Synthesis of Novel 5- and 6-Substituted 3-Arylidene-1,4-oxathiin-2(3*H*)-ones

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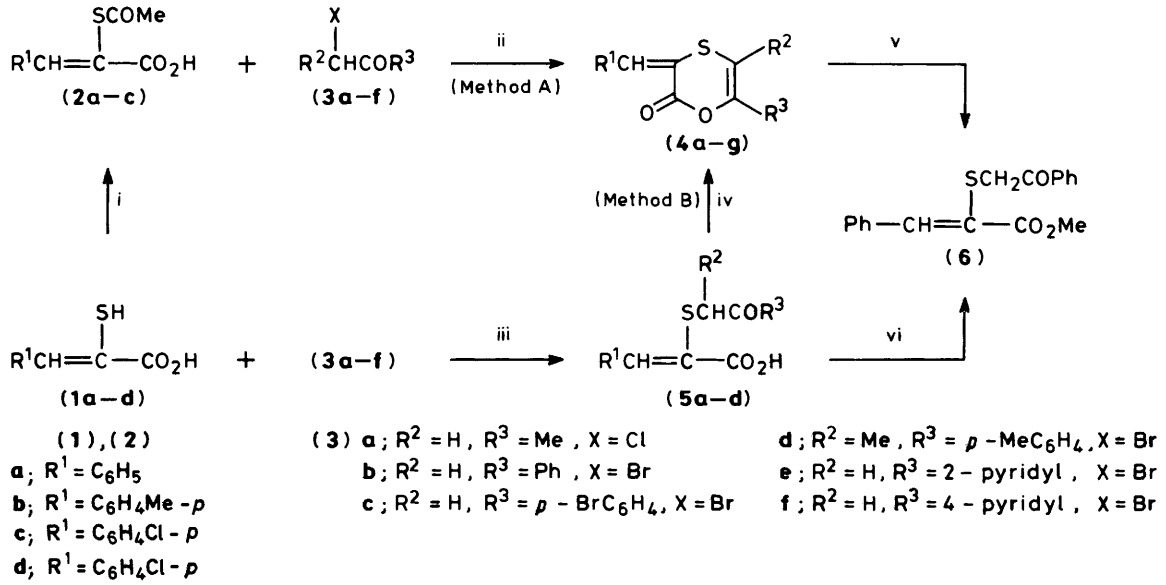
The reactions of α-acetylthio-β-arylacrylic acids (**2a**—**c**) with α-halogeno ketones (**3a**—**f**), α-halogeno-β-keto esters (**7a**—**b**), and α-halogenopyruvate (**9**) afforded the corresponding novel 3-arylidene-1,4-oxathiin-2(3*H*)-ones [(**4a**—**d**), (**8a**—**f**), and (**10a**), respectively] having 5- and/or 6-substituents. The β-aryl-α-thioacrylic acids (**1a**—**d**) were treated with α-halogeno ketones (**3a**—**f**), (**7a**—**b**), and (**9**) to give the corresponding β-aryl-α-alkylthioacrylic acids (**5a**—**d**), (**11a**—**f**), and (**12a**—**c**), which were converted into the respective 3-arylidene-1,4-oxathiin-2(3*H*)-ones (**4a**—**g**), (**8a**—**f**), and (**10a**—**c**) by intramolecular cyclization when treated with thionyl chloride–dimethylformamide. The sulphur atom of the 1,4-oxathiin-2(3*H*)-ones (**4d**), (**4g**), and (**8a**) was smoothly oxidized with *m*-chloroperbenzoic acid to give the corresponding *S*-oxides (**13a**—**c**) in good yields.

Chymotrypsin inhibitors have been widely investigated[1a–e] since they are considered to have potential as clinically useful compounds.[1a,2a–d] In continuation of our earlier syntheses of heterocycles having chymotrypsin inhibiting activity,[3a,b] we report here two new procedures (methods A and B) for the preparation of novel 3-arylidene-1,4-oxathiin-2(3*H*)-ones. Three reports have appeared on the preparation of the 1,4-oxathiin-2(3*H*)-one ring: [4,5,6] 1,4-oxathiin-2(3*H*)-one 4,4-dioxides were obtained by treating α-diazo ketones with sulphur dioxide,[4,5] and 3,5,6-trisubstituted 1,4-oxathiin-2(3*H*)-ones were prepared by the cyclization of α-(chloroacetylmercapto)-acetophenone.[6]

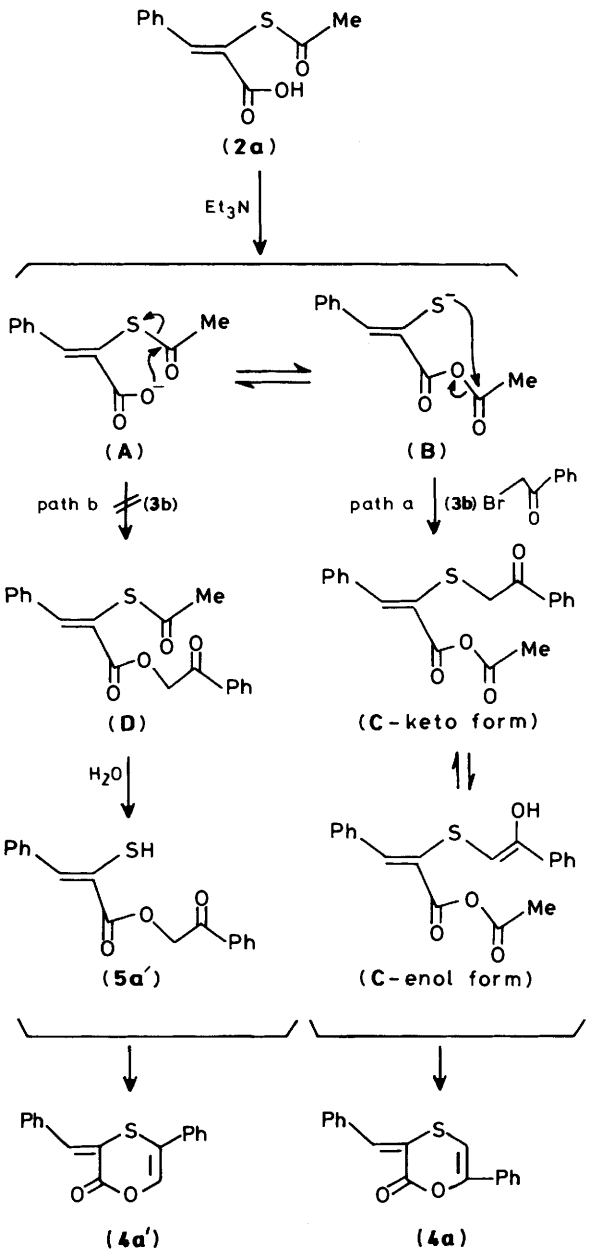
Results and Discussion

Addition of an excess of triethylamine to a solution containing equimolar proportions of α-acetylmercapto-β-arylacrylic acid (**2a**) and 2-bromo-1-phenylethan-1-one (**3b**) (method A), gave light yellow crystals the i.r. spectrum of which showed the presence of a lactone or ester carbonyl group (1 725 cm^{-1}). An elemental analysis and mass spectrum [M^+ (parent peak) at *m/z* 280] of the product established its formula as $C_{17}H_{12}O_2S$, which indicated that the reaction proceeded with the elimination of hydrogen bromide and acetic acid: this evidence suggested two possible structures, (**4a**) and (**4a'**), for the compound. The former might be produced *via* path a which included a transfer of the *S*-acetyl group to the oxygen atom, and the latter might be produced *via* path b which included a hydrolysis step involving the acetyl group (Scheme 2).

The ^1H n.m.r. spectrum (in $CDCl_3$) showed signals corresponding to an exocyclic benzylidene proton and an endocyclic double bond proton at 7.90 and 6.04 p.p.m., respectively. The presence of the endocyclic double bond was confirmed on the basis of the ^{13}C n.m.r. spectrum in which a signal for the secondary carbon at the 5-position appeared at 92.1 p.p.m. as a singlet under decoupling conditions, but was split into a doublet under the off-resonance mode. Furthermore, the presence of the phenyl group at the 6-position of the 1,4-oxathiin ring was confirmed by assignment of the signal at 146.2 p.p.m. as a carbon atom (6-position) which was attached to an oxygen



Scheme 1. *Reagents:* i, Ac_2O–NaOH; ii, Et_3N–CH_2Cl_2; iii, (1) Et_3N–CH_2Cl_2 refluxing, (2) H_3O^+; iv, $SOCl_2$–DMF–C_6H_6; v, LiOH–MeOH; vi, CH_2N_2–Et_2O



Scheme 2. A plausible reaction mechanism for the production of (4)

atom rather than a sulphur atom. Thus, the structure of the product was confirmed as (**4a**). The reaction was extended to other α-acetylthio-β-arylacrylic acids (**2a**—**c**) and α-halogeno ketones (**3a**—**f**) to give good yields of the corresponding novel 1,4-oxathiins (**4b**—**d**), the structures of which were assigned as described above for (**4a**). These results are summarized in Table 1.

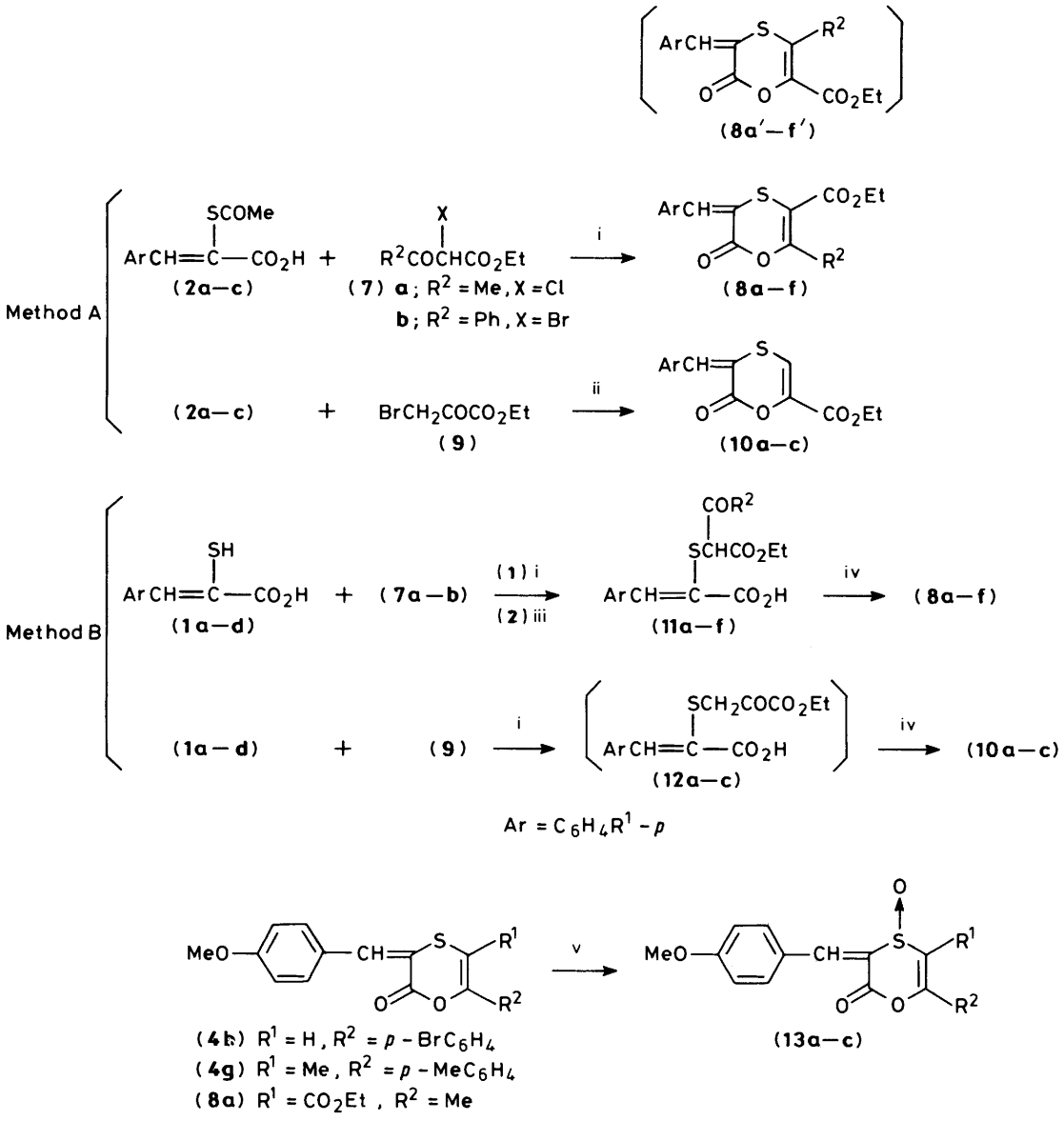
The yield of (**4**) was raised in an alternative synthesis (method B). Treatment at room temperature of β-phenyl-α-thioacrylic acid (**1a**) with α-bromoacetophenone (**3b**) in dichloromethane in the presence of triethylamine afforded (**5a**) which was soluble in aqueous 5% $NaHCO_3$. The ^1H n.m.r. spectrum ($CDCl_3$) of (**5a**) showed the methylene proton signal ($PhCOCH_2$, s, 2 H) at 4.26 p.p.m. and CO_2H (br, 1 H) at 11.0 p.p.m. The mass spectrum of (**5a**) showed M^+ at *m/z* 298, and the i.r. spectrum showed a carboxyl absorption at 2 500—3 300 cm^{-1}. These data clearly support structure (**5a**) rather than (**5a'**) (see Scheme 2). The carboxylic acid (**5a**) was easily cyclized to the 1,4-oxathiin (**4a**) by treatment with thionyl chloride–dimethylformamide in benzene at room temperature; the product was identical with that obtained by method A. The structures of the novel 1,4-oxathiins (**4e**—**g**) obtained by method B were established on the basis of the similarity of their spectra to that of (**4a**).

Treatment of (**4a**) with lithium hydroxide in methanol produced an oily material (**6**) in 72% yield, the ^1H n.m.r. spectrum ($CDCl_3$) of which showed signals at 3.75 p.p.m. (CO_2Me) and 4.15 p.p.m. ($PhCOCH_2$, 2 H); the mass spectrum of (**6**) showed M^+ at *m/z* 312. The product was, therefore, presumed to be the methyl α-phenacylthio-β-phenylacrylate (**6**), a presumption which was confirmed by esterification of (**5a**) with diazomethane to produce (**6**). The olefinic proton of (**6**) appeared at 7.75 p.p.m. in the ^1H n.m.r. spectrum, a value very close to that (7.80 p.p.m.) observed for (*Z*)-α-methylthio-β-phenylacylate rather than that (6.75 p.p.m.) for the *E*-isomer;[7] this establishes that the benzylidene protons of (**4a**) have *Z*-stereochemistry. A plausible reaction mechanism for the production of (**4**) starting from (**2**) and (**3**) is shown in Scheme 2.

It was also found that ethyl α-chloroacetoacetate (**7a**) and ethyl α-bromobenzoylacetate[8] (**7b**) could be used as the α-halogeno ketone in methods A and B. In the reaction of (**2a**) with (**7a**), 3-benzylidene-5-ethoxycarbonyl-6-methyl-1,4-oxathiin-2(3*H*)-one (**8a**) was obtained in 38% yield by method A (Scheme 3). The i.r. spectrum of (**8a**) showed the presence of δ-lactone (1 730 cm^{-1}) and ester carbonyl groups (1 710 cm^{-1}), the mass spectrum showed M^+ at *m/z* 290, and the ^1H n.m.r. spectrum ($CDCl_3$) showed an ethoxy group and olefinic 3-H singlet at 7.82 p.p.m. The ^{13}C n.m.r. spectrum showed the 5-and 6-carbon signals at 101.9 and 158.3 p.p.m. respectively (both singlets for decoupling and off-resonance modes). Since these spectral data are very similar to those of (**4a**), the structure may be tentatively assigned as (**8a**) (see Scheme 3). Similar reactions of (**2**) with (**7a**) and with (**7b**) also afforded the corresponding 6-substituted 3-arylidene-5-ethoxycarbonyl-1,4-oxathiin-2(3*H*)-ones (**8b**—**f**) (method A), whose structures were confirmed in a similar manner as for (**8a**). The compounds (**8a**—**f**) were also synthesized stepwise by method B, *i.e.* the treatment of (**1a**) with (**7a**) in dichloromethane in the presence of triethylamine gave compound (**11a**) in 40% yield. Subsequent treatment of the latter with thionyl chloride–dimethylformamide in benzene gave the cyclized product (**8a**) (93%), identical in all respects with the product obtained by method A. Therefore it was clearly verified that the structure of the product obtained by method A is (**8a**) and not (**8a'**).

The mass spectrum of (**11a**) showed M^+ at *m/z* 308, and the ^1H n.m.r. spectrum ($CDCl_3$) ethoxy group protons as a methine proton (singlet at 4.73 p.p.m.), an olefinic 3-H (singlet at 7.83 p.p.m.), and CO_2H (br at 11.43 p.p.m.). These data clearly support structure (**11a**). The 1,4-oxathiins (**8b**—**f**) were similarly synthesized by method B *via* the *S* alkylated acids (**11b**—**c**) results are summarized in Tables 1 and 2.

We also examined the reaction of ethyl bromopyruvate (**9**) with (**2a**) in dichloromethane in the presence of triethylamine (method A). The yield of the desired 1,4-oxathiin (**10a**) having a 6-ethoxycarbonyl group was only 3% however, much starting material being recovered. As expected, reaction of (**1a**) with (**9**) and treatment of the crude product with thionyl chloride–dimethylformamide in benzene by method B gave an improved yield of (**10a**) (26%); this was identical in all respects with (**10a**) obtained by method A. As expected, the ethoxycarbonyl group was found at the 6-position: in the ^{13}C n.m.r. spectrum C-5 appeared at 108.1 p.p.m. as a singlet under decoupling conditions (doublet under the off-resonance mode). Compounds (**10b**) and (**10c**) were obtained similarly as above *via* (**12b**) and (**12c**), respectively (Table 1 and Scheme 3). In order to examine any enhancement or variation of their pharmacological activity,



Scheme 3. *Reagents:* i, Et_3N–CH_2Cl_2, refluxing; ii, Et_3N–CH_2Cl_2; iii, H_3O^+; iv, $SOCl_2$–DMF–C_6H_6; iv, $SOCl_2$–DMF–C_6H_6; v, *m*-CPBA–CH_2Cl_2

several 3-arylidene-1,4-oxathiin-2(3*H*)-ones (**4b**), (**4g**), and (**8a**) were converted into the corresponding *S*-oxides (**13a**), (**13b**), and (**13c**), respectively by treatment with *m*-chloroperbenzoic acid in dichloromethane (Table 3 and Scheme 3). The i.r. spectrum of (**13a**) showed the presence of the lactone carbonyl group at 1 720 cm^{-1}, the mass spectrum showed M^+ at *m/z* 406, and the ^1H n.m.r. spectrum ($CDCl_3$) showed the signals of the olefinic 5-H (singlet at 6.72 p.p.m.) and the benzylidene 3-H (singlet at 8.43 p.p.m.). These data were all consistent with structure (**13a**) (see Scheme 3). The structures of (**13b**) and (**13c**) were also confirmed in a similar manner as for (**13a**).

The pharmacological activity of the compounds prepared in this work will be published elsewhere.

Experimental

General.—All melting points were measured on a Yanagimoto micromelting point apparatus and are uncorrected. I.r. spectra were taken on a Hitachi 260-50 spectrophotometer. Mass spectra were recorded on a JEOL LMS-01G-2 spectrometer. ^1H and ^{13}C n.m.r. spectra were recorded on a JEOL JMN-FX 100 spectrometer using tetramethylsilane as an internal standard. Elemental analyses were carried out with a Yanagimoto C.H.N. Corder MT-2 analyser.

Kieselgel 60 (230—400 mesh, Merck) was used for open column chromatography.

Materials.—1-Chloropropan-2-one (**3a**), 2-bromo-1-phenylethan-1-one (**3b**), 2-bromo-1-(*p*-bromophenyl)ethan-1-one (**3c**), ethyl α-chloroacetoacetate (**7a**), and ethyl bromopyruvate (**9**) were commercially available.

2-Bromo-1-(p-tolyl)propan-1-one (**3d**). The bromo ketone (**3d**), m.p. 75—77 °C (lit.,[9] 79—80 °C) was prepared by the bromination of 1-(*p*-tolyl)propan-1-one according to Borowitz's procedure.[9]

2-Bromo-2-(2-pyridyl)ethan-1-one hydrobromide (**3e**) *and 2-bromo-1-(4-pyridyl)ethan-1-one hydrobromide* (**3f**). The bromo ketones (**3e**) [m.p. 203—205 °C (lit.,[10] 204—208 °C] and

Table 1. Analytical data for the compounds (**4**), (**8**), and (**10**)

Compd.[a] (Formula)	R^1	R^2	R^3	Method[b]	Yield (%)	M.p. (°C)	M^+ (*m/z*)	Found (%) (Required) C	H	N
(**4a**) ($C_{17}H_{12}O_2S$)	H	H	Ph	A	58	117—118[e]	280	73.05	4.25	
				B	60[c]	118—119[e]		(72.84)	(4.31)	
(**4b**) ($C_{18}H_{13}BrO_3S$)	4-OMe	H	*p*-BrC_6H_4	A	61	169—170[e]	388	55.56	3.35	
								(55.54)	(3.37)	
(**4c**) ($C_{16}H_{11}NO_2S$)	H	H	4-Pyridyl	A	30	180—183[f]	281	68.0	3.85	5.05
								(68.31)	(3.94)	(4.98)
(**4d**) ($C_{16}H_{11}NO_2S$)	H	H	2-Pyridyl	A	36	155—157[f]	281	68.7	3.85	5.25
								(68.31)	(3.94)	(4.98)
(**4e**) ($C_{12}H_{10}O_2S$)	H	H	Me	B	21[c]	68—70[e]	218	66.05	4.55	
								(66.03)	(4.62)	
(**4f**) ($C_{18}H_{14}O_2S$)	4-Me	H	Ph	B	64[c]	134—135[f]	294	75.5	4.85	
								(73.44)	(4.79)	
(**4g**) ($C_{20}H_{18}O_3S$)	4-OMe	Me	*p*-MeC_6H_4	B	66[c]	142—143[f]	338	71.3	5.45	
								(70.98)	(5.36)	
(**8a**) ($C_{15}H_{14}O_4S$)	H	Me		A	38	79—81[f]	290	62.0	4.8	
				B	90[c]	81—82[f]		(62.05)	(4.86)	
(**8b**) ($C_{16}H_{16}O_5S$)	4-OMe	Me		A	58	78—79[f]	320	60.15	4.95	
				B	81[c]	80—81[f]		(59.99)	(5.03)	
(**8c**) ($C_{15}H_{13}ClO_4S$)	4-Cl	Me		B	85[c]	129—130[g]	324	55.2	4.05	
								(55.47)	(4.03)	
(**8d**) ($C_{20}H_{16}O_4S$)	H	Ph		A	53	127—129[f]	352	67.95	4.65	
				B	87[c]	127—128[f]		(68.17)	(4.58)	
(**8e**) ($C_{21}H_{18}O_4S$)	4-Me	Ph		A	71	104—105[f]	366	68.9	4.95	
				B	99[c]	102—103[f]		(68.83)	(4.95)	
(**8f**) ($C_{21}H_{18}O_5S$)	4-OMe	Ph		B	83[c]	79—81[g]	382	66.0	4.9	
								(65.95)	(4.74)	
(**10a**) ($C_{14}H_{12}O_4S$)	H			A	3	106—108[f]	276	60.85	4.35	
				B	26[d]	108—109[f]		(60.86)	(4.38)	
(**10b**) ($C_{15}H_{14}O_4S$)	4-Me			B	38[d]	78—79[f]	290	62.1	4.85	
								(62.05)	(4.86)	
(**10c**) ($C_{15}H_{14}O_5S$)	4-OMe			B	28[d]	96—98[f]	306	58.75	4.65	
								(58.81)	(4.61)	

[a] All compounds are light yellow crystals. [b] For methods A and B, see Experimental section. [c] These yields are from compounds (**5**) or (**11**). [d] These yields are from compound (**1**). [e] Purified by column chromatography. [f] Recrystallized from ethanol. [g] Recrystallized from ethanol–light petroleum.

(**3f**) [m.p. 197—200 °C (lit.,[10] 198—201 °C)] were prepared by bromination of the corresponding ketones according to Dornow's procedure.[11]

Ethyl α-bromobenzoylacetate (**7b**). The bromo keto ester (**7b**) [b.p. 132—134 °C/1 mmHg (lit.,[8] 135—137 °C/1 mmHg)] was prepared by bromination of ethyl benzoylacetate according to Howk's procedure.[8]

β-Aryl-α-mercaptoacrylic acid (**1a**) [m.p. 123—124 °C (lit.,[12] 125 °C)], (**1b**) [m.p. 167—168 °C (lit.,[12] 168—169 °C)], (**1c**) [m.p. 168—170 °C (lit.,[12] 172 °C)] and (**1d**) [m.p. 173—175 °C (lit.,[12] 172—173 °C)] were prepared by the hydrolysis of the corresponding rhodanines, according to Ito's procedure.[12]

Preparation of α-Acetylthio-β-arylacrylic Acids (**2a**—**c**).—The title compounds were prepared by the treatment of the corresponding acrylic acids (**1a**), (**1b**), and (**1c**) with acetic acid anhydride in alkaline solution according to a previous report.[3b] The yields, spectra data, and elemental analyses are as follows. Compounds (**2a**), yield 92%, m.p. 140—143 °C; $\nu_{max.}$(KBr) 2 400—3 100 (CO_2H), 1 690 (sh) (CO), and 1 670 cm^{-1} (CO); δ_H($CDCl_3$) 2.37 (3 H, s, COMe), 7.25—8.75 (5 H, m, ArH), 8.33 (1 H, s, CH=), and 10.28—10.44 (1 H, br, CO_2H) [Found: C, 59.35; H, 4.6%; M^+, 222. $C_{11}H_{10}O_3S$ requires C, 59.44; H, 4.54%; *M*, 222].

Compound (**2b**), yield 82%, m.p. 154—156 °C; $\nu_{max.}$(KBr) 2 400—3 100 (CO_2H), 1700sh (CO), and 1 680 cm^{-1} (CO); δ_H($CDCl_3$) 2.35 (3 H, s, COMe), 2.42 (3 H, s, Me), 7.10 (2 H, d, ArH), 7.50 (2 H, d, ArH), 8.25 (1 H, s, CH=), and 10.25—10.55 (1 H, br, CO_2H) [Found: C, 61.1; H, 5.0%; M^+, 236. $C_{12}H_{12}O_3S$ requires C, 61.02; H, 5.08%; *M*, 236].

Compound (**2c**), yield 92%, m.p. 141—143 °C; $\nu_{max.}$(KBr) 2 400—3 100 (CO_2H), 1 700 (CO), and 1 670 cm^{-1} (CO); δ_H($CDCl_3$) 2.36 (3 H, s, COMe), 3.79 (3 H, s, OMe), 6.79 (2 H, d, ArH), 7.66 (2 H, d, ArH), 8.26 (1 H, s, CH=), and 10.00—10.26 (1 H, br, CO_2H) [Found: C, 57.4; H, 4.9; M^+, 252. $C_{12}H_{12}O_4S$ requires C, 57.13; H, 4.79%; *M*, 252].

α-(*2-Oxo-2-phenylethylthio*)-β-*phenylacrylic Acid* (**5a**): *Typical Procedure for the Synthesis of Compounds* (**5a**—**d**).—Triethylamine (2.1 ml, 15 mmol) was added dropwise to a solution of α-mercapto-β-phenylacrylic acid (**1a**) (1.0 g, 5.6 mmol), 2-bromo-1-phenylethan-1-one (**3b**) (1.2 g, 5.7 mmol), and dichloromethane (50 ml) with stirring and ice cooling. The reaction mixture was then stirred and refluxed for 4 h after which the product (**5a**) was extracted with M-NaOH (20 ml). The aqueous solution was acidified with 6M-HCl, extracted with chloroform (2 × 50 ml), and the combined extracts dried (Na_2SO_4) and evaporated to dryness under reduced pressure. The crude product was recrystallized from ethanol to afford white crystals of (**5a**) (1.3 g, 78%), m.p. 141—142 °C; $\nu_{max.}$(KBr) 2 500—3 000 (CO_2H), 1 720 (CO), and 1 642 cm^{-1} (CO); δ_H($CDCl_3$) 4.26 (2 H, s, CH_2), 7.07—8.00 (10 H, m, ArH), 7.90 (1

Table 2. Analytical data for the compounds (**5**) and (**11**)

Compd. (Formula)	R^1	R^2	R^3	Yield (%)	M.p. (°C)	M^+ (*m/z*)	Found (%) (Required) C	H
(**5a**) ($C_{17}H_{14}O_3S$)	H	H	Ph	78	141—142[a]	298	68.75 (68.44)	4.75 (4.73)
(**5b**) ($C_{12}H_{12}O_3S$)	H	H	Me	92	98—100[b]	236	61.1 (61.00)	5.1 (5.12)
(**5c**) ($C_{18}H_{16}O_3S$)	Me	H	Ph	71	146—147[a]	312	69.35 (69.21)	5.15 (5.16)
(**5d**) ($C_{20}H_{20}O_4S$)	OMe	*p*-Me	*p*-MeC_6H_4	59	134—136[c]	350	67.05 (67.39)	5.75 (5.66)
(**11a**) ($C_{15}H_{16}O_5S$)	H	Me		40	117—118[a]	308	58.45 (58.40)	5.3 (5.23)
(**11b**) ($C_{16}H_{18}O_6S$)	OMe	Me		51	130—132[a]	338	56.95 (56.79)	5.25 (5.36)
(**11c**) ($C_{15}H_{15}ClO_5S$)	Cl	Me		27	131—132[a]	342	52.65 (52.55)	4.3 (4.41)
(**11d**) ($C_{20}H_{18}O_5S$)	H	Ph		39	147—148[a]	370	64.75 (64.85)	4.9 (4.89)
(**11e**) ($C_{21}H_{20}O_5S$)	Me	Ph		74	124—125[a]	384	65.95 (65.60)	5.3 (5.24)
(**11f**) ($C_{21}H_{20}O_6S$)	OMe	Ph		34	122—124[a]	400	63.0 (62.98)	5.05 (5.03)

[a] Recrystallized from ethanol. [b] Recrystallized from ether. [c] Recrystallized from benzene.

Table 3. Analytical data for the compounds (**13**)

Compd.[a] (Formula)	R^1	R^2	Yield (%)	M.p.[b] (°C)	I.r. $\nu_{max.}$(KBr)	M^+ (*m/z*)	Found (%) (Required) C	H
(**13a**) ($C_{18}H_{13}BrO_4S$)	H	*p*-BrC_6H_4	74	162—164	1 720 (CO)	406	53.45 (53.35)	3.2 (3.23)
(**13b**) ($C_{20}H_{18}O_4S$)	Me	*p*-MeC_6H_4	76	152—154	1 725 (CO)	354	67.3 (67.78)	5.1 (5.12)
(**13c**) ($C_{16}H_{16}O_6S$)	CO_2Et	Me	61	141—143	1 720sh (CO) 1 710 (CO)	336	57.15 (57.13)	4.95 (4.79)

[a] All compounds are light yellow crystals. [b] Recrystallized from ethanol.

H, s, CH=), and 10.56—11.50 (1 H, br, CO_2H). Other data are listed in Table 2. A similar procedure was used for the synthesis of compounds (**5b—d**).

Compound (**5b**), $\delta_H(CDCl_3)$ 2.10 (3 H, s, Me), 3.63 (2 H, s, CH_2), 7.00—8.16 (5 H, m, ArH), 7.90 (1 H, s, CH=), and 10.00—10.80 (1 H, br, CO_2H).

Compound (**5c**), $\delta_H(CDCl_3)$ 2.27 (3 H, s, Me), 4.23 (2 H, s, CH_2), 6.90—8.00 (9 H, m, ArH), 7.83 (1 H, s, CH=), and 10.20—11.40 (1 H, br, CO_2H).

Compound (**5d**), $\delta_H(CDCl_3)$ 1.46 (3 H, d, *J* 7.0 Hz, Me), 2.27 (3 H, s, Me), 3.79 (3 H, s, OMe), 4.89 (1 H, q, *J* 7.0 Hz, CH), 6.73 (2 H, d, ArH), 7.86 (2 H, d, ArH), 8.10 (1 H, s, CH=), and 9.86—10.20 (1 H, br, CO_2H). Other data are listed in Table 2.

3-*Benzylidene*-6-*phenyl*-1,4-*oxathiin*-2(3H)-*one* (**4a**): *Typical Procedure for the Synthesis of Compounds* (**4a—g**).—*Method A*. Triethylamine (1.5 ml, 10.8 mmol) was added dropwise to a solution of α-acetylthio-β-phenylacrylic acid (**2a**) (1.1 g, 5.0 mmol) and 2-bromo-1-phenylethan-1-one (**3b**) (1.0 g, 5.0 mmol) in dichloromethane (30 ml) with stirring and ice cooling. The reaction mixture was stirred at room temperature for 24 h and then washed with water (10 ml). The dichloromethane layer was dried (Na_2SO_4), evaporated to dryness under reduced pressure and the crude product chromatographed (SiO_2, $CHCl_3$) to afford light yellow crystals of (**4a**) (0.80 g, 58%), m.p. 117—118 °C; $\nu_{max.}$(KBr) 1 725 cm^{-1} (CO); $\delta_H(CDCl_3)$ 6.04 (1 H, s, CH), 7.10—7.70 (10 H, m, ArH), and 7.90 (1 H, s, CH=); $\delta_C(CDCl_3)$ 92.1 (d), 114.8 (s), 123.9 (d), 128.6 (d), 128.9 (d), 129.5 (d), 130.3 (d), 132.1 (s), 134.1 (s), 136.5 (d), 146.2 (s), and 158.5 (s) p.p.m. Other data are listed in Table 1. Similar procedures were used for the synthesis of (**4b—d**).

(**4b**), $\delta_H(CDCl_3)$ 3.81 (3 H, s, OMe), 6.04 (1 H, s, CH), 6.88 (2 H, d, ArH), 7.39 (4 H, s, ArH), 7.50 (2 H, d, ArH), and 7.82 (1 H, s, CH=). (**4c**), $\delta_H(CDCl_3)$ 6.42 (1 H, s, CH), 7.20—7.70 (7 H, m, ArH), 8.04 (1 H, s, CH=), and 8.64 (2 H, d, ArH). (**4d**), $\delta_H(CDCl_3)$ 7.04 (1 H, s, CH), 7.16—7.86 (8 H, m, ArH), 8.03 (1 H, s, CH=), and 8.55 (1 H, m, ArH). Other data are listed in Table 1.

(*Method B*). $SOCl_2$ (1.0 ml) was added dropwise to a solution of α-(2-oxo-2-phenylethylthio)-β-phenylacrylic acid (**5a**) (1.0 g, 3.4 mmol) in dimethylformamide (3 ml) and benzene (30 ml) with stirring and ice-cooling. The reaction mixture was stirred at room temperature for 8 h after which ice–water (10 ml) was added and the whole extracted with benzene. The benzene layer was dried (Na_2SO_4), evaporated to dryness under reduced pressure, and the residue chromatographed (SiO_2, $CHCl_3$) to

afford light yellow crystals (0.56 g, 60%), identical with (**4a**), obtained by method A as described above. Similar procedures were used for the synthesis of (**4e—g**).

(**4e**), $\delta_H(CDCl_3)$ 2.01 (3 H, s, Me), 5.28 (1 H, s, CH), 7.20—7.60 (5 H, m, ArH), and 7.80 (1 H, s, CH=). (**4f**), $\delta_H(CDCl_3)$ 2.36 (3 H, s, Me), 6.06 (1 H, s, CH), 7.07—7.66 (5 H, m, ArH), and 7.89 (1 H, s, CH=). (**4g**), $\delta_H(CDCl_3)$ 2.00 (3 H, s, Me), 2.33 (3 H, s, Me), 3.79 (3 H, s, OMe), 6.79—7.60 (8 H, m, ArH), and 7.76 (1 H, s, CH=). Other data are listed in Table 1.

Methanolysis of (**4a**).—LiOH (0.018 g, 0.43 mmol) was added to a solution of (**4a**) (0.10 g, 0.36 mmol) in methanol (10 ml) at 0—5 °C. The mixture was stirred at room temperature for 0.2 h after which it was acidified with 2M-HCl and concentrated to *ca.* 2 ml under reduced pressure. The oily layer was extracted with ether (2 × 10 ml) and the extract dried (Na_2SO_4), evaporated to dryness under reduced pressure, and the crude product chromatographed (SiO_2, $CHCl_3$) to afford the oily product, (**6**) (0.080 g, 72%), *m/z* 312 (M^+); $\delta_H(CDCl_3)$ 3.75 (3 H, s, Me), 4.15 (2 H, s, $PhCOCH_2$), 7.00—7.72 (10 H, m, ArH), and 7.75 (1 H, s, CH=).

Esterification of (**5a**).—The acrylic acid (**5a**) (0.10 g, 0.34 mmol) was added to an ethereal solution (10 ml) of diazomethane (prepared from *N*-nitrosomethylurea (0.50 g, 4.8 mmol) at room temperature. After the evolution of nitrogen had ceased, excess of diazomethane was destroyed by addition of acetic acid and the reaction mixture evaporated to dryness under reduced pressure, and the crude product chromatographed (SiO_2, $CHCl_3$) to afford an oily product (0.070 g, 67%) identical in all respects with (**6**) obtained by methanolysis of (**4a**) as described above.

α-(1-*Ethoxycarbonyl*-2-*oxopropylthio*)-β-*phenylacrylic Acid* (**11a**): *Typical Procedure for the Synthesis of Compounds* (**11a—f**).—Triethylamine (0.5 ml, 3.4 mmol) was added dropwise to a solution of α-mercapto-β-phenylacrylic acid (**1a**) (0.59 g, 2.8 mmol) and ethyl α-chloroacetoacetate (**7a**) (0.50 g, 3.3 mmol) in dichloromethane (20 ml) with stirring and ice cooling. The reaction mixture was stirred under reflux for 1 h and then washed with M-HCl (5 ml) and water (5 ml). The dichloromethane layer was dried (Na_2SO_4), evaporated to dryness under reduced pressure, and the crude product recrystallized from ethanol to afford white crystals of (**11a**) (0.40 g, 40%), m.p. 117—118 °C; $\delta_H(CDCl_3)$ 1.07 (3 H, t, *J* 7.0 Hz, CH_2Me), 2.30 (3 H, s, COMe), 4.07 (2 H, q, *J* 7.0 Hz, CH_2Me), 4.73 (1 H, s, CH), 7.16—7.50 (2 H, m, ArH), 7.50—7.92 (2 H, m, ArH), 7.83 (1 H, s, CH=), and 11.43 (1 H, br, CO_2H). Other data are listed in Table 2. Similar procedures were used for the synthesis of (**11b**)—(**11f**).

(**11b**), $\delta_H(CDCl_3)$ 0.97—1.27 (3 H, m, CH_2Me), 2.25, 2.33 (3 H, each s, COMe), 3.86 (3 H, s, OMe), 3.98—4.24 (2 H, m, CH_2Me), 4.77 (1 H, s, CH), 6.94 (2 H, d, ArH), 7.97 (2 H, d, ArH), 8.19 (1 H, s, CH=), and 11.40 (1 H, br, CO_2H).

(**11c**), $\delta_H(CDCl_3)$ 1.09 (3 H, q, *J* 7.3 Hz, CH_2Me), 2.22 (3 H, d, COMe), 4.06 (2 H, q, *J* 7.3 Hz, CH_2Me), 4.75 (1 H, s, CH), 7.51 (2 H, d, ArH), 7.84 (2 H, d, ArH), 7.97 (1 H, s, CH=), and 11.38 (1 H, br, CO_2H).

(**11d**), $\delta_H(CDCl_3)$ 0.97 (3 H, t, *J* 7.0 Hz, CH_2Me), 3.99 (2 H, q, *J* 7.0 Hz, CH_2Me), 5.90 (1 H, br, CH), 7.30—7.60 (5 H, m, ArH), 7.60—7.95 (5 H, m, ArH), 8.02 (1 H, s, CH=), and 11.23 (1 H, br, CO_2H).

(**11e**), $\delta_H(CDCl_3)$ 0.98 (3 H, t, *J* 7.0 Hz, CH_2Me), 2.31 (3 H, s, Me), 3.99 (2 H, q, *J* 7.0 Hz, CH_2Me), 7.21 (2 H, d, ArH), 7.30—7.95 (7 H, m, ArH), 7.98 (1 H, s, CH=), and 11.37 (1 H, br, CO_2H).

(**11f**), $\delta_H(CDCl_3)$ 1.03 (3 H, t, *J* 7.1 Hz, CH_2Me), 3.83 (3 H, s, OMe), 4.02 (2 H, q, *J* 7.1 Hz, CH_2Me), 5.71 (1 H, s, CH), 6.80 (2 H, d, ArH), 7.20—7.60 (3 H, m, ArH), 7.80—8.00 (4 H, m, ArH), 8.19 (1 H, d, CH=), and 11.30 (1 H, br, CO_2H). Other data are listed in Table 2.

3-*Benzylidene*-5-*ethoxycarbonyl*-6-*methyl*-1,4-*oxathiin*-2(3H)-*one* (**8a**): *Typical Procedure for the synthesis of Compounds* (**8a—f**).—*Method A.* Triethylamine (1 ml, 7.1 mmol) was added dropwise to a solution of α-acetylthio-β-phenylacrylic acid (**2a**) (0.30 g, 1.4 mmol) and ethyl α-chloroacetoacetate (**7a**) (0.25 g, 1.5 mmol) in dichloromethane (20 ml) under stirring with ice cooling. The reaction mixture was stirred under reflux for 7 h and then washed with water (5 ml). The dichloromethane layer was dried (Na_2SO_4), evaporated to dryness under reduced pressure, and the crude product chromatographed (SiO_2, $CHCl_3$) to afford light yellow crystals of (**8a**) (0.15 g, 38%), m.p. 79—81 °C; $\nu_{max.}$(KBr) 1 730 (CO), and 1 710 cm^{-1} (CO); $\delta_H(CDCl_3)$ 1.33 (3 H, t, *J* 7.0 Hz, CH_2Me), 2.46 (3 H, s, Me), 4.27 (2 H, q, *J* 7.0 Hz, CH_2Me), 7.25—7.70 (5 H, m, ArH), and 7.82 (1 H, s, CH=); $\delta_C(CDCl_3)$ 14.2 (q), 20.2 (q), 62.0 (t), 101.9 (s), 115.2 (s), 128.6 (d), 129.8 (d), 130.6 (d), 133.8 (s), 137.4 (d), 155.7 (s), 158.3 (s), and 162.9 (s) p.p.m. Other data are listed in Table 1. Similar procedures were used for the synthesis of (**8b**), (**8d**), and (**8e**).

(**8b**), $\delta_H(CDCl_3)$ 1.36 (3 H, t, *J* 7.0 Hz, CH_2Me), 2.46 (3 H, s, Me), 3.86 (3 H, s, OMe), 4.30 (2 H, q, *J* 7.0 Hz, CH_2Me), 6.98 (2 H, d, ArH), 7.64 (2 H, d, ArH), and 7.83 (1 H, s, CH=).

(**8d**), $\delta_H(CDCl_3)$ 1.03 (3 H, t, *J* 7.0 Hz, CH_2Me), 4.09 (2 H, q, *J* 7.0 Hz, CH_2Me), 7.20—7.80 (10 H, m, ArH), and 7.96 (1 H, s, CH=).

(**8e**), $\delta_H(CDCl_3)$ 1.03 (3 H, t, *J* 7.1 Hz, CH_2Me), 2.41 (3 H, s, Me), 4.08 (2 H, q, *J* 7.1 Hz, CH_2Me), 7.20—7.64 (9 H, m, ArH), and 7.93 (1 H, s, CH=). Other data are listed in Table 1.

Method B. $SOCl_2$ (0.3 ml) was added dropwise to a solution of α-(1-ethoxycarbonyl-2-oxopropylthio)-β-phenylacrylic acid (**11a**) (0.20 g, 0.65 mmol) in dimethylformamide (1 ml) and benzene (10 ml) with stirring and ice cooling. The reaction mixture was stirred at room temperature for 1 h and then 4-dimethylaminopyridine (0.030 g, 0.25 mmol) was added. The mixture was stirred at the same temperature for 0.1 h and then added to ice-water (5 ml); the mixture was then extracted with benzene. The benzene layer was dried (Na_2SO_4), evaporated to dryness under reduced pressure, and the crude product recrystallized from ethanol to afford light yellow crystals. This product (0.17 g, 90%) was identical with (**8a**) obtained by method A as described above. Other data are listed in Table 1. Similar procedures were used for the synthesis of (**8b—f**).

(**8c**), $\delta_H(CDCl_3)$ 1.35 (3 H, t, *J* 7.1 Hz, CH_2Me), 2.47 (3 H, s, Me), 4.31 (2 H, q, *J* 7.1 Hz, CH_2Me), 7.42 (2 H, d, ArH), 7.58 (2 H, d, ArH), and 7.81 (1 H, s, CH=).

(**8f**), $\delta_H(CDCl_3)$ 1.03 (3 H, t, *J* 7.0 Hz, CH_2Me), 3.87 (3 H, s, OMe), 4.09 (2 H, q, *J* 7.0 Hz, CH_2Me), 6.99 (2 H, d, ArH), 7.41 (5 H, s, ArH), 7.68 (2 H, d, ArH), and 7.90 (1 H, s, CH=). Other data are listed in Table 1.

3-*Benzylidene*-6-*ethoxycarbonyl*-1,4-*oxathiin*-2(3H)-*one* (**10a**): *Typical Procedure for the Synthesis of Compounds* (**10a—c**).—*Method A.* Ethyl bromopyruvate (**9**) (0.45 g, 2.3 mmol) was added to a solution of α-acetylthio-β-phenylacrylic acid (**2a**) (0.50 g, 2.3 mmol) and triethylamine (0.38 ml, 2.7 mmol) in dichloromethane (20 ml) with stirring and ice cooling. The reaction mixture was stirred at room temperature for 14 h and then washed with M-HCl (5 ml) and water (2 × 5 ml). The dichloromethane layer was dried (Na_2SO_4), evaporated to dryness under reduced pressure, and the crude product recrystallized from ethanol to afford light yellow crystals of (**10a**) (0.018 g, 3%), m.p. 108—109 °C; $\nu_{max.}$(KBr) 1 730sh (CO), and 1 710 cm^{-1} (CO); $\delta_H(CDCl_3)$ 1.36 (3 H, t, *J* 7.1 Hz, CH_2Me), 4.33 (2 H, q, *J* 7.1 Hz, CH_2Me), 7.00 (1 H, s, CH), 7.25—7.66 (5 H, m, ArH), and 8.00 (1 H, s, CH=); $\delta_C(CDCl_3)$ 14.2 (q), 62.0 (t),

108.1 (d), 112.8 (s), 128.8 (d), 130.1 (d), 133.2 (d), 133.5 (s), 137.3 (s), 138.6 (d), 156.7 (s), and 158.8 (s) p.p.m. Other data are listed in Table 1.

Method B. Triethylamine (2.7 ml, 19 mmol) was added to a solution of α-mercapto-β-phenylacrylic acid (**1a**) (3.0 g, 17 mmol) and ethyl bromopyruvate (3.3 g, 17 mmol) in dichloromethane (100 ml) with stirring and ice cooling. The reaction mixture was stirred under reflux for 1 h and then evaporated to dryness under reduced pressure. $SOCl_2$ (4.5 ml) and dimethylformamide (3 ml) were added to a solution of the resulting residue in benzene (90 ml) with stirring and ice cooling after which the reaction mixture was stirred at room temperature for 2 h and washed with water (2 × 30 ml). The dichloromethane layer was dried (Na_2SO_4), evaporated to dryness under reduced pressure, and the crude product recrystallized from ethanol to afford light yellow crystals. This product (1.2 g, 26%) was identical in all respects with (**10a**) obtained by method A as described above. Similar procedures were used for the syntheses of (**10b**) and (**10c**).

(**10b**), $\delta_H(CDCl_3)$ 1.35 (3 H, t, *J* 7.1 Hz, CH_2Me), 2.40 (3 H, s, Me), 4.32 (2 H, q, *J* 7.1 Hz, CH_2Me), 7.00 (1 H, s, CH), 7.26 (2 H, d, ArH), 7.50 (2 H, d, ArH), and 8.00 (1 H, s, CH=).

(**10c**), $\delta_H(CDCl_3)$ 1.35 (3 H, t, *J* 7.1 Hz, CH_2Me), 3.87 (3 H, s, OMe), 4.32 (2 H, q, *J* 7.1 Hz, CH_2Me), 6.97 (2 H, d, ArH), 7.02 (1 H, s, CH), 7.58 (2 H, d, ArH), and 7.99 (1 H, s, CH=).

Oxidation of (**4b**), (**4g**), *and* (**8a**) *with* m-*Chloroperbenzoic Acid.*—*m*-Chloroperbenzoic acid (0.050 g, 0.29 mmol) was added to a solution of (**4b**) (0.10 g, 0.26 mmol) in dichloromethane (10 ml) with stirring at 0—5 °C. The reaction mixture was stirred at this temperature for 2 h and then washed with aqueous sodium hydrogencarbonate (0.030 g, in 5 ml H_2O) and with water (5 ml). The dichloromethane layer was dried (Na_2SO_4), evaporated to dryness under reduced pressure, and the crude product recrystallized from ethanol to afford white crystals of (**13a**) (0.077 g, 74%), m.p. 162—164 °C; $\delta_H(CDCl_3)$ 3.86 (3 H, s, OMe), 6.72 (1 H, s, CH), 6.97 (2 H, d, ArH), 7.56 (4 H, s, ArH), 7.86 (2 H, d, ArH), and 8.43 (1 H, s, CH=). Other data are listed in Table 3. Similar procedures were used for the syntheses of (**13b**) and (**13c**).

(**13b**), $\delta_H(CDCl_3)$ 2.33 (3 H, s, Me), 2.38 (3 H, s, Me), 3.87 (3 H, s, OMe), 7.00 (2 H, d, ArH), 7.20—7.56 (4 H, m, ArH), 7.86 (2 H, d, ArH), and 8.40 (1 H, s, CH=).

(**13c**), $\delta_H(CDCl_3)$ 1.39 (3 H, t, *J* 7.1 Hz, CH_2Me), 2.62 (3 H, s, Me), 3.91 (3 H, s, OMe), 4.38 (2 H, q, *J* 7.1 Hz, CH_2Me), 7.03 (2 H, d, ArH), 7.85 (2 H, d, ArH), and 8.36 (1 H, s, CH=). Other data are listed in Table 3.

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