Some Fatty Acids Having *O*-Heterocycles in their Terminal Positions. III. ω-(2-Benzofuranyl)alkanoic Acids

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Some ω-(2-benzofuranyl)alkanoic acids **1**, n = 2-5 were synthesized by acylation of benzofuran with ω-(ethoxycarbonyl)alkanoic acids in trifluoroacetic anhydride followed by Wolff-Kishner reductions.

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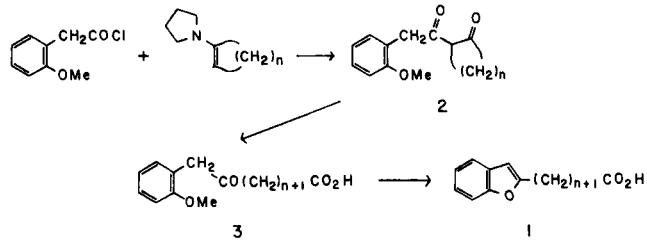
In our studies on *O*-heterocyclic compounds, some carboxylic acids showed antimicrobial activities. So, we planned the syntheses of some fatty acids having *O*-heterocycles in their terminal positions to test their antimicrobial activities. We already reported the syntheses of some ω-(3-chromonyl)alkanoic acids [1], ω-(3-coumarinyl)-alkanoic acids, and ω-(2-chromonyl)alkanoic acids [2]. In this paper, we will report the synthesis of some ω-(2-benzofuranyl)alkanoic acids.

We already reported that ω-(*o*-hydroxybenzoyl)alkanoic acids were prepared from acylation of cyclopentanone or cyclohexanone enamine with *o*-acetoxybenzoyl chloride followed by alkaline cleavage [1]. Similarly, 8-(*o*-methoxyphenyl)-7-oxooctanoic acid **3**, n = 4 was prepared from acylation of cyclohexanone-pyrrolidine enamine with *o*-methoxyphenylacetyl chloride *via* a diketone **2**, n = 4. Demethylation of this keto acid **3**, n = 4 with pyridine hydrochloride gave 6-(2-benzofuranyl)hexanoic acid **1**, n = 4 in 18% yield. But, a similar alkaline cleavage of 2-(*o*-methoxyphenylacetyl)-1-cyclopentanone (diketone) **2**, n = 3 gave *o*-methoxyphenylacetic acid and cyclopentanone only, and the corresponding keto acid **3**, n = 3 was not obtained in this procedure.

So, we tried another procedure for benzofurancarboxylic acids **1** having a side chain of various length *via* acylation of benzofuran with some ω-(ethoxycarbonyl)-



alkanoic acids and the following reductions of the keto esters **4b**. Acylation of benzofuran with some ω-(ethoxycarbonyl)alkanoic acids, n = 2-5 was effective in trifluoroacetic anhydride for 96 hours at room temperature, and the keto esters **4b** were obtained in 23-39% yields. These results are summarized in Table 1. In some cases, 3-acylated products **5** were also obtained. But, ethyl 3-(2-benzofuranyl)-3-oxopropanoate **4b**, n = 1 was not obtained from benzofuran and (ethoxycarbonyl)acetic acid

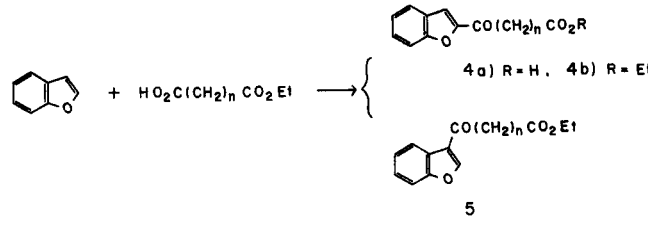


Table 1

Acylations of Benzofuran with an ω-(ethoxycarbonyl)alkanoic Acid and Some Physical Data and Elemental Analyses of the Products **4b** and **5**

Products 4b and 5	Yield	Melting Point (°C)	ν CO (cm^{-1})	M+ (m/z)	Elemental Analysis Found C(%)	Found H(%)	Calcd. C(%)	Calcd. H(%)
4b n = 2	23%	64-64.5	1720, 1675	246	68.56	5.96	68.28	5.73 for $C_{14}H_{14}O_4$
4b n = 3	31%	62.5-63	1720, 1665	260	69.38	6.22	69.22	6.20 for $C_{15}H_{16}O_4$
4b n = 4	30%	55-56	1725, 1680	274	70.10	6.61	70.06	6.61 for $C_{16}H_{18}O_4$
5 n = 4	2%	75-76	1725, 1650	274	70.10	6.61	70.06	6.61 for $C_{16}H_{18}O_4$
4b n = 5	39%	200-210 (4 mm Hg) [a]	1725, 1675	288	70.74	7.02	70.81	6.99 for $C_{17}H_{20}O_4$
5 n = 5	3%	90-91	1725, 1650	288	70.73	7.03	70.81	6.99 for $C_{17}H_{20}O_4$

[a] Boiling Point.

Table 2

Hydrolyses of Keto Esters **4b** to Keto Acids **4a** and Some Physical Data and Elemental Analyses of Keto Acids **4a**

Keto	Acid	Yield	Melting Point (°C)	ν CO (cm^{-1})	M+ (m/z)	Elemental Analysis Found C(%)	Found H(%)	Calcd. C(%)	Calcd. H(%)	
4a	n = 2	73%	152-153	1705, 1670	218	65.78	4.67	66.05	4.62	for $C_{12}H_{10}O_4$
4a	n = 3	97%	183-184	1700, 1670	232	67.40	5.37	67.23	5.21	for $C_{13}H_{12}O_4$
4a	n = 4	85%	141.5-142.5	1715, 1670	246	68.03	5.72	68.28	5.73	for $C_{14}H_{14}O_4$
4a	n = 5	96%	144-145	1715, 1670	260	69.22	6.20	69.25	6.12	for $C_{15}H_{16}O_4$

Table 3

Wolff-Kishner Reduction of Keto Estes **4b** to Benzofurancarboxylic Acids **1** and Some Physical Data and Elemental Analyses of Benzofurancarboxylic Acids **1**

Benzofuran-carboxylic Acid		Yield	Melting Point (°C)	ν CO (cm^{-1})	M+ (m/z)	Elemental Analysis Found C(%)	Found H(%)	Calcd. C(%)	Calcd. H(%)	
1	n = 2	61%	85-86	1685	204	70.55	5.99	70.58	5.92	for $C_{12}H_{12}O_3$
1	n = 3	98%	130-130.5	1710	218	71.56	6.37	71.54	6.47	for $C_{13}H_{14}O_3$
1	n = 4	89%	54.5-55.5	1710	232	72.39	6.94	72.39	6.94	for $C_{14}H_{16}O_3$
1	n = 5	89%	75-76	1700	246	73.22	7.47	73.15	7.37	for $C_{15}H_{18}O_3$

Table 4

PMR Data of New Benzofurancarboxylic Acid Derivatives **1**, **4a,b**, and **5**

Benzofuran Derivative		Solvent	Side Methylenes α	ω	others	Furan	Aromatic Ring 4-H	others	R (ester)
1	(n = 2)	$CDCl_3$	2.8 (t)	2.4 (t)	2.1 (m)	6.4 (s)	7.0-7.6 (m)		10.4 (broad s)
1	(n = 3)	DMSO-d_6	2.8 (t)	2.3 (t)	1.5-1.9 (m)	6.5 (s)	7.0-7.7 (m)		11.7 (broad s)
1	(n = 4)	$CDCl_3$	2.7 (t)	2.3 (t)	1.2-2.0 (m)	6.3 (s)	7.1-7.6 (m)		10.4 (broad s)
1	(n = 5)	DMSO-d_6	2.8 (t)	2.3 (t)	1.2-1.9 (m)	6.5 (s)	7.0-7.7 (m)		——
4a	(n = 2)	DMSO-d_6	2.6 (t)	3.3 (t)	——	7.9 (s)	7.2-7.9 (m)		12.2 (broad s)
4a	(n = 3)	DMSO-d_6	2.3 (t)	3.0 (t)	2.0 (m)	7.8 (s)	7.1-8.0 (m)		12.0 (broad s)
4a	(n = 4)	DMSO-d_6	2.5 (t)	3.0 (t)	1.5-1.9 (m)	7.9 (s)	7.3-7.9 (m)		12.0 (broad s)
4a	(n = 5)	DMSO-d_6	2.2 (t)	3.0 (t)	1.1-2.0 (m)	7.9 (s)	7.2-7.9 (m)		——
4b	(n = 2)	$CDCl_3$	2.8 (t)	3.3 (t)	——	7.5 (s)	7.1-7.8 (m)		1.3 (t) 4.2(q)
4b	(n = 3)	$CDCl_3$	2.4 (t)	3.0 (t)	1.8-2.6 (m)	7.5 (s)	7.2-7.8 (m)		1.3 (t) 4.1 (q)
4b	(n = 4)	$CDCl_3$	2.4 (t)	3.0 (t)	1.7-2.0 (m)	7.5 (s)	7.1-7.8 (m)		1.3 (t) 4.1 (q)
4b	(n = 5)	$CDCl_3$	2.3 (t)	3.0 (t)	1.4-2.1 (m)	7.6 (s)	7.1-7.9 (m)		1.3 (t) 4.1 (q)
5	(n = 4)	$CDCl_3$	2.3 (t)	2.8 (t)	1.6-1.9 (m)	8.2 (s)	8.2 (dd)	7.1-7.5 (m)	1.2 (t) 4.1 (q)
5	(n = 5)	$CDCl_3$	2.3 (t)	2.9 (t)	1.4-2.1 (m)	8.2 (s)	8.2 (dd)	7.2-7.5 (m)	1.2 (t) 4.1 (q)

[3]. These keto esters **4b** were easily converted to the corresponding keto acids **4a** by refluxing in 20% aqueous potassium hydroxide solution for 1 hour and these data are summarized in Table 2.

The reduction of keto esters **4b** was effective by the Wolff-Kishner method, and the corresponding benzofurancarboxylic acids **1** were obtained in 61-98% yield **8**. These results are summarized in Table 3.

EXPERIMENTAL

All melting points were measured on a Yanagimoto micro melting point apparatus, and the melting points and boiling points are uncorrected. The ir spectra were taken on a Hitachi 260-50 infrared spectrophotometer as liquid films or potassium bromide disks. Mass spectra were recorded on a JEOL JMS-OISG-2 mass spectrometer. Some physical data and elemental analyses were summarized in Table 1-3. The pmr spectra were recorded on a JEOL PMX-60Si nmr spectrometer, and the data

Table 5
UV Spectral Data of New Benzofuran Derivatives

Benzofuran Derivative	λ max (log ε) (nm)
1 (n = 2)	246 (4.24) 270 sh (3.58) 277 (3.67) 283 (3.66)
1 (n = 3)	246 (4.17) 270 sh (3.54) 276 (3.61) 283 (3.61)
1 (n = 4)	246 (4.15) 270 sh (3.49) 276 (3.59) 283 (3.58)
1 (n = 5)	246 (4.16) 270 sh (3.50) 276 (3.60) 283 (3.59)
4a (n = 2)	222 (3.86) 292 (4.28)
4a (n = 3)	223 (3.81) 293 (4.22)
4a (n = 4)	223 (3.84) 293 (4.30)
4a (n = 5)	223 (3.87) 292 (4.30)
4b (n = 2)	222 (3.98) 288 (4.23)
4b (n = 3)	223 (3.87) 292 (4.31)
4b (n = 4)	223 (3.92) 292 (4.26)
4b (n = 5)	223 (3.91) 292 (4.28)
5 (n = 4)	224 (4.25) 242 (3.79) 264 (3.84)
5 (n = 5)	224 (4.26) 243 (3.81) 264 (3.85)

are summarized in Table 4. The uv spectra were recorded on a Hitachi 220A spectrophotometer in 95% ethanol, and their data are summarized in Table 5.

Preparation of 6-(2-Benzofuranyl)hexanoic Acid from *o*-Methoxyphenylacetyl Chloride and Cyclohexanone-pyrrolidine Enamine.

To a solution of cyclohexanone-pyrrolidine enamine (18.2 g, 121 mmoles), triethylamine (18.2 g, 164 mmoles) in dry benzene (400 ml) *o*-methoxyphenylacetyl chloride (11.1 g, 60.2 mmoles) was added with cooling, and the mixture was refluxed for 5 hours. After cooling the reaction mixture was treated with 20% dilute hydrochloric acid (300 ml) and refluxed again for 2 hours. After cooling, the benzene layer was collected and treated with saturated aqueous copper(II) acetate solution. The precipitate of the copper complex was collected by filtration and washed well with ether. This precipitate was treated with 20% sulfuric acid to decompose the complex and extracted with ether. The ether layer was washed with saturated aqueous sodium hydrogencarbonate solution and saturated aqueous sodium chloride solution, and dried over anhydrous sodium sulfate. After removal of the ether, the residue was distilled under reduced pressure to give 2-(*o*-methoxyphenylacetyl)-1-cyclohexanone **2**, n = 4 (6.77 g, 46%), bp 185-186° (7 mm Hg); ir: 1700, 1675 cm^{-1}; ms: m/z 246 (M^+).

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 72.88; H, 7.59.

To a solution of **2** (2.84 g, 11.3 mmoles) in ethanol (19 ml) potassium hydroxide (2.35 g, 41.9 mmoles) was added, and the mixture was refluxed for 1.5 hours. After removing most of the ethanol, the residue was acidified with hydrochloric acid and extracted with chloroform. The chloroform layer was extracted twice with a saturated aqueous sodium hydrogencarbonate solution. The combined alkaline extracts were acidified and reextracted with ether. This ether layer was washed with saturated aqueous sodium chloride solution and dried over anhydrous sodium sulfate. After removal of the ether, the residue was distilled under reduced pressure to provide 8-(*o*-methoxyphenyl)-7-oxooctanoic acid **3**, n = 4 (2.85 g, 96%) as a yellow oil, bp 196-200° (3 mm Hg); ir: 1720 cm^{-1}; ms: m/z 264 (M^+).

Anal. Calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.38; H, 7.76.

A mixture of 8-(*o*-methoxyphenyl)-7-oxooctanoic acid (**3**), n = 4 (1.00 g, 3.79 mmoles) and pyridine hydrochloride (10 g) was refluxed for 1.5 hours. After cooling the mixture was diluted with water and extracted with ether. The ether layer was washed with 10% hydrochloric acid and saturated aqueous sodium chloride solution, and then extracted twice with 5% aqueous sodium hydroxide solution. The combined alkaline extracts were acidified with hydrochloric acid and the precipitates were collected by filtration and recrystallized from hexane to give 6-(2-benzofuranyl)hexanoic acid **1**, n = 4 (150 mg, 18%) as pale yellow needles, mp 52-52.5°; ir: 1710 cm^{-1}; ms: m/z 232 (M^+).

Anal. Calcd. for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.53; H, 7.20.

Acylations of Benzofuran with ω-(Ethoxycarbonyl)alkanoic Acids.

To a mixture of benzofuran (2.00 g, 16.9 mmoles) and ω-(ethoxycarbonyl)alkanoic acid (17.0 mmoles) was added trifluoroacetic anhydride (7.10 g, 33.8 mmoles) with cooling. The mixture was stirred at room temperature for 96 hours (4 days). After the reaction the mixture was treated with dilute aqueous potassium carbonate solution and stirred for overnight to decompose the acid anhydride and extracted with ether. The ether layer was washed with saturated aqueous sodium chloride solution and dried over anhydrous sodium sulfate. After removal of the ether, the residue was chromatographed on a silica-gel column. The fractions eluted with benzene gave ethyl ω-(3-benzofuranyl)-ω-oxoalkanoate and ethyl ω-(2-benzofuranyl)-ω-oxoalkanoate as colorless crystals, which were recrystallized from cyclohexane. These results are summarized in Table 1. The acylation of benzofuran with 3-(ethoxycarbonyl)propionic acid (ethyl hydrogen succinate) was checked at room temperature during several reaction times, and the yields of 2-acylated products, ethyl 4-(2-benzofuranyl)-4-oxobutanoate **4b**, n = 2 were 4% (2 hours), 8% (4 hours), 9% (12 hours), 20% (48 hours), and 23% (96 hours).

Hydrolysis of Keto Esters **4b** to Keto Acids **4a**.

To a solution of ethyl ω-(2-benzofuranyl)-ω-oxoalkanoate **4b** (2.00 mmoles) in ethanol (5 ml) was added 20% aqueous potassium hydroxide solution (30 g), and the mixture was refluxed for 1 hour. After cooling the mixture was acidified with 10% hydrochloric acid. The precipitate was collected by filtration and recrystallized from cyclohexane to give ω-(2-benzofuranyl)-ω-oxoalkanoic acids **4a**. These results are listed in Table 2.

Wolff-Kisher Reduction of **4b** to Benzofurancarboxylic Acids **1**.

To a solution of keto ester **4b** (3.00 mmoles) in diethylene glycol (10.0 g) was added 80% hydrazine hydrate (690 mg, 11.0 mmoles), and the mixture was heated at once to reflux. Then potassium hydroxide (710 mg, 12.7 mmoles) was added to the cooled reaction mixture, and the mixture was refluxed again for 2 hours with removing water. The cooled mixture was poured into ice water and washed with ether. The alkaline aqueous layer was acidified with 10% hydrochloric acid. The precipitate was recrystallized from cyclohexane to give ω-(2-benzofuranyl)alkanoic acid **1** as colorless crystals. These data are summarized in Table 3.

REFERENCES AND NOTES

[1] S. Yamaguchi, M. Mutoh, M. Shimakura, K. Tsuzuki and Y. Kawase, *J. Heterocyclic Chem*, **28**, 119 (1991).

[2] S. Yamaguchi, M. Saitoh, and Y. Kawase, *J. Heterocyclic Chem.*, **28**, 125 (1991).

[3] The active methylene group involved might cause further reactions.