Chem. Pharm. Bull.
30(2) 552—558 (1982)

Reaction of 4-Haloacetoacetate with Phenols in the Presence of Aluminum Chloride

HITOSHI KIMURA, HIROTOSHI SATO, CHIZUKO TSUCHIYA, TAKUO CHIBA, and TETSUZO KATO*

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

(Received July 13, 1981)

Reaction of ethyl 4-bromoacetoacetate (**1**) with phenol in the presence of aluminum chloride gave ethyl 4-bromo-3-hydroxy-3-(2-hydroxyphenyl)butyrate (**3a**), which can be regarded as an intermediate of the Pechmann reaction. Similar reaction of ethyl 4-chloroacetoacetate (**7**) with phenol in the presence of aluminum chloride gave the 4-chloro derivative **8a.**

Compound **3a** was treated with either hydrogen chloride in ethanol or triethylamine followed by treatment with *p*-toluenesulfonic acid to give 4-bromomethylcoumarin (**4a**) or ethyl 3-benzo[*b*]furanacetate (**6a**), respectively.

Similarly, reactions of phenol derivatives **2** with **1** gave the corresponding 3-hydroxybutyrates **3**, which were transformed to the coumarins **4** and the 3-benzo[*b*]furanacetates **6**.

Keywords——Pechmann reaction; ethyl 4-haloacetoacetate; phenols; ethyl 3-hydroxy-3-phenylbutyrates; 4-halomethylcoumarins; ethyl 3-benzo[*b*]furanacetates; mechanism of Pechmann reaction

Previously, we have reported that treatment of ethyl 4-bromoacetoacetate (**1**) in benzene under the conditions of the Friedel–Crafts reaction gave a number of products, from which 3,4-diphenylbutyric acid was isolated.[1] This result indicates that the carbonyl carbon at the 3-position of the ester **1** adds to benzene as an electrophile, accompanied by the Friedel–Crafts reaction of the 4-bromocarbon with benzene. On the other hand, the reaction of β-ketoesters such as ethyl acetoacetate with phenol is well documented as the Pechmann reaction[2] and gives coumarin derivatives such as 4-methylcoumarin.[3,4] Dey *et al.*[5] and Seshadri *et al.*[6] reported the reaction of **1** with *m*-cresol and resorcinol to give the corresponding 4-bromomethylcomarins.

We now report that the reaction of **1** with phenol (**2a**) in the presence of aluminum chloride gave an adduct **3a** which can be regarded as an intermediate in the Pechmann reaction.

When ethyl 4-bromoacetoacetate (**1**) was allowed to react with phenol (**2a**) in nitrobenzene in the presence of aluminum chloride at 60°C, ethyl 4-bromo-3-hydroxy-3-(2-hydroxyphenyl)-

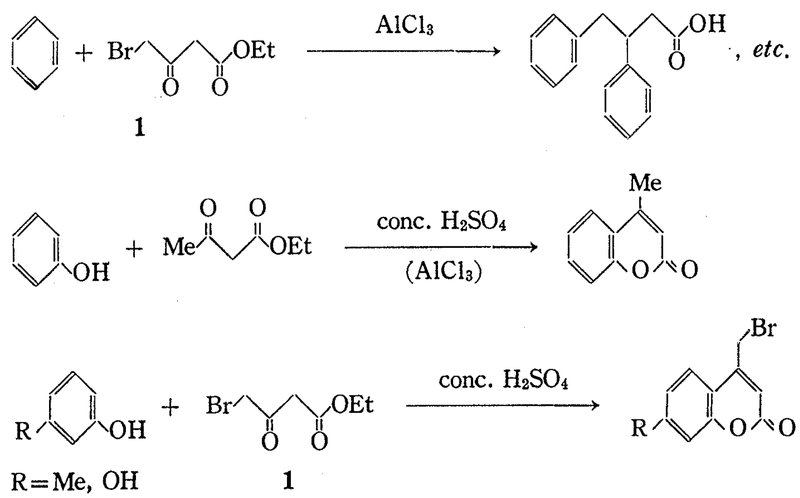


Chart 1

butyrate (**3a**) was obtained in 71% yield. As detailed in the experimental section, elemental analyses and spectroscopic data were consistent with this structure.

Treatment of compound **3a** with hydrogen chloride in ethanol afforded 4-bromomethylcoumarin (**4a**) in 91% yield. Treatment of **3a** with triethylamine in benzene gave ethyl 2,3-dihydro-3-hydroxybenzo[*b*]furan-3-acetate (**5a**) in 96% yield. This product was dehydrated, on heating in benzene in the presence of *p*-toluenesulfonic acid, to give ethyl 3-benzo[*b*]furanacetate (**6a**) in 97% yield. These chemical properties are also consistent with the structure **3a**.

Similar reaction of ethyl 4-chloroacetoacetate (**7**) with phenol (**2a**) in the presence of aluminum chloride gave a 42% yield of ethyl 4-chloro-3-hydroxy-3-(2-hydroxyphenyl)butyrate (**8a**), which was transformed to 4-chloromethylcoumarin (**9a**) and **6a** in 82 and 88% yields, respectively.

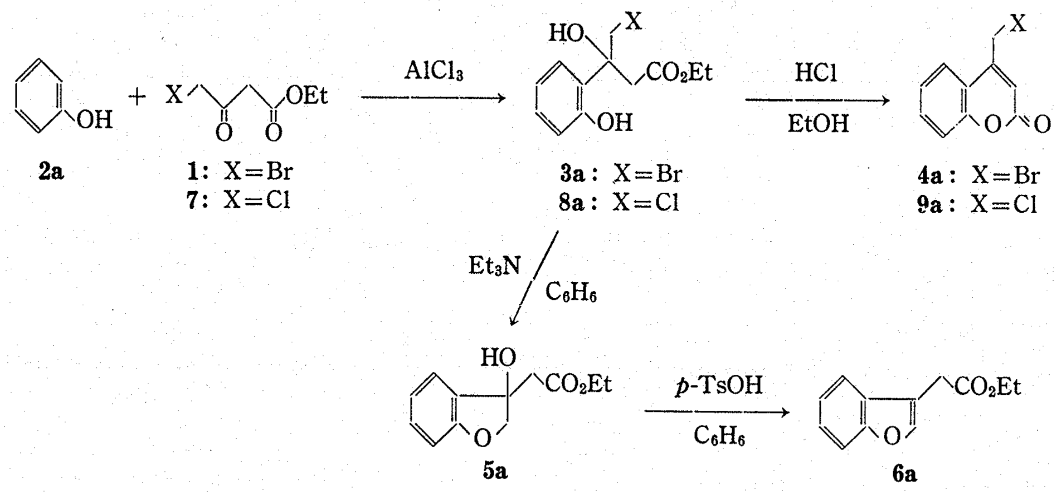
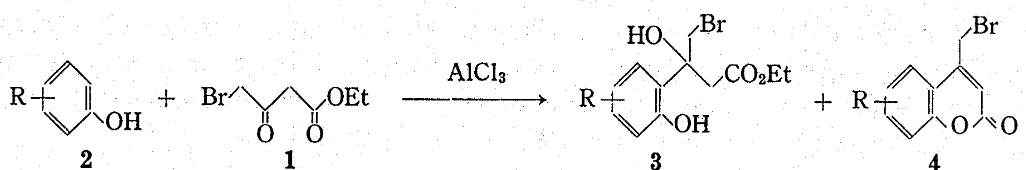


Chart 2

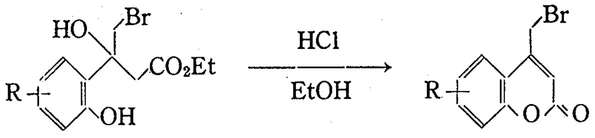
Similarly, reactions of phenol derivatives such as cresols (**2b**, **c**, **d**), methoxyphenols (**2e**, **f**, **g**), and chlorophenols (**2h**, **i**, **j**) with **1** were carried out. Of these, the reactions of **1** with *o*- and *m*-methoxyphenol (**2e** and **2f**) and *o*-chlorophenol (**2h**) did not give the hydroxybutyrates corresponding to **3a**. The results are summarized in Table I.

TABLE I.



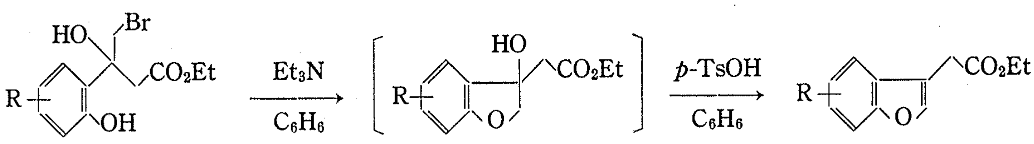
R–C_6H_4–OH		Temp. (°C)	Time (h)	Yield (%)	
2,	R			3,	4
a	H	60	3	71	—
b	*o*-Me	20	20	34	—
c	*m*-Me	60	3	—	36
		20	7	63	5
d	*p*-Me	40	20	61	6
e	*o*-MeO	60	72	—	—
f	*m*-MeO	20	3	—	51
g	*p*-MeO	60	20	36	6
h	*o*-Cl	60	72	—	—
i	*m*-Cl	60	24	41	6
j	*p*-Cl	60	72	27	7

Table II.



4	R	Yield (%)	mp (°C)
a	H	91	178
b	8-Me	86	163—164
c	7-Me	94	233 (dec.)
d	6-Me	82	178—179
g	6-MeO	86	171—172
i	7-Cl	87	217—218
j	6-Cl	80	177—178

Table III.



6	R	Yield (%)	bp (°C/mmHg) or mp (°C)
a	H	93	73/0.07
b	7-Me	87	118/1
c	6-Me	92	113/1
d	5-Me	89	110/1
g	5-MeO	85	115/1
i	6-Cl	95	120/1
j	5-Cl	93	35—36

The 3-hydroxybutyrates **3** thus obtained were cyclized with hydrogen chloride in ethanol to give the corresponding coumarins **4**, whereas treatment of **3** with triethylamine in benzene followed by treatment with *p*-toluenesulfonic acid gave the corresponding 3-benzo[*b*]furan-acetates **6**. These results are summarized in Tables II and III.

Several views have been reported regarding the mechanism of the Pechmann synthesis of coumarins from phenols and *β*-ketoesters.[2] For instance, Pechmann and Duisberg[3] suggested that the 3-hydroxy-3-(2-hydroxyphenyl)butyrate **A** is an intermediate, while Robertson *et al.*[7] speculated that the cinnamate **B** might be formed as an intermediate. Another intermediate, phenyl acetoacetate **C** was also proposed.[8] However, these intermediates **A**, **B**, and **C** could not be isolated under the reported conditions of the Pechmann reaction. Therefore, it may be concluded from the results of our investigation that the 3-hydroxy-3-(2-hydroxyphenyl)butyrate **A** is probably the real intermediate in the Pechmann reaction.

Since the addition of ethyl 4-bromoacetoacetate (**1**) always occurs at the *ortho* positions of phenols, the pathway of the formation of **3a** from phenol and **1** may be as shown in Chart 3. Namely, co-ordination of aluminum chloride with phenol gives phenoxyaluminum dichloride (**D**), which reacts with **1** *via* a *quasi* six-membered concerted mechanism followed by hydrolysis to give **3a**.

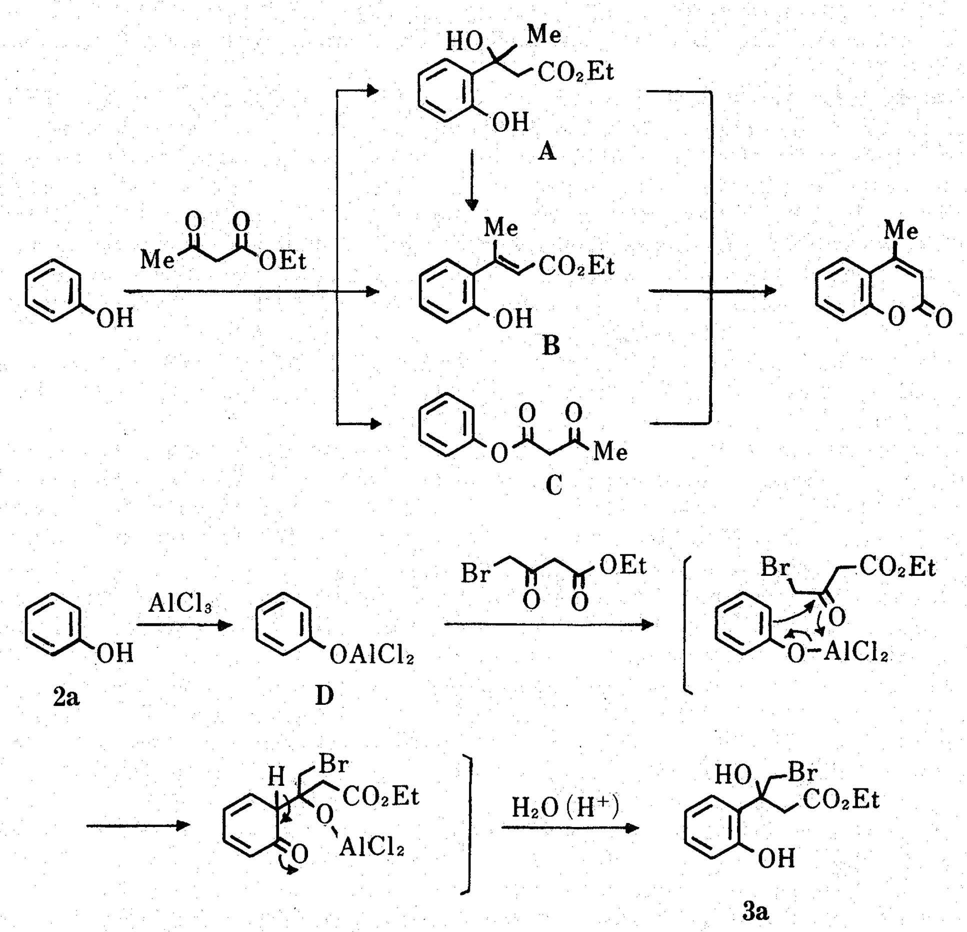


Chart 3

Experimental

Melting points and boiling points are uncorrected. Infrared (IR) spectra were taken on a JASCO IR-S spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on JEOL JNM-PMX60 and Hitachi R-20 instruments using tetramethylsilane or 3-(trimethylsilyl)propanesulfonic acid sodium salt as an internal standard.

Ethyl 4-Bromo-3-hydroxy-3-(2-hydroxyphenyl)butyrate (3a)——A solution of ethyl 4-bromoacetoacetate (**1**) (2.1 g, 0.01 mol) in dry nitrobenzene (8 ml) was added dropwise to a mixture of anhydrous aluminum chloride (6.7 g, 0.05 mol) and phenol (**2a**) (4.7 g, 0.05 mol) in dry nitrobenzene (12 ml) with stirring at 60°C. After being stirred at 60°C for 3 h, the reaction mixture was poured into a mixture of concentrated hydrochloric acid (20 ml) and ice (50 g). The mixture was extracted with ether (50 ml $\times$ 3), and the ether layer was dried over sodium sulfate. After removal of the ether by evaporation, the oily residue was distilled under reduced pressure (at 0.3 mmHg) to remove nitrobenzene and phenol. The resulting residue was subjected to silica gel (60 g) column chromatography using chloroform as an eluent to afford the product **3a** as a pale purple oil. Yield, 2.15 g (71%). *Anal.* Calcd for $C_{12}H_{15}BrO_4$: C, 47.54; H, 4.99; Br, 26.36. Found: C, 47.42; H, 4.98; Br, 26.49. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3360, 1710. ^{1}H-NMR ($CDCl_3$) δ: 1.20 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 3.20 (2H, s, CH_2CO), 3.58, 3.86 (2H, ABq, J=11 Hz, CH_2Br), 4.15 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 5.87 (1H, s, OH), 6.60—7.40 (4H, m, Ar–H), 8.85 (1H, s, OH).

4-Bromomethylcoumarin (4a)——A solution of **3a** (0.31 g, 1 mmol) in absolute ethanol (20 ml) saturated with dry hydrogen chloride was stirred at room temperature for 24 h. After the solvent had been removed *in vacuo*, the residue was recrystallized from ether to give the product **4a** as colorless needles, mp 177—178°C (lit.[9] mp 176°C). Yield, 0.22 g (91%).

Ethyl 2,3-Dihydro-3-hydroxybenzo[*b*]furan-3-acetate (5a)——A mixture of **3a** (0.31 g, 1 mmol) and triethylamine (0.2 g, 2 mmol) in benzene (10 ml) was stirred at room temperature for 4 h. The precipitates were filtered off, and the filtrate was concentrated under reduced pressure. The residual oil was purified by silica gel column chromatography using benzene as an eluent to afford the product **5a** as a colorless oil. Yield, 0.21 g (96%). *Anal.* Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 65.02; H, 6.54. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3560, 1720. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.82, 3.08 (2H, ABq, J=16 Hz, CH_2CO), 3.50—3.75 (1H, br, OH), 4.21 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 4.44, 4.56 (2H, ABq, J=11 Hz, 2-H $\times$ 2), 6.75—7.45 (4H, m, Ar–H). Similarly, reaction of **8a** (0.26 g, 1 mmol) with triethylamine (0.2 g, 2 mmol) gave **5a**. Yield, 0.20 g (91%).

Ethyl 3-Benzo[*b*]furanacetate (6a)——A mixture of **5a** (0.21 g, 0.96 mmol) and *p*-toluenesulfonic acid (0.1 g) in benzene (20 ml) was refluxed for 3 h. The reaction mixture was washed with 2% sodium bicarbonate solution and then with saturated sodium chloride solution. The benzene layer was dried over sodium sulfate and concentrated *in vacuo*. The residual oil was distilled under reduced pressure to give the product **6a** as a colorless oil, bp 73°C (0.07 mmHg) (lit.[10] bp 140—145°C (12 mmHg)). Yield, 0.19 g (97%).

Ethyl 4-Chloro-3-hydroxy-3-(2-hydroxyphenyl)butyrate (8a)——Following a procedure similar to that given for compound **3a**, ethyl 4-chloroacetoacetate (**7**) (3.3 g, 0.02 mol) was allowed to react with phenol (**2a**) (9.4 g, 0.10 mol) in the presence of anhydrous aluminum chloride (13.4 g, 0.10 mol) to afford the product **8a** as a pale yellow oil. Yield, 2.20 g (42%). *Anal.* Calcd for $C_{12}H_{15}ClO_4$: C, 55.71; H, 5.84; Cl, 13.70. Found: C, 55.57; H, 5.89; Cl, 13.57. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3320, 1705. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 3.13 (2H, s, CH_2CO), 3.71, 3.87 (2H, ABq, J=12 Hz, CH_2Cl), 4.08 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 5.70 (1H, s, OH), 6.60—7.33 (4H, m, Ar–H), 8.76 (1H, s, OH).

4-Chloromethylcoumarin (9a)[11]——In the manner described for **4a**, **8a** (0.26 g, 1 mmol) was treated with dry hydrogen chloride in absolute ethanol to give the product **9a** as colorless needles (recrystallized from benzene), mp 144—145°C. Yield, 1.60 g (82%). *Anal.* Calcd for $C_{10}H_7ClO_2$: C, 61.72; H, 3.63; Cl, 18.22. Found: C, 61.84; H, 3.71; Cl, 18.25. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725, 1610. ^{1}H-NMR ($CDCl_3$) δ: 4.70 (2H, s, CH_2Cl), 6.61 (1H, s, 3-H), 7.32—7.84 (4H, m, Ar–H).

Reaction of 1 with *o*-Cresol (2b)——As described for **3a**, a mixture of **1** (2.1 g, 0.01 mol), **2b** (5.4 g, 0.05 mol), and anhydrous aluminum chloride (6.7 g, 0.05 mol) in dry nitrobenzene (20 ml) was stirred at 20°C for 20 h. After removal of ether, nitrobenzene, and **2b**, the residue was subjected to silica gel column chromatography using *n*-hexane–benzene (1: 2) as an eluent to afford ethyl 4-bromo-3-hydroxy-3-(2-hydroxy-3-methylphenyl)butyrate (**3b**) as a colorless oil. Yield, 1.10 g (34%). *Anal.* Calcd for $C_{13}H_{17}BrO_4$: C, 49.23; H, 5.40. Found: C, 49.10; H, 5.26. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3340, 1705. ^{1}H-NMR ($CDCl_3$) δ: 1.20 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.24 (3H, s, CH_3), 3.17 (2H, s, CH_2CO), 3.53, 3.81 (2H, ABq, J=11 Hz, CH_2Br), 4.13 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 5.88 (1H, s, OH), 6.50—7.30 (3H, m, Ar–H), 9.03 (1H, s, OH).

Reaction of 1 with *m*-Cresol (2c)——a) A mixture of **1** (2.1 g, 0.01 mol), **2c** (5.4 g, 0.05 mol), and anhydrous aluminum chloride (6.7 g, 0.05 mol) in dry nitrobenzene (20 ml) was stirred at 60°C for 3 h. The reaction mixture was poured into a mixture of concentrated hydrochloric acid and ice. Ether was added to this mixture with stirring, and the crystals that separated were collected and recrystallized from benzene to give 4-bromomethyl-7-methylcoumarin (**4c**) as colorless plates, mp 233°C (dec.) (lit.[9] mp 236°C (dec.)), 0.85 g. The ether-soluble fraction was concentrated and the oily residue was distilled *in vacuo* to remove nitrobenzene and **2c**. The resulting residue was recrystallized from benzene to give **4c**, 0.05 g. Total yield, 0.90 g (36%).

b) In the manner described for **3a**, a mixture of **1** (2.1 g, 0.01 mol), **2c** (5.4 g, 0.05 mol), and anhydrous aluminum chloride (6.7 g, 0.05 mol) in dry nitrobenzene (20 ml) was stirred at 20°C for 7 h. After removal of ether, nitrobenzene, and **2c**, ether was added to the residue. The ether-insoluble material was collected and recrystallized from benzene to give **4c**. Yield, 0.12 g (5%). The ether solution was concentrated and the residue was recrystallized from cyclohexane to give ethyl 4-bromo-3-hydroxy-3-(2-hydroxy-4-methylphenyl)butyrate (**3c**) as colorless needles, mp 101—102°C. Yield, 2.00 g (63%). *Anal.* Calcd for $C_{13}H_{17}BrO_4$: C, 49.23; H, 5.40. Found: C, 48.86; H, 5.65. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3340, 1705. ^{1}H-NMR ($CDCl_3$) δ: 1.18 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.24 (3H, s, CH_3), 3.15 (2H, s, CH_2CO), 3.50, 3.80 (2H, ABq, J=11 Hz, CH_2Br), 4.12 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 5.76 (1H, s, OH), 6.46—6.95 (3H, m, Ar–H), 8.70 (1H, s, OH).

Reaction of 1 with *p*-Cresol (2d)——As described for **3a**, a mixture of **1** (2.1 g, 0.01 mol), **2d** (5.4 g, 0.05 mol), and anhydrous aluminum chloride (6.7 g, 0.05 mol) in dry nitrobenzene (20 ml) was stirred at 40°C for 20 h. After removal of ether, nitrobenzene, and **2d**, the residue was subjected to silica gel column chromatography. Elution with *n*-hexane–ethyl acetate (19: 1) gave ethyl 4-bromo-3-hydroxy-3-(2-hydroxy-5-methylphenyl)butyrate (**3d**) as a colorless oil. Yield, 1.95 g (61%). *Anal.* Calcd for $C_{13}H_{17}BrO_4$: C, 49.23; H, 5.40. Found: C, 48.84; H, 5.48. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3340, 1705. ^{1}H-NMR ($CDCl_3$) δ: 1.10 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.13 (3H, s, CH_3), 3.16 (2H, s, CH_2CO), 3.49, 3.75 (2H, ABq, J=11 Hz, CH_2Br), 4.08 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 5.66 (1H, s, OH), 6.60—7.05 (3H, m, Ar–H), 8.50 (1H, s, OH). Subsequent elution with *n*-hexane–ethyl acetate (19: 1) gave 4-bromomethyl-6-methylcoumarin (**4d**) as colorless needles (recrystallized from cyclohexane), mp 178—179°C (lit.[9] mp 177°C). Yield, 0.15 g (6%).

Reaction of 1 with *m*-Methoxyphenol (2f)——A mixture of **1** (2.1 g, 0.01 mol), **2f** (6.2 g, 0.05 mol), and anhydrous aluminum chloride (6.7 g, 0.05 mol) in dry nitrobenzene (20 ml) was stirred at 20°C for 3 h. The reaction mixture was poured into a mixture of concentrated hydrochloric acid and ice. Ether was added to this mixture with stirring, and the crystals that separated were collected and recrystallized from benzene to give 4-bromomethyl-7-methoxycoumarin (**4f**) as colorless needles, mp 208°C (dec.) (lit.[9] mp 204°C), 1.15 g. The ether-soluble fraction was concentrated and the oily residue was distilled *in vacuo* to remove nitrobenzene and **2f**. The residue was subjected to silica gel column chromatography using benzene as an eluent to afford **4f**, 0.21 g, Total yield, 1.36 g (51%).

Reaction of 1 with *p*-Methoxyphenol (2g)——In the manner described for **3a**, a mixture of **1** (2.1 g, 0.01

mol), **2g** (6.2 g, 0.05 mol), and anhydrous aluminum chloride (6.7 g, 0.05 mol) in dry nitrobenzene (20 ml) was stirred at 60°C for 20 h. After removal of ether, nitrobenzene, and **2g**, the residue was subjected to silica gel column chromatography. Elution with *n*-hexane–benzene (1: 2) gave ethyl 4-bromo-3-hydroxy-3-(2-hydroxy-5-methoxyphenyl)butyrate (**3g**) as a pale yellow oil. Yield, 1.20 g (36%). *Anal.* Calcd for $C_{13}H_{17}BrO_5$: C, 46.86; H, 5.14. Found: C, 46.66; H, 4.85. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3360, 1710. ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 3.18 (2H, s, CH_2CO), 3.72 (3H, s, OCH_3), 3.59, 3.83 (2H, ABq, J=11 Hz, CH_2Br), 4.18 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 5.74 (1H, s, OH), 6.53—6.83 (3H, m, Ar–H), 8.24 (1H, s, OH). Elution was continued with benzene to give 4-bromomethyl-6-methoxycoumarin (**4g**) as colorless needles, mp 171—172°C. Yield, 0.16 g (6%). *Anal.* Calcd for $C_{11}H_9BrO_3$: C, 49.09; H, 3.37; Br, 29.69. Found: C, 49.07; H, 3.41; Br, 29.47. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1580. ^{1}H-NMR ($CDCl_3$) δ: 3.87 (3H, s, OCH_3), 4.47 (2H, s, CH_2Br), 6.50 (1H, s, 3-H), 7.05—7.40 (3H, m, Ar–H).

Reaction of 1 with *m*-Chlorophenol (2i)——A mixture of **1** (2.1 g, 0.01 mol), **2i** (6.4 g, 0.05 mol), and anhydrous aluminum chloride (6.7 g, 0.05 mol) in dry nitrobenzene (20 ml) was stirred at 60°C for 24 h. The reaction mixture was poured into a mixture of concentrated hydrochloric acid and ice. Ether was added to this mixture with stirring, and the crystals that separated were collected and recrystallized from benzene to give 4-bromomethyl-7-chlorocoumarin (**4i**) as colorless needles, mp 217—218°C. Yield, 0.17 g (6%). *Anal.* Calcd for $C_{10}H_6BrClO_2$: C, 43.91; H, 2.21. Found: C, 43.99; H, 2.16. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730, 1605. ^{1}H-NMR (CF_3CO_2H) δ: 4.56 (2H, s, CH_2Br), 6.80 (1H, s, 3-H), 7.40—8.00 (3H, m, Ar–H). The ether-soluble fraction was concentrated and the oily residue was distilled *in vacuo* to remove nitrobenzene and **2i**. The residue was subjected to silica gel column chromatography using *n*-hexane–chloroform (4: 1) as an eluent to afford ethyl 4-bromo-3-(4-chloro-2-hydroxyphenyl)-3-hydroxybutyrate (**3i**) as colorless needles (recrystallized from cyclohexane), mp 103—104°C. Yield, 1.40 g (41%). *Anal.* Calcd for $C_{12}H_{14}BrClO_4$: C, 42.69; H, 4.18. Found: C, 42.92; H, 4.12. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300, 1710. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 3.15 (2H, s, CH_2CO), 3.58, 3.80 (2H, ABq, J=11 Hz, CH_2Br), 4.16 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 5.88 (1H, s, OH), 6.70—7.13 (3H, m, Ar–H), 8.98 (1H, s, OH).

Reaction of 1 with *p*-Chlorophenol (2j)——In the manner described for **3a**, a mixture of **1** (2.1 g, 0.01 mol), **2j** (6.4 g, 0.05 mol), and anhydrous aluminum chloride (6.7 g, 0.05 mol) in dry nitrobenzene (20 ml) was stirred at 60°C for 72 h. After removal of ether, nitrobenzene, and **2j**, the residue was subjected to silica gel column chromatography. Elution with *n*-hexane–ethyl acetate (19: 1) gave ethyl 4-bromo-3-(5-chloro-2-hydroxyphenyl)-3-hydroxybutyrate (**3j**) as colorless prisms (recrystallized from cyclohexane), mp 67—68°C. Yield, 0.90 g (27%). *Anal.* Calcd for $C_{12}H_{14}BrClO_4$: C, 42.69; H, 4.18. Found: C, 42.48; H, 4.21. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3340, 1705. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 3.18 (2H, s, CH_2CO), 3.59, 3.81 (2H, ABq, J=11 Hz, CH_2Br), 4.19 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 5.85 (1H, s, OH), 6.73—7.30 (3H, m, Ar–H), 8.75 (1H, s, OH). Subsequent elution with *n*-hexane–ethyl acetate (19: 1) gave 4-bromomethyl-6-chlorocoumarin (**4j**) as colorless needles (recrystallized from ethyl acetate), mp 177—178°C. Yield, 0.20 g (7%). *Anal.* Calcd for $C_{10}H_6BrClO_2$: C, 43.91; H, 2.21. Found: C, 44.03; H, 2.17. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725, 1605. ^{1}H-NMR ($CDCl_3$) δ: 4.43 (2H, s, CH_2Br), 6.53 (1H, s, 3-H), 7.16—7.75 (3H, m, Ar–H).

4-Bromomethylcoumarin Derivatives 4b-d, g, i, j: General Procedure——In the manner described for **4a**, **3** (1 mmol) was treated with dry hydrogen chloride in absolute ethanol to give the product **4**. Yields and melting points are summarized in Table II. **4b** (R=8-Me): colorless needles (recrystallized from *n*-hexane–benzene (1: 1)), *Anal.* Calcd for $C_{11}H_9BrO_2$: C, 52.20; H, 3.58; Br, 31.58. Found: C, 52.48; H, 3.55; Br, 31.45. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725, 1605. ^{1}H-NMR ($CDCl_3$) δ: 2.30 (3H, s, CH_3), 4.48 (2H, s, CH_2Br), 6.49 (1H, s, 3-H), 7.05—7.70 (3H, m, Ar–H).

TABLE IV

6	R	Formula	Analysis (%) Calcd (Found) C	H	IR $\nu_{max}^{CHCl_3}$ cm^{-1}	^{1}H-NMR ($CDCl_3$) δ
b	7-Me	$C_{13}H_{14}O_3$	71.54 (71.48	6.47 6.29)	1730	1.24 (3H, t, J=7 Hz), 2.50 (3H, s), 3.65 (2H, s), 4.16 (2H, q, J=7 Hz), 6.87—7.53 (3H, m), 7.60 (1H, s)
c	6-Me	$C_{13}H_{14}O_3$	71.54 (71.24	6.47 6.41)	1730	1.26 (3H, t, J=7 Hz), 2.46 (3H, s), 3.67 (2H, s), 4.19 (2H, q, J=7 Hz), 6.96—7.48 (3H, m), 7.55 (1H, s)
d	5-Me	$C_{13}H_{14}O_3$	71.54 (77.27	6.47 6.72)	1730	1.22 (3H, t, J=7 Hz), 2.40 (3H, s), 3.62 (2H, s), 4.16 (2H, q, J=7 Hz), 6.95—7.42 (3H, m), 7.55 (1H, s)
g	5-MeO	$C_{13}H_{14}O_4$	66.66 (66.48	6.02 6.10)	1730	1.26 (3, t, J=7 Hz), 3.64 (2H, s), 3.82 (3H, s), 4.17 (2H, q, J=7 Hz), 6.74—7.10 (2H, m), 7.33 (1H, d, J=9 Hz), 7.57 (1H, s)
i	6-Cl	$C_{12}H_{11}ClO_3$	60.39 (60.14	4.65 4.61)	1730	1.25 (3H, t, J=7 Hz), 3.65 (2H, s), 4.18 (2H, q, J=7 Hz), 7.09—7.56 (3H, m), 7.59 (1H, s)
j	5-Cl	$C_{12}H_{11}ClO_3$	60.39 (60.60	4.65 4.80)	1730	1.28 (3H, t, J=7 Hz), 3.65 (2H, s), 4.09 (2H, q, J=7 Hz), 7.20—7.56 (3H, m), 7.62 (1H, s)

Ethyl 3-Benzo[*b*]furanacetate Derivatives 6b-d, g, i, j: General Procedure——A mixture of 3 (1 mmol) and triethylamine (0.2 g, 2 mmol) in benzene (10 ml) was stirred at room temperature for 4 h. After the precipitates had been filtered off, the filtrate was concentrated under reduced pressure. *p*-Toluenesulfonic acid (0.1 g) and benzene (20 ml) were added to the residual oil **5**. After refluxing for 3 h, the reaction mixture was washed with 2% sodium bicarbonate and then with saturated sodium chloride. The benzene layer was dried and concentrated *in vacuo*. The oily residue was subjected to silica gel column chromatography using *n*-hexane–ether (9: 1) as an eluent to give the product **6**. Yields and boiling points (or melting point) are summarized in Table III. Elemental analysis, IR and ^{1}H-NMR spectral data are listed in Table IV.

Acknowledgement We are indebted to the Central Analysis Room of the Institute for elemental analyses. This research was supported in part by a Grant from the Takeda Science Foundation.

References

1) T. Kato and H. Kimura, *Chem. Lett.*, **1979**, 337.
2) S. Sethna and R. Phadke, "Organic Reactions," Vol. 7, ed. by R. Adams, John Wiley and Sons, Inc., New York, 1953, p. 1.
3) H.v. Pechmann and C. Duisberg, *Ber.*, **16**, 2119 (1883).
4) E.H. Woodruff, "Organic Syntheses," Coll. Vol. III, ed. by E.C. Horning, John Wiley and Sons, Inc., New York, 1955, p. 581.
5) B.B. Dey and Y.S. Sankarnarayan, *J. Indian Chem. Soc.*, **11**, 687 (1934).
6) T.R. Seshadri and S. Varadarajan, *J. Sci. Ind. Research* (India), **11**, 39 (1952).
7) A. Robertson, R.B. Waters, and E.T. Jones, *J. Chem. Soc.*, **1932**, 1681.
8) R.N. Lacey, *J. Chem. Soc.*, **1954**, 854.
9) B.B. Dey and K. Radhabai, *J. Indian Chem. Soc.*, **11**, 635 (1934).
10) V. Titoff, H. Müller, and T. Reichstein, *Helv. Chim. Acta*, **20**, 883 (1937).
11) P. Hardt and K.J. Boosen, Ger. Patent 2243203 (1973) [*C.A.*, **79**, 42196e (1973)].