was dried over magnesium sulfate and the solvent was evaporated. The residue was purified by recrystallization from dilute methanol to give 4 g. (19%) of VIIa as colorless plates, m.p. 85-86°; ir (potassium bromide: ν 3500, 3370 (NH_2), 1700 cm^{-1} (C=O); nmr (deuteriochloroform): δ 7.50 (1H, m, benzene-H), 7.26 (1H, d, J = 3.6 Hz, furan C_3-H), 7.11 (1H, m, benzene-H), 6.76 (2H, m, benzene-H), 6.66 (1H, d, J = 3.6 Hz, furan C_4-H), 4.62 (2H, br, NH_2), 3.89 (3H, s, CH_3); ms: (m/e) 217 (M^+).

Anal. Calcd. for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.29; H, 4.92; N, 6.31.

b. Hydrogenation of IIIa.

A solution of 24.7 g. (0.1 mole) of IIIa in 250 ml. of ethanol was hydrogenated over 3 g. of 5% palladium on carbon at room temperature. 6720 Ml. (0.3 mole) of hydrogen had been absorbed, the catalyst was filtered off from the solution. The condensed solution by distillation gave 19.5 g. (90%) of VIIa as yellow prisms, m.p. 85-86°, which was identified by a mixed melting point test and an ir spectral comparison with VIIa prepared *via* method *a*.

Ethyl 5-(2-Aminophenyl)-2-furoate (VIIb).

a. Esterification of VI.

Compound VI was esterified with ethanol to give VIIb as colorless needles, m.p. 96-98° (from dilute ethanol), in 16.7% yield; ir (potassium bromide): ν 3500, 3370 (NH_2), 1700 cm^{-1} (C=O); nmr (deuteriochloroform): δ 7.48 (1H, m, benzene-H), 7.22 (1H, d, J = 3.6 Hz, furan C_3-H), 7.07 (1H, m, benzene-H), 6.74 (2H, m, benzene-H), 6.62 (1H, d, J = 3.6 Hz, furan C_4-H), 4.58 (2H, br, NH_2), 4.35 and 1.37 (5H, q and t, C_2H_5); ms: (m/e) 231 (M^+).

Anal. Calcd. for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.22; H, 5.38; N, 6.01.

b. Hydrogenation of IIIb.

The procedure described for the preparation of VIIa was employed to convert 26 g. (0.1 mole) of IIIb to 21.4 g. (93%) of VIIb as yellow prisms, m.p. 97-98°. This compound was identified by a mixed melting point test and an ir spectral comparison with VIIb prepared *via* method *a*.

Methyl 5-(2-Azidophenyl)-2-furoate (VIIIa).

A mixture of 4.4 g. (0.02 mole) of VIIa in 10 ml. of concentrated hydrochloric acid was cooled in an ice-salt bath. To the cold solution was added 1.52 g. of sodium nitrite in 10 ml. of water. The cold reaction mixture was then allowed to stand with frequent stirring for 45 minutes, after which time a solution of 2.6 g. of sodium azide in 10 ml. of water was added dropwise to the cold diazonium solution. After all the azide had been added, the mixture was allowed to stand at room temperature for half an hour. The resulting product was filtered and purified by recrystallization from petroleum ether to give 3.8 g. (77%) of VIIIa as colorless needles, m.p. 110-111°; ir (potassium bromide): ν 2120, 2070 (N_3), 1733 cm^{-1} (C=O); nmr (deuteriochloroform): δ 8.03 (1H, m, benzene-H), 7.30 (5H, m, other aromatic-H), 3.94 (3H, s, CH_3); ms: (m/e) 243 (M^+).

Anal. Calcd. for $C_{12}H_9N_3O_3$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.13; H, 3.62; N, 17.20.

Ethyl 5-(2-Azidophenyl)-2-furoate (VIIIb).

The procedure described for the preparation of VIIIa was employed to convert 4.6 g. (0.02 mole) of VIIb to 4.2 g. (82%) of VIIIb as colorless needles, m.p. 72-73° (from petroleum ether); ir (potassium bromide): ν 2120, 2090 (N_3), 1710 cm^{-1} (C=O); nmr (deuteriochloroform): δ 7.97 (1H, m, benzene-H), 7.25 (5H, m, other aromatic-H), 4.36 and 1.39 (5H, q and t, C_2H_5); ms: (m/e) 257 (M^+).

Anal. Calcd. for $C_{13}H_{11}N_3O_3$: C, 60.69; H, 4.31; N, 16.34. Found: C, 60.51; H, 4.20; N, 16.39.

Methyl 4*H*-furo[3,2-*b*]indole-2-carboxylate (Va).

A solution of 4.9 g. (0.02 mole) of VIIIa in 20 ml. of *o*-dichlorobenzene was added dropwise to 20 ml. of boiling *o*-dichlorobenzene with stirring. During the reaction, nitrogen gas evolved and the solution became reddish brown in color. After cooling, 80 ml. of petroleum ether was added to the reaction mixture, and the solution was allowed to stand overnight. The resulting product was filtered and purified by recrystallization from benzene to give 3.3 g. (76%) of Va as colorless scales, m.p. 199-200°. This compound was identified by a mixed melting point test and an ir comparison with Va prepared previously from IIIa and triethyl phosphite.

Ethyl 4*H*-Furo[3,2-*b*]indole-2-carboxylate (Vb).

The procedure described for Va was employed to convert 5.1 g. (0.02

mole) of VIIIb to 3.5 g. (77%) of Vb as colorless scales, m.p. 143-144° (from benzene). This compound was previously identified by a mixed melting point test and an ir comparison with Vb previously prepared from IIIb and triethyl phosphite.

4*H*-Furo[3,2-*b*]indole-2-carboxylic Acid (IX).

A mixture of 4.3 g. (0.02 mole) of Va in 40 ml. of 10% sodium hydroxide solution was heated in a water-bath for 2 hours. After cooling, the solution was poured into 200 ml. of ice-water and acidified with dilute hydrochloric acid. The resulting product was filtered and purified by recrystallization from acetone to give 3.5 g. (87%) of IX as colorless scales, m.p. 229-230°; ir (potassium bromide): ν 3410, (NH), 2990 (OH), 1660 cm^{-1} (C=O); nmr (DMSO-d_6): δ 11.13 (1H, br, NH), 7.83 (1H, m, C_8-H), 7.55 (1H, s, C_3-H), 7.35 (3H, m, C_{5-7}-H); ms: (m/e) 201 (M^+).

Anal. Calcd. for $C_{11}H_7NO_3$: C, 65.67; H, 3.51; N, 6.96. Found: C, 65.83; H, 3.28; N, 6.72.

4*H*-Furo[3,2-*b*]indole-2-carboxoyl Chloride (X).

A mixture of 15 g. (0.075 mole) of IX in 90 ml. of thionyl chloride was refluxed for 2 hours. After evaporation of excess thionyl chloride, the residue was purified by recrystallization from ether to give 12 g. (73%) of X as green flakes, m.p. 143-144°; ir (potassium bromide): ν 3440 (NH), 1720 cm^{-1} (C=O); ms: (m/e) 219 (M^+).

Anal. Calcd. for $C_{11}H_6ClNO_2$: C, 60.15; H, 2.75; N, 6.38. Found: C, 60.01; H, 2.61; N, 6.25.

4*H*-Furo[3,2-*b*]indole-2-carboxylic Acid Amides (XIa-h).

To a solution of 1 g. (5 mmoles) of X in 30 ml. of acetone was added equimolar amounts of the appropriate amines. The reaction mixture was treated as usual to give XIa-h, which are shown in Table I.

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