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Benzofuran Derivatives. I. On the Effects of Substituents in Benzofuran Syntheses

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The Rössing's reaction of 4-substituted 2-acylphenoxyacetic acids give a mixture of benzofurans and 2-benzofurancarboxylic acids. The relative yields of benzofurans and 2-benzofurancarboxylic acids depend on the substituents on the benzene ring of the 2-acylphenoxyacetic acids. Electron-withdrawing substituents such as nitro groups favor the formation of 2-benzofurancarboxylic acids. On the other hand, the formation of benzofurans is favored by the steric hindrance of 2-acyl groups in the reaction of 2-acyl-4-nitrophenoxyacetic acids with anhydrous sodium acetate and acetic anhydride.

Benzofurans are well-known heterocyclic compounds and have been prepared by Rössing's method.[1] This is a general procedure to obtain benzofurans from 2-acylphenoxyacetic acids by heating them with anhydrous sodium acetate and acetic anhydride. In this method 2-benzofurancarboxylic acids were obtained as minor products. The formation of 2-benzofurancarboxylic acids has not been noted because of their poor yields.[2] Burgstahler and Worden, however, reported that 2-benzofurancarboxylic acid was obtained in high yield (45%) by the reaction of 2-formylphenoxyacetic acid with anhydrous sodium acetate and acetic anhydride.[3] Recently, we reported that 2-acetyl-5-nitrophenoxyacetic acid gave 3-methyl-6-nitrobenzofuran and 3-methyl-6-nitro-2-benzofurancarboxylic acid in 58 and 42% yields, respectively.[4] Thus, substituents in 2-acylphenoxyacetic acids influence the relative yields of benzofurans and 2-benzofurancarboxylic acids. In the present paper, we examined the electronic and steric effects on the relative yields of benzofurans (**2**) and 2-benzofurancarboxylic acids (**3**) in the Rössing's method.

Results and Discussion

Some 2-acylphenoxyacetic acid derivatives (**1a**—**j**) were prepared in order to investigate substituent effects (R^1 and R^2) on the syntheses of benzofurans (**2a**—**j**) and 2-benzofurancarboxylic acids (**3a**—**j**). The syntheses of **1a**,[5] **1c**,[6] **1d**,[7] **1g**,[8] and **1h**[9], were carried out according to reported methods. The synthetic methods of **1b**, **1e**, **1f**, **1i**, and **1j**, are summarized in Scheme 1.

When 4-substituted 2-acylphenoxyacetic acids (**1a**—**j**) were heated with anhydrous sodium acetate and acetic anhydride at 110±1 °C for 3 h, benzofurans (**2a**—**j**) and 2-benzofurancarboxylic acids (**3a**—**j**) were obtained. The isolated and relative yields of **2a**—**j** and **3a**—**j** are summarized in Table 1.

Table 1. The reaction of 4-substituted 2-acylphenoxyacetic acids with anhydrous sodium acetate and acetic anhydride

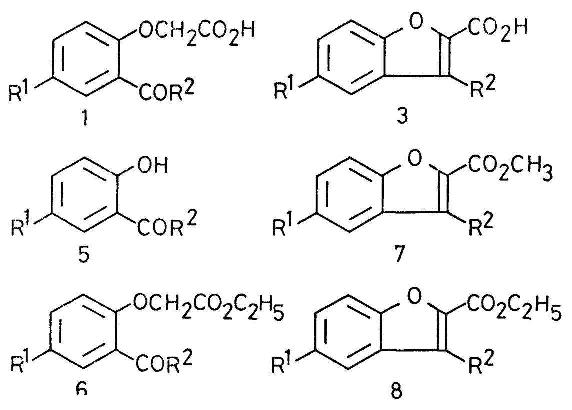
a) $R^1=CH_3O, R^2=CH_3$
b) $R^1=CH_3, R^2=CH_3$
c) $R^1=H, R^2=CH_3$
d) $R^1=Cl, R^2=CH_3$
e) $R^1=NO_2, R^2=CH_3$
f) $R^1=CH_3, R_2=H$
g) $R^1=H, R^2=H$
h) $R^1=NO_2, R^2=H$
i) $R^1=NO_2, R^2=CH_2CH_3$
j) $R^1=NO_2, R^2=CH(CH_3)_2$

Starting materials	Isolated yields[a]/%		Relative yields/%	
	2	**3**	**2**	**3**
1a	96.6	3.2	96.8	3.2
1b	96.0	1.7	98.3	1.7
1c	93.8	1.4	98.5	1.5
1d	91.3	7.4	92.5	7.5
1e	56.9[b]	34.2[b]	62.5	37.5
1f	27.2[c]	55.5	44.5[d]	55.5
1g	22.2[c]	53.0	47.0[d]	53.0
1h	25.3[b]	73.9[b]	25.5	74.5
1i	64.7[b]	32.8[b]	66.4	33.6
1j	84.8[b]	13.6[b]	86.2	13.8

a) Benzofuran **2** and methyl ester of **3** were analyzed by GLPC and the yields of **3** were calculated from those of methyl esters. b) Analyzed by usual method. c) The yields are low because of the high volatility. d) Calculated in equation 100-**3f**, **g** (%).

Initially, the effects of R^2 were examined for $R^1=NO_2$ by changing R^2 from hydrogen to methyl, ethyl, or isopropyl groups. In the case of $R^2=H$, the relative yields of benzofuran (**2h**) and 2-benzofurancarboxylic acid (**3h**) were 25.5 and 74.5%, respectively. Therefore, the latter was the major product, whereas the yield (86.2%) of benzofuran (**2j**) exceeded that (13.8%) of 2-benzofurancarboxylic acid (**3j**) when R^2 was an isopropyl group. When R^2 were methyl or ethyl groups, the yields of **2e** and **3e** were 62.5 and 37.5%, and those of **2i** and **3i** were 66.4 and 33.6%, respectively. Thus, the formation of benzofurans (**2**) was favored as the steric bulk of R^2 increased. The results are explained in terms of steric effects of R^2, since the electronic effects of methyl, ethyl, and isopropyl groups are similar.

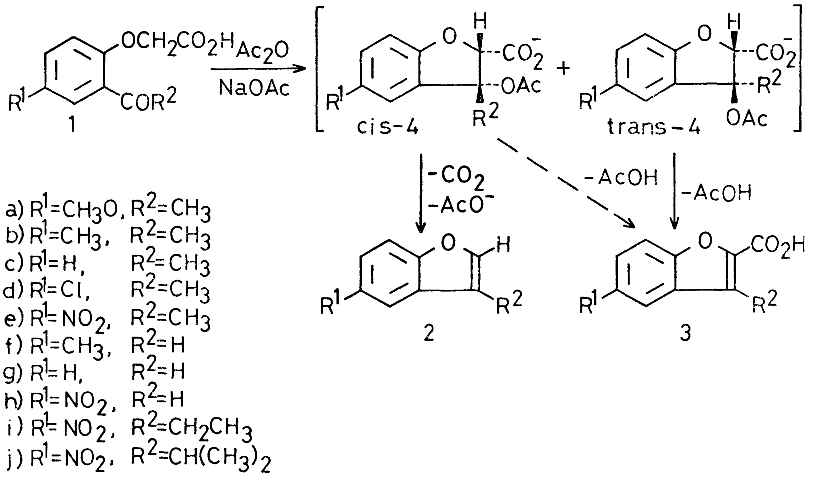
Although little information[10] is available concerning reaction mechanisms of formation of the furan ring, 3-hydroxy-2,3-dihydro-2-benzofurancarboxylate ion (**4**)



b) $R^1=CH_3$, $R^2=CH_3$ f) $R^1=CH_3$, $R^2=H$
c) $R^1=H$, $R^2=CH_3$ g) $R^1=H$, $R^2=H$
d) $R^1=Cl$, $R^2=CH_3$ i) $R^1=NO_2$, $R^2=CH_2CH_3$
e) $R^1=NO_2$, $R^2=CH_3$ j) $R^1=NO_2$, $R^2=CH(CH_3)_2$

5b ⟶ 1b
5e,f ⟶ 6e,f ⟶ 1e,f
p-Nitrophenol → 5i,j ⟶ 6i,j ⟶ 1i,j
3b,c,d ⟶ 7b,c,d
5f ⟶ 8f ⟶ 3f ⟶ 7f
5g ⟶ 3g ⟶ 7g

Scheme 1. The synthetic pathways of 4-substituted 2-acylphenoxyacetic acids (**1**) and methyl 2-benzofurancarboxylates (**7**).



a) $R^1=CH_3O$, $R^2=CH_3$
b) $R^1=CH_3$, $R^2=CH_3$
c) $R^1=H$, $R^2=CH_3$
d) $R^1=Cl$, $R^2=CH_3$
e) $R^1=NO_2$, $R^2=CH_3$
f) $R^1=CH_3$, $R^2=H$
g) $R^1=H$, $R^2=H$
h) $R^1=NO_2$, $R^2=H$
i) $R^1=NO_2$, $R^2=CH_2CH_3$
j) $R^1=NO_2$, $R^2=CH(CH_3)_2$

Scheme 2. The reaction pathways for the production of benzofurans (**2**) and 2-benzofurancarboxylic acids (**3**).

was assumed as an intermediate in the formation of benzofurans.[11] A similar intermediate was isolated recently in the syntheses of 4,5-dihydro-3*H*-naphtho[1,8-*bc*]furan.[12]

A proposed reaction mechanism is depicted in Scheme 2. The reaction of 2-acylphenoxyacetic acids (**1**) with anhydrous sodium acetate and acetic anhydride will afford two intermediates (*cis*-**4** and *trans*-**4**). The relative ratio of *cis*-**4** to *trans*-**4** will be varied by changing R^2. In the case of **1h** ($R^2=H$), *trans*-**4h** will be preferentially produced because the steric repulsion between the acetoxyl group and the carboxylate ion of *cis*-**4h** is larger than that of *trans*-**4h**. On the other hand, **1j** ($R^2=CH(CH_3)_2$) will preferentially give *cis*-**4j** because of the steric repulsion between the isopropyl group and the carboxylate ion. Preferential formation of benzofuran (**2j**) suggests that **2j** must be produced mainly through *cis*-**4j** by *syn* elimination of carbon dioxide and acetate ion, while 2-benzofurancarboxylic acid (**3h**) must be produced exclusively through *trans*-**4h** by *syn* elimination of acetic acid.$^{13)}$

Secondly, the effects of R^1 were examined. In the first case, R^2 was fixed as a methyl group, and R^1 was varied from hydrogen to methoxyl, methyl, nitro groups, or a chlorine atom. The reaction of **1a**—**d** with anhydrous sodium acetate and acetic anhydride gave a mixture of 3-methylbenzofurans (**2a**—**d**) and 3-methyl-2-benzofurancarboxylic acid (**3a**—**d**) in relative yields of 98.5—92.5 and 1.5—7.5%, respectively. Electronic effects of substituents R^1 did not influence the relative yields of **2a**—**d** and **3a**—**d**, while compound **1e** ($R^1=NO_2$) gave benzofuran (**2e**) and 2-benzofurancarboxylic acid (**3e**) in relative yields of 62.5 and 37.5%, respectively. The strongly electron-withdrawing nitro group makes the hydrogen atom attached at the C_2 carbon atom of *cis*-**4e** more acidic than that of *cis*-**4a**—**d** as illustrated in Scheme 2, and facile *anti* elimination of acetic acid gives 2-benzofurancarboxylic acid (**3e**).

In the second case, R^2 was fixed as hydrogen and R^1 was varied from hydrogen to methyl or nitro groups. The reaction of **1f** ($R^1=CH_3$) with anhydrous sodium acetate and acetic anhydride gave benzofuran (**2f**) and 2-benzofurancarboxylic acid (**3f**) in 44.5 and 55.5 % relative yields, respectively. Compound **1g** also afforded **2g** and **3g** in similar relative yields. On the other hand, compound **1h** ($R^1=NO_2$) gave benzofuran (**2h**) and 2-benzofurancarboxylic acid (**3h**) in relative yields of 25.5 and 74.5%, respectively. Therefore, nitro group of **1h** also favored the formation of 2-benzofurancarboxylic acid (**3h**) by its electron-withdrawing nature.

We wish to try to trap intermediates, *cis*-**4** and *trans*-**4**, and are continuing further research on the mechanism of furan ring formation.

Experimental

All melting points are uncorrected. The infrared absorption spectra were determined on a JASCO Model DS402G infrared spectrometer and a HITACHI EP1-G grating infrared spectrometer. Nuclear magnetic resonance spectra were determined at 100 MHz on a JEOL Model 4H-100 NMR spectrometer, using tetramethylsilane as an internal standard. GLC analyses were performed on a YANACO Gas Chromatograph Model G 80-FP equipped with a glass column (1.5 m; $\phi=4$ mm) packed with 5% Silicone Gum SE-30 on Chromosorb W AW-DMCS (80—100 mesh) at 110—200 °C for each case. The column chromatography was performed on silica gel (Wakogel C-200).

General Procedure for Determination of the Ratio of 3 to 2 in the Reaction of 1. A typical procedure will be described for the reaction of **1b**. A mixture of **1b** (1.04 g, 0.5 mmol), anhydrous sodium acetate (2.6 g, 31.6 mmol), and acetic anhydride (17 ml) was heated at 110±1 °C for 3 h. After cooling, the reaction mixture was poured into 100 ml of water and stirred for 1 h. This mixture was extracted with 250 ml of ether, and the ethereal solution was washed with water (40 ml×5). The ethereal solution was concentrated by evaporation to approximately 50 ml. An ethereal solution of diazomethane was added dropwise to the residue until the color of the solution turned yellow. The resulting solution was diluted with ether exactly to a total volume of 200 ml (sample 1). Five ml of the sample 1 was pipetted and was diluted with ether exactly to a total volume of 50 ml (sample 2). The quantity of **2b** in the sample 2 and that of **7b** in the sample 1 were determined by gas chromatography and the yield of **3b** was calculated from the quantity of **7b**. The resulting chromatograms were compared by measuring the areas of peaks by triangulation with those of the standard sample for which the concentration was known. The yield of **2b** was 96.0% and that of **3b** was 1.7%. The results of the reaction of **1a,c,d,f** and **1g** with anhydrous sodium acetate and acetic anhydride were obtained similarly and are listed in Table 1. Nitro compounds (**1e**, **1h**—**j**) were run in the same manner as described above. The separation and quantitative analyses of the products were carried out in the usual manner and the results are summarized in Table 1. Compounds **2h**$^{14)}$ and **3h**$^{14)}$ were identified by comparison of their IR and NMR spectra with those of authentic samples.

2e: Mp 89—90 °C. IR(KBr): ν_{max} 3088, 2920, 1625, 1586, 1516 (NO_2), 1442 (C=C), 1334 (NO_2), 887 (furan ring), 804 cm^{-1} (two adjacent aromatic hydrogen atoms). Found: C, 61.02; H, 4.04%. Calcd for $C_9H_7NO_3$: C, 61.02; H, 3.98%.

3e: Mp 285—286 °C (decomp). IR(KBr): ν_{max} 3100, 2800—2400, 1692 (CO_2H), 1620, 1580, 1525 and 1329 (NO_2), 903 (CO_2H), 832 cm^{-1} (two adjacent aromatic hydrogen atoms). Found: C, 54.32; H, 3.23%. Calcd for $C_{10}H_7NO_5$: C, 54.30; H, 3.19%.

2i: Mp 89—90 °C. IR (KBr): ν_{max} 3095, 2960, 1578, 1515 (NO_2), 1445 (C=C), 1342 (NO_2), 887 (furan ring), 830 cm^{-1} (two adjacent aromatic hydrogen atoms). Found: C, 62.72; H, 4.76%. Calcd for $C_{10}H_9NO_3$: C, 62.82; H, 4.74%.

3i: Mp 240—243 °C. IR (KBr): ν_{max} 3100, 2970, 2800—2400, 1678 (CO_2H), 1617, 1584, 1520 (NO_2), 1447, 1340 (NO_2), 924 (CO_2H), 831 cm^{-1} (two adjacent aromatic hydrogen atoms). Found: C, 56.12; H, 3.99%. Calcd for $C_{11}H_9NO_5$: C, 56.17; H, 3.85%.

2j: Mp 110.5—111.0 °C. IR (KBr): ν_{max} 3105, 2960, 2875, 1623, 1585, 1508 (NO_2), 1444 (C=C), 1335 (NO_2), 885 (furan ring), 818 cm^{-1} (two adjacent aromatic hydrogen atoms). Found: C, 64.34; H, 5.40%. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40%.

3j: Mp 249—250 °C. IR (KBr): ν_{max} 3080, 2960, 2800—2400, 1674 (CO_2H), 1608, 1585, 1515 and 1340 (NO_2), 908 (CO_2H), 832 cm^{-1} (two adjacent aromatic hydrogen atoms). Found: C, 57.89; H, 4·48%. Calcd for $C_{12}H_{11}NO_5$: C, 57.83; H, 4.44%.

Preparation of Materials (1a—j). 2-Acetyl-4-methoxyphenoxyacetic acid (**1a**) was prepared by Whalley's method,$^{5)}$ 2-acetylphenoxyacetic acid (**1c**) by Rosseels' method,$^{6)}$ and 2-acetyl-4-chlorophenoxyacetic acid (**1d**) by Deorha's method.$^{7)}$ 2-Formylphenoxyacetic acid (**1g**) was prepared by Dumont's method,$^{8)}$ and 2-formyl-4-nitrophenoxyacetic acid (**1h**) by Jacobs' method.$^{9)}$

2-Acetyl-4-methylphenoxyacetic Acid (1b). A mixture of 2-hydroxy-5-methylacetophenone$^{15)}$ (**5b**) (10 g), ethyl bromoacetate (16.5 g), anhydrous potassium carbonate (40 g), and acetone (200 ml) was refluxed at 70 °C for 6 h. After cooling, the insoluble salts were removed by filtration and the filtrate was concentrated under evaporation. The residue was treated with ethanol (50 ml) and 3 M (1 M= 1 mol dm^{-3}) sodium hydroxide solution (50 ml) at room temperature for 30 min. The reaction mixture was poured into cold water (100 ml) and acidified with 6 M hydrochloric acid. The precipitates were filtered, washed with cold water, and dried under vacuum to give 12.9 g (92%) of **1b** as crystals. Recrystallization from aqueous methanol gave colorless plates, mp 156—157 °C. IR (KBr): ν_{max} 1773 (CO_2H), 1654 cm^{-1} (CO). NMR (CD_3COCD_3): δ= 2.29 (3H, s, $PhCH_3$), 2.67 (3H, s, $COCH_3$), 4.76 (2H, s, CH_2), 6.88 (1H, d, J=8.5 Hz, C_6-H), 7.28 (1H, dd, J= 8.5 and 2.5 Hz, C_5-H), 7.47 (1H, J=2.5 Hz, C_3-H). Found: C, 63.21; H, 5.89%. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81%.

*Ethyl 2-Acetyl-4-nitrophenoxyacetate (**6e**).* 2-Hydroxy-5-nitroacetophenone (**5e**) was prepared by Joshi's method.[16] A mixture of **5e** (10 g), ethyl bromoacetate (11 g), anhydrous potassium carbonate (30.4 g), and acetone (200 ml) was refluxed at 70 °C for 3 h. After cooling, insoluble salts were removed by filtration. The residue obtained upon evaporation of the acetone was purified by recrystallization from hexane-ethanol to give 12.4 g (84.3%) of **6e** as pale yellow short needles, mp 88.0—89.5 °C. IR (KBr): ν_{max} 1760 ($-CO_2-$), 1674 (CO), 1507 and 1338 (NO_2), 836 cm^{-1} (two adjacent aromatic hydrogen atoms). Found: C, 53.97; H, 4.97%. Calcd for $C_{12}H_{13}NO_6$: C, 53.93; H, 4.90%.

*2-Acetyl-4-nitrophenoxyacetic Acid (**1e**).* A mixture of **6e** (1 g), anhydrous potassium carbonate (0.5 g), and water (10 ml) was refluxed for 40 min. Insoluble material in the reaction mixture was filtered while hot, and the filtrate was acidified after cooling with 6 M hydrochloric acid. The precipitates were filtered, washed with cold water, and dried under vacuum to give 0.8 g (90%) of **1e** as crystals. Recrystallization from aqueous ethanol gave pale yellow short needles, mp 198—200 °C (decomp). IR (KBr): ν_{max} 1739 (CO_2H), 1675 (CO), 1516 and 1340 cm^{-1} (NO_2). NMR (CD_3OD): δ=2.72 (3H, s, $COCH_3$), 4.99 (2H, s, CH_2), 7.24 (1H, d, J=8.7 Hz, C_6-H), 8.35 (1H, dd, J=8.7 and 3.7 Hz, C_5-H), 8.51 (1H, d, J=3.7 Hz, C_3-H). Found: C, 50.31; H, 3.86%. Calcd for $C_{10}H_9NO_6$: C, 50.21; H, 3.79%.

*Ethyl 2-Formyl-4-methylphenoxyacetate (**6f**).* From 5-methylsalicylaldehyde[17] (**5f**) (3 g), **6f** (4 g, 81.6%) was obtained in the same manner as has been described for **6e** except that tetrahydrofuran was used as solvent instead of acetone. Recrystallization from aqueous ethanol gave colorless short needles, mp 51.5—52.5 °C. IR (KBr): ν_{max} 1767 ($-CO_2-$), 1671 (CHO), 837 cm^{-1} (two adjacent aromatic hydrogen atoms). Found: C, 65.01; H, 6.39%. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.34%.

*2-Formyl-4-methylphenoxyacetic Acid (**1f**).* A mixture of **6f** (2.61 g), 20% potassium hydroxide solution (10 ml) and ethanol (12 ml) was warmed at 60 °C for 30 min. After cooling, 150 ml of water was poured into the reaction mixture and the mixture was acidified with 6 M hydrochloric acid. Resulting precipitates were filtered, washed with cold water, and dried under vacuum to give 1.9 g (83.3%) of **1f** as crystals. Recrystallization from aqueous acetone gave colorless plates, mp 147—148 °C (lit,[18] mp 151 °C). IR (KBr): ν_{max} 1745 and 1720 (CO_2H), 1690 (CHO), 927 (CO_2H), 822 cm^{-1} (two adjacent aromatic hydrogen atoms), (Found: C, 61.83; H, 5.29%).

*2′-Hydroxy-5′-nitropropiophenone (**5i**).* By the modified method of Joshi[16], **5i** (7.5 g, 35.7%) was prepared from the reaction of *p*-nitrophenol (15 g) with propionyl chloride (18.6 g) in nitrobenzene (150 ml) in the presence of anhydrous aluminium chloride (41 g) as catalyst. Recrystallization from methanol gave colorless short needles, mp 94.5—95.0 °C. IR (KBr): ν_{max} 3070, 1640 (CO), 1615, 1576, 1510 and 1338 (NO_2), 825 cm^{-1} (two adjacent aromatic hydrogen atoms). Found: C, 55.38; H, 4.71%. Calcd for $C_9H_9NO_4$: C, 55.38; H, 4.64%.

*Ethyl 4-Nitro-2-propionylphenoxyacetate (**6i**).* In the same manner as has been described for **6e**, **6i** (12.3 g, 63.4%) was prepared from **5i** (13.5 g). Recrystallization from aqueous ethanol gave colorless short needles, mp 58—59 °C. IR (KBr): ν_{max} 1730 ($-CO_2-$), 1682 (CO), 1510 and 1334 (NO_2), 833 cm^{-1} (two adjacent aromatic hydrogen atoms). Found: C, 55.59; H, 5.37%. Calcd for $C_{13}H_{15}NO_6$: C, 55.51; H, 5.38%.

*4-Nitro-2-propionylphenoxyacetic Acid (**1i**).* Acid **1i** (8.1 g, 90%) was obtained from **6i** (10 g) in the same way as described for the preparation of **1e**. Recrystallization of **1i** from benzene-acetone gave colorless plates, mp 128—129 °C. IR (KBr): ν_{max} 1752 and 1720 (CO_2H), 1663 (CO), 1522 and 1345 (NO_2), 834 cm^{-1} (two adjacent aromatic hydrogen atoms). Found: C, 52.27; H, 4.41%. Calcd for $C_{11}H_{11}NO_6$: C, 52.17; H, 4.37%.

*2′-Hydroxy-5′-nitroisobutyrophenone (**5j**).* By the modified method of Joshi[16], **5j** (2.7 g, 8.6%) was prepared from the reaction of *p*-nitrophenol (15 g) with isobutyryl chloride (21.3 g) in nitrobenzene (170 ml) in the presence of anhydrous aluminium chloride (41 g) as a catalyst. Recrystallization from methanol gave pale yellow short needles, mp 74.0—74.5 °C. IR (KBr): ν_{max} 3080, 1636 (CO), 1615, 1575, 1506 and 1334 (NO_2), 821 cm^{-1} (two adjacent aromatic hydrogen atoms). NMR (CD_3COCD_3): δ=1.28 (6H, d, J=7.5 Hz, $-CH(C\underline{H}_3)_2$), 3.95 (1H, m, J= 7.5 Hz, $-C\underline{H}(CH_3)_2$), 7.20 (1H, d, J=10 Hz, C_3-H), 8.42 (1H, dd, J=10 and 2.5 Hz, C_4-H), 8.86 (1H, d, J=2.5 Hz, C_6-H). Found: C, 57.37; H, 5.34%. Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.29%.

*Ethyl 2-Isobutyryl-4-nitrophenoxyacetate (**6j**).* In the same manner as has been described for **6e**, **6j** (4.5 g, 77.7%) was prepared from **5j** (4.1 g). Recrystallization of **6j** from ethanol gave colorless short needles, mp 58—60 °C. IR (KBr): ν_{max} 1730 ($-CO_2-$), 1667 (CO), 1510 and 1334 cm^{-1} (NO_2). Found: C, 57.01; H, 5.87%. Calcd for $C_{14}H_{17}NO_6$: C, 56.94; H, 5.80%.

*2-Isobutyryl-4-nitrophenoxyacetic Acid (**1j**).* Acid **1j** (5.8 g, 95%) was obtained from **6j** (6.8 g) in the same way as described for the preparation of **1e**. Recrystallization of **1j** from benzene gave colorless short needles, mp 108—109 °C. IR (KBr): ν_{max} 1739 (CO_2H), 1667 (CO), 1515 and 1334 (NO_2), 910 (CO_2H), 826 cm^{-1} (two adjacent aromatic hydrogen atoms). Found: C, 53.86; H, 4.96%. Calcd for $C_{12}H_{13}NO_6$: C, 53.93; H, 4.90%.

*Preparation of Standard Compounds (**2a**—**d**, **2f**,**g**, **7a**—**d**, and **7f**,**g**) for Gas Chromatography Analyses.* 5-Methoxy-3-methylbenzofuran (**2a**) was prepared by Whalley's method,[5] **2c** by Rosseels' method,[6] **2d** by Deorha's method,[7] **2f** by Auwer's method,[19] and **2g** by Tanaka's method.[20] methyl ester **7a** was prepared by methylation of **3a** with diazomethane in ether.[5]

*3,5-Dimethylbenzofuran (**2b**).* A mixture of **1b** (5.0 g), anhydrous sodium acetate (13.0 g), and acetic anhydride (85.0 ml) was heated at 110±1 °C for 3 h. After cooling, the reaction mixture was poured into 200 ml of water and stirred for 1 h and then extracted with 300 ml of ether. The ethereal solution was washed with 3% potassium carbonate solution (40 ml×3), with water (40 ml×3), and dried over anhydrous sodium sulfate. Ether was removed by evaporation and the residue was distilled under reduced pressure to give 2.74 g (72%) of **2b** as colorless oil, bp 83 °C at 12 Torr.† IR (neat): ν_{max} 3120, 3022, 2950, 2923, 1580, 1450, 1289, 868 (furan ring), 804 cm^{-1} (two adjacent aromatic hydrogen atoms). Found: C, 82.03; H, 6.96%. Calcd for $C_{10}H_{10}O$: C, 82.16; H, 6.89%.

*Methyl 3,5-Dimethyl-2-benzofurancarboxylate (**7b**).* Diazomethane in ether was added to an ethereal solution of **3b**[21] (1 g) until the reaction mixture turned yellow and the solution was allowed to stand at room temperature for 20 min. The residue (1.2 g) obtained upon evaporation of ether was recrystallized from aqueous methanol to give 0.7 g (84%) of **7b** as colorless short needles, mp 50—51 °C. IR (KBr): ν_{max} 1713 (-CO_2-), 844 (furan ring), 808 cm^{-1} (two adjacent aromatic hydrogen atoms). Found: C, 70.45; H, 5.94%. Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92%.

*Methyl 3-Methyl-2-benzofurancarboxylate (**7c**).* In the same manner as has been described for **7b**, **7c** (3.82 g, 93%) was prepared from **3c**[22] (3.34 g). Recrystallization of **7c** from methanol gave colorless short needles, mp 69—70 °C. IR (KBr): ν_{max} 1705 (-CO_2-), 837 (furan ring), 763 cm^{-1} (four adjacent aromatic hydrogen atoms). Found: C, 69.41; H, 5.38%. Calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.29%.

*Methyl 5-Chloro-3-methyl-2-benzofurancarboxylate (**7d**).* In the same procedure as the preparation of **7b**, ester **7d** (1 g, 94%) was obtained from **3d**[7] (1 g). Recrystallization of **7d** from methanol gave colorless short needles, mp 95.0—95.8 °C. IR (KBr): ν_{max} 1708 (-CO_2-), 813 cm^{-1} (two adjacent aromatic hydrogen atoms). Found: C, 58.89; H, 4.15%. Calcd for $C_{11}H_9ClO_3$: C, 58.81; H, 4.03%.

*Ethyl 5-Methyl-2-benzofurancarboxylate (**8f**).* A mixture of 5-methylsalicylaldehyde[17] (**5f**) (3 g), ethyl bromoacetate (10 g), and anhydrous potassium carbonate (12 g) was heated at 140 °C for 6 h. After cooling, acetone (100 ml) was added to the reaction mixture and the insoluble salts were removed by filtration. The residue obtained upon evaporation of acetone was purified by column chromatography and eluted with benzene to give crude **8f** (3.6 g, 80%). Recrystallization from hexane gave colorless short needles, mp 41—42 °C. IR (KBr): ν_{max} 3003, 2950, 2880, 1728 (-CO_2-), 1297, 1214, 820 cm^{-1} (two adjacent aromatic hydrogen atoms). Found: C, 70.52; H, 5.92%. Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92%.

*5-Methyl-2-benzofurancarboxylic Acid (**3f**).* A mixture of **8f** (2.2 g) and 20% potassium hydroxide solution (25 ml) was refluxed for 1 h. After cooling, the reaction mixture was acidified with 6 M hydrochloric acid and the precipitates were filtered, washed with cold water, and dried under vacuum to give crude **3f** (1.8 g, 94.8%). Recrystallization from acetone gave colorless plates, mp 237—238 °C (lit,[23] mp 237 °C). IR (KBr): ν_{max} 1693 (CO_2H), 1623, 1585, 921 (CO_2H), 827 cm^{-1} (two adjacent aromatic hydrogen atoms), (Found: C, 68.29; H, 4.67%).

*Methyl 5-Methyl-2-benzofurancarboxylate (**7f**).* In the same procedure as the preparation of **7b**, ester **7f** (1.4 g, 87.5%) was obtained from **3f** (1.5 g). Recrystallization of **7f** from aqueous methanol gave colorless short needles, mp 58.5—59.5 °C. IR (KBr): ν_{max} 1723 (-CO_2-), 808 cm^{-1} (two adjacent aromatic hydrogen atoms). Found: C, 69.38; H, 5.34%. Calcd for $C_{11}H_{10}O_3$: C, 69.47; H, 5.29%.

*2-Benzofurancarboxylic Acid (**3g**).* A mixture of salicylaldehyde (**5g**) (10 g), ethyl bromoacetate (54.7 g), and anhydrous potassium carbonate (45 g) was heated at 100 °C for 1.5 h then at 140 °C for 4.5 h. After cooling, water (300 ml) was added to the reaction mixture, which was extracted with ether. The ethereal solution was washed with water, dried over anhydrous sodium sulfate, and concentrated by evaporation. The residue was hydrolyzed without purification as has been described for **3f** to give 7.4 g of **3g** in a 55.7% yield. Recrystallization from aqueous acetone gave colorless plates, mp 193.0—193.5 °C (lit,[20] mp 192—193 °C). IR (KBr): ν_{max} 1680 and 943 (CO_2H), 745 cm^{-1} (four adjacent aromatic hydrogen atoms), (Found: C, 66.77; H, 3.93%).

*Methyl 2-Benzofurancarboxylate (**7g**).* By the same procedure as the preparation of **7b**, ester **7g** (0.8 g, 82%) was prepared from **3g** (0.9 g). Recrystallization from aqueous methanol gave colorless short needles, mp 52—53 °C. IR (KBr): ν_{max} 1732 (-CO_2-), 758 cm^{-1} (four adjacent aromatic hydrogen atoms). Found: C, 68.36; H, 4.64%. Calcd for $C_{10}H_8O_3$: C, 68.17; H, 4.57%.

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† 1 Torr = 133.322 Pa.

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