Some Fatty Acids Having an *O*-Heterocycle in their Terminal Positions. IV. (2-Methyl-2*H*-chromen-2-yl)acetic Acids

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(2-Methyl-2*H*-chromen-2-yl)acetic acid **2a** was prepared by condensations of salicylaldehyde with diethyl isopropylidenemalonate followed by hydrolyses. Similarly three methoxy derivatives **2c**, **2d**, and **2e** were also prepared from the corresponding salicylaldehyde.

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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*-heterocycle in their terminal positions to test their antimicrobial activities. We have synthesized some ω-(3-chromonyl)alkanoic acids [1], ω-(3-coumarinyl)alkanoic acids [2], and ω-(2-benzofuranyl)alkanoic acids [3]. In our previous paper [4], we reported a new one-step preparation of ethyl (2-methyl-2*H*-chromen-2-yl)acetate **1a**. In this paper, we report the syntheses of some (2-methyl-2-chromen-2-yl)acetic acids.

Three methoxy derivatives **1c**, **1d**, and **1e** of ethyl (2-methyl-2*H*-chromen-2-yl)acetate **1a** were prepared by similar condensations of the corresponding methoxysalicylaldehydes with diethyl isopropylidenemalonate. Small amounts of non-cyclized products were also obtained in the reactions and their structures were determined by comparing their spectra with that of **3a** and **4a** in our previous paper [4]. These data are summarized in Tables 1-3. But 3-methoxysalicylaldehyde did not afford any cyclized product. These cyclizations, we thought, were probably derived from double nucleophilic attacks, the attack of the carbanion at the C=O double bond of salicylaldehyde and the attack of phenoxide ion at the conjugated C=C dou-

Table 1

Preparations and Hydrolyses of Ethyl (2-Methyl-2*H*-chromen-2-yl)acetates

Starting Salicyladehyde	Chrome	Non-Cyclized Products	Hydrolyses
Salicylaldehyde	**1a** (35%)	**3a** + **4a** (2:1) (16%) **5a** (9%) **6a** (3%)	**2a** (75%)
3-Methoxysalicylaldehyde	-------	**3b** + **4b** (3:1) (1%)	-------
4-Methoxysalicylaldehyde	**1c** (22%)	**5c** (2%)	**2c** (65%)
5-Methoxysalicylaldehyde	**1d** (31%)	**5d** (2%)	**2d** (65%)
6-Methoxysalicylaldehyde	**1e** (42%)	-----	**2e** (67%)

Table 2

Some Physical Data and Elemental Analyses of New Compounds

Compound	Boiling Point (C°)	IR (cm^{-1})	Mass M+ (m/z)	Elemental Analyses Found C(%)	Found H(%)	Cald. C(%)	Cald. H(%)	
1c	150-160 (5 mm Hg)	1720	262	68.80	6.96	68.68	6.92	for $C_{15}H_{18}O_4$
1d	ca 172 (5 mm Hg) [a]	1740	262	68.96	7.09	68.68	6.92	for $C_{15}H_{18}O_4$
1e	220-230 (5 mm Hg)	1720	262	68.57	7.09	68.68	6.92	for $C_{15}H_{18}O_4$
2a	69.5-70.5 [b]	1690	204	70.63	6.16	70.57	5.92	for $C_{12}H_{12}O_3$
2c	---------- [c]	1700	234	---------- [c]				
2d	---------- [c]	1700	234	---------- [c]				
2e	---------- [c]	1700	--- [d]	---------- [c]				
5c	209-211 [b]	1640	192	66.53	6.18	66.65	6.02	for $C_{13}H_{14}O_4$
5d	180-183 [b]	1640	192	66.74	6.15	66.65	6.02	for $C_{13}H_{14}O_4$

[a] Bath temperature. [b] Melting point. [c] Oily acids caused decarboxylation on distillation, and furthermore **2e** showed only the decarboxylated ion peak in its mass spectrum.

Table 3

PMR Spectral Data of New Chromenes, δ/ppm (J/Hz)

Compound	2-Me	2-CH_2	3-H	4-H	Ar-H	Ar-OMe	Others
1a [a]	1.5 (s)	2.6 (d, 15) 2.7 (d, 15)	5.7 (d, 10)	6.3 (d, 10)	6.5-7.3 (m)	-----	1.2 (t, 7) 4.1 (q, 7)
1c	1.5 (s)	2.6 (d, 14) 2.7 (d, 14)	5.6 (d, 10)	6.8 (d, 10)	6.2-6.4 (m)	3.8 (s)	1.2 (t, 7) 4.1 (q, 7)
1d	1.5 (s)	2.6 (d, 14) 2.8 (d, 14)	5.7 (d, 10)	6.2 (d, 10)	6.5-6.6 (m)	3.7 (s)	1.2 (t, 7) 4.1 (q, 7)
1e	1.5 (s)	2.6 (d, 14) 2.8 (d, 14)	5.6 (d, 10)	6.6 (d, 10)	6.2-7.1 (m)	3.8 (s)	1.2 (t, 7) 4.0 (q, 7)
2a	1.6 (m)	2.8 (s)	5.7 (d, 10)	6.3 (d, 10)	6.6-7.2 (m)	-----	9.8 (br s)
2c	1.5 (s)	2.8 (s)	5.6 (d, 10)	6.9 (d, 10)	6.3-6.6 (m)	3.8 (s)	8.9 (br s)
2d	1.5 (s)	2.7 (s)	5.7 (d, 10)	6.3 (d, 10)	6.5-6.7 (m)	3.7 (s)	8.2 (br s)
2e	1.5 (s)	2.7 (s)	5.7 (d, 10)	6.6 (d, 10)	6.2-7.2 (m)	3.8 (s)	8.6 (br s)

[a] Already reported in our previous paper [4].

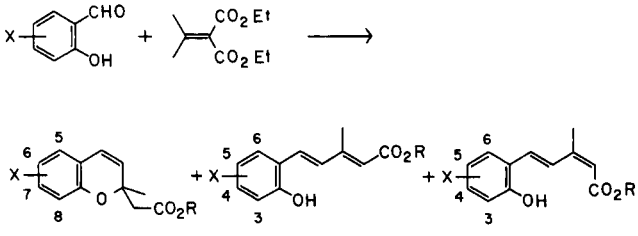
Table 4

PMR Spectral Data of Non-Cylized Products, δ/ppm (J/Hz)

Compound	Solvent	α-H	β-Me	γ-H	δ-H	Ar-H	Ar-OH or Ar-OMe	Others
3a [a]	CCl_4	5.8 (s)	2.4 (s)	6.8 (s)		6.5-7.5 (m)	------	1.3 (t, 7) 4.2 (q, 7)
4a [a]	DMSO-d_6	5.9 (s)	2.3 (s)	6.8 (s)		6.7-7.6 (m)	9.8 (br s)	11.9 (br s)
3b [b]	$CDCl_3$	5.8 (s)	2.2 (s)	7.3 (d, 16)	6.9 (d, 16)	6.8-75(m)	3.9 (s)	1.4 (t, 7) 4.3 (q, 7)
4b [b]		6.0 (s)	2.5 (s)	8.6 (d, 16)	6.9 (d, 16)			
5c	DMSO-d_6	5.9 (s)	2.3 (s)	7.1 (d, 16)	7.0 (d, 16)	6.7-7.5 (m)	3.7 (s)	10.0 (br s)
5d	DMSO-d_6	5.9 (s)	2.3 (s)	7.1 (d, 16)	7.0 (d, 16)	6.7-6.8 (m)	3.7 (s)	

[a] Already reported in our previous paper [4]. [b] Data obtained from a sample mixture.

ble bond. In 3-methoxysalicylaldehyde, after the first nucleophilic attack the hydrogen bonding between the phenolic hydroxy and methoxy groups might prevent the second nucleophilic attack. These three esters **1c**, **1d**, and **1e** were readily hydrolyzed to the corresponding acids **2c**, **2d**, and **2e** by refluxing with 30% potassium hydroxide solution, and these data are also summarized in Table 1.



1 R = Et 3 R = Et 4 R = Et

2 R = H 5 R = H 6 R = H

a) X = H

b) X = 8-MeO (in 1 or 2), 3-MeO (in 3-6)

c) 7-MeO (in 1 or 2), 4-MeO (in 3-6)

d) 6-MeO (in 1 or 2), 5-MeO (in 3-6)

e) 5-MeO (in 1 or 2), 6-MeO (in 3-6)

In the pmr spectra of these chromenes (Table 3), two protons of the methylene exhibited non-equivalent AB type signals in the esters, but showed equivalent A_2 signals in the acids. The ethoxycarbonyl group might be too bulky to rotate freely and the carboxyl group might be small enough to rotate freely.

EXPERIMENTAL

All melting points were measured on a micro melting point apparatus (Yanagimoto), and the melting points and the boiling points are uncorrected. The ir spectra were taken on a Hitachi 260-50 spectrophotometer as liquid films or as potassium bromide disks. Mass spectra were recorded on a JEOL JMS-OISG-2 spectrometer. Some physical data and elemental analysis data of the new compounds are summarized in Table 2. The pmr spectra were recorded on a JEOL PMX-60Si spectrometer, and the data of the new compounds are listed in Tables 3 and 4.

General Procedure for Condensations of Salicylaldehydes with Diethyl Isopropylidenemalonate.

A mixture of salicylaldehyde (*ca.* 10 mmoles), diethyl isopropylidenemalonate (*ca.* 10 mmoles), anhydrous potassium carbonate (4.0 g), and DMF (100 ml) was heated at 130° for 8 hours. After removing the solvent *in vacuo*, the mixture was diluted with water, acidified with 10% hydrochloric acid, and extracted with

ether. The ether solution was washed with a 5% sodium hydroxide solution and a saturated sodium chloride solution, and then dried over anhydrous sodium sulfate. After removing the ether, the residual oil was chromatographed on a silica-gel column. Oily chromenes **1a**, **1c**, **1d**, and **1e** were obtained as the fractions eluted with benzene. These data are summarized in Tables 1, 2 and 3. The alkaline washings were acidified with 10% hydrochloric acid and extracted with ether. After removing the ether, the crystalline residue was recrystallized from ethyl acetate to give pure acids **5a**, **6a**, **5c**, and **5d**, and the oily residue was chromatographed on silica-gel to give a mixture of **3a** and **4a**, **3b** and **4b** as the fractions eluted with benzene. Thus the geometrical isomers could not be isolated, and the ratios were determined from the pmr signal ratios. These data are also summarized in Tables 1, 2 and 4.

Hydrolyses of Ethyl (2-Methyl-2*H*-chromen-2-yl)acetates **1a**, **1c**, **1d**, and **1e** to the Corresponding Acids **2a**, **2c**, **2d**, and **2e**.

A solution of an ethyl (2-methyl-2*H*-chromenyl)acetate (2 mmoles) in ethanol (20 ml) was mixed with a 30% aqueous potassium hydroxide solution (5 ml) and refluxed for 2 hours. After removing the ethanol under reduced pressure, the residual cooled solution was carefully acidified with 10% hydrochloric acid and then extracted with ether. The ether solution was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. After removing the ether, the residual oil was chromatogramed on a silica-gel column to give pure **2a** as crystals (recrystallized from hexane) and **2c**, **2d**, and **2e** as oils. The distillations of the acids **2a**, **2c**, **2d**, and **2e** caused thermal decarboxylation to give the corresponding methoxy-2,2-dimethyl-2*H*-chromenes [5].

REFERENCES AND NOTES

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