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Antiulcer Activity of 5-Benzylthiazolidine-2,4-dione Derivatives

TAKASHI SOHDA, KATSUTOSHI MIZUNO, TAKEO HIRATA, YOSHITAKA MAKI and YUTAKA KAWAMATSU*

Central Research Division, Takeda Chemical Industries, Ltd., 17-85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka 532, Japan

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5-Benzylthiazolidine-2,4-dione derivatives were prepared and examined for antisecretory and antiulcer activities using pylorus-ligated rats and water-immersion stress rats. Some of these compounds, in particular, 5-(2,4,5-tripropoxybenzyl)thiazolidine-2,4-dione (**4**) and 5-(2,4-dimethoxybenzyl)thiazolidine-2,4-dione (**23**), exhibited pronounced pharmacological activities. Structure–activity relationships are discussed.

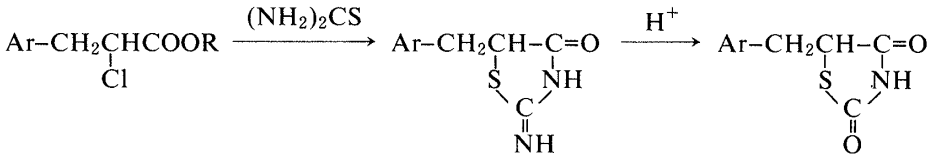
Keywords——antiulcer activity; 5-benzylthiazolidine-2,4-dione; structure–activity relationship; antisecretory activity; 3-aryl-2-chloropropionic acid

In the preceding paper,[1] we reported that 5-benzylthiazolidine-2,4-dione derivatives bearing a 4-oxy group in the benzyl moiety had potent hypoglycemic and hypolipidemic activities. 5-(Polyalkoxybenzyl)thiazolidine-2,4-diones such as **3** and **6** (Table I) were also prepared because some hydrophobic moieties seemed to be essential for activity. Although these compounds did not exhibit the above activities, they did show antisecretory and antiulcer effects on pylorus-ligated rats and water-immersion stress rats. We therefore prepared and evaluated a number of analogues to find an effective compound with minimal side effects.

Chemistry

Most thiazolidine-2,4-diones (I) were prepared by reaction of 3-aryl-2-chloropropionic acids (III) with thiourea (Chart 1). The reaction gave the 2-iminothiazolidin-4-ones (II), which either were (method A) or were not (method B) isolated and then subjected to acid hydrolysis to obtain the thiazolidine-2,4-diones (I).[2]

methods A and B



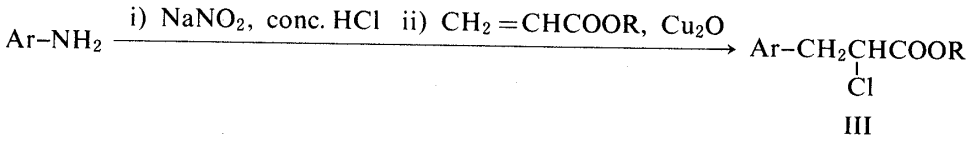
III II I

Ar=substituted phenyl, R=H, Me or Et

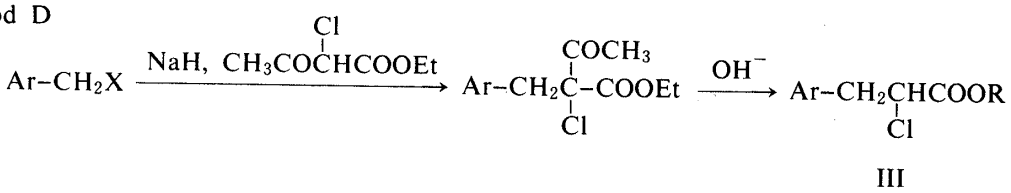
Chart 1

The preparation of the starting 3-aryl-2-chloropropionic acids (III) is summarized in Chart 2 (methods C, D and E). The method was chosen based on the substituents present on the benzene ring. For example, Meerwein arylation reaction (method C) of the aniline derivatives having alkoxy substituents at the *ortho* or the *para* position was mostly avoided because of known side reactions.[3] In method E, chlorination of the diethyl malonates was accompanied by partial chlorination on the benzene nucleus in some cases. 2-Chloro-3-(3-chloro-4-hydroxy-5-methoxyphenyl)propionic acid was prepared by taking advantage of this side reaction (Chart 3).

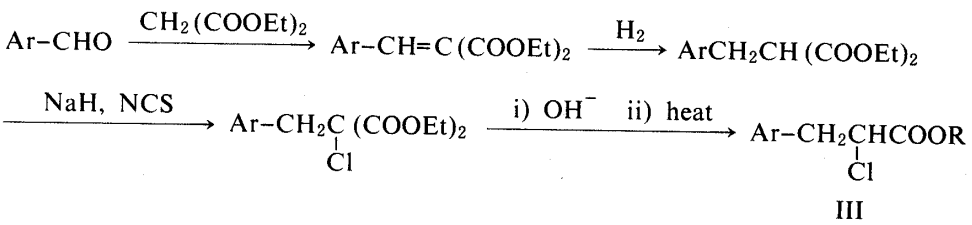
method C



method D



method E



Ar=substituted phenyl, R=H, Me or Et, X=Cl or Br

Chart 2

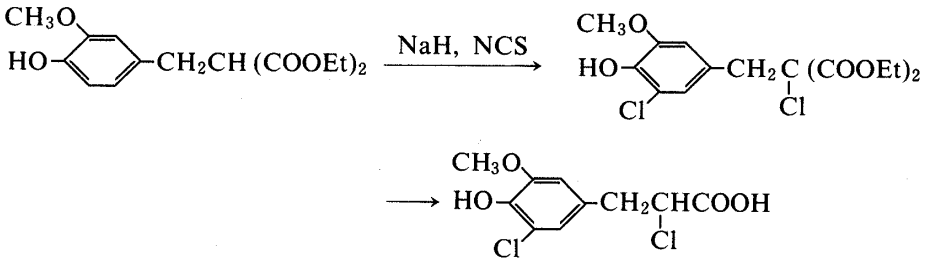
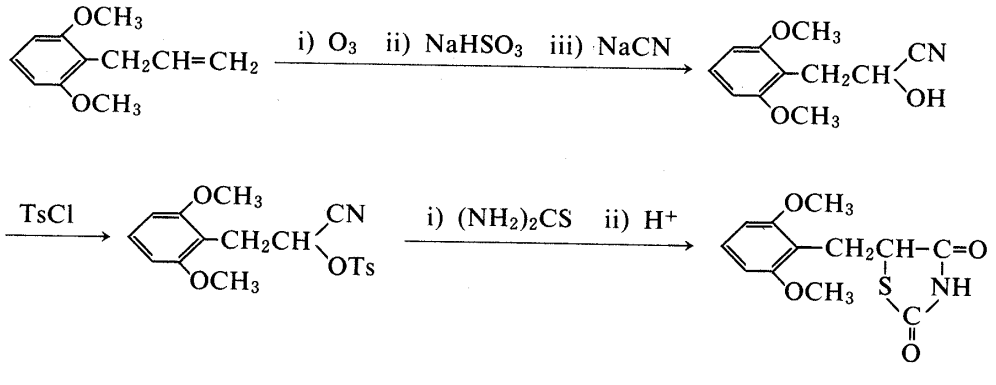


Chart 3

Most 2-chloro-3-phenylpropionic acids obtained by method E were mixtures of the acids and the esters, and the mixtures were used for the subsequent reaction without purification. Representative examples are described in the experimental section, but no efforts were made to optimize the yields.

The phenolic compound **13** and the amino compound **21** were obtained by acid hydrolysis of the *O*- and *N*-protected 2-iminothiazolidin-4-ones, respectively. Acetylations of **8**, **13**, **15**, **17** and **21** afforded **9**, **14**, **16**, **18** and **22**, respectively. Compound **17** was obtained by de-



34

Chart 4

alkylation of **15** with BBr_3. Compound **34** (Table II) was prepared starting from 2,6-dimethoxyallylbenzene[4] as shown in Chart 4.

Biological Method

Male Spraque-Dawley rats (7 weeks old) weighing 190—240 g were fasted but allowed free access to water for 24 h before the experiment. Each test compound was administered as a suspension in 5% gum arabic solution. The antisecretory or antiulcer activity of each compound was expressed as the % inhibition relative to the control group given the vehicle only.

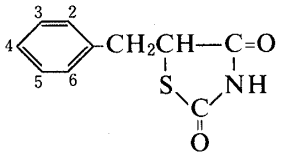
Gastric Secretion in Pylorus-ligated Rats[5]

Under light ether anesthesia, the rats were subjected to laparotomy and the pylorus was ligated. After 3 h, the gastric juice that had accumulated in the stomach was collected and the volume was measured after centrifugation at 3000 rpm for 10 min. The test compounds were given intraduodenally at 50 mg/kg immediately after the pylorus ligation. The effect of the compounds was estimated from the change in the volume of gastric juice (ml) compared with the control group.

Water-immersion Stress Ulcer[6]

Each rat was placed in a stress cage and immersed to the level of the xiphoid process for 5 h in a water bath maintained at 23 °C. After this stress condition, the rats were injected with 1 ml of 0.5% Evan's blue solution into the tail vein to enhance the contrast of the mucosal lesions. Ten min later, the animals were sacrificed under ether anesthesia and the stomach was removed. It was fixed by instilling it with 10 ml of 1% formalin solution and then immersing it in the formalin solution for 10 min, after which it was incised along the greater curvature. The length of each lesion in the glandular portion was measured under a dissecting

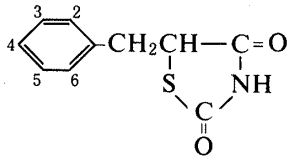
TABLE I. Physical and Biological Properties of 5-Benzylthiazolidine-2,4-dione Derivatives (I)



No.	Substituents 2	3	4	5	6	Method[a]	Yield[b] (%)	mp (°C)	Recrystn. solvent[c]	Formula[d]	Activity: Antiulcer activity[e]	Activity: Antisecretory activity[f]	Toxicity[g]
1	CH_3O	CH_3O	CH_3O	H	H	D-A	40.1	92—93	F	$C_{13}N_{15}NO_5S$	3	14	
2	CH_3O	H	CH_3O	CH_3O	H	E-A	57.2[h]	141—142	A	$C_{13}H_{15}NO_5S$	92***[i]	81*	100
3	C_2H_5O	H	C_2H_5O	C_2H_5O	H	D-B	81.4	104—105	A	$C_{16}H_{21}NO_5S$[j]	85*	19	80
4	C_3H_7O	H	C_3H_7O	C_3H_7O	H	D-B	69.3	91—92	F	$C_{19}H_{27}NO_5S$	70*	14	0
5	CH_3O	H	CH_3O	H	CH_3O	E-B	43.6[h]	157—158	A	$C_{13}H_{15}NO_5S$	35**	56	
6	H	CH_3O	CH_3O	CH_3O	H	D-B	66.7	161—162	A	$C_{13}H_{15}NO_5S$	90*	50*	100
7	H	C_2H_5O	C_2H_5O	C_2H_5O	H	D-A	50.7	113—114	A	$C_{16}H_{21}NO_5S$	40	14	
8	H	Cl	HO	CH_3O	H	A	33.0[h]	157—158	A	$C_{11}H_{10}ClNO_4S$	−19		
9	H	Cl	CH_3O	CH_3O	H		92.3[k]	155—156	B	$C_{13}H_{12}ClNO_5S$	−2		

a) See "Experimental".
b) Overall yield based on the corresponding 3-aryl-2-chloropropionic acid (III).
c) A=AcOEt–hexane, B=MeOH, C=EtOH, D=cyclohexane, E=hexane, F=EtOH–H_2O, G=Et_2O–hexane, H=AcOEt–hexane, I=DMF–H_2O.
d) All compounds were analyzed for C, H and N: analytical results obtained for these elements were within ±0.4% of calculated values.
e) % Inhibition in the formation of water-immersion stress ulcer, 50 mg/kg(*p.o.*).
f) % Inhibition of gastric secretion in 3 h pylorus-ligated rats, 50 mg/kg(*i.d.*).
g) Mortality (%) in mice orally given 500 mg/kg of each compound.
h) Overall yield based on the corresponding 2-benzyl-2-chloromalonate.
i) Statistically significant at * $p<0.05$, ** $p<0.01$, *** $p<0.001$.
j) See ref. 1).
k) Yield from **8**.

TABLE II. Physical and Biological Properties of 5-Benzylthiazolidine-2,4-dione Derivatives (I)



No.	Substituents 2	3	4	5	6	Method[a]	Yield[b] (%)	mp (°C)	Recrystn. solvent[c]	Formula[d]	Activity: Antiulcer activity[e]	Activity: Antisecretory activity[f]	Toxicity[g]
10	H	CH_3O	CH_3O	H	H	D-B	80.4	162—164	B	$C_{12}H_{13}NO_4S$[h]	76*[i]	38*	0
11	H	C_2H_5O	C_2H_5O	H	H	D-B	56.1	98—99	A	$C_{14}H_{17}NO_4S$	67**	22	0
12	H	C_3H_7O	C_3H_7O	H	H	D-A	63.4	79—80	G	$C_{16}H_{21}NO_4S$	−13	−15	
13	H	CH_3O	HO	H	H	D-B	65.0	109—110	A	$C_{11}H_{11}NO_4S$	36		
14	H	CH_3O		H	H		90.5[j]	142—143	A	$C_{13}H_{13}NO_5S$	5		
15	H	C_2H_5O	HO	H	H	E-A	18.5[k]	75—76	F	$C_{12}H_{13}NO_4S \cdot H_2O$	41	3	
16	H	C_2H_5O		H	H		90.5[l]	113—114	A	$C_{14}H_{15}NO_5S$	62**	24	0
17	H	HO	HO	H	H		89.4[m]	165—166	E	$C_{10}H_9NO_4S$	63**	35	0
18	H			H	H		60.1[n]	117—118	C	$C_{14}H_{13}NO_6S$	37	19	
19	H	CH_3	CH_3	H	H	C-A	35.3	119—120	B	$C_{12}H_{13}NO_2S$	53*	23	0
20	H	Cl	CH_3O	H	H	C-A	55.4	136—137	A	$C_{11}H_{10}ClNO_3S$	−38		
21	H	CH_3O	NH_2	H	H	C-A	37.2	172—173	B	$C_{11}H_{12}N_2O_3S$	61	13	100
22	H	CH_3O		H	H		39.2[o]	157—158	A	$C_{13}H_{14}N_2O_4S$	80	71***	100
23	CH_3O	H	CH_3O	H	H	E-B	57.7	171—172	C	$C_{12}H_{13}NO_4S$	61*	19	0
24	C_2H_5O	H	C_2H_5O	H	H	E-A	22.3[p]	115—116	A	$C_{14}H_{17}NO_4S$	−32		
25	CH_3O	CH_3O	H	H	H	E-A	79.7	112—113	A	$C_{12}H_{13}NO_4S$	38	22	
26	C_2H_5O	C_2H_5O	H	H	H	D-A	54.4	71—72	G	$C_{14}H_{12}NO_4S$	12		
27	HO	CH_3O	H	H	H	E-B	22.4	137—138	A	$C_{11}H_{11}NO_4S$	45*	−14	
28	H	CH_3O	H	CH_3O	H	C-A	49.9	110—111	A	$C_{12}H_{13}NO_4S$	58	36	
29	H	C_2H_5O	H	C_2H_5O	H	E-A	37.0	121—122	C	$C_{14}H_{17}NO_4S$	50	41	
30	CH_3O	H	H	CH_3O	H	C-B	20.8[q]	123—124	H	$C_{12}H_{13}NO_4S$	−2	36	
31	C_2H_5O	H	H	C_2H_5O	H	C-A	45.0	109—110	A	$C_{14}H_{17}NO_4S$	33		
32	CH_3O	H	H	CH_3	H	C-A	33.6	126—127	A	$C_{12}H_{13}NO_3S$	35	6	
33	H	$-OCH_2O-$		H	H	D-A	42.1	119—120[r]	C	$C_{11}H_{19}NO_4S$	28		
34	CH_3O	H	H	H	CH_3O		33.4[s]	152—153	F	$C_{12}H_{13}NO_4S$	−63	30	
35	H	H		H	H	E-B	25.2	125—126	F	$C_{12}H_{14}N_2O_2S$	89***	65*	100

a—*g*) See the corresponding footnote in Table I.
h) See ref. 1).
i) See footnote in Table I.
j) Yield based on **13**.
k) Overall yield based on diethyl 2-(4-acetoxy-3-ethoxy)-2-chloromalonate.
l) Yield based on **15**.
m) Yield of dealkylation of **15**.
n) Yield based on **17**.
o) Yield based on **21**.
p) Overall yield based on diethyl 2-chloro-2-(2,4-diethoxybenzyl)malonate.
q) Overall yield based on 2,5-diethoxyaniline.
r) Lit.[7] mp 116—117°C.
s) Overall yield based on 3-(2,6-dimethoxyphenyl)-2-(*p*-toluenesulfonyloxy)propionitrile.

microscope. The sum of the length (mm) of all lesions for each rat was used as an ulcer index. The test compounds were given orally at 50 mg/kg at 30 min before the water immersion.

Results and Discussion

The structures, physical constants and biological data of 5-benzylthiazolidine-2,4-dione derivatives are shown in Tables I and II.

Since compounds **3** and **6** were first found to possess potent biological activities, various 5-benzylthiazolidine-2,4-diones mainly having alkoxy groups in the benzene ring have been prepared. Table I shows the activities of trisubstituted benzyl derivatives. Among these compounds, 5-(2,4,5-trimethoxybenzyl)thiazolidine-2,4-dione (**2**) showed the most potent activities, but had toxicity comparable to those of **3** and **6**. An increase in the number of

carbon atoms in the alkoxy moieties reduced the toxicity (**4** *vs.* **3** *vs.* **2**), but resulted in loss of the activities (**2**>**3**>**4**; **6**>**7**). As for the position of the substituents, 2,4,5-trisubstitution seems to be most favorable for the activities (**2**>**1**, **5**, **6**).

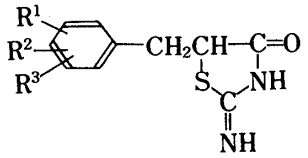
Table II shows the activities of mono- or disubstituted benzylthiazolidine-2,4-dione derivatives. The toxicity levels of this series of compounds were less than those of trisubstituted benzyl derivatives, except for the compounds having an amino or an acetamido group (**21**, **22**, **35**). Although the relationship between the substituents and the activities is not clear from the data shown in Table II, 3,4-disubstituted compounds were, in general, more potent than the others (**10**>**23**, **25**, **28**, **30**, **34**; **11**>**24**, **26**, **31**). In particular, 3,4-dialkoxy substitution seems to be desirable in terms of high activity and low toxicity. An increase of carbon number in the alkoxy chain caused a decrease of the activities (**10**>**11**>**12**; **23**>**24**; **25**>**26**) as in the case of trialkoxybenzyl derivatives (Table I).

Among the compounds listed in Tables I and II, compounds **4**, **10**, **11**, **16**, **17**, **19** and **23**, especially 5-(2,4,5-tripropoxybenzyl)thiazolidine-2,4-dione (**4**) and 5-(2,4-dimethoxybenzyl)thiazolidine-2,4-dione (**23**), showed good antiulcer activity without an antisecretory activity. These compounds therefore seem worthy of further pharmacological evaluation as a new type of antiulcer agent.

Experimental

Melting points were determined on Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were taken on a Hitachi IR-215 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian T-60 NMR spectrometer in $CDCl_3$ unless otherwise noted. Chemical shifts are given in ppm with tetramethylsilane as an internal standard, and the following abbreviations are used: s=singlet, br s=broad singlet, d=doublet, t=triplet, q=quartet, m=multiplet.

TABLE III. 5-Benzyl-2-iminothiazolidin-4-ones (II)



No.	R^1, R^2, R^3	Yield[a] (%)	mp (°C)	Recrystn. solvent[b]	Formula[c]
36	2,3,4-$(CH_3O)_3$	54.7	230—231	M	$C_{13}H_{16}N_2O_4S$
37	3,4-$(C_2H_5O)_2$	65.2	171—172	Et	$C_{14}H_{18}N_2O_3S$
38	3,4-$(C_3H_7O)_2$	71.4	165—166	Et	$C_{16}H_{22}N_2O_3S$
39	3-C_2H_5O, 4-HO	32.1	205—206	Et	$C_{12}H_{14}N_2O_3S$
40	3,4-$(CH_3)_2$	60.3	226—227	Et	$C_{12}H_{14}N_2OS$
41	3-CH_3O, 4-Cl	63.3	242—243	C-M	$C_{11}H_{11}ClN_2O_2S$
42	3-CH_3O, 4-CH_3CONH	57.5	204—205	M	$C_{13}H_{15}N_3O_3S$
43	3,5-$(CH_3O)_2$	55.7	193—194	Et	$C_{12}H_{14}N_2O_3S$
44	3,5-$(C_2H_5O)_2$	57.3	187—188	M	$C_{14}H_{18}N_2O_3S$
45	2,5-$(C_2H_5O)_2$	62.0	263—264	DMF-W	$C_{14}H_{18}N_2O_3S$
46	2-CH_3O, 5-CH_3	53.7	238—239	C-M	$C_{12}H_{14}N_2O_2S$
47	2,3-$(C_2H_5O)_2$	59.3	215—216	M	$C_{14}H_{18}N_2O_3S$
48	3,4-(OCH_2O)	90.1	220—221	Et	$C_{11}H_{10}N_2O_3S$
49	3-Cl, 4-HO, 5-CH_3O	35.7	250—251	DMF-W	$C_{11}H_{11}ClN_2O_3S$
50	2,4-$(C_2H_5O)_2$	25.2	222—223	M	$C_{14}H_{18}N_2O_3S$
51	2,3-$(CH_3O)_2$	23.0	213—214	M	$C_{12}H_{14}N_2O_3S$

a) Yield based on the corresponding 3-aryl-2-chloropropionic acid (III) (**36**—**48**) or 2-benzyl-2-chloromalonate (**49**—**51**).
b) C=$CHCl_3$, DMF=*N*,*N*-dimethylformamide, E=EtOH, M=MeOH, W=H_2O.
c) All compounds were analyzed for C, H and N; analytical results obtained for these elements were within ±0.4% of calculated values.

Thiazolidine-2,4-diones (I)

Typical examples are given to illustrate the general procedures.

Method A———2-Imino-5-(3,4,5-triethoxybenzyl)thiazolidin-4-one: A mixture of ethyl 2-chloro-3-(3,4,5-triethoxyphenyl)propionate (9.3 g), AcONa (2,65 g), thiourea (3.1 g) and 2-methoxyethanol (100 ml) was stirred at 100 °C or 16 h, then concentrated, diluted with H_2O and extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) and the solvent was evaporated off to give crystals (7.0 g, 76.9%). Recrystallization from MeOH gave colorless needles, mp 205—206 °C. IR ν_{max}^{Nujol} cm^{-1}: 3230, 1670. NMR (d_6-DMSO) δ: 1.23 (3H, t, J=7), 1.34 (6H, t, J=7), 2.75 (1H, q, J=14 and 9), 3.45 (1H, q, J=14 and 4), 3.90 (2H, q, J=7), 4.02 (4H, q, J=7), 4.53 (1H, q, J=9 and 4), 6.50 (2H, s), 8.66 (1H, br), 8.95 (1H, br). *Anal.* Calcd for $C_{16}H_{22}N_2O_4S$: C, 56.79; H, 6.55; N, 8.28. Found: C, 56.75; H, 6.62; N, 8.29.

The 5-benzyl-2-iminothiazolidin-4-ones (II) listed in Table III (**36**—**48**) were similarly prepared.

5-(3,4,5-Triethoxybenzyl)thiazolidine-2,4-dione (**7**): A mixture of 2-imino-5-(3,4,5-triethoxybenzyl)thiazolidin-4-one (5.0 g), 1N HCl (70 ml) and EtOH (70 ml) was refluxed for 10 h, then diluted with H_2O and extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated to give crystals (3.3 g, 66.0%). Recrystallization from AcOEt–hexane gave colorless prisms, mp 113—114 °C. IR ν_{max}^{Nujol} cm^{-1}: 3180, 3070, 1750, 1700. NMR δ: 1.33 (3H, t, J=7), 1.40 (6H, t, J=7), 2.97 (1H, q, J=14 and 10), 3.50 (1H, q, J=14 and 4), 4.06 (6H, q, J=7), 4.50 (1H, q, J=10 and 4), 6.43 (2H, s), 9.20 (1H, br s). *Anal.* Calcd for $C_{16}H_{21}NO_5S$: C, 56.63; H,6.24; N, 4.13. Found: C, 56.62; H, 6.18; N, 4.06.

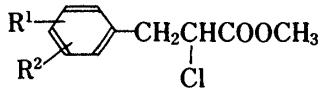
Method B———5-(3,4,5-Trimethoxybenzyl)thiazolidine-2,4-dione (**6**): A mixture of ethyl 2-chloro-3-(3,4,5-trimethoxyphenyl)propionate (3.8 g), thiourea (1.4 g) and sulfolane (50 ml) was stirred at 110 °C or 8 h and 1N HCl(40 ml) was added thereto. The mixture was refluxed for 8 h, diluted with H_2O and extracted with Et_2O. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated to give crystals (2.5 g, 66.7%). Recrystallization from AcOEt–hexane gave colorless prisms, mp 161—162 °C. IR ν_{max}^{Nujol} cm^{-1}: 3220, 3080, 1750, 1695. NMR δ: 3.02 (1H, q, J=14 and 9), 3.52 (1H, q, J=14 and 4), 3.83 (9H, s), 4.55 (1H, q, J=9 and 4), 6.45 (2H, s), 9.30 (1H, br s). *Anal.* Calcd for $C_{13}H_{15}NO_5S$: C, 52.52; H, 5.09; N, 4.71. Found: C, 52.64; H, 5.23; N, 4.56.

3-Aryl-2-chloropropionic Acids (III)

Typical examples are given to illustrate the general procedures.

Method C———Methyl 2-Chloro-3-(2,5-diethoxyphenyl)propionate: A solution of $NaNO_2$ (4.55 g) in H_2O (10 ml) was added to a stirred and ice-cooled mixture of 2,5-diethoxyaniline (10.9 g), conc. HCl (15 ml) and acetone (100 ml) below 5 °C. After the mixture had been stirred at 5 °C for 15 min, methyl acrylate (31 g) was added thereto and the temperature was raised to 35 °C. Cu_2O (0.1 g) was added to the mixture in small

TABLE IV. 3-Aryl-2-chloropropionic Acids (III)



R^1	R^2	Yield[a] (%)	Formula[b]
3-CH_3	4-CH_3	66.2	$C_{12}H_{15}ClO_2$
3-CH_3O	4-Cl	72.8	$C_{11}H_{12}Cl_2O_3$
3-CH_3O	4-CH_3CONH	42.9	$C_{13}H_{16}ClNO_4$
3-CH_3O	5-CH_3O	53.3	$C_{12}H_{15}ClO_4$
2-CH_3O	5-CH_3O	49.5	$C_{12}H_{15}ClO_4$
2-CH_3O	5-CH_3	34.7	$C_{12}H_{14}ClO_3$

a) Yield based on the corresponding aniline derivative.
b) All compounds are oils and were purified by column chromatography.

portions with vigorous stirring. After evolution of N_2 gas had ceased, the reaction mixture was concentrated and extracted with Et_2O. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated to leave the title compound as a crude oil. Purification by column chromatography on SiO_2 (150 g) using Et_2O–hexane (1:4, v/v) as an eluent gave a pure oil (9.2 g, 53.5%). IR ν_{max}^{neat} cm^{-1}: 1745. NMR δ: 1.37 (3H, t, J=7), 1.39 (3H, t, J=7), 3.05 (1H, q, J=14 and 7), 3.33 (1H, q, J=14 and 7), 3.65 (3H, s), 3.90 (2H, q, J=7), 3.93 (2H, q, J=7), 4.57 (1H, t, J=7), 6.63 (3H, s).

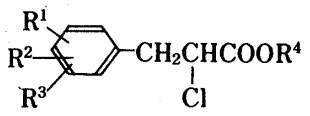
The 3-aryl-2-chloropropionic acids (III) listed in Table IV were similarly prepared.

Method D———Ethyl 2-Acetyl-2-chloro-3-(3,4-methylenedioxyphenyl)propionate: A solution of ethyl 2-chloroacetoacetate (9.9 g) in DMF(100 ml) was treated with 60% NaH in oil (2.4 g) at room temperature for 20 min. A solution of 3,4-methylenedioxybenzyl chloride (10.2 g) in DMF (10 ml) was added thereto, and the mixture was stirred at 60 °C for 2 h, poured into ice-H_2O and extracted with AcOEt. The extract was washed

with H_2O, dried($MgSO_4$) and concentrated. The residual oil was chromatographed on SiO_2 (150 g) using Et_2O–hexane (1:2, v/v) as an eluent to give a pure oil (11.3 g, 63.1%). IR ν_{max}^{neat} cm^{-1}: 1740, 1720. NMR δ: 1.28 (3H, t, J=7), 2.27 (3H, s), 3.43 (2H, s), 4.28 (2H, q, J=7), 5.93 (2H, s), 6.7 (3H, m).

2-Chloro-3-(3,4-methylenedioxyphenyl)propionic Acid: A stirred solution of ethyl 2-acetyl-2-chloro-3-(3,4-methylenedioxyphenyl)propionate (11.2 g) in EtOH (100 ml) was treated with 2N NaOH (20 ml) at room temperature for 30 min, diluted with H_2O and acidified with conc.HCl to give crystals (8.3 g, 96.5%). Recrystallization from 80% EtOH gave colorless prisms, mp 136—137°C. IR ν_{max}^{Nujol} cm^{-1}: 1720. NMR δ: 3.13 (1H, q, J=14 and 7), 3.22 (1H, q, J=14 and 7), 4.43 (1H, t, J=7), 5.95 (2H, s), 6.7 (3H, m), 10.6 (1H, b s). *Anal.* Calcd for $C_{10}H_9ClO_4$: C, 52.53; H, 3.97. Found: C, 52.78; H, 3.94.

TABLE V. 3-Aryl-2-chloropropionic Acids (III)



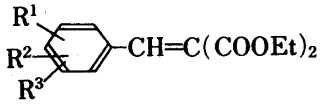
R^1, R^2, R^3	R^4	Yield[a] (%)	mp (°C)	Recrystn. solvent	Formula[b]
2,3,4-$(CH_3O)_3$	H	63.7	Oil	—	$C_{12}H_{15}ClO_5$
2,4,5-$(C_2H_5O)_3$	H	69.6	98—99	AcOEt–hexane	$C_{15}H_{21}ClO_5$[c]
2,4,5-$(C_3H_7O)_3$	Et	70.9	Oil	—	$C_{20}H_{31}ClO_5$
3,4,5-$(CH_3O)_3$	Et	35.8	Oil	—	$C_{14}H_{19}ClO_5$
3,4,5-$(C_2H_5O)_3$	Et	45.0	Oil	—	$C_{17}H_{25}ClO_5$
3,4-$(CH_3O)_2$	Et	38.8	Oil	—	$C_{13}H_{17}ClO_4$[c]
3,4-$(C_3H_7O)_2$	Et	64.5	Oil	—	$C_{17}H_{25}ClO_4$
3-CH_3O, 4-C_2H_5OCOO	Et	33.6	Oil	—	$C_{15}H_{19}ClO_6$
2,3-$(C_2H_5O)_2$	Et	38.2	Oil	—	$C_{15}H_{21}ClO_4$
3,5-$(C_2H_5O)_2$	H	55.4	Oil	—	$C_{13}H_{17}ClO_4$

a) Overall yield based on the corresponding benzyl halide.
b) Oily compounds were purified by column chromatography.
c) See ref. 1).

Ethyl 2-Chloro-3-(3,4-diethoxyphenyl)propionate: A stirred solution of ethyl 2-acetyl-2-chloro-3-(3,4-diethoxyphenyl)propionate (14.0 g) in EtOH (150 ml) was treated with $Ba(OH)_2$ (3.5 g) at room temperature for 1 h, diluted with H_2O and extracted with Et_2O. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated to give the title compound as an oil (12.0 g, 97.6%). IR ν_{max}^{neat} cm^{-1}: 1740. NMR δ: 1.20 (3H, t, J=7), 1.38 (6H, t, J=7), 3.00 (1H, q, J=14 and 7), 3.30 (1H, q, J=14 and 7), 4.02 (4H, q, J=7), 4.14 (2H, q, J=7), 4.33 (1H, t, J=7), 6.67 (3H, s).

The 3-aryl-2-chloropropionic acids (III) listed in Table V were similarly prepared.

TABLE VI. Benzylidenemalonates



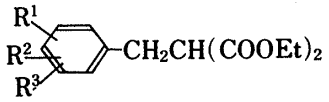
R^1, R^2, R^3	Yield[a] (%)	mp(°C)	Recrystn. solvent[b]	Formula[c]
2,4,6-$(CH_3O)_3$	77.4	118—119	Et	$C_{17}H_{22}O_7$
3-CH_3O, 4-HO	95.2	108—109	Et	$C_{15}H_{18}O_6$
3-C_2H_5O, 4-HO	82.6	61—62	H	$C_{16}H_{20}O_6$
2,4-$(CH_3O)_2$	92.9	53—54	E–H	$C_{16}H_{20}O_6$
2,4-$(C_2H_5O)_2$	73.7	74—75	H	$C_{18}H_{24}O_6$
2,3-$(CH_3O)_2$	85.5	Oil	—	$C_{16}H_{20}O_6$
2-HO, 3-CH_3O	84.4	83—84	Et	$C_{15}H_{18}O_6$
4-$(CH_3)_2N$	87.6	108—109	EA–H	$C_{16}H_{21}NO_4$

a) Yield based on the corresponding benzaldehyde.
b) E=Et_2O, EA=AcOEt, Et=EtOH, H=hexane.
c) All compounds were analyzed for C, H and N; analytical results obtained for these elements were within ±0.4% of calculated values.

Method E——Diethyl 2,4,5-Trimethoxybenzylidenemalonate: A mixture of 2,4,5-trimethoxybenzaldehyde (5.9 g), diethyl malonate (4.8 g), piperidine (0.3 ml), benzoic acid (0.3 g) and toluene (80 ml) was refluxed for 4 h and concentrated *in vacuo* to give crystals (8.9 g, 87.3%). Recrystallization from AcOEt–hexane gave colorless prisms, mp 99—100 °C. IR ν_{max}^{Nujol} cm^{-1}: 1705. NMR δ: 1.30 (3H, t, J=7), 1.33 (3H, t, J=7), 3.80 (3H, s), 3.85 (3H,s), 3.92 (3H, s), 3,98 (2H, q, J=7), 4.01 (2H, q, J=7), 6.50 (1H, s), 7.02 (1H, s), 8.05 (1H, s). *Anal.* Calcd for $C_{17}H_{22}O_7$: C, 60.34; H, 6.55. Found: C, 60.73; H,6.69.

The benzylidenemalonates listed in Table VI were similarly prepared.

TABLE VII. Benzylmalonates



R^1, R^2, R^3	Yield[a] (%)	mp (°C)	Recrystn. solvent[b]	Formula[c]
2,4,6-$(CH_3O)_3$	82.4	68—69	E-H	$C_{17}H_{24}O_7$
3-CH_3O, 4-HO	Quant.	Oil	—	$C_{15}H_{20}O_6$[d]
3-C_2H_5O, 4-HO	Quant.	Oil	—	$C_{16}H_{22}O_6$[d]
2,4-$(CH_3O)_2$	Quant.	Oil	—	$C_{16}H_{22}O_6$[d]
2,4-$(C_2H_5O)_2$	96.3	Oil	—	$C_{18}H_{26}O_6$[d]
2,3-$(CH_3O)_2$	96.1	Oil	—	$C_{16}H_{22}O_6$
4-$(CH_3)_2N$	Quant.	Oil	—	$C_{16}H_{23}NO_4$[d]

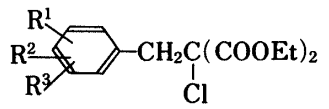
a) Yield based on the corresponding benzylmalonate.
b, c) See the corresponding footnote in Table VI.
d) The crude oil was used for the subsequent chlorination without purification.

Diethyl 2,4,5-Trimethoxybenzylmalonate: A mixture of diethyl 2,4,5-trimethoxybenzylidenemalonate (8.5 g), 10% Pd-C (1.0 g) and MeOH (100 ml) was hydrogenated at room temperature and atmospheric pressure. The catalyst was filtered off and the filtrate was concentrated to give crystals (7.0 g, 82.4%). Recrystallization from EtOH gave colorless needles, mp 56—57 °C. IR ν_{max}^{Nujol} cm^{-1}: 1720. NMR δ: 1.22 (6H, t, J=7), 3.12 (2H, d, J=7), 3.75 (1H, t, J=7), 3.78 (6H, s), 3.85 (3H, s), 4.15 (4H, q, J=7), 6.47 (1H, s), 6.68 (1H, s). *Anal.* Calcd for $C_{17}H_{24}O_7$: C, 59.99; H, 7.11. Found: C, 59.77; H, 6.83.

The benzylmalonates listed in Table VII were similarly prepared.

Diethyl 2-Chloro-2-(2,4,5-trimethoxybenzyl)malonate: A stirred solution of diethyl 2,4,5-trimethoxybenzylmalonate (6.5 g) in anhydrous tetrahydrofuran (THF) (70 ml) was treated with 60% NaH in oil

TABLE VIII. 2-Benzyl-2-chloromalonates



R^1, R^2, R^3	Yield[a] (%)	mp (°C)	Recrystn. solvent[b]	Formula[c]
2,4,6-$(CH_3O)_3$	31.4	83—84	E-H	$C_{17}H_{23}ClO_7$
3-C_2H_5O, 4-$OCOCH_3$	Quant.	Oil	—	$C_{18}H_{23}ClO_7$[d]
2,4-$(CH_3O)_2$	74.2	46—47	Et	$C_{16}H_{21}ClO_7$
2,4-$(C_2H_5O)_2$	Quant.	Oil	—	$C_{18}H_{25}ClO_6$[d]
2,3-$(CH_3O)_2$	71.4	53—54	Et	$C_{16}H_{21}ClO_6$
4-$(CH_3)_2N$	84.4	Oil	—	$C_{16}H_{22}ClNO_4$

a) Yield based on the corresponding benzylmalonate.
b, c) See the corresponding footnotes in Table VII.
d) The crude oil was used for the subsequent chlorination without purification.

(0.76 g) at room temperature for 15 min. Then NCS (2.5 g) was added thereto. The mixture was stirred at room temperature for 30 min, poured into H_2O and extracted with Et_2O. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated to give crystals (6.5 g, 91.5%). Recrystallization from EtOH gave colorless prisms, mp 97—98 °C. IR ν_{max}^{Nujol} cm^{-1}: 1740. NMR δ: 1.30 (6H, t, J=7), 3.25 (2H, s), 3.73 (3H, s), 3.80 (3H, s), 3.86 (3H, s), 4.26 (4H, q, J=7), 6.45 (1H, s), 6.80 (1H, s). *Anal.* Calcd for $C_{17}H_{23}ClO_7$: C, 54.48; H,

6.19. Found: C, 54.48; H,6.02.

The 2-benzyl-2-chloromalonates listed in Table VIII were similarly prepared.

2-Imino-5-(2,4,5-trimethoxybenzyl)thiazolidin-4-one: A mixture of diethyl 2-chloro-2-(2,4,5-trimethoxybenzyl)malonate (6.0 g), 2N KOH (20 ml) and MeOH (60 ml) was stirred at room temperaure for 1 h, diluted with H_2O, acidified with conc.HCl and extracted with AcOEt. The usual work-up gave an oily residue (5.5 g) as a mixture of the monoacid and the diacid of the starting compound. The oil was dissolved in AcOH (60 ml) and the solution was refluxed for 3 h. Thiourea (1.8 g) was added thereto, and the mixture was refluxed for 15 h then concentrated *in vacuo*. The residue was diluted with sat. aq. $NaHCO_3$ (50 ml) to give crystals (4.0 g, 85.1%). Recrystallization from MeOH gave colorless prisms, mp 207—208 °C. IR ν_{max}^{Nujol} cm^{-1}: 3380, 1690, 1650. NMR (d_6-DMSO) δ: 2.63 (1H, q, J=14 and 10), 3.40 (1H, q, J=14 and 4), 3.66 (3H, s), 3.78 (6H, s), 4.49 (1H, q, J=10 and 4), 6.64 (1H, s), 6.78 (1H, s), 8.60 (1H, br s), 8.82 (1H, br s). *Anal.* Calcd for $C_{13}H_{16}N_2O_4S$: C, 52.69; H, 5.44; N, 9.45. Found: C,52.57; H, 5.47; N, 9.33.

The 2-iminothiazolidin-4-ones (II) (**49**, **50** and **51**) listed in Table III were similarly prepared starting from the corresponding 2-benzyl-2-chloromalonate.

Diethyl 2-Chloro-3-(3-chloro-4-hydroxy-5-methoxybenzyl)malonate: A stirred and ice-cooled solution of diethyl 4-hydroxy-3-methoxybenzylmalonate (24.7 g) in anhydrous THF (200 ml) was treated with 60% NaH in oil (6.66 g) for 30 min. *N*-Chlorosuccinimide (NCS) (22.2 g) was added thereto and the stirring was continued for 1 h. The reaction mixture was poured into H_2O, acidified with 6N HCl and extracted with Et_2O. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated. The residue was chromatographed on SiO_2 (200 g) using cyclohexane–AcOEt (8:1, v/v) as an eluent to yield crystals (17.0 g, 55.7%). Recrystallization from AcOEt–hexane gave colorless prisms, mp 86—87 °C. IR ν_{max}^{Nujol} cm^{-1}: 3450, 1735. NMR δ: 1.30 (6H, t, J=7), 3.46 (2H, s), 3.86 (3H, s), 4.27 (4H, q, J=7), 5.82 (1H, s), 6.70 (1H, d, J=2), 6.80 (1H, d, J=2). *Anal.* Calcd for $C_{15}H_{18}Cl_2O_6$: C, 49.33; H, 4.97. Found: C, 49.15; H,4.97.

This compound was saponified and used for the subsequent reaction with thiourea to give **49** (Table III) according to Method E.

5-(4-Hydroxy-3-methoxybenzyl)thiazolidine-2,4-dione (**13**): A mixture of ethyl 2-chloro-3-(4-ethoxycarbonyloxy-3-methoxyphenyl)propionate (7.8 g), thiourea (3.6 g) and sulfolane (80 ml) was stirred at 110 °C for 10 h and 3N HCl (80 ml) was added thereto. The mixture was refluxed for 8 h, diluted with H_2O and extracted with Et_2O. The usual work-up gave **13** as crystals (3.9 g, 65.0%). Recrystallization from AcOEt–hexane gave colorless prisms, mp 109—110 °C. IR ν_{max}^{Nujol} cm^{-1}: 3510, 3200, 3060, 1750, 1670. NMR (d_6-DMSO) δ: 2.90 (1H, q, J=14 and 9), 3.32 (1H, q, J=14 and 4), 3.73 (3H, s), 4.76 (1H, q, J=9 and 4), 6.5—6.8 (3H, m), 8.70 (1H, br s), 11.7 (1H, br s). *Anal.* Calcd for $C_{11}H_{11}NO_4S$: C, 52.16; H, 4.38; N, 5.53. Found: C, 52.19; H, 4.29; N, 5.31.

5-(4-Amino-3-methoxybenzyl)thiazolidine-2,4-dione (**21**): A mixture of 5-(4-acetamido-3-methoxybenzyl)-2-iminothiazolidin-4-one (4.0 g), 6N HCl (30 ml) and EtOH (40 ml) was stirred under reflux for 20 h, concentrated *in vacuo*, neutralized with sat. aq. $NaHCO_3$ and extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated to give crystals (2.2 g, 64.7%). Recrystallization from MeOH gave colorless needles, mp 172—173 °C. IR ν_{max}^{Nujol} cm^{-1}: 3380, 3305, 2650 (br), 1760, 1730, 1700, 1685. NMR (d_6-DMSO) δ: 2.90 (1H, q, J=14 and 9), 3.33 (1H, q, J=14 and 4), 3.75 (3H, s), 4.82 (1H, q, J=9 and 4), 6.5—6.8 (3H, m), 6.7—7.7 (3H, br). *Anal.* Calcd for $C_{11}H_{12}N_2O_3S$: C, 52.38; H, 4.80; N,11.11. Found: C, 52.21; H, 4.76; N, 10.92.

5-(4-Acetoxy-3-chloro-5-methoxybenzyl)thiazolidine-2,4-dione (**9**): A solution of **8** (1.7 g) in a mixture of pyridine (20 ml) and Ac_2O (1.2 g) was allowed to stand at room temperature overnight. The mixture was concentrated *in vacuo*, diluted with H_2O and extracted with AcOEt. The usual work-up gave **9** as crystals (1.8 g, 92.3%). Recrystallization from MeOH gave colorless prisms, mp 155—156 °C. IR ν_{max}^{Nujol} cm^{-1}: 3160, 1760, 1745, 1670. NMR (d_6-DMSO) δ: 2.30 (3H, s), 3.03 (1H, q,J=14 and 9), 3.45 (1H, q, J=14 and 4), 3.80 (3H, s), 4.93 (1H, q, J=9 and 4), 7.0 (2H, s), 12.04 (1H, br). *Anal.* Calcd for $C_{13}H_{12}ClNO_5S$: C, 47.35; H, 3.67; N, 4.25. Found: C, 47.25; H, 3.61; N,4.13.

5-(4-Acetoxy-3-methoxybenzyl)thiazolidine-2,4-dione (**14**): Similar acetylation of **13** gave **14** in 90.5% yield. mp 142—143 °C (from AcOEt–hexane). IR ν_{max}^{Nujol} cm^{-1}: 3200, 3060, 1760, 1670. NMR δ: 2.30 (3H, s), 3.05 (1H, q, J=14 and 9), 3.53 (1H, q, J=14 and 4), 3.80 (3H, s), 4.48 (1H, q, J=9 and 4), 6.6—7.1 (3H, m), 8.85 (1H, br). *Anal.* Calcd for $C_{13}H_{13}NO_5S$: C, 52.88; H, 4.44; N, 4.74. Found: C, 52.87; H, 4.34; N, 4.75.

5-(4-Acetoxy-3-ethoxybenzyl)thiazolidine-2,4-dione (**16**): Similar acetylation of **15** gave **16** in 90.5% yield. mp 113—114 °C (from AcOEt–hexane). IR ν_{max}^{Nujol} cm^{-1}: 3170, 3060, 1770, 1745, 1685. NMR δ: 1.40 (3H, t, J=7), 2.32 (3H, s), 3.06 (1H, q, J=14 and 9), 3.55 (1H, q, J=14 and 4), 4.09 (2H, q, J=7), 4.52 (1H, q, J=9 and 4), 6.8—7.2 (3H, m), 9.0 (1H, br s). *Anal.* Calcd for $C_{14}H_{15}NO_5S$: C, 54.36; H, 4.89; N, 4.53. Found: C, 54.51; H, 4.95; N, 4.68.

5-(3,4-Diacetoxybenzyl)thiazolidine-2,4-dione (**18**): Similar acetylation of **17** gave **18** in 60.1% yield. mp 117—118 °C (from EtOH–H_2O). IR ν_{max}^{Nujol} cm^{-1}: 3150, 3030, 1770, 1750, 1650. NMR δ: 2.30 (6H, s), 3.17 (1H, q, J=14 and 9), 3.60 (1H, q, J=14 and 4), 4.53 (1H, q,J=9 and 4), 7.17 (3H, m), 8.7 (1H, br s). *Anal.* Calcd for $C_{14}H_{13}NO_6S$: C, 52.01; H, 4.05; N, 4.33. Found: C, 52.15; H, 4.02; N, 4.29.

5-(4-Acetamido-3-methoxybenzyl)thiazolidine-2,4-dione (**22**): Similar acetylation of **21** gave **22** in 88.9%

yield. mp 157—158 °C (from AcOEt–hexane). IR ν_{max}^{Nujol} cm^{-1}: 3380, 3120, 1735, 1685, 1650. NMR (d_6-DMSO) δ: 2.05 (3H, s), 3.01 (1H, q, J=14 and 9), 3.37 (1H, q, J=14 and 4), 3.80 (3H, s), 4.88 (1H, q, J=9 and 4), 6.73 (1H, q, J=8 and 2), 6.90 (1H, d, J=2), 7.83 (1H, d, J=8), 9.00 (1H, s), 12.0 (1H, br s). *Anal.* Calcd for $C_{13}H_{14}N_2O_4S$: C, 53.06; H, 4.80; N, 9.52. Found: C, 53.01; H, 4.74; N, 9.25.

5-(3,4-Dihydroxybenzyl)thiazolidine-2,4-dione (**17**): BBr_3 (2 ml) was added dropwise to a stirred and ice-cooled solution of **15** (2.0 g) in $CHCl_3$ (20 ml). The mixture was stirred at 5 °C for 30 min and at room temperature for 1 h, diluted with 2N HCl (30 ml) and extracted with $CHCl_3$. The extract was washed with H_2O dried ($MgSO_4$) and concentrated. The residual oil was chromatographed on SiO_2 (40 g) using cyclohexane–AcOEt (1:1, v/v) as an eluent to give crystals of **17** (0.55 g, 25.5%). Recrystallization from Et_2O–hexane gave colorless prisms, mp 165—166 °C. IR ν_{max}^{Nujol} cm^{-1}: 3300, 1740, 1680. NMR (d_6-DMSO) δ: 2.85 (1H, q, J=14 and 9), 3.30 (1H, q, J=14 and 4), 4.77 (1H, q, J=9 and 4), 6.63 (3H, m), 8.73 (2H, br), 11.7 (1H, br). *Anal.* Calcd for $C_{10}H_9NO_4S$: C, 50.20; H, 3.79; N, 5.85. Found: C, 50.48; H, 3.97; N, 5.74.

3-(2,6-Dimethoxyphenyl)-2-hydroxypropionitrile: O_3 gas was bubbled into a solution of 2,6-dimethoxyallylbenzene,[4] (3.56 g) in MeOH (200 ml) at −70 °C for 2 h. After N_2 gas had been bubbled into the mixture for 5 min, a solution of $NaHSO_3$ (6.24 g) in H_2O (100 ml) was added dropwise thereto. The cooling bath was removed, and NaCN (3.0 g) was added to the reaction mixture. The mixture was stirred at room temperature for 50 min, then concentrated *in vacuo,* diluted with H_2O and extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated to give the title compound as a crude oil (2.76 g, 67.0%). IR ν_{max}^{neat} cm^{-1}: 3430, 2240. NMR δ: 3.36 (2H, d, J=7), 3.73 (1H, br s), 3.91 (6H, s), 4.76 (1H, t, J=7), 6.73 (2H, m), 7.35 (1H, m).

3-(2,6-Dimethoxyphenyl)-2-(*p*-toluenesulfonyloxy)propionitrile: Tosyl chloride (1.91 g) was added to a stirred and ice-cooled solution of 3-(2,6-dimethoxyphenyl)-2-hydroxypropionitrile (2.07 g) in pyridine (9 ml). The mixture was allowed to stand at 5 °C for 3 d, then diluted with H_2O and extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated to give crystals (2.07 g, 68.8%). Recrystallization from cyclohexane–AcOEt gave colorless prisms, mp 126—127 °C. IR ν_{max}^{Nujol} cm^{-1}: 2150, 1375, 1120. NMR δ: 2.48 (3H, s), 3.37 (2H, d, J=8), 3.81 (6H, s), 5.37 (1H, t, J=8), 6.6 (2H, m), 7.3 (1H, m), 7.41 (2H, d, J=9), 7.81 (2H, d, J=9). *Anal.* Calcd for $C_{18}H_{19}NO_5S$: C, 59.82; H, 5.30; N, 3.88. Found: C, 59.73; H,5.12; N, 3.91.

5-(2,6-Dimethoxybenzyl)thiazolidine-2,4-dione (**34**): A mixture of 3-(2,6-dimethoxyphenyl)-2-(*p*-toluenesulfonyloxy)propionitrile (8.64 g), thiourea (2.28 g) and 2-methoxyethanol (100 ml) was stirred under reflux for 7 h and conc.HCl (12 ml) was added thereto. After being refluxed for 5 h, the mixture was diluted with H_2O and extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated to give a crystalline residue, which was recrystallized from 60% (v/v) EtOH to afford colorless prisms (2.14 g, 33.4%), mp 152—153 °C. IR ν_{max}^{Nujol} cm^{-1}: 3170, 3050, 1750, 1690. NMR δ: 3.40 (1H, q, J=14 and 9), 3.63 (1H, q, J=14 and 5), 3.89 (6H, s), 4.82 (1H, q, J=9 and 5), 6.6 (2H, m), 7.4 (1H, m), 9.30 (1H, br s). *Anal.* Calcd for $C_{12}H_{13}NO_4S$: C, 53.92; H, 4.90; N, 5.24. Found: C, 53.75; H, 4.76; N, 5.25.

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