Some Fatty Acids Having an *O*-Heterocycle in their Terminal Positions. II. ω-(3-Coumarinyl)alkanoic Acids and ω-(2-Chromonyl)alkanoic Acids

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Some ω-(3-coumarinyl)alkanoic acids **1a**, n = 3-6 were synthesized by cyclization of corresponding ethyl *o*-formylphenyl alkanedioate **3** with DBU followed by hydrolysis. By a similar cyclization, some ω-(2-chromonyl)alkanoic acids **2a**, n = 3-6 were also obtained from the cyclization of corresponding *o*-acetylphenyl ethyl alkanedioate **4**.

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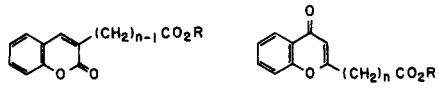
In our studies on *O*-heterocyclic compounds, some carboxylic acid derivatives showed antimicrobial activities. So, we planned the syntheses of some fatty acids having an *O*-heterocycles in their terminal positions to test their antimicrobial activities. We already reported the synthesis of some ω-(3-chromonyl)alkanoic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



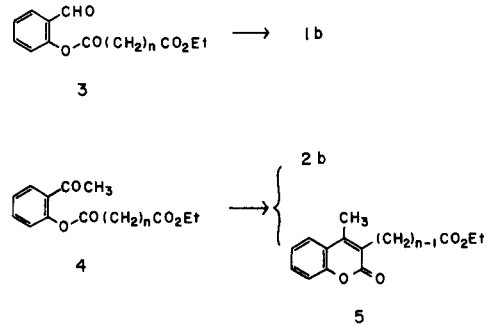
1 a R = H
b R = Et

2 a R = H
b R = Et

We planned the synthesis of ω-(3-coumarinyl)alkanoic acids and ω-(2-chromoyl)alkanoic acids from ethyl *o*-formylphenyl alkanedioates **3** or *o*-acetylphenyl ethyl alkanedioates **4**. The preparations of **3**, n = 2-6 were successful from salicylaldehyde and ethyl ω-chloroformylalkanoates in 20-68% yield. Similarly, *o*-acetylphenyl ethyl alkandioates **4** were prepared from *o*-hydroxyacetophenone and ethyl ω-chloroformylalkanoates in 21-49% yield. These results are summarized in Table 1.

The cyclizations of compounds **3**, n = 2-5 to the corresponding ethyl ω-(3-coumarinyl)alkanoates **1b**, n = 3-6 were effective in refluxing with DBU (1,8-diazabicyclo-[5.4.0]-7-undecene) (*ca.* 0.8 molar equivalents) in toluene. But, ethyl (3-coumarinyl)acetate, **1b**, n = 2 was not obtained, because this might cause further reactions of its active methylene. These results are summarized in Table 2.

The similar cyclization of *o*-acetylphenyl ethyl alkanedioates **4** in refluxing with DBU gave mixtures of ethyl ω-(2-chromonyl)alkanoates **2b**, n = 3-6 and ethyl ω-(4-methyl-3-coumarinyl)alkanoates **5** and the results are also summarized in Table 2.



3

4

5

The coumarin esters **1b** and the chromone ester **2b**, thus obtained, were hydrolyzed to the corresponding acids. The coumarin esters **1b** were effectively converted to the acids **1a** by refluxing in 5% aqueous sodium hydroxide solution for 1 hour and the chromone esters **2b** were converted to the acids **2a** by refluxing in 20% aqueous sulfuric acid [2]. These results are summarized in Table 3.

Table 1

Preparation of Ethyl *o*-Formyl- or *o*-Acetylphenylalkandioates (3 and 4) and their Physical Data

	Yield	Bp/°C	IR/cm^{-1}	M$^+$ (m/z)
3 n 2	25%	165-171 (3 mm Hg)	1755, 1725, 1690	250
3 n 3	20%	*ca* 185 (3 mm Hg)	1755, 1720, 1690	264
3 n 4	38%	180-183 (3 mm Hg)	1755, 1725, 1695	278
3 n 5	68%	182-185 (2 mm Hg)	1755, 1725, 1695	292
3 n 6	68%	216-217 (2 mm Hg)	1760, 1730, 1700	306
4 n 3	49%	165-175 (4 mm Hg)	1760, 1730, 1685	278
4 n 4	21%	160-170 (15mm Hg)	1760, 1730, 1685	292
4 n 5	35%	131-132 (3 mm Hg)	1760, 1730, 1685	306
4 n 6	39%	165-178 (2 mm Hg)	1760, 1730, 1690	320

EXPERIMENTAL

All melting points were measured on a Yanagimoto micro melting point apparatus, and they are uncorrected. The ir spectra were taken on a Hitachi EPI-S2 spectrophotometer as liquid films or as potassium bromide disks. Mass spectra were recorded on a JOEL JMS-OISG-2 spectrometer. Some physical data and elemental analyses are summarized in Tables 1-3. The pmr spectra of the new coumarins and chromones were recorded on a JOEL JNM-MH-60 or a JEOL PMX-60Si spectrometer, and their data are summarized in Tables **4a** and **4b**.

Table 2

Cyclization of **3** and **4** and some Physical Data of their products

Substrate	Product	Yield	Melting Point (°C)	ν CO (cm^{-1})	M^+ (m/z)	Elemental Analysis Found C%	Found H%	Calcd. C%	Calcd. H%	
3 n = 3	**1b** n = 3	24%	61-61.5	1735, 1715	246	68.50	5.90	68.28	5.73	for $C_{14}H_{14}O_4$
3 n = 4	**1b** n = 4	23%	43-44	1725, 1710	260	69.20	6.16	69.21	6.20	for $C_{15}H_{16}O_4$
3 n = 5	**1b** n = 5	34%	50-50.5	1735, 1710	274	69.83	6.67	70.05	6.61	for $C_{16}H_{18}O_4$
3 n = 6	**1b** n = 6	32%	37-37.5	1725, 1710	288	70.58	7.03	70.81	6.99	for $C_{17}H_{20}O_4$
4 n = 3	**2b** n = 3	16%	63-64	1730, 1650	260	68.99	6.24	69.21	6.20	for $C_{15}H_{16}O_4$
	3 n = 3	2%	43-44	1725, 1710	260	69.11	6.25	69.21	6.20	for $C_{15}H_{16}O_4$
4 n = 4	**2b** n = 4	6%	180-195 (1 mm Hg) [a]	1730, 1655	274	69.78	6.64	70.05	6.61	for $C_{16}H_{18}O_4$
	5 n = 4	1%	77-78	1720, 1700	274	69.80	6.78	70.05	6.61	for $C_{16}H_{18}O_4$
4 n = 5	**2b** n = 5	11%	38-39	1740, 1650	288	70.75	6.75	70.81	6.99	for $C_{17}H_{20}O_4$
	5 n = 5	2%	50-51	1730, 1710	288	70.81	6.79	70.81	6.99	for $C_{17}H_{20}O_4$
4 n = 6	**2b** n = 6	20%	213-225 (1 mm Hg) [a]	1725, 1650	302	71.43	7.20	71.50	7.33	for $C_{18}H_{22}O_4$
	5 n = 6	4%	212-238 (1 mm Hg) [a]	1700 broad	302	71.35	7.24	71.50	7.33	for $C_{18}H_{22}O_4$

[a] Boiling Point.

Table 3

Hydrolysis and Some Physical Data of the Acid Derivatives

Acid	Yield	Melting Point (°C)	ν CO (cm^{-1})	M^+ (m/z)	Elemental Analysis Found C%	Found H%	Calcd. C%	Calcd. H%	
1a n = 3	54%	148-149	1710 broad	218	66.06	4.50	66.05	4.62	for $C_{12}H_{10}O_4$
1a n = 4	90%	131-131.5	1720, 1690	232	67.00	5.20	67.23	5.21	for $C_{13}H_{12}O_4$
1a n = 5	63%	123-124	1710 broad	246	68.53	5.70	68.28	5.73	for $C_{14}H_{14}O_4$
1a n = 6	41%	121-122	1710 broad	260	69.41	6.22	69.21	6.20	for $C_{15}H_{16}O_4$
2a n = 3	22%	122-123	1735, 1630	232	67.25	5.33	67.23	5.21	for $C_{13}H_{12}O_4$
2a n = 4	75%	119-120	1725, 1630	246	67.99	5.76	68.28	5.73	for $C_{14}H_{14}O_4$
2a n = 5	54%	91-92	1720, 1630	260	69.21	6.28	69.21	6.20	for $C_{15}H_{16}O_4$
2a n = 6	42%	90-91 [a]	1720, 1630	274	65.67	6.89	65.74	6.90	for $C_{16}H_{18}O_4 \cdot H_2O$ [a]

[a] Crystals contains one mole of water.

Table 4a

DMR Data of New Coumarin Derivatives

Coumarin	Solvent	Side Methylenes α and ω	Side Methylenes others	4-R'	Aromatic Protones	R (ester)
1a n = 3	acetone-d_6	2.5-2.8	-----	7.6	7.0-7.5	
1b n = 3	CCl_4	2.5-2.8	-----	7.7	7.0-7.5	1.2 (t), 4.0 (q)
1a n = 4	acetone-d_6	2.2-2.7	1.7-2.1	7.8	6.9-7.8	
1b n = 4	CCl_4	2.2-2.8	1.7-2.2	7.5	7.2-7.6	1.2 (t), 4.0 (q)
1a n = 5	$CDCl_3$	2.3-2.9	1.6-2.0	7.7	7.4-7.8	10.1 broad s)
1b n = 5	CCl_4	2.1-2.7	1.5-1.9	7.4	7.0-7.6	1.2 (t), 4.0 (q)
1a n = 6	acetone-d_6	1.9-2.7	1.4-1.8	7.7	7.1-7.7	
1b n = 6	CCl_4	2.1-2.7	1.2-1.8	7.6	7.3-7.7	1.2 (t), 4.1 (q)
5 n = 3	CCl_4	2.4-3.2	-----	2.5	7.4-7.9	1.3 (t), 4.2 (q)
5 n = 4	CCl_4	2.2-2.8	1.6-2.1	2.4	7.1-7.7	1.2 (t), 4.0 (q)
5 n = 5	CCl_4	2.2-2.9	1.4-1.9	2.5	7.3-8.0	1.3 (t), 4.2 (q)
5 n = 6	CCl_4	2.1-2.9	1.0-1.9	2.4	7.2-7.9	1.2 (t), 4.1 (q)

Preparation of Ethyl *o*-Formyl- and *o*-Acetylalkanedioates **3** and **4**.

To a solution of salicylaldehyde or *o*-hydroxyacetophenone (*ca.* 0.10 mole) in dry pyridine (50 ml) was added a molar equivalent of ethyl ω-chloroformylalkanoate with cooling in ice-water during 30 minutes. After the evolution of heat ceased, the reaction mixture was stirred at room temperature for an additional hour. The mixture was then treated with cold 10% hydrochloric acid and extracted with ether. The ether layer was washed with 5% aqueous sodium hydroxide solution and then with saturated aqueous sodium chloride solution and dried over anhydrous sodium sulfate. After removal of the solvent, the oily residue was distilled under reduced pressure to give pure ethyl *o*-formylphenyl alkanedioates **3** and *o*-acetylphenyl ethyl alkanedioates **4**. These results are summarized in Table 1.

Table 4b

DMR Data of New Coumarin Derivatives

Chrome	Solvent	Side Methylenes α and ω	others	3-H	Aromatic Protones 5-H	others	R (ester)
2a n = 3	$CDCl_3$	2.4-2.9	1.9-2.5	6.3	8.2	7.3-7.7	8.6-8.8 (broad)
2b n = 3	CCl_4	1.9-2.9	0.9-1.5	6.0	8.2	7.3-7.8	1.3 (t), 4.2 (q)
2a n = 4	$CDCl_3$	2.3-2.9	1.6-2.1	6.4	8.3	7.4-7.9	8.2-8.5 (broad)
2b n = 4	CCl_4	2.2-2.8	1.6-1.9	5.9	7.9	7.0-7.5	1.2 (t), 3.9 (q)
2a n = 5	$CDCl_3$	2.3-2.9	1.5-2.1	6.3	8.2	7.2-7.8	11.2 (s)
2b n = 5	CCl_4	2.1-3.0	1.4-2.1	6.2	8.3	7.4-8.0	1.3 (t), 4.2 (q)
2a n = 6	$CDCl_3$	2.2-2.8	1.3-2.0	6.2	8.2	7.3-7.7	6.0-6.6 (broad)
2b n = 6	CCl_4	2.1-2.8	1.3-2.0	6.2	8.3	7.4-7.9	1.3 (t), 4.1 (q)

Cyclization of **3** and **4**.

To a solution of **3** or **4** (*ca.* 20 mmoles) in dry toluene (10 ml), DBU (16 mmoles) was added, and the mixture was refluxed for 4 hours. After cooling, the mixture was treated with cold 10% hydrochloric acid and extracted with ether. The ether layer was washed with 5% aqueous sodium hydroxide solution and then with saturated sodium chloride solution and dried over anhydrous sodium sulfate. After removal of the solvent, the residue from **3** was purified by distillation or/and recrystallization from cyclohexane to give pure ethyl ω-(3-coumarinyl)alkanoates **1b**. The residue from **4** was chromatographed on a silica-gel column, and the fractions when eluted with benzene gave ethyl ω-(4-methyl-3-coumarinyl)alkanoates **5** and the fractions eluted with chloroform gave ethyl ω-(4-chromenon-2-yl)alkanoates **2b**. They were purified by distillation or recrystallization from cyclohexane and their data are summarized in Table 2.

Hydrolysis of Coumarin Esters **1b** Chromone Esters **2b**.

Hydrolysis of coumarin ester **1b** was successful by refluxing in a 5% aqueous sodium hydroxide solution for 1 hour. After cooling, the mixture washed with ether and acidified with concentrated hydrochloric acid to give the coumarin carboxylic acids **1b**, which were recrystallized from benzene. Hydrolysis of chromone esters **2b** was successful by refluxing in 20% dilute sulfuric acid for 8 hours. After the reaction, the mixture was diluted with water and the precipitate was recrystallized from benzene to give the corresponding chromone acids **2a**. These results are summarized in Table 3.

REFERENCES AND NOTES

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

[2] Alkaline hydrolysis might cause the ring-opening of the chromone ring.