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Syntheses and Chemical Properties of Novel 1,3-Oxathiolan-5-one Derivatives[1)]

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2-Aklylidene-4-arylidene-1,3-oxathiolan-5-one (III-1a—m) and 2,4-diarylidene-1,3-oxathiolan-5-one (III-2a—i) derivatives were synthesized by treating β-aryl-α-mercaptoacrylic acids (I) with alkanoic acid anhydrides (II) or by treating α-acylthio-β-arylacrylic acids (V) with thionyl chloride in dimethylformamide. Basic hydrolysis and methanolysis of III-1 and III-2 in the presence of lithium hydroxide easily occurred to give the corresponding ring-cleaved products, the carboxylic acid (I and II) and the ester (VII and VIII), respectively.

The catalytic hydrogenation of the two olefinic bonds of III-2 in the presence of 10% palladium charcoal proceeded easily without ring cleavage to give 1,3-oxathiolan-5-one (IXa—e) derivatives. The oxidation of III-1 and III-2 with *m*-chloroperbenzoic acid afforded the corresponding 1,3-oxathiolan-5-one *S*-oxide (Xa, b) derivatives.

Keywords——1,3-oxathiolan-5-one; β-aryl-α-mercaptoacrylic acid; α-acylthio-β-arylacrylic acid; heterocyclization; 1,3-oxathiolane ring cleavage; *m*-chloroperbenzoic acid; 1,3-oxathiolan-5-one *S*-oxide

β-Aryl-α-mercaptoacrylic acids have attracted considerable attention from pharmacists and chemists as useful intermediates for the synthesis of clinically useful compounds. Many α-mercaptoacrylic acid derivatives have been prepared and pharmacologically investigated by many groups.[2-6)] Several groups have prepared 4-arylidene-1,3-oxathiolan-5-one derivatives,[6-8)] 5-arylidene-4-thiazolidinone derivatives[8)] and benzothiophene-2-carboxylic acid derivatives[4)] by starting from β-aryl-α-mercaptoacrylic acids. During studies on the synthesis of new heterocyclic compounds possessing antihyperlipidemic activity,[9)] we found that β-aryl-α-mercaptoacrylic acids (I) reacted with an excess of alkanoic acid anhydrides (II) to give novel 1,3-oxathiolan-5-one derivatives (III-1)[10)] having a 2,4-di-*exo*-methylene group, and we reported some of the results in a communication.[10)] In the present paper we would like to report two general procedures for synthesizing 1,3-oxathiolan-5-one derivatives (III-1, III-2) having a 2,4-di-*exo*-methylene group. The reactions of β-aryl-α-mercaptoacrylic acids (I) with aldehydes producing 4-arylidene-1,3-oxathiolan-5-one derivatives are known,[6-8)] whereas the reactions of I with alkanoic acid anhydrides (II) have not been reported. Thus, the reactions of β-aryl-α-mercaptoacrylic acids (Ia—g) with an excess of alkanoic acid anhydrides (IIa—c) were carried out by heating at 130—150 °C for 0.5—1.0 h in the absence of solvent. From the reaction mixtures, novel cyclized products, 1,3-oxathiolan-5-one derivatives (III-1a—m) having alkylidene groups at the 2- and 4-positions, were obtained in significant yields. The infrared (IR) spectrum of III-1a showed the presence of a lactone carbonyl group at 1778 cm^{-1}. Elemental analysis and the mass spectrum (MS) *m/e*: 209 (M^+) established the formula $C_9H_7NO_3S$, which indicated that the reaction between Ia and IIa proceeded with eliminations of water and acetic acid. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum of III-1a in $CDCl_3$ showed the signal of the vinyl proton on the isoxazolylmethylene

at δ 7.37 ppm as a singlet. On the other hand, the signals of the *exo*-cyclic vinyl protons appeared at δ 4.65 (d, J=4 Hz) and 5.18 ppm (d, J=4 Hz). The presence of the *exo*-cyclic double bond of III-1a at the 2-position was also confirmed by analysis of the carbon nuclear magnetic resonance (^{13}C-NMR) spectrum. The signal of a secondary carbon of III-1a at the 2-position at δ 89.5 ppm (singlet under decoupling conditions) changed into a triplet on application of the off-resonance technique. These spectral and analytical observations clearly support the structural assignment of III-1a. The structures of III-1b—m were confirmed similarly. The physical data for the products (III-1a—m) are listed in Table I. We consider that *Z*-geometry of the double bond substituents of I[7] might be retained in the geometry of the double bond of III at the 4-position.[11]

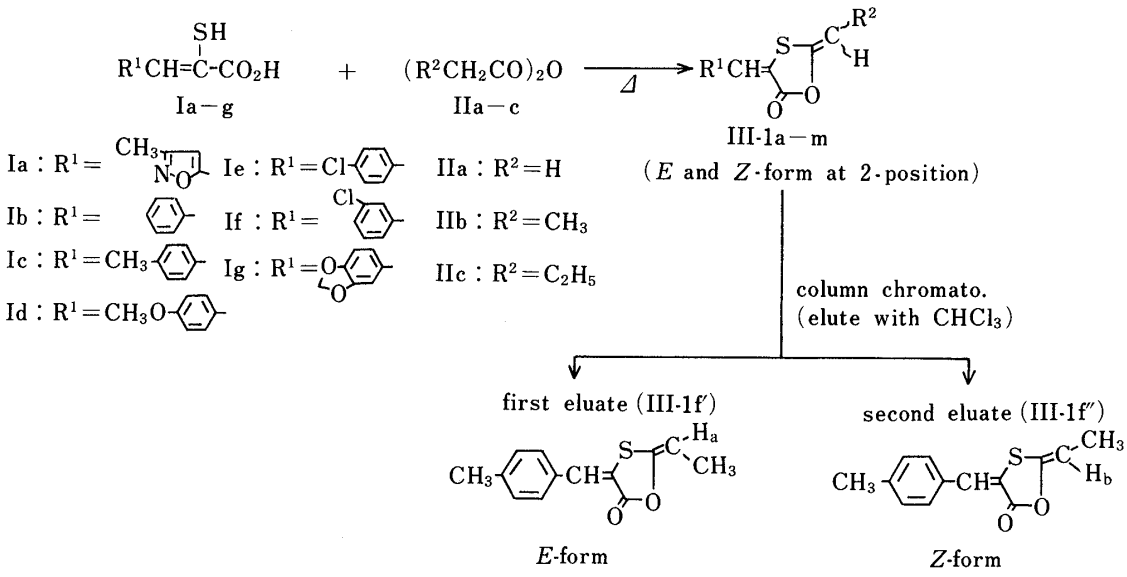
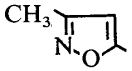
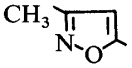
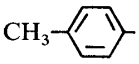
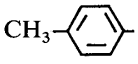
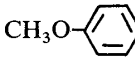
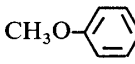
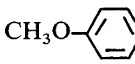
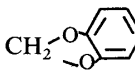
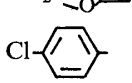
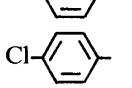
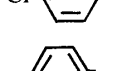


Chart 1

Reaction of propanoic acid anhydride (IIb) with Ic gave an isomeric mixture of III-1f′ and III-1f″; the ^{1}H-NMR spectrum of the crude product indicated a 1 : 1 mixture. These isomers could be separated by silica gel column chromatography to give III-1f′ as yellow crystals (mp 90—91.5 °C) and III-1f″ as yellow crystals (mp 113—115 °C). The geometries at the 2-position of III-1f′ and III-1f″ were confirmed by known principles. Thus, Pascual's method[12] was applied, namely, the olefinic geometry was estimated by comparing the observed δ value deviations of the geometric isomers from the standard δ value of ethylene protons with the calculated ones based on the substituents and geometries. The calculated ^{1}H-NMR δ values for proton H_a of III-1f′ and for proton H_b of III-1f″ are 4.81 and 5.28 ppm, respectively. On the other hand, the observed δ values of the vinyl protons in the ^{1}H-NMR spectra were 4.79 ppm (q, J=7 Hz) in III-1f′ and 5.46 ppm (q, J=7 Hz) in III-1f″. Therefore, the assigned structures for III-1f′ (*E*-form) and III-1f″ (*Z*-form) were established. The *E*/*Z* ratios of other products (III-1b, 1d, 1h, 1i, 1e) were similarly determined (Table I). The present reaction probably proceeds *via* formation of a mixed acid anhydride followed by intramolecular acylation.

We planned to synthesize III by using acid chlorides (IV) instead of the anhydrides (II) in order to increase the scope of the reaction.[13] Considering the reaction mechanism in the case of II, excess of anhydride presumably effects dehydration for intramolecular cyclization *via* the formation of a mixed anhydride as an intermediate (Chart 2). Thus, in the case of acid chlorides, an appropriate dehydrating agent may be necessary. When Ic was allowed to react with acetic anhydride in 3 N NaOH, the intermediate Va (mp 154—156 °C) was obtained in

TABLE I. 2-Alkylidene-4-arylidene-1,3-oxathiolan-5-one Derivatives (III-1)

Product[a] No.	R^1	R^2	mp (°C) (recryst. solv.)	Yield (%)	E/Z[b]	Formula	Analysis (%) Calcd (Found) C	H	N
III-1a		H	143—145 (CCl_4)	44.3		$C_9H_7NO_3S$	51.61 (51.15	3.37 3.34	6.69 6.58)
III-1b		CH_3	133—136 (CCl_4)	58.2	5/3	$C_{10}H_9NO_3S$	53.80 (53.75	4.06 4.10	6.27 6.30)
III-1c		H	57—59 (CCl_4)	42.1		$C_{11}H_8O_2S$	64.69 (64.72	3.95 3.81	— —)
III-1d		CH_3	45—46 (CCl_4)	64.8	1/1	$C_{12}H_{10}O_2S$	66.03 (66.01	4.62 4.56	— —)
III-1e		H	91—93 (EtOH)	69.7		$C_{12}H_{10}O_2S$	66.03 (66.12	4.62 4.88	— —)
III-1f		CH_3	79—85 (EtOH)	65.9	1/1	$C_{13}H_{12}O_2S$	67.24 (67.38	5.17 5.30	— —)
III-1g		H	94—95 (EtOH)	42.3		$C_{12}H_{10}O_3S$	61.52 (61.62	4.30 4.17	— —)
III-1h		CH_3	94—96 (EtOH)	76.4	1/1	$C_{13}H_{12}O_3S$	62.88 (62.65	4.87 4.78	— —)
III-1i		C_2H_5	79—81 (EtOH)	50.5	1/1	$C_{14}H_{14}O_3S$	64.12 (64.01	5.34 5.57	— —)
III-1j		H	139—141 (MeOH)	44.8		$C_{12}H_8O_4S$	58.06 (58.26	3.25 3.18	— —)
III-1k		H	132—134 (EtOH)	30.4		$C_{11}H_7ClO_2S$	55.35 (55.12	2.96 3.05	— —)
III-1l		CH_3	116—119 (EtOH)	60.1	1/1	$C_{12}H_9ClO_2S$	57.03 (56.83	3.59 3.57	— —)
III-1m		H	109—110 (EtOH)	50.3		$C_{11}H_7ClO_2S$	55.35 (55.30	2.96 2.97	— —)

a) The products (III-1a—m) were all yellow needles. *b*) The ratio of the geometrical isomers (*E*/*Z*) involving R^2 was calculated from the ^{1}H-NMR results.

88.2% yield, and could be characterized by elemental analysis, MS, IR and ^{1}H-NMR. Intermediates Va—i were also obtained by treating Ia—g with the corresponding acyl chloride in the presence of triethylamine. Although ethyl chlorocarbonate, dicyclohexyl carbodiimide or *p*-toluenesulfonic acid were not effective for the intramolecular cyclization to III, thionyl chloride was effective for this purpose. For example, IIIa (mp 91—93 °C) was obtained in 80.0% yield by treating Va with thionyl chloride in dimethylformamide at room temperature, and Vb—i were also converted to the corresponding III in high yields by similar treatment (Table IV). It is interesting that the *Z*-form was produced predominantly (based on the ^{1}H-NMR spectra of the crude products (Table IV)). The ratio of the geometrical isomers formed may be affected by the steric hindrance of the starting carboxylic acid; namely, in the case of a large group as R^4 and a small group as R^3 (for example, R^3=H, R^4=naphthyl and the like) in Chart 3, intermediate (B) would predominate reather than intermediate (A). Thus, more *Z*-form than *E*-form at the 2-position of III-2 would be produced on 1,3-oxathiolane formation.

We have also studied the chemical properties of the 1,3-oxathiolan-5-ones (III-1, III-2). It was found that cleavage of the heterocyclic ring of III occurred on treatment with 3 N

TABLE II. IR and ^{1}H-NMR Spectral Data for 1,3-Oxathiolan-5-one Derivatives (III-1)

Product No.	IR ν_{max}^{KBr} cm^{-1} (CO)	^{1}H-NMR ($CDCl_3$) δ ppm
III-1a	1778	2.35 (3H, s), 4.65 and 5.18 (2H, each d, each J=4 Hz), 6.28 (1H, s), 7.37 (1H, s)
III-1b	1776	1.74 and 1.89 (3H, each d, each J=7 Hz), 2.35 and 2.36 (3H, each s), 4.91 and 5.64 (1H, each q, each J=7 Hz), 6.31 and 6.36 (1H, each s), 7.41 and 7.42 (1H, each s)
III-1c	1775	4.51 and 5.06 (2H, each d, each J=4 Hz), 7.33 (5H, s), 7.54 (1H, s)
III-1d	1772	1.69 and 1.85 (3H, each d, each J=7 Hz), 4.78 and 5.48 (1H, each q, each J=7 Hz), 7.10—7.45 (5H, m), 7.46 and 7.51 (1H, each s)
III-1e	1774	2.32 (3H, s), 4.51 and 5.05 (2H, each d, each J=4 Hz), 7.00—7.40 (4H, m), 7.55 (1H, s)
III-1f	1775	1.66 and 1.85 (3H, each d, each J=7.8 Hz), 2.33 (3H, s), 4.78 and 5.45 (1H, each q, each J=7.8 Hz), 7.17 (4H, d), 7.50 (1H, s)
III-1g	1772	3.80 (3H, s), 4.51 and 5.06 (2H, each d, each J=4 Hz), 6.39 (2H, d, J=8 Hz), 7.35 (2H, d, J=8 Hz), 7.55 (1H, s)
III-1h	1772	1.66 and 1.81 (3H, each d, each J=7 Hz), 3.80 (3H, s), 4.80 and 5.48 (1H, each q, each J=7 Hz), 6.86—7.45 (5H, m), 7.47 and 7.49 (1H, each s)
III-1i	1770	1.04 and 1.07 (3H, each t), 1.67—2.56 (2H, m), 3.79 (3H, s), 4.75 and 5.41 (1H, each t, each J=7.7 Hz), 6.73—7.43 (4H, m), 7.44 (1H, s)
III-1j	1775	4.50 and 5.05 (2H, each d, each J=4 Hz), 5.96 (2H, s), 6.72—6.96 (3H, m), 7.42 (1H, s)
III-1k	1770	4.56 and 5.13 (2H, each d, each J=4 Hz), 7.44 (4H, s), 7.58 (1H, s)
III-1l	1770	1.70 and 1.85 (3H, each d, each J=7 Hz), 4.84 and 5.54 (1H, each q, each J=7 Hz), 7.40 and 7.46 (4H, each s), 7.52 and 7.54 (1H, each s)
III-1m	1771	4.60 and 5.13 (2H, each d, each J=4 Hz), 7.10—7.45 (4H, m), 7.51 (1H, s)

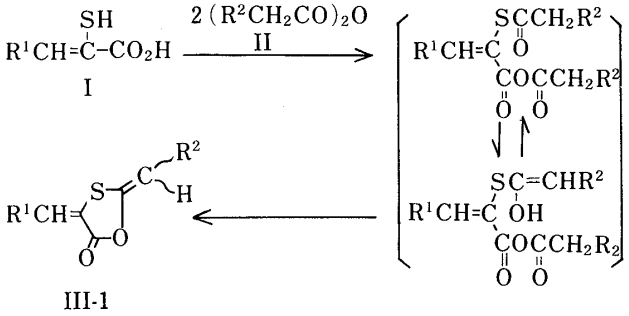


Chart 2. Possible Pathway for the Formation of Product III-1

NaOH in methanol to yield α-mercapto-β-(4-methylphenyl)acrylic acid (Ic, raw material) and β-phenylpropionic acid (VI).[14] When III-1c and III-2e were treated with lithium hydroxide in methanol, similar ring cleavage occurred to produce methyl α-mercapto-β-(4-methylphenyl)acrylate (VII) and methyl propionate (VIIIa) or methyl phenoxyacetate (VIIIb).[15] The ^{1}H-NMR spectrum ($CDCl_3$) of VII showed the signal of CO_2CH_3 at δ 3.86 ppm and the signal of SH at δ 4.68 ppm. The MS of VII showed m/e 208 (M^+). These data clearly support the structure of VII. Compound VIIIa could not be isolated, but considering the formation of VIIIb by methanolysis of III-2e, we presume that similar methanolysis of III-1c occurs, producing VIIIa.

Olefinic bonds of the product (III-2c) were easily hydrogenated over 10% palladium

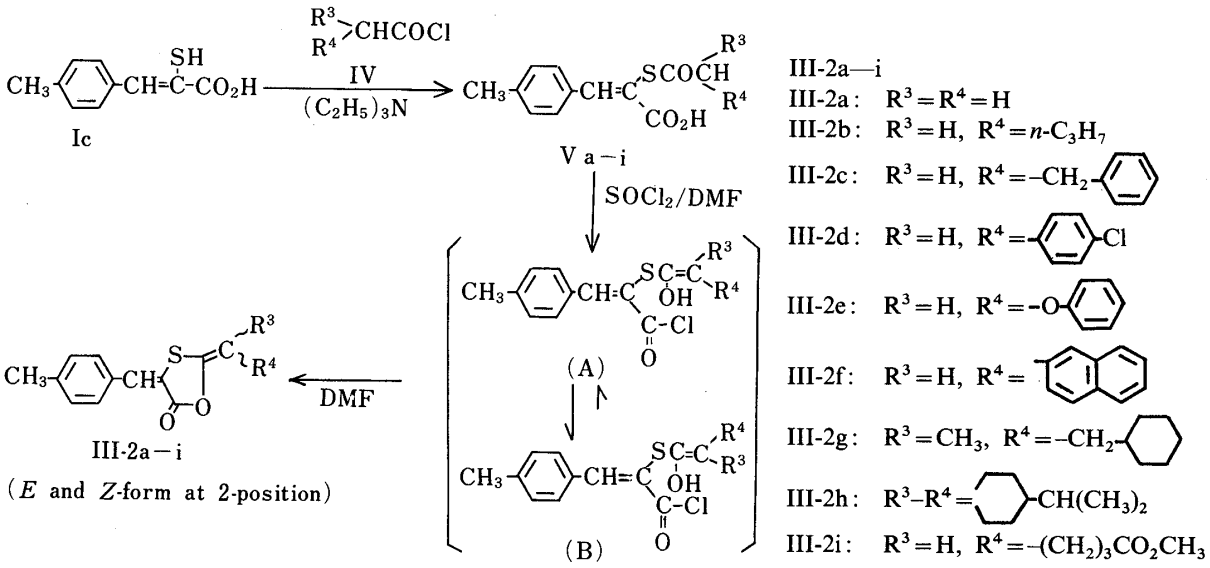


Chart 3

TABLE III. α-Acylthio-β-(4-methylphenyl)acrylic Acid Derivatives (V)

Compd. No.	R^3	R^4	mp (°C)	Yield (%)	MS (M^+)	Formula	Analysis (%) Calcd (Found) C	H
Va[a)]	H	H	154—156	82.2	236	$C_{12}H_{12}O_3S$	61.02 (61.12)	5.08 (5.01)
Vb	H	n-C_3H_7	101—102	54.8	278	$C_{15}H_{18}O_3S$	64.72 (64.71)	6.52 (6.62)
Vc	H	-CH_2-C$_6$H$_5$	155—157	44.6	326	$C_{19}H_{20}O_3S$	69.91 (69.72)	5.56 (5.51)
Vd	H	-C$_6$H$_4$-Cl	157—158	83.9	346	$C_{18}H_{15}ClO_3S$	62.33 (62.27)	4.36 (4.49)
Ve	H	-O-C$_6$H$_5$	147—148	88.8	328	$C_{18}H_{16}O_4S$	65.84 (65.29)	4.91 (5.14)
Vf	H	C$_{10}$H$_7$	185—187	89.3	362	$C_{22}H_{18}O_3S$	72.91 (72.87)	5.01 (5.07)
Vg	CH_3	-CH_2-C$_6$H$_5$	136—137	65.4	346	$C_{20}H_{26}O_3S$	69.33 (69.01)	7.56 (7.52)
Vh	C$_6$H$_5$	-$CH(CH_3)_2$	157—159	58.8	346	$C_{20}H_{26}O_3S$	69.33 (68.91)	7.56 (7.57)
Vi	H	-$(CH_2)_3CO_2CH_3$	76—77	42.4	336	$C_{17}H_{20}O_5S$	60.70 (60.22)	5.99 (5.79)

a) This compound only was prepared by treatment of Ic with acetic anhydride in NaOH solution.

charcoal to give a diastereomeric mixture of 4-(4-methylbenzyl)-2-(2-phenethyl)-1,3-oxathiolan-5-one (IXa) without cleavage of the 1,3-oxathiolane ring in 74.1% yield. The IR spectrum of IXa showed the presence of a lactone carbonyl group at 1755 cm^{-1}, the MS showed m/e 312 (M^+) and the ^{1}H-NMR spectrum ($CDCl_3$) showed the signals of the methine protons at the 2- and 4-positions of the product (IXa) at δ 5.30, 4.85 ppm and δ 4.30, 4.15 ppm, respectively. The ^{1}H-NMR of IXa indicated that the product (IXa) was a diastereomeric mixture at the newly produced asymmetric carbons. The ^{1}H-NMR spectrum ($CDCl_3$) of IXa

TABLE IV. 2-Substituted-4-(4-methylphenylmethylene)-1,3-oxathiolan-5-one Derivatives (III-2)

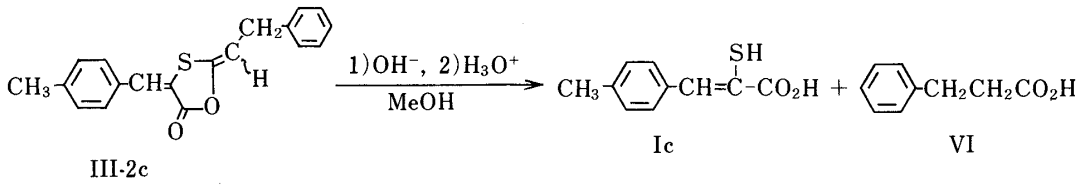
Product[a] No.	R^3	R^4	mp (°C)	Yield (%)	E/Z[b]	Formula	Analysis (%) Calcd (Found) C	H
III-2a	H	H	91—93 (EtOH)	80.0	—	$C_{12}H_{10}O_2S$	III-1e	
III-2b	H	n-C_3H_7	43—49 (CCl_4)	92.9	2/5	$C_{15}H_{16}O_2S$	69.20 (69.30	6.19 6.35)
III-2c	H	$-CH_2-C_6H_5$	95—99 (EtOH)	88.2	2/3	$C_{19}H_{16}O_2S$	74.00 (73.99	5.23 5.20)
III-2d	H	$-C_6H_4Cl$	169—175 (EtOH)	87.9	1/2	$C_{18}H_{13}ClO_2S$	65.75 (65.92	3.99 4.13)
III-2e	H	$-O-C_6H_5$	98—102 (EtOH)	76.5	1/6	$C_{18}H_{14}O_3S$	69.66 (69.37	4.55 4.68)
III-2f	H	$-C_{10}H_7$	136—142 (EtOH)	91.2	1/6	$C_{22}H_{16}O_2S$	76.72 (76.82	4.68 4.82)
III-2g	CH_3	$-CH_2-C_6H_{11}$	107—109 (EtOH)	91.4	1/6	$C_{20}H_{24}O_2S$	73.13 (73.34	7.36 7.69)
III-2h	$-C_6H_{11}$	$-CH(CH_3)_2$	129—132 (EtOH)	98.5	—	$C_{20}H_{24}O_2S$	73.13 (72.77	7.36 7.54)
III-2i	H	$-(CH_2)_3CO_2CH_3$	52—54 (CCl_4)	84.5	2/3	$C_{17}H_{18}O_4S$	64.13 (63.93	5.70 5.82)

a) The products (III-2a—i) were all yellow needles and their isomers (*E*/*Z*) could not be isolated, so the listed data are for the mixtures. *b*) The ratio of the geometrical isomers (*E*/*Z*) involving R^3 (R^4) was calculated from the ^{1}H-NMR results.

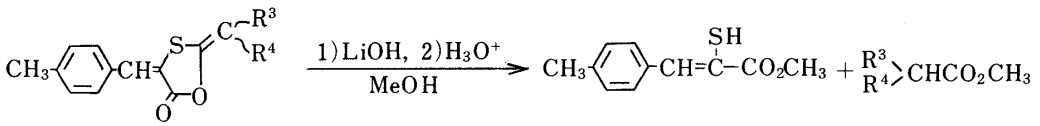
TABLE V. IR and ^{1}H-NMR Spectral Data for 1,3-Oxathiolan-5-one Derivatives (III-2)

Product No.	IR ν_{max}^{KBr} cm^{-1} (CO)	^{1}H-NMR ($CDCl_3$) δ ppm
III-2b	1760	0.94 and 0.96 (3H, each t, each J=7.8 Hz), 1.20—1.68 (2H, m), 2.05 and 2.32 (2H, each q, each J=7.8 Hz), 2.40 (3H, s), 4.84 and 5.53 (1H, each t, each J=7.8 Hz), 7.10—7.48 (2H, m), 7.60 (1H, s)
III-2c	1776	2.40 (3H, s), 3.41 and 3.67 (2H, each d, each J=7.8 Hz), 5.02 and 5.74 (1H, each t, each J=7.8 Hz), 7.10—7.50 (9H, m), 7.64 (1H, s)
III-2d	1785 1770 1755	2.41 (3H, s), 5.68 and 6.57 (1H, each s), 7.16—7.54 (8H, m), 7.69 (1H, s)
III-2e	1765	2.39 (3H, s), 6.16 and 7.00 (1H, each s), 6.90—7.48 (9H, m), 7.66 (1H, s)
III-2f	1780	2.37 (3H, s), 6.44 and 7.12 (1H, each s), 7.08—8.08 (11H, m), 7.68 (1H, s)
III-2g	1770	0.70—2.00 (11H, m), 1.88—1.96 (3H, each s), 2.40 (3H, s), 2.22 and 2.90 (2H, each d, each J=6.6 Hz), 7.14—7.44 (4H, m), 7.57 (1H, s)
III-2h	1770 1765	0.84 (3H, s), 0.90 (3H, s), 1.00—2.30 (9H, m), 2.39 (3H, s), 2.84—3.18 (1H, m), 7.10—7.46 (4H, m), 7.58 (1H, s)
III-2i	1770 1735	1.60—2.50 (6H, m), 2.40 (3H, s), 3.68 (3H, s), 4.82 and 5.50 (1H, each t, each J=7.8 Hz), 7.12—7.44 (4H, m), 7.62 (1H, s)

was quite similar to those of 2-ethyl-4-methyl-1,3-oxathiolan-5-one (δ 5.43 and 4.05 ppm), which was obtained from the reaction of 2-mercaptopropionic acid with propionaldehyde by Satsumabayashi and his coworkers,[16] and 2,4-dimethyl-1,3-oxathiolan-5-one (*cis*; δ 5.47 and



III-2c Ic VI



III-1c, III-2e VII VIIIa, b

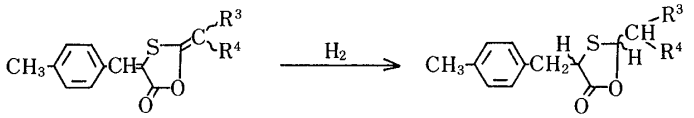
III-1c: $R^3=H$, $R^4=CH_3$

III-2e: $R^3=H$, $R^4=-O-C_6H_5$

VIIIa: $R^3=H$, $R^4=CH_3$

VIIIb: $R^3=H$, $R^4=-O-C_6H_5$

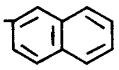
Chart 4

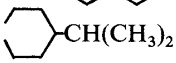


III-2c, e, f, h, i IXa—e

III-2c: $R^3=H$, $R^4=-CH_2-C_6H_5$

III-2e: $R^3=H$, $R^4=-O-C_6H_5$

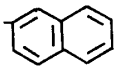
III-2f: $R^3=H$, $R^4=$ 

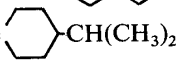
III-2h: $R^3-R^4=$ 

III-2i: $R^3=H$, $R^4=-(CH_2)_3CO_2CH_3$

IXa: $R^3=H$, $R^4=-CH_2-C_6H_5$

IXb: $R^3=H$, $R^4=-O-C_6H_5$

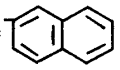
IXc: $R^3=H$, $R^4=$ 

IXd: $R^3-R^4=$ 

IXe: $R^3=H$, $R^4=-(CH_2)_3CO_2CH_3$

III-1i, 2f Xa, b

III-1i: $R^3=H$, $R^4=C_2H_5$, $R^5=OCH_3$

III-2f: $R^3=H$, $R^4=$  , $R^5=CH_3$

Xa: $R^3=H$, $R^4=C_2H_5$, $R^5=OCH_3$

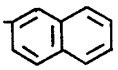
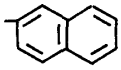
Xb: $R^3=H$, $R^4=$  , $R^5=CH_3$

Chart 5

3.97 ppm, *trans*; δ 5.57 and 3.91 ppm), which was obtained by Pihlaja and his coworkers.[17] Unfortunately, the isomers (*cis* and *trans*) for IXa could not be separated by column chromatography. Similar hydrogenations of III-2e, III-2f, III-2h and III-2i were carried out to give IXb, IXc, IXd and IXe, respectively. The structures of IXb—e were confirmed similarly.

We carried out oxidation of III-1i and III-2f with *m*-chloroperbenzoic acid to afford the corresponding *S*-oxides, Xa and Xb, in 43.5% and 66.9% yields, respectively.[18] The IR spectrum of Xa showed a lactone carbonyl absorption at 1740 cm^{-1}, the MS showed *m/e* 278 (M^+) and the ^1H-NMR spectrum ($CDCl_3$) showed the signals of two vinyl protons at the 2- and 4-positions of the product (Xa) at δ 6.04 and 5.76 ppm, and δ 8.30 ppm, respectively (the

TABLE VI. 2-Substituted-4-(4-methylbenzyl)-1,3-oxathiolan-5-one Derivatives (IX)

Product[a] No.	R^3	R^4	Yield (%)	IR $\nu_{max}^{CHCl_3}$ cm^{-1} (CO)	MS (M^+)	^{1}H-NMR ($CDCl_3$) δ ppm
IXa	H	$-CH_2-C_6H_5$	74.1	1755	312	1.80—2.25 (2H, m), 2.31 (3H, s), 2.60—3.65 (4H, m), 4.15 and 4.30 (1H, each d), 4.85 and 5.30 (1H, each t), 6.80—7.40 (9H, m)
IXb	H	$-O-C_6H_5$	65.8	1760	314	2.32 (3H, s), 2.80—3.50 (2H, m), 3.75 (2H, d), 4.10—4.35 (1H, m), 5.35 and 5.60 (1H, each t), 6.70—7.40 (9H, m)
IXc	H		72.5	1755	348	3.38 (3H, s), 2.60—3.90 (4H, m), 4.10 and 4.20 (1H, each d), 5.28 and 5.73 (1H, each t), 6.90—8.00 (11H, m)
IXd		$-CH(CH_3)_2$	74.1	1760	332	0.84 (6H, d), 0.70—1.90 (11H, m), 2.33 (3H, s), 2.75—3.60 (2H, m), 4.13 and 4.24 (1H, each d), 5.09 and 5.36 (1H, each d), 7.12 (4H, s)
IXe	H	$-(CH_2)_3CO_2CH_3$	71.1	1755 1725	322	1.15—2.00 (6H, m), 2.30 (2H, t), 2.33 (3H, s), 2.75—3.60 (4H, m), 3.66 (3H, s), 4.15 and 4.25 (1H, each d), 4.90 and 5.30 (1H, each t), 7.11 (4H, s)

a) All products except IXc (mp 67—70 °C) were oils. Their diastereomeric mixtures could not be separated, so the listed data are for the mixtures.

product was an isomeric mixture). The structure of Xb was also determined in the same manner as described for Xa. The ratio (*E*/*Z*)[19] of geometry of the products (Xa, b) agreed with that of III-1i and III-2f found from the ^{1}H-NMR spectra. From the above results, it can be concluded that the 1,3-oxathiolan-5-one ring having two *exo*-methylene groups at the 2- and 4-positions is very unstable under basic conditions, but in other experiments the ring was relatively stable to mild reduction and oxidation.

These products (III-1) possessed considerable chymotrypsin inhibitory activity;[20] the data will be reported in detail in a later paper.

Experimental

All melting points were recorded with a Yanagimoto micromelting point apparatus and are uncorrected. Spectral data were obtained with the following instruments: IR with a Hitachi 260-50 spectrophotometer; MS with a JEOL LMS-01G-2 spectrometer; ^{1}H-NMR, ^{13}C-NMR with a JEOL LMN-FX 100 spectrometer (using tetramethylsilane as an internal standard). Chemical shifts are given in δ values (ppm) and the abbreviations of signal patterns are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Elemental analyses were carried out with a Yanagimoto C H N Corder MT-2 analyzer.

Starting Materials——β-Aryl-α-mercaptoacrylic acids (Ib—g) were prepared by the reported procedure[6] and they are known compounds except for Ia. The preparation of Ia has been reported elsewhere.[9] 4-Isopropylcyclohexanecarboxylic acid, bp 131—134 °C/1 mmHg (literature bp 133 °C/2.5 mmHg)[21] was prepared by hydrogenation of cuminic acid over PtO_2 in AcOH.[21] β-Cyclohexyl-α-methylpropionic acid, bp 117—121 °C/0.5 mmHg (literature, bp 178—179 °C/2 mmHg)[22] was prepared *via* diethyl α-methyl-α-cyclohexylmethylmalonate, which was obtained by the condensation of diethyl methylmalonate with cyclohexylmethylbromide,[23] according to Reid's procedure.[24] Acid chlorides (IVc, d, f—i) were prepared by treatment of the corresponding carboxylic acids with $SOCl_2$. IVb and IVe were commercial products.

α-Acetylthio-β-(4-methylphenyl)acrylic Acid (Va)——Acetic anhydride (7 ml) was added dropwise to a 20% NaOH solution (40 ml) of Ic (1.6 g) under stirring at room temperature. After being stirred for 1 h, the reaction mixture was poured into cold 6 N HCl (100 ml). The precipitates were collected by suction and washed with water. Colorless needles of Va were obtained by recrystallization from ethanol–water. Yield 1.6 g (82.2%), mp 154—156 °C. MS *m*/*e*: 236 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 2.40 (3H, s, CH_3), 2.41 (3H, s, $COCH_3$), 7.10 (2H, d), 7.52 (2H, d), 7.70—8.30 (1H, br, CO_2H), 8.31 (1H, s, CH=). Other data are listed in Table III.

β-(4-Methylphenyl)-α-(*n*-valeroylthio)acrylic Acid (Vb)——Typical Procedure for Syntheses of Vb—i: A solution

of *n*-valeroyl chloride (2.5 g) in ether (5 ml) was added dropwise to a suspension of Ic (3.0 g) in NaOH solution (NaOH, 1.4 g in H_2O, 30 ml) and ether (5 ml) under stirring with ice-water cooling. The mixture was stirred at the same temperature for 1 h then poured into cold 6 N HCl (30 ml) and extracted with ether. The ether layer was dried over sodium sulfate and evaporated to dryness under reduced pressure. The residue was chromatographed on a silica gel column with chloroform. From the eluate, colorless needles of Vb were obtained. Yield 2.3 g (54.8%), mp 101—102 °C (ethanol–water). MS *m/e*: 278 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, t, J=6.6 Hz, $CO(CH_2)_3C\underline{H}_3$), 1.10—1.85 (4H, m, $COCH_2(C\underline{H}_2)_2CH_3$), 2.39 (3H, s, CH_3), 2.66 (2H, t, J=6.6 Hz, $COC\underline{H}_2(CH_2)_2CH_3$), 7.20—7.80 (1H, br, CO_2H), 7.21 (2H, d), 7.65 (2H, d), 8.33 (1H, s, CH=). Other data are listed in Table III.

2-Methylene-4-(3-methyl-5-isoxazolylmethylene)-1,3-oxathiolan-5-one (III-1a)——Typical Procedure for Syntheses of III-1a, 1b, 1e—m: A solution of α-mercapto-β-(3-methyl-5-isoxazolyl)acrylic acid, Ia (9.0 g) in an excess of acetic anhydride, IIa (50 ml) was heated at 120 °C for 1 h. After cooling, the reaction mixture was concentrated to about 5 ml and poured into ice-cold water. The precipitates were collected by suction and washed with water. Yellow needles of III-1a were obtained by recrystallization from carbon tetrachloride. Yield 4.5 g (44.3%), mp 143—145 °C. MS *m/e*: 209 (M^+). ^{13}C-NMR ($CDCl_3$) δ: 10.7 (q), 89.5 (t), 106.8 (d), 112.4 (d), 125.0 (s), 145.1 (s), 148.7 (s), 159.3 (s), 163.3 (s). Other data are listed in Tables I and II. Similar procedures were used for the syntheses of III-1b, 1e—m.

In the cases of the syntheses of III-1c and III-1d, the acidified solution was extracted with chloroform. The chloroform layer was washed with water, dried over sodium sulfate and evaporated to dryness under reduced pressure. The residue was chromatographed on a silica gel column with chloroform. From the eluate, yellow crystals of III-1c and III-1d, respectively, were obtained. Other data are listed in Tables I and II.

Separation of *E* and *Z* Isomers for Product III-1f——The product III-1f (1.0 g) was chromatographed on a long silica gel column with chloroform. From the first eluate, yellow crystals of III-1f′ (*E*-form) were obtained. Yield 0.45 g, mp 90—91.5 °C. MS *m/e*: 232 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.86 (3H, d, J=7.8 Hz, $C\underline{H}_3CH$=), 2.33 (3H, s, CH_3), 4.79 (1H, q, J=7.8 Hz, $CH_3C\underline{H}_2$ at 2-position), 7.20 (4H, s), 7.50 (1H, s, CH= at 4-position). From the second eluate, yellow crystals of III-1f″ (*Z*-form) were obtained. Yield 0.50 g, mp 113—115 °C. MS *m/e*: 232 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.66 (3H, d, J=7.8 Hz, $C\underline{H}_3CH$=), 2.34 (3H, s, CH_3), 5.46 (1H, q, J=7.8 Hz, $CH_3C\underline{H}$= at 2-position), 7.23 (4H, d), 7.50 (1H, s, CH= at 4-position).

4-(4-Methylphenylmethylene)-2-(2-phenylethylene)-1,3-oxathiolan-5-one (III-2c)——Typical Procedure for Syntheses of III-2a—i: $SOCl_2$ (0.2 ml) was added dropwise to a solution of Vc (0.6 g) in dimethylformamide (8 ml) under stirring with ice cooling. The reaction mixture was stirred at room temperature for 1 h then poured into ice-water, followed by extraction with chloroform. The chloform layer was dried over sodium sulfate and evaporated to dryness under reduced pressure. The residue was chromatographed on a silica gel column with chloroform. From the eluate, yellow needles of III-2c were obtained. Yield 0.50 g (88.2%), mp 95—99 °C (ethanol). Other data are listed in Tables IV and V. Similar procedures were used for the syntheses of III-2b—i.

Hydrolysis of III-2c——Aqueous 2 N NaOH (1 ml) was added dropwise to a solution of III-2c (0.2 g) in dioxane (5 ml) under stirring at 0—5 °C. The reaction mixture was stirred at room temperature for 0.5 h then acidified with 6 N HCl followed by extraction with ether. The ether layer was dried over sodium sulfate and evaporated to dryness under reduced pressure. The residue was chromatographed on a silica gel column with chloroform–ethanol (10 : 1, v/v). From the first eluate, VI was obtained as an oily product. Yield 0.07 g (88.2%). The product was identical with authentic 3-phenylpropionic acid. From the second eluate, light yellow crystals were obtained. This product was identical with authentic α-mercapto-β-(4-methylphenyl)acrylic acid (Ic).

Methanolysis of III-1c and III-2e——LiOH (0.56 g) was added to a solution of III-1c (0.21 g) in methanol (20 ml) at 0—5 °C. The mixture was stirred at the same temperature for 2 h then acidified with 2 N HCl followed by concentration to about 5 ml under reduced pressure. The oily layer was extracted with ether. The ether layer was dried over sodium sulfate and it was evaporated to dryness under reduced pressure. The residue was chromatographed on a silica gel column using chloroform. From the eluate, VII was obtained as an oily product. Yield 0.16 g (80.4%). MS *m/e*: 208 (M^+). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1690 (CO). ^{1}H-NMR ($CDCl_3$) δ: 2.36 (3H, s, CH_3), 3.86 (3H, s, CO_2CH_3), 4.68 (1H, s, SH), 7.23 (2H, d), 7.56 (2H, d), 7.73 (1H, s, CH=).

In the case of the reaction starting from III-2e (0.25 g), LiOH (0.5 g) and methanol (20 ml) were used. From the first eluate, VIIIb was obtained as an oily product. Yield 0.10 g (74.7%). The product was identical with authentic methyl phenoxyacetate. From the second eluate, VII was obtained as an oily product. Yield 0.12 g (71.9%). This product was identical with VII obtained by methanolysis of III-1c as described above.

Hydrogenation of III-2c, 2e, 2f, 2h and 2i——Typical Procedure for Syntheses of IXa—e: A solution of III-2c (1.6 g) in ethyl acetate (200 ml) was shaken with 10% palladium charcoal (4.0 g) under a hydrogen atmosphere (1 atm) at room temperature for 4 h. The reaction mixture was filtered and the filtrate was evaporated to dryness under reduced pressure. The residue was chromatographed on silica gel using chloroform. From the eluate, IXa was obtained as an oily product. Yield 1.2 g (74.1%). Other data are listed in Table VI. Similar procedures were used for the syntheses of IXb—e.

Oxidation of III-1i and III-2f with *m*-Chloroperbenzoic Acid——*m*-Chloroperbenzoic acid (0.16 g) was added to a solution of III-1i (0.22 g) in dichloromethane (20 ml) under stirring at 0—5 °C. The reaction mixture was stirred at room temperature for 3 h then evaporated to dryness under reduced pressure. The residue was chromatographed on a

silica gel column with chloroform. From the eluate, light yellow crystals of Xa were obtained. Yield 0.10 g (42.8%), mp 123—128 °C (ethanol). MS *m/e*: 278 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1740 (CO). ^{1}H-NMR ($CDCl_3$) δ: 1.14 and 1.19 (3H, each t, $CH_3CH_2CH=$), 2.24—2.75 (1H, m, $CH_3CH_2CH=$), 3.92 (3H, s, CH_3), 5.76 and 6.04 (1H, each t, $CH_3CH_2CH=$), 7.05 (2H, d), 7.79 (2H, d), 8.30 (1H, s, CH= at 4-position). *Anal.* Calcd for $C_{14}H_{14}O_4S$: C, 60.42; H, 5.07. Found: C, 60.23; H, 5.12. Similar procedures were used for the synthesis of Xb. Yield 0.12 g (66.9%), mp 175—180 °C (ethanol). MS *m/e*: 360 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1775 (CO). ^{1}H-NMR ($CDCl_3$) δ: 2.40 and 2.48 (3H, each s, CH_3), 7.10—8.20 (12H, m), 8.33 and 8.60 (1H, each s, CH=). *Anal.* Calcd for $C_{22}H_{16}O_3S$: C, 73.31; H, 4.47. Found: C, 73.38; H, 4.57.

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References and Notes

1) A part of the present work was presented at the 104th Annual Meeting of the Pharmaceutical Society of Japan, Sendai, March 1984, Abstracts of Papers, p. 259.
2) M. Girand, *Ann. Chim.* (Paris), **16**, 326 (1941).
3) E. Campaigne and R. E. Cline, *J. Org. Chem.*, **21**, 32 (1956).
4) E. Campaigne and W. E. Kregbaum, *J. Org. Chem.*, **26**, 1326 (1961).
5) N. Campbell and J. E. Mckail, *J. Chem. Soc.*, **1948**, 1251.
6) T. Ito, T. Ishii and M. Nishio, *Agric. Biol. Chem.*, **29**, 728 (1965).
7) L. Jensen, I. Thomsen and S. O. Lawesson, *Bull. Soc. Chim. Belg.*, **86**, 639 (1977).
8) H. Abdel H., E. Mohamed H. and A. Sanna O., *Indian J. Chem.*, **11**, 128 (1973).
9) Taiho Pharmaceutical Co., Ltd., Japan Patent 30171 (1979) [*Chem. Abstr.*, **91**, 74595*y* (1979)].
10) K. Ogawa, S. Yamada, T. Terada, T. Yamazaki and T. Honna, *Synthesis*, **1984**, 595.
11) We could not determine the geometry of III at the 4-position because only a single isomer was obtained.
12) C. Pascual, J. Meier and W. Shimon, *Helv. Chim. Acta*, **49**, 164 (1966).
13) In general, syntheses of symmetric acid anhydrides (II) are tendious compared with those of acid chlorides (IV).
14) E. Schwenk and D. Papa, *J. Org. Chem.*, **11**, 798 (1946).
15) C. M. Eaker, Brit. Patent 682282 (1952) [*Chem. Abstr.*, **48**, 2776 (1954)].
16) S. Satsumabayashi, S. Irioka, H. Kudo, K. Tsujimoto and S. Motoki, *Bull. Chem. Soc. Jpn.*, **45**, 913 (1972).
17) K. Pihlaja, A. Nikkilä, K. Neuvonen and R. Keskinen, *Acta Chem. Scand., Ser. A*, **30**, 457 (1976).
18) In the oxidations of III-**1i** and III-**2f**, we presumed that the ease of oxidation of sulfur might be affected by steric hindrance due to the substituent at the 2-position of the 1,3-oxathiolane ring.
19) The *E*/*Z* ratios involving R^3(R^4) for Xa and Xb were calculated on the basis of the ^{1}H-NMR integration values as done for III-**1**, and were 1/1 and 1/6, respectively.
20) Taiho Pharmaceutical Co., Ltd., Japan. Patent 193474 (1982) [*Chem. Abstr.*, **99**, 38447*h* (1983)].
21) R. G. Cooke and A. K. Macbeth, *J. Chem. Soc.*, **1939**, 1245.
22) L. F. Fieser and M. T. Lefeler, *J. Am. Chem. Soc.*, **70**, 3181 (1948).
23) E. E. Royals and A. H. Neal, *J. Org. Chem.*, **21**, 1448 (1956).
24) E. M. Reid and J. R. Ruhoff, "Organic Syntheses," Coll. Vol. II, ed. by A. H. Blatt, John Wiley and Sons, Inc., New York, 1943, p. 474.