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### Studies on Hypolipidemic Agents. III. $\omega$ -(4-Phenoxybenzoyl)-alkanoic Acid Derivatives

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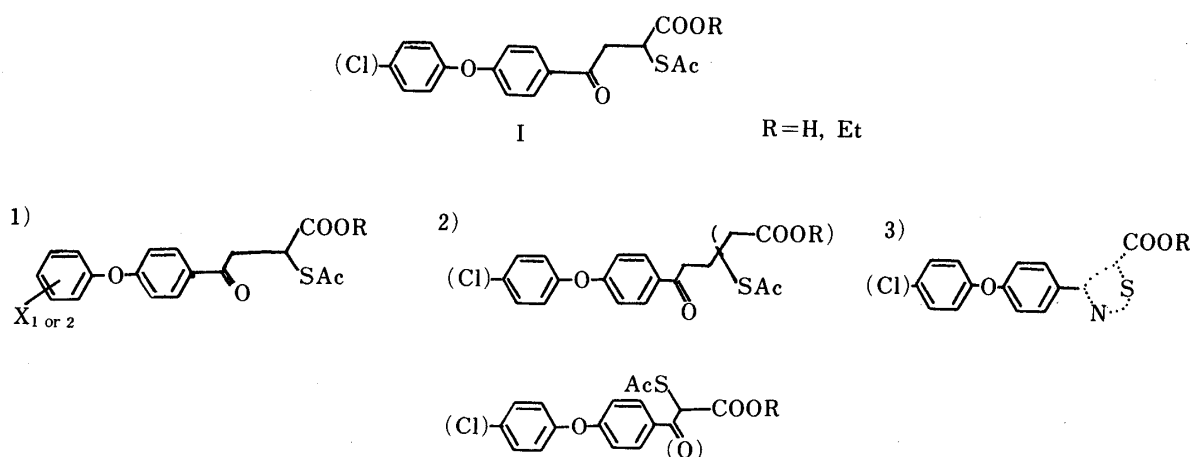
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2-Acetylthio-3-(4-substituted phenoxybenzoyl)propionic acids and various other  $\omega$ -(4-phenoxybenzoyl)alkanoic acid derivatives were prepared, and tested for hypolipidemic activity in normal rats. Some of these compounds were active. 2-Acetylthio-3-(4-phenoxybenzoyl)propionic acid derivatives seemed to have the most potent hypocholesterolemic activities, and halogen substitution on the phenoxy group increased the activity.

**Keywords**—2-acetylthio-3-(4-phenoxybenzoyl)propionic acid; 2-acetylthio-3-(4-phenoxyphenyl)propionic acid; 3-[2-methyl-4-(4-phenoxyphenyl)-5-thiazolyl]propionic acid; structure-activity relationship; hypolipidemic activity

In the previous work,<sup>1,2)</sup> we synthesized various derivatives of 3-(4-phenoxybenzoyl)propionic acid and found that 2-acetylthio-3-(4-phenoxybenzoyl)propionic acids (I) have potent hypocholesterolemic activities. This paper reports the synthesis and hypocholesterolemic activities of chemically modified derivatives of I, *i.e.*, 1) 2-acetylthio-3-(4-substituted phenoxybenzoyl)propionic acids, 2) acetylthio-substituted derivatives of  $\omega$ -(4-phenoxybenzoyl)butyric acids and acetic acids, 3) isothiazole derivatives and thiazole derivatives, as shown in Chart 1.



#### Chemistry

2-Acetylthio-3-(4-substituted phenoxybenzoyl)propionic acids (III) were prepared by means of the Michael addition reaction<sup>2)</sup> using the corresponding 3-benzoylacrylic acids (II)

method A

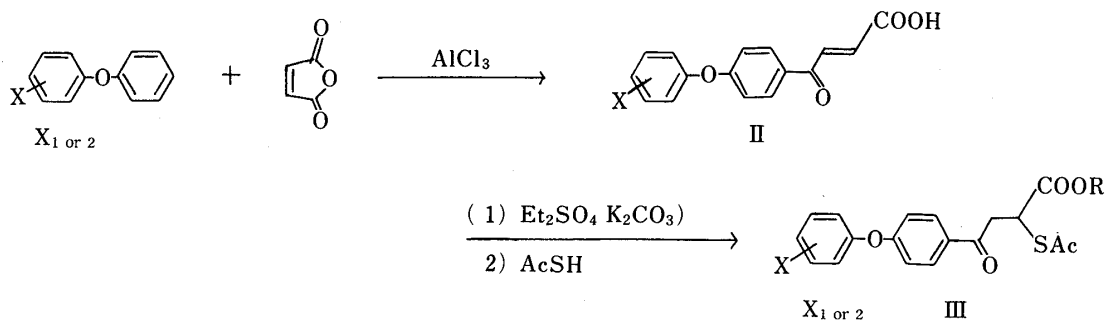
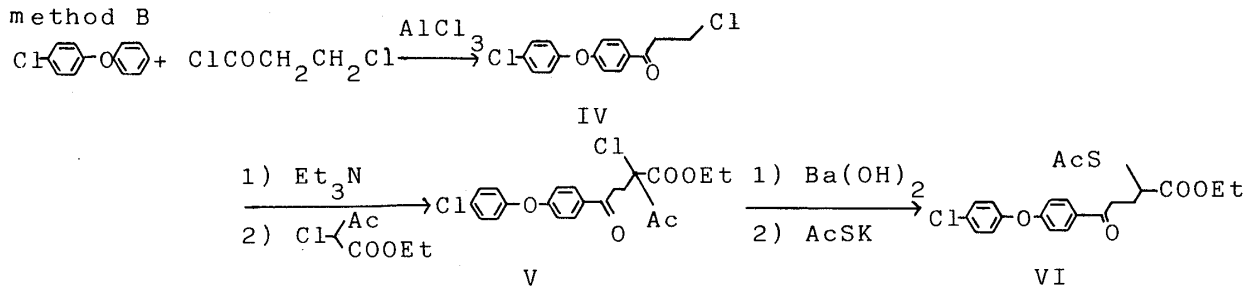


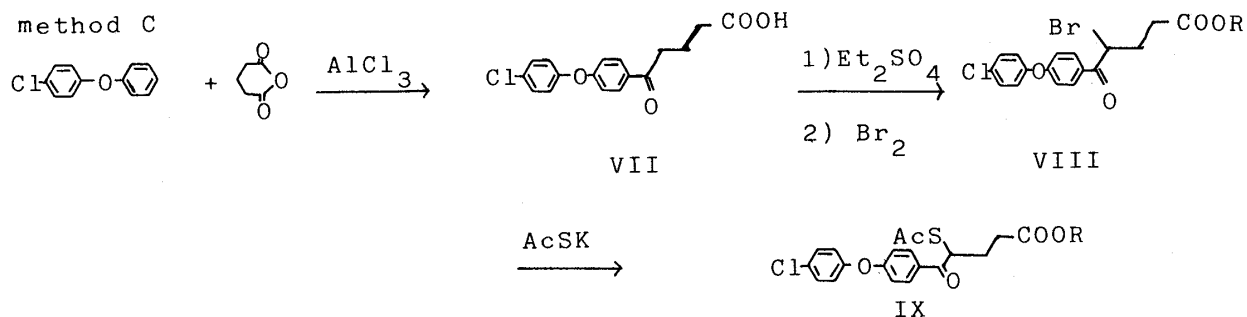
Chart 2

and thioacetic acid, as shown in Chart 2 (method A). The acetylthio-substituted derivatives of  $\omega$ -(4-phenoxybenzoyl)butyric acids and acetic acids were synthesized by the methods shown in Chart 3. 2-Chloroethyl 4-(4-chlorophenoxy)phenyl ketone (IV), which was prepared by Friedel-Crafts acylation, was dehydrochlorinated and reacted with ethyl 2-chloroacetate<sup>3)</sup> in the presence of sodium hydride to give ethyl 2-acetyl-2-chloro-4-[4-(4-chlorophenoxy)benzoyl]butyrate (V). Compound V was deacetylated<sup>4)</sup> and then reacted with potassium thioacetate to give ethyl 2-acetylthio-4-[4-(4-chlorophenoxy)benzoyl]butyrate (VI) (method B). 4-[4-(4-Chlorophenoxy)benzoyl]butyric acid<sup>4)</sup> (VII) was brominated at the 4-position and then reacted with potassium thioacetate to give 4-acetylthio-4-[4-(4-chlorophenoxy)benzoyl]butyric acids (IX) (method C). Ethyl 4-bromo-4-[4-(4-chlorophenoxy)benzoyl]butyric acid (VIII) was converted to the 4-phenylthio derivative by the reaction with sodium thiophenoxide, then oxidized with *m*-chloroperbenzoic acid and desulfinylated to give mixtures of the two olefin derivatives. The mixtures were reacted with thioacetic acid to give 3-acetylthio-4-[4-(4-chlorophenoxy)benzoyl]butyric acids (X) (method D). 2-Methylene-3-(4-phenoxybenzoyl)propionic acids<sup>5)</sup> (XI) were prepared by the Friedel-Crafts acylation of diphenyl ethers with itaconic anhydride. Compounds XI were reacted with thioacetic acid in *N,N*-dimethylformamide (DMF) at 30 °C by the addition of 0.1 eq of potassium carbonate aqueous solution to give 2-acetylthiomethyl-3-(4-phenoxybenzoyl)propionic acids (XII) (method E). 4-Phenoxyacetophenones (XIII) were reacted with carbon disulfide and methyl iodide in the presence of sodium hydride to give 4-phenoxyphenyl 2,2-bis(methylthio)vinyl ketones<sup>6)</sup> (XIV). Treatment of XIV with sulfuric acid in ethanol provided ethyl (4-phenoxybenzoyl)acetates (XV). Compounds XV were brominated, and reacted with potassium thioacetate to give ethyl 2-acetylthio-2-(4-phenoxybenzoyl)acetates (XVI) (method F). Ethyl 2-chloro-3-(4-phenoxyphenyl)propionates (XVII), which were prepared by the method of Kawamatsu *et al.*,<sup>4)</sup> and 2-chloroethyl 4-(4-chlorophenoxy)phenyl ketone (IV) were also reacted with potassium thioacetate to give the decarbonylated and decarboxylated derivatives (XVIII, XIX) (methods G and H). The isothiazole and thiazole derivatives were synthesized by the methods shown in Chart 4. 4-Phenoxybenzaldehyde (XX) was converted to the rhodanide<sup>7)</sup> (XXI), then reacted with sodium hydroxide to give the 2-thioxopropionic acid (XXII). Treatment of XXII with hydroxylamine in ethanol and acetic anhydride provided 4-phenoxybenzyl cyanide (XXIII). According to the method of Beck *et al.*,<sup>8)</sup> XXIII was converted to 3-(4-phenoxyphenyl)isothiazole-5-carboxylic acids (XXIV) (method I).  $\omega$ -(4-Phenoxybenzoyl)propionic acids and butyric acids were brominated and reacted with thioacetamide or thiourea to give the thiazole derivatives (XXV) (method J).

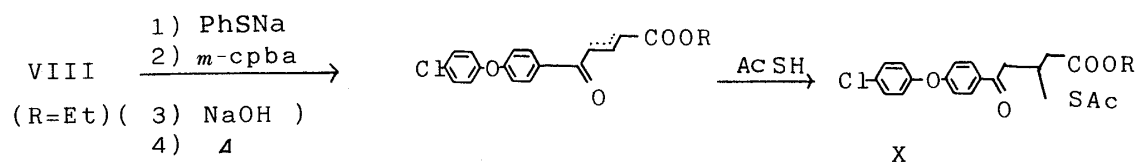
method B



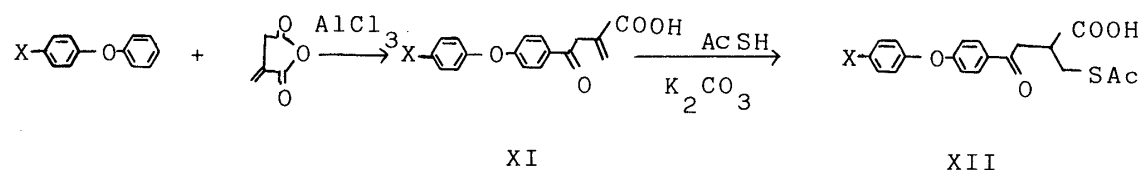
method C



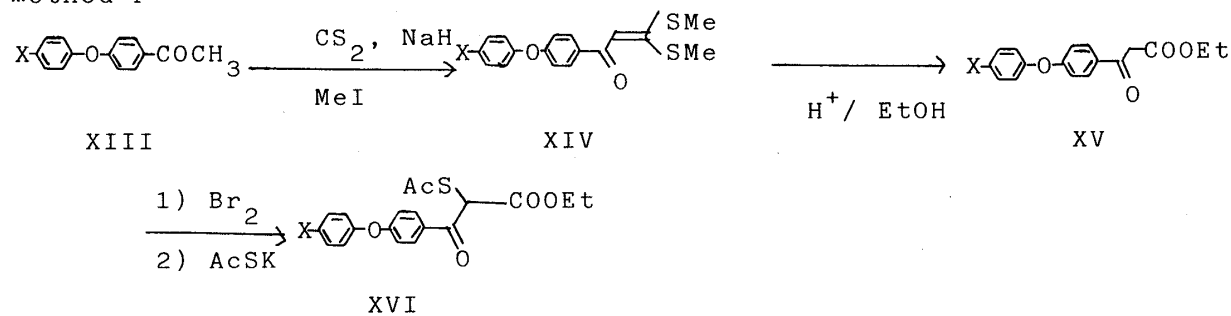
method D



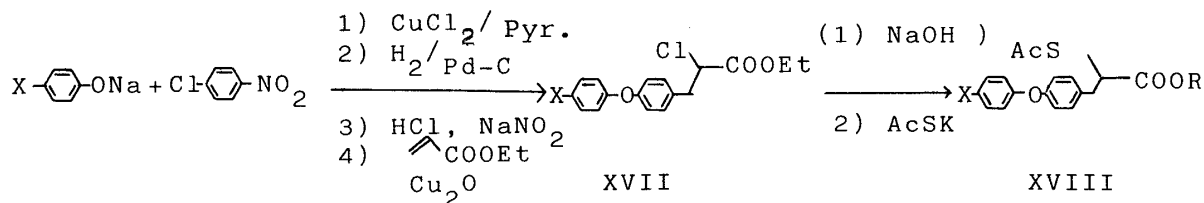
method E



method F



method G



method H

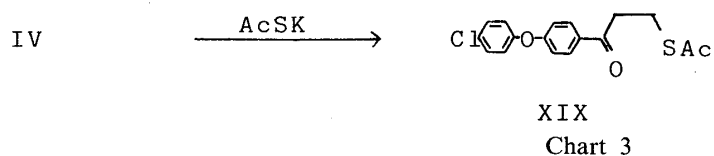
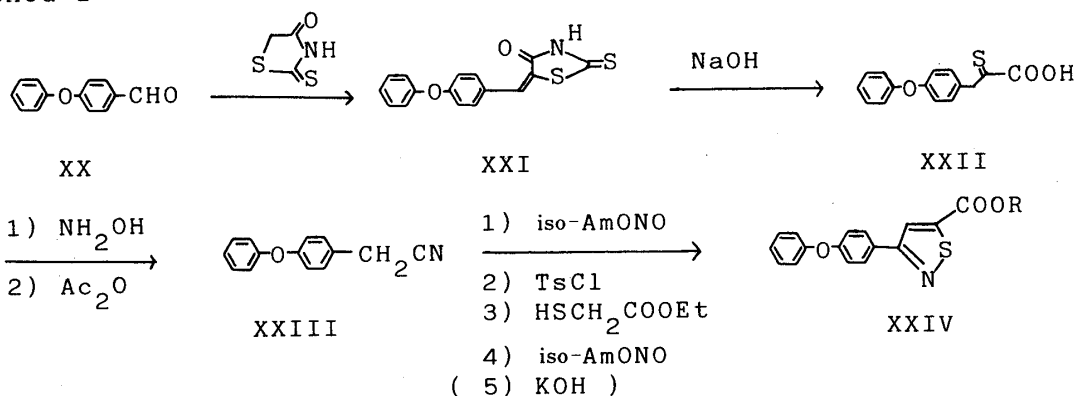


Chart 3

## method I



## method J

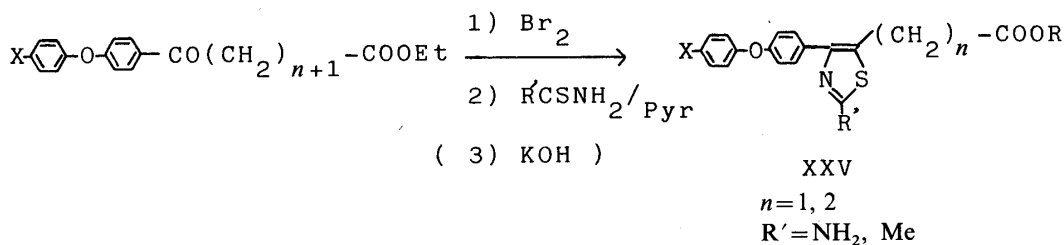


Chart 4

**Biological Method**

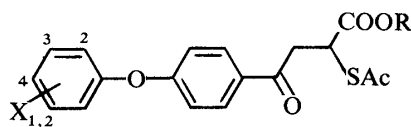
Five-week-old male rats (five rats per group) were used. After prefeeding for a week, the test compounds, which were prepared as a suspension in 0.2% sodium carboxymethylcellulose (CMC-Na) solution, were orally administered to the rats at a daily dose of 100 mg/kg for 3 d. A 0.2% CMC-Na solution was orally administered to rats in the control group. Eighteen hours 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).

**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, introduction of halogen substituents into the phenoxy group increased the hypocholesterolemic activities in the following order: *para* > *meta* > *ortho*. However, methyl, methoxy, or isopropyl substitution decreased the activities. The activity of the free acid was stronger than that of the ethyl ester, and the activities of **3** and **10** were stronger than that of clofibrate.<sup>1,9)</sup> As shown in Table II, the butyric acids and the acetic acids did not show hypocholesterolemic activity, and 3-acetylthiobutyric acids (**19**, **20**) and ethyl 2-acetylthio-2-[4-(4-chlorophenoxy)benzoyl]acetate (**26**) considerably increased the serum triglyceride levels. The decarboxylated derivatives (**27**, **29**) showed hypocholesterolemic activities, but the ketone moiety increased these activities (compare **2—4** with **28—30**). Because the decarboxylated derivative (**31**) had no activity, the carboxylic acid moiety must be essential for the activity. These results suggest that the partial structure  $-\text{COCH}_2\text{CH}(\text{SAc})-\text{COOH}$  is the most favorable structural feature for hypocholesterolemic activity. As shown in Table III, some of the thiazole derivatives ( $\text{R}=\text{Me}$ ) showed hypocholesterolemic activities. Among

TABLE I. Physical and Biological Properties of 2-Acetylthio-3-(4-phenoxybenzoyl)propionic Acids



Compd. No.	X	R	mp (°C)	Recrystn. <sup>a)</sup> solvent	Formula	Hypolipidemic activity rank <sup>b)</sup>	
						Cholesterol	Triglyceride
1	H	H	105.5—106.5	D-H	C <sub>18</sub> H <sub>16</sub> O <sub>5</sub> S	2	2
2	H	Et	78—79	E-H	C <sub>20</sub> H <sub>20</sub> O <sub>5</sub> S	1	2
3	4-Cl	H	91—94	E-H	C <sub>18</sub> H <sub>15</sub> ClO <sub>5</sub> S	4	4
4	4-Cl	Et	75.5—77	E-H	C <sub>20</sub> H <sub>19</sub> ClO <sub>5</sub> S	3	2
5	3-Cl	H	122—125	D-H	C <sub>18</sub> H <sub>15</sub> ClO <sub>5</sub> S	3	2
6	3-Cl	Et		Oil <sup>c)</sup>	C <sub>20</sub> H <sub>19</sub> ClO <sub>5</sub> S	2	3
7	2-Cl	Et		Oil <sup>c)</sup>	C <sub>20</sub> H <sub>19</sub> ClO <sub>5</sub> S	1	1
8	3,4-Cl <sub>2</sub>	Et		Oil <sup>c)</sup>	C <sub>20</sub> H <sub>18</sub> Cl <sub>2</sub> O <sub>5</sub> S	1	1
9	4-Br	Et	67—68.5	E-H	C <sub>20</sub> H <sub>19</sub> BrO <sub>5</sub> S	3	1
10	4-F	H	142—143	EA-H	C <sub>18</sub> H <sub>15</sub> FO <sub>5</sub> S	4	2
11	4-F	Et	71—72	D-H	C <sub>20</sub> H <sub>19</sub> FO <sub>5</sub> S	1	2
12	3-F	H	131—132.5	D-H	C <sub>18</sub> H <sub>15</sub> FO <sub>5</sub> S	3	2
13	4-Me	Et	85—86.5	A-H	C <sub>21</sub> H <sub>22</sub> O <sub>5</sub> S	0	3
14	4-MeO	H	110—111	D-H	C <sub>19</sub> H <sub>18</sub> O <sub>6</sub> S	0	1
15	4-MeO	Et		Oil <sup>c)</sup>	C <sub>21</sub> H <sub>22</sub> O <sub>6</sub> S	0	2
16	4-iso-Pr	H	110—111.5	D-H	C <sub>21</sub> H <sub>22</sub> O <sub>5</sub> S	0	2
17	4-iso-Pr	Et		Oil <sup>c)</sup>	C <sub>23</sub> H <sub>26</sub> O <sub>5</sub> S	0	2
Clofibrate						3	1

a) A=acetone, B=benzene, D=dichloromethane, E=ethyl ether, EA=ethyl acetate, H=hexane. b) Reduction levels were calculated as percentages with respect to the control value; less than 14% reduction=0, 15—24% reduction=1, 25—34% reduction=2, 35—44% reduction=3, 45—54% reduction=4, more than 55% reduction=5. d) Purified by column chromatography.

these derivatives, the activities of propionic acids (38—41) were stronger than those of acetic acids (34—37). Chloro substitution at the *para* position on the phenoxy group increased the activities (40, 41), and the ester derivatives (39, 41) were found to be as active as the free acid derivatives (38, 40).

### Experimental

All the melting points are uncorrected. Infrared (IR) spectra were measured with a JASCO DS-301 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were taken at 200 MHz with tetramethylsilane (TMS) as an internal standard on a Varian XL-200 spectrometer, in CDCl<sub>3</sub> unless otherwise noted. 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. The unit (Hz) of coupling constant (*J*Hz) is omitted. Lipid concentrations in serum were estimated by the enzyme method (Daitest Series Kit, Dai-ichi Co., Ltd., Tokyo). The oily products were purified by column chromatography on silica gel (Wako gel, C-200).

**Method A<sup>2)</sup>**—(1) 3-[4-(3-Chlorophenoxy)benzoyl]acrylic Acid: AlCl<sub>3</sub> (7.90 g) was added to a stirred solution of 3-chlorodiphenylether<sup>1)</sup> (10.00g) and maleic anhydride (4.80 g) in CH<sub>2</sub>Cl<sub>2</sub> (300 ml) over 30 min at room temperature. Stirring was continued for an additional 4 h and the CH<sub>2</sub>Cl<sub>2</sub> was removed under reduced pressure. The residue was poured into conc. HCl-ice, and the whole was extracted with AcOEt. The extract was washed with H<sub>2</sub>O, dried (MgSO<sub>4</sub>) and concentrated. The residue was recrystallized from acetone-hexane to give yellow needles (8.67 g, 58.5%), mp 110—111 °C.

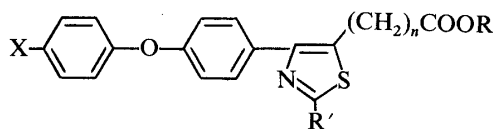
The following compounds were similarly prepared. 3-[4-(2-Chlorophenoxy)benzoyl]acrylic acid: mp 145—147 °C (from AcOEt-hexane), 58.4%. 3-[4-(3,4-Dichlorophenoxy)benzoyl]acrylic acid: mp 155—156 °C (from AcOEt-

TABLE II. Physical and Biological Properties of  $\omega$ -(4-Phenoxybenzoyl)alkanoic Acids

Compd. No.	X	R	mp (°C)	Recrystn. <sup>a)</sup> solvent	Formula	Hypolipidemic activity rank <sup>b)</sup>	
						Cholesterol	Triglyceride
18	Cl		58.5—59.5	E-H	C <sub>21</sub> H <sub>21</sub> ClO <sub>5</sub> S	1	1
19	Cl		106—108	D-H	C <sub>19</sub> H <sub>17</sub> ClO <sub>5</sub> S	0	-5 <sup>d)</sup>
20	Cl			Oil <sup>c)</sup>	C <sub>21</sub> H <sub>21</sub> ClO <sub>5</sub> S	0	-5 <sup>d)</sup>
21	Cl		115.5—117	D-H	C <sub>19</sub> H <sub>17</sub> ClO <sub>5</sub> S	0	0
22	Cl			Oil <sup>c)</sup>	C <sub>21</sub> H <sub>21</sub> ClO <sub>5</sub> S	0	0
23	H		92—93.5	E-H	C <sub>19</sub> H <sub>18</sub> O <sub>5</sub> S	0	0
24	Cl		108—110	E-H	C <sub>19</sub> H <sub>17</sub> ClO <sub>5</sub> S	0	-1 <sup>d)</sup>
25	H			Oil <sup>c)</sup>	C <sub>19</sub> H <sub>18</sub> O <sub>5</sub> S	0	0
26	Cl			Oil <sup>c)</sup>	C <sub>19</sub> H <sub>17</sub> ClO <sub>5</sub> S	0	-5 <sup>d)</sup>
27	H		121.5—122.5	E-H	C <sub>17</sub> H <sub>16</sub> O <sub>4</sub> S	2	0
28	H			Oil <sup>c)</sup>	C <sub>19</sub> H <sub>20</sub> O <sub>4</sub> S	0	0
29	Cl		142—143	E-H	C <sub>17</sub> H <sub>15</sub> ClO <sub>4</sub> S	2	2
30	Cl			Oil <sup>c)</sup>	C <sub>19</sub> H <sub>19</sub> ClO <sub>4</sub> S	1	1
31	Cl		76—77.5	D-H	C <sub>17</sub> H <sub>15</sub> ClO <sub>3</sub> S	0	0
32	H		181—183	D-H	C <sub>16</sub> H <sub>11</sub> NO <sub>3</sub> S	0	0
33	H		89—91	E-H	C <sub>18</sub> H <sub>15</sub> NO <sub>3</sub> S	0	0

<sup>a-c)</sup> See footnotes to Table I. <sup>d)</sup> The triglyceride levels were increased; -1=25—34% increases, -5=more than 55% increase.

TABLE III. Physical and Biological Properties of 4-(4-Phenoxybenzoyl)thiazole Derivatives



Compd. No.	X	R'	n	R	mp (°C)	Recrystn. <sup>a)</sup> solvent	Formula	Hypolipidemic activity rank <sup>b)</sup>	
								Cholesterol	Triglyceride
34	H	Me	1	H	176—178	B	C <sub>18</sub> H <sub>15</sub> NO <sub>2</sub> S	0	0
35	H	Me	1	Et	Oil <sup>c)</sup>		C <sub>20</sub> H <sub>19</sub> NO <sub>3</sub> S	1	3
36	Cl	Me	1	H	164—165	B	C <sub>18</sub> H <sub>14</sub> ClNO <sub>3</sub> S	2	3
37	Cl	Me	1	Et	82—84	E-H	C <sub>20</sub> H <sub>18</sub> ClNO <sub>3</sub> S	0	2
38	H	Me	2	H	119—121	E	C <sub>19</sub> H <sub>17</sub> NO <sub>3</sub> S	1	1
39	H	Me	2	Et	Oil <sup>c)</sup>		C <sub>21</sub> H <sub>21</sub> NO <sub>3</sub> S	1	1
40	Cl	Me	2	H	147—148	EtOH	C <sub>19</sub> H <sub>16</sub> ClNO <sub>3</sub> S	2	1
41	Cl	Me	2	Et	Oil <sup>c)</sup>		C <sub>21</sub> H <sub>20</sub> ClNO <sub>3</sub> S	2	2
42	H	NH <sub>2</sub>	1	Et	103—105	D-H	C <sub>19</sub> H <sub>18</sub> N <sub>2</sub> O <sub>3</sub> S	1	2
43	Cl	NH <sub>2</sub>	1	Et	107—109	D-H	C <sub>19</sub> H <sub>17</sub> ClN <sub>2</sub> O <sub>3</sub> S	0	1
44	H	NH <sub>2</sub>	2	Et	107—108	EtOH	C <sub>20</sub> H <sub>20</sub> N <sub>2</sub> O <sub>3</sub> S	0	3
45	Cl	NH <sub>2</sub>	2	Et	122—123	EtOH	C <sub>20</sub> H <sub>19</sub> ClN <sub>2</sub> O <sub>3</sub> S	0	3

a—c) See footnotes to Table I.

hexane), 33.2%. 3-[4-(4-Bromophenoxy)benzoyl]acrylic acid: mp 171—172 °C (from AcOEt-hexane), 66.7%. 3-[4-(4-Fluorophenoxy)benzoyl]acrylic acid: mp 142—143 °C (from AcOEt-hexane), 74.7%. 3-[4-(3-Fluorophenoxy)benzoyl]acrylic acid: 119—120 °C (from AcOEt-hexane), 66.8%. 3-[4-(4-Methylphenoxy)benzoyl]acrylic acid: mp 145—146.5 °C (from acetone-hexane), 54.4%. 3-[4-(4-Methoxyphenoxy)benzoyl]acrylic acid: mp 139—139.5 °C (from Et<sub>2</sub>O-hexane), 35.2%. 3-[4-(4-Isopropylphenoxy)benzoyl]acrylic acid: mp 133—134.5 °C (from acetone-hexane), 56.1%.

(2) Ethyl 3-[4-(3-Chlorophenoxy)benzoyl]acrylate: 3-[4-(3-Chlorophenoxy)benzoyl]acrylic acid (7.57 g) and Et<sub>2</sub>SO<sub>4</sub> (4.62 g) were dissolved in DMF (60 ml), then K<sub>2</sub>CO<sub>3</sub> (2.01 g) was added under stirring. The mixture was stirred for an additional 3 h at room temperature, then suspended in H<sub>2</sub>O, and the whole was extracted with Et<sub>2</sub>O. The extract was washed with H<sub>2</sub>O, dried (MgSO<sub>4</sub>) and concentrated. The residue was purified by column chromatography on silica gel using Et<sub>2</sub>O-hexane (1:5, v/v) as an eluent to give a colorless oil (7.17 g, 86.7%).

The following compounds were similarly prepared. Ethyl 3-[4-(2-chlorophenoxy)benzoyl]acrylate: mp 50—52 °C (from Et<sub>2</sub>O-hexane), 82.2%. Ethyl 3-[4-(3,4-dichlorophenoxy)benzoyl]acrylate: oil, 94.3%. Ethyl 3-[4-(4-bromophenoxy)benzoyl]acrylate: mp 67—68.5 °C (from Et<sub>2</sub>O-hexane), 79.7%. Ethyl 3-[4-(4-fluorophenoxy)benzoyl]acrylate: mp 65—67 °C (from Et<sub>2</sub>O-hexane), 75.2%. Ethyl 3-[4-(3-fluorophenoxy)benzoyl]acrylate: oil, 97.5%. Ethyl 3-[4-(4-methylphenoxy)benzoyl]acrylate: oil, 91.0%. Ethyl 3-[4-(4-methoxyphenoxy)benzoyl]acrylate: oil, 77.3%. Ethyl 3-[4-(4-isopropylphenoxy)benzoyl]acrylate: oil, 73.0%.

(3) 2-Acetylthio-3-[4-(3-chlorophenoxy)benzoyl]propionic Acid (5): 3-[4-(3-Chlorophenoxy)benzoyl]acrylic acid (3.00 g) and thioacetic acid (0.71 ml) were dissolved in CH<sub>2</sub>Cl<sub>2</sub> (30 ml), then the mixture was stirred for 4 h at room temperature. The mixture was concentrated and the residue was recrystallized from CH<sub>2</sub>Cl<sub>2</sub>-hexane to give 5 (3.14 g, 83.0%), mp 122—125 °C. IR  $\nu_{\max}^{\text{KBr}}$  cm<sup>-1</sup>: 2500, 1705, 1690, 1670. NMR  $\delta$ : 2.40 (3H, s), 3.54 (1H, dd, *J* = 16, 4), 3.68 (1H, dd, *J* = 16, 6), 4.76 (1H, dd, *J* = 6, 4), 6.92—7.40 (6H, m), 7.95 (2H, d, *J* = 8), 7.80 (1H, br s). Anal. Calcd for C<sub>18</sub>H<sub>15</sub>ClO<sub>5</sub>S: C, 57.07; H, 3.99. Found: C, 57.15; H, 4.09.

The following compounds were similarly prepared.

Ethyl 2-Acetylthio-3-[4-(3-chlorophenoxy)benzoyl]propionate (6): Oil, 94.3%. IR  $\nu_{\max}^{\text{neat}}$  cm<sup>-1</sup>: 1750—1670. NMR  $\delta$ : 1.27 (3H, t, *J* = 7), 2.39 (3H, s), 3.53 (1H, dd, *J* = 16, 4), 3.69 (1H, dd, *J* = 16, 6), 4.23 (2H, q, *J* = 7), 4.72 (1H, dd, *J* = 6, 4), 6.90—7.00 (6H, m), 7.98 (2H, d, *J* = 8). Anal. Calcd for C<sub>20</sub>H<sub>19</sub>ClO<sub>5</sub>S: C, 59.04; H, 4.71. Found: C, 59.18; H, 4.83.

Ethyl 2-Acetylthio-3-[4-(2-chlorophenoxy)benzoyl]propionate (7): Oil, 90.3%. IR  $\nu_{\max}^{\text{neat}}$  cm<sup>-1</sup>: 1740—1680. NMR  $\delta$ : 1.25 (3H, t, *J* = 7), 2.37 (3H, s), 3.52 (1H, dd, *J* = 18, 5), 3.68 (1H, dd, *J* = 18, 8), 4.71 (1H, dd, *J* = 8, 5), 6.94 (2H, d, *J* = 9), 7.13 (1H, d, *J* = 8), 7.15—7.37 (2H, m), 7.52 (1H, *J* = 8), 7.95 (2H, d, *J* = 9). Anal. Calcd for C<sub>20</sub>H<sub>19</sub>ClO<sub>5</sub>S: C, 59.04; H, 4.71. Found: C, 59.19; H, 4.88.

Ethyl 2-Acetylthio-3-[4-(3,4-dichlorophenoxy)benzoyl]propionate (8): Oil, 88.4%. IR  $\nu_{\max}^{\text{neat}}$  cm<sup>-1</sup>: 1750—1670.

NMR  $\delta$ : 1.27 (3H, t,  $J=7$ ), 2.18 (3H, s), 3.52 (1H, dd,  $J=16, 4$ ), 3.70 (1H, dd,  $J=16, 6$ ), 4.23 (2H, q,  $J=7$ ), 4.72 (1H, dd,  $J=6, 4$ ), 6.93 (1H, dd,  $J=8, 3$ ), 7.04 (2H, d,  $J=8$ ), 7.18 (1H, d,  $J=3$ ), 7.47 (1H, d,  $J=8$ ), 7.98 (2H, d,  $J=8$ ). *Anal.* Calcd for  $C_{20}H_{18}Cl_2O_5S$ : C, 54.43; H, 4.11. Found: C, 54.48; H, 4.29.

Ethyl 2-Acetylthio-3-[4-(4-bromophenoxy)benzoyl]propionate (**9**): mp 67—68.5°C (from  $Et_2O$ -hexane), 78.4%. IR  $\nu_{max}^{KBr} cm^{-1}$ : 1725, 1700, 1670. NMR  $\delta$ : 1.25 (3H, t,  $J=7$ ), 2.37 (3H, s), 3.49 (1H, dd,  $J=18, 5$ ), 3.67 (1H, dd,  $J=18, 7$ ), 4.21 (2H, q,  $J=7$ ), 4.70 (1H, dd,  $J=7, 5$ ), 6.92—7.53 (6H, m), 7.94 (2H, d,  $J=9$ ). *Anal.* Calcd for  $C_{20}H_{19}BrO_5S$ : C, 53.22; H, 4.24. Found: C, 53.34; H, 4.32.

2-Acetylthio-3-[4-(4-fluorophenoxy)benzoyl]propionic Acid (**10**): mp 99.5—101.5°C (from  $CH_2Cl_2$ -hexane), 71.2%. IR  $\nu_{max}^{KBr} cm^{-1}$ : 2500, 1700—1660. NMR  $\delta$ : 3.38 (3H, s), 3.50 (1H, dd,  $J=16, 4$ ), 3.65 (1H, dd,  $J=16, 7$ ), 4.75 (1H, dd,  $J=7, 4$ ), 6.97 (2H, d,  $J=8$ ), 7.00—7.15 (4H, m), 7.93 (2H, d,  $J=8$ ), 9.65 (1H, br s). *Anal.* Calcd for  $C_{18}H_{15}FO_5S$ : C, 59.66; H, 4.17. Found: C, 59.86; H, 4.42.

Ethyl 2-Acetylthio-3-[4-(4-fluorophenoxy)benzoyl]propionate (**11**): mp 71—72°C (from  $CH_2Cl_2$ -hexane), 70.8%. IR  $\nu_{max}^{KBr} cm^{-1}$ : 1710, 1690, 1670. NMR  $\delta$ : 1.27 (3H, t,  $J=7$ ), 2.38 (3H, s), 3.50 (1H, dd,  $J=16, 5$ ), 3.67 (1H, dd,  $J=16, 7$ ), 4.22 (2H, q,  $J=7$ ), 4.71 (1H, dd,  $J=7, 5$ ), 6.96—7.16 (6H, m), 7.95 (2H, d,  $J=9$ ). *Anal.* Calcd for  $C_{20}H_{19}FO_5S$ : C, 61.35; H, 4.90. Found: C, 61.35; H, 4.98.

2-Acetylthio-3-[4-(3-fluorophenoxy)benzoyl]propionic Acid (**12**): mp 131.5—133.5°C (from  $CH_2Cl_2$ -hexane), 89.7%. IR  $\nu_{max}^{KBr} cm^{-1}$ : 2500, 1700, 1670. NMR  $\delta$ : 2.39 (3H, s), 3.53 (1H, dd,  $J=16, 5$ ), 3.69 (1H, dd,  $J=16, 7$ ), 4.76 (1H, dd,  $J=7, 5$ ), 6.72—6.97 (3H, m), 7.05 (2H, d,  $J=8$ ), 7.37—7.44 (1H, m), 7.45 (1H, br s), 7.96 (2H, d,  $J=8$ ). *Anal.* Calcd for  $C_{18}H_{15}FO_5S$ : C, 59.66; H, 4.17. Found: C, 59.59; H, 4.39.

Ethyl 2-Acetylthio-3-[4-(4-methylphenoxy)benzoyl]propionate (**13**): mp 85—86.5°C (from  $AcOEt$ -hexane), 86.3%. IR  $\nu_{max}^{KBr} cm^{-1}$ : 1730, 1700, 1670. NMR  $\delta$ : 1.27 (3H, t,  $J=7$ ), 2.38 (6H, s), 3.52 (1H, dd,  $J=18, 4$ ), 3.62 (1H, dd,  $J=18, 8$ ), 4.22 (2H, q,  $J=7$ ), 4.71 (1H, dd,  $J=18, 4$ ), 6.96—7.28 (6H, m), 7.93 (2H, d,  $J=9$ ). *Anal.* Calcd for  $C_{21}H_{22}O_5S$ : C, 65.27; H, 5.74. Found: C, 65.29; H, 5.71.

2-Acetylthio-3-[4-(4-methoxyphenoxy)benzoyl]propionic Acid (**14**): mp 110—111°C (from  $CH_2Cl_2$ -hexane), 68.3%. IR  $\nu_{max}^{KBr} cm^{-1}$ : 2500, 1735, 1710, 1670. NMR  $\delta$ : 2.38 (3H, s), 3.53 (1H, dd,  $J=16, 4$ ), 3.65 (1H, dd,  $J=16, 6$ ), 3.85 (3H, s), 4.70 (1H, dd,  $J=6, 4$ ), 6.90—7.08 (6H, m), 7.70 (1H, br s), 7.91 (2H, d,  $J=9$ ). *Anal.* Calcd for  $C_{19}H_{18}O_6S$ : C, 60.95; H, 4.85. Found: C, 61.11; H, 4.86.

Ethyl 2-Acetylthio-3-[4-(4-methoxyphenoxy)benzoyl]propionate (**15**): Oil, 95.5%. IR  $\nu_{max}^{neat} cm^{-1}$ : 1740—1670. NMR  $\delta$ : 1.25 (3H, t,  $J=7$ ), 2.36 (3H, s), 3.51 (1H, dd,  $J=18, 5$ ), 3.67 (1H, dd,  $J=18, 8$ ), 3.82 (3H, s), 4.20 (2H, q,  $J=7$ ), 4.70 (1H, dd,  $J=8, 5$ ), 6.90—7.04 (6H, m), 7.91 (2H, d,  $J=9$ ). *Anal.* Calcd for  $C_{21}H_{22}O_6S$ : C, 62.67; H, 5.51. Found: C, 62.61; H, 5.66.

2-Acetylthio-3-[4-(4-isopropylphenoxy)benzoyl]propionic Acid (**16**): mp 110—111.5°C (from  $CH_2Cl_2$ -hexane) 88.7%. IR  $\nu_{max}^{KBr} cm^{-1}$ : 2500, 1720, 1695, 1685. NMR  $\delta$ : 1.28 (6H, d,  $J=6$ ), 2.38 (3H, s), 2.97 (1H, m), 3.55 (1H, dd,  $J=16, 4$ ), 3.67 (1H, dd,  $J=16, 6$ ), 4.77 (1H, dd,  $J=6, 4$ ), 6.99 (4H, d,  $J=8$ ), 7.25 (2H, d,  $J=8$ ), 7.92 (2H, d,  $J=8$ ), 9.20 (1H, br s). *Anal.* Calcd for  $C_{21}H_{22}O_5S$ : C, 65.27; H, 65.45. Found: C, 65.45; H, 5.81.

Ethyl 2-Acetylthio-3-[4-(4-isopropylphenoxy)benzoyl]propionate (**17**): Oil, 91.2%. IR  $\nu_{max}^{neat} cm^{-1}$ : 1730, 1680. NMR  $\delta$ : 1.26 (3H, t,  $J=7$ ), 1.27 (6H, d,  $J=6$ ), 2.38 (3H, s), 2.94 (1H, m), 3.51 (1H, dd,  $J=16, 4$ ), 3.65 (1H, dd,  $J=16, 6$ ), 4.21 (2H, q,  $J=7$ ), 4.70 (1H, dd,  $J=6, 4$ ), 6.98 (4H, d,  $J=8$ ), 7.25 (2H, d,  $J=8$ ), 7.92 (2H, d,  $J=8$ ). *Anal.* Calcd for  $C_{23}H_{26}O_5S$ : C, 66.64; H, 6.32. Found: C, 66.58; H, 6.51.

**Method B**—(1) 2-Chloroethyl 4-(4-chlorophenoxy)phenyl Ketone: 4-Chlorodiphenylether (40.0 g) and 3-chloropropionyl chloride (27.9 g) were dissolved in  $CH_2Cl_2$  (200 ml), then  $AlCl_3$  (40.0 g) was added to the mixture at room temperature under stirring. Stirring was continued for an additional 2 h, and the  $CH_2Cl_2$  was removed under reduced pressure. The residue was poured into conc. 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 hexane to give colorless needles (53.4 g, 90.7%), mp 75.5—77°C. IR  $\nu_{max}^{KBr} cm^{-1}$ : 1670. NMR  $\delta$ : 3.43 (2H, t,  $J=7$ ), 3.94 (2H, t,  $J=7$ ), 7.04 (4H, d,  $J=8$ ), 7.40 (2H, d,  $J=8$ ), 7.98 (2H, d,  $J=8$ ).

(2) Ethyl 2-Acetyl-2-chloro-4-[4-(4-chlorophenoxy)benzoyl]butyrate: Triethylamine (5.6 ml) was added to a stirred solution of 2-chloroethyl 4-(4-chlorophenoxy)phenyl ketone (10.7 g) in acetone (70 ml) at room temperature. The mixture was stirred for an additional 1 h and the acetone was removed under reduced pressure. The residue was dissolved in  $Et_2O$  and the precipitate was filtered off. The filtrate was concentrated under reduced pressure. The residue was dissolved in a mixture of ethyl 2-chloroacetoacetate (6.4 g) and  $CCl_4$  (300 ml), then a 40% aqueous solution of Triton B (0.3 ml) was added, and the whole was stirred for an additional 18 h at room temperature. The mixture was washed with 10% HCl aq. and  $H_2O$ , then dried ( $MgSO_4$ ) and concentrated. The residue was purified by column chromatography on silica gel with hexane- $Et_2O$ - $CH_2Cl_2$  (6 : 1 : 1, v/v) to give a colorless oil (10.2 g, 67%). IR  $\nu_{max}^{neat} cm^{-1}$ : 1750, 1730, 1680. NMR  $\delta$ : 1.30 (3H, t,  $J=7$ ), 2.38 (2H, s), 2.64 (2H, m), 3.12 (2H, m), 4.30 (2H, q,  $J=7$ ), 7.01 (2H, d,  $J=8$ ), 7.02 (2H, d,  $J=8$ ), 7.37 (2H, d,  $J=8$ ), 7.47 (2H, d,  $J=8$ ).

(3) Ethyl 2-Chloro-4-[4-(4-chlorophenoxy)benzoyl]butyrate: A mixture of ethyl 2-acetyl-2-chloro-4-[4-(4-chlorophenoxy)benzoyl]butyrate (3.0 g),  $Ba(OH)_2 \cdot 8H_2O$  (1.1 g) and  $EtOH$  (50 ml) was stirred at 5°C for 30 min, then the  $EtOH$  was removed under reduced pressure. The residue was dissolved in  $Et_2O$  and the whole was washed with 10% HCl aq. and  $H_2O$ , then dried ( $MgSO_4$ ) and concentrated. The residue was purified by column chromatography



on silica gel using ether-hexane (1:7, v/v) as an eluent to give a colorless oil (1.9 g, 69%). IR  $\nu_{\max}^{\text{neat}} \text{cm}^{-1}$ : 1740, 1675. NMR  $\delta$ : 1.31 (3H, t,  $J=7$ ), 2.36 (1H, m), 2.54 (1H, m), 3.16 (1H, d,  $J=8$ ), 3.20 (1H, dd,  $J=8, 2$ ), 4.29 (2H, q,  $J=7$ ), 4.50 (1H, dd,  $J=8, 5$ ), 7.02 (4H, d,  $J=9$ ), 7.38 (2H, d,  $J=9$ ), 7.99 (2H, d,  $J=9$ ).

(4) Ethyl 2-Acetylthio-4-[4-(4-chlorophenoxy)benzoyl]butyrate (**18**): Ethyl 2-chloro-4-[4-(4-chlorophenoxy)benzoyl]butyrate (1.00 g) was dissolved in DMF (5 ml), then AcSK (0.33 g) was added to the solution under stirring. Stirring was continued for an additional 3.5 h at room temperature, and the mixture was suspended in H<sub>2</sub>O. The whole was extracted with AcOEt and the extract was washed with H<sub>2</sub>O, dried (MgSO<sub>4</sub>) and concentrated. The residue was recrystallized from Et<sub>2</sub>O-hexane to give **18** (0.98 g, 86.3%), mp 58.5–59.5°C. IR  $\nu_{\max}^{\text{KBr}} \text{cm}^{-1}$ : 1725, 1690, 1670. NMR  $\delta$ : 1.27 (3H, t,  $J=7$ ), 2.22 (1H, dt,  $J=22, 8$ ), 2.37 (3H, s), 2.41 (1H, dt,  $J=22, 8$ ), 3.04 (1H, d,  $J=8$ ), 3.08 (1H, d,  $J=8$ ), 4.21 (2H, q,  $J=7$ ), 4.32 (1H, t,  $J=8$ ), 7.01 (2H, d,  $J=9$ ), 7.02 (2H, d,  $J=9$ ), 7.38 (2H, d,  $J=9$ ), 7.96 (2H, d,  $J=9$ ). Anal. Calcd for C<sub>21</sub>H<sub>21</sub>ClO<sub>5</sub>S: C, 59.93; H, 5.03. Found: C, 59.72; H, 5.09.

**Method C**—(1) Ethyl 4-[4-(4-Chlorophenoxy)benzoyl]butyrate: (Prepared from 4-[4-(4-chlorophenoxy)benzoyl]butyric acid<sup>4</sup>) in a manner similar to that described under method A-(2)), mp 55–57°C (from Et<sub>2</sub>O-hexane), 74.2%. IR  $\nu_{\max}^{\text{KBr}} \text{cm}^{-1}$ : 1720, 1675. NMR  $\delta$ : 1.26 (3H, t,  $J=8$ ), 2.08 (2H, quintet,  $J=8$ ), 2.44 (2H, t,  $J=8$ ), 3.02 (2H, t,  $J=8$ ), 4.16 (2H, q,  $J=8$ ), 7.01 (2H, d,  $J=9$ ), 7.02 (2H, d,  $J=9$ ), 7.18 (2H, d,  $J=9$ ), 7.98 (2H, d,  $J=9$ ).

(2) 4-Bromo-4-[4-(4-chlorophenoxy)benzoyl]butyric Acid: A solution of Br<sub>2</sub> (8.7 g) in CHCl<sub>3</sub> (30 ml) was added dropwise to a stirred solution of 4-[4-(4-chlorophenoxy)benzoyl]butyric acid<sup>4</sup> (17.3 g) in CHCl<sub>3</sub> (200 ml). The mixture was stirred for an additional 3 h at room temperature, then the CHCl<sub>3</sub> was removed under reduced pressure. The residue was dissolved in Et<sub>2</sub>O, and the whole was washed with H<sub>2</sub>O, dried (MgSO<sub>4</sub>) and concentrated. The residue was recrystallized from Et<sub>2</sub>O-hexane to give colorless needles (18.7 g, 88.3%), mp 118–120°C. IR  $\nu_{\max}^{\text{KBr}} \text{cm}^{-1}$ : 2500, 1700, 1665. NMR  $\delta$ : 2.46 (2H, m), 2.69 (2H, m), 5.31 (1H, dd,  $J=8, 6$ ), 7.02 (2H, d,  $J=9$ ), 7.38 (2H, d,  $J=9$ ), 8.03 (2H, d,  $J=9$ ), 9.00 (1H, br s).

Ethyl 4-Bromo-4-[4-(4-chlorophenoxy)benzoyl]butyrate: mp 76–77.5°C (from Et<sub>2</sub>O-hexane), 64.1%. IR  $\nu_{\max}^{\text{KBr}} \text{cm}^{-1}$ : 1730, 1665. NMR  $\delta$ : 1.26 (3H, t,  $J=7$ ), 2.46 (2H, m), 2.58 (2H, m), 4.16 (2H, q,  $J=7$ ), 5.35 (1H, dd,  $J=8, 6$ ), 7.02 (2H, d,  $J=9$ ), 7.04 (2H, d,  $J=9$ ), 7.38 (2H, d,  $J=9$ ), 8.04 (2H, d,  $J=9$ ).

(3) (Prepared in a manner similar to that described under method B-(4)).

4-Acetylthio-4-[4-(4-chlorophenoxy)benzoyl]butyric Acid (**21**): mp 115.5–117°C (from Et<sub>2</sub>O-hexane), 70.6%. IR  $\nu_{\max}^{\text{KBr}} \text{cm}^{-1}$ : 2500, 1705, 1690, 1660. NMR  $\delta$ : 2.11 (2H, m), 2.38 (3H, s), 2.50 (2H, m), 5.29 (1H, dd,  $J=8, 5$ ), 7.01 (2H, d,  $J=9$ ), 7.03 (2H, d,  $J=9$ ), 8.00 (2H, d,  $J=9$ ), 9.50 (1H, br s). Anal. Calcd for C<sub>19</sub>H<sub>17</sub>ClO<sub>5</sub>S: C, 58.09; H, 4.36. Found: C, 58.24; H, 4.53.

Ethyl 4-Acetylthio-4-[4-(4-chlorophenoxy)benzoyl]butyrate (**22**): Oil, 96.7%. IR  $\nu_{\max}^{\text{neat}} \text{cm}^{-1}$ : 1730, 1690, 1675. NMR  $\delta$ : 1.25 (3H, t,  $J=7$ ), 2.10 (2H, m), 2.36 (3H, s), 2.43 (2H, m), 4.16 (2H, q,  $J=7$ ), 5.39 (1H, dd,  $J=8, 5$ ), 7.01 (2H, d,  $J=9$ ), 7.03 (2H, d,  $J=9$ ), 7.38 (2H, d,  $J=9$ ), 8.02 (2H, d,  $J=9$ ). Anal. Calcd for C<sub>21</sub>H<sub>21</sub>ClO<sub>5</sub>S: C, 59.93; H, 5.03. Found: C, 60.12; H, 5.22.

**Method D**—(1) Ethyl 4-[4-(4-Chlorophenoxy)benzoyl]-4-phenylthiobutyrate: A solution of PhSNa (1.6 g) in EtOH (25 ml) was added to a stirred and ice-cooled mixture of ethyl 4-bromo-4-[4-(4-chlorophenoxy)benzoyl]butyrate (5.00 g), EtOH (25 ml) and tetrahydrofuran (THF) (25 ml). Stirring was continued for an additional 30 min at room temperature. The mixture was suspended in H<sub>2</sub>O, and the whole was extracted with Et<sub>2</sub>O. The extract was washed with H<sub>2</sub>O, dried (MgSO<sub>4</sub>) and concentrated. The residue was purified by column chromatography on silica gel with Et<sub>2</sub>O-hexane (4:1, v/v) to give a colorless oil (5.33 g, 93.2%). IR  $\nu_{\max}^{\text{neat}} \text{cm}^{-1}$ : 1730, 1670. NMR  $\delta$ : 1.23 (3H, t,  $J=8$ ), 2.16 (1H, m), 2.51 (1H, m), 2.60 (1H, m), 4.13 (2H, q,  $J=8$ ), 4.64 (1H, dd,  $J=8, 6$ ), 6.98 (2H, d,  $J=9$ ), 7.03 (2H, d,  $J=9$ ), 7.31 (5H, m), 7.38 (2H, d,  $J=9$ ), 7.94 (2H, d,  $J=9$ ).

(2) Ethyl 4-[4-(4-Chlorophenoxy)benzoyl]-4-phenylsulfinylbutyrate: *m*-Chloroperbenzoic acid (0.8 g) was added to a stirred and ice-cooled solution of ethyl 4-[4-(4-chlorophenoxy)benzoyl]-4-phenylthiobutyrate (1.80 g), and stirring was continued for an additional 30 min under ice-cooling. The mixture was suspended in satd. NaHCO<sub>3</sub> aq., and the whole was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The extract was washed with H<sub>2</sub>O, dried (MgSO<sub>4</sub>) and concentrated. The residue was purified by column chromatography on silica gel using CH<sub>2</sub>Cl<sub>2</sub>-Et<sub>2</sub>O-hexane (1:1:2, v/v) and recrystallized from Et<sub>2</sub>O-hexane to give colorless needles (1.48 g, 79.2%), mp 90–91.5°C.

(3) 4-[4-(4-Chlorophenoxy)benzoyl]-4-phenylsulfinylbutyric Acid: A mixture of ethyl 4-[4-(4-chlorophenoxy)benzoyl]-4-phenylsulfinylbutyrate (3.90 g), NaOH (0.34 g) and EtOH (20 ml) was stirred for 3 h at room temperature, then the EtOH was removed under reduced pressure. The residue was dissolved in H<sub>2</sub>O and the whole was washed with Et<sub>2</sub>O. The aqueous layer was acidified with 10% HCl aq., and the whole was extracted with EtOAc. The extract was washed with H<sub>2</sub>O, dried (MgSO<sub>4</sub>) and concentrated. The residue was recrystallized from acetone-hexane to give colorless needles (3.06 g, 83.5%), mp 127°C.

(4) Desulfinylation of the Sulfoxide: A solution of the sulfoxide (10 mmol) in CCl<sub>4</sub> (100 ml) was heated under reflux for 10 h. Then CH<sub>2</sub>Cl<sub>2</sub> (100 ml) was added, and the whole was washed with H<sub>2</sub>O, dried (MgSO<sub>4</sub>) and concentrated. The residue was purified by column chromatography on silica gel with Et<sub>2</sub>O-hexane (1:5, v/v) to give a mixture<sup>10</sup> of desulfinylated derivatives. A 3:2 mixture of 4-[4-(4-chlorophenoxy)benzoyl]-3-butenoic acid and 4-[4-(4-chlorophenoxy)benzoyl]-2-butenoic acid: 55%. A 3:1 mixture of ethyl 4-[4-(4-chlorophenoxy)benzoyl]-3-butenoate and ethyl 4-[4-(4-chlorophenoxy)benzoyl]-2-butenoate: 65%.

These mixtures were reacted with thioacetic acid in a manner similar to that described under method A-(3).

(5) 3-Acetylthio-4-[4-(4-chlorophenoxy)benzoyl]butyric Acid (**19**): mp 106—108 °C (from CH<sub>2</sub>Cl<sub>2</sub>-hexane), 40.3%. IR  $\nu_{\max}^{\text{KBr}}$  cm<sup>-1</sup>: 2500, 1720, 1685, 1670. NMR  $\delta$ : 2.32 (2H, s), 2.96 (2H, d, *J*=7), 3.44 (1H, dd, *J*=17, 7), 3.50 (1H, dd, *J*=17, 7), 4.35 (1H, m), 7.02 (2H, d, *J*=9), 7.07 (2H, d, *J*=9), 7.39 (2H, d, *J*=9), 7.98 (2H, d, *J*=9), 9.00 (1H, br s). *Anal.* Calcd for C<sub>19</sub>H<sub>17</sub>ClO<sub>5</sub>S: C, 58.09; H, 4.36. Found: C, 58.33; H, 4.49.

Ethyl 3-Acetylthio-4-[4-(4-chlorophenoxy)benzoyl]butyrate (**20**): Oil, 83.1%. IR  $\nu_{\max}^{\text{neat}}$  cm<sup>-1</sup>: 1730, 1685. NMR  $\delta$ : 1.25 (3H, t, *J*=7), 2.31 (2H, s), 2.88 (2H, d, *J*=6), 3.46 (1H, d, *J*=6), 3.47 (1H, d, *J*=6), 4.25 (2H, q, *J*=8), 4.36 (1H, m), 7.00 (2H, d, *J*=9), 7.01 (2H, d, *J*=9), 7.37 (2H, d, *J*=9), 7.98 (2H, d, *J*=9). *Anal.* Calcd for C<sub>21</sub>H<sub>21</sub>ClO<sub>5</sub>S: C, 59.93; H, 5.03. Found: C, 60.09; H, 5.05.

**Method E**—(1) 2-Methylene-3-(4-phenoxybenzoyl)propionic Acid: (Prepared from diphenylether and itaconic anhydride in a manner similar to that described under method A-(1)<sup>5</sup>), mp 92—93.5 °C (from AcOEt-hexane), 48.5%).

3-[4-(4-Chlorophenoxy)benzoyl]-2-methylenepropionic Acid: mp 145—146 °C (from Et<sub>2</sub>O-hexane), 44.0%.

(2) 2-Acetylthiomethyl-3-(4-phenoxybenzoyl)propionic Acid (**23**): 2-Methylene-3-(4-phenoxybenzoyl)propionic acid (20.0 g) and thioacetic acid (6.00 ml) were dissolved in DMF (50 ml), then a solution of K<sub>2</sub>CO<sub>3</sub> (1 g) in H<sub>2</sub>O (5 ml) was added dropwise to the solution under stirring at 30 °C for 30 min. Stirring was continued for an additional 2 h, then the mixture was suspended in H<sub>2</sub>O and acidified with 10% HCl aq. The whole was extracted with AcOEt, and the extract was washed with H<sub>2</sub>O, dried (MgSO<sub>4</sub>) and concentrated. The residue was recrystallized from Et<sub>2</sub>O-hexane to give **23** (19.5 g, 77.8%), mp 92—93.5 °C. IR  $\nu_{\max}^{\text{KBr}}$  cm<sup>-1</sup>: 1700, 1675. NMR  $\delta$ : 2.33 (3H, s), 3.11—3.56 (5H, m), 7.00 (2H, d, *J*=9), 7.05—7.24 (5H, m), 7.93 (2H, d, *J*=9), 8.98 (1H, br s). *Anal.* Calcd for C<sub>19</sub>H<sub>18</sub>O<sub>5</sub>S: C, 63.67; H, 5.06. Found: C, 63.70; H, 5.18.

2-Acetylthiomethyl-3-[4-(4-chlorophenoxy)benzoyl]propionic Acid (**24**): mp 108—110 °C (from Et<sub>2</sub>O-hexane), 84.7%. IR  $\nu_{\max}^{\text{KBr}}$  cm<sup>-1</sup>: 2500, 1685. NMR  $\delta$ : 2.35 (3H, s), 3.33 (5H, m), 6.95 (4H, d, *J*=9), 7.40 (2H, d, *J*=9), 7.94 (2H, d, *J*=9), 8.70 (1H, br s). *Anal.* Calcd for C<sub>19</sub>H<sub>17</sub>ClO<sub>5</sub>S: C, 58.10; H, 4.36. Found: C, 58.19; H, 4.46.

**Method F**—(1) 2,2-Bis(methylthio)vinyl 4-Phenoxyphenyl Ketone: *N,N*-Dimethylacetamide (30 ml) was added to a stirred solution of 4'-phenoxyacetophenone (31.8 g), 50% NaH (16 g), CS<sub>2</sub> (15 ml) and MeI (31 ml) in benzene (200 ml) at 25—30 °C for 30 min. Stirring was continued for an additional 2 h, then the mixture was poured into ice-water. The whole mixture was extracted with AcOEt and the extract was washed with H<sub>2</sub>O, dried (MgSO<sub>4</sub>) and concentrated. The residue was recrystallized from EtOH to give yellow prisms (38.9 g, 88.8%), mp 105—107 °C. IR  $\nu_{\max}^{\text{KBr}}$  cm<sup>-1</sup>: 1612, 1580. NMR  $\delta$ : 2.54 (3H, s), 2.56 (3H, s), 6.75 (1H, s), 7.02 (2H, d, *J*=9), 7.07 (2H, d, *J*=9), 7.17 (1H, t, *J*=9), 7.39 (2H, t, *J*=9), 7.93 (2H, d, *J*=9).

4-(4-Chlorophenoxy)phenyl 2,2-Bis(methylthio)vinyl Ketone: mp 94—95 °C (from EtOH), 79.8%. IR  $\nu_{\max}^{\text{KBr}}$  cm<sup>-1</sup>: 1610, 1595, 1580. NMR  $\delta$ : 2.55 (3H, s), 2.57 (3H, s), 6.74 (1H, s), 7.01 (4H, d, *J*=9), 7.34 (2H, d, *J*=9), 7.94 (2H, d, *J*=9).

(2) Ethyl 4-Phenoxybenzoylacetate: A mixture of 2,2-bis(methylthio)vinyl 4-phenoxyphenyl ketone (31.6 g), conc. H<sub>2</sub>SO<sub>4</sub> (4 ml) and EtOH (200 ml) was heated for 3 h under reflux, then the EtOH was removed under reduced pressure. The residue was dissolved in Et<sub>2</sub>O, and the whole was washed with H<sub>2</sub>O, dried (MgSO<sub>4</sub>) and concentrated. The residue was purified by column chromatography on silica gel with Et<sub>2</sub>O-hexane (5:1, v/v) to give a colorless oil (25.8 g, 84.0%). IR  $\nu_{\max}^{\text{neat}}$  cm<sup>-1</sup>: 1735, 1675. NMR  $\delta$ : 1.28 (3H, t, *J*=8), 3.95 (2H, s), 4.23 (2H, q, *J*=8), 7.02 (2H, d, *J*=9), 7.08 (2H, d, *J*=9), 7.22 (2H, d, *J*=9), 7.42 (2H, d, *J*=9), 7.94 (2H, d, *J*=9).

Ethyl 4-(4-Chlorophenoxy)benzoylacetate: Oil, 84.4%. IR  $\nu_{\max}^{\text{neat}}$  cm<sup>-1</sup>: 1735, 1680. NMR  $\delta$ : 1.28 (3H, t, *J*=8), 3.96 (2H, s), 4.23 (2H, q, *J*=8), 7.01 (2H, d, *J*=9), 7.03 (2H, d, *J*=9), 7.38 (2H, d, *J*=9), 7.96 (2H, d, *J*=9).

(3) (Prepared in a manner similar to that described under method C-(3) and B-(4)).

Ethyl 2-Acetylthio-2-(4-phenoxybenzoyl)acetate (**25**): Oil, 57.3%. IR  $\nu_{\max}^{\text{neat}}$  cm<sup>-1</sup>: 1740, 1700—1670. NMR  $\delta$ : 1.24 (3H, t, *J*=7), 2.40 (3H, s), 4.23 (2H, q, *J*=7), 5.86 (1H, s), 7.01 (2H, d, *J*=8), 7.09 (2H, d, *J*=8), 7.23 (1H, t, *J*=8), 7.43 (2H, t, *J*=8), 7.99 (2H, d, *J*=8). *Anal.* Calcd for C<sub>19</sub>H<sub>18</sub>O<sub>5</sub>S: C, 63.67; H, 5.06. Found: C, 63.40; H, 5.19.

Ethyl 2-Acetylthio-2-[4-(4-chlorophenoxy)benzoyl]acetate (**26**): Oil, 31.4%. IR  $\nu_{\max}^{\text{neat}}$  cm<sup>-1</sup>: 1740, 1700—1670. NMR  $\delta$ : 1.25 (3H, t, *J*=7), 2.40 (3H, s), 4.24 (2H, q, *J*=7), 5.86 (1H, s), 7.00 (2H, d, *J*=8), 7.03 (2H, d, *J*=8), 7.37 (2H, d, *J*=8), 8.00 (2H, d, *J*=8). *Anal.* Calcd for C<sub>19</sub>H<sub>17</sub>ClO<sub>5</sub>S: C, 58.09; H, 4.36. Found: C, 57.90; H, 4.50.

**Method G, H (Prepared in a Manner Similar to That Described under Method B-(4))**—2-Acetylthio-3-(4-phenoxyphenyl)propionic Acid (**27**): mp 121.5—122.5 °C (from Et<sub>2</sub>O-hexane), 78.3%. IR  $\nu_{\max}^{\text{KBr}}$  cm<sup>-1</sup>: 2500, 1690. NMR  $\delta$ : 2.35 (3H, s), 3.00 (1H, dd, *J*=14, 7), 3.26 (1H, dd, *J*=14, 8), 4.42 (1H, dd, *J*=8, 7), 6.93 (2H, d, *J*=8), 7.00 (2H, d, *J*=8), 7.10 (1H, t, *J*=8), 7.20 (2H, d, *J*=8), 7.34 (2H, t, *J*=8). *Anal.* Calcd for C<sub>17</sub>H<sub>16</sub>O<sub>4</sub>S: C, 64.54; H, 5.10. Found: C, 64.43; H, 5.16.

Ethyl 2-Acetylthio-3-(4-phenoxyphenyl)propionate (**28**): Oil, 50.5%. IR  $\nu_{\max}^{\text{neat}}$  cm<sup>-1</sup>: 1735, 1695. NMR  $\delta$ : 1.20 (3H, t, *J*=7), 2.35 (3H, s), 3.01 (1H, dd, *J*=13, 7), 3.22 (1H, dd, *J*=13, 8), 4.14 (2H, q, *J*=7), 4.41 (1H, dd, *J*=8, 7), 6.92 (2H, d, *J*=8), 6.99 (2H, d, *J*=8), 7.10 (1H, t, *J*=8), 7.20 (2H, d, *J*=8), 7.34 (2H, t, *J*=8). *Anal.* Calcd for C<sub>19</sub>H<sub>20</sub>O<sub>4</sub>S: C, 66.26; H, 5.85. Found: C, 66.13; H, 5.85.

2-Acetylthio-3-[4-(4-chlorophenoxy)phenyl]propionic Acid (**29**): mp 142—143 °C (from Et<sub>2</sub>O-hexane). IR  $\nu_{\max}^{\text{KBr}}$  cm<sup>-1</sup>: 2500, 1695. NMR  $\delta$ : 2.36 (3H, s), 3.01 (1H, dd, *J*=14, 7), 3.27 (1H, dd, *J*=14, 8), 4.22 (1H, dd, *J*=8, 7),

6.93 (4H, d,  $J=8$ ), 7.21 (2H, d,  $J=8$ ), 7.30 (2H, d,  $J=8$ ), 8.17 (1H, br s). *Anal.* Calcd for  $C_{17}H_{15}ClO_4S$ : C, 58.20; H, 4.31. Found: C, 58.40; H, 4.40.

Ethyl 2-Acetylthio-3-[4-(4-chlorophenoxy)phenyl]propionate (**30**): Oil, 87.2%. IR  $\nu_{\max}^{\text{neat}} \text{cm}^{-1}$ : 1735, 1695. NMR  $\delta$ : 1.20 (3H, t,  $J=7$ ), 2.34 (3H, s), 3.00 (1H, dd,  $J=14, 7$ ), 3.22 (1H, dd,  $J=14, 8$ ), 4.14 (2H, q,  $J=7$ ), 4.41 (1H, dd,  $J=8, 7$ ), 6.92 (4H, d,  $J=8$ ), 7.21 (2H, d,  $J=8$ ), 7.39 (2H, d,  $J=8$ ). *Anal.* Calcd for  $C_{19}H_{19}ClO_4S$ : C, 60.22; H, 5.05. Found: C, 60.44; H, 5.10.

2-Acetylthioethyl 4-(4-Chlorophenoxy)phenyl Ketone (**31**): mp 76–77.5 °C (from  $CH_2Cl_2$ –hexane), 76.7%. IR  $\nu_{\max}^{\text{KBr}} \text{cm}^{-1}$ : 1685, 1665. NMR  $\delta$ : 2.33 (3H, s), 3.26 (4H, t,  $J=3$ ), 8.01 (4H, d,  $J=9$ ), 7.38 (2H, d,  $J=9$ ), 7.97 (2H, d,  $J=9$ ). *Anal.* Calcd for  $C_{17}H_{15}ClO_3S$ : C, 60.99; H, 4.52. Found: C, 61.02; H, 4.56.

**Method I**—(1) 5-[4-Phenoxyphenyl)methylene]rhodanine: A solution of rhodanine (33.3 g) in benzene (240 ml) was added to a solution of ammonium acetate (4.8 g) in AcOH (17 ml), and the mixture was heated for 10 min under reflux, then 4-phenoxybenzaldehyde (49.6 g) was added. The whole was heated at reflux for 2 h, using a Dean–Stark apparatus to remove the separated water. After cooling of the mixture, the precipitated crystals were collected by filtration and washed with benzene to give yellow needles (71.5 g, 91.3%), mp 193.5–195 °C.

(2) 4-Phenoxybenzyl Cyanide: A solution of 5-[4-(4-phenoxyphenyl)methylene]rhodanine (11.8 g) and NaOH (4.5 g) in  $H_2O$  (200 ml) was heated for 40 min under reflux. After cooling, the solution was acidified with 10% HCl aq. and the whole was extracted with AcOEt. The extract was washed with  $H_2O$ , dried ( $MgSO_4$ ) and concentrated to give crude 3-(4-phenoxyphenyl)-2-thioxopropionic acid (9.4 g). NMR (acetone- $d_6$ )  $\delta$ : 7.11 (4H, d,  $J=9$ ), 7.15 (2H, s), 7.22 (1H, t,  $J=8$ ), 7.46 (2H, t,  $J=8$ ), 7.77 (2H, d,  $J=9$ ). A solution of  $NH_2OH \cdot HCl$  (8.2 g) in  $H_2O$  (6 ml) was added to a solution of NaOEt (7.8 g) in EtOH (50 ml) and the precipitate (NaCl) was filtered off. To the filtrate was added a solution of the crude 3-(4-phenoxyphenyl)-2-thioxopropionic acid (9.4 g) in EtOH (60 ml). The mixture was refluxed for 1 h, then the EtOH was removed under reduced pressure. The residue was dissolved in 5% KOH aq. (100 ml) and the whole was extracted with  $Et_2O$ . The extract was washed with  $H_2O$ , dried ( $MgSO_4$ ) and concentrated. The residue was dissolved in  $Ac_2O$  (50 ml) and the solution was refluxed for 1 h, then poured into  $H_2O$ . 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 (2:1, v/v) to give a colorless oil (2.0 g, 25%). IR  $\nu_{\max}^{\text{neat}} \text{cm}^{-1}$ : 2320. NMR  $\delta$ : 3.62 (2H, s), 7.02 (4H, d,  $J=8$ ), 7.14 (1H, t,  $J=8$ ), 7.31 (2H, d,  $J=8$ ), 7.37 (2H, t,  $J=8$ ).

(3) Ethyl 4-Amino-3-(4-phenoxyphenyl)isothiazole-5-carboxylate: A solution of 4-phenoxybenzyl cyanide (2.1 g) in EtOH (20 ml) was added to a stirred and ice-cooled solution of NaOEt (0.68 g) in EtOH (20 ml), then isoamyl nitrite (1.17 g) was added to the mixture. The whole was allowed to stand overnight under ice-cooling. The EtOH was removed under reduced pressure. The residue was recrystallized from  $Et_2O$  and dissolved in toluene (50 ml), and azeotropic evaporation of the toluene solution gave a solid. This solid and *p*-toluenesulfonyl chloride (1.27 g) were dissolved in toluene (50 ml), and the mixture was heated for 5 h under reflux, then washed with  $H_2O$ , dried ( $MgSO_4$ ) and concentrated. The residue was purified by column chromatography on silica gel with  $Et_2O$ –hexane (1:3, v/v), and dissolved in a mixture of ethyl thioglycolate (0.83 g), triethylamine (1.2 g) and EtOH (30 ml). The whole mixture was stirred for 1 h at room temperature and allowed to stand overnight. The mixture was concentrated, then the residue was suspended in  $H_2O$ , and 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 (1:3, v/v) and the product was recrystallized from  $Et_2O$ –hexane to give colorless needles (0.62 g, 18%), mp 66.5–67 °C. IR  $\nu_{\max}^{\text{KBr}} \text{cm}^{-1}$ : 3350, 1680. NMR  $\delta$ : 1.38 (3H, t,  $J=7$ ), 4.38 (2H, q,  $J=7$ ), 5.40 (2H, s), 7.12 (4H, d,  $J=8$ ), 7.16 (1H, t,  $J=8$ ), 7.39 (2H, t,  $J=8$ ), 7.71 (2H, d,  $J=8$ ).

(4) Ethyl 3-(4-Phenoxyphenyl)isothiazole-5-carboxylate (**33**): Isoamyl nitrite (1.75 g) was added to a solution of ethyl 4-amino-3-(4-phenoxyphenyl)isothiazole-5-carboxylate (1.7 g) in THF (20 ml) under stirring, and the mixture was refluxed for 30 min, then evaporated to dryness. The residue was purified by column chromatography on silica gel with  $Et_2O$ –hexane (1:3, v/v) and recrystallized from  $Et_2O$ –hexane to give **33** (1.12 g, 69%), mp 89–91 °C. IR  $\nu_{\max}^{\text{KBr}} \text{cm}^{-1}$ : 1720. NMR  $\delta$ : 1.42 (3H, t,  $J=7$ ), 4.24 (2H, q,  $J=7$ ), 7.08 (4H, d,  $J=8$ ), 7.15 (1H, t,  $J=8$ ), 7.39 (2H, t,  $J=8$ ), 7.94 (2H, d,  $J=8$ ), 8.08 (1H, s). *Anal.* Calcd for  $C_{18}H_{15}NO_3S$ : C, 66.44; H, 4.65; N, 4.30. Found: C, 66.25; H, 4.76; N, 4.33.

(5) 3-(4-Phenoxyphenyl)isothiazole-5-carboxylic Acid (**32**): A solution of **33** (0.77 g) and KOH (0.43 g) in 95% EtOH aqueous solution (20 ml) was stirred for 30 min at room temperature, and acidified with 10% HCl aq. The whole was extracted with  $Et_2O$ , and the extract was washed with  $H_2O$ , dried ( $MgSO_4$ ) and concentrated. The residue was recrystallized from  $CH_2Cl_2$ –hexane to give **32** (0.62 g, 88%), mp 181–183 °C (dec.). IR  $\nu_{\max}^{\text{KBr}} \text{cm}^{-1}$ : 2500, 1710. NMR  $\delta$ : 7.10 (4H, d,  $J=8$ ), 7.19 (1H, t,  $J=8$ ), 7.40 (2H, t,  $J=8$ ), 7.96 (2H, d,  $J=8$ ), 8.15 (1H, s). *Anal.* Calcd for  $C_{16}H_{11}NO_3S$ : C, 63.67; H, 3.84; N, 4.62. Found: C, 63.60; H, 4.02; N, 4.62.

**Method J**—2-[2-Methyl-4-(4-phenoxyphenyl)-5-thiazolyl]acetic Acid (**34**): A mixture of 3-bromo-3-(4-phenoxybenzoyl)propionic acid<sup>21</sup> (5.00 g), thioacetamide (1.10 g), pyridine (2.3 g) and MeOH (15 ml) was refluxed for 2 h under stirring, then concentrated under reduced pressure. The residue was suspended in  $Et_2O$  and the whole was extracted with saturated  $NaHCO_3$  aq. The extract was washed with  $Et_2O$ , and acidified with 10% HCl aq., then extracted with AcOEt. The extract was washed with  $H_2O$ , dried ( $MgSO_4$ ) and concentrated. The residue was recrystallized from benzene to give **34** (1.62 g, 36.6%), mp 176–178 °C. IR  $\nu_{\max}^{\text{KBr}} \text{cm}^{-1}$ : 2500, 1715. NMR (DMSO- $d_6$ )

$\delta$ : 2.64 (3H, s), 3.87 (2H, s), 7.13 (5H, m), 7.44 (2H, t,  $J=8$ ), 7.63 (2H, d,  $J=8$ ). *Anal.* Calcd for  $C_{18}H_{15}NO_3S$ : C, 66.44; H, 4.65; N, 4.30. Found: C, 66.32; H, 4.71; N, 4.19.

The following compounds were similarly prepared.

Ethyl 2-[2-Methyl-4-(4-phenoxyphenyl)-5-thiazolyl]acetate (**35**): Oil, 83.6%. IR  $\nu_{\max}^{\text{neat}} \text{cm}^{-1}$ : 1730. NMR  $\delta$ : 1.29 (3H, t,  $J=7$ ), 2.73 (3H, s), 3.85 (2H, s), 4.22 (2H, q,  $J=7$ ), 7.10 (5H, m), 7.37 (2H, t,  $J=8$ ), 7.58 (2H, d,  $J=8$ ). *Anal.* Calcd for  $C_{20}H_{19}NO_3S$ : C, 67.96; H, 5.42; N, 3.96. Found: C, 67.78; H, 5.57; N, 3.99.

2-[4-[4-(4-Chlorophenoxy)phenyl]-2-methyl-5-thiazolyl]acetic Acid (**36**): mp 164–165 °C (from benzene), 31.4%. IR  $\nu_{\max}^{\text{KBr}} \text{cm}^{-1}$ : 1708. NMR (DMSO- $d_6$ )  $\delta$ : 2.64 (3H, s), 3.86 (2H, s), 7.12 (4H, d,  $J=8$ ), 7.48 (2H, d,  $J=8$ ), 7.68 (2H, d,  $J=8$ ). *Anal.* Calcd for  $C_{18}H_{14}ClNO_3S$ : C, 60.08; H, 3.92; N, 3.89. Found: C, 59.95; H, 3.98; N, 3.88.

Ethyl 2-[4-[4-(4-Chlorophenoxy)phenyl]-2-methyl-5-thiazolyl]acetate (**37**): mp 82–84 °C (from Et<sub>2</sub>O-hexane), 89.2%. IR  $\nu_{\max}^{\text{KBr}} \text{cm}^{-1}$ : 1735. NMR  $\delta$ : 1.28 (3H, t,  $J=7$ ), 2.70 (3H, s), 4.22 (2H, q,  $J=8$ ), 6.98 (2H, d,  $J=8$ ), 7.08 (2H, d,  $J=8$ ), 7.32 (2H, d,  $J=8$ ), 7.58 (2H, d,  $J=8$ ). *Anal.* Calcd for  $C_{20}H_{18}ClNO_3S$ : C, 61.93; H, 4.68; N, 3.61. Found: C, 61.85; H, 4.79; N, 3.58.

3-[2-Methyl-4-(4-phenoxyphenyl)-5-thiazolyl]propionic Acid (**38**): mp 119–121 °C (from Et<sub>2</sub>O), 82.7%. IR  $\nu_{\max}^{\text{KBr}} \text{cm}^{-1}$ : 1705. NMR (DMSO- $d_6$ )  $\delta$ : 2.60 (2H, t,  $J=7$ ), 2.64 (3H, s), 3.12 (2H, t,  $J=7$ ), 7.08 (4H, m), 7.18 (1H, t), 7.44 (2H, t,  $J=8$ ), 7.62 (2H, d,  $J=8$ ), 12.25 (1H, br s). *Anal.* Calcd for  $C_{19}H_{17}NO_3S$ : C, 67.24; H, 5.05; N, 4.13. Found: C, 67.17; H, 5.17; N, 4.05.

Ethyl 3-[2-Methyl-4-(4-phenoxyphenyl)-5-thiazolyl]propionate (**39**): Oil, 73.0%. IR  $\nu_{\max}^{\text{neat}} \text{cm}^{-1}$ : 1733. NMR  $\delta$ : 1.15 (3H, t,  $J=7$ ), 2.64 (2H, t,  $J=7$ ), 2.68 (3H, s), 3.12 (2H, t,  $J=7$ ), 4.15 (2H, q,  $J=7$ ), 7.08 (5H, m), 7.35 (2H, t,  $J=8$ ), 7.55 (2H, d,  $J=8$ ). *Anal.* Calcd for  $C_{21}H_{21}NO_3S$ : C, 68.64; H, 5.76; N, 3.81. Found: C, 68.39; H, 5.76; N, 3.77.

3-[4-[4-(4-Chlorophenoxy)phenyl]-2-methyl-5-thiazolyl]propionic Acid (**40**): mp 147–148 °C (from Et<sub>2</sub>O), 86.7%. IR  $\nu_{\max}^{\text{KBr}} \text{cm}^{-1}$ : 1705. NMR  $\delta$ : 2.63 (3H, s), 2.60 (2H, t,  $J=7$ ), 3.12 (2H, t,  $J=7$ ), 7.10 (4H, d,  $J=8$ ), 7.46 (2H, d,  $J=8$ ), 7.63 (2H, d,  $J=8$ ), 12.24 (1H, br s). *Anal.* Calcd for  $C_{19}H_{16}ClNO_3S$ : C, 61.04; H, 4.31; N, 3.75. Found: C, 61.03; H, 4.45; N, 3.74.

Ethyl 3-[4-[4-(4-Chlorophenoxy)phenyl]-2-methyl-5-thiazolyl]propionate (**41**): Oil, 75.3%. IR  $\nu_{\max}^{\text{neat}} \text{cm}^{-1}$ : 1730. NMR  $\delta$ : 1.16 (3H, t,  $J=7$ ), 2.68 (3H, s), 2.64 (2H, t,  $J=7$ ), 3.12 (2H, t,  $J=7$ ), 4.15 (2H, q,  $J=7$ ), 6.97 (2H, d,  $J=8$ ), 7.06 (2H, d,  $J=8$ ), 7.30 (2H, d,  $J=8$ ), 7.57 (2H, d,  $J=8$ ). *Anal.* Calcd for  $C_{21}H_{20}ClNO_3S$ : C, 62.76; H, 5.02; N, 3.49. Found: C, 62.64; H, 5.09; N, 3.47.

Ethyl 2-[2-Amino-4-(4-phenoxyphenyl)-5-thiazolyl]acetate (**42**): mp 103–105 °C (from CH<sub>2</sub>Cl<sub>2</sub>-hexane), 90.1%. IR  $\nu_{\max}^{\text{KBr}} \text{cm}^{-1}$ : 3400, 3360, 3270, 1720. NMR  $\delta$ : 1.29 (3H, t,  $J=7$ ), 3.73 (2H, s), 4.21 (2H, q,  $J=7$ ), 5.24 (2H, br s), 7.05 (4H, d,  $J=8$ ), 7.12 (1H, t,  $J=8$ ), 7.36 (2H, t,  $J=8$ ), 7.53 (2H, d,  $J=8$ ). *Anal.* Calcd for  $C_{19}H_{18}N_2O_3S$ : C, 64.39; H, 5.12; N, 7.90. Found: C, 64.09; H, 5.15; N, 7.65.

Ethyl 2-[2-Amino-4-[4-(4-chlorophenoxy)phenyl]-5-thiazolyl]acetate (**43**): mp 107–109 °C (from CH<sub>2</sub>Cl<sub>2</sub>-hexane), 84.6%. IR  $\nu_{\max}^{\text{KBr}} \text{cm}^{-1}$ : 3420, 3260, 1725. NMR  $\delta$ : 1.19 (3H, t,  $J=7$ ), 3.72 (2H, s), 4.21 (2H, q,  $J=7$ ), 5.17 (2H, br s), 6.97 (2H, d,  $J=8$ ), 7.02 (2H, d,  $J=8$ ), 7.31 (2H, d,  $J=8$ ), 7.53 (2H, d,  $J=8$ ). *Anal.* Calcd for  $C_{19}H_{17}ClN_2O_3S$ : C, 58.69; H, 4.41; N, 7.20. Found: C, 58.40; H, 4.54; N, 7.09.

Ethyl 3-[2-Amino-4-(4-phenoxyphenyl)-5-thiazolyl]propionate (**44**): mp 107–108 °C (from EtOH), 74%. IR  $\nu_{\max}^{\text{KBr}} \text{cm}^{-1}$ : 3380, 3260, 3100, 1705. NMR  $\delta$ : 1.16 (3H, t,  $J=7$ ), 2.58 (2H, t,  $J=7$ ), 2.98 (2H, t,  $J=7$ ), 4.06 (2H, q,  $J=7$ ), 6.86 (2H, br s), 7.02 (2H, d,  $J=8$ ), 7.07 (2H, d,  $J=8$ ), 7.17 (1H, t,  $J=8$ ), 7.42 (2H, t,  $J=8$ ), 7.54 (2H, t,  $J=8$ ). *Anal.* Calcd for  $C_{20}H_{20}N_2O_3S$ : C, 65.20; H, 5.47; N, 7.60. Found: C, 65.28; H, 5.50; N, 7.68.

Ethyl 3-[2-Amino-4-[4-(4-chlorophenoxy)phenyl]-5-thiazolyl]propionate (**45**): mp 122–123 °C (from EtOH), 85%. IR  $\nu_{\max}^{\text{KBr}} \text{cm}^{-1}$ : 3360, 3290, 3100, 1708. NMR (DMSO- $d_6$ )  $\delta$ : 1.17 (3H, t,  $J=7$ ), 2.58 (2H, t,  $J=7$ ), 2.98 (2H, t,  $J=7$ ), 6.85 (2H, br s), 7.04 (2H, d,  $J=8$ ), 7.09 (2H, d,  $J=8$ ), 7.46 (2H, d,  $J=8$ ), 7.55 (2H, d,  $J=8$ ). *Anal.* Calcd for  $C_{20}H_{19}ClN_2O_3S$ : C, 59.62; H, 4.75; N, 6.95. Found: C, 59.74; H, 4.86; N, 6.93.

#### References and Notes

- 1) K. Tomisawa, K. Kameo, M. Goi and K. Sota, *Chem. Pharm. Bull.*, **32**, 3066 (1984).
- 2) K. Tomisawa, K. Kameo, T. Matsunaga, S. Saito, K. Hosoda, Y. Asami and K. Sota, *Chem. Pharm. Bull.*, **33**, 2386 (1985).
- 3) T. Sohda, K. Mizuno, E. Imamiya, Y. Sugiyama, T. Fujita and Y. Kawamatsu, *Chem. Pharm. Bull.*, **30**, 3580 (1982).
- 4) Y. Kawamatsu, T. Saraie, E. Imamiya, K. Nishikawa and Y. Hamuro, *Arzneim.-Forsch./Drug Res.*, **30**, 454 (1980).
- 5) R. E. Lutz, P. S. Bailey, C-K. Dien and J. W. Rinker, *J. Am. Chem. Soc.*, **75**, 5039 (1953).
- 6) I. Shahak and Y. Sasson, *Tetrahedron Lett.*, **1973**, 4207.
- 7) J. Plucker, III and E. D. Amstutz, *J. Am. Chem. Soc.*, **62**, 1512 (1940).
- 8) J. R. Beck, R. P. Gajewski and R. E. Hackler, Eur. Patent 48615 (1982) [*Chem. Abstr.*, **97**, 55798 (1982)].
- 9) J. M. Thorp and W. S. Waring, *Nature* (London), **194**, 948 (1962).
- 10) A ratio of the mixture was established on the basis of the NMR spectra.