Benzofuran Derivatives. Part 4 [1]. Synthesis of Benzofurans and 2,3,4,5-Tetrahydro-1-benzoxepin-3,5-diones

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By treatment of ethyl 4- or 5-substituted 2-acetylphenoxyacetates **1** with potassium hydroxide in dry dioxane, benzofurans **2-7** and 2,3,4,5-tetrahydro-1-benzoxepin-3,5-diones **8** were obtained. The relative yields of benzofurans **2-7** and 2,3,4,5-tetrahydro-1-benzoxepin-3,5-diones **8** varied with the types of 4- or 5-substituents. The electron-donating 4-methoxyl group favored the formation of benzoxepins. On the other hand, electron-withdrawing substituents such as the 4-nitro group favored the formation of benzofurans. When esters **1** were treated with sodium amide, 2,3-dihydrobenzofurans **2** were obtained exclusively regardless of 4- or 5-substituents.

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Introduction.

Benzofurans [2] and benzoxepins [3a-k] are oxygen heterocycles and their syntheses, reactivities, physiological properties [3l-m], and pharmacological activities [3n-s] have been widely investigated.

Generally, ethyl 3-alkyl-2-benzofurancarboxylates are prepared by the reaction of ethyl 2-acylphenoxyacetates with ethanolic sodium ethoxide [4]. By using the above method, 2,3,4,5-tetrahydro-1-benzoxepin-3,5-diones are also obtained together with benzofuran derivatives. For example, Tymann and Pickles isolated 2,3,4,5-tetrahydro-1-benzoxepin-3,5-dione in a low yield by the action of ethanolic sodium ethoxide on ethyl 2-acetylphenoxyacetate together with benzofuran, ethyl 2-benzofurancarboxylate, and its carboxylic acid [5]. Wasson obtained 6-hydroxy-2,3,4,5-tetrahydro-1-benzoxepin-3,5-dione in 58% yield by refluxing ethyl 2-acetyl-3-hydroxyphenoxyacetate with sodium ethoxide in toluene [6]. Heinrich-Wilhelm prepared fourteen kinds of 2,3,4,5-tetrahydro-1-benzoxepin-3,5-diones in 47-64% yields by the reaction of methyl 2-acetylphenoxyacetates with lithium *tert*-butylate in tetrahydrofuran or sodium hydride in dimethylformamide [7]. However, the detailed investigation on substituent effects for the formation of benzofurans and 2,3,4,5-tetrahydro-1-benzoxepin-3,5-diones have not been performed. In this paper, we report substituent and base effects on the production of benzofurans and benzoxepins in the cyclization of ethyl 2-acetylphenoxyacetates with bases.

Results and Discussion.

Table 1

Synthesis of Benzofurans and 1-Benzoxepin-3,5-diones in the Reaction of Ethyl Esters **1a-i** with Potassium Hydroxide in Dry Dioxane [a]

Compound	Isolated Yield of Products (%)								Relative Yield (%)		Total Yield (%)
1 (R)	**2** + **3**	(**2**:**3**) [b]	**4** [c]	**5**	**6**	**7** [c]	**8**	**9** [c]	**2-7**	**8**	**2-8**
1a (4-MeO)	0		0	25	0	4	55	1	35	65	84
1b (4-Me)	0		0	39	0	5	41	1	52	48	85
1c (5-Me)	0		0	54	0	4	35	1	62	38	93
1d (H)	0		0	24	0	4	32	trace	47	53	60
1e (5-MeO)	0		0	61	0	6	25	0	73	27	92
1f (4-Cl)	0		10	23	0	7	34	1	54	46	74
1g (5-Cl)	0		0	50	0	8	26	1	69	31	84
1h (5-NO_2) [d]	50	(6:1)	7	0	9	<1	21	<1	76	24	88
1i (4-NO_2)	27	(5:1)	28	trace	19	2	8	trace	90	10	84

[a] Esters **1a-i** were stirred at 60° for 6 hours with two equivalents of potassium hydroxide in dry dioxane. [b] Ratios of the two isomers **2** and **3** were determined by the ^1H nmr measurements of the mixture, which was obtained by the column chromatography of benzene soluble parts. [c] Acids **4**, **7**, and **9** were estimated as the corresponding methyl esters **18**, **19**, and **17**, respectively. [d] Five percent of ester **1h** was recovered.

Table 2

Synthesis of Benzofurans and 1-Benzoxepin-3,5-diones in the Reaction of Ethyl Esters **1a-i** with Potassium Hydroxide in Dry Dioxane [a]

Compound	Recovery	Isolated Yield of Products (%)								Relative Yield (%)		Total Yield (%)
1 (R)	of **1** (%)	**2** + **3**	(**2**:**3**) [b]	**4** [c]	**5**	**6**	**7** [c]	**8**	**9** [c]	**2-7**	**8**	**2-8**
1a (4-MeO)	6	11	(6:1)	0	17	trace	trace	50	5	36	64	78
1b (4-Me)	1	13	(6:1)	0	29	2	2	40	4	53	47	86
1c (5-Me)	trace	8	(3:1)	0	39	2	2	34	3	60	40	85
1d (H)	3	15	(16:1)	0	20	2	1	33	4	54	46	71
1e (5-MeO)	1	19	(13:1)	0	44	3	2	25	2	73	27	93
1f (4-Cl)	0	13	(5:1)	26	8	3	1	33	7	61	39	84
1g (5-Cl)	0	2	(1:1.3)	6	30	6	1	35	2	56	44	80
1h (5-NO_2)	82	13	(10:1)	trace	0	trace	trace	3	1	81	19	16
1i (4-NO_2)	57	32	(15:1)	1	1	trace	1	1	1	97	3	36

[a] Esters **1a-i** were stirred at 60° for 6 hours with one equivalent of potassium hydroxide in dry dioxane. [b] Ratios of the two isomers **2** and **3** were determined by the ^1H nmr measurements of the mixture, which was obtained by the column chromatography of benzene soluble parts. [c] Acids **4**, **7**, and **9** were estimated as the corresponding methyl esters **18**, **19**, and **17**, respectively.

Some ethyl 2-acetylphenoxyacetates **1a-i** were prepared in order to investigate substituent effects on the synthesis of benzofurans **2a-i-7a-i** and 1-benzoxepin-3,5-diones **8a-i**, respectively. The syntheses of **1a** [8], **1c** [9], **1d** [10], **1e** [11], **1f** [12], **1g** [13], **1h** [14], and **1i** [15] were carried out according to reported methods.

Initially, when esters **1a-i** were stirred with two equivalents of potassium hydroxide in dry dioxane at 60° for 6 hours, benzofurans **2**, **3**, and **6** were obtained from the dioxane solution and benzofurans **4**, **5**, and **7**, benzoxepins **8**, and phenoxyacetic acids **9** were isolated from the precipitate after treatment with 6*M* hydrochloric acid. The results are summarized in Table 1.

The relative yields of benzofurans **2-7** and benzoxepins **8** varied with the types of 4- or 5-substituents. In the case of **1a** (R = 4-MeO), the relative yields of benzofurans **2a-7a** to benzoxepin **8a** were 35 and 65% yields, respectively. However, when ester **1i** (R = 4-NO_2) was treated with the base, benzofurans **2i-7i** and benzoxepin **8i** were obtained in relative yields of 90:10%. In the cases of **1b** (R = 4-Me), **1c** (R = 5-Me), **1d** (R = H), **1e** (R = 5-MeO), **1f** (R = 4-Cl), **1g** (R = 5-Cl), and **1h** (R = 5-NO_2), benzofurans and benzoxepins were obtained in the relative yields of 47-76 and 53-24%. Thus, especially compound **1i** (R = 4-NO_2) gave benzofurans **2i-7i** predominantly. The relative yields of benzofurans **2-7** decreased with an increase of electron-donating character of 4- or 5-substituents. The acidity of methylene proton of **1a** would be weaker than that of **1b-1i** by electron-donating effects of the 4-methoxyl group and the furan ring formation is less favorable than that of oxepin ring. On the other hand, the 4-nitro group of **1i** increased the acidity of methylene proton by electron-withdrawing effects compared with that of **1a-1h** and benzofurans **2i-7i** were produced exclusively.

Secondly, esters **1a-i** were treated with one equivalent of potassium hydroxide in order to clarify the reaction pathways for the formation of benzofurans **2-7** and benzoxepins **8**. The results are listed in Table 2.

The relative yields of benzofurans **2a-g**, **3a-g**, **4f** and **g**, **5a-g**, **6a-g**, and **7a-g** to benzoxepins **8a-g** (73-36:27-64%) were similar to those obtained from the reactions of esters **1a-g** with two equivalents of potassium hydroxide. While, in the case of compounds **1h** (5-NO_2) and **1i** (4-NO_2), relative yields of benzofurans **2h-7h** and **2i-7i** to benzoxepins **8h** and **8i** were 81:19 and 97:3%, respectively. The relative yields of benzofurans and benzoxepins were not so influenced by quantity of the base. By using one equivalent of potassium hydroxide, 2,3-dihydrobenzofurans **2a-i** and **3a-i** were prepared in 2-32% yields. The ratios of **2a-i** to **3a-i** varied from 1:1.3 to 16:1. *cis*-2,3-Dihydrobenzofurans **2** were produced exclusively by the steric repulsion between the C_2-ethoxycarbonyl group and the C_3-methyl group in the furan ring formation. Benzofurans **5a-g**, **6a-g**, and **7a-g** were obtained in 2-6 and 1-2% yields, respectively. In the case of **1f** and **1g**, compounds **4f** and **4g** were obtained in 26 and 6% yields, respectively. Thus, these results suggested that the composition of benzofurans **2-7** depends on the facility of saponification or dehydration of esters **2** and **3** by bases and the reactivity of salt **12** with acids.

The formation of furan ring and oxepin ring will be explained as one of the aldol-type condensation and suitable mechanisms are illustrated in Scheme 1 [16]. Potassium hydroxide abstracts hydrogen adjacent to ethoxycarbonyl group in **1** to give an anion **10**. The anion **10** attacks the carbonyl group to afford benzofurans **2** and **3** *via* compound **11**. Compound **2** is saponified with potassium hydroxide to give salt **12** [1,17,18]. Benzofuran **5** and 2,3-dihydro-2-benzofurancarboxylic acid **4** are obtained by the treatment of **12** with 6*M* hydrochloric acid [17]. Acid **7** is produced by saponification of ester **6**, which is obtained

Scheme 1

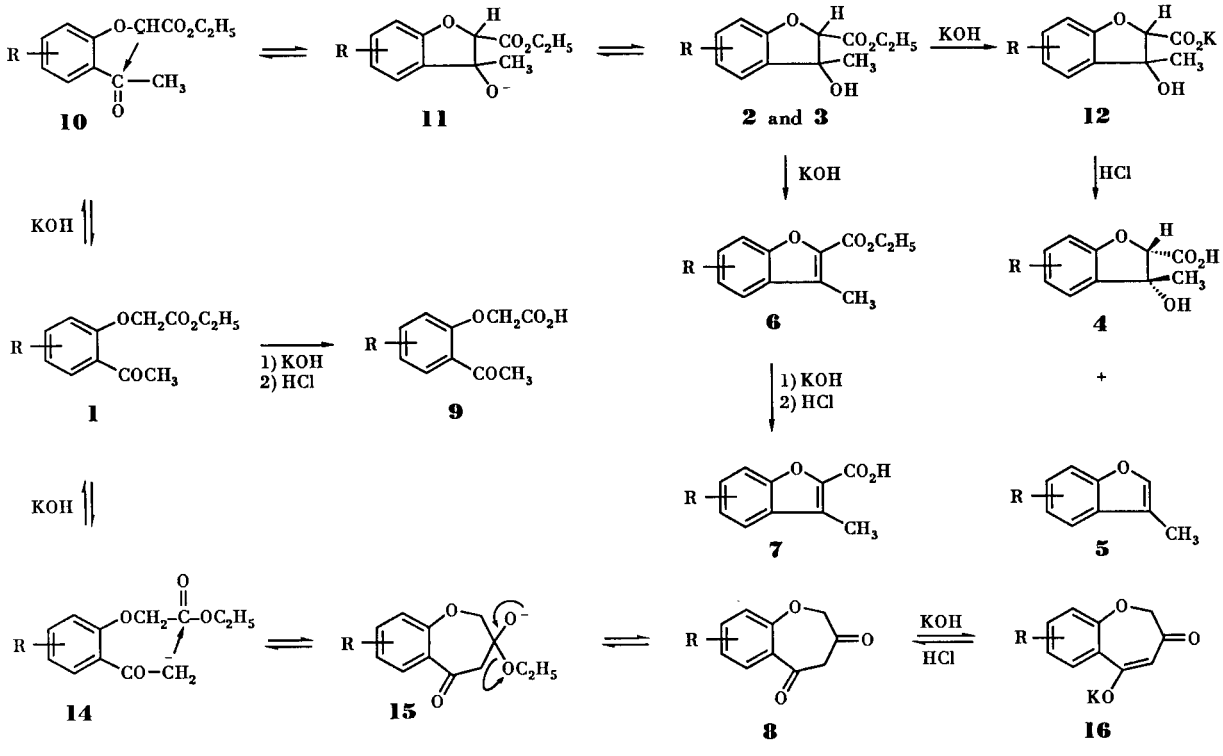


Table 3

Synthesis of Benzofurans and 1-Benzoxepin-3,5-diones in the Reaction of Ethyl Esters **1a-i** with Sodium Amide in Dry Dioxane [a]

Compound	Recovery	Isolated Yield of Products (%)								Relative Yield (%)		Total Yield (%)
1 (R)	of **1** (%)	**2** + **3**	(**2**:**3**) [b]	**4** [c]	**5**	**6**	**7** [c]	**8**	**9** [c]	**2-7**	**8**	**2-8**
1a (4-MeO)	64	13	(1:0)	0	trace	trace	0	5	2	72	28	18
1b (4-Me)	48	24	(1:0)	0	trace	0	trace	4	3	86	14	28
1c (5-Me)	29	41	(1:0)	0	trace	trace	0	7	0	85	15	48
1d (H)	46	29	(1:0)	0	trace	0	0	2	2	94	6	31
1e (5-MeO)	2	55	(1:0)	0	9	1	3	8	2	89	11	76
1f (4-Cl)	14	42	(100:1)	0	trace	trace	3	12	6	79	21	57
1g (5-Cl)	12	47	(300:1)	0	2	trace	0	8	3	86	14	57
1h (5-NO_2)	92	3	(25:1)	1	0	0	trace	0	<1	100	0	4
1h (5-NO_2) [d]	50	33	(27:1)	1	1	trace	trace	0	2	100	0	35
1i (4-NO_2)	3	78	(33:1)	3	trace	3	1	0	2	100	0	85

[a] Esters **1a-i** were stirred with sodium amide in a 1:1 molar ratio at 60° for 6 hours in dry dioxane. [b] Ratios of the two isomers **2** and **3** were determined by the ^1H nmr measurements. [c] Compounds **4**, **7**, and **9** were estimated as the corresponding methyl esters **18**, **19**, and **17**, respectively. [d] Three equivalents of sodium amide was used.

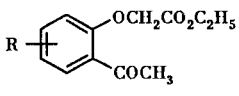
by dehydration of compounds **2** and **3** [19]. While, the base abstracts protons of 2-acetyl group in **1** to give an anion **14**. Attack of the anion **14** to the carbonyl group of ester produces benzoxepin **8** *via* **15**. Compound **8** is present as potassium salt **16** in the reaction mixture [17].

Finally, the reactions of esters **1a-i** with one equivalent of sodium amide were examined and the results are listed in Table 3. In all cases, benzofurans **2a-i**-**7a-i** were produced in good relative yields (72-100%). However, benzoxepins **8a-g** were obtained in low relative yields (28-6%) and esters **1h** and **1i** did not produce benzoxepins **8h** and **8i**, respectively. Poor-nucleophilic sodium amide is an useful base for preparation of 2,3-dihydrobenzofurans **2a-i**.

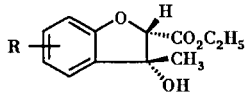
The stereochemistry of 2,3-dihydrobenzofurans **2a-i** and **3a-i** was determined from the comparison of their chemical shifts of C_2-H and C_3-Me protons as shown in Table 4. The chemical shifts of the C_2 methine proton of compounds **3a-i** are located 0.13-0.19 downfield from that

of the methine proton of **2a-i** by the anisotropic effect of C_3-methyl group [20a,20b]. The C_3-methyl protons of **2a-i** appeared at low field (δ 1.77-1.88) than that of **3a-i** (δ 1.52-1.65) by the anisotropic effect of C_2-C bond of C_2-ethoxycarbonyl group [20b]. Compound **2i** is already concluded to be *cis* and compound **3i** to be *trans* by the NOE measurement [19]. The *cis* isomer refers *cis* relationship between C_2-alkoxycarbonyl groups or carboxyl groups and C_3-hydroxyl groups. Acids **4f, g,** and **h** were assigned to *cis* stereochemistry by methylation followed by comparison with authentic samples obtained from the reactions of methyl esters **17f, 17g,** and **17h** with sodium amide or potassium hydroxide, respectively.

Formula 1



1, R
a, 4-CH_3O **g**, 5-Cl
b, 4-CH_3 **h**, 5-NO_2
c, 5-CH_3 **i**, 4-NO_2
d, H
e, 5-CH_3O
f, 4-Cl



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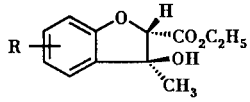

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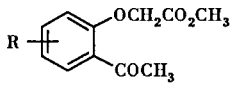

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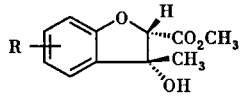

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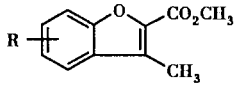

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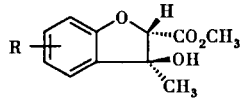

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Thus, the relative yields of benzofurans **2-7** and benzoxepins **8** varied by the kinds of substituents. Ester **1a** (R = 4-MeO) favored the production of benzoxepin **8a** rather than benzofurans **2a-7a**. On the other hand, ester **1i** (R = 4-NO_2) produced benzofurans **2i-7i** predominantly. By using sodium amide, 2,3-dihydrobenzofurans **2a-i** were exclusively obtained. Detailed investigation concerning substituent effects of 2-acyl groups and α substituents of acetate in esters **1** for the distribution of benzofurans and benzoxepins is now in progress.

EXPERIMENTAL

Melting points are uncorrected. Column chromatography was performed on silica gel (Wakogel C-200). Unless otherwise stated anhydrous sodium sulfate was employed as the drying agent. 1,4-Dioxane was dried by refluxing with sodium [21]. The infrared absorption spectra were determined on a JASCO Model DS402G infrared spectrometer. The nuclear magnetic resonance spectra (^1H) were determined at 90 MHz on a JEOL JNM-FX 90Q FT NMR spectrometer and at 60 MHz on a HITACHI R-24B NMR spectrometer, using tetramethylsilane as the internal standard.

Table 4
Structure of 2,3-Dihydrobenzofurans **2** and **3**

Compound	^1H nmr ppm in deuteriochloroform [a] C_2-H	C_3-Me
2a	4.82	1.79
3a	4.98	1.55
2b	4.81	1.78
3b	4.96	1.53
2c	4.82	1.78
3c	4.98	1.55
2d	4.82	1.79
3d	4.97	1.54
2e	4.85	1.77
3e	4.98	1.52
2f	4.84	1.78
3f	4.99	1.53
2g	4.83	1.77
3g	4.99	1.54
2h	4.91	1.82
3h	5.06	1.56
2i	4.99	1.88
3i	5.18	1.65

[a] Tetramethylsilane was used as the internal standard.

General Procedure for the Reaction of Esters **1a-i** with Potassium Hydroxide in Dry Dioxane.

A typical procedure is described for the reaction of **1e**. A mixture of **1e** (300 mg, 1.19 mmoles), potassium hydroxide powder (67 mg, 1.19 mmoles), and dry dioxane (25 ml) was stirred at 60° for 6 hours. After cooling, the insoluble materials in the reaction mixture were filtered and the filtrate was concentrated by evaporation. The residue was dissolved in benzene and the insoluble materials were removed by filtration. The residue (69 mg) obtained upon evaporation of benzene was chromatographed on silica gel (30 g). Esters **6e** (7 mg, 3%) and **1e** (3 mg, 1%) were obtained by elution with benzene-ether (30:1), respectively. 2,3-Dihydrobenzofurans **2e** and **3e** (58 mg, 19%; **2e**:**3e** = 13:1) were eluted with benzene-ether (5:1). A mixture of **2e** and **3e** was recrystallized from benzene-hexane to give colorless plates of **2e**, mp 87.2-88.0°; ir (potassium bromide): 3440 (OH), 1733 ($CO_2C_2H_5$), 1618, 1595, 1154 cm^{-1}; ^1H nmr (deuteriochloroform): 90 MHz, δ 1.34 (t, J = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 1.77 (s, 3H, C_3-CH_3), 2.58 (broad s, 1H, OH), 3.76 (s, 3H, C_6-OCH_3), 4.30 (q, J = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 4.85 (s, 1H, C_2-H), 6.47 (d, J = 2.2 Hz, 1H, C_7-H), 6.52 (dd, J = 6.4 and 2.2 Hz, 1H, C_5-H), 7.18 (d, J = 6.4 Hz, 1H, C_4-H).

Anal. Calcd. for $C_{13}H_{16}O_5$: C, 61.89; H, 6.39. Found: C, 62.10; H, 6.50.

The insoluble materials obtained above were combined and dissolved in water and acidified with 6*M* hydrochloric acid. The resulting precipitate was extracted with ether (300 ml). The ethereal solution was washed with water and dried. The residue (175 mg) obtained upon evaporation of ether was chromatographed on silica gel (20 g). Firstly, benzofuran **5e** (85 mg, 44%)

was obtained by elution with benzene. Secondly, benzoxepin **8e** (61 mg, 25%) was obtained by elution with benzene-ether (100:3). Thirdly, a mixture of acids **7e** and **9e** was obtained by elution with acetone. Acids **7e** and **9e** were methylated with diazomethane in ether and chromatographed on silica gel (15 g). Methyl esters **20e** (5 mg, 2%) and **18e** (7 mg, 2%) were obtained by elution with benzene and then with benzene-ether (30:1), respectively.

The reactions of compounds **1a-d** and **f-i** with potassium hydroxide in a 1:1 molar ratio were carried out in a similar manner to the reaction of **1e** with one equivalent of potassium hydroxide. The results are listed in Table 2. Similarly, esters **1a-i** were stirred with two equivalents of potassium hydroxide and the reaction mixture was worked up as described above. The results are summarized in Table 1. In the case of **1f-i**, compounds **17f-i**, **18f-i**, and **19f-i** were obtained by the elution of residue obtained by methylation of the corresponding acids **9f-i**, **4f-i**, and **7f-i** with benzene, benzene-ether (30:1) and then with benzene-ether (5:1), respectively.

Compounds **5a** [8], **6a** [8], **8a** [7], **17a** [7], **19a** [8], **5b** [15], **8b** [7], **17b** [7], **19b** [15], **5c** [9], **6c** [9], **8c** [7], **17c** [7], **5d** [10], **8d** [7], **17d** [7], **19d** [15], **5e** [11], **6e** [4d], **8e** [7], **17e** [7], **19e** [22], **5f** [23], **6f** [23], **8f** [7], **17f** [7], **19f** [15], **5g** [13], **8g** [7], **17g** [7], **5h** [14], **2i** [19], **5i** [15], **6i** [19], **17i** [19], **18i** [19], **19i** [19] were identified by comparison with authentic samples obtained by reported procedures, respectively.

The Reactions of Esters **1a-i** with Sodium Amide.

In the same manner as has been described for the reaction of **1e** with one equivalent of potassium hydroxide, the reactions of esters **1a-i** and sodium amide in a ratio of 1:1 were carried out and the results are summarized in Table 3.

Compound **2a** was obtained as colorless plates, mp 90.8-91.4° (from benzene-hexane); ir (potassium bromide): 3450 (OH), 1759 ($CO_2C_2H_5$), 1484, 1202, 1060, 817 cm^{-1}; ^1H nmr (deuteriochloroform): 90 MHz, δ 1.34 (t, J = 7.0 Hz, 3H, $CO_2CH_2CH_3$), 1.79 (s, 3H, C_3-CH_3), 2.67 (broad s, 1H, OH), 3.75 (s, 3H, C_5-OCH_3), 4.31 (q, J = 7.0 Hz, 2H, $CO_2CH_2CH_3$), 4.82 (s, 1H, C_2-H), 6.82 (s, 3H, Ar-H_3).

Anal. Calcd. for $C_{13}H_{16}O_5$: C, 61.89; H, 6.39. Found: C, 61.79; H, 6.47.

Compound **2b** was obtained as colorless plates, mp 82.0-83.0° (from benzene-hexane); ir (potassium bromide): 3460 (OH), 1743 ($CO_2C_2H_5$), 1479, 1213, 1107, 1068, 1047, 811 cm^{-1}; ^1H nmr (deuteriochloroform): 90 MHz, δ 1.33 (t, J = 7.0 Hz, 3H, $CO_2CH_2CH_3$), 1.78 (s, 3H, C_3-CH_3), 2.31 (s, 3H, C_5-CH_3), 2.45 (s, 1H, OH), 4.30 (q, J = 7.0 Hz, 2H, $CO_2CH_2CH_3$), 4.81 (s, 1H, C_2-H), 6.82 (d, J = 9.0 Hz, 1H, C_7-H), 7.03-7.11 (m, 2H, C_4-H and C_5-H).

Anal. Calcd. for $C_{13}H_{16}O_4$: C, 66.08; H, 6.82. Found: C, 65.94; H, 6.96.

Compound **2c** was obtained as colorless short needles, mp 61.5-62.5° (benzene-hexane); ir (potassium bromide): 3425 (OH), 1747 ($CO_2C_2H_5$), 1382, 1246, 1223, 1207, 1141, 1104, 1073, 1049, 825 cm^{-1}; ^1H nmr (deuteriochloroform): 90 MHz, δ 1.33 (t, J = 7.0 Hz, 3H, $CO_2CH_2CH_3$), 1.78 (s, 3H, C_3-CH_3), 2.33 (s, 3H, C_6-CH_3), 2.48 (s, 1H, OH), 4.30 (q, J = 7.0 Hz, 2H, $CO_2CH_2CH_3$), 4.82 (s, 1H, C_2-H), 6.74-6.83 (m, 2H, C_5-H and C_7-H), 7.18 (d, J = 8.1 Hz, 1H, C_4-H).

Anal. Calcd. for $C_{13}H_{16}O_4$: C, 66.08; H, 6.82. Found: C, 65.92; H, 6.87.

Compound **2d** was obtained as colorless plates, mp 74.0-75.0° (from benzene-hexane); ir (potassium bromide): 3440 (OH), 1742 ($CO_2C_2H_5$), 1598, 1447, 1214, 1112, 1071, 1050, 767 cm^{-1}; ^1H nmr (deuteriochloroform): 90 MHz, δ 1.33 (t, J = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 1.79 (s, 3H, C_3-CH_3), 2.69 (s, 1H, OH), 4.29 (q, J = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 4.82 (s, 1H, C_2-H), 6.89-7.35 (m, 4H, Ar-H_4).

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.57; H, 6.42.

Compound **2f** was obtained as colorless short needles, mp 98.0-99.5° (from benzene-hexane); ir (potassium bromide): 3420 (OH), 1740 ($CO_2C_2H_5$), 1466, 1215, 1082, 1061, 1043, 838 cm^{-1}; ^1H nmr (deuteriochloroform): 90 MHz, δ 1.33 (t, J = 7.0 Hz, 3H, $CO_2CH_2CH_3$), 1.78 (s, 3H, C_3-CH_3), 2.70 (s, 1H, OH), 4.29 (q, J = 7.0 Hz, 2H, $CO_2CH_2CH_3$), 4.84 (s, 1H, C_2-H), 6.86 (d, J = 7.2 Hz, 1H, C_7-H), 7.20 (dd, J = 7.2 and 2.5 Hz, 1H, C_6-H), 7.26 (d, J = 2.5 Hz, 1H, C_4-H).

Anal. Calcd. for $C_{12}H_{13}ClO_4$: C, 56.15; H, 5.10. Found: C, 56.40; H, 5.20.

Compound **2g** was obtained as colorless plates, mp 108.0-109.0° (from benzene-hexane); ir (potassium bromide): 3450 (OH), 1739 ($CO_2C_2H_5$), 1604, 1593, 1473, 1214, 1057, 1043, 900, 849, 819 cm^{-1}; ^1H nmr (deuteriochloroform): 90 MHz, δ 1.32 (t, J = 7.0 Hz, 3H, $CO_2CH_2CH_3$), 1.77 (s, 3H, C_3-CH_3), 2.91 (s, 1H, OH), 4.25 (q, J = 7.0 Hz, 2H, $CO_2CH_2CH_3$), 4.83 (s, 1H, C_2-H), 6.91-6.99 (m, 2H, C_5-H and C_7-H), 7.19 (d, J = 8.6 Hz, 1H, C_4-H).

Anal. Calcd. for $C_{12}H_{13}ClO_4$: C, 56.15; H, 5.10. Found: C, 56.35; H, 5.18.

Compound **6g** was obtained as colorless short needles, mp 52.8-53.3° (from benzene-hexane); ir (potassium bromide): 1723 and 1702 ($CO_2C_2H_5$), 1594, 1284, 1150, 1136, 1097, 916, 817, 804 cm^{-1}; ^1H nmr (deuteriochloroform): 90 MHz, δ 1.42 (t, J = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 2.54 (s, 3H, C_3-CH_3), 4.44 (q, J = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 7.22 (dd, J = 8.4 and 2.4 Hz, 1H, C_5-H), 7.49 (d, J = 2.4 Hz, 1H, C_7-H), 7.50 (d, J = 8.4 Hz, 1H, C_4-H).

Anal. Calcd. for $C_{12}H_{11}ClO_3$: C, 60.39; H, 4.65. Found: C, 60.33; H, 4.67.

Compound **2h** was obtained as colorless plates, mp 110.5-111.5° (from benzene); ir (potassium bromide): 3420 (OH), 1735 ($CO_2C_2H_5$), 1520 (NO_2), 1343 (NO_2), 1212, 1042, 819 cm^{-1}; ^1H nmr (deuteriochloroform): 60 MHz, δ 1.32 (t, J = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 1.82 (s, 3H, C_3-CH_3), 2.84 (s, 1H, OH), 4.27 (q, J = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 4.91 (s, 1H, C_2-H), 7.40 (d, J = 8.4 Hz, 1H, C_4-H), 7.68 (d, J = 2.4 Hz, 1H, C_7-H), 7.85 (dd, J = 8.4 and 2.4 Hz, 1H, C_5-H).

Anal. Calcd. for $C_{12}H_{13}NO_6$: C, 53.93; H, 4.90. Found: C, 53.86; H, 5.14.

Compound **6h** was obtained as pale yellow short needles, mp 100.0-100.5° (from benzene-hexane); ir (potassium bromide): 1722 ($CO_2C_2H_5$), 1523 (NO_2), 1342 (NO_2), 1294, 1161, 870, 831, 827 cm^{-1}; ^1H nmr (deuteriochloroform): 60 MHz, δ 1.46 (t, J = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 2.59 (s, 3H, C_3-CH_3), 4.46 (q, J = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 7.70 (d, J = 9.0 Hz, 1H, C_4-H), 8.18 (dd, J = 9.0 and 1.8 Hz, 1H, C_5-H), 8.37 (d, J = 1.8 Hz, 1H, C_7-H).

Anal. Calcd. for $C_{12}H_{11}NO_5$: C, 57.83; H, 4.45. Found: C, 57.77; H, 4.59.

Compound **8h** was obtained as pale yellow long needles, mp 155-156° dec (from benzene); ir (potassium bromide): 1718 (OCH_2CO), 1675 (ArCO), 1515 (NO_2), 1347 (NO_2), 1275, 1039, 926, 807 cm^{-1}; ^1H nmr (deuteriochloroform): 60 MHz, δ 4.36 (s, 2H, $ArCOCH_2CO$), 4.61 (s, 2H, OCH_2CO), 8.10-8.14 (m, 3H, Ar-H_3).

Anal. Calcd. for $C_{10}H_7NO_5$: C, 54.30; H, 3.19. Found: C, 54.58; H, 3.40.

Compound **19h** was obtained as pale yellow short needles, mp 178-180° (from benzene); ir (potassium bromide): 1712 ($CO_2C_2H_5$), 1588, 1512 (NO_2), 1439, 1368, 1339 (NO_2), 1293, 1231, 1150, 1100, 827 cm^{-1}; ^1H nmr (deuteriochloroform): 60 MHz, δ 2.59 (s, 3H, C_3-CH_3), 3.98 (s, 3H, CO_2CH_3), 7.69 (d, J = 9.0 Hz, 1H, C_4-H), 8.17 (dd, J = 9.0 and 1.8 Hz, 1H, C_5-H), 8.35 (d, J = 1.8 Hz, 1H, C_7-H).

Anal. Calcd. for $C_{11}H_9NO_5$: C, 56.17; H, 3.86. Found: C, 56.30; H, 3.97.

Compound **8i** was obtained as pale yellow short needles, mp 131-132° dec (from benzene); ir (potassium bromide): 1727 (OCH_2CO), 1678 (ArCO), 1615, 1523 (NO_2), 1356, 1344, 1281, 1086, 1031, 862 cm^{-1}; ^1H nmr (deuteriochloroform): 60 MHz, δ 4.33 (s, 2H, $COCH_2CO$), 4.62 (s, 2H, OCH_2CO), 7.39 (d, J = 8.4 Hz, 1H, C_9-H), 8.41 (dd, J = 8.4 and 3.0 Hz, C_6-H), 8.86 (d, J. = 3.0 Hz, 1H, C_6-H).

Anal. Calcd. for $C_{10}H_7NO_5$: C, 54.30; H, 3.19. Found: C, 54.48; H, 3.23.

Ethyl 4-Methyl-2-acetylphenoxyacetate (**1b**).

A mixture of 2-hydroxy-5-methylacetophenone [24] (20 g), ethyl bromoacetate (26.6 g), anhydrous potassium carbonate (80 g), and acetone (400 ml) was refluxed at 70° for 6 hours. After cooling, insoluble materials were removed by filtration. The residue obtained upon evaporation of the acetone was purified by recrystallization from ethanol to give 25.1 g (80%) of **1b** as colorless short needles, mp 41.5-42.5°; ir (potassium bromide): 1758 ($CO_2C_2H_5$), 1660 ($COCH_3$), 1611, 1449, 819 cm^{-1}.

Anal. Calcd. for $C_{13}H_{16}O_4$: C, 66.08; H, 6.82. Found: C, 66.09; H, 6.85.

Ethyl 3,5-Dimethyl-2-benzofurancarboxylate (**6b**).

A mixture of 2-hydroxy-5-methylacetophenone [24] (1.0 g), ethyl bromoacetate (4.4 g), and anhydrous potassium carbonate (3.6 g) was heated at 105° for 1.5 hours and then at 140° for 4.5 hours. After cooling, the reaction mixture was poured into ice water and extracted with ether. The ethereal solution was washed with cold water and dried. The residue obtained upon evaporation of ether was chromatographed and eluted with benzene to give **6b** (0.84 g, 57.9%). Recrystallization from aqueous ethanol gave colorless flakes, mp 51.5-52.5° (lit [25], 52.5-54.0°); ir (potassium bromide): 1720 ($CO_2C_2H_5$), 1577, 1474, 1290, 813 cm^{-1}; ^1H nmr (deuteriochloroform): 60 MHz, δ 1.41 (t, J = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 2.43 (s, 3H, C_5-CH_3), 2.52 (s, 3H, C_3-CH_3), 4.41 (q, J = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 7.09-7.47 (m, 3H, Ar-H_3).

Anal. Calcd. for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.58; H, 6.53.

Ethyl 3-Methyl-2-benzofurancarboxylate (**6d**).

A mixture of 2-hydroxyacetophenone (10.0 g), ethyl bromoacetate (35.0 g), and anhydrous potassium carbonate (40.0 g) was heated at 80° for 1 hour and then at 160° for 5 hours. The reaction mixture was worked up similarly as described for the preparation of **6b**. Crude **6d** obtained by column chromatography was recrystallized from benzene-hexane to give 6.5 g (43%) of **6d** as colorless short needles, mp 50.8-51.5° (lit [26] mp 49-51°); ir (potassium bromide): 1714 ($CO_2C_2H_5$), 854, 746 cm^{-1}; ^1H nmr (deuteriochloroform): 60 MHz, δ 1.41 (t, J = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 2.54 (s, 3H, C_3-CH_3), 4.42 (q, J = 7.2 Hz, 2H, $CO_2CH_2CH_3$), 7.07-7.65 (m, 4H, Ar-H_4).

Anal. Calcd. for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.53; H, 6.03.

Methyl 2-Acetyl-5-nitrophenoxyacetate (**17h**).

A mixture of 2-hydroxy-4-nitroacetophenone [27] (1 g, 5.5 mmoles), methyl bromoacetate (1.1 g, 7.0 mmoles), anhydrous potassium carbonate (4.0 g, 28.9 mmoles), and acetone (30 ml) was refluxed at 70° for 3.5 hours. After cooling, insoluble materials were removed by filtration and the filtrate was concentrated by evaporation. The residue was extracted with ether (200 ml). The ether layer was washed with water and dried. The residue obtained upon evaporation of ether was column chromatographed on silica gel (75 g). Crude **17h** (1.3 g, 93%), obtained by elution with benzene-ether (60:1) and then benzene-ether (30:1), was recrystallized from benzene-hexane to give pale yellow long needles of **17h** (1.1 g, 79%), mp 126.0-127.5°; ir (potassium bromide): 1767 ($CO_2C_2H_5$), 1661 ($COCH_3$), 1507 (NO_2), 1351 (NO_2), 1217, 1067, 1051, 877, 820 cm^{-1}; ^1H nmr (deuteriochloroform): 60 MHz, δ 2.69 (s, 3H, C_3-CH_3), 3.82 (s, 3H, CO_2CH_3), 4.83 (s, 2H, OCH_2CO_2), 7.65-7.81 (m, 3H, Ar-H_3).

Anal. Calcd. for $C_{11}H_{11}NO_6$: C, 52.17; H, 4.38. Found: C, 52.20; H, 4.35.

Methyl 5-Chloro-*c*-3-hydroxy-3-methyl-2,3-dihydro-*r*-2-benzofurancarboxylate (**18f**).

A mixture of **17f** [7] (289 mg, 1.19 mmoles), sodium amide (143 mg, 3.62 mmoles), and dry dioxane (25 ml) was stirred at 60° for 6 hours. The reaction mixture was worked up according to the reaction of **2e** with potassium hydroxide. Methyl ester **18f** (85 mg, 29%) was obtained. Recrystallization from benzene-hexane gave colorless prisms, mp 128.8-129.8°; ir (potassium bromide): 3410 (OH), 1753 ($CO_2C_2H_5$), 1466, 1224, 1199, 1084, 1060, 830 cm^{-1}; ^1H nmr (deuteriochloroform): 90 MHz, δ 1.78 (s, 3H, C_3-CH_3), 2.69 (s, 1H, OH), 3.87 (s, 3H, CO_2CH_3), 4.87 (s, 1H, C_2-H), 6.86 (d, J = 9.4 Hz, 1H, C_7-H), 7.17-7.27 (m, 2H, C_4-H and C_6-H).

Anal. Calcd. for $C_{11}H_{11}ClO_4$: C, 54.45; H, 4.57. Found: C, 54.62; H, 4.64.

Methyl 6-Chloro-*c*-3-hydroxy-3-methyl-2,3-dihydro-*r*-2-benzofurancarboxylate (**18g**).

In the similar manner to that described for **18f**, compound **18g** (88 mg, 30%) was obtained from **17g** [7] (289 mg, 1.19 mmoles). Recrystallization from benzene-hexane gave colorless short needles, mp 110.0-112.0°; ir (potassium bromide): 3460 (OH), 1740 (CO_2CH_3), 1610, 1593, 1475, 1218, 1113, 1061, 1046, 896, 849, 838, 816 cm^{-1}; ^1H nmr (deuteriochloroform): 90 MHz, δ 1.77 (s, 3H, C_3-CH_3), 2.85 (broad s, 1H, OH), 3.81 (s, 3H, CO_2CH_3), 4.87 (s, 1H, C_2-H), 6.91-7.00 (m, 2H, C_5-H and C_7-H), 7.21 (d, J = 8.6 Hz, 1H, C_4-H).

Anal. Calcd. for $C_{11}H_{11}ClO_4$: C, 54.45; H, 4.57. Found: C, 54.36; H, 4.51.

Methyl *c*-3-Hydroxy-3-methyl-6-nitro-2,3-dihydro-*r*-2-benzofurancarboxylate (**18h**).

A mixture of **17h** (301 mg, 1.19 mmoles), potassium hydroxide (201 mg, 3.57 mmoles), and dry dioxane (25 ml) was refluxed for 5 hours. The reaction mixture was treated by a method similar to

the reaction of **2e** with potassium hydroxide. A mixture of **18h** and **20h** (98 mg, 33%, **18h**:**20h** = 9:1) was obtained. Recrystallization from benzene gave colorless plates of **18h**, mp 129.0-129.5°; ir (potassium bromide): 3425 (OH), 1746 (CO_2CH_3), 1517 (NO_2), 1342 (NO_2), 1220, 1046, 872, 824, 814 cm^{-1}; ^1H nmr (deuteriochloroform): 60 MHz, δ 1.84 (s, 3H, C_3-CH_3), 2.69 (s, 1H, OH), 3.84 (s, 3H, CO_2CH_3), 4.96 (s, 1H, C_2-H), 7.41 (d, J = 8.4 Hz, 1H, C_4-H), 7.71 (d, J = 1.8 Hz, 1H, C_7-H), 7.87 (dd, J = 8.4 and 1.8 Hz, 1H, C_5-H).

Anal. Calcd. for $C_{11}H_{11}NO_6$: C, 52.17; H, 4.38. Found: C, 52.30; H, 4.47.

Methyl 3,6-Dimethyl-2-benzofurancarboxylate (**19c**).

A mixture of 2-hydroxy-4-methylacetophenone [24] (1.0 g, 6.7 mmoles), methyl bromoacetate (4 g, 26.8 mmoles), and anhydrous potassium carbonate (3.5 g, 25.3 mmoles) was heated at 100° for 1 hour and then at 140° for 5 hours. The reaction mixture was worked up similarly as described for the preparation of **6b**. Ester **19c** was obtained in 45% yield (0.62 g). Recrystallization from benzene-hexane gave colorless short needles, mp 54.5-55.5°; ir (potassium bromide): 1706 (CO_2CH_3), 1595, 1293, 1235, 1098, 812 cm^{-1}; ^1H nmr (deuteriochloroform): 60 MHz, δ 2.46 (s, 3H, C_6-CH_3), 2.63 (s, 3H, C_3-CH_3), 3.93 (s, 3H, CO_2CH_3), 7.07 (broad d, J = 8.4 Hz, 1H, C_4-H), 7.28 (broad s, 1H, C_7-H), 7.46 (d, J = 8.4 Hz, 1H, C_5-H).

Anal. Calcd. for $C_{12}H_{12}O_3$: C, 70.58; H, 5.92. Found: C, 70.53; H, 5.85.

Methyl 6-Chloro-3-methyl-2-benzofurancarboxylate (**19g**).

To a suspension of acid **7g** [14] (0.24 g, 1.14 mmoles) in ether (30 ml) was added diazomethane in ether until the reaction mixture turned yellow and the solution was maintained at room temperature for 20 minutes. The residue obtained upon evaporation of ether was chromatographed on silica gel (30 g). Compound **19g** (0.25 g) was obtained in 98% yield by elution with benzene. Recrystallization from benzene-hexane gave colorless plates, mp 82.3-83.5°; ir (potassium bromide): 1711 (CO_2CH_3), 1598, 1294, 1226, 1104, 919, 852, 813, 807, 772 cm^{-1}; ^1H nmr (deuteriochloroform): 60 MHz, δ 2.53 (s, 3H, C_3-CH_3), 3.95 (s, 3H, CO_2CH_3), 7.23 (dd, J = 8.2 and 2.4 Hz, 1H, C_5-H), 7.49 (d, J = 2.4 Hz, 1H, C_7-H), 7.51 (d, J = 8.2 Hz, 1H, C_4-H).

Anal. Calcd. for $C_{11}H_9ClO_3$: C, 58.81; H, 4.04. Found: C, 58.81; H, 4.07.

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