

[Chem. Pharm. Bull.]
36(6)2050—2060(1988)

Studies on Antirheumatic Agents: 3-Benzoylpropionic Acid Derivatives

KAZUYA KAMEO,* KUNIO OGAWA, KIMIYO TAKESHITA,
SHIRO NAKAIKE, KAZUYUKI TOMISAWA
and KAORU SOTA

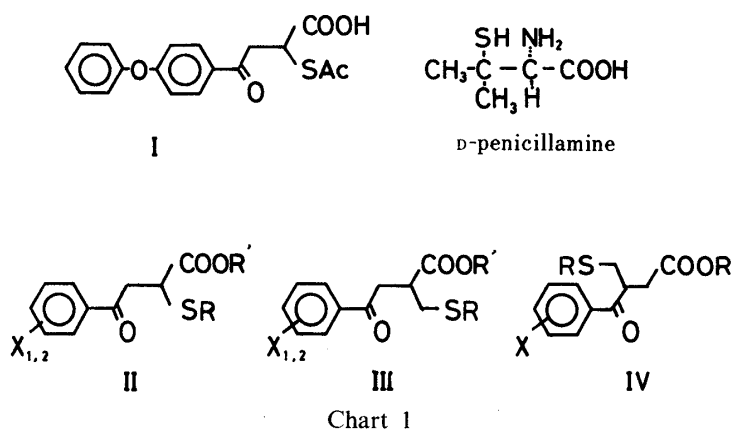
Research Center, Taisho Pharmaceutical Co., Ltd.,
1-403 Yoshino-cho, Ohmiya, Saitama 330, Japan

(Received December 2, 1987)

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

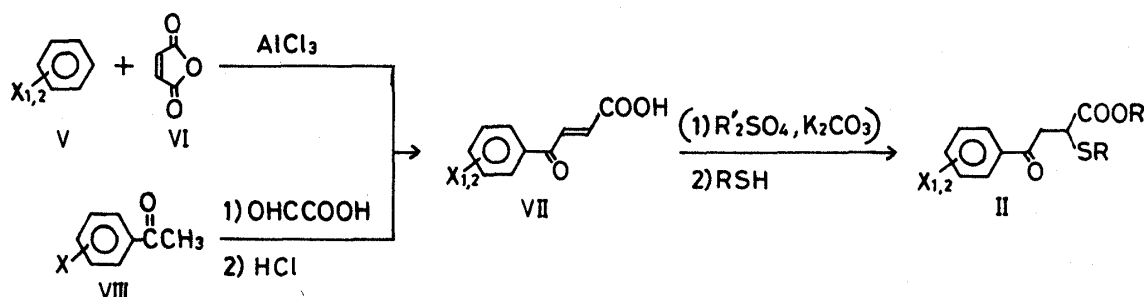
In the previous paper,¹⁾ we reported that 2-acetylthio-3-(4-phenoxybenzoyl)propionic acid (I) (Chart 1) and its derivatives, having mercapto and carboxylic acid moieties in their structures, have potent hypolipidemic activities. In further pharmacological studies, we found that I has an immunomodulative 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).



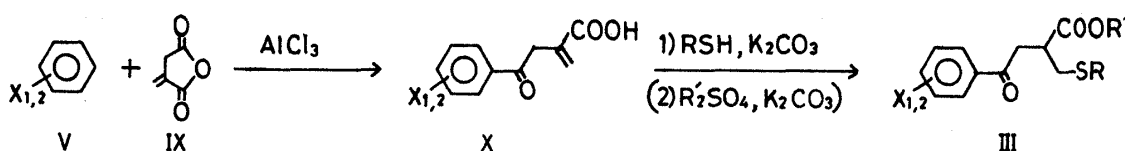
Chemistry

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 acids⁴⁾ (VII). Treatment of VII with mercapto

method A



method B



method C

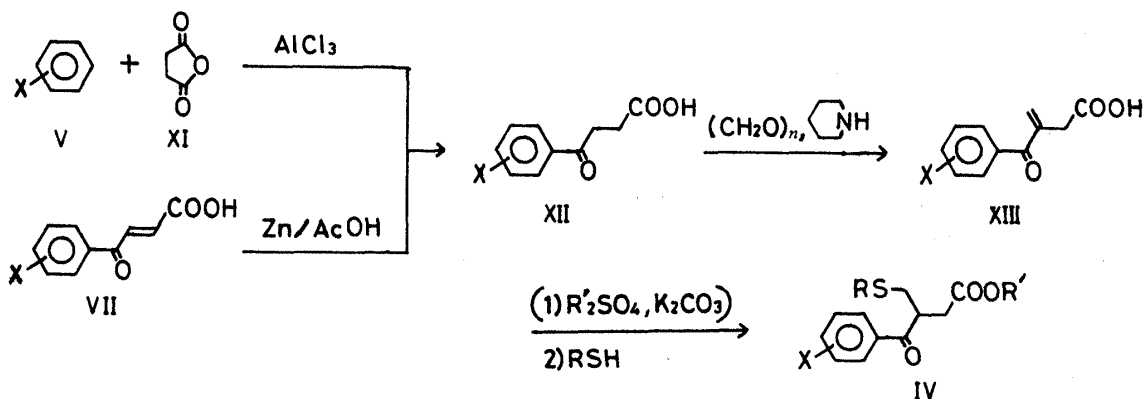


Chart 2

compounds provided 2-mercapto-3-benzoylpropionic acids (II) (method A). 2-Methylene-3-benzoylpropionic acids⁵⁾ (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 acylation⁶⁾ 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-butenic acids (XIII), which were treated with mercapto compounds to give 3-benzoyl-4-mercaptobutyric acids (IV) (method C).

Biological Method⁸⁾

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 paraffin. 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

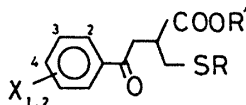
The physical constants and biological data of the derivatives prepared in this work are listed in Tables I—III. As shown in Tables I—III, the suppressing activities of the ester derivatives were mostly weaker than those of the corresponding free carboxylic acids, and in comparison with acetylthio derivatives, 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-mercapto-3-phenylpropionic 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 ₄ S	1
2	4-Br	Ac	H	98—99	H-E	C ₁₂ H ₁₁ BrO ₄ S	3
3	3-Br	Ac	H	90—91	CCl ₄	C ₁₂ H ₁₁ BrO ₄ S	2
4	2-Br	Ac	H	130—131	PhH	C ₁₂ H ₁₁ BrO ₄ S	1
5	3,4-Br ₂	Ac	H	119—121	H-E	C ₁₂ H ₁₀ Br ₂ O ₄ S	3
6	4-Cl	Ac	H	68—69	H-E	C ₁₂ H ₁₁ ClO ₄ S	2
7	4-F	Ac	H	108—110	H-D	C ₁₂ H ₁₁ FO ₄ S	0
8	3-CF ₃	Ac	H	96.5—97	H-E	C ₁₃ H ₁₁ F ₃ O ₄ S	0
9	4-Me	Ac	H	81—85	H-E	C ₁₃ H ₁₄ O ₄ S	0
10	4-	Ac	H	91—93	H-E	C ₁₈ H ₂₂ O ₄ S	1
11	4-MeO	Ac	H	122—123.5	H-E	C ₁₃ H ₁₄ O ₅ S	0
12	H	H	H	145—147	H-E	C ₁₀ H ₁₀ O ₃ S	1
13	H	Et	H	115—115.5	H-E	C ₁₂ H ₁₄ O ₃ S	1
14	4-Br	Ac	Et	Oil ^{c)}		C ₁₄ H ₁₅ BrO ₄ S	3
15	4-Br	Et	H	114.5—115	H-E	C ₁₂ H ₁₃ BrO ₃ S	0
16	4-Br	COEt	H	133—135	H-D	C ₁₃ H ₁₃ BrO ₄ S	3
17	4-Br	COPh	H	164.5—166	H-E	C ₁₇ H ₁₃ BrO ₄ S	3
18				125.5—126	H-E	C ₁₂ H ₁₁ BrO ₄ S	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-mercaptopropionic 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 ₄ S	3
20	H	Ac	Et	Oil ^{c)}		C ₁₅ H ₁₈ O ₄ S	0
21	4-Br	Ac	H	126.5—128	H-E	C ₁₃ H ₁₃ BrO ₄ S	3
22	4-Br	Ac	Me	Oil ^{c)}		C ₁₄ H ₁₅ BrO ₄ S	0
23	4-Br	Ac	Et	Oil ^{c)}		C ₁₅ H ₁₇ BrO ₄ S	0
24	4-Br	Ac	iso-Pr	Oil ^{c)}		C ₁₆ H ₁₉ BrO ₄ S	0
25	4-Br	Ac	CH ₂ Ph	79—80	H-E	C ₂₀ H ₁₉ BrO ₄ S	1
26	4-Cl	Ac	H	109.5—110	H-E	C ₁₃ H ₁₃ ClO ₄ S	0
27	4-F	Ac	H	106.5—108	H-E	C ₁₃ H ₁₃ FO ₄ S	0
28	4-Me	Ac	H	94—95.5	H-E	C ₁₄ H ₁₆ O ₄ S	4
29	3,4-Me ₂	Ac	H	111—113	H-EA	C ₁₅ H ₁₈ O ₄ S	3
30	2,4-Me ₂	Ac	H	76—77.5	H-EA	C ₁₅ H ₁₈ O ₄ S	1
31	2,5-Me ₂	Ac	H	60—90	H-E	C ₁₅ H ₁₈ O ₄ S	—
32	4-Et	Ac	H	76—77	H-E	C ₁₅ H ₁₈ O ₄ S	1
33	4-iso-Pr	Ac	H	78—79	H-E	C ₁₆ H ₂₀ O ₄ S	0
34	4-MeO	Ac	H	88—90	H-E	C ₁₄ H ₁₆ O ₅ S	0
35	4-PhO	Ac	H	92—93.5	H-E	C ₁₉ H ₁₈ O ₅ S	1
36	H	COEt	H	76—78	H-E	C ₁₄ H ₁₆ O ₄ S	—
37	H	COPh	H	110—111	H-E	C ₁₈ H ₁₆ O ₄ S	1
38	4-Br	COEt	H	125.5—123	H-EA	C ₁₄ H ₁₅ BrO ₄ S	0
39	4-Br	COPh	H	133—135	H-EA	C ₁₈ H ₁₅ BrO ₄ S	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.)

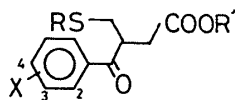
Experimental

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 CDCl₃. 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: AlCl₃ (13.3 g) was added to a stirred solution of anisole (5.40 g) and maleic anhydride (4.89 g) in CH₂Cl₂ (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 H₂O, dried (MgSO₄)

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 ₄ S	2
41	H	Ac	Et	Oil ^{c)}		C ₁₅ H ₁₈ O ₄ S	0
42	4-Br	Ac	H	93—94.5	H-E	C ₁₃ H ₁₃ BrO ₄ S	2
43	3-Br	Ac	H	Oil ^{c)}		C ₁₃ H ₁₃ BrO ₄ S	—
44	4-Cl	Ac	H	75—76	H-E	C ₁₃ H ₁₃ ClO ₄ S	1
45	4-Cl	Ac	Et	Oil ^{c)}		C ₁₅ H ₁₇ ClO ₄ S	1
46	4-F	Ac	H	90—91	H-E	C ₁₃ H ₁₃ FO ₄ S	—
47	4-F	Ac	Et	Oil ^{c)}		C ₁₅ H ₁₇ FO ₄ S	0
48	4-Me	Ac	H	Oil ^{c)}		C ₁₄ H ₁₆ O ₄ S	2
49	3-Me	Ac	H	Oil ^{c)}		C ₁₄ H ₁₆ O ₄ S	0
50	2-Me	Ac	H	78—79	H-E	C ₁₄ H ₁₆ O ₄ S	0
51	4-Et	Ac	H	Oil ^{c)}		C ₁₅ H ₁₈ O ₄ S	1
52	4-iso-Pr	Ac	H	89—92	H-E	C ₁₆ H ₂₀ O ₄ S	2
53	4-MeO	Ac	H	102—103	H-EA	C ₁₄ H ₁₆ O ₅ S	0
54	4-PhS	Ac	H	81—82	H-E	C ₁₉ H ₁₈ O ₄ S ₂	0
55	H	iso-Pr	H	80—81	H-E	C ₁₄ H ₁₈ O ₃ S	0
56	H	EtCO	H	82—83	H-E	C ₁₄ H ₁₆ O ₄ S	0
57	H	PhCO	H	101—102	H-E	C ₁₈ H ₁₆ O ₄ S	0
58	4-Ph	Ac	H	122—123	H-E	C ₁₉ H ₁₈ O ₄ S	0
59	4-Br-	Ac	H	114—115	H-EA	C ₁₉ H ₁₇ BrO ₄ S	3
60	4-	Ac	H	118—120	H-EA	C ₁₉ H ₁₇ BrO ₄ S	3
61	4-Cl-	Ac	H	113—115	H-E	C ₁₉ H ₁₇ ClO ₄ S	4
62	4-Me-	Ac	H	184—186	H-E	C ₂₀ H ₂₀ O ₄ S	0

a—c) See the footnotes to Table I.

and concentrated. The residue was recrystallized from Et₂O–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% K₂CO₃, and washed with AcOEt. The aqueous layer was acidified with aqueous 10% HCl, and the whole was extracted with AcOEt. The extract was washed with H₂O, dried (MgSO₄) 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 H₂O, dried (MgSO₄) 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 CCl₄), 47%. 3-(3-Trifluoromethylbenzoyl)acrylic acid⁴⁾: mp 112—113°C (from Et₂O–hexane), 22%. 3-(3-Methylbenzoyl)acrylic acid: mp 115—117°C (from Et₂O–hexane), 59%. 3-(2-Methylbenzoyl)acrylic acid: mp 106—108°C (from Et₂O–hexane), 51%.

(3) Ethyl 3-Benzoylacrylate⁹⁾: 3-Benzoylacrylic acid (15.0 g) and Et₂SO₄ (15.7 g) was dissolved in DMF (90 ml), then K₂CO₃ (6.0 g) was added with stirring. The mixture was stirred for an additional 3 h at room temperature, then suspended in H₂O, and the whole was extracted with Et₂O. The extract was washed with H₂O, dried (MgSO₄) and concentrated. The residue was purified by column chromatography using Et₂O–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 Et₂O (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 Et₂O–hexane (1:5, v/v) as an eluent, then recrystallized from Et₂O–hexane to give **1** (2.09 g, 82.9%), mp 90–92 °C. IR $\nu_{\text{max}}^{\text{KBr}}$ 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, brs). *Anal.* Calcd for C₁₂H₁₂O₄S: 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 Et₂O–hexane), 76.6%. IR $\nu_{\text{max}}^{\text{KBr}}$ 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 C₁₂H₁₁BrO₄S: 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 CCl₄), 97.1%. IR $\nu_{\text{max}}^{\text{KBr}}$ 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, brs). *Anal.* Calcd for C₁₂H₁₁BrO₄S: 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 $\nu_{\text{max}}^{\text{KBr}}$ 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, brs). *Anal.* Calcd for C₁₂H₁₁O₄S: 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 Et₂O–hexane), 27.7%. IR $\nu_{\text{max}}^{\text{KBr}}$ 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 C₁₂H₁₀Br₂O₄S: 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 Et₂O–hexane), 92.4%. IR $\nu_{\text{max}}^{\text{KBr}}$ 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 C₁₂H₁₁ClO₄S: 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 CH₂Cl₂–hexane), 81.7%. IR $\nu_{\text{max}}^{\text{KBr}}$ 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, brs). *Anal.* Calcd for C₁₂H₁₁FO₄S: 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 Et₂O–hexane), 97.6%. IR $\nu_{\text{max}}^{\text{KBr}}$ 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, brs), 7.64 (1H, t, $J=8$ Hz), 8.15 (1H, d, $J=8$ Hz), 8.21 (1H, s). *Anal.* Calcd for C₁₃H₁₁F₃O₄S: 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 Et₂O–hexane), 59.5%. IR $\nu_{\text{max}}^{\text{KBr}}$ 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 C₁₃H₁₄O₄S: 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 Et₂O–hexane), 93.8%. IR $\nu_{\text{max}}^{\text{KBr}}$ 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 C₁₈H₂₂O₄S: 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 Et₂O–hexane), 74.8%. IR $\nu_{\text{max}}^{\text{KBr}}$ 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, d, $J=8$ Hz). *Anal.* Calcd for C₁₃H₁₄O₅S: 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 Et₂O–hexane), 71.4%. IR $\nu_{\text{max}}^{\text{KBr}}$ 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, brs). *Anal.* Calcd for C₁₂H₁₄O₅S: 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 $\nu_{\text{max}}^{\text{neat}}$ 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 C₁₄H₁₅BrO₄S: 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 Et₂O–hexane), 64.7%. IR $\nu_{\text{max}}^{\text{KBr}}$ 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, brs). *Anal.* Calcd for C₁₂H₁₃BrO₃S: 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 CH₂Cl₂–hexane), 66.8%. IR $\nu_{\text{max}}^{\text{KBr}}$ 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, brs). *Anal.* Calcd for C₁₃H₁₃BrO₄S: 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 Et₂O–hexane), 64.6%. IR $\nu_{\text{max}}^{\text{KBr}}$ 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 C₁₇H₁₃BrO₄S: C, 51.92; H, 3.33. Found: C, 51.65; H, 3.53.

Method B—(1) 3-Benzoyl-2-methylenepropionic Acid⁵: This compound was prepared from benzene and itaconic anhydride using CH₂ClCH₂Cl 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 acid⁵: mp 146.5–149 °C (from AcOEt–hexane), 63.1%. 3-(4-Chlorobenzoyl)-2-methylenepropionic acid⁵: 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 acid⁵: 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 K₂CO₃ (1.6 g) in H₂O (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 H₂O and acidified with aqueous 10% HCl. The whole was extracted with AcOEt and the extract was washed with H₂O, dried (MgSO₄) and concentrated. The residue was recrystallized from Et₂O–hexane to give **19** (15.4 g, 92.5%), mp 100–101 °C. IR $\nu_{\text{max}}^{\text{KBr}}$ 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 C₁₃H₁₄O₄S: 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 Et₂O–hexane), 89.4%. IR $\nu_{\text{max}}^{\text{KBr}}$ 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 C₁₃H₁₃BrO₄S: 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 Et₂O–hexane), 66.0%. IR $\nu_{\text{max}}^{\text{KBr}}$ 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 C₁₃H₁₃ClO₄S: 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 Et₂O–hexane), 70.8%. IR $\nu_{\text{max}}^{\text{KBr}}$ 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 C₁₃H₁₃FO₄S: 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 $\nu_{\text{max}}^{\text{KBr}}$ 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 C₁₄H₁₆O₄S: 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 $\nu_{\text{max}}^{\text{KBr}}$ 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 C₁₅H₁₈O₄S: 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 $\nu_{\text{max}}^{\text{KBr}}$ 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 C₁₅H₁₈O₄S: 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 Et₂O–hexane), 93.3%. IR $\nu_{\text{max}}^{\text{KBr}}$ 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 C₁₅H₁₈O₄S: 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 Et₂O–hexane), 90.8%. IR $\nu_{\text{max}}^{\text{KBr}}$ 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 C₁₅H₁₈O₄S: 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 Et₂O–hexane), 69.8%. IR $\nu_{\text{max}}^{\text{KBr}}$ 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 C₁₆H₂₀O₄S: 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 Et₂O–hexane), 61.5%. IR $\nu_{\text{max}}^{\text{KBr}}$ 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 C₁₄H₁₆O₅S: 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 Et₂O–hexane), 77.8%. IR $\nu_{\text{max}}^{\text{KBr}}$ 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 C₁₉H₁₈O₅S: C, 63.67; H, 5.06. Found: C, 63.70; H, 5.18.

3-Benzoyl-2-propionylthiomethylpropionic Acid (**36**): mp 76–78 °C (from Et₂O–hexane), 68.1%. IR $\nu_{\text{max}}^{\text{KBr}}$ 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 C₁₄H₁₆O₄S: C, 59.98; H, 5.75. Found: C, 60.21; H, 5.69.

3-Benzoyl-2-benzoylthiomethylpropionic Acid (**37**): mp 110–111 °C (from Et₂O–hexane), 33.8%. IR $\nu_{\text{max}}^{\text{KBr}}$ 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 C₁₈H₁₆O₄S: 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 $\nu_{\text{max}}^{\text{KBr}}$ 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 C₁₄H₁₅BrO₄S: 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 $\nu_{\text{max}}^{\text{KBr}}$ 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 C₁₈H₁₅BrO₄S: 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 $\nu_{\text{max}}^{\text{KBr}}$ 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 C₁₅H₁₈O₄S: 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 $\nu_{\text{max}}^{\text{neat}}$ 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 C₁₄H₁₅BrO₄S: 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 $\nu_{\text{max}}^{\text{neat}}$ 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 C₁₅H₁₇BrO₄S: 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 $\nu_{\text{max}}^{\text{neat}}$ 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 C₁₆H₁₉BrO₄S: 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 Et₂O–hexane). IR $\nu_{\text{max}}^{\text{KBr}}$ 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 C₂₀H₁₉BrO₄S: 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 H₂O (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 H₂O, and the whole was extracted with AcOEt. The extract was washed with H₂O, dried (MgSO₄) 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 Et₂O–hexane), 73.8%.

(2) 3-Benzoyl-3-butenic Acid¹¹: 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 H₂O, dried (MgSO₄) and concentrated. The residue was purified by column chromatography using CH₂Cl₂–hexane (1:1, v/v) as an eluent, then recrystallized from Et₂O–hexane to give colorless needles (4.12 g, 75.4%), mp 61–62 °C. The following compounds were similarly prepared. 3-(4-Bromobenzoyl)-3-butenic acid¹¹: mp 85–87 °C (from Et₂O–hexane), 65.7%. 3-(3-Bromobenzoyl)-3-butenic acid: mp 124–125 °C (from Et₂O–hexane), 66.8%. 3-(4-Chlorobenzoyl)-3-butenic acid: 81–83 °C (from Et₂O–hexane), 37.9%. 3-(4-Fluorobenzoyl)-3-butenic acid: mp 111–112 °C (from Et₂O–hexane), 46.0%. 3-(4-Methylbenzoyl)-3-butenic acid: mp 60–62 °C (from Et₂O–hexane), 75.9%. 3-(3-Methylbenzoyl)-3-butenic acid: mp 60–67 °C (from Et₂O–hexane), 76.5%. 3-(2-Methylbenzoyl)-3-butenic acid¹¹: Oil, 88.3%. 3-(4-Ethylbenzoyl)-3-butenic acid: mp 62–64 °C (from Et₂O–hexane), 65.9%. 3-(4-Isopropylbenzoyl)-3-butenic acid: mp 65–66.5 °C (from Et₂O–hexane), 60.8%. 3-(4-Methoxybenzoyl)-3-butenic acid: mp 107–108 °C (from Et₂O–hexane), 66.2%. 3-[4-(Phenylthio)benzoyl]-3-butenic acid: mp 97–98 °C (from Et₂O–hexane), 65.4%. 3-(4-Phenylbenzoyl)-3-butenic acid¹²: mp 142–143 °C (from Et₂O–hexane), 66.0%. 3-[4-(4-Bromophenyl)benzoyl]-3-butenic acid: mp 136–138 °C (from CH₂Cl₂–hexane), 72.5%. 3-[4-(2-Bromophenyl)benzoyl]-3-butenic acid: mp 129.5–130.5 °C (from CH₂Cl₂), 73.7%. 3-[4-(4-Chlorophenyl)benzoyl]-3-butenic acid: mp 133–134 °C (from CH₂Cl₂–hexane), 68.6%. 3-[4-(4-Methylphenyl)benzoyl]-3-butenic acid: mp 154–156 °C (from CH₂Cl₂–hexane), 47.7%.

(3) Ethyl 3-Benzoyl-3-butenate: This compound was prepared from 3-benzoyl-3-butenic 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-butenate: Oil, 94.1%. Ethyl 3-(4-Fluorobenzoyl)-3-butenate: Oil, 78.4%.

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

manner similar to that described under method A (4), mp 87–88 °C (from Et₂O–hexane), 71.2%. IR $\nu_{\text{max}}^{\text{KBr}}$ 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 C₁₃H₁₄O₄S: 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 $\nu_{\text{max}}^{\text{neat}}$ 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 C₁₅H₁₈O₄S: 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 Et₂O–hexane), 75.2%. IR $\nu_{\text{max}}^{\text{KBr}}$ 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 C₁₃H₁₃BrO₄S: 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 $\nu_{\text{max}}^{\text{neat}}$ 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 C₁₃H₁₃BrO₄S: 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 Et₂O–hexane), 78.3%. IR $\nu_{\text{max}}^{\text{KBr}}$ 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 C₁₃H₁₃ClO₄S: 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 $\nu_{\text{max}}^{\text{KBr}}$ 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 C₁₅H₁₆ClO₄S: 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 Et₂O–hexane), 75.4%. IR $\nu_{\text{max}}^{\text{KBr}}$ 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 C₁₃H₁₃FO₄S: 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 $\nu_{\text{max}}^{\text{KBr}}$ 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 C₁₅H₁₇FO₄S: 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 $\nu_{\text{max}}^{\text{KBr}}$ 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 C₁₄H₁₆O₄S: 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 $\nu_{\text{max}}^{\text{KBr}}$ 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 C₁₄H₁₆O₄S: 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 Et₂O–hexane), 58.4%. IR $\nu_{\text{max}}^{\text{KBr}}$ 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 C₁₄H₁₆O₄S: 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 Et₂O–hexane), 97.6%. IR $\nu_{\text{max}}^{\text{KBr}}$ 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 C₁₅H₁₈O₄S: 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 Et₂O–hexane), 79.4%. IR $\nu_{\text{max}}^{\text{KBr}}$ 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 C₁₆H₂₀O₄S: 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 $\nu_{\text{max}}^{\text{KBr}}$ 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 C₁₄H₁₆O₅S: 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 Et₂O–hexane), 70.0%. IR $\nu_{\text{max}}^{\text{KBr}}$ 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 C₁₉H₁₈O₄S: C, 60.94; H, 4.84. Found: C, 60.92; H, 4.93.

3-Benzoyl-4-isopropylthiobutyric Acid (**55**): mp 80—81 °C (from Et₂O–hexane), 80.3%. IR $\nu_{\text{max}}^{\text{KBr}}$ 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 C₁₄H₁₈O₃S: C, 63.13; H, 6.81. Found: C, 62.98; H, 6.80.

3-Benzoyl-4-propionylthiobutyric Acid (**56**): mp 82—83 °C (from Et₂O–hexane), 58.4%. IR $\nu_{\text{max}}^{\text{KBr}}$ 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 C₁₄H₁₆O₄S: C, 59.98; H, 5.75. Found: C, 59.95; H, 5.67.

3-Benzoyl-4-benzoylthiobutyric Acid (**57**): mp 101—102 °C (from Et₂O–hexane), 76.8%. IR $\nu_{\text{max}}^{\text{KBr}}$ 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 C₁₈H₁₆O₄S: 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 Et₂O–hexane), 53.0%. IR $\nu_{\text{max}}^{\text{KBr}}$ 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 C₁₉H₁₈O₄S: 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 $\nu_{\text{max}}^{\text{KBr}}$ 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 C₁₉H₁₇BrO₄S: 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 $\nu_{\text{max}}^{\text{KBr}}$ 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 C₁₉H₁₇BrO₄S: 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 Et₂O–hexane), 82.6%. IR $\nu_{\text{max}}^{\text{KBr}}$ 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 C₁₉H₁₇ClO₄S: 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 Et₂O–hexane), 39.8%. IR $\nu_{\text{max}}^{\text{KBr}}$ 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 C₂₀H₂₀O₄S: C, 67.39; H, 5.66. Found: C, 67.29; H, 5.71.

3-Benzoyl-2-mercaptopropionic Acid (**12**): An 80% N₂H₄ 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 H₂O and the whole was extracted with AcOEt. The extract was washed with H₂O, dried (MgSO₄) and concentrated. The residue was purified by column chromatography using Et₂O–hexane (1:1, v/v) as an eluent, then crystallized from Et₂O–hexane to give colorless prisms (3.1 g, 41%), mp 145—146 °C. IR $\nu_{\text{max}}^{\text{KBr}}$ 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 C₁₀H₁₀O₃S: C, 57.12; H, 4.79. Found: C, 57.24; H, 4.92.

3-Acetylthio-3-(4-bromobenzoyl)propionic Acid (**18**): A solution of Br₂ (6.2 g) in CHCl₃ (20 ml) was added dropwise to a stirred solution of 3-(4-bromobenzoyl)propionic acid¹³⁾ (10.0 g) in CHCl₃ (100 ml). The mixture was stirred for an additional 3 h at room temperature, and CHCl₃ was removed under reduced pressure. The residue was dissolved in Et₂O and the whole was washed with H₂O, dried (MgSO₄) 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 H₂O. The whole was extracted with AcOEt and the extract was washed with H₂O, dried (MgSO₄) and concentrated. The residue was recrystallized from Et₂O–hexane to give colorless needles (6.5 g, 50.5%), mp 125.5—126 °C. IR $\nu_{\text{max}}^{\text{KBr}}$ 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 C₁₂H₁₁BrO₄S: C, 43.52; H, 3.35. Found: C, 43.54; H, 3.46.

References and Notes

- 1) K. Tomisawa, K. Kameo, T. Matsunaga, S. Saito, K. Hosoda, T. Asami and K. Sota, *Chem. Pharm. Bull.*, **33**, 2386 (1985).
- 2) a) Y. Shiokawa, Y. Horiuchi, M. Honma, T. Kageyama, T. Okada and T. Azuma, *Arthritis Rheum.*, **20**, 1464 (1979); b) R. Baumgartner, H. Obenaus and H. C. Staerk, *Proc. Soc. Exp. Biol. Med.*, **146**, 241 (1974); c) S. Otomo, S. Nakaike, I. Tsuji, C. Mori and M. Ohzeki, *Folia Pharmacol. Jpn.*, **77**, 313 (1981); d) H-C. Liu, *Nippon*

- Seikeigeka Gakkai Zasshi*, **51**, 161 (1977); e) F. Capasso, N. Mascolo and G. Autore, *Pharmacol. Res. Commun.*, **13**, 385 (1981).
- 3) O. Grummitt, E. I. Becker and C. Miesse, "Organic Syntheses," Coll. Vol. III, ed. by E. C. Horning, John Wiley and Sons, Inc., New York, 1955, p. 109.
 - 4) A. Markovac, M. P. LaMontagne, P. Blumbergs, A. B. Ash and C. L. Stevens, *J. Med. Chem.*, **15**, 918 (1972).
 - 5) H. Cousse, G. Mouzin, J-P. Pieu, A. Delhon, F. Brunnguel and F. Fauran, *Eur. J. Med. Chem.*, **22**, 45 (1987).
 - 6) L. F. Somerville and C. F. H. Allen, "Organic Syntheses," Coll. Vol. II, ed. by A. H. Blatt, John Wiley and Sons, Inc., New York, 1955, p. 81.
 - 7) R. E. Lutz, P. S. Bailey, C-K. Dien and J. W. Rinker, *J. Am. Chem. Soc.*, **75**, 5039 (1953).
 - 8) W. Mohr and A. Wild, *Arzneim.-Forsch./Drug Res.*, **26**, 1860 (1976).
 - 9) G. P. Rice, *J. Am. Chem. Soc.*, **45**, 222 (1923).
 - 10) The other 3-benzoylpropionic acids were prepared from succinic anhydride in a manner similar to that described under method A (1).
 - 11) G. Cignarella, G. Grella and M. M. Curzu, *Synthesis*, **1980**, 825.
 - 12) H. Henri, M. Gilbert and R. J. Pierre, Fr. Patent 2503140 (1980) [*Chem. Abstr.*, **98**, 178950 (1983)].
 - 13) D. Papa, E. Schwenk, F. Villani and E. Klingsberg, *J. Am. Chem. Soc.*, **70**, 3356 (1948).