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Studies on Antirheumatic Agents: 3-Benzoylpropionic Acid Derivatives

Kazuya Kameo,* Kunio Ogawa, Kimiyo Takeshita,
Shiro Nakaike, Kazuyuki Tomisawa
and Kaoru Sota

*Research Center, Taisho Pharmaceutical Co., Ltd.,
1-403 Yoshino-cho, Ohmiya, Saitama 330, Japan*

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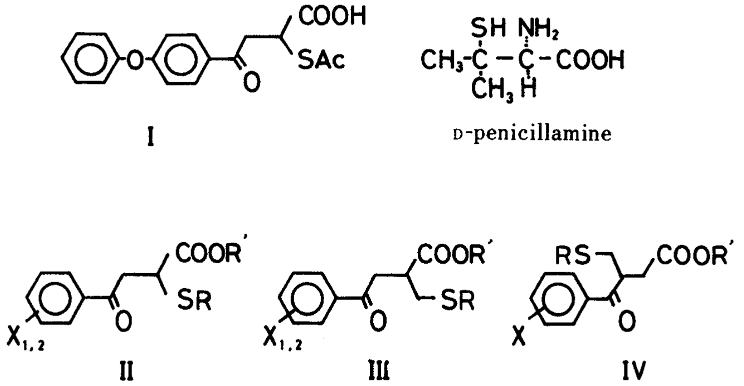
As part of the search for new antirheumatic agents, three types of 3-benzoylpropionic acid derivatives having a mercapto moiety in their structures were prepared, and tested for suppressing activity on adjuvant arthritis in Sprague-Dawley rats. A structure–activity relationship study showed that substitution on the phenyl ring contributed to the activity and the most favorable substituent was different in each type of derivative.

Keywords——3-benzoylpropionic acid; D-penicillamine; antirheumatic agent; structure–activity relationship; adjuvant arthritis

In the previous paper,[1] we reported that 2-acetylthio-3-(4-phenoxybenzoyl)propionic acid (I) (Chart 1) and its derivatives, having mercapto and carboxylic acid moieties in their structures, have potent hypolipidemic activities. In further pharmacological studies, we found that I has an immunomodulative activity and suppresses adjuvant arthritis. It is known that D-penicillamine,[2] an antirheumatic agent having mercapto and carboxylic acid moieties, also has an immunomodulative activity and suppresses adjuvant arthritis. These structural and biological similarities led us to study derivatives of I in the hope of finding new antirheumatic agents. This paper reports the synthesis and inhibitory activities against rat adjuvant arthritis of chemically modified derivatives (II—IV) (Chart 1).



I

D-penicillamine

II III IV

Chart 1

Chemistry

The 3-benzoylpropionic acid derivatives listed in Tables I—III were synthesized by the methods shown in Chart 2. 3-Benzoylacrylic acids (VII) were mostly prepared by Friedel–Crafts acylation using maleic anhydride.[3] Acetophenones (VIII) were reacted with glyoxylic acid at 95 °C and dehydrated to give acrylic acids[4] (VII). Treatment of VII with mercapto

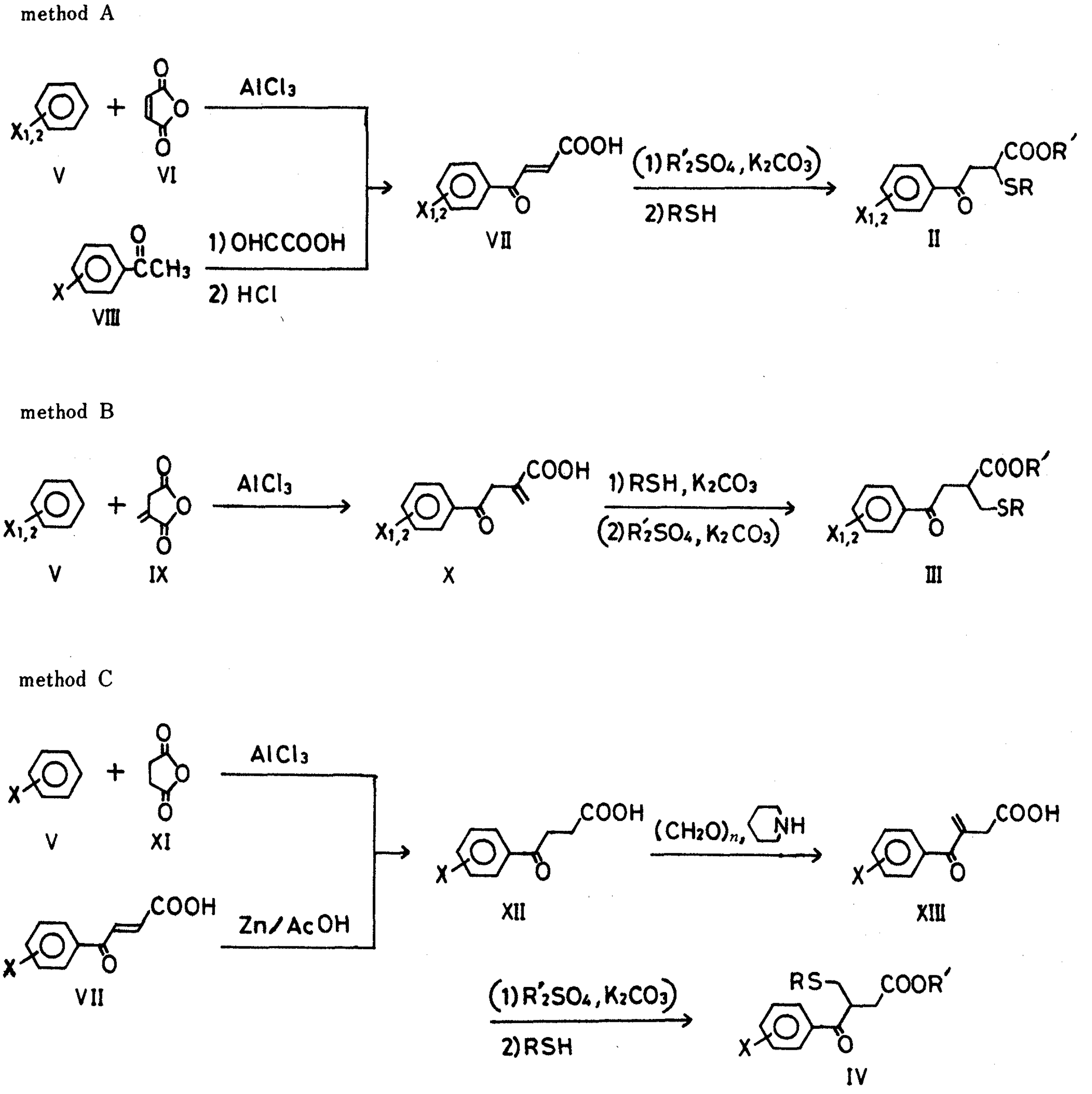


Chart 2

compounds provided 2-mercapto-3-benzoylpropionic acids (II) (method A). 2-Methylene-3-benzoylpropionic acids[5] (X), which were prepared from itaconic anhydride, were reacted with carbothioic S-acids in *N*,*N*-dimethylformamide (DMF) in the presence of 0.1 eq of aqueous potassium carbonate solution to give 2-acylthiomethyl-3-benzoylpropionic acids (III) (method B). The preparation of 3-benzoylpropionic acids (XII) was carried out by Friedel–Crafts acylation[6] or by reduction (zinc dust–acetic acid)[7] of the acrylic acids (VII). Compounds XII were reacted with paraformaldehyde in pyridine in the presence of 0.2 eq of piperidine at 50 °C to give 3-benzoyl-3-butenoic acids (XIII), which were treated with mercapto compounds to give 3-benzoyl-4-mercaptobutyric acids (IV) (method C).

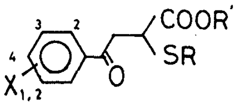
Biological Method[8]

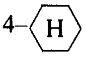
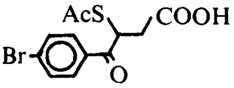
Eight-week-old female Sprague-Dawley rats (ten rats per group) were used. Rats of each group were administered subcutaneously into the tail with a suspension of 0.6 mg of thermally killed *Mycobacterium butyricum* in liquid parafin. The test compounds, which were prepared as a suspension in 5% gum arabic solution, were orally administered to the rats at a daily dose of 100 mg/kg for 20 d. A 5% gum arabic solution was orally administered to rats after sensitization in the control group. Twenty-one days later, the edema volume of the hind paw of rats in the test compound-treated groups and the control was measured for evaluating edema-suppressing activity.

Results and Discussion

The physical constants and biological data of the derivatives prepared in this work are listed in Tables I—III. As shown in Tables I—III, the suppressing activities of the ester derivatives were mostly weaker than those of the corresponding free carboxylic acids, and in comparison with acetylthio derivatives, the other mercapto derivatives did not show especially strong activities. However, substitution in the phenyl ring seemed to have a considerable influence on the activities and these influences were different in each type of derivative. As shown in Table I (2-acetylthio-3-benzoylpropionic acid derivatives), a bromo substituent (**2**—**5**) increased the activity in the following order: *para*>*meta*>*ortho*, and a chloro substituent (**6**) also increased the activity, but the introduction of the other substituents (**7**—**11**) did not increase the activity. In 2-acetylthiomethyl-3-benzoylpropionic acid derivatives, as shown in Table II, methyl substitution (**28**) strongly increased the activity and bromo substitution (**21**) also increased it, but chloro (**26**) and the other substituents (**27**, **32**—**35**) decreased the activity. In 4-acetylthio-3-benzoylbutyric acid derivatives, as shown in Table III, bromo (**42**,

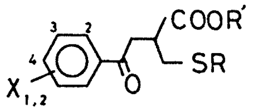
TABLE I. Physical and Biological Properties of 3-Benzoyl-2-mercaptopropionic Acid



No.	X	R	R′	mp (°C)	Recrystn.[a] solvent	Formula	Activity[b] rank
1	H	Ac	H	90—92	H–E	$C_{12}H_{12}O_4S$	1
2	4-Br	Ac	H	98—99	H–E	$C_{12}H_{11}BrO_4S$	3
3	3-Br	Ac	H	90—91	CCl_4	$C_{12}H_{11}BrO_4S$	2
4	2-Br	Ac	H	130—131	PhH	$C_{12}H_{11}BrO_4S$	1
5	3,4-Br_2	Ac	H	119—121	H–E	$C_{12}H_{10}Br_2O_4S$	3
6	4-Cl	Ac	H	68—69	H–E	$C_{12}H_{11}ClO_4S$	2
7	4-F	Ac	H	108—110	H–D	$C_{12}H_{11}FO_4S$	0
8	3-CF_3	Ac	H	96.5—97	H–E	$C_{13}H_{11}F_3O_4S$	0
9	4-Me	Ac	H	81—85	H–E	$C_{13}H_{14}O_4S$	0
10	4-	Ac	H	91—93	H–E	$C_{18}H_{22}O_4S$	1
11	4-MeO	Ac	H	122—123.5	H–E	$C_{13}H_{14}O_5S$	0
12	H	H	H	145—147	H–E	$C_{10}H_{10}O_3S$	1
13	H	Et	H	115—115.5	H–E	$C_{12}H_{14}O_3S$	1
14	4-Br	Ac	Et	Oil[c]		$C_{14}H_{15}BrO_4S$	3
15	4-Br	Et	H	114.5—115	H–E	$C_{12}H_{13}BrO_3S$	0
16	4-Br	COEt	H	133—135	H–D	$C_{13}H_{13}BrO_4S$	3
17	4-Br	COPh	H	164.5—166	H–E	$C_{17}H_{13}BrO_4S$	3
18				125.5—126	H–E	$C_{12}H_{11}BrO_4S$	0
I	4-PhO	Ac	H				2
D-Penicillamine							3

a) D=dichloromethane, E=ethyl ether, EA=ethyl acetate, H=hexane. *b*) Edema suppression rates were calculated as percentages with respect to the control value; less than 10% suppression=0, 10—25% suppression=1, 26—40% suppression=2, 41—55% suppression=3, more than 55% suppression=4. *c*) Purified by column chromatography.

Table II. Physical and Biological Properties of 3-Benzoyl-2-mercaptomethylpropionic Acid



No.	X	R	R'	mp (°C)	Recrystn.[a] solvent	Formula	Activity[b] rank
19	H	Ac	H	110—101	E–EA	$C_{13}H_{14}O_4S$	3
20	H	Ac	Et	Oil[c]		$C_{15}H_{18}O_4S$	0
21	4-Br	Ac	H	126.5—128	H–E	$C_{13}H_{13}BrO_4S$	3
22	4-Br	Ac	Me	Oil[c]		$C_{14}H_{15}BrO_4S$	0
23	4-Br	Ac	Et	Oil[c]		$C_{15}H_{17}BrO_4S$	0
24	4-Br	Ac	iso-Pr	Oil[c]		$C_{16}H_{19}BrO_4S$	0
25	4-Br	Ac	CH_2Ph	79—80	H–E	$C_{20}H_{19}BrO_4S$	1
26	4-Cl	Ac	H	109.5—110	H–E	$C_{13}H_{13}ClO_4S$	0
27	4-F	Ac	H	106.5—108	H–E	$C_{13}H_{13}FO_4S$	0
28	4-Me	Ac	H	94—95.5	H–E	$C_{14}H_{16}O_4S$	4
29	3,4-Me_2	Ac	H	111—113	H–EA	$C_{15}H_{18}O_4S$	3
30	2,4-Me_2	Ac	H	76—77.5	H–EA	$C_{15}H_{18}O_4S$	1
31	2,5-Me_2	Ac	H	60—90	H–E	$C_{15}H_{18}O_4S$	—
32	4-Et	Ac	H	76—77	H–E	$C_{15}H_{18}O_4S$	1
33	4-iso-Pr	Ac	H	78—79	H–E	$C_{16}H_{20}O_4S$	0
34	4-MeO	Ac	H	88—90	H–E	$C_{14}H_{16}O_5S$	0
35	4-PhO	Ac	H	92—93.5	H–E	$C_{19}H_{18}O_5S$	1
36	H	COEt	H	76—78	H–E	$C_{14}H_{16}O_4S$	—
37	H	COPh	H	110—111	H–E	$C_{18}H_{16}O_4S$	1
38	4-Br	COEt	H	125.5—123	H–EA	$C_{14}H_{15}BrO_4S$	0
39	4-Br	COPh	H	133—135	H–EA	$C_{18}H_{15}BrO_4S$	1

a—c) See footnotes to Table I.

43), chloro (**44**, **45**), and methyl (**48**, **50**) substitution did not increase the activity, while bromophenyl (**59**, **60**) and chlorophenyl (**61**) substitution did increased it.

Conclusion

Three types of compounds (II—IV) (Chart 1) were prepared and tested for biological activities on adjuvant arthritis. In each type of compound, some derivatives (**2**, **21**, **28**, **61**) showed strong activities. (These compounds did not have anti-inflammatory activity in the carrageenin test,[2e] and further biological study showed that these derivatives have different immunomodulative effects. Detailed pharmacological data will be reported elsewhere.)

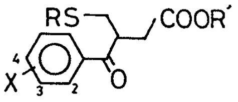
Experimental

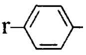
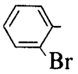
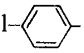
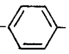
All the melting points are uncorrected. Infrared (IR) spectra were measured with a JASCO DS-301 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were taken at 200 MHz with tetramethylsilane (TMS) as an internal standard on a Varian XL-200 spectrometer, in $CDCl_3$. The chemical shifts are expressed as ppm downfield from TMS. The following abbreviations are used: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet and br = broad. For column chromatography, silica gel (Wako gel, C-200) was used.

Typical examples are given to illustrate the general procedure.

Method A——(1) 3-(4-Methoxybenzoyl)acrylic Acid: $AlCl_3$ (13.3 g) was added to a stirred solution of anisole (5.40 g) and maleic anhydride (4.89 g) in CH_2Cl_2 (200 ml) over 30 min at room temperature. Stirring was continued for an additional 4 h and the solvents were removed under reduced pressure. The residue was poured into concentrated HCl–ice, and the whole was extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$)

TABLE III. Physical and Biological Properties of 3-Benzoyl-4-mercaptobutyric Acid



No.	X	R	R′	mp (°C)	Recrystn.[a] solvent	Formula	Activity[b] rank
40	H	Ac	H	87—88	H–E	$C_{13}H_{14}O_4S$	2
41	H	Ac	Et	Oil[c]		$C_{15}H_{18}O_4S$	0
42	4-Br	Ac	H	93—94.5	H–E	$C_{13}H_{13}BrO_4S$	2
43	3-Br	Ac	H	Oil[c]		$C_{13}H_{13}BrO_4S$	—
44	4-Cl	Ac	H	75—76	H–E	$C_{13}H_{13}ClO_4S$	1
45	4-Cl	Ac	Et	Oil[c]		$C_{15}H_{17}ClO_4S$	1
46	4-F	Ac	H	90—91	H–E	$C_{13}H_{13}FO_4S$	—
47	4-F	Ac	Et	Oil[c]		$C_{15}H_{17}FO_4S$	0
48	4-Me	Ac	H	Oil[c]		$C_{14}H_{16}O_4S$	2
49	3-Me	Ac	H	Oil[c]		$C_{14}H_{16}O_4S$	0
50	2-Me	Ac	H	78—79	H–E	$C_{14}H_{16}O_4S$	0
51	4-Et	Ac	H	Oil[c]		$C_{15}H_{18}O_4S$	1
52	4-iso-Pr	Ac	H	89—92	H–E	$C_{16}H_{20}O_4S$	2
53	4-MeO	Ac	H	102—103	H-EA	$C_{14}H_{16}O_5S$	0
54	4-PhS	Ac	H	81—82	H–E	$C_{19}H_{18}O_4S_2$	0
55	H	iso-Pr	H	80—81	H–E	$C_{14}H_{18}O_3S$	0
56	H	EtCO	H	82—83	H–E	$C_{14}H_{16}O_4S$	0
57	H	PhCO	H	101—102	H–E	$C_{18}H_{16}O_4S$	0
58	4-Ph	Ac	H	122—123	H–E	$C_{19}H_{18}O_4S$	0
59	4-Br-	Ac	H	114—115	H-EA	$C_{19}H_{17}BrO_4S$	3
60	4-	Ac	H	118—120	H-EA	$C_{19}H_{17}BrO_4S$	3
61	4-Cl-	Ac	H	113—115	H–E	$C_{19}H_{17}ClO_4S$	4
62	4-Me-	Ac	H	184—186	H–E	$C_{20}H_{20}O_4S$	0

a—c) See the footnotes to Table I.

and concentrated. The residue was recrystallized from Et_2O–hexane to give yellow needles (5.85 g, 57.9%), mp 108—110 °C.

(2) 3-(3-Bromobenzoyl)acrylic Acid: A mixture of 3-bromoacetophenone (9.95 g) and glyoxylic acid monohydrate (4.60 g) was stirred at 95 °C under reduced pressure (9 mmHg) for 2 h. After cooling, the mixture was dissolved in aqueous 5% K_2CO_3, and washed wtih AcOEt. The aqueous layer was acidified with aqueous 10% HCl, and the whole was extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated. The residue was dissolved in acetic acid (10 ml), and concentrated HCl (1 ml) was added, then the whole was heated for 3 h under reflux. The acetic acid was removed under reduced pressure and the residue was dissolved in AcOEt, then the whole was washed with H_2O, dried ($MgSO_4$) and concentrated. The residue was recrystallized from AcOEt to give yellow needles (7.43 g, 58.3%), mp 149—150 °C.

The following compounds were similarly prepared. 3-(2-Bromobenzoyl)acrylic acid: mp 88—89 °C (from CCl_4), 47%. 3-(3-Trifluoromethylbenzoyl)acrylic acid[4]: mp 112—113 °C (from Et_2O–hexane), 22%. 3-(3-Methylbenzoyl)acrylic acid: mp 115—117 °C (from Et_2O–hexane), 59%. 3-(2-Methylbenzoyl)acrylic acid: mp 106—108 °C (from Et_2O–hexane), 51%.

(3) Ethyl 3-Benzoylacrylate[9]: 3-Benzoylacrylic acid (15.0 g) and Et_2SO_4 (15.7 g) was dissolved in DMF (90 ml), then K_2CO_3 (6.0 g) was added with stirring. The mixture was stirred for an additional 3 h at room temperature, then suspended in H_2O, and the whole was extracted with Et_2O. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography using Et_2O–hexane (1 : 10, v/v) as an eluent to give a yellow oil (16.4 g, 93.4%).

(4) 2-Acetylthio-3-benzoylpropionic Acid (**1**): 3-Benzoylacrylic acid (1.76 g) and thioacetic acid (0.8 ml) were

dissolved in Et_2O (30 ml), then the mixture was stirred for 5 h at room temperature. The mixture was concentrated and the residue was purified by column chromatography using Et_2O–hexane (1 : 5, v/v) as an eluent, then recrystallized from Et_2O–hexane to give **1** (2.09 g, 82.9%), mp 90—92 °C. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1700, 1685, 1670. NMR δ: 2.39 (3H, s), 3.58 (1H, dd, $J=16$, 4 Hz), 3.72 (1H, dd, $J=16$, 6 Hz), 4.77 (1H, dd, $J=6$, 4 Hz), 7.42—7.70 (3H, m), 7.95 (2H, d, $J=8$ Hz), 8.95 (1H, br s). *Anal.* Calcd for $C_{12}H_{12}O_4S$: C, 57.13; H, 4.80. Found: C, 57.18; H, 4.84.

The following compounds were similarly prepared.

2-Acetylthio-3-(4-bromobenzoyl)propionic Acid (**2**): mp 98—99 °C (from Et_2O–hexane), 76.6%. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1700, 1680. NMR δ: 2.38 (3H, s), 3.51 (1H, dd, $J=17$, 5 Hz), 3.67 (1H, dd, $J=17$, 7 Hz), 4.75 (1H, dd, $J=7$, 5 Hz), 7.67 (2H, d, $J=8$ Hz), 7.82 (2H, d, $J=8$ Hz). *Anal.* Calcd for $C_{12}H_{11}BrO_4S$: C, 43.52; H, 3.35. Found: C, 43.70; H, 3.37.

2-Acetylthio-3-(3-bromobenzoyl)propionic Acid (**3**): mp 90—91 °C (from CCl_4), 97.1%. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1720—1670. NMR δ: 2.40 (3H, s), 3.56 (1H, dd, $J=18$, 4 Hz), 3.68 (1H, dd, $J=18$, 8 Hz), 4.76 (1H, dd, $J=8$, 4 Hz), 7.37 (1H, t, $J=8$ Hz), 7.72 (1H, d, $J=8$ Hz), 7.88 (1H, d, $J=8$ Hz), 8.09 (1H, t, $J=1$ Hz), 9.50 (1H, br s). *Anal.* Calcd for $C_{12}H_{11}BrO_4S$: C, 43.52; H, 3.35. Found: C, 43.43; H, 3.43.

2-Acetylthio-3-(2-bromobenzoyl)propionic Acid (**4**): mp 130—131 °C (from benzene), 83.7%. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1720—1670. NMR δ: 2.40 (3H, s), 3.54 (1H, dd, $J=18$, 4 Hz), 3.66 (1H, dd, $J=18$, 8 Hz), 4.76 (1H, dd, $J=8$, 4 Hz), 7.37 (2H, m), 7.50 (1H, dd, $J=8$, 2 Hz), 7.64 (1H, dd, $J=8$, 1 Hz), 8.62 (1H, br s). *Anal.* Calcd for $C_{12}H_{11}O_4S$: C, 43.52; H, 3.35. Found: C, 43.30, H, 3.48.

2-Acetylthio-3-(3,4-dibromobenzoyl)propionic Acid (**5**): mp 119—121 °C (from Et_2O–hexane), 27.7%. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1700—1680. NMR δ: 2.39 (3H, s), 3.50 (1H, dd, $J=16$, 5 Hz), 3.67 (1H, dd, $J=16$, 7 Hz), 4.72 (1H, dd, $J=7$, 5 Hz), 7.73 (2H, s), 8.16 (1H, s). *Anal.* Calcd for $C_{12}H_{10}Br_2O_4S$: C, 35.15; H, 2.46. Found: C, 35.48; H, 2.60.

2-Acetylthio-3-(4-chlorobenzoyl)propionic Acid (**6**): mp 68—69 °C (from Et_2O–hexane), 92.4%. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1710—1680. NMR δ: 2.40 (3H, s), 3.53 (1H, dd, $J=18$, 5 Hz), 3.70 (1H, dd, $J=18$, 8 Hz), 4.7—4.8 (1H, m), 7.48 (2H, d, $J=8$ Hz), 7.92 (2H, d, $J=8$ Hz). *Anal.* Calcd for $C_{12}H_{11}ClO_4S$: C, 50.28, H, 3.48. Found: C, 50.40; H, 3.91.

2-Acetylthio-3-(4-fluorobenzoyl)propionic Acid (**7**): mp 108—110 °C (from CH_2Cl_2–hexane), 81.7%. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1700, 1680, 1670. NMR δ: 2.39 (3H, s), 3.53 (1H, dd, $J=16$, 5 Hz), 3.68 (1H, dd, $J=16$, 7 Hz), 4.76 (1H, dd, $J=7$, 5 Hz), 7.10—8.02 (4H, m), 9.84 (1H, br s). *Anal.* Calcd for $C_{12}H_{11}FO_4S$: C, 53.33; H, 4.10. Found: C, 53.10; H, 4.17.

2-Acetylthio-3-(3-trifluoromethylbenzoyl)propionic Acid (**8**): mp 96.5—97 °C (from Et_2O–hexane), 97.6%. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1700, 1685. NMR δ: 2.20 (3H, s), 3.58 (1H, dd, $J=17$, 4 Hz), 3.76 (1H, dd, $J=17$, 8 Hz), 4.79 (1H, dd, $J=8$, 4 Hz), 6.60—7.30 (1H, br s), 7.64 (1H, t, $J=8$ Hz), 8.15 (1H, d, $J=8$ Hz), 8.21 (1H, s). *Anal.* Calcd for $C_{13}H_{11}F_3O_4S$: C, 48.75; H, 4.46. Found: C, 48.83; H, 3.58.

2-Acetylthio-3-(4-methylbenzoyl)propionic Acid (**9**): mp 81—85 °C (from Et_2O–hexane), 59.5%. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1700, 1670. NMR δ: 2.38 (3H, s), 2.42 (3H, s), 3.55 (1H, dd, $J=17$, 5 Hz), 3.68 (1H, dd, $J=17$, 7 Hz), 4.76 (1H, dd, $J=7$, 5 Hz), 7.28 (2H, d, $J=8$ Hz), 7.86 (2H, d, $J=8$ Hz). *Anal.* Calcd for $C_{13}H_{14}O_4S$: C, 58.63; H, 5.30. Found: C, 58.88; H, 5.33.

2-Acetylthio-3-(4-cyclohexylbenzoyl)propionic Acid (**10**): mp 91—93 °C (from Et_2O–hexane), 93.8%. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1715, 1680. NMR δ: 1.42 (5H, m), 1.86 (5H, m), 2.38 (3H, s), 2.57 (1H, m), 3.58 (1H, dd, $J=18$, 5 Hz), 3.66 (1H, dd, $J=18$, 8 Hz), 4.76 (1H, dd, $J=8$, 5 Hz), 7.31 (2H, d, $J=8$ Hz), 7.89 (2H, d, $J=8$ Hz). *Anal.* Calcd for $C_{18}H_{22}O_4S$: C, 64.64; H, 6.63. Found: C, 64.52; H, 6.88.

2-Acetylthio-3-(4-methoxybenzoyl)propionic Acid (**11**): mp 122—123 °C (from Et_2O–hexane), 74.8%. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1700, 1660. NMR δ: 2.38 (3H, s), 3.53 (1H, dd, $J=17$, 5 Hz), 3.65 (1H, dd, $J=17$, 7 Hz), 3.87 (3H, s), 4.75 (1H, dd, $J=7$, 5 Hz), 6.85 (2H, d, $J=8$ Hz), 7.94 (2H, $J=8$ Hz). *Anal.* Calcd for $C_{13}H_{14}O_5S$: C, 55.31; H, 5.00. Found: C, 55.54; H, 5.08.

3-Benzoyl-2-ethylthiopropionic Acid (**13**): mp 115—115.5 °C (from Et_2O–hexane), 71.4%. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1710—1670. NMR δ: 1.31 (3H, t, $J=7$ Hz), 2.70—2.95 (2H, m), 3.33 (1H, dd, $J=16$, 4 Hz), 3.70 (1H, dd, $J=16$, 9 Hz), 3.91 (1H, dd, $J=9$, 4 Hz), 7.43—7.70 (3H, m), 7.98 (2H, d, $J=8$ Hz), 10.00 (1H, br s). *Anal.* Calcd for $C_{12}H_{14}O_5S$: C, 60.48; H, 5.92. Found: C, 60.56; H, 6.06.

Ethyl 2-Acetylthio-3-(4-bromobenzoyl)propionate (**14**): Oil, 87.4%. IR $\nu_{\max}^{\mathrm{neat}}$ cm^{-1}: 1735, 1690. NMR δ: 1.26 (3H, t, $J=7$ Hz), 2.38 (3H, s), 3.50 (1H, dd, $J=17$, 4 Hz), 3.69 (1H, dd, $J=17$, 7 Hz), 4.21 (2H, q, $J=7$ Hz), 4.69 (1H, dd, $J=7$, 4 Hz), 7.62 (2H, d, $J=8$ Hz), 7.83 (2H, d, $J=8$ Hz). *Anal.* Calcd for $C_{14}H_{15}BrO_4S$: C, 46.82; H, 4.21. Found: C, 46.72; H, 4.24.

3-(4-Bromobenzoyl)-2-ethylthiopropionic Acid (**15**): mp 114.5—115 °C (from Et_2O–hexane), 64.7%. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1695, 1670. NMR δ: 1.31 (3H, t, $J=7$ Hz), 2.67—2.95 (2H, m), 3.28 (1H, dd, $J=20$, 5 Hz), 3.65 (1H, dd, $J=20$, 10 Hz), 3.99 (1H, dd, $J=10$, 5 Hz), 7.64 (2H, d, $J=8$ Hz), 7.85 (2H, d, $J=8$ Hz), 9.00 (1H, br s). *Anal.* Calcd for $C_{12}H_{13}BrO_3S$: C, 45.44; H, 4.13. Found: C, 45.58; H, 4.09.

3-(4-Bromobenzoyl)-2-propionylthiopropionic Acid (**16**): mp 133—135 °C (from CH_2Cl_2–hexane), 66.8%. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1710—1670. NMR δ: 1.20 (3H, t, $J=7$ Hz), 2.64 (2H, q, $J=7$ Hz), 3.53 (1H, dd, $J=18$, 4 Hz), 3.66 (1H, dd, $J=18$, 8 Hz), 4.76 (1H, dd, $J=8$, 4 Hz), 7.61 (2H, d, $J=8$ Hz), 7.81 (2H, d, $J=8$ Hz), 9.86 (1H, br s). *Anal.* Calcd for $C_{13}H_{13}BrO_4S$: C, 45.23; H, 3.80. Found: 45.15; H, 3.84.

2-Benzoylthio-3-(4-bromobenzoyl)propionic Acid (**17**): mp 164.5—166 °C (from Et_2O–hexane), 64.6%. IR $\nu_{\max}^{\mathrm{KBr}}\,\mathrm{cm}^{-1}$: 1690, 1670. NMR δ: 3.59 (1H, dd, $J=14$, 4 Hz), 3.81 (1H, dd, $J=14$, 6 Hz), 4.97 (1H, dd, $J=6$, 4 Hz), 7.47 (2H, d, $J=8$ Hz), 7.62 (3H, m), 7.85 (2H, d, $J=8$ Hz), 7.95 (2H, d, $J=8$ Hz), 8.20 (1H, br s). *Anal.* Calcd for $C_{17}H_{13}BrO_4S$: C, 51.92; H, 3.33. Found: C, 51.65; H, 3.53.

Method B——(1) 3-Benzoyl-2-methylenepropionic Acid[5]: This compound was prepared from benzene and itaconic anhydride using CH_2ClCH_2Cl as a solvent in a manner similar to that described under method A (1), mp 163—164 °C (from acetone–hexane), 50.1%. The following compounds were similarly prepared. 3-(4-Bromobenzoyl)-2-methylenepropionic acid[5]: mp 146.5—149 °C (from AcOEt–hexane), 63.1%. 3-(4-Chlorobenzoyl)-2-methylenepropionic acid[5]: mp 150—154 °C (from acetone–hexane), 38.3%. 3-(4-Fluorobenzoyl)-2-methylenepropionic acid: mp 107—108 °C (from acetone–hexane), 40.4%. 3-(4-Methylbenzoyl)-2-methylenepropionic acid: mp 137—138 °C (from acetone–hexane), 52.4%. 3-(3,4-Dimethylbenzoyl)-2-methylenepropionic acid: mp 144—146 °C (from AcOEt–hexane), 22.4%. 3-(2,4-Dimethylbenzoyl)-2-methylenepropionic acid: mp 108.5—109.5 °C (from AcOEt–hexane), 8.2%. 3-(2,5-Dimethylbenzoyl)-2-methylenepropionic acid: mp 124—126 °C (from AcOEt), 92.6%. 3-(4-Ethylbenzoyl)-2-methylenepropionic acid: mp 145—147 °C (from AcOEt–hexane), 67.7%. 3-(4-Isopropylbenzoyl)-2-methylenepropionic acid: mp 144—146 °C (from acetone–hexane), 51.3%. 3-(4-Methoxybenzoyl)-2-methylenepropionic acid[5]: mp 138—140 °C (from acetone–hexane), 44.0%. 2-Methylene-2-(4-phenoxybenzoyl)propionic acid: mp 92—93.5 °C (from AcOEt–hexane), 48.5%.

(2) 2-Acetylthiomethyl-3-benzoylpropionic acid (**19**): 3-Benzoyl-2-methylenepropionic acid (14.0 g) and thioacetic acid (6.3 ml) were dissolved in DMF (100 ml), then a solution of K_2CO_3 (1.6 g) in H_2O (6 ml) was added dropwise under stirring at 30 °C for 30 min. Stirring was continued for an additional 2 h, then the mixture was suspended in H_2O and acidified with aqueous 10% HCl. The whole was extracted with AcOEt and the extract was washed with H_2O, dried ($MgSO_4$) and concentrated. The residue was recrystallized from Et_2O–hexane to give **19** (15.4 g, 92.5%), mp 100—101 °C. IR $\nu_{\max}^{\mathrm{KBr}}\,\mathrm{cm}^{-1}$: 1700, 1680. NMR δ: 2.35 (3H, s), 3.35 (5H, m), 7.28—7.68 (3H, m), 7.98 (2H, d, $J=8$ Hz). *Anal.* Calcd for $C_{13}H_{14}O_4S$: C, 58.63; H, 5.30. Found: C, 58.84; H, 5.29.

The following compounds were similarly prepared.

2-Acetylthiomethyl-3-(4-bromobenzoyl)propionic Acid (**21**): mp 126.5—128 °C (from Et_2O–hexane), 89.4%. IR $\nu_{\max}^{\mathrm{KBr}}\,\mathrm{cm}^{-1}$: 1670. NMR δ: 2.34 (3H, s), 3.12—3.55 (5H, m), 7.62 (2H, d, $J=8$ Hz), 7.82 (2H, d, $J=8$ Hz), 8.20 (1H, br s). *Anal.* Calcd for $C_{13}H_{13}BrO_4S$: C, 45.23; H, 3.79. Found: C, 45.35; H, 3.97.

2-Acetylthiomethyl-3-(4-chlorobenzoyl)propionic Acid (**26**): mp 109.5—110 °C (from Et_2O–hexane), 66.0%. IR $\nu_{\max}^{\mathrm{KBr}}\,\mathrm{cm}^{-1}$: 1700, 1670. NMR δ: 2.34 (3H, s), 3.15—3.55 (5H, m), 7.47 (2H, d, $J=8$ Hz), 7.91 (2H, d, $J=8$ Hz), 8.20 (1H, br s). *Anal.* Calcd for $C_{13}H_{13}ClO_4S$: C, 51.92; H, 4.36. Found: C, 52.09; H, 4.41.

2-Acetylthiomethyl-3-(4-fluorobenzoyl)propionic Acid (**27**): mp 106.5—108 °C (from Et_2O–hexane), 70.8%. IR $\nu_{\max}^{\mathrm{KBr}}\,\mathrm{cm}^{-1}$: 1700, 1680. NMR δ: 2.34 (3H, s), 3.15—3.55 (5H, m), 7.15 (2H, t, $J=8$ Hz), 7.99 (2H, dd, $J=8$, 6 Hz), 9.00 (1H, br s). *Anal.* Calcd for $C_{13}H_{13}FO_4S$: C, 54.92; H, 4.61. Found: C, 54.93; H, 4.76.

2-Acetylthiomethyl-3-(4-methylbenzoyl)propionic Acid (**28**): mp 94—95.5 °C, 72.8%. IR $\nu_{\max}^{\mathrm{KBr}}\,\mathrm{cm}^{-1}$: 1705, 1690, 1670. NMR δ: 2.33 (3H, s), 2.41 (3H, s), 3.15—3.55 (5H, m), 7.26 (2H, d, $J=8$ Hz), 7.86 (2H, d, $J=8$ Hz), 8.00 (1H, br s). *Anal.* Calcd for $C_{14}H_{16}O_4S$: C, 59.98; H, 5.75. Found: C, 60.19; H, 5.71.

2-Acetylthiomethyl-3-(3,4-dimethylbenzoyl)propionic Acid (**29**): mp 111—113 °C (from AcOEt–hexane), 69.1%. IR $\nu_{\max}^{\mathrm{KBr}}\,\mathrm{cm}^{-1}$: 1710, 1690, 1670. NMR δ: 2.30 (6H, s), 2.32 (3H, s), 3.12—3.52 (5H, m), 7.22 (1H, d, $J=8$ Hz), 7.65—7.76 (2H, m), 10.70 (1H, br s). *Anal.* Calcd for $C_{15}H_{18}O_4S$: C, 61.12; H, 6.16. Found: C, 61.27; H, 6.09.

2-Acetylthiomethyl-3-(2,4-dimethylbenzoyl)propionic Acid (**30**): mp 76—77.5 °C (from AcOEt–hexane), 59.5%. IR $\nu_{\max}^{\mathrm{KBr}}\,\mathrm{cm}^{-1}$: 1695, 1665. NMR δ: 2.35 (3H, s), 2.36 (3H, s), 2.50 (3H, s), 3.12—3.52 (5H, m), 7.06—7.12 (3H, m), 7.64 (1H, d, $J=9$ Hz). *Anal.* Calcd for $C_{15}H_{18}O_4S$: C, 61.12; H, 6.16. Found: C, 61.16; H, 6.21.

2-Acetylthiomethyl-3-(2,5-dimethylbenzoyl)propionic Acid (**31**): mp 69—90 °C (from Et_2O–hexane), 93.3%. IR $\nu_{\max}^{\mathrm{KBr}}\,\mathrm{cm}^{-1}$: 1720, 1690, 1670. NMR δ: 2.34 (3H, s), 2.36 (3H, s), 2.45 (3H, s), 3.07—3.51 (5H, m), 7.13 (1H, d, $J=8$ Hz), 7.19 (1H, d, $J=8$ Hz), 7.46 (1H, s), 10.30 (1H, br s). *Anal.* Calcd for $C_{15}H_{18}O_4S$: C, 61.21; H, 6.16. Found: C, 61.12; H, 6.12.

2-Acetylthiomethyl-3-(4-ethylbenzoyl)propionic Acid (**32**): mp 76—77 °C (from Et_2O–hexane), 90.8%. IR $\nu_{\max}^{\mathrm{KBr}}\,\mathrm{cm}^{-1}$: 1710, 1670. NMR δ: 1.25 (3H, t, $J=7$ Hz), 2.34 (3H, s), 2.72 (2H, q, $J=7$ Hz), 3.15—3.56 (5H, m), 7.30 (2H, d, $J=9$ Hz), 7.90 (2H, d, $J=9$ Hz), 9.50 (1H, br s). *Anal.* Calcd for $C_{15}H_{18}O_4S$: C, 61.20; H, 6.16. Found: C, 61.30; H, 6.10.

2-Acetylthiomethyl-3-(4-isopropylbenzoyl)propionic Acid (**33**): mp 78—79 °C (from Et_2O–hexane), 69.8%. IR $\nu_{\max}^{\mathrm{KBr}}\,\mathrm{cm}^{-1}$: 1695, 1675. NMR δ: 1.27 (6H, d, $J=6$ Hz), 2.33 (3H, s), 2.97 (1H, septet, $J=6$ Hz), 3.15—3.55 (5H, m), 7.32 (2H, d, $J=8$ Hz), 7.86 (2H, d, $J=8$ Hz). *Anal.* Calcd for $C_{16}H_{20}O_4S$: C, 62.32; H, 6.54. Found: C, 62.28; H, 6.33.

2-Acetylthiomethyl-3-(4-methoxybenzoyl)propionic Acid (**34**): mp 88—90 °C (from Et_2O–hexane), 61.5%. IR $\nu_{\max}^{\mathrm{KBr}}\,\mathrm{cm}^{-1}$: 1690, 1665. NMR δ: 2.34 (3H, s), 3.26—3.50 (5H, m), 3.84 (3H, s), 6.95 (2H, d, $J=8$ Hz), 7.95 (2H, d, $J=8$ Hz). *Anal.* Calcd for $C_{14}H_{16}O_5S$: C, 56.74; H, 5.44. Found: C, 56.86; H, 5.48.

2-Acetylthiomethyl-3-(4-phenoxybenzoyl)propionic Acid (**35**): mp 92—93.5 °C (from Et_2O–hexane), 77.8%. IR $\nu_{\max}^{\mathrm{KBr}}\,\mathrm{cm}^{-1}$: 1700, 1675. NMR δ: 2.33 (3H, s), 3.11—3.56 (5H, m), 7.00 (2H, d, $J=9$ Hz), 7.05—7.24 (5H, m), 7.93 (2H, d, $J=9$ Hz), 8.98 (1H, br s). *Anal.* Calcd for $C_{19}H_{18}O_5S$: C, 63.67; H, 5.06. Found: C, 63.70; H, 5.18.

3-Benzoyl-2-propionylthiomethylpropionic Acid (**36**): mp 76—78 °C (from Et_2O–hexane), 68.1%. IR ν_{max}^{KBr} cm^{-1}: 1720, 1690. NMR δ: 1.18 (3H, t, $J=7$ Hz), 2.60 (2H, q, $J=7$ Hz), 3.17—3.64 (5H, m), 7.50 (3H, m), 7.98 (2H, m). *Anal.* Calcd for $C_{14}H_{16}O_4S$: C, 59.98; H, 5.75. Found: C, 60.21; H, 5.69.

3-Benzoyl-2-benzoylthiomethylpropionic Acid (**37**): mp 110—111 °C (from Et_2O–hexane), 33.8%. IR ν_{max}^{KBr} cm^{-1}: 1700, 1660. NMR δ: 3.26—3.68 (5H, m), 7.38—7.64 (6H, m), 7.96 (2H, d, $J=9$ Hz), 7.97 (2H, d, $J=9$ Hz), 9.80 (1H, br s). *Anal.* Calcd for $C_{18}H_{16}O_4S$: C, 65.84; H, 4.91. Found: C, 66.12; H, 5.07.

3-(4-Bromobenzoyl)-2-propionylthiomethylpropionic Acid (**38**): mp 125.5—123 °C (from AcOEt–hexane), 70.6%. IR ν_{max}^{KBr} cm^{-1}: 1700, 1670. NMR δ: 1.16 (3H, t, $J=7$ Hz), 2.58 (2H, q, $J=7$ Hz), 3.10—3.52 (5H, m), 7.61 (2H, d, $J=8$ Hz), 7.82 (2H, d, $J=8$ Hz), 9.80 (1H, br s). *Anal.* Calcd for $C_{14}H_{15}BrO_4S$: C, 46.81; H, 4.21. Found: C, 46.77; H, 4.37.

3-(4-Bromobenzoyl)-2-benzoylthiomethylpropionic Acid (**39**): mp 133—135 °C (from AcOEt–hexane), 35.8%. IR ν_{max}^{KBr} cm^{-1}: 1660. NMR δ: 3.20—3.70 (5H, m), 7.41—7.52 (2H, m), 7.54—7.69 (2H, m), 7.79—7.88 (2H, m), 7.92—8.01 (2H, m), 8.50 (1H, br s). *Anal.* Calcd for $C_{18}H_{15}BrO_4S$: C, 53.08; H, 3.71. Found: C, 53.11; H, 3.87.

(3) Ethyl 2-Acetylthiomethyl-3-benzoylpropionate (**20**): This compound was prepared from **19** in a manner similar to that described under method A (3), oil, 75.6%. IR ν_{max}^{KBr} cm^{-1}: 1730, 1685. NMR δ: 1.27 (3H, t, $J=7$ Hz), 2.36 (3H, s), 3.12—3.60 (5H, m), 4.16 (2H, q, $J=7$ Hz), 7.52 (3H, m), 7.98 (2H, d, $J=8$ Hz). *Anal.* Calcd for $C_{15}H_{18}O_4S$: C, 61.20; H, 6.16. Found: C, 61.10; H, 6.13.

Compounds **22**—**25** were similarly prepared.

Methyl 2-Acetylthiomethyl-3-(4-bromobenzoyl)propionate (**22**): Oil, 69.1%. IR ν_{max}^{neat} cm^{-1}: 1710, 1690, 1670. NMR δ: 2.33 (3H, s), 3.03—3.56 (5H, m), 3.71 (3H, s), 7.62 (2H, d, $J=8$ Hz), 7.82 (2H, d, $J=8$ Hz). *Anal.* Calcd for $C_{14}H_{15}BrO_4S$: C, 46.81; H, 4.21. Found: C, 46.53; H, 4.16.

Ethyl 2-Acetylthiomethyl-3-(4-bromobenzoyl)propionate (**23**): Oil, 74.9%. IR ν_{max}^{neat} cm^{-1}: 1740, 1685. NMR δ: 1.26 (3H, t, $J=7$ Hz), 2.35 (3H, s), 3.06—3.54 (5H, m), 4.18 (2H, q, $J=7$ Hz), 7.62 (2H, d, $J=8$ Hz), 7.83 (2H, d, $J=8$ Hz). *Anal.* Calcd for $C_{15}H_{17}BrO_4S$: C, 48.27; H, 4.59. Found: C, 48.43; H, 4.63.

Isopropyl 2-Acetylthiomethyl-3-(4-bromobenzoyl)propionate (**24**): Oil, 78.2%. IR ν_{max}^{neat} cm^{-1}: 1725, 1685. NMR δ: 1.25 (6H, d, $J=6$ Hz), 2.34 (3H, s), 3.04—3.54 (5H, m), 5.03 (1H, septet, $J=6$ Hz), 7.63 (2H, d, $J=8$ Hz), 7.84 (2H, d, $J=8$ Hz). *Anal.* Calcd for $C_{16}H_{19}BrO_4S$: C, 49.62; H, 4.94. Found: C, 49.65; H, 4.94.

Benzyl 2-Acetylthiomethyl-3-(4-bromobenzoyl)propionate (**25**): mp 79—80 °C (from Et_2O–hexane). IR ν_{max}^{KBr} cm^{-1}: 1730, 1680, 1665. NMR δ: 2.31 (3H, s), 3.10—3.56 (5H, m), 5.15 (2H, s), 7.35 (5H, s), 7.60 (2H, d, $J=8$ Hz), 7.80 (2H, d, $J=8$ Hz). *Anal.* Calcd for $C_{20}H_{19}BrO_4S$: C, 55.18; H, 4.40. Found: C, 55.19; H, 4.58.

Method C——(1) 3-(3-Bromobenzoyl)propionic Acid: Zinc dust (3.6 g) was added to a stirred mixture of 3-(3-bromobenzoyl)acrylic acid (12.4 g), AcOH (70 ml) and H_2O (25 ml) at room temperature for 1 h. The stirring was continued for an additional 2 h, then the precipitate was filtered off. The filtrate was added to H_2O, and the whole was extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was recrystallized from AcOEt–hexane to give colorless needles (8.86 g, 67.2%), mp 115—117 °C.

The following compounds were similarly prepared.[10] 3-(3-Methylbenzoyl)propionic acid: mp 71—72 °C (from AcOEt), 74.4%. 3-(2-Methylbenzoyl)propionic acid: mp 113—114 °C (from Et_2O–hexane), 73.8%.

(2) 3-Benzoyl-3-butenoic Acid[11]: Piperidine (0.1 ml) was added to a stirred mixture of 3-benzoylpropionic acid (5.00 g), paraformaldehyde (1.20 g) and pyridine (5 ml) at 50 °C. Stirring was continued at 50 °C for an additional 6 h, then the mixture was poured into concentrated HCl–ice. The whole was extracted with AcOEt and the extract was washed with H_2O, dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography using CH_2Cl_2–hexane (1 : 1, v/v) as an eluent, then recrystallized from Et_2O–hexane to give colorless needles (4.12 g, 75.4%), mp 61—62 °C. The following compounds were similarly prepared. 3-(4-Bromobenzoyl)-3-butenoic acid[11]: mp 85—87 °C (from Et_2O–hexane), 65.7%. 3-(3-Bromobenzoyl)-3-butenoic acid: mp 124—125 °C (from Et_2O–hexane), 66.8%. 3-(4-Chlorobenzoyl)-3-butenoic acid: 81—83 °C (from Et_2O–hexane), 37.9%. 3-(4-Fluorobenzoyl)-3-butenoic acid: mp 111—112 °C (from Et_2O–hexane), 46.0%. 3-(4-Methylbenzoyl)-3-butenoic acid: mp 60—62 °C (from Et_2O–hexane), 75.9%. 3-(3-Methylbenzoyl)-3-butenoic acid: mp 60—67 °C (from Et_2O–hexane), 76.5%. 3-(2-Methylbenzoyl)-3-butenoic acid[11]: Oil, 88.3%. 3-(4-Ethylbenzoyl)-3-butenoic acid: mp 62—64 °C (from Et_2O–hexane), 65.9%. 3-(4-Isopropylbenzoyl)-3-butenoic acid: mp 65—66.5 °C (from Et_2O–hexane), 60.8%. 3-(4-Methoxybenzoyl)-3-butenoic acid: mp 107—108 °C (from Et_2O–hexane), 66.2%. 3-[4-(Phenylthio)benzoyl]-3-butenoic acid: mp 97—98 °C (from Et_2O–hexane), 65.4%. 3-(4-Phenylbenzoyl)-3-butenoic acid[12]: mp 142—143 °C (from Et_2O–hexane), 66.0%. 3-[4-(4-Bromophenyl)benzoyl]-3-butenoic acid: mp 136—138 °C (from CH_2Cl_2–hexane), 72.5%. 3-[4-(2-Bromophenyl)benzoyl]-3-butenoic acid: mp 129.5—130.5 °C (from CH_2Cl_2), 73.7%. 3-[4-(4-Cholorophenyl)benzoyl]-3-butenoic acid: mp 133—134 °C (from CH_2Cl_2–hexane), 68.6%. 3-[4-(4-Methylphenyl)benzoyl]-3-butenoic acid: mp 154—156 °C (from CH_2Cl_2–hexane), 47.7%.

(3) Ethyl 3-Benzoyl-3-butenoate: This compound was prepared from 3-benzoyl-3-butenoic acid in a manner similar to that described under method A (3), oil, 84.4%.

The following compounds were similarly prepared. Ethyl 3-(4-Chlorobenzoyl)-3-butenoate: Oil, 94.1%. Ethyl 3-(4-Fluorobenzoyl)-3-butenoate: Oil, 78.4%.

(4) 4-Acetylthio-3-benzoylbutyric Acid (**40**): This compound was prepared from 3-benzoyl-3-butenoic acid in a

manner similar to that described under method A (4), mp 87—88 °C (from Et_2O–hexane), 71.2%. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1710, 1670. NMR δ: 2.33 (3H, s), 2.67 (1H, dd, J=18, 9 Hz), 3.36 (1H, dd, J=14, 5 Hz), 4.08 (1H, m), 7.54 (3H, m), 8.07 (2H, d, J=8 Hz), 9.50 (1H, br s). *Anal.* Calcd for $C_{13}H_{14}O_4S$: C, 58.63; H, 5.30. Found: C, 58.81; H, 5.19.

The following compounds were similarly prepared.

Ethyl 4-Acetylthio-3-benzoylbutyrate (**41**): Oil, 80.5%. IR $\nu_{\max}^{\text{neat}}$ cm^{-1}: 1735, 1680, 1595. NMR δ: 1.17 (3H, t, J=7 Hz), 2.33 (3H, s), 2.44 (1H, dd, J=16, 4 Hz), 2.91 (1H, dd, J=12, 9 Hz), 2.95 (1H, dd, J=16, 9 Hz), 3.35 (1H, dd, J=12, 6 Hz), 4.08 (2H, q, J=7 Hz), 4.06—4.20 (1H, m), 7.46—7.64 (3H, m), 8.10 (2H, d, J=8 Hz). *Anal.* Calcd for $C_{15}H_{18}O_4S$: C, 61.21; H, 6.16. Found: C, 61.06; H, 6.13.

4-Acetylthio-3-(4-bromobenzoyl)butyric Acid (**42**): mp 93—94.5 °C (from Et_2O–hexane), 75.2%. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1700. NMR δ: 2.33 (3H, s), 2.66 (1H, dd, J=18, 5 Hz), 2.79 (1H, dd, J=14, 9 Hz), 2.99 (1H, dd, J=18, 9 Hz), 3.34 (1H, dd, J=14, 5 Hz), 4.01 (1H, m), 7.65 (2H, d, J=8 Hz), 7.96 (2H, d, J=8 Hz), 9.70 (1H, br s). *Anal.* Calcd for $C_{13}H_{13}BrO_4S$: C, 45.23; H, 3.79. Found: C, 45.29; H, 3.82.

4-Acetylthio-3-(3-bromobenzoyl)butyric Acid (**43**): Oil, 77.1%. IR $\nu_{\max}^{\text{neat}}$ cm^{-1}: 1690, 1565. NMR δ: 2.33 (3H, s), 2.67 (1H, dd, J=16, 4 Hz), 2.81 (1H, dd, J=14, 5 Hz), 3.00 (1H, dd, J=16, 10 Hz), 3.35 (1H, dd, J=14, 6 Hz), 3.94—4.10 (1H, m), 7.39 (1H, t, J=8 Hz), 7.74 (1H, d, J=8 Hz), 8.03 (1H, d, J=8 Hz), 8.21 (1H, s). *Anal.* Calcd for $C_{13}H_{13}BrO_4S$: C, 45.23; H, 3.80. Found: C, 45.08; H, 3.83.

4-Acetylthio-3-(4-chlorobenzoyl)butyric Acid (**44**): mp 75—76 °C (from EtO_2–hexane), 78.3%. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1710, 1680. NMR δ: 2.34 (3H, s), 2.69 (1H, dd, J=18, 5 Hz), 2.79 (1H, dd, J=14, 9 Hz), 3.01 (1H, dd, J=18, 9 Hz), 3.35 (1H, dd, J=14, 5 Hz), 4.03 (1H, m), 7.50 (2H, d, J=9 Hz), 8.05 (2H, d, J=9 Hz), 9.00 (1H, br s). *Anal.* Calcd for $C_{13}H_{13}ClO_4S$: C, 51.91; H, 4.36. Found: C, 51.93; H, 4.36.

Ethyl 4-Acetylthio-3-(4-chlorobenzoyl)butyrate (**45**): Oil, 91.3%. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1725, 1680, 1585. NMR δ: 1.17 (3H, t, J=7 Hz), 2.33 (3H, s), 2.66 (1H, dd, J=18, 5 Hz), 2.86 (1H, dd, J=12, 8 Hz), 2.96 (1H, dd, J=18, 8 Hz), 3.31 (1H, dd, J=12, 6 Hz), 4.08 (2H, q, J=7 Hz), 3.99—4.18 (1H, m), 7.50 (2H, d, J=9 Hz), 8.06 (2H, d, J=9 Hz). *Anal.* Calcd for $C_{15}H_{16}ClO_4S$: C, 54.80; H, 5.21. Found: C, 54.58; H, 5.16.

4-Acetylthio-3-(4-fluorobenzoyl)butyric Acid (**46**): 90—91 °C (from Et_2O–hexane), 75.4%. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1710, 1675. NMR δ: 2.34 (3H, s), 2.68 (1H, dd, J=17, 5 Hz), 2.70 (1H, dd, J=14, 8 Hz), 3.00 (1H, dd, J=17, 10 Hz), 3.36 (1H, dd, J=14, 6 Hz), 4.05 (1H, m), 7.19 (2H, t, J=8 Hz), 8.15 (2H, m). *Anal.* Calcd for $C_{13}H_{13}FO_4S$: C, 54.92; H, 4.61. Found: C, 55.12; H, 4.58.

Ethyl 4-Acetylthio-3-(4-fluorobenzoyl)butyrate (**47**): Oil, 59.0%. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1730, 1680, 1595. NMR δ: 1.28 (3H, t, J=7 Hz), 2.34 (3H, s), 2.66 (1H, dd, J=16, 5 Hz), 2.87 (1H, dd, J=14, 9 Hz), 2.97 (1H, dd, J=16, 10 Hz), 3.13 (1H, dd, J=14, 6 Hz), 4.09 (2H, q, J=7 Hz), 4.10 (1H, m), 7.20 (2H, t, J=8 Hz), 8.17 (2H, dd, J=8, 5 Hz). *Anal.* Calcd for $C_{15}H_{17}FO_4S$: C, 57.68; H, 5.49. Found: C, 57.90; H, 5.51.

4-Acetylthio-3-(4-methylbenzoyl)butyric Acid (**48**): Oil, 96.2%. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1710, 1680. NMR δ: 2.32 (3H, s), 2.42 (3H, s), 2.64 (1H, dd, J=18, 5 Hz), 2.85 (1H, dd, J=14, 8 Hz), 2.98 (1H, dd, J=18, 8 Hz), 3.38 (1H, dd, J=14, 5 Hz), 4.09 (1H, m), 7.30 (2H, d, J=9 Hz), 7.98 (2H, d, J=9 Hz), 9.00 (1H, br s). *Anal.* Calcd for $C_{14}H_{16}O_4S$: C, 59.98; H, 5.75. Found: C, 60.03; H, 5.49.

4-Acetylthio-3-(3-methylbenzoyl)butyric Acid (**49**): Oil, 96.9%. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1700, 1600. NMR δ: 2.33 (3H, s), 2.43 (3H, s), 2.66 (1H, dd, J=18, 4 Hz), 2.84 (1H, dd, J=14, 8 Hz), 2.95 (1H, dd, J=18, 8 Hz), 3.39 (1H, dd, J=14, 4 Hz), 4.09 (1H, m), 7.35—7.45 (2H, m), 7.80 (2H, m), 9.50 (1H, br s). *Anal.* Calcd for $C_{14}H_{16}O_4S$: C, 59.98; H, 5.75. Found: C, 59.43; H, 5.76.

4-Acetylthio-3-(2-methylbenzoyl)butyric Acid (**50**): mp 78—79 °C (from Et_2O–hexane), 58.4%. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1670, 1596. NMR δ: 2.31 (3H, s), 2.45 (3H, s), 2.62 (1H, dd, J=17, 4 Hz), 2.92 (1H, dd, J=14, 9 Hz), 2.96 (1H, dd, J=17, 8 Hz), 3.31 (1H, dd, J=14, 6 Hz), 3.96 (1H, m), 7.24—7.46 (3H, m), 7.80 (1H, d, J=8 Hz). *Anal.* Calcd for $C_{14}H_{16}O_4S$: C, 59.98; H, 5.75. Found: C, 60.04; H, 5.80.

4-Acetylthio-3-(4-ethylbenzoyl)butyric Acid (**51**): mp 53—55 °C (from Et_2O–hexane), 97.6%. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1700, 1675. NMR δ: 1.26 (3H, t, J=7 Hz), 2.32 (3H, s), 2.65 (1H, dd, J=16, 4 Hz), 2.74 (2H, q, J=7 Hz), 2.88 (1H, dd, J=14, 8 Hz), 2.99 (1H, dd, J=16, 8 Hz), 3.39 (1H, dd, J=14, 4 Hz), 4.08 (1H, m), 7.23 (2H, d, J=9 Hz), 8.01 (2H, d, J=9 Hz). *Anal.* Calcd for $C_{15}H_{18}O_4S$: C, 61.20; H, 6.16. Found: C, 60.97; H, 6.33.

4-Acetylthio-3-(4-isopropylbenzoyl)butyric Acid (**52**): mp 89—92 °C (from Et_2O–hexane), 79.4%. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1705, 1690, 1670, 1600. NMR δ: 1.28 (6H, d, J=6 Hz), 2.32 (3H, s), 2.69 (1H, dd, J=16, 4 Hz), 2.82 (1H, dd, J=14, 8 Hz), 3.00 (1H, m), 3.01 (1H, dd, J=16, 4 Hz), 3.41 (1H, dd, J=14, 4 Hz), 4.09 (1H, m), 7.37 (2H, d, J=8 Hz), 8.04 (2H, d, J=8 Hz), 10.00 (1H, br s). *Anal.* Calcd for $C_{16}H_{20}O_4S$: C, 62.31; H, 6.54. Found: C, 62.66; H, 6.41.

4-Acetylthio-3-(4-methoxybenzoyl)butyric Acid (**53**): mp 102—103 °C (from AcOEt–hexane), 84.0%. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1700, 1660, 1600. NMR δ: 2.35 (3H, s), 2.66 (1H, dd, J=18, 6 Hz), 2.83 (1H, dd, J=16, 8 Hz), 3.00 (1H, dd, J=18, 8 Hz), 3.38 (1H, dd, J=16, 4 Hz), 3.88 (3H, s), 4.00 (1H, m), 7.00 (2H, d, J=9 Hz), 8.10 (2H, d, J=9 Hz). *Anal.* Calcd for $C_{14}H_{16}O_5S$: C, 56.74; H, 5.44. Found: C, 56.27; H, 5.49.

4-Acetylthio-3-[4-(phenylthio)benzoyl]butyric Acid (**54**): mp 81—82 °C (from Et_2O–hexane), 70.0%. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1695, 1678, 1665. NMR δ: 2.32 (3H, s), 2.65 (1H, dd, J=18, 4 Hz), 2.77 (1H, dd, J=14, 9 Hz), 2.98 (1H, dd, J=18, 8 Hz), 3.36 (1H, dd, J=14, 5 Hz), 3.92—4.08 (1H, m), 7.23 (2H, d, J=9 Hz), 7.38—7.60 (5H, m), 7.97 (2H, d, J=9 Hz). *Anal.* Calcd for $C_{19}H_{18}O_4S$: C, 60.94; H, 4.84. Found: C, 60.92; H, 4.93.

3-Benzoyl-4-isopropylthiobutyric Acid (**55**): mp 80—81 °C (from Et_2O–hexane), 80.3%. IR $\nu_{\max}^{\mathrm{KBr}}\,\mathrm{cm}^{-1}$: 1705, 1677, 1592. NMR δ: 1.20 (6H, d, J=6 Hz), 2.56 (1H, dd, J=14, 8 Hz), 2.75—2.97 (3H, m), 3.01 (1H, dd, J=14, 8 Hz), 3.94—4.12 (1H, m), 7.43—7.66 (3H, m), 7.99 (1H, d, J=9 Hz). *Anal.* Calcd for $C_{14}H_{18}O_3S$: C, 63.13; H, 6.81. Found: C, 62.98; H, 6.80.

3-Benzoyl-4-propionylthiobutyric Acid (**56**): mp 82—83 °C (from Et_2O–hexane), 58.4%. IR $\nu_{\max}^{\mathrm{KBr}}\,\mathrm{cm}^{-1}$: 1700, 1675, 1590. NMR δ: 1.14 (3H, t, J=8 Hz), 2.56 (2H, q, J=8 Hz), 2.66 (1H, dd, J=17, 6 Hz), 2.86 (1H, dd, J=15, 8 Hz), 3.00 (1H, dd, J=17, 8 Hz), 3.38 (1H, dd, J=15, 6 Hz), 4.10 (1H, m), 7.30 (3H, m), 8.10 (2H, d, J=9 Hz). *Anal.* Calcd for $C_{14}H_{16}O_4S$: C, 59.98; H, 5.75. Found: C, 59.95; H, 5.67.

3-Benzoyl-4-benzoylthiobutyric Acid (**57**): mp 101—102 °C (from Et_2O–hexane), 76.8%. IR $\nu_{\max}^{\mathrm{KBr}}\,\mathrm{cm}^{-1}$: 1700, 1650, 1580. NMR δ: 2.74 (1H, dd, J=16, 6 Hz), 3.03 (1H, dd, J=14, 9 Hz), 3.05 (1H, dd, J=16, 10 Hz), 3.57 (1H, dd, J=14, 6 Hz), 4.12—4.30 (1H, m), 7.20—7.68 (6H, m), 7.94 (2H, d, J=8 Hz), 8.14 (2H, d, J=8 Hz). *Anal.* Calcd for $C_{18}H_{16}O_4S$: C, 65.84; H, 4.91. Found: C, 65.68; H, 4.82.

4-Acetylthio-3-(4-phenylbenzoyl)butyric Acid (**58**): mp 122—123 °C (from Et_2O–hexane), 53.0%. IR $\nu_{\max}^{\mathrm{KBr}}\,\mathrm{cm}^{-1}$: 1700, 1670, 1600. NMR δ: 2.33 (3H, s), 2.69 (1H, dd, J=18, 4 Hz), 2.77 (1H, dd, J=14, 9 Hz), 2.99 (1H, dd, J=18, 8 Hz), 3.42 (1H, dd, J=14, 5 Hz), 4.04—4.21 (1H, m), 7.27—7.46 (2H, m), 7.50—7.76 (3H, m), 8.16 (2H, d, J=8 Hz). *Anal.* Calcd for $C_{19}H_{18}O_4S$: C, 66.65; H, 5.30. Found: C, 66.70; H, 5.28.

4-Acetylthio-3-[4-(4-bromophenyl)benzoyl]butyric Acid (**59**): mp 114—115 °C (from AcOEt–hexane), 81.6%. IR $\nu_{\max}^{\mathrm{KBr}}\,\mathrm{cm}^{-1}$: 1700. NMR δ: 2.34 (3H, s), 2.69 (1H, dd, J=16, 4 Hz), 2.84 (1H, dd, J=14, 9 Hz), 3.03 (1H, dd, J=16, 9 Hz), 3.41 (1H, dd, J=14, 5 Hz), 4.11 (1H, m), 7.50 (2H, d, J=9 Hz), 7.61 (2H, d, J=9 Hz), 7.69 (2H, d, J=9 Hz), 8.18 (2H, d, J=9 Hz), 8.50 (1H, br s). *Anal.* Calcd for $C_{19}H_{19}BrO_4S$: C, 54.16; H, 4.09. Found: C, 54.21; H, 3.99.

3-Acetylthio-4-[4-(2-bromophenyl)benzoyl]butyric Acid (**60**): mp 118—120 °C (from AcOEt–hexane), 87.1%. IR $\nu_{\max}^{\mathrm{KBr}}\,\mathrm{cm}^{-1}$: 1700, 1670, 1600. NMR δ: 2.37 (3H, s), 2.70 (1H, dd, J=16, 4 Hz), 2.92 (1H, dd, J=13, 8 Hz), 3.40 (1H, dd, J=16, 8 Hz), 3.44 (1H, dd, J=13, 4 Hz), 4.09—4.24 (1H, m), 7.20—7.44 (3H, m), 7.57 (2H, d, J=9 Hz), 7.71 (1H, d, J=9 Hz), 8.10 (2H, d, J=9 Hz). *Anal.* Calcd for $C_{19}H_{17}BrO_4S$: C, 54.16; H, 4.07. Found: C, 54.23; H, 3.98.

4-Acetylthio-3-[4-(4-chlorophenyl)benzoyl]butyric Acid (**61**): mp 113—115 °C (from Et_2O–hexane), 82.6%. IR $\nu_{\max}^{\mathrm{KBr}}\,\mathrm{cm}^{-1}$: 1700, 1670, 1600. NMR δ: 2.34 (3H, s), 2.69 (1H, dd, J=17, 4 Hz), 2.83 (1H, dd, J=14, 8 Hz), 3.03 (1H, dd, J=17, 8 Hz), 3.40 (1H, dd, J=14, 8 Hz), 4.10 (1H, m), 7.44 (2H, d, J=8 Hz), 7.57 (2H, d, J=8 Hz), 7.67 (2H, d, J=8 Hz), 8.16 (2H, d, J=8 Hz), 9.00 (1H, br s). *Anal.* Calcd for $C_{19}H_{17}ClO_4S$: C, 60.55; H, 4.55. Found: C, 60.74; H, 4.51.

4-Acetylthio-3-[4-(4-methylphenyl)benzoyl]butyric Acid (**62**): mp 184—186 °C (from Et_2O–hexane), 39.8%. IR $\nu_{\max}^{\mathrm{KBr}}\,\mathrm{cm}^{-1}$: 1670, 1600. NMR δ: 2.34 (3H, s), 2.45 (3H, s), 2.68 (1H, dd, J=18, 5 Hz), 2.87 (1H, dd, J=14, 8 Hz), 3.03 (1H, dd, J=18, 8 Hz), 3.42 (1H, dd, J=14, 5 Hz), 4.04—4.21 (1H, m), 7.29 (2H, d, J=8 Hz), 7.55 (2H, d, J=8 Hz), 7.72 (2H, d, J=8 Hz), 8.15 (2H, d, J=8 Hz), 10.00 (1H, br s). *Anal.* Calcd for $C_{20}H_{20}O_4S$: C, 67.39; H, 5.66. Found: C, 67.29; H, 5.71.

3-Benzoyl-2-mercaptopropionic Acid (**12**): An 80% N_2H_4 aqueous solution (3.2 g) was added to a stirred and ice-cooled solution of **1** (8.5 g) in tetrahydrofuran (THF) (100 ml). The mixture was stirred for 30 min at room temperature and THF was removed under reduced pressure. The residue was suspended in H_2O and the whole was extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography using Et_2O–hexane (1 : 1, v/v) as an eluent, then crystallized from Et_2O–hexane to give colorless prisms (3.1 g, 41%), mp 145—146 °C. IR $\nu_{\max}^{\mathrm{KBr}}\,\mathrm{cm}^{-1}$: 1700, 1670. NMR δ: 2.36 (1H, d, J=8 Hz), 3.20 (1H, br s), 3.45 (1H, dd, J=17, 5 Hz), 3.77 (1H, dd, J=17, 8 Hz), 4.01 (1H, dd, J=8, 5 Hz), 7.45—7.65 (3H, m), 7.98 (2H, d, J=8 Hz). *Anal.* Calcd for $C_{10}H_{10}O_3S$: C, 57.12; H, 4.79. Found: C, 57.24; H, 4.92.

3-Acetylthio-3-(4-bromobenzoyl)propionic Acid (**18**): A solution of Br_2 (6.2 g) in $CHCl_3$ (20 ml) was added dropwise to a stirred solution of 3-(4-bromobenzoyl)propionic acid[13] (10.0 g) in $CHCl_3$ (100 ml). The mixture was stirred for an additional 3 h at room temperature, and $CHCl_3$ was removed under reduced pressure. The residue was dissolved in Et_2O and the whole was washed with H_2O, dried ($MgSO_4$) and concentrated. The residue was dissolved in DMF (40 ml), and AcSK (3.20 g) was added to the solution under stirring. The stirring was continued for 3 h at room temperature, and the mixture was suspended in H_2O. The whole was extracted with AcOEt and the extract was washed with H_2O, dried ($MgSO_4$) and concentrated. The residue was recrystallized from Et_2O–hexane to give colorless needles (6.5 g, 50.5%), mp 125.5—126 °C. IR $\nu_{\max}^{\mathrm{KBr}}\,\mathrm{cm}^{-1}$: 1695, 1670. NMR δ: 2.35 (3H, s), 2.79 (1H, dd, J=16, 4 Hz), 3.33 (1H, dd, J=16, 10 Hz), 5.45 (1H, dd, J=10, 4 Hz), 7.60 (2H, d, J=8 Hz), 7.81 (2H, d, J=8 Hz). *Anal.* Calcd for $C_{12}H_{11}BrO_4S$: C, 43.52; H, 3.35. Found: C, 43.54; H, 3.46.

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