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Studies on Hypolipidemic Agents. IV. 3-[4-(Phenylthio)benzoyl]propionic Acid Derivatives

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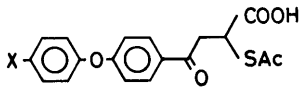
2-Acetylthio-3-benzoylpropionic acid derivatives having two benzene rings or condensed-ring moieties were prepared, and tested for hypolipidemic activity in normal rats. Some of these compounds were active. 2-Acetylthio-3-[4-(phenylthio)benzoyl]propionic acid (10) and its derivatives seemed to have the most potent hypocholesterolemic activities. Compound 10 showed strong activity, especially in cholesterol-fed rats.

Keywords 3-[4-(phenylthio)benzoyl]propionic acid; 2-acetylthio-3-[4-(4-chlorophenoxy)benzoyl]propionic acid; hypolipidemic activity; structure–activity relationship; clofibrate

In the previous work,[1] we found that 2-acetylthio-3-(4-phenoxybenzoyl)propionic acids (I) (Chart 1) have hypocholesterolemic activities, and studies of chemically modified derivatives having the diphenyl ether moiety indicated that the partial structure $-CH_2CH(SAc)COOH$ is the most favorable feature for the activity. During studies on antirheumatic agents,[2] we synthesized 2-acetylthio-3-benzoylpropionic acid derivatives, having one benzene ring moiety, and found that these derivatives lack hypolipidemic activities. It is known that some hypolipidemic compounds,



Ia: X=H
Ib: X=Cl

Chart 1

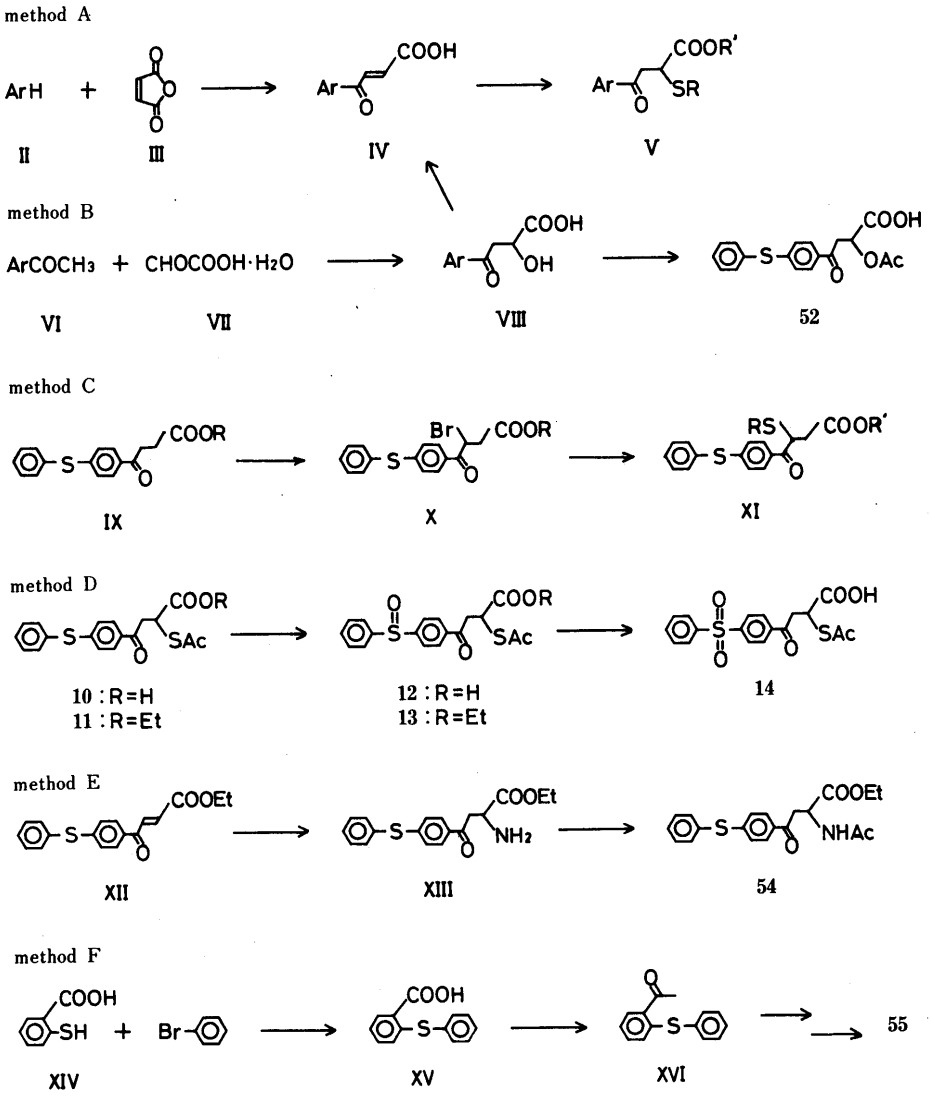
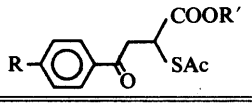
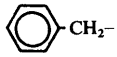
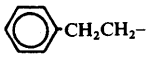
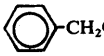
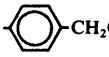
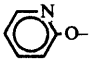
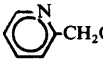
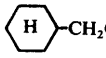
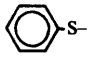
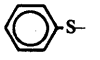
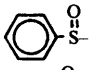
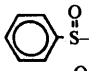
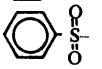
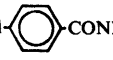
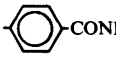
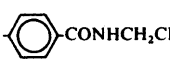
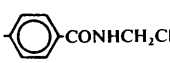
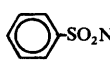
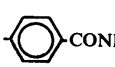


Chart 2

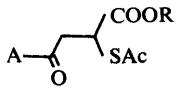
TABLE I. Physical and Biological Properties of 2-Acetylthio-3-benzoylpropionic Acids

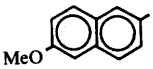
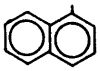
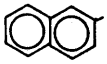
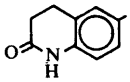
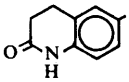
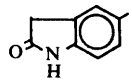
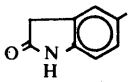
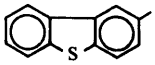
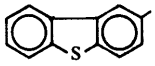
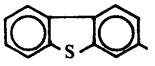
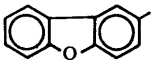
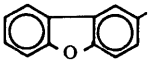
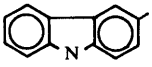
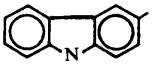
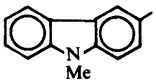
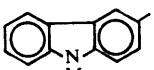


No.	R	R′	Formula[a]	mp (°C) (Recrystn.[b] solvent)	Hypolipidemic activity rank[c]	
					Cholesterol	Triglyceride
1		H	$C_{18}H_{16}O_4S$	156—159 (A–H)	3	3
2		H	$C_{19}H_{18}O_4S$	110—113 (A–H)	2	1
3		H	$C_{20}H_{20}O_4S$	129—130 (AE–H)	2	0
4		H	$C_{19}H_{18}O_5S$	132.5—133.5 (D–H)	0	0
5 Cl		H	$C_{19}H_{17}ClO_5S$	128—129.5 (D–H)	1	3
6		H	$C_{17}H_5NO_5S$	138—139 (D–H)	0	0
7		H	$C_{18}H_7NO_5S$	153—155 (D–H)	0	0
8		H	$C_{18}H_{22}O_4S$	91—93 (E–H)	0	0
9		H	$C_{19}H_{24}O_5S$	88—89 (E–H)	1	0
10		H	$C_{18}H_{16}O_4S_2$	116.5—118.5 (AE–H)	4	2
11		Et	$C_{20}H_{20}O_4S_2$	71—72.5 (D–H)	3	0
12		H	$C_{18}H_{16}O_5S_2$	Oil[d]	0	0
13		Et	$C_{20}H_{20}O_5S_2$	Oil[d]	1	0
14		H	$C_{18}H_{16}O_6S_2$	143—144 (AE–H)	0	0
15 Cl		H	$C_{19}H_{16}ClNO_5S$	202 (dec.) (THF)	1	0
16 Cl		Et	$C_{21}H_{20}ClNO_5S$	142—144 (D–H)	0	0
17		H	$C_{21}H_{21}NO_5S$	183—184 (dec.) (THF)	0	0
18		Et	$C_{23}H_{35}NO_5S$	140—141 (AE)	0	0
19 Cl		H	$C_{21}H_{20}ClNO_5S$	186—187 (A)	0	0
20 Cl		Et	$C_{23}H_{24}ClNO_5S$	106—108 (AE)	0	0
21		H	$C_{18}H_{17}NO_6S_2$	167—169 (dec.) (AE)	0	0
22 Cl		H	$C_{20}H_{18}NO_5S$	Oil[d]	0	0

a) All compounds were analyzed for C, H and N: analytical results obtained for these elements were within ±0.4% of calculated values. *b*) A=acetone, AE=AcOEt, D=CH_2Cl_2, E=Et_2O, H=*n*-hexane. *c*) Reduction levels were calculated as percentages with respect to the control value; less than 9% reduction=0, 10—19% reduction=1, 20—29% reduction=2, 30—39% reduction=3, 40—49% reduction=4. *d*) Purified by column chromatography.

TABLE II. Physical and Biological Properties of 2-Acetylthio-3-benzoylpropionic Acids

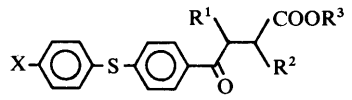


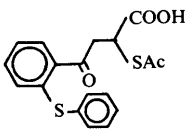
No.	A	R	Formula[a]	mp (°C) (Recrystn.[b] solvent)	Hypolipidemic activity rank[c]	
					Cholesterol	Triglyceride
23		H	$C_{17}H_{16}O_5S$	115—117 (D–H)	0	0
24		H	$C_{16}H_{14}O_4S$	149—150 (AE)	0	0
25		H	$C_{16}H_{14}O_4S$	118—120 (AE)	0	0
26		H	$C_{15}H_{15}NO_5S$	193—195 (AE)	0	0
27		Et	$C_{17}H_{19}NO_5S$	133—135 (D–H)	0	1
28		H	$C_{14}H_{13}NO_5S$	134—137 (AE)	0	0
29		Et	$C_{16}H_{17}NO_5S$	103—107 (AE–H)	0	1
30		H	$C_{18}H_{14}O_4S_2$	160 (dec.) (AE–H)	3	1
31		Et	$C_{20}H_{18}O_4S_2$	96—98 (E–H)	2	0
32		H	$C_{18}H_{14}O_4S_2$	167.5—168 (AE–H)	2	3
33		H	$C_{18}H_{14}O_5S$	157—159 (AE–H)	3	0
34		Et	$C_{20}H_{18}O_5S$	Oil[d]	1	0
35		H	$C_{20}H_{19}NO_5S$	189—191 (A)	1	0
36		Et	$C_{22}H_{21}NO_5S$	104—108 (AE–H)	1	0
37		H	$C_{19}H_{17}NO_4S$	185—188 (dec.) (A)	0	0
38		Et	$C_{21}H_{21}NO_4S$	104—105 (AE–H)	0	0

a—*d*) See footnotes in Table I.

such as Beclobrate,[3] Bezafibrate[4] and Itanoxone,[5] have two benzene rings in their structure. Since it was considered that the presence of two benzene rings is important for the hypolipidemic activity, in an attempt to find a new hypolipidemic agent we investigated a series of 2-acetylthio-3-benzoylpropionic acid derivatives having two benzene rings and condensed-ring moieties in place of the diphenyl ether

TABLE III. Physical and Biological Properties of 3-(4-Phenylthiobenzoyl)propionic Acids



No.	X	R^1	R^2	R^3	Formula[a]	mp (°C) (Recrystn.[b] solvent)	Hypolipidemic activity rank[c] Cholesterol	Triglyceride
10	H	H	SAc	H			4	2
39	Me	H	SAc	H	$C_{19}H_{18}O_4S_2$	127—129 (D–H)	2	3
40	Cl	H	SAc	H	$C_{18}H_{15}ClO_4S_2$	111—114 (D–H)	4	4
11	H	H	SAc	Et			3	0
41	H	H	SAc	iso-Pr	$C_{21}H_{22}O_4S_2$	82—82.5 (E–H)	1	0
42	H	H	SAc	*n*-Bu	$C_{22}H_{24}O_4S_2$	50—51.5 (E–H)	1	0
43	H	H	SAc	CH_2Ph	$C_{25}H_{22}O_4S_2$	126—127 (AE–H)	0	0
44	H	H	SCOEt	H	$C_{18}H_{18}O_4S_2$	94—95 (E–H)	2	1
45	H	H	SCOEt	Et	$C_{21}H_{22}O_4S_2$	56—57 (E–H)	3	0
46	H	H	SCOPh	H	$C_{23}H_{18}O_4S_2$	128—129 (AE–H)	2	0
47	H	H	SH	H	$C_{16}H_{14}O_3S_2$	146—147 (AE–H)	3	0
48	H	H	SH	Et	$C_{18}H_{18}O_3S_2$	49—50 (E–H)	1	2
49	H	H	SMe	H	$C_{17}H_{16}O_3S_2$	110—111 (D–H)	3	0
50	H	H	SEt	H	$C_{18}H_{18}O_3S_2$	84—86 (E–H)	3	3
51	H	H	S-iso-Pr	H	$C_{19}H_{20}O_3S_2$	124—125 (E–H)	1	0
52	H	H	OAc	H	$C_{18}H_{16}O_5S$	122—124 (AE)	2	0
53	H	H	OH	H	$C_{16}H_{14}O_4S$	135—137 (AE)	0	1
54	H	H	NHAc	Et	$C_{20}H_{21}NO_4S$	87—88 (E)	1	0
55					$C_{18}H_{16}O_4S_2$	150—151 (D–H)	2	1
56	H	SH	H	H	$C_{16}H_{14}O_3S_2$	109—111 (E–H)	1	3
57	H	SH	H	Et	$C_{18}H_{18}O_3S_2$	Oil[d]	2	2
58	H	SAc	H	H	$C_{18}H_{16}O_4S_2$	109—110 (E–H)	2	2
59	H	SAc	H	Et	$C_{20}H_{20}O_4S_2$	Oil[d]	1	0
60	H	SCOEt	H	H	$C_{19}H_{18}O_4S_2$	91 (E–H)	0	0
61	H	SCOPh	H	H	$C_{23}H_{18}O_4S_2$	57—158 (D–H)	0	3
62	H	SMe	H	H	$C_{17}H_{16}O_3S_2$	114—116 (E–H)	1	2

a—d) See footnotes in Table I.

moiety of I.

Chemistry The test compounds listed in Tables I—III were synthesized by the methods shown in Chart 2. 3-Benzoylacrylic acids (IV) were mostly prepared by Friedel–Crafts acylation using maleic anhydride (method A). Acetophenones (VI) were allowed to react with glyoxylic acid at 95 °C and dehydrated to give acrylic acids (IV) (method B). Treatment of IV with mercapto compounds provided 2-mercapto-3-propionic acids (V). 3-[4-(phenylthio)benzoyl]propionic acids (IX) were brominated at the 3-position and allowed to react with mercapto compounds in the presence of potassium carbonate to give 3-mercapto-3-[4-(phenylthio)benzoyl]propionic acids (XI) (method C). The acetylthio derivatives (V, R=Ac) were easily converted to the corresponding mercapto derivatives (R=H) by treatment with hydrazine. 2-Acetylthio-3-[4-(phenylthio)benzoyl]propionic acid and its ester (**10**, **11**) were oxidized with *m*-chloroperbenzoic acid to give the sulfinyl (**12**,**13**) and sulfonyl (**14**) derivatives (method D). Treatment of ethyl 3-[4-(phenylthio)benzoyl]acrylate (XII) with ammonia water, and then acetyl chloride provided the 2-acetamido derivative (**54**) (method E). 2-Acetylphenyl phenyl sulfide (XVI) was prepared from 2-mercaptobenzoic acid (XIV) in 2 steps (method F) and converted to 2-acetylthio-3-[2-(phenylthio)benzoyl]propionic acid (**55**) by the same reactions as in method B.

Biological Methods 1) In Normal Rats (Tables I—III, Fig. 1): Five-week-old male rats (five rats per group) were used. After prefeeding for a week, the test compounds, which were prepared as a suspension in 0.2% sodium carboxymethylcellulose (CMC-Na) solution, were orally administered to the rats at a daily dose of 100 mg/kg for 3 d. A 0.2% CMC-Na solution was orally administered to the rats in the control group. At 18 h after the final drug administration, the rats were anesthetized with diethyl ether and their blood was collected. The lipid concentration in serum was then determined with an autoanalyzer (Hitachi model 105).

2) In Cholesterol-Fed Rats (Fig. 2): Seven-week-old male rats (six rats per group) were used. The high-cholesterol diet was prepared from normal rat food (Oriental Yeast Co., Ltd.) by adding 1% cholesterol and 0.5% Na cholate. The animals were fed on the high-cholesterol diet *ad lib.* for 10 d. For the following 6 d, the test compounds, which were prepared as a suspension in 0.2% CMC-NA solution, were orally administered to the rats at a daily dose of 50 or 100 mg/kg. A 0.2% CMC-Na solution was orally administered to the cholesterol-fed rats in the control group. At the end of the experimental period, they were treated as in 1).

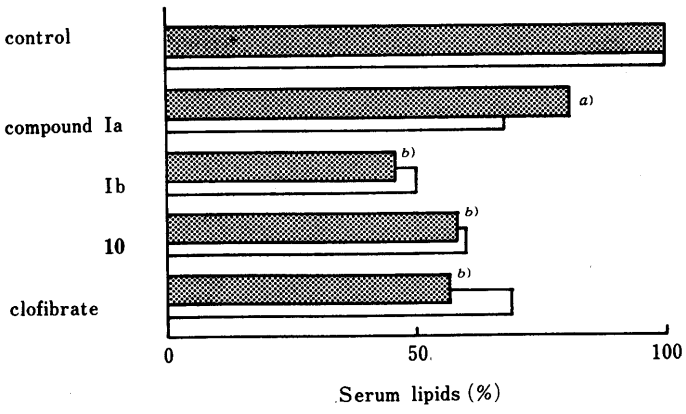


Fig. 1. Effect of Compounds Ia, Ib and **10** on Serum Lipids in Normal Rats

▒, cholesterol; □, triglyceride; *a*) $p<0.01$, *b*) $p<0.001$.

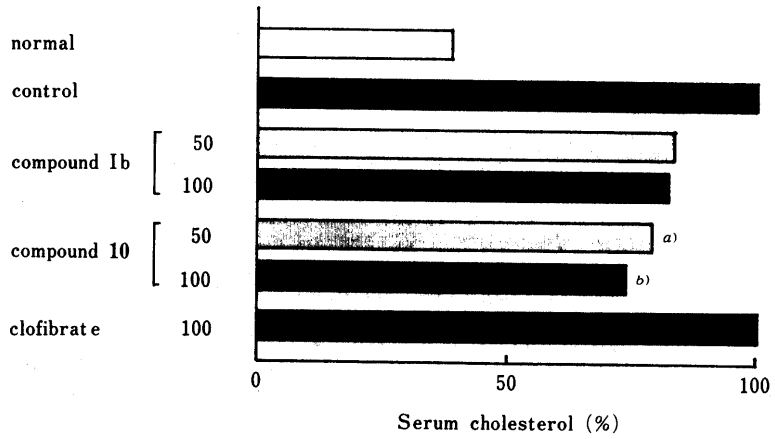


Fig. 2. Effect of Compounds Ib and **10** on Serum Total Cholesterol in Cholesterol-Fed Rats
a) $p<0.05$, *b*) $p<0.01$.

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 Table I, with regard to the effects of the structure between the two benzene rings, the methylene (**2**)-, ethylene (**3**)- and sulfide (**10**, **11**)-linked derivatives showed potent hypocholesterolemic activities, and the diphenyl derivative (**1**) revealed comparable activity. But the other linkages, such as methyleneoxy (**4**, **5**), sulfinyl (**12**, **13**), sulfonyl (**14**), amido (**15**, **16**), *etc.*, resulted in diminished activities, and the 2-pyridyloxy (**6**) and the cyclohexyl (**8**) derivatives also displayed only slight activities. Among the condensed-ring derivatives, as shown in Table II, the dibenzothiophene (**30**—**32**) and the dibenzofuran (**33**, **34**) derivatives showed activity. In the series of Tables I and II, compound **10**, containing the diphenyl sulfide group, was found to be the most active analogue. We then further investigated derivatives of the diphenyl sulfide, as shown in Table III, and the following structure–activity relationships were found. (i) Methyl or chloro substitution at the *para* position on the diphenyl sulfide had little influence on the activity (**39**, **40**). (ii) The activities of the ester derivatives are weaker than those of the corresponding free carboxylic acid. (iii) Like the 2-acylthio derivatives (**44**—**46**), the 2-methylthio (**49**) and 2-ethylthio (**50**) derivatives are active. (iv) The 3-acylthio derivatives (**56**—**62**) are less active than the 2-acylthio derivatives. (v) Replacement of the 3-acylthio moiety of **10** with an acetoxy or acetamido group lowered the activity. (vi) The activity of the *ortho*-phenylthio derivative (**55**) is weaker than that of the *para*-phenylthio compound (**10**). Most of these tendencies were similarly found in the diphenyl ether derivatives (I), but (i) and (iii) were not applicable.[1] (In the derivatives of I, chloro substitution at the *para* position on the diphenyl ether greatly increased the activity and the 2-alkylthio derivatives were inactive.)

Next, we compared the hypocholesterolemic activities of **10**, Ia, Ib and clofibrate[6] (CPIB, ethyl 2-(4-chlorophenoxy)-2-methylpropionate) using normal rats (Fig. 1) and cholesterol-fed rats (Fig. 2). As shown in Fig. 1, the potencies of their activities in the normal rats were in the order Ib > **10** = CPIB > Ia.

In cholesterol-fed rats (Fig. 2), however, the activity of **10** was stronger than that of Ib, and CPIB showed no activity. In the normal rats, CPIB increased the weight of the liver by 25% over the control value, while **10** increased it 5.7%. From these biological results, it is concluded that compound **10** shows strong activity, especially in cholesterol-fed rats, and has no liver toxicity, so it is likely that the mechanism of hypocholesterolemic activity of **10** is different from that of CPIB. Detailed pharmacological data will be reported elsewhere.[7]

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 Varian XL-200 spectrometer. The chemical shifts are expressed as ppm down field 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. IR and ^{1}H-NMR spectral data for the compounds **1**—**62** are listed in Tables IV—VI.

Method A (1) 3-[4-(Phenylthio)benzoyl]acrylic Acid: $AlCl_3$ (6.7 g) was added to a stirred solution of diphenyl sulfide (5.23 g) and maleic anhydride (2.45 g) in CH_2Cl_2 (150 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 ($MgSO_4$) and concentrated. The residue was recrystallized from AcOEt–hexane to give yellow needles (5.11 g, 71.9%), mp 157—159 °C. IR ν_{max}^{KBr} cm^{-1}: 1690, 1660. NMR (acetone-d_6) δ: 6.77 (1H, d, J=16 Hz), 7.30—7.62 (7H, m), 7.93 (1H, d, J=16 Hz), 8.02 (2H, d, J=9 Hz), 13.00 (1H, br s).

The following compounds were similarly prepared. 3-(4-Phenylbenzoyl)acrylic Acid[8]: mp 172—175 °C (form AcOEt–hexane), 42%. 3-(4-Benzylbenzoyl)acrylic Acid: Oil, 94%. 3-[4-(2-Phenylethyl)]-benzoylacrylic Acid: mp 72—74 °C (from Et_2O–hexane), 83%. 3-(4-Cyclohexylbenzoyl)acrylic Acid[9]: mp 138—140 °C (from Et_2O–hexane), 62%. 3-(4-Cyclohexylmethylbenzoyl)acrylic Acid: mp 151.5—153 °C (from acetone–hexane), 23%. 3-[4-(4-Chlorobenzoylamino)benzoyl]-acrylic Acid: >220 °C (from AcOEt), 74%. 3-[4-(2-Benzoylaminoethyl)-benzoyl]acrylic Acid: mp 163—165 °C (from AcOEt), 86%. 3-[4-(2-(4-Chlorobenzoyl)aminoethyl)benzoyl]acrylic Acid: mp 174—175 °C (from AcOEt), 95%. 3-(4-Phenylsulfonylaminobenzoyl)acrylic Acid: mp 177—178 °C (from AcOEt), 38%. 3-[4-(4-Chlorobenzoyl)aminomethylbenzyl]-acrylic Acid: mp 178—181 °C (from AcOEt), 81%. 3-(1-Naphthoyl)acrylic Acid[10]: mp 144—145 °C (from AcOEt), 25%. 3-(2-Naphthoyl)acrylic Acid[10]: mp 164—165 °C (from AcOEt), 21%. 4-(3,4-Dihydro-2(*H*)-quinolon-6-yl)-4-oxo-2-butenoic Acid: mp *ca.* 210 °C (dec.) (from AcOEt). 4-(5-Oxaindolyl)-4-oxo-2-butenoic Acid: mp > 220 °C (from AcOEt), 91%. 4-(3-Dibenzothienyl)-4-oxo-2-butenoic Acid: mp 192—195 °C (dec.) (from acetone–hexane), 16%. 4-(2-Dibenzothienyl)-4-oxo-2-butenoic Acid: mp 205 °C (dec.) (from acetone–hexane), 5%. 4-[3-(9-Acetylcarba-

TABLE IV. IR and ^{1}H-NMR Spectral Data for the Compounds in Table I

No.	Method	Yield (%)	IR ν_{max} cm^{-1}	NMR	
				Solv.[a]	Chemical shift δ ppm
1	A	81.8	(KBr) 1720, 1680	C	2.21 (3H, s), 3.66 (1H, dd, J=16, 4Hz), 3.75 (1H, dd, J=16, 6Hz), 6.80 (1H, brs), 7.40—7.75 (7H, m), 8.04 (2H, d, J=8Hz)
2	A	64.1	(KBr) 1700—1670	C	2.37 (3H, s), 3.55 (1H, dd, J=18, 6Hz), 3.68 (1H, dd, J=18, 8Hz), 4.04 (2H, s), 4.75 (1H, dd, J=8, 6Hz), 7.16—7.31 (7H, m), 7.88 (2H, d, J=8Hz)
3	A	94.3	(KBr) 1700, 1680	C	2.38 (3H, s), 2.92—3.03 (4H, m), 3.55 (1H, dd, J=18, 5Hz), 3.69 (1H, dd, J=18, 7Hz), 4.76 (1H, dd, J=7, 5Hz), 7.13—7.34 (7H, m), 7.87 (2H, d, J=9Hz), 8.66 (1H, brs)
4	B	79.7	(KBr) 1700, 1670	A	2.38 (3H, s), 3.52 (1H, dd, J=17, 5Hz), 3.70 (1H, dd, J=17, 8Hz), 4.74 (1H, dd, J=8, 5Hz), 5.25 (2H, s), 7.14 (2H, d, J=8Hz), 7.45 (5H, m), 8.02 (2H, d, J=8Hz)
5	B	70.7	(KBr) 1720, 1700, 1660	C	2.36 (3H, s), 3.51 (1H, dd, J=17, 5Hz), 3.62 (1H, dd, J=17, 8Hz), 4.72 (1H, dd, J=8, 5Hz), 5.08 (2H, s), 6.98 (2H, d, J=8Hz), 7.36 (4H, m), 7.92 (2H, d, J=8Hz)
6	B	78.2	(KBr) 1710—1640	C	2.37 (3H, s), 3.56 (1H, dd, J=18, 7Hz), 3.66 (1H, dd, J=18, 7Hz), 4.53 (1H, t, J=7Hz), 6.99 (1H, d, J=8Hz), 7.09 (1H, dd, J=8, 5Hz), 7.77 (1H, td, J=8, 2Hz), 8.26 (1H, dd, J=5, 2Hz)
7	B	78.6	(KBr) 1720, 1682, 1662	D	2.36 (3H, s), 3.48 (1H, dd, J=17, 5Hz), 3.62 (1H, dd, J=17, 8Hz), 4.53 (1H, dd, J=8, 5Hz), 5.29 (2H, s), 7.15 (2H, d, J=8Hz), 7.37 (1H, dd, J=8, 5Hz), 7.54 (1H, d, J=8Hz), 7.85 (1H, td, J=8, 2Hz), 7.96 (2H, d, J=8Hz), 8.60 (1H, m)
8	A	93.5	(KBr) 1715, 1680	C	1.42 (5H, m), 1.86 (5H, m), 2.38 (3H, s), 2.57 (1H, m), 3.58 (1H, dd, J=18, 5Hz), 3.66 (1H, dd, J=18, 8Hz), 4.76 (1H, dd, J=8, 5Hz), 7.31 (2H, d, J=8Hz), 7.89 (2H, d, J=8Hz)
9	A	68.7	(KBr) 1700, 1675	C	0.95—1.42 (5H, m), 1.64—1.95 (6H, m), 2.38 (3H, s), 3.52 (1H, dd, J=17, 5Hz), 3.65 (1H, dd, J=17, 7Hz), 3.81 (2H, d, J=6Hz), 4.75 (1H, dd, J=7, 5Hz), 6.92 (2H, d, J=8Hz), 7.51 (2H, d, J=8Hz), 8.80 (1H, brs)
10	A	94.8	(KBr) 1700, 1675	C	2.38 (3H, s), 3.50 (1H, dd, J=18, 6Hz), 3.64 (1H, dd, J=18, 7Hz), 4.74 (1H, dd, J=7, 6Hz), 7.19—7.55 (7H, m), 7.81 (2H, d, J=9Hz), 8.80 (1H, brs)
11	A	88.9	(KBr) 1735, 1700, 1670	C	1.24 (3H, t, J=7Hz), 2.36 (3H, s), 3.48 (1H, dd, J=18, 4Hz), 3.64 (1H, dd, J=18, 8Hz), 4.20 (2H, q, J=7Hz), 4.69 (1H, dd, J=8, 4Hz), 7.21 (2H, d, J=9Hz), 7.40—7.54 (5H, m), 7.82 (2H, d, J=9Hz)
12	D	94.8	(KBr) 1700—1690	C	2.35 (3H, s), 3.52 (1H, dd, J=14, 8Hz), 3.67 (1H, dd, J=14, 7Hz), 4.74 (1H, dd, 7.47—7.70 (5H, m), 7.75 (2H, d, J=9Hz), 8.02 (2H, d, J=9Hz)
13	D	57.1	(KBr) 1725, 1690—1670	C	1.24 (3H, t, J=7Hz), 2.36 (3H, s), 3.50 (1H, dd, J=16, 5Hz), 3.69 (1H, dd, J=16, 7Hz), 4.19 (2H, q, J=7Hz), 4.69 (1H, dd, J=7, 5Hz), 7.46—7.70 (5H, m), 7.76 (2H, d, J=9Hz), 8.04 (2H, d, J=9Hz)
14	D	45.8	(KBr) 1700—1680	A	2.17 (3H, s), 3.58 (1H, dd, J=19, 4Hz), 3.82 (1H, dd, J=19, 8Hz), 4.73 (1H, dd, J=8, 4Hz), 7.60—7.73 (3H, m), 8.04 (1H, d, J=8Hz), 8.05 (1H, d, J=8Hz), 8.19 (4H, m)
15	A	59.1	(KBr) 3320, 1720—1640	D	2.38 (3H, s), 3.52 (1H, dd, J=18, 4Hz), 3.66 (1H, dd, J=18, 8Hz), 4.55 (1H, dd, J=8, 4Hz), 7.65 (2H, d, J=8Hz), 8.02 (6H, m), 10.57 (1H, s), 12.84 (1H, brs)
16	A	92.5	(KBr) 3350, 1740, 1695, 1680, 1660	D	1.15 (3H, t, J=7Hz), 2.38 (3H, s), 3.56 (1H, dd, J=18, 4Hz), 3.70 (1H, dd, J=18, 8Hz), 4.10 (2H, q, J=7Hz), 4.58 (1H, dd, J=8, 2Hz), 7.64 (2H, d, J=8Hz), 8.00 (6H, m), 10.57 (1H, s)
17	A	87.8	(KBr) 3340, 2900, 1700, 1675	D	2.38 (1H, s), 2.94 (2H, t, J=7Hz), 3.50 (3H, m), 3.65 (1H, dd, J=18, 8Hz), 4.52 (1H, J=8, 5Hz), 7.40 (2H, d, J=8Hz), 7.48 (3H, m), 7.80 (2H, dd, J=8, 2Hz), 7.92 (2H, d, J=8Hz), 8.53 (1H, t, J=5Hz), 12.85 (1H, brs)
18	A	93.4	(KBr) 3280, 2970, 1730, 1710, 1680	D	1.14 (3H, t, J=7Hz), 2.40 (3H, s), 2.96 (2H, t, 7Hz), 3.55 (3H, m), 3.70 (1H, dd, J=18, 8Hz), 4.10 (2H, q, J=7Hz), 4.60 (1H, dd, J=8, 5Hz), 7.44 (2H, d, J=8Hz), 7.50 (3H, m), 7.82 (2H, dd, J=8, 2Hz), 7.94 (2H, d, J=8Hz), 8.60 (1H, t, J=5Hz)
19	A	92.7	(KBr) 3320, 2900, 1700, 1680, 1665	D	2.38 (3H, s), 2.95 (2H, t, J=7Hz), 3.52 (3H, m), 3.67 (1H, dd, J=18, 8Hz), 4.55 (1H, dd, J=8, 4Hz), 7.42 (2H, d, J=8Hz), 7.55 (2H, d, J=8Hz), 7.85 (2H, d, J=8Hz), 7.94 (2H, d, J=8Hz), 8.66 (1H, t, J=5Hz), 12.88 (1H, s)
20	A	97.6	(KBr) 3320, 2920, 1735, 1690, 1675	D	1.14 (3H, t, J=8Hz), 2.40 (3H, s), 2.95 (2H, t, J=7Hz), 3.56 (3H, m), 3.71 (1H, dd, J=18, 8Hz), 4.10 (2H, q, J=8Hz), 4.60 (1H, dd, J=8, 4Hz), 7.43 (2H, d, J=8Hz), 7.85 (2H, d, J=8Hz), 7.94 (2H, d, J=8Hz), 8.67 (1H, t, J=5Hz)
21	A	73.4	(KBr) 3420, 3210, 2900, 1700, 1670	D	2.36 (3H, s), 3.42 (1H, dd, J=18, 5Hz), 3.58 (1H, dd, J=18, 8Hz), 4.50 (1H, dd, J=8, 5Hz), 7.24 (2H, d, J=8Hz), 7.62 (3H, m), 7.88 (4H, m), 10.8 (1H, s), 12.8 (1H, brs)
22	A	95.6	(neat) 3340, 3000, 1730, 1660	D	2.38 (3H, s), 3.51 (1H, dd, J=18, 5Hz), 3.67 (1H, dd, J=18, 8Hz), 4.56 (3H, m), 7.48 (2H, d, J=8Hz), 7.58 (2H, d, J=8Hz), 7.94 (2H, d, J=8Hz), 7.98 (2H, d, J=8Hz), 9.24 (1H, t, J=5Hz), 12.8 (1H, brs)

a) C=$CDCl_3$: A=acetone-d_6; D=DMSO-d_6.

zolyl)]-4-oxo-2-butenoic Acid: mp 223 °C (dec.) (from AcOEt), 74%. 4-[3-(9-Methylcarbazolyl)]-4-oxo-2-butenoic Acid: mp 210 °C (dec.) (from AcOEt), 19%. 3-[4-(4-Methylphenylthio)benzoyl]acrylic Acid: mp 146—147 °C (from AcOEt), 84%. 3-[4-(4-Chlorophenylthio)benzoyl]acrylic Acid: mp 164—165 °C (from AcOEt), 87%.

(2) 2-Acetylthio-3-[4-(phenylthio)benzoyl]propionic Acid (**10**): 3-[4-Phenylthio)benzoyl]acrylic acid (5.12 g) and thioacetic acid (1.44 ml) were dissolved in CH_2Cl_2 (100 ml), then the mixture was stirred for 5 h at room temperature. The mixture was concentrated and the residue was recrystallized from AcOEt–hexane to give **10** (6.16 g, 94.8%), mp 116.5—118.5 °C. (*Anal.* Calcd for $C_{18}H_{16}O_4S_2$: C, 59.98; H, 4.47. Found: C, 59.84; H, 4.70).

Method B 3-(4-Benzyloxybenzoyl)-2-hydroxypropionic Acid: A mixture of 4-benzyloxyacetophenone (10.00 g) and glyoxylic acid monohydrate (5.15 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 with AcOEt. The aqueous layer was acidified with aqueous 10% HCl, and the whole was extracted with AcOEt. The extract was washed

TABLE V. IR and ^{1}H-NMR Spectral Data for the Compounds in Table II

No.	Method	Yield (%)	IR ν_{max} cm^{-1}	NMR	
				Solv.[a]	Chemical shift δ ppm
23	B	85.4	1720—1670	C	2.38 (3H, s), 3.70 (1H, dd, J=18, 6 Hz), 3.82 (1H, dd, J=18, 8 Hz), 3.94 (3H, s), 4.82 (1H, dd, J=8, 6 Hz), 7.21 (2H, m), 7.78 (1H, d, J=8 Hz), 7.84 (1H, J=8 Hz), 7.99 (1H, d, J=8 Hz), 8.40 (1H, s)
24	A	90.3	1720—1660	A	2.38 (3H, s), 3.64 (1H, dd, J=18, 4 Hz), 3.84 (1H, dd, J=18, 8 Hz), 4.84 (1H, dd, J=8, 4 Hz), 7.60 (3H, m), 7.98 (1H, m), 8.13 (d, J=8 Hz), 8.64 (1H, m)
25	A	89.1	1720—1660	A	2.40 (3H, s), 3.72 (1H, dd, J=18, 4 Hz), 3.94 (1H, dd, J=18, 8 Hz), 4.82 (1H, dd, J=8, 4 Hz), 7.67 (2H, m), 8.09 (4H, m), 8.74 (1H, s)
26	A	61.4	3400, 1720—1650	D	2.38 (3H, s), 2.52 (2H, t, J=8 Hz), 2.96 (2H, t, J=8 Hz), 3.46 (1H, dd, J=18, 4 Hz), 3.63 (1H, dd, J=18, 8 Hz), 4.53 (1H, dd, J=8, 4 Hz), 6.95 (1H, d, J=8 Hz), 7.83 (2H, m), 10.41 (1H, s), 12.86 (1H, brs)
27	A	88.1	1725, 1685—1665	D	1.13 (3H, t, J=7 Hz), 2.38 (3H, s), 2.52 (2H, t, J=8 Hz), 2.96 (2H, t, J=8 Hz), 3.50 (1H, dd, J=18, 4 Hz), 3.64 (1H, dd, J=18, 8 Hz), 4.08 (2H, q, J=7 Hz), 4.56 (1H, dd, J=8, 4 Hz), 6.94 (1H, m), 7.80 (2H, m), 10.40 (1H, s)
28	A	61.8	3300, 1730—1660	D	2.37 (3H, s), 3.46 (1H, dd, J=18, 4 Hz), 3.54 (2H, s), 3.60 (1H, dd, J=18, 8 Hz), 4.52 (1H, d, J=8 Hz), 7.83 (1H, s), 7.88 (1H, d, J=8 Hz), 10.75 (1H, s), 12.85 (1H, brs)
29	A	30.3	1740—1670	A	1.20 (3H, t, J=7 Hz), 2.38 (3H, s), 3.52 (1H, dd, J=18, 4 Hz), 3.56 (2H, s), 3.70 (1H, dd, J=18, 8 Hz), 4.14 (2H, q, J=7 Hz), 4.68 (1H, dd, J=8, 4 Hz), 7.02 (1H, d, J=8 Hz), 7.94 (2H, m), 9.80 (1H, brs)
30	A	90.1	1700, 1690, 1670	C	2.41 (3H, s), 3.72 (1H, dd, J=16, 4 Hz), 3.86 (1H, dd, J=16, 8 Hz), 4.85 (1H, dd, J=8, 4 Hz), 7.53 (2H, m), 7.89 (1H, m), 7.94 (1H, d, J=8 Hz), 8.05 (1H, d, J=8 Hz), 8.46 (1H, m), 8.76 (1H, s)
31	A	65.8	1720, 1705, 1675	C	1.29 (3H, t, J=7 Hz), 2.40 (3H, s), 3.71 (1H, dd, J=16, 4 Hz), 3.86 (1H, dd, J=16, 8 Hz), 4.25 (2H, q, J=7 Hz), 4.79 (1H, dd, J=8, 4 Hz), 7.53 (2H, m), 7.88 (1H, m), 7.93 (1H, d, J=8 Hz), 8.05 (1H, d, J=8 Hz), 8.25 (1H, m), 8.76 (1H, s)
32	A	77.1	1715, 1690, 1675	C	2.42 (3H, s), 3.70 (1H, dd, J=16, 4 Hz), 3.48 (1H, dd, J=16, 8 Hz), 4.40 (1H, brs), 4.83 (1H, dd, J=8, 4 Hz), 7.54 (2H, m), 7.91 (1H, m), 8.05 (1H, d, J=8 Hz), 8.22 (1H, m), 8.23 (1H, d, J=8 Hz), 8.48 (1H, s)
33	B	90.8	1710—1650	A	2.40 (3H, s), 3.77 (1H, dd, J=18, 4 Hz), 3.92 (1H, dd, J=18, 8 Hz), 4.82 (1H, dd, J=8, 4 Hz), 7.49 (1H, td, J=8, 5 Hz), 7.75 (2H, m), 8.26 (1H, d, J=2 Hz), 8.89 (1H, d, J=2 Hz)
34	B	85.0	1740—1670	C	1.28 (3H, t, J=7 Hz), 2.40 (3H, s), 3.70 (1H, dd, J=18, 4 Hz), 3.83 (1H, dd, J=18, 8 Hz), 4.24 (2H, q, J=7 Hz), 4.78 (1H, dd, J=8, 4 Hz), 7.40 (1H, td, J=8, 2 Hz), 7.52 (1H, td, J=8, 2 Hz), 7.60 (2H, d, J=8 Hz), 8.00 (1H, d, J=8 Hz), 8.12 (1H, d, J=8, 2 Hz), 8.58 (1H, d, J=2 Hz)
35	A	88.3	1710—1650	D	2.41 (3H, s), 2.94 (3H, s), 3.69 (1H, dd, J=18, 5 Hz), 3.84 (1H, dd, J=18, 8 Hz), 4.64 (1H, dd, J=8, 5 Hz), 7.50 (1H, t, J=8 Hz), 7.64 (1H, td, J=8, 2 Hz), 8.08 (1H, dd, J=8, 2 Hz), 8.30 (3H, m), 8.86 (1H, s), 13.0 (1H, brs)
36	A	82.4	1720—1670	D	1.18 (3H, t, J=8 Hz), 2.43 (3H, s), 2.95 (3H, s), 3.73 (1H, dd, J=18, 5 Hz), 3.86 (1H, dd, J=18, 8 Hz), 4.14 (2H, q, J=8 Hz), 4.67 (1H, dd, J=8, 5 Hz), 7.50 (1H, t, J=8 Hz), 7.64 (1H, t, J=8 Hz), 8.08 (1H, d, J=8 Hz), 8.30 (3H, m), 8.86 (1H, s)
37	A	92.9	1700, 1650	D	2.40 (3H, s), 3.67 (1H, dd, J=18, 5 Hz), 3.84 (1H, dd, J=18, 8 Hz), 3.94 (3H, s), 4.64 (1H, dd, J=8, 5 Hz), 7.32 (1H, t, J=8 Hz), 7.70 (2H, m), 8.12 (1H, dd, J=8, 2 Hz), 8.35 (1H, d, J=8 Hz), 8.96 (1H, d, J=2 Hz), 12.8 (1H, brs)
38	A	81.3	1735, 1685, 1660	D	1.17 (3H, t, J=8 Hz), 2.43 (3H, s), 3.72 (1H, dd, J=18, 5 Hz), 3.88 (1H, dd, J=18, 8 Hz), 3.94 (3H, s), 4.13 (2H, q, J=8 Hz), 4.68 (1H, dd, J=8, 5 Hz), 7.32 (1H, t, J=8 Hz), 7.56 (1H, t, J=8 Hz), 7.70 (2H, m), 8.12 (1H, d, J=8 Hz), 8.34 (1H, d, J=8 Hz), 8.95 (1H, s)

a) See footnote in Table IV.

with H_2O, dried ($MgSO_4$) and concentrated. The residue was recrystallized from AcOEt–hexane to give colorless needles (8.94 g, 66.4%), mp 164—165 °C.

2-Acetoxy-3-[4-(phenylthio)benzoyl]propionic Acid (**52**): Acetic anhydride (5.0 ml) was added to a stirred solution of 2-hydroxy-3-[4-(phenylthio)benzoyl]propionic acid (5.00 g) pyridine (30 ml) at 0 °C, and the stirring was continued for 1 h at 0°C. The mixture was poured into concentrated HCl-ice, and the whole was extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated. The residue was recrystallized from AcOEt–hexane to give **52** (5.58 g, 98.2%), mp 122—123 °C. *Anal.* Calcd for $C_{18}H_{16}O_5S$: C, 62.79; H, 4.68. Found: C, 62.79; H, 4.61.

3-(4-Benzyloxybenzoyl)acrylic Acid: A mixed solution of 3-(4-benzyloxybenzoyl)-2-hydroxypropionic acid (8.94 g) and $KHSO_4$ (4.6 g) in toluene (100 ml) was heated for 2 h under reflux, then the whole was washed with H_2O, dried ($MgSO_4$) and concentrated. The residue was recrystallized from benzene to give yellow needles (5.25 g, 60.1%), mp 180—182 °C. IR ν_{max}^{KBr} cm^{-1}: 1695, 1668. NMR (acetone-d_6) δ: 5.30 (2H, s), 6.78 (1H, d, J=16 Hz), 7.22 (2H, d, J=8 Hz), 7.46 (5H, m), 7.98 (1H, d, J=16 Hz), 8.12 (2H, d, J=8 Hz).

The following compounds were similarly prepared. 3-[4-(4-Chlorobenzyloxy)benzoyl]acrylic Acid: mp 173—174 °C (from benzene), 71%. 3-[4-(2-Pyridyloxy)benzoyl]acrylic Acid: mp 128—130 °C (from benzene), 6.5%. 3-[4-(2-Pyridylmethoxy)benzoyl]acrylic Acid: mp 197—198 °C, 31%. 3-(6-Methoxy-2-naphtoyl)acrylic Acid: mp 120—127 °C (dec.) (from AcOEt), 19%. 4-(3-Dibenzofuranyl)-4-oxo-2-butanoic Acid: mp 215 °C (dec.) (from AcOEt), 55%.

Method C 3-Acetylthio-3-(4-phenylthiobenzoyl)propionic Acid (**58**): A solution of Br_2 (11 ml) in $CHCl_3$ (30 ml) was added dropwise to a stirred solution of 3-(4-phenylthiobenzoyl)propionic acid (prepared from succinic anhydride in a manner similar to that described under method A-(1), mp 141—142 °C (from AcOEt–hexane)) (6.32 g) in $CHCl_3$ (70 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 dimethylformamide (DMF) (50 ml), and added to a mixed solution of thioacetic acid (1.6 ml) and K_2CO_3 (2.00 g) with stirring. The stirring was continued for 10 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 purified by column chromatography on silica gel with acetone–hexane (1 : 10, v/v) as an eluent and recrystallized from Et_2O–hexane to give **58** (6.25 g), 82.9%. *Anal.* Calcd for $C_{18}H_{16}O_4S_2$: C, 59.98; H, 4.47. Found: C, 59.80; H, 4.54.

Method D 2-Acetylthio-3-(4-phenylsulfinylbenzoyl)propionic Acid (**12**): A solution of *m*-chloroperbenzoic acid (1.72 g) in CH_2Cl_2 (20 ml) was added dropwise to a stirred and ice-cooled solution of **10** (3.60 g) in CH_2Cl_2 (20 ml). The mixture was stirred for 2 h at room temperature and CH_2Cl_2 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 on silica gel with Et_2O–hexane (1 : 5, v/v) as an eluent to give **12** as an oil (3.57 g, 94.8%). *Anal.* Calcd for $C_{18}H_{16}O_4S_2$: C, 57.43; H, 4.28. Found: C, 57.80; H, 4.59.

TABLE VI. IR and ^{1}H-NMR Spectral Data for the Compounds in Table III

No.	Method	Yield (%)	IR ν_{max} cm^{-1}	NMR Solv.[a]	NMR Chemical shift δ ppm
39	A	52.3	1700, 1680, 1665	C	2.37 (3H, s), 2.40 (3H, s), 3.49 (1H, dd, J=18, 6 Hz), 3.63 (1H, dd, J=18, 8 Hz), 4.74 (1H, dd, J=8, 6 Hz), 7.15 (2H, d, J=9 Hz), 7.24 (2H, d, J=9 Hz), 7.42 (2H, d, J=9 Hz), 7.78 (2H, d, J=9 Hz)
40	A	92.3	1720—1660	C	2.38 (3H, s), 3.52 (1H, dd, J=18, 4 Hz), 3.62 (1H, dd, J=18, 8 Hz), 4.47 (1H, dd, J=8, 4 Hz), 7.21 (2H, d, J=9 Hz), 7.40 (4H, m), 7.80 (2H, d, J=9 Hz)
41	A	83.2	1725, 1700, 1670	C	1.22 (3H, d, J=7 Hz), 1.24 (3H, d, J=7 Hz), 2.36 (3H, s), 3.48 (1H, dd, J=18, 5 Hz), 3.65 (1H, dd, J=18, 8 Hz), 4.65 (1H, dd, J=8, 5 Hz), 5.04 (1H, m), 7.22 (2H, d, J=9 Hz), 7.39—7.56 (5H, m), 7.84 (2H, d, J=9 Hz)
42	A	86.7	1735, 1700, 1670	C	0.89 (3H, t, J=7 Hz), 1.24—1.44 (2H, m), 1.53—1.66 (2H, m), 2.34 (3H, s), 3.47 (1H, dd, J=18, 5 Hz), 3.64 (1H, dd, J=18, 7 Hz), 4.13 (2H, t, J=7 Hz), 4.69 (1H, dd, J=7, 5 Hz), 7.20 (2H, d, J=9 Hz), 7.36—7.53 (5H, m), 7.81 (2H, d, J=9 Hz)
43	A	94.1	1730, 1690, 1660	C	2.32 (3H, s), 3.50 (1H, dd, J=16, 5 Hz), 3.64 (1H, dd, J=16, 7 Hz), 4.75 (1H, dd, J=7, 5 Hz), 5.17 (2H, s), 7.19 (2H, d, J=9 Hz), 7.26—7.52 (10H, m), 7.79 (2H, J=9 Hz)
44	A	51.6	1705, 1670	C	1.19 (3H, t, J=7 Hz), 2.63 (2H, q, J=7 Hz), 3.49 (1H, dd, J=17, 4 Hz), 3.65 (1H, dd, J=17, 7 Hz), 4.75 (1H, dd, J=7, 4 Hz), 7.22 (2H, d, J=9 Hz), 7.38—7.58 (5H, m), 7.82 (2H, d, J=9 Hz)
45	A	57.4	1725, 1680	C	1.18 (3H, t, J=7 Hz), 1.23 (3H, t, J=7 Hz), 2.61 (2H, q, J=7 Hz), 3.48 (1H, dd, J=17, 4 Hz), 3.65 (1H, dd, J=17, 7 Hz), 4.19 (2H, q, J=7 Hz), 4.69 (1H, dd, J=7, 4 Hz), 7.21 (2H, d, J=9 Hz), 7.36—7.56 (4H, m), 7.83 (2H, d, J=9 Hz)
46	A	92.7	1700, 1665, 1645	C	3.59 (1H, dd, J=18, 5 Hz), 3.75 (1H, dd, J=18, 7 Hz), 4.97 (1H, dd, J=7, 5 Hz), 7.21 (2H, d, J=9 Hz), 7.39—7.63 (8H, m), 7.83 (2H, d, J=9 Hz), 7.96 (2H, d, J=9 Hz), 10.62 (1H, br s)
47	A	75.0	2550, 1700, 1665	A	2.68 (1H, d, J=9 Hz), 3.45 (1H, dd, J=18, 4 Hz), 3.71 (1H, dd, J=18, 9 Hz), 3.93 (1H, m), 7.29 (2H, d, J=8 Hz), 7.53 (5H, m), 7.96
48	A	74.8	2540, 1735, 1660	C	1.28 (3H, t, J=7 Hz), 2.23 (1H, d, J=9 Hz), 3.33 (1H, dd, J=18, 5 Hz), 3.64 (1H, dd, J=18, 9 Hz), 3.86—3.98 (1H, m), 4.21 (2H, q, J=7 Hz), 7.20 (2H, d, J=9 Hz), 7.38—7.52 (5H, m), 7.81 (2H, d, J=9 Hz)
49	A	53.4	1700, 1665	C	2.29 (3H, s), 3.24 (1H, dd, J=18, 4 Hz), 3.62 (1H, dd, J=18, 10 Hz), 3.79 (1H, dd, J=10, 4 Hz), 7.21 (2H, d, J=9 Hz), 7.39—7.54 (5H, m), 7.83 (2H, d, J=9 Hz)
50	A	85.9	1700, 1660	C	2.28 (3H, t, J=7 Hz), 2.66—2.92 (2H, m), 3.24 (1H, dd, J=18, 4 Hz), 3.61 (1H, dd, J=18, 10 Hz), 3.87 (1H, dd, J=10, 4 Hz), 7.21 (2H, d, J=9 Hz), 7.39—7.54 (5H, m), 7.83 (2H, d, J=9 Hz)
51	A	97.8	1690, 1673	C	1.28 (3H, d, J=7 Hz), 1.35 (3H, d, J=7 Hz), 3.23 (1H, dd, J=18, 5 Hz), 3.28 (1H, m), 3.60 (1H, dd, J=18, 9 Hz), 3.91 (1H, dd, J=9, 5 Hz), 7.20 (2H, d, J=8 Hz), 7.42 (3H, m), 7.50 (2H, m), 7.83 (2H, d, J=8 Hz)
52	B	98.2	1750—1700, 1670	D	2.04 (3H, s), 3.52 (1H, dd, J=18, 4 Hz), 3.65 (1H, dd, J=18, 8 Hz), 5.47 (1H, dd, J=8, 4 Hz), 7.28 (2H, d, J=8 Hz), 7.53 (5H, m), 7.96 (2H, d, J=8 Hz)
53	B	38.4	3380, 1725, 1685	D	3.29 (2H, d, J=6 Hz), 4.49 (1H, t, J=6 Hz), 5.45 (1H, br s), 7.28 (2H, d, J=8 Hz), 7.53 (5H, m), 7.92 (2H, d, J=8 Hz), 12.5 (1H, br s)
54	E	59.3	3360, 1725, 1675	A	1.17 (3H, t, J=8 Hz), 1.91 (3H, s), 2.86 (1H, s), 3.51 (1H, dd, J=18, 4 Hz), 3.58 (1H, dd, J=18, 6 Hz), 4.12 (2H, q, J=8 Hz), 4.92 (1H, m), 7.52 (5H, m), 7.92 (2H, d, J=8 Hz), 7.94 (2H, d, J=8 Hz)
55	F	88.1	3000, 1685, 1650	C	2.40 (3H, s), 3.59 (1H, dd, J=18, 5 Hz), 3.77 (1H, dd, J=18, 8 Hz), 4.80 (1H, dd, J=8, 5 Hz), 6.92 (1H, d, J=8 Hz), 7.19 (1H, t, J=8 Hz), 7.29 (1H, t, J=8 Hz), 7.43 (3H, m), 7.54 (2H, m), 7.84 (1H, d, J=8 Hz), 7.16—7.98 (1H, br s)
56	C	62.3	1710, 1670	C	1.99 (1H, d, J=12 Hz), 2.95 (1H, dd, J=18, 6 Hz), 3.28 (1H, dd, J=18, 9 Hz), 4.45—4.58 (1H, m), 7.22 (2H, d, J=9 Hz), 7.39—7.58 (5H, m), 7.87 (2H, d, J=9 Hz), 10.10 (1H, br s)
57	C	77.8	2550, 1720, 1675	C	1.20 (3H, t, J=8 Hz), 1.99 (1H, d, J=12 Hz), 2.90 (1H, dd, J=16, 5 Hz), 3.24 (1H, dd, J=16, 9 Hz), 4.12 (2H, q, J=8 Hz), 4.58 (1H, dd, J=9, 5 Hz), 7.24 (2H, d, J=9 Hz), 7.42 (2H, d, J=9 Hz), 7.42 (1H, m), 7.52 (2H, m), 7.90 (2H, d, J=9 Hz)
58	C	82.9	1700—1660	C	2.32 (3H, s), 2.76 (1H, dd, J=16, 5 Hz), 3.29 (1H, dd, J=16, 10 Hz), 5.43 (1H, dd, J=10, 5 Hz), 7.16 (2H, d, J=9 Hz), 7.39—7.55 (5H, m), 7.80 (2H, d, J=9 Hz)
59	C	87.8	1725, 1680, 1670	C	1.19 (3H, t, J=7 Hz), 2.31 (3H, s), 2.72 (1H, dd, J=16, 5 Hz), 3.27 (1H, dd, J=16, 10 Hz), 4.10 (2H, q, J=7 Hz), 5.50 (1H, dd, J=10, 5 Hz), 7.19 (2H, d, J=9 Hz), 7.40—7.55 (5H, m), 7.88 (2H, d, J=9 Hz)
60	C	58.4	1690, 1677	C	1.15 (3H, t, J=8 Hz), 2.59 (2H, q, J=8 Hz), 2.76 (1H, dd, J=16, 5 Hz), 3.30 (1H, dd, J=16, 10 Hz), 5.44 (1H, dd, J=10, 5 Hz), 7.16 (2H, d, J=9 Hz), 7.36—7.60 (5H, m), 7.81 (2H, d, J=8 Hz)
61	C	70.0	1710, 1667	C	2.87 (1H, dd, J=16, 5 Hz), 3.41 (1H, dd, J=16, 10 Hz), 5.69 (1H, dd, J=10, 5 Hz), 7.17 (2H, d, J=9 Hz), 7.35—7.72 (8H, m), 7.83—8.20 (4H, m)
62	C	85.6	1693, 1665	C	1.92 (3H, s), 2.83 (1H, dd, J=18, 5 Hz), 3.29 (1H, dd, J=18, 10 Hz), 4.52 (1H, dd, J=10, 5 Hz), 7.21 (2H, d, J=9 Hz), 7.36—7.60 (5H, m), 7.89 (2H, d, J=9 Hz)

a) See footnote in Table IV.

Compound **14** was similarly prepared from compound **12**.

Method E Ethyl 2-Acetamido-3-[4-(phenylthio)benzoyl]propionate (**54**): A 28% NH_4OH aqueous solution (14 ml) was added dropwise to a stirred solution of ethyl 3-[4-(phenylthio)-benzoyl]acrylate (7.21 g) in acetone (50 ml). The mixture was stirred for 3 h at room temperature and acetone 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 dissolved in Et_2O (100 ml), and a mixture of pyridine (5 ml) and acetyl chloride (5.0 g) was added with stirring. The stirring was continued for 3 h at room temperature, and the reaction mixture was washed with H_2O, dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography on silica gel with Et_2O–hexane (1 : 6, v/v) as an eluent, then recrystallized from Et_2O–hexane to give **54** (5.07 g, 59.3%). *Anal.* Calcd for $C_{20}H_{21}NO_4S$: C, 64.67; H, 5.70; N, 3.77. Found: C, 64.80; H, 5.68; N, 3.76.

Method F 2-(Phenylthio)benzoic Acid: A mixture of 2-mercaptobenzoic acid (30.3 g), bromobenzene (23.1 ml), CuCl (3.0 g), K_2CO_3 (40.0 g) and DMF (450 ml) was refluxed for 6 h, and the precipitate was filtered off. The filtrate was added to H_2O, and the whole was acidified with aqueous 10% HCl. The reaction mixture was extracted with AcOEt, dried ($MgSO_4$)

and concentrated. The residue was recrystallized from AcOEt–hexane to give colorless needles (32.4 g, 74.0%), mp 120—125 °C.

2-(Phenylthio)acetophenone: A tetrahydrofuran (THF) solution of 1.6 M methyllithium (151 ml) was added dropwise to a stirred solution of 2-(phenylthio)acetophenone (25.0 g) in THF (110 ml) at −50 °C in an atmosphere of nitrogen, and the mixture was stirred for 1 h at room temperature. The mixture was neutralized with aqueous NH_4Cl, 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 on silica gel with Et_2O–hexane (1 : 4, v/v) to give a colorless oil (18.0 g, 71.6%).

3-[2-(Phenylthio)benzoyl]acrylic Acid: Prepared from 2-(phenylthio)-acetophenone and glyoxylic acid monohydrate according to method B, (51.3%), mp 119—120 °C (from Et_2O–hexane). IR ν_{max}^{KBr} cm^{-1}: 1690, 1655. NMR ($CDCl_3$) δ: 6.80 (1H, d, J=16 Hz), 7.10 (1H, d, J=8 Hz), 7.24—7.51 (7H, m), 7.80 (2H, J=8 Hz), 7.90 (1H, J=8 Hz), 9.70 (1H, br s).

Preparation of the Ester Derivatives of 3-Benzoylacrylic Acid Ethyl 3-[4-(Phenylthio)benzoyl]acrylate: 3-[4-(Phenylthio)-benzoyl]acrylic acid (56.8 g) and Et_2SO_4 (37.0 g) were dissolved in DMF (50 ml), then K_2CO_3 (16.6 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 recrystallized from CH_2Cl_2–hexane to give yellow needles (5.17 g, 82.8%), mp 74—75 °C. IR ν_{max}^{KBr} cm^{-1}: 1720, 1660. NMR ($CDCl_3$) δ: 1.33 (3H, t, J=7 Hz), 4.29 (2H, q, J=7 Hz), 6.86 (1H, d, J= 16 Hz), 7.23 (2H, d, J=9 Hz), 7.41—7.56 (5H, m), 7.87 (1H, d, J=16 Hz), 7.88 (2H, d, J=9 Hz).

The following compounds were similarly prepared. Ethyl 3-[4-(4-Chlorobenzoylamino)benzoyl]acrylate: mp 186—187 °C (from AcOEt), 67%. Ethyl 3-[4-(2-Benzoylaminoethyl)benzoyl]acrylate: mp 151—152 °C (from AcOEt), 87%. Ethyl 3-[4-(2-(4-Chlorobenzoyl)aminoethyl)benzoyl]-acrylate: mp 128—129 °C (from AcOEt), 86%. Ethyl 4-[6-(3,4-Dihydro-2-(1*H*)-quinolone)]-4-oxo-2-butenoate: mp 190—192 °C (from AcOEt), 71%. Ethyl 4-(5-Oxindole-4-oxo-2-butenoate: Oil, 89%. Ethyl 4-(2-Dibenzothienyl)-4-oxo-2-butenoate: mp 87.5—88.5 °C (from $CHCl_3$–hexane), 77%. Ethyl 4-(2-Dibenzofuranyl)-4-oxo-butenoate: mp 100—102 °C (from AcOEt–hexane), 80%. Ethyl 4-[3-(9-Acetylcarbazoyl)]-4-oxo-2-butenoate: mp 124—127 °C, 74%. Ethyl 4-[3-(9-Methylcarbazoyl)]-4-oxo-2-butenoate: mp 120—122 °C (from AcOEt–hexane), 85%. Isopropyl 3-[4-(Phenylthio)benzoyl]acrylate: mp 59—60 °C (from CH_2Cl_2–hexane), 80%. *n*-Butyl 3-[4-(Phenylthio)benzoyl]acrylate: mp 40—43 °C (from CH_2Cl_2–hexane), 73%. Benzyl 3-[4-(Phenylthio)benzoyl]acrylate: mp 85—86 °C (from CH_2Cl_2–hexane), 83%.

References and Notes

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