A Novel Synthesis of Benzofuran and Related Compounds. I. The Vilsmeier Reaction of Phenoxyacetonitriles

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A novel synthesis of 2-benzofurancarboxylic acid derivatives by the Vilsmeier reaction of phenoxyacetonitriles is described.

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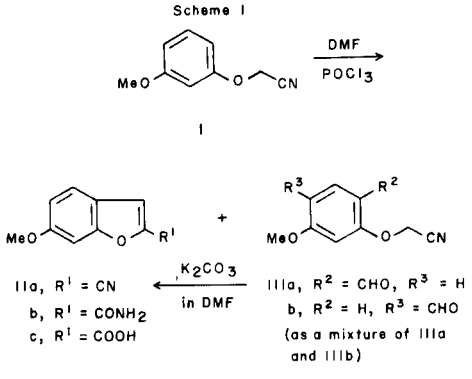
The Vilsmeier reaction is a moderate method for formylation of aromatic and active aliphatic compounds. Sometimes unexpected cyclizations under the Vilsmeier conditions were reported, which were recently reviewed [1]. Previously we reported a novel synthesis of isoquinoline derivatives by the Vilsmeier reaction of phenylacetonitriles [2]. In the course of our work, we were interested in an attempt to use this reaction for phenoxyacetonitriles.

Scheme 1

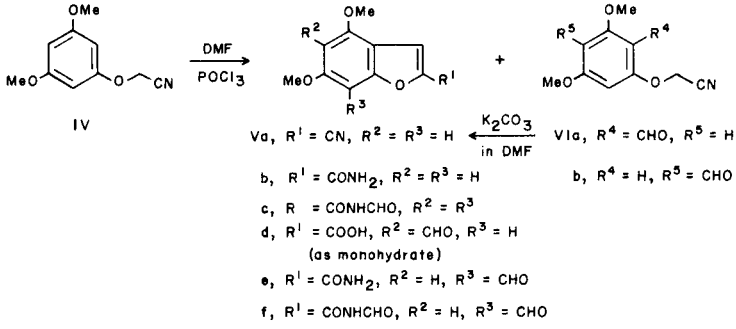


As shown in Scheme 1, the Vilsmeier reaction of 3-methoxyphenoxyacetonitrile (I) [3] with dimethylformamide (DMF, large excess) and phosphoryl chloride (3 molar excess) afforded 6-methoxy-2-benzofurancarboxylic acid derivatives IIa [4], IIb [4], IIc [5] and formylated compounds IIIa and IIIb. Although IIIa and IIIb could not be separated by column or thin-layer chromatography (tlc), nuclear magnetic resonance (nmr) spectrum of the mixture showed almost equal proportion. Bourguignon *et al.* [6] obtained ethyl thieno[2,3-*b*]pyrazine-6-caroboxylate by heating ethyl *S*-(3-formylpyrazin-2-yl)thioglycolate with potassium carbonate in DMF. This method was applied to the mixture of IIIa and IIIb, and cyclized product, IIa, and unchanged IIIb were isolate.

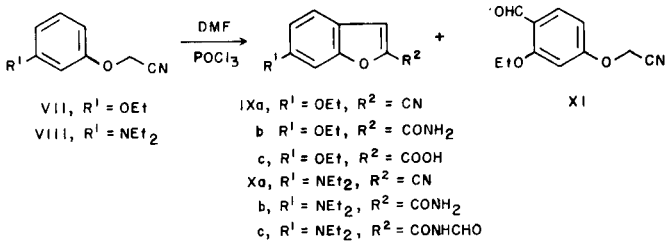
To investigate better reaction conditions of the novel benzofuran synthesis, the Vilsmeier reaction was applied to 3,5-dimethoxyphenoxyacetonitrile (IV) [7], which is more reactive than I on electrophilic cyclization. As shown in Scheme 2 and Table I, good results were obtained in the total yield of benzofurans when compound IV, DMF, and phosphoryl chloride were used in a molar ratio of 1:1.2:3.6. 2-Formyl-3,5-dimethoxyphenoxyacetonitrile (VIa) obtained in runs A and B could be converted to benzofuran, Va, by heating with potassium carbonate in DMF in good yield.

Since Elvidge and Foster reported the existence of coupling between the C-3 and C-7 protons (~1 Hz) in the nmr spectrum [8], the position of the formyl groups of 5-formyl-4,6-dimethoxy-2-benzofurancarboxylic acid (Vd), 7-formyl-4,6-dimethoxy-2-benzofurancarboxamide (Ve), and *N*,7-diformyl-4,6-dimethoxy-2-benzofuancarboxamide (Vf) was determined by the existence of Vd and the nonexistence of Ve and Vf of the coupling between protons of C-3 and C-7.

Scheme 2



Scheme 3



VII, R^1 = OEt
VIII, R^1 = NEt_2

IXa, R^1 = OEt, R^2 = CN
b R^1 = OEt, R^2 = $CONH_2$
c, R^1 = OEt, R^2 = COOH
Xa, R^1 = NEt_2, R^2 = CN
b, R^1 = NEt_2, R^2 = $CONH_2$
c, R^1 = NEt_2, R^2 = CONHCHO

XI

Table I

Conditions and Yields in the Reaction of 10 mmoles of 3,5-Dimethoxyphenoxyacetonitrile (IV)

Run	Molar Ratio		Reaction time (hours)	Reaction temp (°C)	Products and Yields
A	IV	1	9	75	Vc, 7%; Vd, 14% (21%) [a]; VIa, 29%; VIb, 7.5%
	DMF	solvent			
	$POCl_3$	3			
B	IV	1	6	75	Va, 11%; Vb, 2.5%; Vc, 1.5%; Vf, 15.5% (31%) [a]; VIa, 36%; VIb, 13%
	DMF	3			
	$POCl_3$	1			
C	IV	1	3	70	Va, 52.5%; Vb, 0.5%; Vc, 2.5% (56%) [a]; VIb, 13%;
	DMF	1			
	$POCl_3$	2			
D	IV	1	3	70	Va, 61%; Vb, 0.5%; Vc, 2%; Ve, 2%; (66%) [a]; VIb, 8.5%
	DMF	1.2			
	$POCl_3$	3.6			

[a] The total yield of benzofurans are represented in parentheses. Most of the products were isolated with silica gel column chromatography and recrystallized from appropriate solvent.

To generalize this benzofuran synthesis, further studies were carried out using 3-ethoxy- (VII) and 3-diethylaminophenoxyacetonitriles (VIII). As shown in Scheme 3, 2-benzofurancarboxylic acid derivatives IXa,b,c and Xa,b,c and the formylated compound XI were obtained as expected. The nmr spectrum of XI indicated that the formylated position was situated at C-4 and C-6, however, reaction of XI with potassium carbonate in DMF did not afford IXa (recovery of starting material) which differed from IIIa and VIa. Thus, the position of the formyl group was shown to be at C-4.

Further work in this novel synthesis of benzofurans is in progress.

EXPERIMENTAL

The melting points were recorded on a Yanagimoto micro melting point apparatus and are uncorrected. Elemental analyses were performed on a Yanagimoto MT-2 CHN Corder elemental analyzer. The infrared (ir) absorption spectra were obtained with a Japan Spectroscopic A-102 diffraction grating infrared spectrophotometer. The nmr spectra were measured on a Hitachi R-22FTS FT-NMR spectrometer (90 MHz). The chemical shifts (δ) in ppm were measured relative to tetramethylsilane as an internal standard. The mass spectra (ms) were taken with a Shimadzu LKB-9000 instrument at 70eV. The ultraviolet (uv) abosorption spectra were taken on a Hitachi ESP-2 spectrophotometer in ethanol.

General Procedure for Preparation of Phenoxyacetonitriles.

A mixture of 10 mmoles of the corresponding phenol, 15 mmoles of dry potassium carbonate, 15 mmoles of chloroacetonitrile, and 0.3 mmole of potassium iodide in 15 ml of dry dimethylsulfoxide was stirred at 70-75° for the appropriate number of hours (tlc check) under a nitrogen stream. After cooling, the precipitated solid was filtered and washed with benzene. The filtrate and washings were combined and water was added to the mixture, which was extracted with benzene. The benzene layer was shaken with 1*N* sodium hydroxide and then with water. The organic layer was dried and evaporated.

3-Methoxyphenoxyacetonitrile (I) [3].

The reacion conditions were: stirring at 75° for 11 hours, yield 53%, colorless oil, bp 135-136° 5 mm Hg (lit 167-168°/15 mm Hg [3]); ms: m/z 163 (M^+); nmr (deuteriochloroform): 3.81 (3H, s, OCH_3), 4.75 (2H, s, OCH_2), 6.60, 7.25 (3H, m, 1H, m, Ar-H).

3,5-Dimethoxyphenoxyacetonitrile (IV) [7].

The reaction conditions were: stirring at room temperature for 1 day, yield 97%, colorless needles from benzene-*n*-hexane, mp 44-45° (no mp in the literature [7]); ms: m/z 193 (M^+); nmr (deuteriochloroform): 3.78 (6H, s, 2 × OCH_3), 4.72 (2H, s, OCH_2), 6.16 (3H, br s, Ar-H).

3-Ethoxyphenoxyacetonitrile (VII).

The reaction conditions were: stirring at room temperature for 6.5 hours, yield 98%, colorless oil, bp 131-131.5°/3 mm Hg; ms: m/z 177 (M^+); nmr (deuteriochloroform): 1.41 (3H, t, J = 7 Hz, OCH_2CH_3), 4.04 (2H, q, J = 7 Hz, OCH_2CH_3), 4.75 (2H, s, CH_2CN), 6.56, 7.26 (3H, m, 1H, br t, J = 8.5 Hz, Ar-H).

Anal. Calcd. for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.57; H, 6.27; N, 7.81.

3-Diethylaminophenoxyacetonitrile (VIII) [9].

The reaction conditions were: stirring at 75-80° of 20 hours, yield 65%, colorless oil, bp 145-147°/2.5 mm Hg (no bp in the literature [9]); ms: m/z 204 (M^+); nmr (deuteriochloroform): 1.16 (6H, t, J = 7 Hz, 2 × CH_2CH_3), 3.35 (4H, q, J = 7 Hz, 2 × CH_2CH_3), 4.75 (2H, s, CH_2CN), 6.32, 7.17 (3H, m, 1H, br t, J = 9 Hz, Ar-H).

General Procedure of the Vilsmeier Reaction for Phenoxyacetonitriles I, IV, VII, and VIII.

To the Vilsmeier reagent prepared from DMF and phosphoryl chloride at 0-5° for 0.5 hour, was added 10 mmoles of phenoxyacetonitrile at once and the mixture was stirred under the appropriate condition. After cooling, *ca.* 50 ml of water was added to the reaction mixture and the mixture was warmed at 40-50° for 10-20 minutes. The resulting mixture was extracted with chloroform. The aqueous layer was basified with sodium bicarbonate and extracted with chloroform. Each organic layer was washed with water, dried over anhydrous sodium sulfate, and evaporated, independently. Since the amount of the latter extract was very small and similar spots were observed in both extracts on tlc, each residue was combined and chromatographed on silica gel starting with benzene folllowed by dichloromethane, chloroform, ethyl acetate (or acetone), and ethanol.

Vilsmeier Reaction of I.

To the Vilsmeier reagent prepared from 10 ml of DMF and 4.61 g (30 mmoles) of phosphoryl chloride, was added 1.63 g (10 mmoles) of I and the mixture was stirred at 100° for 15 hours. The reaction mixture was worked up as described in the general procedure. The benzene eluate was recrystallized from *n*-hexane to give 46 mg (2.7%) of 6-methoxy-2-

benzofurancarbonitrile (IIa) as colorless needles, mp 72-73° (lit 74° [3]); ms: m/z 173 (M^+); ir (potassium bromide): cm^{-1} 2240 (C≡N); nmr (deuteriochloroform): 3.89 (3H, s, OCH_3), 7.01 (1H, br d, J = 9.5 Hz, 5-H), 7.04 (1H, br s, 7-H), 7.39 (1H, br s, 3-H), 7.54 (1H, d, J = 9.5 Hz, 4-H); uv: λ max nm (log ε) 220 (3.34), 274 (3.18), 296 (3.20), 3.06 (3.23).

Anal. Calcd. for $C_{10}H_7NO_2$: C, 69.36; H, 4.07; N, 8.09. Found: C, 69.24; H,4.05; N, 7.99.

The benzene-dichloromethane (1:2) eluate was recrystallized from benzene-cyclohexane to give 353 mg (19%) of a mixture of 2-formyl-5-methoxyphenoxyacetonitrile (IIIa) and 4-formyl-3-methoxyphenoxyacetonitrile (IIIb) as colorless needles. The mixture could not be separated because they behaved very similarly on tlc with several developing solvent systems. The product ratio was *ca.* 1:1 by nmr measurement of the mixture. The benzene-acetone (3:1) eluate was recrystallized from benzene to give 86 mg (4.5%) of 6-methoxy-2-benzofurancarboxamide (IIb) as pale brown needles, mp 176-177° (lit 178° [3]); ms: m/z 191 (M^+); ir (potassium bromide): cm^{-1} 3440, 3170 1615 (N-H), 1673 (C=O); nmr (deuteriochloroform): 3.88 (1H, s, OCH_3), 6.35 (2H, br, deuterium oxide exchangeable, NH_2), 6.96 (1H, br d, J = 8 Hz, 5-H), 7.02 (1H, br s, 7-H), 7.49 (1H, br s, 3-H), 7.56 (1H, d, J = 8 Hz, 4-H); uv: λ max nm (log ε) 220 (4.15), 270 (4.03), 277 (4.08), 300 (4.27), 307 (4.27).

Anal. Calcd. for $C_{10}H_9NO_3$: C, 62.82; H, 4.75; N, 7.33. Found: C, 62.55; H, 4.61; N, 7.04.

The acetone eluate was recrystallized from dichloromethane to give 259 mg (14%) of 6-methoxy-2-benzofurancarboxylic acid (IIc) as colorless needles, mp 195-197° (lit 195.5-196.5° [4]); ms: m/z 192 (M^+); ir (potassium bromide): cm^{-1} 1680 (C=O); nmr (deuteriochloroform): 3.92 (3H, s, OCH_3), 7.00 (1H, dd, J = 8.5 Hz, 2.5 Hz, 5-H), 7.19 (1H, br s, 7-H), 7.59 (1H, br s, 3-H), 7.67 (1H, d, J = 8.5 Hz, 4-H); uv: λ max nm (log ε) 236 (3.64), 272 (3.92), 300 (4.13), 305 (4.15).

Anal. Calcd. for $C_{10}H_8O_4$: C, 62.50; H, 4.20. Found: C, 62.51; H, 4.12.

Reaction of the Mixture of IIIa and IIIb with Potassium Carbonate.

A solution of 100 mg of the mixture of IIIa and IIIb in 5 ml of DMF was heated at 100° for 2.5 hours in the presence of 100 mg of potassium carbonate. After cooling, the deposited solid was filtered and washed with chloroform. Water was added to the combined filtrate and the mixture was extracted with chloroform. The organic layer was washed with water, dried over anhydrous sodium sulfate, and evaporated. The residue was separated by preparative tlc (Wakogel B-5FM, 20 cm × 20 cm × 1 mm, solvent system: benzene:chloroform:acetone:ethanol = 5:5:1:1). The fraction with Rf value *ca.* 0.6-0.7, which indicated blue fluorescence with a PAN-UV lamp, was collected and recrystallized from *n*-hexane to give 45.5 mg of IIa, which was identified with the crystals described above (mixed mp, tlc, and ir). The fraction with Rf value *ca.* 0.4-0.5, which indicated bluish violet fluoresence with a PAN-UV lamp, was collected and recrystallized from benzene-cyclohexane to give 41 mg of IIIb as colorless needles, mp 70-72°; ms: m/z 191 (M^+); ir (potassium bromide): cm^{-1} 1675 (C=O); nmr (deuteriochloroform): 3.95 (3H, s, OCH_3), 4.87 (2H, s, OCH_2), 6.56 (1H, d, J = 1.5 Hz, 2-H), 6.67 (1H, dd, J = 8 Hz, 1.5 Hz, 6-H), 7.91 (1H, d, J = 8 Hz, 5-H), 10.37 (1H, s, CHO).

Anal. Calcd. for $C_{10}H_9NO_3$: C, 62.82; H, 4.75; N, 7.33. Found: C, 62.71; H, 4.82; N, 7.19.

Vilsmeier Reaction of 3,5-Dimethoxyphenoxyacetonitrile (IV).

Reaction conditions, products, and yields are summarized in Scheme 2 and Table I.

Run A.

5-Formyl-4,6-dimethoxy-2-benzofurancarboxylic acid (Vd) was precipitated when water was added to the reaction mixture. The solid was recrystallized from acetone to give colorless needles as the monohydrate of Vd, mp 252-254° dec; ms: parent peak was not observed in free acid. Methyl ester of Vd gave the parent peak at m/z 250; ir (potassium bromide): cm^{-1} 1680, 1675 (C=O); nmr (DMSO-d_6): 4.05, 4.09 (each 3H, s, 2 × OCH_3), 6.71 (1H, d, J = 0.7 Hz, 7-H), 7.51 (1H, d, J = 0.7 Hz, 3-H), 10.32 (1H, s, CHO); uv: λ max nm (log ε) 222 (4.03), 231 (4.02), 238 (4.01), 273 (4.34), 295 (4.32), 329 (4.08).

Anal. Calcd. for $C_{12}H_{10}O_6 \cdot H_2O$: C, 53.73; H, 4.51. Found: C, 53.51; H, 4.46.

The filtrate of the crude Vd was extracted with chloroform. The organic layer and the mother liquor of recrystallization of Vd were combined and evaporated. The residue was chromatographed on silica gel. The dichloromethane eluate was recrystallized from benzene to give *N*-formyl-4,6-dimethoxy-2-benzofurancarboxamide (Vc) was colorless fine needles, mp 208-209° dec; ms: m/z 249 (M^+); ir (potassium bromide): cm^{-1} 3240, 1625 (N-H), 1732, 1695 (C=O); nmr (deuteriochloroform): 3.89, 3.93 (each 3H, s, 2 × OCH_3), 6.36 (1H, d, J = 2 Hz, 5-H), 6.61 (1H, br s, 7-H), 7.77 (1H, d, J = 0.7 Hz, 3-H), 8.94 (1H, br, deuterium oxide exchangeable, NH), 9.34 (1H, d, J = 10 Hz, changed to singlet with deuterium oxide, CHO); uv: λ max nm (log ε) 288 (4.07), 315 (4.03), 333 (4.03).

Anal. Calcd. for $C_{12}H_{11}NO_5$: C, 57.83; H, 4.45; N, 5.62. Found: C, 57.61; H, 4.29; N, 5.44.

Continuous elution with dichloromethane gave 2-formyl-3,5-dimethoxyacetonitrile (VIa), which was recrystallized from benzene-cyclohexane to give colorless granules, mp 108-110°; ms: m/z 221 (M^+); ir (potassium bromide): cm^{-1} 2270 (C≡N), 1682 (C=O); nmr (deuteriochloroform): 3.89, 3.91 (each 3H, s, 2 × OCH_3), 4.85 (2H, s, OCH_2), 6.23 (2H, br s, Ar-H), 10.31 (1H, s, CHO).

Anal. Calcd. for $C_{11}H_{11}NO_4$: C, 59.72; H, 5.01; N, 6.33. Found: C, 59.93; H, 4.99; N, 6.11.

Further continuous elution with dichloromethane gave 4-formyl-3,5-dimethoxyphenoxyacetonitrile (VIb), which was recrystallized from benzene-cyclohexane to give colorless needles, mp 131-132°; ms: m/z 221 (M^+); ir (potassium bromide): cm^{-1} 2270 (C≡N), 1685 (C=O); nmr (deuteriochloroform): 3.92 (6H, s, 2 × OCH_3), 4.87 (2H, s, OCH_2), 6.19 (2H, s, Ar-H), 10.29 (1H, s, CHO).

Anal. Calcd. for $C_{11}H_{11}NO_4$: C, 59.72; H, 5.01; N, 6.33. Found: C, 59.68; H, 4.82; N, 6.12.

Run B.

The combined chloroform extract was chromatographed on silica gel. The benzene eluate was recrystallized from *n*-hexane to give 4,6-dimethoxy-2-benzofurancarbonitrile (Va) as colorless needles, mp 161-163°; ms: m/z 203 (M^+); ir (potassium bromide): cm^{-1} 2240 (C≡N); nmr (deuteriochloroform): 3.85, 3.90 (each 3H, s, 2 × OCH_3), 6.37 (1H, d, J = 2 Hz, 5-H), 6.63 (1H, br s, 7-H), 7.46 (1H, d, J = 0.6 Hz, 3-H); uv: λ max nm (log ε) 235 (4.31), 240 (4.30), 2.90 (4.43).

Anal. Calcd. for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 64.80; H, 4.29; N, 6.65.

The dichloromethane eluate was recrystallized from benzene to give Vc as colorless needles, which was identical with the product obtained in run A. Continuous elution with dichloromethane gave VIa and VIb, which was identical with the product obtained in run A. Further continuous elution with dichloromethane gave 4,6-dimethoxy-2-benzofurancarboxamide (Vb) as colorless needles (from benzene), mp 146-148°; ms: m/z 221 (M^+); ir (potassium bromide): cm^{-1} 3450, 3170, 1630 (N-H), 1670 (C=O); nmr (deuteriochloroform): 3.87, 3.92 (each 3H, s, 2 × OCH_3), 6.17 (2H, br, deuterium oxide exchangeable, NH_2), 6.35 (1H, d, J = 2 Hz, 5-H), 6.61 (1H, br s, 7-H), 7.54 (1H, d, J = 0.7 Hz, 3-H); uv: λ max nm (log ε) 234 (4.21), 297 (4.39).

Anal. Calcd. for $C_{11}H_{11}NO_4$: C, 59.72; H, 5.01; N, 6.33. Found: C, 59.46; H, 4.90; N, 6.10.

The chloroform eluate was recrystallized from ethanol to give *N*,7-diformyl-4,6-dimethoxy-2-benzofurancarboxamide (Vf) as pale yellow needles, mp 221-222°; ms: m/z: 277 (M^+); ir (potassium bromide): cm^{-1} 3430, 1602 (N-H), 1734, 1680 (sh), 1668 (C=O); nmr (deuteriochloroform): 4.06, 4.08 (each 3H, s, 2 × OCH_3), 6.39 (1H, s, 5-H), 7.76 (1H, s, 3-H), 9.38 (1H, d, J = 9.5 Hz, changed to singlet with deuterium oxide, N-CHO), 10.41 (1H, s, Ar-CHO), 10.59 (1H, br, deuterium oxide exchangeable, NH); uv: λ max nm (log ε) 223 (4.12), 290 (4.16), 315 (4.04), 332 (4.06).

Anal. Calcd. for $C_{13}H_{11}NO_6$: C, 56.32; H, 4.00; N, 5.05. Found: C, 56.13; H, 3.90; N, 4.89.

Run C.

The chloroform extract was chromatographed on silica gel. The benzene eluate was recrystallized from *n*-hexane to give Va as colorless needles. The dichloromethane eluate was recrystallized from benzene to give Vc as colorless needles. Continuous elution with dichloromethane gave VIb as colorless needles (from benzene-cyclohexane). The dichloromethane-chloroform (1:1) eluate was recrystallized from benzene to give Vb as colorless needles. These compounds were identified with the products obtained in run A and B.

Run D.

The chloroform extract was chromatographed on silica gel. The benzene eluate was recrystallized from *n*-hexane to give Va. The dichloromethane eluate was recrystallized from benzene to give Vc. Continuous elution with dichloromethane gave VIb, which was recrystallized from benzene-cyclohexane. The chloroform eluate was recrystallized from benzene to give Vb as colorless needles. These compounds were identified with the products obtained in run A and B. The chloroform-acetone (2:1) eluate was recrystallized from acetone-benzene to give 7-formyl-4,6-dimethoxy-2-benzofurancarboxamide (Ve) as pale yellow powder, mp 260-261.5° dec; ms: m/z 249 (M^+); ir (potassium bromide): cm^{-1} 3400, 3290 (N-H), 1665, 1645 (C=O); nmr (DMSO-d_6): 4.03, 4.08 (each 3H, s, 2 × OCH_3), 6.70 (1H, s, 5-H), 7.54 (1H, s, 3-H), 7.72 (2H, br, deuterium oxide exchangeable, NH_2), 10.43 (1H, s, CHO); uv: λ max nm (log ε) 221 (3.42), 277 (3.73), 298 (3.67), 332 (3.42).

Anal. Calcd. for $C_{12}H_{11}NO_5$: C, 57.83; H, 4.45; N, 5.62. Found: C, 57.61; H, 4.33; N, 5.48.

Reaction of VIa with Potassium Carbonate.

A mixture of 110 mg (0.5 mmole) of VIa, 150 mg of potassium carbonate, and 5 ml of DMF was stirred at 100° for 3 hours. After cooled, the deposited solid was filtered and rinsed with chloroform. Water was added to the combined filtrate and the mixture was extracted with chloroform. The organic layer was washed with water, dried over anhydrous sodium sulfate, and evaporated. The residue was recrystallized from *n*-hexane to give 93 mg (92%) of Va as colorless needles, which was identical with the product described above.

Vilsmeier Reaction of 3-Ethoxyphenoxyacetonitrile (VII).

To the Vilsmeier reagent prepared from 0.88 g (12 mmoles) of DMF and 5.50 g (36 mmoles) of phosphoryl chloride, was added 1.77 g (10 mmoles) of VII and the mixture was stirred at 95-100° for 10 hours. The reaction mixture was worked up as described in general procedure. The combined extract was chromatographed on silica gel. The benzene eluate was recrystallized from *n*-hexane to give 57 mg (3%) of 6-ethoxy-2-benzofurancarbonitrile (IXa) as colorless needles, mp 70-71.5°; ms; m/z 187 (M^+); ir (potassium bromide): cm^{-1} 2240 (C N); nmr (deuteriochloroform): 1.47 (3H, t, J = 7.5 Hz, CH_3), 4.10 (2H, q, J = 7.5 Hz, CH_2), 6.99 (1H, dd, J = 9 Hz, 2 Hz, 5-H), 7.03 (1H, br s, 7-H), 7.38 (1H, br s, 3-H), 7.53 (1H, d, J = 9 Hz, 4-H); uv: λ max nm (log ε) 222 (3.18), 236 (3.15), 269 (3.36), 275 (3.43), 298 (3.60), 307 (3.63).

Anal. Calcd. for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.39; H, 4.63; N, 7.22.

The benzene-dichloromethane (4:1) eluate was recrystallized from benzene-cyclohexane to give 226 mg (11%) of 3-ethoxy-4-formylphenoxyacetonitrile (XI) as colorless needles, mp 125-126°; ms: m/z 205 (M^+); ir (potassium bromide) cm^{-1}: 1675 (C=O); nmr (deuteriochloroform): 1.49 (3H, t, J = 7 Hz, CH_3), 4.16 (2H, q, J = 7 Hz, CH_2CH_3), 4.98 (2H, s, CH_2CN), 6.56 (1H, d, J = 2 Hz, 2-H), 6.60 (1H, dd, J = 9 Hz, 2 Hz, 6-H), 7.88 (1H, d, J = 9 Hz, 5-H), 10.39 (1H, s, CHO).

Anal. Calcd. for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.40; H, 5.42; N, 6.49.

The chloroform eluate was recrystallized from benzene-cyclohexane to give 391 mg (19%) of 6-ethoxy-2-benzofurancarboxamide (IXb) as pale yellow needles, mp 153-154°; ms: m/z 205 (M^+); ir (potassium bromide): cm^{-1} 3380, 3200, 1615 (N-H), 1655 (C=O); nmr (deuteriochloroform): 1.45 (3H, t, J = 7 Hz, CH_3), 4.11 (2H, q, J = 7 Hz, CH_2), 6.18 (2H, br, deuterium oxide exchangeable, NH_2), 6.94 (1H, dd, J = 8.5 Hz, 2.5 Hz, 5-H), 7.00 (1H, br s, 7-H), 7.47 (1H, br s, 3-H), 7.55 (1H, d, J = 8.5 Hz, 4-H); uv: λ max nm (log ε) 270 (3.93), 278 (3.98), 302 (4.19), 3.08 (4.19).

Anal. Calcd. for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.12; H, 5.38; N, 6.81.

Further eluate with chloroform was recrystallized from benzene to give 236 mg (12%) of 6-ethoxy-2-benzofurancarboxylic acid (IXc) as colorless needles, mp 164.5-165.5° (lit 162-163° [4]); ms: m/z 206 (M^+); ir (potassium bromide): cm^{-1} 1690 (C=O); nmr (deuteriochloroform): 1.47 (3H, t, J = 7 Hz, CH_3), 4.11 (2H, q, J = 7 Hz, CH_2), 6.97 (1H, dd, J = 9 Hz, 2.5 Hz, 5-H), 7.07 (1H, br s, 7-H), 7.48 (1H, br, deuterium oxide exchangeable, COOH), 7.58 (1H, d, J = 9 Hz, 4-H), 7.64 (1H, br s, 3-H); uv λ max nm (log ε): 235 (3.56), 264 (3.90), 271 (3.94), 299 (4.11), 304 (4.12).

Anal. Calcd. for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89. Found: C, 63.91; H, 4.82.

Vilsmeier Reaction of 3-Diethylaminophenoxyacetonitrile (VIII).

To the Vilsmeier reagent prepared from 0.88 g (12 mmoles) of DMF and 5.50 g (36 mmoles) of phosphoryl chloride, was added 2.04 g (10 mmoles) of VIII and the mixture was stirred at 95-100° for 8 hours. The reaction mixture was worked up as described in general procedure. The combined chloroform extract was chromatographed on silica gel. The benzene eluate gave 87 mg (4%) of 6-diethylamino-2-benzofurancarbonitrile (Xa) as viscous oil; ms; m/z 214.091 (M^+, Calcd. for $C_{13}H_{14}N_2O$: 214.1106); ir (liquid) cm^{-1}: 2240 (C≡N); nmr (carbon tetrachloride): 1.22 (6H, t, J = 7 Hz, 2 × CH_3), 3.43 (4H, q, J = 7 Hz, 2 × CH_2), 6.64 (1H, br s, 7-H), 6.69 (1H, br d, J = 9 Hz, 5-H), 7.19 (1H, br s, 3-H), 7.39 (1H, d, J = 9 Hz, 4-H); uv: λ max nm (log ε) 230 (3.75), 302 (3.65), 346 (3.79).

The benzene-chloroform (1:1) eluate was recrystallized from benzene-cyclohexaen to give 133 mg (5%) of 6-diethylamino-*N*-formyl-2-benzofurancarboxamide (Xc) as orange rhombs, mp 181-183°; ms: m/z 260 (M^+); ir (potassium bromide) cm^{-1}: 3230, 1620 (N-H), 1718, 1680 (C=O); nmr (deuteriochloroform): 1.22 (6H, t, J = 7.5 Hz, 2 × CH_3), 3.46 (4H, q, J = 7.5 Hz, 2 × CH_2), 6.69 (1H, br s, 7-H), 6.78 (1H, dd, J = 9 Hz, 2 Hz, 5-H), 7.50 (1H, d, J = 9 Hz, 4-H), 7.64 (1H, br s, 3-H), 9.05 (1H, br, deuterium oxide exchangeable, NH), 9.35 (1H, d, J = 9 Hz, changed to singlet with deuterium oxide, CHO); uv: λ max nm (log ε) 246 (3.82), 300 (2.90), 311 (2.90), 387 (4.07).

Anal. Calcd. for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.54; H. 6.20; N, 10.73.

The ethyl acetate eluate was recrystallized from benzene to give 513 mg (22%) of 6-diethylamino-2-benzofurancarboxamide (Xb) as pale brown needles, mp 185-187° (lit 187-188° [10]); ms: m/z 232 (M^+); ir (potassium bromide): cm^{-1} 3390, 3200, 1612 (N-H), 1642 (C=O); nmr (deuteriochloroform): 1.20 (6H, t, J = 7 Hz, 2 × CH_3), 3.43 (4H, q, J = 7 Hz, 2 × CH_2), 6.19 (2H, br, deuterium oxide exchangeable, NH_2), 6.71 (1H, br s, 7-H), 6.74 (1H, br d, J = 9 Hz, 5-H), 7.41 (1H, br s, 3-H), 7.47 (1H, d, J = 9 Hz, 4-H); uv: λ max nm (log ε) 228 (3.99), 302 (3.66); 352 (4.16).

Anal. Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.12; H, 7.02; N, 12.05.

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REFERENCES AND NOTES

[1] O. Meth-Cohn and B. Tarnowski, "Advances in Heterocyclic Chemistry", Vol **31**, A. R. Katritzky, ed, Academic Press, Inc., New York, 1982, p 207.

[2a] T. Koyama, T. Hirota, Y. Shinohara, M. Yamato, and S. Ohmori, *Chem. Pharm. Bull.*, **23**, 497 (1975); [b] T. Hirota, T. Koyama, T. Namba and M. Yamato, *ibid.*, **25**, 2838 (1977).

[3] P. Pfeiffer and H. Simons, *J. Prakt. Chem.*, **160**, 83 (1942).

[4] L. Rene and R. Royer, *Bull. Soc. Chem. France*, 1971, 4329.

[5] W. Will and O. Beck, *Chem. Ber.*, **19**, 1777 (1886).

[6a] J. Bourguignon, M. Lemarchand, and G. Queguiner, *J. Heterocyclic Chem.*, **17**, 257 (1980); [b] J. D. Brewer and J. A. Elix, *Aust. J. Chem.*, **25**, 545 (1972).

[7] A. Waefelaer, J. Pecher, A. Dubois, J. Semet, and P. Pouttier, *Bull. Soc., Chim. Belg.*, **85**, 421 (1976).

[8] J. A. Elvidge and R. G. Foster, *J. Chem. Soc.*, 590 (1963); *ibid.*, 981 (1964).

[9] P. Mischke, E. Fleckenstein, and R. Mohr, German Patent 2,525,557 (1976); *Chem. Abstr.*, **86**, 91739n (1977).

[10] K. Grychtol, German Patent 2,244,371 (1974); *Chem. Abstr.*, **81**, 137603r (1974).