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Studies on Antidiabetic Agents. III.[1] 5-Arylthiazolidine-2,4-diones as Potent Aldose Reductase Inhibitors

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Central Research Division, Takeda Chemical Industries, Ltd.,[a] 17-85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka 532, Japan and Senju Pharmaceutical Co., Ltd.,[b] 1-1, Sakuragaoka, Oshika, Itami 664, Japan

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Thiazolidine-2,4-dione derivatives having one or two substituent(s) such as phenyl, heteryl and alkyl group(s) at the 5-position were synthesized and evaluated as aldose reductase inhibitors. Inhibition by the active compounds of the swelling of the lens in a rat-lens-culture assay was also measured. Among these compounds, a series of 5-(3,4-dialkoxyphenyl)thiazolidine-2,4-diones showed pronounced activities in both assays. Structure–activity relationships are discussed and a new approach to the synthesis of 5-arylthiazolidine-2,4-diones is described.

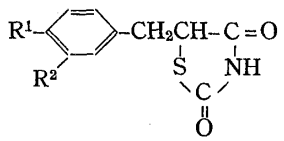
Keywords——aldose reductase; 5-arylthiazolidine-2,4-diones; diabetic cataract; structure–activity relationship ; rat-leus-culture

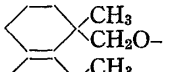
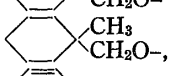
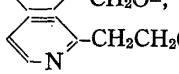
Introduction

Much effort has been expended searching for antidiabetic agents, but these studies have mostly been limited to compounds possessing hypoglycemic activity. Only a few compounds are known to be effective on certain chronic symptoms due to diabetes, such as diabetic cataract, neuropathy and retinopathy.

Recently, some aldose reductase inhibitors have been found useful for preventing or treating some chronic complications of diabetes, though they do not lower the blood glucose level.[2] The metabolic conversion of aldoses to ketoses is catalyzed in the lens,[3,4] sciatic nerve,[5] kidney[6] and other locations[7–9] by enzymes of the polyol pathway, aldose reductase and polyol dehydrogenase. Sorbitol, the intermediate in the metabolism of glucose to fructose by this pathway, diffuses poorly out of the cell and thus accumulates in certain tissues where

TABLE I. Biological Properties of 5-Benzylthiazolidine-2,4-diones



No.	R^1	R^2	Activity (% inhibition)			
			Aldose reductase			Lens swelling
			10^{-4} M	10^{-5} M	10^{-6} M	10^{-6} M
1	Cl	H	79.3	38.8	14.0	
2		H	38.7	0		7.1
3		C_2H_5O–		16.7		
4		H			18.0	6.9

there is hyperglycemia. This contributes to the pathological changes in diabetes mellitus and galactocemia,[10] particularly cataract formation, because high sugar alcohol concentration in the lens exerts strong osmotic effects, causing ingress of water and eventual disruption of lens fiber membranes.[11–13]

Many acidic compounds, *i.e.*, carboxylic acid derivatives,[14] imidazolidine-2,4-diones[15] and oxazolidine-2,4-diones,[16] are known to be aldose reductase inhibitors. Based on the structural analogy to these compounds, some 5-benzylthiazolidine-2,4-diones (Table I, **1**—**4**) which we previously reported as potential antidiabetic agents,[1] were screened and found to show some aldose reductase inhibition. We therefore synthesized various 5-substituted thiazolidine-2,4-dione derivatives as potential inhibitors of the enzyme. Inhibition of lens swelling was also evaluated using a rat-lens-culture assay.

Chemistry

Most of the thiazolidine-2,4-diones (I) listed in Tables II-VI were prepared by reaction of 2-chloroacetonitrile derivatives (II) or 2-haloacetic acid derivatives (III) with thiourea followed by acid hydrolysis (Chart 1).

The reaction of 2-chloroacetonitrile derivatives (II) with thiourea gave 2,4-diiminothiazolines (IV) which, without isolation, were hydrolyzed to the desired thiazolidine-2,4-diones (I) (method A). The intermediate compounds (IV) could not be isolated in pure forms since they were easily hydrolyzed to the monoiminothiazolidines (V) under acidic conditions and were unstable under basic conditions. The reaction of 2-haloacetic acid derivatives (III) with thiourea afforded the 2-iminothiazolidin-4-ones (V), which were (method B) or were not (method C) isolated and then subjected to acid hydrolysis to obtain the thiazolidine-2,4-diones (I) in good yields.

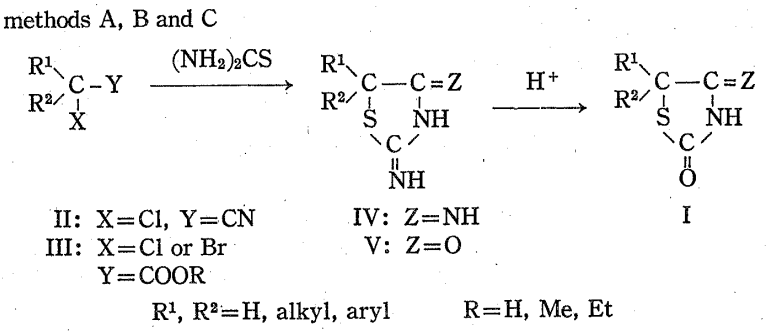


Chart 1

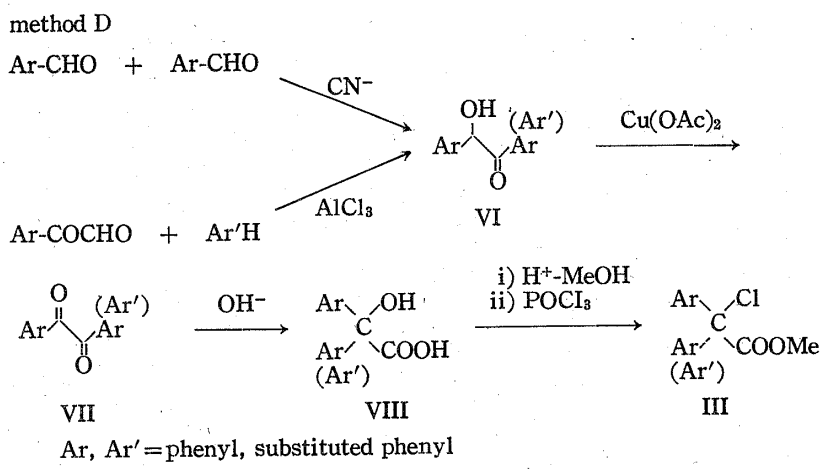


Chart 2

The starting 2,2-diphenyl-2-haloacetic acids (III) required for the preparation of the series of 5,5-diphenylthiazolidine-2,4-diones listed in Table II were obtained as shown in Chart 2 (method D), which includes the benzil-benzilic acid rearrangement.

The synthesis of 2-chloroacetonitrile derivatives (II) and 2-haloacetic acid derivatives (III), required for the preparation of the series of 5-arylthiazolidine-2,4-diones (I) listed in Tables III—VI, is summarized in Chart 3 (methods E, F and G).

Most 5-(alkoxyphenyl)thiazolidine-2,4-diones (I) were prepared according to method E followed by method A, starting from the corresponding aldehydes (IX). In these reactions, the hydrocyanation of the alkoxybenzaldehyde (IX) was not complete and the subsequent chlorination was accompanied with many side reactions, probably due to stable benzyl cations. Thus, these intermediates (X) and (II) were not isolated before being subjected to the subsequent reactions in most cases. Representative examples are described in the experimental section, but no efforts were made to obtain optimal yields. Method F, the Hell–Volhard–Zelinsky reaction, was used only for the preparation of compounds having no electron-donating substituents on the benzene ring, since such substituents cause bromination on the benzene nucleus. The methods used are shown in Tables II—VI.

The required aldehydes (IX) for method E were mainly prepared by alkylation of the corresponding hydroxybenzaldehydes. But the starting aldehydes for the preparation of

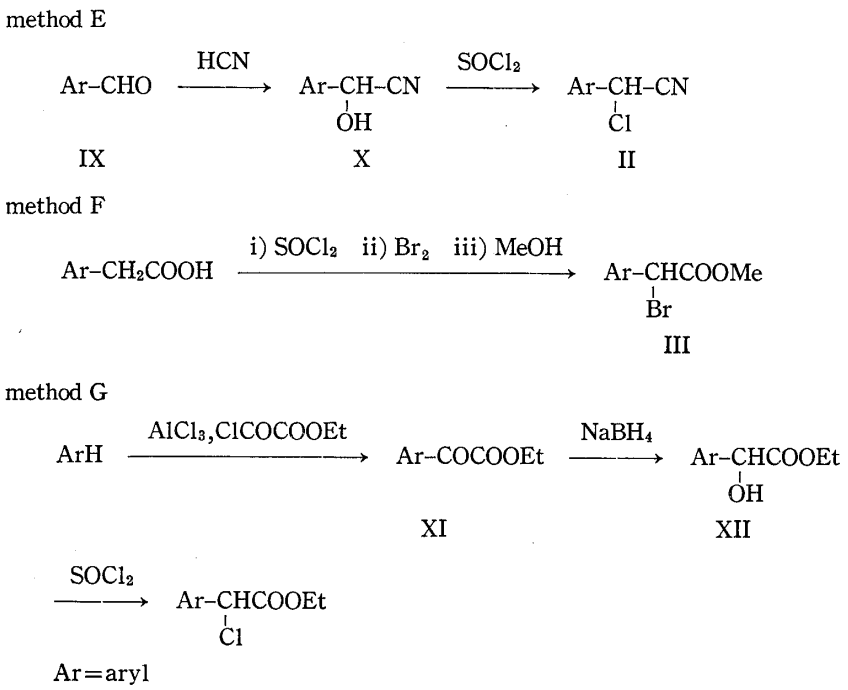


Chart 3

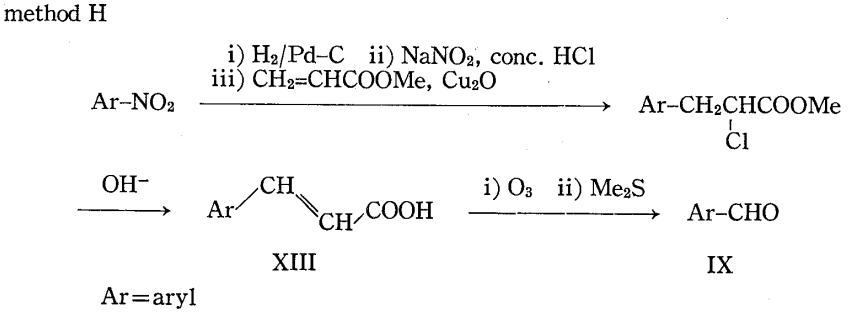


Chart 4

33, **34** (Table III), **47** (Table IV) and a series of 5-(2-alkoxy-5-pyridyl)thiazolidine-2,4-diones (**69**—**74**, Table V) were obtained by method H, which includes the Meerwein arylation reaction followed by ozonolysis (Chart 4).

5-Aryl-5-ethylthiazolidine-2,4-diones (**15**, Table III; **50**, Table IV) were prepared by ethylation of the dianions derived from **14** and **49**, respectively. Catalytic reduction of **19** gave **20** and acetylation of **20**, **38** and **48** afforded **21**, **39** and **40**, respectively. Compound **22** (Table III) was prepared by alkaline hydrolysis of the corresponding ester, and compounds **23** (Table III) and **38** (Table IV) were obtained from **24** and **48**, respectively, by dealkylation (see "Experimental").

As mentioned previously, the synthesis of 5-(alkoxyphenyl)thiazolidine-2,4-diones (I) (Tables III and IV) according to method E followed by method A was accompanied by the formation of many by-products, and the yields were low. Since these compounds, especially the 5-(3,4-dialkoxyphenyl) derivatives (Table IV), exhibited the most favorable activities (*vide infra*), we sought an alternative method suitable for their large-scale production, and we considered nucleophilic substitution (S_N1) on a benzylic cation with thiourea. Since a benzylic cation, which is stabilized by the electronic effect of the alkoxy group(s) on the benzene ring, was expected to be a good substrate for the S_N1 reaction, we tried the reaction of 2-(alkoxyphenyl)-2-hydroxyacetonitriles (method I) or 2-(alkoxyphenyl)-2-hydroxyacetic acid derivatives (methods J and K) with thiourea in the presence of a mineral acid. The reaction proceeded smoothly to give the thiazolidine-2,4-diones (I). The imino intermediate (V) was isolated under mild conditions. The sequence of this reaction is depicted in Chart 5.

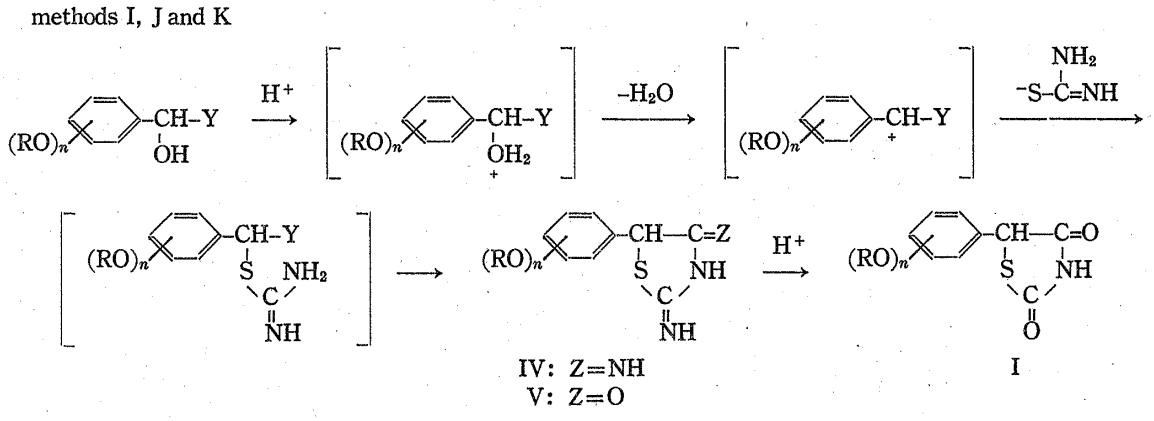


Chart 5

Using these methods, the desired thiazolidine-2,4-diones (I) were prepared from starting hydroxyacetonitriles or hydroxyacetic acid derivatives in more than 70% overall yields.

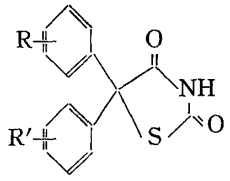
Method I also permitted one-pot preparation (method L) of 5-(3,4-dialkoxyphenyl)-thiazolidine-2,4-diones starting with alkoxybenzaldehydes. The alkoxybenzaldehydes in a protic solvent containing a small excess of acid were allowed to react with an aqueous solution of NaCN (or KCN) below 25°C and then conc. HCl and thiourea were added to this solution. After being stirred for 2—3 h at 60°C, the reaction mixture was subjected to hydrolysis by heating at a higher temperature. This one-pot synthesis is a simple method for large-scale production of thiazolidine-2,4-diones (I) in good yields.

The starting 2-(alkoxyphenyl)-2-hydroxyacetic acid derivatives used for methods J and K were prepared by method G and the method of Compere,[17] respectively.

Biological Method

The inhibitory effect of each compound on aldose reductase was evaluated by the methods of Hayman *et al.*[18] and Kinoshita *et al.*[19] Partially purified aldose reductase from human placenta was used in the assay. The swelling-inhibitory effect in a rat-lens-culture assay was evaluated by the method of Obazawa *et al.*[20] The results, expressed as the percent inhibition at each concentration, are shown in Tables I—VI.

TABLE II. Physical and Biolgical Propeties of Thiazolidine-2,4-dione Derivatives



No.	R	R′	Method[a]	Yield[b] (%)	mp (°C)	Recrystn. solvent[c]	Formula[d]	Activity (% inhibition) Aldose reductase 10^{-6} M	10^{-7} M	10^{-8} M	Lens swelling 10^{-6} M	10^{-7} M
5	H	H	D–C	63.1	154—155	Et	$C_{15}H_{11}NO_2S$	53.3	23.8		54.1	5.5
6	3-Cl	3-Cl	D–C	20.8	150—151	Et–W	$C_{15}H_9Cl_2NO_2S$	72.5	39.5	0	0	
7	4-CH_3	4-CH_3	D–C	26.9	125—126	IPE	$C_{17}H_{15}NO_2S$	22.0	0		7.2	
8	4-Cl	H	D–C	48.3	110—111	Et–W	$C_{15}H_{10}ClNO_2S$	42.7	15.0	0		
9	3-Cl	H	D–C	39.9	103—104	E–H	$C_{15}H_{10}ClNO_2S$	55.1	22.2	0	7.7	
10	2-Cl	H	D–C	17.1	195—196	Et	$C_{15}H_{10}ClNO_2S$	25.1	0			

a) See experimental section.
b) Overall yield from the corresponding benzylic acid (VIII).
c) C=$CHCl_3$, Cy=cyclohexane, E=Et_2O, Et=EtOH, H=hexane, IPE=isopropyl ether, M=MeOH, W=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.

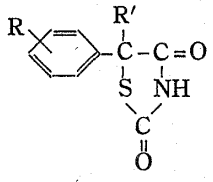
Results and Discussion

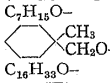
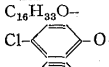
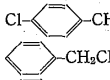
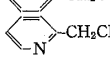
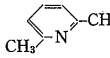
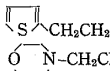
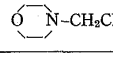
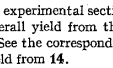
The structures, physical constants and biological data of the thiazolidine-2,4-dione derivatives are shown in Tables II—VI.

The activities of 5,5-diphenylthiazolidine-2,4-diones are shown in Table II. Compound **5** exhibited potent activities in both assays, but the other compounds (**6**—**10**) had weaker activities than **5**, except for the aldose reductase inhibition of **6**, indicating that the introduction of substituent(s) on the benzene ring(s) has no potentiating effect.

Table III lists the activities of a series of 5-(monosubstituted phenyl)thiazolidine-2,4-dione derivatives. Most of these compounds are more active than the unsubstituted compound **11**. In compounds **12**—**36**, changes in the electron density of the benzene ring and hydrophilicity of the molecule do not much alter the activities, while 5-(*p*-alkoxyphenyl)thiazolidine-2,4-dione derivatives with a proper length of carbon chain exhibited rather potent activities. Compounds with a branched *p*-alkoxy side chain (**26**) and a cyclic alkoxy chain (**28**) had almost the same activities as the compounds with a linear alkoxy chain. However, the potency decreased in the compound (**29**) with a long *p*-alkoxy chain. Introduction of a phenyl (**31** and **32**), a pyridyl (**33** and **34**), a thienyl (**35**) or an amino moiety (**36**) into the aliphatic chain did not cause significant effects. Compound **15** with an additional alkyl substituent at the 5-position of the thiazolidine-2,4-dione ring displayed aldose reductase inhibition almost equivalent to

TABLE III. Physical and Biological Properties of Thiazolidine-2,4-dione Derivatives



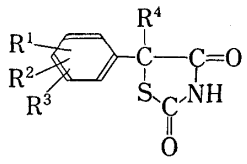
No.	Position of R	R	R′	Mehod[a]	Yield[b] (%)	mp (°C)	Recrystn. solvent[c]	Formula[d]	Activity (% inhibition) Aldose reductase 10^{-6} M	10^{-7} M	10^{-8} M	Lens swelling 10^{-6} M	10^{-7} M
11	—	H	H	F–C	86.7*	125—127	Et–W	$C_9H_7NO_2S$	29.2	0			
12	2	Cl–	H	F–B	76.6*	128—129	EA–H	$C_9H_6ClNO_2S$	59.4	4.3			
13	4	Cl–	H	F–C	89.3*	127—129	Et–W	$C_9H_6ClNO_2S$	48.9	13.4	0		
14	3	F–	H	E–A	40.7***	129—130	E–H	$C_9H_6FNO_2S$	38.5	4.6		10.7	
15	3	F–	C_2H_5	M	54.2[e]	90—91	E–H	$C_{11}H_{10}FNO_2S$	38.0	6.4			
16	4	F–	H	G–C	46.9****	145—146	E–H	$C_9H_6FNO_2S$	27.6	2.3		2.5	
17	3	CF_3–	H	F–B	73.5*	139—140	E–H	$C_{10}H_7F_3NO_2S$	39.4	0			
18	4	C_2H_5–	H	G–C	45.1*	122—123	Et–W	$C_{11}H_{11}NO_2S$	45.9	6.0			
19	4	NO_2–	H	F–B	58.2*	114—115	EA–H	$C_9H_6N_2O_4S$	50.2	0.9			
20	4	NH_2–	H	N	56.8[f]	206—207	M	$C_9H_8N_2O_2S$	34.7	0			
21	4	CH_3CONH–	H	O	78.3[g]	225—226	M	$C_{11}H_{10}N_2O_3S$	64.4	7.8			
22	4	HOOC–	H	P	65.8[h]	252—253	M–E	$C_{10}H_7NO_4S$	30.0			4.0	
23	4	HO–	H	Q	56.0[i]	239—240	M	$C_9H_7NO_3S$	49.3	2.3		0.6	
24	4	C_2H_5O–	H	E–A	35.4**	167—168	Et	$C_{11}H_{11}NO_3S$	53.6	10.4		6.0	
25	4	$C_5H_{11}O$–	H	E–A	48.8***	101—102	Et–W	$C_{14}H_{17}NO_3S$	51.3	0		15.3	
				L	67.9*****								
26	4	$(CH_3)_3CCH_2O$–	H	E–A	33.1***	164—165	Et–W	$C_{14}H_{17}NO_3S$	50.4	16.7		7.9	7.8
27	4	$C_7H_{15}O$–	H	E–A	39.7***	104—105	Et	$C_{16}H_{21}NO_3S$	17.6				
28	4		H	E–A	27.0**	127—128	Et–W	$C_{17}H_{21}NO_3S$	53.0	15.9			
29	4	$C_{16}H_{33}O$–	H	E–A	22.1***	112—113	Et	$C_{25}H_{39}NO_3S$	14.3			0	
30	4		H	G–C	64.1*	174—175	Et	$C_{15}H_{10}ClNO_3S$	60.7	4.1			
31	4		H	E–A	58.8***	135—136	M	$C_{16}H_{12}ClNO_3S$	79.7	20.0			
32	4		H	J	86.7****	136—137	Et	$C_{17}H_{15}NO_3S$	64.6	17.2	0	1.9	
33	4		H	H–E–A	50.0**	175—176	M	$C_{16}H_{14}N_2O_3S$	36.2			28.0	
34	4		H	H–E–A	54.5**	158—159	M	$C_{17}H_{16}N_2O_3S$	0				
35	4		H	E–A	31.3***	114—115	EA–H	$C_{15}H_{13}NO_3S_2$	6.5				
36	4		H	E–A	6.7***	166—167	M	$C_{15}H_{18}N_2O_4S$	8.1			4.0	

a) See experimental section.
b) Overall yield from the corresponding haloacetate (III) (*), hydroxynitrile (X) (**), chloronitrile (II) (***), hydroxy acid derivative (****) or aldehyde (IX) (*****).
c, *d*) See the corresponding footnote in Table II.
e) Yield from **14**.
f) Yield from **19**.
g) Yield from **20**.
h) Yield from the corresponding ester (see experimental section).
i) Yield from **24**.

that of the parent compound. From these results, the appropriate lipophilic alkoxy chain seemed to be the most promising functional group for high activities. Thus, further study was focused on the 5-(*p*-alkoxyphenyl)thiazolidine-2,4-dione derivatives.

Table IV shows the activities of the compounds with a di- or trisubstituted phenyl group. Generally, 5-(3,4-diakoxyphenyl)thiazolidine-2,4-dione derivatives exhibited more potent activities than 5-(*p*-alkoxyphenyl)thiazolidine-2,4-diones (**24**—**29**, Table III), especially in the rat-lens-culture assay. In contrast, the 2,4-dialkoxyphenyl derivative (**51**) and trialkoxyphenyl derivatives (**67** and **68**) had inferior biological properties. Introduction of the phenyl group(s) into the aliphatic chain (**60** and **66**) and an alkyl group at the 5-position of the thiazolidine-2,4-dione ring (**50**) did not enhance the activities, as in the case of 5-(monosubstituted phenyl)thiazolidine-2,4-dione derivatives (Table III). In a series of 5-(3,4-dialkoxyphenyl)-thiazolidine-2,4-dione derivatives, compounds with alkyl groups containing less than six carbon atoms showed almost equivalent activities. However, an abrupt drop in aldose reductase inhibition was observed when the 4-alkoxy chain had seven carbon atoms (**59**).

TABLE IV. Physical and Biological Properties of Thiazolidine-2,4-dione Derivatives



No.	R^1	R^2	R^3	R^4	Method[a]	Yield[b] (%)	mp (°C)	Recrystn. solvent[c]	Formula[d]	Activity (% inhibition) Aldose reductase 10^{-6} M	10^{-7} M	10^{-8} M	Lens swelling 10^{-6} M	10^{-7} M
37	3-CH_3	4-CH_3	H	H	G–C	60.0*	121—122	EA–Cy	$C_{11}H_{11}NO_2S$	35.8	0		1.8	
38	3-OH	4-OH	H	H	Q	72.2[e]	186—187	EA–H	$C_9H_7NO_4S$	41.8	0		10.2	
					L	42.0*****								
39	3-$OCOCH_3$	4-$OCOCH_3$	H	H	O	82.9[f]	134—135	EA–H	$C_{13}H_{11}NO_6S$	60.1	15.1		4.0	
40	3-OC_2H_5	4-$OCOCH_3$	H	H	O	59.3[e]	120—121	EA–H	$C_{13}H_{13}NO_5S$	59.0	10.7	0	23.7	
41	3,4-OCH_2O–		H	H	E–A	30.3**	177—178	Et–W	$C_{10}H_7NO_4S$	47.4	30.8	16.2	16.5	
42	3-OCH_3	4-OCH_3	H	H	E–A	14.7**	177—178	M	$C_{11}H_{11}NO_4S$	57.1	15.8	0	30.3	0
43	3-OCH_3	4-OC_4H_9	H	H	E–A	32.0***	150—151	EA–H	$C_{14}H_{17}NO_4S$	38.7	0		49.7	
44	3-OCH_3	4-OC_5H_{11}	H	H	E–A	35.8***	143—144	Et	$C_{15}H_{19}NO_4S$	40.6	0		49.9	9.0
45	3-OCH_3	4-OC_6H_{13}	H	H	E–A	19.1***	133—134	Et	$C_{16}H_{21}NO_4S$	32.2	0		39.0	
46	3-OCH_3	4-O-*i*-C_6H_{13}	H	H	E–A	22.4***	137—138	Et–W	$C_{16}H_{21}NO_4S$	68.1	19.5		46.5	
47	3-OC_2H_5	4-Cl	H	H	H–E–A	13.0*****	124—125	Et–W	$C_{11}H_{10}ClNO_3S$	19.5				
48	3-OC_2H_5	4-OH	H	H	E–A	8.0**	195—196	Et–EA	$C_{11}H_{11}NO_4S$	51.6	8.5	0	13.8	
					L	57.0****								
49	3-OC_2H_5	4-OC_2H_5	H	H	E–A	73.7***	142—143	Et	$C_{13}H_{15}NO_4S$	57.0	21.7		37.0	6.2
					I	90.6**								
					K	83.6****								
50	3-OC_2H_5	4-OC_2H_5	H	Et	M	53.2[g]	79—80	E–H	$C_{15}H_{19}NO_4S$	29.3			8.7	
51	2-OC_2H_5	4-OC_2H_5	H	H	K	91.4****	137—138	E–H	$C_{13}H_{15}NO_4S$	4.1				
52	3-OC_2H_5	4-OC_3H_7	H	H	E–A	14.7***	118—119	Et	$C_{14}H_{17}NO_4S$	45.7	0			
53	3-OC_2H_5	4-OC_4H_9	H	H	E–A	21.2**	111—112	EA–H	$C_{15}H_{19}NO_4S$	55.2	20.6		59.6	7.8
					J	90.9****								
54	3-OC_2H_5	4-OC_5H_{11}	H	H	E–A	56.2**	105—106	Et–W	$C_{16}H_{21}NO_4S$	34.6	0		44.6	4.3
					I	85.9**								
					J	78.9****								
					L	68.9*****								
55	3-OC_2H_5	4-O-iso-C_5H_{11}	H	H	E–A	52.4***	129—130	Et–W	$C_{16}H_{21}NO_4S$	34.0			57.2	
					J	89.1****								
					L	86.0*****								
56	3-OC_2H_5	4-$OCH_2C(CH_3)_3$	H	H	E–A	25.4**	115—116	Et–W	$C_{16}H_{21}NO_4S$	28.0			25.3	
57	3-OC_2H_5	4-OC_6H_{13}	H	H	E–A	19.0**	93—94	Et–W	$C_{17}H_{23}NO_4S$	37.7	0		33.0	0
58	3-OC_2H_5	4-O-iso-C_6H_{13}	H	H	E–A	26.3***	114—115	Et–W	$C_{17}H_{23}NO_4S$	60.6	11.5		49.2	
					L	54.8*****								
59	3-OC_2H_5	4-OC_7H_{15}	H	H	E–A	26.2**	98—99	Et–W	$C_{18}H_{25}NO_4S$	2.2			10.1	
60	3-OC_2H_5	4-(4-Cl-$C_6H_4CH_2O$)–	H	H	E–A	13.7***	125—126	M	$C_{18}H_{16}ClNO_4S$	19.0			22.5	
61	3-OC_3H_7	4-OC_3H_7	H	H	E–A	44.0*****	111—112	Et–W	$C_{15}H_{19}NO_4S$	53.5	21.5		32.4	4.8
62	3-OC_4H_9	4-OCH_3	H	H	E–A	38.3***	118—119	Et–W	$C_{14}H_{17}NO_4S$	42.9	0		37.9	
63	3-OC_4H_9	4-OC_4H_9	H	H	E–A	40.0***	119—120	Et–W	$C_{17}H_{23}NO_4S$	51.7	18.3		30.7	0
					J	81.6****								
64	3-OC_5H_{11}	4-OCH_3	H	H	E–A	22.3***	109—110	EA–H	$C_{15}H_{19}NO_4S$	30.0	0		30.7	
65	3-OC_6H_{13}	4-OCH_3	H	H	E–A	44.2***	83—84	EA–H	$C_{16}H_{21}NO_4S$	28.0	0		31.6	
66	3-($C_6H_5CH_2CH_2O$)–	4-($C_6H_5CH_2CH_2CH_2O$)–	H	H	E–A	13.5***	120—121	M	$C_{25}H_{23}NO_4S$	55.8			8.2	
67	2-OC_2H_5	4-OC_2H_5	5-OC_2H_5	H	K	90.6****	134—135	EA–H	$C_{15}H_{19}NO_5S$	10.0	0			
68	3-OC_2H_5	4-OC_2H_5	5-OC_2H_5	H	E–A	41.6***	124—125	EA–H	$C_{15}H_{19}NO_5S$	25.1	0			

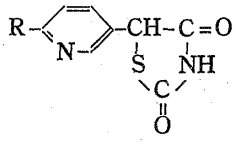
a—*d*) See the corresponding footnote in Table III.
e) Yield from **48**.
f) Yield from **38**.
g) Yield from **49**.

Replacement of the benzene ring in the above-mentioned compounds with pyridine (**69**—**74**, Table V) or thiophene (**77**—**79**, Table VI) did not enhance the potency of either activity. Replacement with alkyl groups (**75** and **76**, Table VI) resulted in complete loss of the activities. The structure-activity relationships among the 5-(2-alkoxy-5-pyridyl)thiazolidine-2,4-dione derivatives appear to parallel those of the 5-(*p*-alkoxyphenyl)thiazolidine-2,4-dione derivatives.

Conclusion

In a search for antidiabetic agents, we prepared various 5-substituted thiazolidine-2,4-dione derivatives as aldose reductase inhibitors; such inhibitors were expected to be useful for preventing or treating some chronic complications of diabetes such as diabetic cataract and neuropathy. Inhibition of the swelling of the lens in a rat-lens-culture assay was also

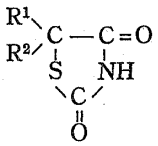
Table V. Physical and Biological Properties of Thiazolidine-2,4-dione Derivatives

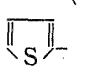
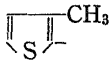
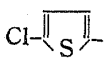


No.	R	Method[a]	Yield[b] (%)	mp (°C)	Recrystn. solvent[c]	Formula[d]	Activity (% inhibition) Aldose reductase 10^{-6}M	10^{-7}M	10^{-8}M	Lens swelling 10^{-6}M	10^{-7}M
69	H	C	22.2**	219—221	W	$C_7H_6O_2N_2S\cdot HCl$	36.5	5.9		5.1	
70	C_2H_5O–	H–E–C	22.2***	151—152	EA–H	$C_{10}H_{10}N_2O_3S$	67.6	21.1		18.3	
71	C_3H_7O–	H–E–C	40.3*	146—147	EA–H	$C_{11}H_{12}N_2O_3S$	39.1	0		38.5	
72	C_4H_9O–	H–E–C	18.0*	86—87	EA–H	$C_{12}H_{14}N_2O_3S$	43.0	0		40.0	
73	$C_5H_{11}O$–	H–E–C	21.0*	83—84	EA–H	$C_{13}H_{16}N_2O_3S$	36.7				
74	$C_7H_{15}O$–	H–E–C	2.0*	73—74	H	$C_{15}H_{20}N_2O_3S$	26.7				

a) See experimental section. *b*) Overall yield from the corresponding hydroxynitrile (X) (*), aldehyde (IX)(**), or chloroacetate (III) (***). *c*, *d*) See the corresponding footnotes in Table II.

Table VI. Physical and Biological Propeties of Thiazolidine-2,4-dione Derivatives



No.	R^1	R^2	Method[a]	Yield[b] (%)	mp (°C)	Recrystn. solvent[c]	Formula[d]	Activity (% inhibition) Aldose reductase 10^{-6}M	10^{-7}M	10^{-8}M	Lens swelling 10^{-6}M	10^{-7}M
75	CH_3	CH_3	C	17.5*	78—79	IPE–H	$C_5H_7NO_2S$	0				
76	$-(CH_2)_5-$		C	2.0*	126—127	M–W	$C_8H_{11}NO_2S$	0				
77		H	G–C	7.6**	108—109	C–H	$C_7H_5NO_2S_2$	53.2	8.7		8.4	
78		H	E–A	5.5***	118—119	E–H	$C_8H_7NO_2S_2$	31.3			10.4	
79		H	G–C	12.1**	126—127	E–H	$C_7H_4ClNO_2S_2$	45.7	4.6		0	

a) See experimental section. *b*) Overall yield from the corresponding haloacetate (III) (*), hydroxyacetate (XII) (**) or hydroxynitrile (X) (***). *c*, *d*) See the corresponding footnotes in Table II.

measured. 5,5-Diphenylthiazolidine-2,4-dione (**5**) and some 5-(3,4-dialkoxyphenyl)thiazolidine-2,4-diones, such as compounds **43**, **44**, **46**, **53**—**55** and **58**, showed potent activities in both assays. Further pharmacological evaluation of these compounds using an *in vivo* assay system will be continued in order to select compounds with the best bioavailability with the aim of developing a new antidiabetic agent for clinical use.

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 the internal standard and the following abbreviations are used: s=singlet, br s=broad singlet, d=doublet, t=triplet, q=quartet, m=multiplet.

Method A——The following experiment is an example of the general procedure used to prepare thiazolidine-2,4-diones in Tables III, IV and VI.

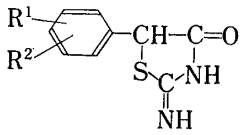
5-[4-(4-Chlorobenzyloxy)phenyl]thiazolidine-2,4-dione (**31**): A mixture of 2-chloro-2-[4-(4-chlorobenzyloxy)phenyl]acetonitrile (1.5 g), thiourea (0.43 g) and EtOH (50 ml) was refluxed for 30 min, then 2 N HCl (50 ml) was added thereto and the mixture was refluxed for 15 h. After cooling, the mixture was diluted with H_2O and extracted with $CHCl_3$. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated to give crystals (1.0 g, 58.8%). Recrystallization from MeOH gave colorless plates, mp 135—136°C. IR ν_{max}^{Nujol} cm^{-1}: 3130, 3090, 1740, 1715. NMR δ: 5.04 (2H, s), 5.64 (1H, s), 6.92 (2H, d, J=9), 7.28 (2H, d, J=9), 7.35 (4H, s), 12.1 (1H, br s). *Anal.* Calcd for $C_{16}H_{12}ClNO_3S$: C, 57.57; H, 3.62; N, 4.20. Found: C, 57.65; H, 3.51; N, 4.44.

Method B——The following experiments are examples of the general procedure used to prepare thiazolidine-2,4-diones listed in Table III.

5-(2-Chlorophenyl)-2-iminothiazolidin-4-one: A mixture of methyl 2-bromo-2-(2-chlorophenyl)acetate (13.0 g), thiourea (4.5 g) and EtOH (150 ml) was refluxed for 1 h, cooled and diluted with aq. sat. $NaHCO_3$ (300 ml) to give crystals (10.2 g, 91.9%). Recrystallization from $CHCl_3$–MeOH gave colorless prisms, mp 269—270°C. IR ν_{max}^{Nujol} cm^{-1}: 3270, 1685. NMR (d_6-DMSO) δ: 5.64 (1H, s), 7.2—7.5 (4H, m), 8.9 (1H, br s), 9.1 (1H, br s). *Anal.* Calcd for $C_9H_7Cl\,N_2OS$: C, 47.69; H, 3.11; N, 12.36. Found: C, 47.79; H, 3.09; N, 12.34.

The 2-iminothiazolidin-4-ones (**85** and **86**) listed in Table VII were similarly prepared.

Table VII. 5-Aryl-2-iminothiazolidin-4-ones (V)



No.	R^1	R^2	Yield[a] (%)	mp (°C) (dec.)	Recrystn. solvent[b]	Formula[c]
80	2-C_2H_5O–,	4-C_2H_5O–,	85.7*	190—191	iso-Pr	$C_{13}H_{16}N_2O_3S$
81	3-C_2H_5O–,	4-C_4H_9O–,	82.8**	218—219	Et	$C_{15}H_{20}N_2O_3S$
82	3-C_4H_9O–,	4-C_4H_9O–,	46.7**	208—209	Et	$C_{17}H_{24}N_2O_3S$
83	3-C_2H_5O–,	4-iso-$C_5H_{11}O$–,	43.8**	220—222	Et	$C_{16}H_{22}N_2O_3S$
84	4-$C_6H_5CH_2CH_2O$–,	H,	62.5**	219—220	Et	$C_{17}H_{16}N_2O_3S$
85	4-NO_2,	H,	93.7***	241—243	M–E	$C_9H_7N_3O_3S\cdot HBr$
86	3-CF_3,	H,	79.0***	245—246	M	$C_{10}H_7F_3N_2OS$

a) Yield from the corresponding mandelic acid ethyl ester (*). mandelic acid (**) or 2-bromoacetate (***). *b*) E=Et_2O, Et=EtOH, iso. Pr=isopropanol, M=MeOH. *c*) All compounds were analyzed for C, H and N; analytical results obtained for these elements were within ±0.4% of calculated values.

5-(2-Chlorophenyl)thiazolidine-2,4-dione (**12**): A mixture of 5-(2-chlorophenyl)-2-iminothiazolidin-4-one (9.0 g), 2 N HCl (80 ml) and EtOH (80 ml) was refluxed for 12 h, cooled and diluted with H_2O to give a precipitate (7.5 g, 83.3%). Recrystallization from AcOEt–hexane gave colorless prisms, mp 128—129°C. IR ν_{max}^{Nujol} cm^{-1}: 3270, 1690, 1660. NMR (d_6-DMSO) δ: 6.07 (1H, s), 7.4—7.7 (4H, m), 12.3 (1H, br s). *Anal.* Calcd for $C_9H_6ClNO_2S$: C, 47.48; H, 2.66; N, 6.15. Found: C, 47.44; H, 2.70; N, 5.85.

Method C——Typical examples are given below to illustrate the general procedure.

5-(3-Chlorophenyl)-5-phenylthiazolidine-2,4-dione (**9**): A mixture of 3-chlorobenzylic acid (14.0 g), conc.H_2SO_4 (8 ml) and MeOH (280 ml) was allowed to stand at room temperature for 1 d, then diluted with H_2O and extracted with Et_2O. The usual work-up gave the oily methyl ester (11.8 g). NMR δ: 3.85 (3H, s), 4.29 (1H, s), 7.1—7.5 (9H, m). The ester was dissolved in $POCl_3$ (30 ml). The mixture was stirred at 70°C for 2 h, poured into ice-H_2O and extracted with Et_2O. The usual work-up gave an oily residue. A mixture of the oil, BuOH (100 ml) and thiourea (4.7 g) was stirred at 110°C for 6 h then concentrated to leave a crystalline residue. The residue was dissolved in EtOH (130 ml)–2 N HCl (130 ml) and the solution was refluxed for 16 h. The reaction mixture was diluted with H_2O and extracted with AcOEt. The usual work-up gave crystals of **9** (6.46 g, 39.9%). Recrystallization from Et_2O–hexane gave colorless prisms, mp 103—104°C. IR ν_{max}^{Nujol} cm^{-1}: 3150, 3040, 1740, 1680. *Anal.* Calcd for $C_{15}H_{10}ClNO_2S$: C, 59.31; H, 3.32; N, 4.61. Found: C, 59.30; H, 3.14; N, 4.73.

5-[4-(4-Chlorophenoxy)phenyl]thiazolidine-2,4-dione (**30**): A mixture of ethyl 2-chloro-2-[4-(4-chlorophenoxy)phenyl]acetate[21] (2.15 g), thiourea (0.99 g) and sulfolane (10 ml) was stirred at 110°C for 2 h, then 6 N HCl (10 ml) was added thereto. The mixture was stirred at 100°C for 8 h and poured into H_2O. The usual work-up gave **30** as crystals (1.35 g, 64.1%). Recrystallization from EtOH gave colorless prisms, mp 174—175°C. IR ν_{max}^{Nujol} cm^{-1}: 3170, 3050, 1750, 1680. NMR (d_6-DMSO) δ: 5.86 (1H, s), 7.0—7.7 (8H, m), 9.0 (1H, br s). *Anal.* Calcd for $C_{15}H_{10}ClNO_3S$: C, 56.34; H, 3.15; N, 4.38. Found: C, 56.43; H, 3.08; N, 4.49.

Method D——Typical examples are given below to illustrate the general procedure.

Benzoins (VI): 4,4′-Dimethylbenzoin: A mixture of 4-methylbenzaldehyde (18.0 g), KCN (3.0 g) and 80% EtOH (200 ml) was refluxed for 3 h, diluted with H_2O and extracted with AcOEt. The usual work-up gave crystals (6.5 g, 36.1%), mp 86—87°C (lit.[22] mp 88—89°C).

4-Chlorobenzoin: 4-Chlorophenylglyoxal monohydrate (1.86 g) was dissolved in C_6H_6 (70 ml) and the solution was concentrated to 15 ml. $AlCl_3$ (2.7 g) was added to the stirred and ice-cooled concentrate, and the mixture was stirred for 1 h. The temperature was raised to room temperature and stirring was continued for 5 h. The reaction mixture was poured into ice-H_2O and extracted with AcOEt. The usual work-up gave crystals (2.0 g, 81.6%) of the title compound, mp 90—91°C (lit.[23] mp 90—91°C).

Benzils (VII): 4,4′-Dimethylbenzil: A mixture of 4,4′-dimethylbenzoin (6.0 g), cupric acetate monohydrate (10.0 g) and 70% AcOH v/v, 125 ml) was stirred under reflux for 1 h, diluted with H_2O and extracted with AcOEt. The usual work-up gave crystals (5.28 g, 88.7%) of the title compound, mp 99—100°C (lit.[22] mp 103°C).

3,3′-Dichlorobenzil, 4-chlorobenzil, 3-chlorobenzil and 2-chlorobenzil were prepared by a known method.[24]

Benzilic Acids (VIII): 4,4′-Dimethylbenzilic acid: A mixture of 4,4′-dimethylbenzil (5.2 g), KOH (10.0 g), H_2O (20 ml) and EtOH (20 ml) was refluxed for 1 h, diluted with H_2O and extracted with Et_2O. The usual work-up gave crystals (4.5 g, 80.4%) of the title compound, mp 130—131°C (lit.[25] mp 132—133.8°C).

3,3′-Dichlorobenzilic acid, 4-chlorobenzilic acid, 3-chlorobenzilic acid and 2-chlorobenzilic acid were prepared by known methods.[26,27]

Methyl Benzilates and Methyl 2-Chloro-2,2-diphenylacetates (III): These compounds were prepared according to method C and the crude materials were used for the subsequent reaction.

Method E——2-[4-(4-Chlorobenzyloxy)phenyl]-2-hydroxyacetonitrile: Solutions of $NaHSO_3$ (26.0 g) in H_2O (50 ml) and KCN (16.3 g) in H_2O (30 ml) were added to a stirred solution of 4-(4-chlorobenzyloxy)-benzaldehyde[28] (12.2 g) in AcOEt (100 ml). The mixture was stirred at room temperature for 24 h and the organic layer was separated. The usual work-up gave crystals (12.0 g, 87.6%). Recrystallization from AcOEt–hexane gave colorless plates, mp 102—103°C. IR ν_{max}^{Nujol} cm^{-1}: 3380, 2250. NMR (d_6-DMSO) δ: 5.07 (2H, s), 5.55 (1H, d, $J=6$), 6.77 (1H, d, $J=6$), 6.95 (2H, d, $J=9$), 7.35 (2H, d, $J=9$), 7.37 (4H, s). *Anal.* Calcd for $C_{15}H_{12}ClNO_2$: C, 65.82; H, 4.42; N, 5.12. Found: C, 65.78; H, 4.24; N, 5.08.

2-Chloro-2-[4-(4-chlorobenzyloxy)phenyl]acetonitrile: A solution of 2-[4-(4-chlorobenzyloxy)phenyl]-2-hydroxyacetonitrile (5.5 g) in $CHCl_3$ (80 ml) was treated with $SOCl_2$ (2.2 ml). After refluxing for 30 min, the mixture was washed with H_2O and dried ($MgSO_4$). Evaporation of the solvent left an oily residue which was chromatographed on SiO_2 (50 g) using Et_2O–hexane (1: 3, v/v) as an eluent to give crystals (1.6 g, 27.4%), mp 94—95°C. NMR (d_6-DMSO) δ: 5.10 (2H, s), 6.48 (1H, s), 7.03 (2H, d, $J=9$), 7.37 (4H, s), 7.45 (2H, d, $J=9$). *Anal.* Calcd for $C_{15}H_{11}Cl_2NO$: C, 61.67; H, 3.80; N, 4.79. Found: C, 61.51; H, 3.75; N, 4.68.

The starting *p*-alkoxybenzaldehydes and 3,4-dialkoxybenzaldehydes were mainly prepared by alkylation of *p*-hydroxybenzaldehyde, vanillin, ethyl vanillin, isovanillin or protocatechualdehyde. Typical examples are given below to illustrate the general procedure.

3-Ethoxy-4-pentyloxybenzaldehyde: A mixture of ethyl vanillin (100.5 g), pentyl bromide (96 g), K_2CO_3 (91.8 g) and dimethylformamide (DMF) (300 ml) was stirred at 110°C for 3 h, poured into ice-H_2O and extracted with hexane. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated to give the title compound (127.7 g, 89.4%) as a crude oil. A pure oil was obtained by distillation [bp 141—143°C (0.3 mmHg), lit.[29] bp 195°C (11 mmHg)].

3,4-Dibutoxybenzaldehyde: A mixture of protocatechualdehyde (29.0 g), butyl bromide (96.6 g), K_2CO_3 (41.5 g) and DMF (200 ml) was stirred at 110°C for 5 h, poured into ice-H_2O and extracted with Et_2O. The usual work-up gave an oil (38.3 g, 72.8%), bp 147—149°C (0.5 mmHg) [lit.[30] bp 165—172°C (2.5 mmHg)].

4-[2-(2-Thienyl)ethoxy]benzaldehyde: A mixture of 2-(2-thienyl)ethanol methanesulfonate (3.5 g), *p*-hydroxybenzaldehyde (2.1 g), K_2CO_3 (2.4 g) and dimethylsulfoxide (DMSO) (50 ml) was stirred at 80°C for 4 h and poured into H_2O. The usual work-up gave the title compound as an oil (3.3 g, 83.5%). NMR δ: 3.35 (2H, t, $J=7$), 4.28 (2H, t, $J=7$), 6.8—7.3 (5H, m), 7.85 (2H, d, $J=9$), 9.93 (1H, s).

3-Ethoxy-4-neopentyloxybenzaldehyde: A mixture of ethyl vanillin (16.6 g), neopentyl alcohol *p*-toluenesulfonate (24.2 g), K_2CO_3 (13.8 g) and DMSO (300 ml) was stirred at 150°C for 24 h and poured into H_2O. The usual work-up gave an oily residue (14 g). Purification by column chromatography on silica gel (200 g) using AcOEt–hexane (1: 10, v/v) as an eluent gave a pure oil (11.0 g, 46.6%). IR ν_{max}^{neat} cm^{-1}: 1690. NMR δ: 1.06 (9H, s), 1.43 (3H, t, $J=7$), 3.70 (2H, s), 4.10 (2H, q, $J=7$), 6.86 (1H, d, $J=9$), 7.2—7.4 (2H, m), 9.76 (1H, s).

4-(1-Methylcyclohexylmethoxy)benzaldehyde: Ac_2O (20 ml) was added to a solution of 4-(1-methylcyclohexylmethoxy)benzyl alcohol (11.7 g) in DMSO (100 ml). The mixture was allowed to stand at room temperature for 1 d, diluted with H_2O and extracted with Et_2O. The usual work-up gave the title compound as a crude oil, which was chromatographed on silica gel (100 g) using Et_2O–hexane (1: 2, v/v) as an eluent to afford a pure oil (10.0 g, 86.2%). IR ν_{max}^{neat} cm^{-1}: 1685. NMR δ: 1.05 (3H, s), 1.47 (10H, br s), 3.73 (2H, s), 6.93 (2H, d, J=9), 7.76 (2H, d, J=9), 9.83 (1H, s).

The starting material used for this method was prepared as follows:

4-(1-Methylcyclohexylmethoxy)benzoic Acid: A mixture of 4-(1-methylcyclohexylmethoxy)benzonitrile[31] (6.8 g), a solution of KOH (15 g) in H_2O (70 ml) and ethylene glycol (70 ml) was refluxed for 10 h, cooled, diluted with H_2O, acidified with conc.HCl and extracted with AcOEt. The usual work-up gave crystals (6.0 g, 81.8%). Recrystallization from EtOH gave colorless prisms, mp 180—181°C. IR ν_{max}^{Nujol} cm^{-1}: 1675. NMR δ: 1.01 (3H, s), 1.44 (10H br s), 3.67 (2H, s), 6.90 (2H, d, J=9), 7.96 (2H, d, J=9), 9.0 (1H, br s). *Anal.* Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.77; H, 8.24.

4-(1-Methylcyclohexylmethoxy)benzyl Alcohol: A solution of 4-(1-methylcyclohexylmethoxy)benzoic acid (11.0 g) in Et_2O (200 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (1.7 g) in Et_2O (200 ml), and the mixture was stirred at room temperature for 1 h. The usual work-up gave the title compound (9.8 g, 94.2%) as an oil. IR ν_{max}^{neat} cm^{-1}: 3300. NMR δ: 1.05 (3H, s), 1.46 (10H, br s), 3.40 (1H, br s), 3.60 (2H, s), 4.40 (2H, s), 6.78 (2H, d, J=9), 7.14 (2H, d, J=9).

Method F——Methyl 2-Bromo-2-(2-chlorophenyl)acetate: A mixture of (2-chlorophenyl)acetic acid (10.2 g) and thionyl chloride (7.7 g) was refluxed for 1 h, then cooled. Bromine (9.6 g) was added thereto and the mixture was stirred at 70°C for 16 h. The reaction mixture was cautiously poured into MeOH (100 ml) and the MeOH was evaporated off to leave an oily residue which was dissolved in Et_2O. The solution was washed with H_2O, dried ($MgSO_4$) and concentrated to give a crude oil (13.2 g, quant.). IR ν_{max}^{neat} cm^{-1}: 1750. NMR δ: 3.77 (3H, s), 5.80 (1H, s), 7.0—7.4 (4H, m).

The following compound was similarly prepared and the crude oil was used for the subsequent reaction without purification.

Methyl 2-Bromo-2-(4-nitrophenyl)acetate: Oil. Yield (98.7%). IR ν_{max}^{neat} cm^{-1}: 1745. NMR δ: 3.83 (3H, s), 5.42 (1H, s), 7.84 (2H, d, J=9), 8.31 (2H, d, J=9).

Methyl 2-bromo-2-(4-chlorophenyl)acetate and methyl 2-bromo-2-(3-trifluoromethylphenyl)acetate were prepared by known methods.[32,33]

Method G——Arylglyoxylates (XI): Ethyl (2,4-Diethoxyphenyl)glyoxylate: Ethoxalyl chloride (6.0 g) and a solution of *m*-diethoxybenzene (7.3 g) in CH_2Cl_2 (20 ml) were added to a stirred and ice-cooled suspension of $AlCl_3$ (5.9 g) in CH_2Cl_2 (80 ml) in that order. The mixture was stirred at room temperature for 1 h, then poured into ice-H_2O. The organic layer was separated, washed with H_2O, dried ($MgSO_4$) and concentrated to give crystals (6.5 g, 55.6%). Recrystallization from Et_2O–hexane gave colorless plates, mp 56—57°C. IR ν_{max}^{Nujol} cm^{-1}: 1720, 1645. NMR δ: 1.37 (6H, t, J=7), 1.40 (3H, t, J=7), 4.04 (4H, q, J=7), 4.30 (2H, q, J=7), 6.2—6.6 (2H, m), 7.75 (1H, d, J=9). *Anal.* Calcd for $C_{14}H_{18}O_5$: C, 63.15; H, 6.81. Found: C, 63.42; H, 6.76.

The following compound was similarly prepared.

Ethyl (2,4,5-Triethoxyphenyl)glyoxylate: mp 58—59°C (from hexane). Yield 69.4%. IR ν_{max}^{Nujol} cm^{-1}: 1730, 1650. NMR δ: 1.40 (6H, t, J=7), 1.44 (3H, t, J=7), 1.51 (3H, t, J=7), 4.05 (4H, q, J=7), 4.13 (2H, q, J=7), 4.32 (2H, q, J=7), 6.40 (1H, s), 7.33 (1H, s). *Anal.* Calcd for $C_{16}H_{22}O_6$: C, 61.92; H, 7.15. Found: C, 62.08; H, 7.20.

Ethyl (4-fluorophenyl)glyoxylate, ethyl (4-ethylphenyl)glyoxylate, ethyl [4-(4-chlorophenoxy)phenyl]-glyoxylate, ethyl (3,4-diethoxyphenyl)glyoxylate, ethyl (2-thienyl)glyoxylate and ethyl (5-chloro-2-thienyl)-glyoxylate were prepared by known methods.[21,34-36]

Ethyl 2-Aryl-2-hydroxyacetates (XII): Ethyl 2-(2,4-Diethoxyphenyl)-2-hydroxyacetate: $NaBH_4$ (0.355 g) was added to a stirred and ice-cooled solution of ethyl (2,4-diethoxyphenyl)glyoxylate (5.0 g) in MeOH (50 ml). The mixture was stirred at room temperature for 30 min, diluted with H_2O and extracted with Et_2O. The usual work-up gave the title compound (5.1 g, quant.) as an oil. IR ν_{max}^{neat} cm^{-1}: 3480, 1725. NMR δ: 1.17 (3H, t, J=7), 1.35 (6H, t, J=7), 3.61 (1H, d, J=7), 3.95 (4H, q, J=7), 4.13 (2H, q, J=7), 5.12 (1H, d, J=7), 6.35 (2H, m), 7.03 (1H, d, J=9).

The following compounds were similarly prepared.

Ethyl 2-Hydroxy-2-(2,4,5-triethoxyphenyl)acetate: Oil. Yield quant., IR ν_{max}^{neat} cm^{-1}: 3480, 1730. NMR δ: 1.21 (3H, t, J=7), 1.37 (6H, t, J=7), 1.43 (3H, t, J=7), 3.61 (1H, d, J=7), 4.01 (4H, q, J=7), 4.08 (2H, q, J=7), 4.18 (2H, q, J=7), 5.23 (1H, d, J=7), 6.50 (1H, s), 6.83 (1H, s).

Ethyl 2-(5-Chloro-2-thienyl)-2-hydroxyacetate: mp 59—60°C (from Et_2O–hexane). Yield 85.9%. IR ν_{max}^{Nujol} cm^{-1}: 3400, 1725. NMR δ: 1.23 (3H, t, J=7), 4.02 (1H, d, J=7), 4.20 (2H, q, J=7), 5.23 (1H, d, J=7), 6.66 (1H, d, J=3.5), 6.78 (1H, d, J=3.5).

Ethyl 2-(4-fluorophenyl)-2-hydroxyacetate, ethyl 2-(4-ethylphenyl)-2-hydroxyacetate, ethyl 2-[4-(4-chlorophenoxy)phenyl]-2-hydroxyacetate, ethyl 2-(3,4-diethoxyphenyl)-2-hydroxyacetate and ethyl 2-hydroxy-2-(2-thienyl)acetate were prepared by known methods.[21,35,37,38]

2-Aryl-2-chloroacetates (III): Ethyl 2-Chloro-2-(5-chloro-2-thienyl)acetate: A solution of ethyl 2-(5-chloro-2-thienyl)-2-hydroxyacetate (6.8 g) in Et_2O (50 ml) was treated with thionyl chloride (4.4 ml). The mixture was refluxed for 2 h, cooled and concentrated to leave an oily residue, which was chromatographed on silica gel (60 g) using Et_2O–hexane (1: 5, v/v) as an eluent to give the title compound as an oil (5.1 g, 69.3%). IR ν_{max}^{neat} cm^{-1}: 1745. NMR δ: 1.33 (3H, t, $J=7$), 4.27 (2H, q, $J=7$), 5.47 (1H, s), 6.70 (1H, d, $J=3.5$), 6.90 (1H, d, $J=3.5$).

The following compounds were similarly prepared.

Ethyl 2-Chloro-2-(4-ethylphenyl)acetate: Oil. Yield 91.9%. IR ν_{max}^{neat} cm^{-1}: 1750. NMR δ: 1.25 (3H, t, $J=7$), 1.30 (3H, t, $J=7$), 2.73 (2H, q, $J=7$), 4.32 (2H, q, $J=7$), 5.43 (1H, s), 7.30 (2H, d, $J=9$), 7.45 (2H, d, $J=9$).

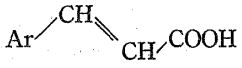
Ethyl 2-Chloro-2-(2-thienyl)acetate: Oil. Yield 58.5%. IR ν_{max}^{neat} cm^{-1}: 1745. NMR δ: 1.30 (3H, t, $J=7$), 4.24 (2H, q, $J=7$), 5.62 (1H, s), 6.8—7.5 (3H, m).

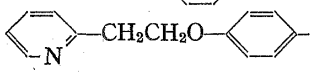
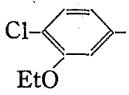
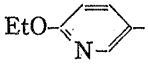
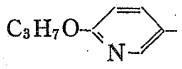
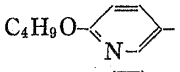
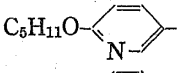
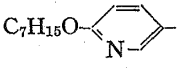
Ethyl 2-Chloro-2-(4-fluorophenyl)acetate, ethyl 2-chloro-2-[4-(4-chlorophenoxy)phenyl]acetate and methyl 2-chloro-(3,4-dimethylphenyl)acetate were prepared by known methods.[21,33,37]

Method H——3-Arylacrylic Acids (XIII): 4-[2-(6-Methyl-2-pyridyl)ethoxy]cinnamic Acid: A mixture of methyl 2-chloro-3-{4-[2-(6-methyl-2-pyridyl)ethoxy]phenyl}propionate[1] (12.5 g), 4 N KOH (100 ml) and EtOH (100 ml) was refluxed for 2 h, concentrated *in vacuo*, neutralized with AcOH and extracted with AcOEt. The extract was washed with brine, dried ($MgSO_4$) and concentrated to give crystals (5.55 g, 52.4%). Recrystallization from AcOEt gave colorless rods, mp 160—161°C. IR ν_{max}^{Nujol} cm^{-1}: 1670. NMR (d_6-DMSO) δ: 2.52 (3H, s), 3.22 (2H, t, $J=7$), 4.47 (2H, t, $J=7$), 6.43 (1H, d, $J=16$), 7.12 (1H, d, $J=16$), 7.0—7.9 (7H, m). *Anal.* Calcd for $C_{17}H_{17}NO_3$: C, 72.06; H, 6.05; N, 4.94. Found: C, 72.01; H, 6.06; N, 5.16.

The other new 3-arylacrylic acids (XIII) listed in Table VIII were similarly prepared.

Table VIII. 3-Arylacrylic Acids (XIII)



No.	Ar	Yield[a] (%)	mp (°C)	Recrystn. solvent[b]	Formula[c]
87	$(CH_3)_3CCH_2O$–	78.5	200—202	Et	$C_{14}H_{18}O_2$
88		41.9	156—157	EA–H	$C_{16}H_{15}NO_3$
89		45.8	127—128	Et	$C_{11}H_{11}ClO_3$
90		43.1	182—183	Et	$C_{10}H_{11}NO_3$
91		78.0	173—174	M	$C_{11}H_{13}NO_3$
92		74.0	151—152	Cy–H	$C_{12}H_{15}NO_3$
93		55.0	136—137	M	$C_{13}H_{17}NO_3$
94		50.6	136—137	M	$C_{15}H_{21}NO_3$

a) Overall yield from the corresponding nitro compound. *b*) Cy=cyclohexane, EA=AcOEt, Et=EtOH, H=hexane, M=MeOH. *c*) See the corresponding footnote in Table VII.

4-[2-(6-Methyl-2-pyridyl)ethoxy]benzaldehyde: A solution of 4-[2-(6-methyl-2-pyridyl)ethoxy]cinnamic acid (5.3 g) in MeOH (300 ml)–CH_2Cl_2 (300 ml) was treated with O_3 at −70°C for 2 h. Me_2S (10 ml) was added to the mixture and stirring was continued for 30 min at −50°C. The temperature was raised to room temperature and the solvent was evaporated off. The oily residue was partitioned between AcOEt and sat. aq. $NaHCO_3$. The organic layer was separated, washed with H_2O, dried ($MgSO_4$) and concentrated to give crystals (3.4 g, 75.6%). Recrystallization from Et_2O–hexane gave colorless plates, mp 59—60°C. IR ν_{max}^{Nujol} cm^{-1}: 1680. NMR δ: 2.57 (3H, s), 3.30 (2H, t, $J=7$), 4.52 (2H, t, $J=7$), 7.0—8.0 (7H, m), 10.0 (1H, s). *Anal.* Calcd for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.27; N, 5.81. Found: C, 74.53; H, 6.19; N, 5.63.

The following aldehydes were similarly prepared from 3-arylacrylic acids (XIII) listed in Table VIII.

4-Neopentyloxybenzaldehyde: Oil. Yield 67.8%. IR ν_{max}^{neat} cm^{-1}: 1685. NMR δ: 1.00 (9H, s), 3.68 (2H, s), 7.03 (2H, d, J=9), 7.87 (2H, d, J=9), 10.08 (1H, s).

4-[2-(2-Pyridyl)ethoxy]benzaldehyde: Oil. Yield quant., IR ν_{max}^{neat} cm^{-1}: 1685. NMR δ: 3.27 (2H, t, J=7), 4.45 (2H, d, J=7), 6.8—7.9 (7H, m), 9.80 (1H, s).

4-Chloro-3-ethoxybenzaldehyde: Oil. Yield 69.4%. IR ν_{max}^{neat} cm^{-1}: 1720. NMR δ: 1.50 (3H, t, J=7), 4.20 (2H, q, J=7), 7.2—7.9 (3H, m), 10.10 (1H, s).

2-Ethoxy-5-pyridinecarbaldehyde: mp 78—79°C (from Et_2O–hexane). Yield 47.7%. IR ν_{max}^{Nujol} cm^{-1}: 1685. NMR δ: 1.42 (3H, t, J=7), 4.45 (2H, q, J=7), 6.72 (1H, d, J=8), 8.00 (1H, dd, J=8 and 2), 8.57 (1H, d, J=2), 9.88 (1H, s). *Anal.* Calcd for $C_8H_9NO_2$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.71; H, 5.88; N, 9.15.

2-Propoxy-5-pyridinecarbaldehyde: Oil. Yield 62.8%. IR ν_{max}^{neat} cm^{-1}: 1690. NMR δ: 1.05 (3H, t, J=7), 1.88 (2H, m), 4.43 (2H, t, J=7), 6.90 (1H, d, J=8), 8.15 (1H, dd, J=8 and 2), 8.71 (1H, d, J=2), 10.10 (1H, s).

2-Butoxy-5-pyridinecarbaldehyde: Oil. Yield 93.0%. IR ν_{max}^{neat} cm^{-1}: 1680. NMR δ: 0.96 (3H, t, J=7), 1.2—2.0 (4H, m), 4.41 (2H, t, J=7), 6.83 (1H, d, J=8), 8.07 (1H, dd, J=8 and 2), 8.73 (1H, d, J=2), 10.05 (1H, s).

2-Pentyloxy-5-pyridinecarbaldehyde: Oil. Yield 89.0%. IR ν_{max}^{neat} cm^{-1}: 1695. NMR δ: 0.92 (3H, t, J=7), 1.1—2.0 (6H, m), 4.37 (2H, t, J=7), 6.73 (1H, d, J=8), 7.95 (1H, dd, J=8 and 2), 8.50 (1H, d, J=2), 9.83 (1H, s).

2-Heptyloxy-5-pyridinecarbaldehyde: Oil. Yield 52.6%. IR ν_{max}^{neat} cm^{-1}: 1680. NMR δ: 0.95 (3H, t, J=7), 1.1—2.0 (10H, m), 4.36 (2H, t, J=7), 6.88 (1H, d, J=8), 8.00 (1H, dd, J=8 and 2), 8.66 (1H, d, J=2), 10.15 (1H, s).

Method I——A typical example is given to illustrate the general procedure.

5-(3,4-Diethoxyphenyl)thiazolidine-2,4-dione (**49**): Conc.HCl (0.5 ml) and thiourea (0.288 g) were added to a stirred suspension of 2-(3,4-diethoxyphenyl)-2-hydroxyacetonitrile[39] (0.443 g) in 2-methoxyethanol (5 ml). The mixture was stirred at 60°C for 3 h and 2 N HCl (5 ml) was added thereto. After being stirred at 100°C for 8 h, the reaction mixture was diluted with H_2O to give crystals of **49**. Recrystallization from EtOH gave colorless prisms (0.51 g, 90.6%), mp 140—141°C. IR ν_{max}^{Nujol} cm^{-1}: 3170, 3040, 1740, 1700. NMR δ: 1.30 (6H, t, J=7), 4.01 (4H, q, J=7), 5.68 (1H, s), 6.9 (3H, m), 12.1 (1H, br s). *Anal.* Calcd for $C_{13}H_{15}NO_4S$: C,55.50; H, 5.37; N, 4.98. Found: C, 55.57; H, 5.28; N, 5.13.

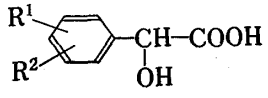
Method J——Typical examples are given to illustrate the general procedure.

5-(3-Ethoxy-4-pentyloxyphenyl)-2-iminothiazolidin-4-one: Conc.HCl (3.3 ml) and thiourea (1.5 g) were added to a stirred solution of 2-(3-ethoxy-4-pentyloxyphenyl)-2-hydroxyacetic acid (2.8 g) in 2-methoxyethanol (30 ml). The mixture was stirred at 60°C for 4 h and poured into sat.aq.$NaHCO_3$ (100 ml) to give crystals. Recrystallization from EtOH gave colorless needles (1.85 g, 57.5%), mp 220—222°C (dec.). IR ν_{max}^{Nujol} cm^{-1}: 3250, 1680. NMR (d_6-DMSO) δ: 0.87 (3H, t, J=7), 1.30 (3H, t, J=7), 1.2—1.9 (6H, m), 3.93 (2H, t, J=7), 3.97 (2H, q, J=7), 5.30 (1H, s), 6.7—7.0 (3H, m), 8.83 (1H, br s), 9.07 (1H, br s). *Anal.* Calcd for $C_{16}H_{22}N_2O_3S$: C, 59.61; H, 6.88; N, 8.69. Found: C, 59.70; H, 6.99; N, 8.74.

5-Aryl-2-iminothiazolidin-4-ones (**82**—**84**, Table VII) were similarly prepared. These compounds were easily hydrolyzed to thiazolidine-2,4-diones as described under method B.

5-(3-Ethoxy-4-pentylphenyl)thiazolidine-2,4-dione (**54**): A mixture of 2-(3-ethoxy-4-pentyloxyphenyl)-2-hydroxyacetic acid (2.8 g), thiourea (1.5 g), conc.HCl (3.3 ml) and 2-methoxyethanol (30 ml) was stirred at 60°C for 4 h, then 2 N HCl (15 ml) was added thereto. After refluxing for 8 h, the reaction mixture was poured into H_2O to give crystals. Recrystallization from 80% EtOH gave colorless plates (2.5 g, 78.1%), mp 106—107°C. IR ν_{max}^{Nujol} cm^{-1}: 3170, 3030, 1740, 1700. NMR δ: 0.90 (3H, t, J=7), 1.40 (3H, t, J=7),

Table IX. Substituted Mandelic Acids



No.	R^1	R^2	Yield[a] (%)	mp (°C)	Recrystn. solvent[b]	Formula[c]
95	3-C_4H_9O–,	4-C_4H_9O–	59.1	88—89	EA–H	$C_{16}H_{24}O_5$
96	3-C_2H_5O–,	4-C_4H_9O–	51.9	94—95	EA–H	$C_{14}H_{20}O_5$
97	3-C_2H_5O–,	4-iso-$C_5H_{11}O$–	60.3	90—91	EA–H	$C_{15}H_{22}O_5$

a) Overall yield from the corresponding aldehyde.
b) EA=AcOEt, H=hexane.
c) See the corresponding footnote in Table VII.

1.2—1.9 (6H, m), 3.97 (2H, t, J=7), 4.07 (2H, q, J=7), 5.27 (1H, s), 6.7—7.0 (3H, m), 8.80 (1H, br s). *Anal.* Calcd for $C_{16}H_{21}NO_4S$: C, 59.43; H, 6.55; N, 4.33. Found: C, 59.66; H, 6.65; N, 4.40.

The starting compounds used for this method were prepared as follows:

2-(3-Ethoxy-4-pentyloxyphenyl)-2-hydroxyacetic Acid: Bromoform (24.3 g) and a solution of 3-ethoxy-4-pentyloxybenzaldehyde[29] (22.7 g) in dioxane (80 ml) were added to a stirred and ice-cooled solution of KOH (21.5 g), LiCl (8.1 g) in H_2O (80 ml). The mixture was stirred at 5°C for 25 h and at 35°C for 25 h. The reaction mixture was diluted with H_2O and extracted with Et_2O. The aqueous layer was acidified with 6 N HCl and extracted with Et_2O. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated to give crystals (18.5 g, 68.3%). Recrystallization from AcOEt–hexane gave colorless needles, mp 90—91°C. IR ν_{max}^{Nujol} cm^{-1}: 3450, 1750. NMR δ: 0.91 (3H, t, J=7), 1.37 (3H, t, J=7), 1.2—2.0 (6H, m), 3.95 (2H, t, J=7), 4.02 (2H, q, J=7), 5.10 (1H, s), 6.7—7.1 (3H, m), 7.2 (2H, br s). *Anal.* Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.70; H, 8.13.

The other new mandelic acid derivatives listed in Table IX were similarly prepared.

Method K——Typical examples are given to illustrate the general procedure.

5-(3,4-Diethoxyphenyl)-2-iminothiazolidin-4-one: Conc.HCl (3.3 ml) and thiourea (1.5 g) were added to a stirred solution of ethyl 2-(3,4-diethoxyphenyl)-2-hydroxyacetate[35] (2.7 g) in 2-methoxyethanol (25 ml). The mixture was stirred at 60°C for 4 h and poured into sat. aq. $NaHCO_3$ (100 ml) to give crystals. Recrystallization from EtOH gave colorless plates (1.55 g, 55.4%), mp 222—223°C (dec.). IR ν_{max}^{Nujol} cm^{-1}: 3230, 1670. NMR (d_6-DMSO) δ: 1.30 (6H, t, J=7), 3.97 (2H, q, J=7), 4.00 (2H, q, J=7), 5.30 (1H, s), 6.7—7.0 (3H, m), 8.85 (1H, br s), 9.10 (1H, br s). *Anal.* Calcd for $C_{13}H_{16}N_2O_3S$: C, 55.70; H, 5.75; N, 9.99. Found: C, 55.49; H, 5.62; N, 9.88.

5-(2,4-Diethoxyphenyl)-2-iminothiazolidin-4-one (**80**, Table VII) was similarly prepared.

5-(3,4-Diethoxyphenyl)thiazolidine-2,4-dione (**49**): A mixture of ethyl 2-(3,4-diethoxyphenyl)-2-hydroxyacetate[35] (2.8 g), thiourea (1.5 g), conc.HCl (3.3 ml) and 2-methoxyethanol (30 ml) was stirred at 60°C for 3 h, then 2 N HCl (10 ml) was added thereto and the mixture was refluxed for 6 h. After cooling, the reaction mixture was diluted with H_2O to give **49** as crystals. Recrystallization from EtOH gave colorless prisms (2.35 g, 83.6%), mp 140—141°C. This sample was identical with an authentic sample of **49** prepared by Method I.

Method L——5-(3-Ethoxy-4-pentyloxyphenyl)thiazolidine-2,4-dione (**54**): AcOH (195.3 g, 3.26 mol) and a solution of NaCN (160 g, 3.26 mol) in H_2O (330 ml) were added dropwise to a solution of 3-ethoxy-4-pentyloxybenzaldehyde [29] (668 g, 2.83 mol) in 2-methoxyethanol (1.35 l) below 25°C. The mixture was stirred at room temperature for 30 min, then conc.HCl (1.01 l, 12.12 mol) and thiourea (237 g, 3.11 mol) were added thereto. The temperature was raised to 60°C and stirring was continued for 2 h. The reaction mixture was then refluxed for 4 h, cooled to 70°C and poured into a mixture of H_2O (3 l) and hexane–AcOEt (15: 2, v/v, 2.7 l). The whole was stirred for 10 min, then the crystalline precipitate was filtered off and recrystallized twice from EtOH (1 l) to give colorless plates (582 g, 68.3%), mp 106—107°C. This sample was identical with an authentic sample of **54** prepared by method J.

Method M——5-(3,4-Diethoxyphenyl)-5-ethylthiazolidine-2,4-dione (**50**): Compound **49** (2.8 g) and 60% NaH in oil (0.44 g) were added to a stirred solution of diisopropylamine (1.0 g) in anhydrous tetrahydrofuran (THF) (20 ml) under an N_2 atmosphere. The mixture was stirred at 50°C for 30 min and cooled to 0°C. A solution of *n*-butyllithium in hexane (1.6 M, 6.2 ml) was added dropwise thereto and the mixture was stirred at 30°C for 15 min. A solution of ethyl iodide (1.6 g) in anhydrous THF (10 ml) was then added to the above stirred mixture below 0°C. The whole was stirred at 35°C for 1 h, then 1 N HCl (40 ml) was added dropwise below 15°C and the mixture was extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated. The oily residue was chromatographed on silica gel (50 g) using AcOEt–cyclohexane (1: 4, v/v) as an eluent to give **50** as crystals (1.65 g, 53.2%). Recrystallization from Et_2O–hexane gave colorless prisms, mp 79—80°C. IR ν_{max}^{Nujol} cm^{-1}: 3170, 3060, 1730, 1680. NMR δ: 1.05 (3H, t, J=7), 1.42 (6H, t, J=7), 2.42 (2H, q, J=7), 4.15 (4H, q, J=7), 6.87 (1H, d, J=9), 7.1—7.4 (2H, m), 9.15 (1H, br s). *Anal.* Calcd for $C_{15}H_{19}NO_4S$: C, 58.24; H, 6.19; N, 4.53. Found: C, 58.04; H, 5.99; N, 4.52.

5-Ethyl-5-(3-fluorophenyl)thiazolidine-2,4-dione (**15**): Compound **15** was similarly prepared by reaction of **14** with ethyl iodide. mp 90—91°C (from Et_2O–hexane). Yield 54.2%. IR ν_{max}^{Nujol} cm^{-1}: 3175, 3050, 1740, 1690. NMR δ: 1.10 (3H, t, J=7), 2.45 (2H, q, J=7), 7.3—7.6 (4H, m), 9.25 (1H, br s). *Anal.* Calcd for $C_{11}H_{10}FNO_2S$: C, 55.22; H, 4.21; N, 5.85. Found: C, 55.28; H, 4.20; N, 5.75.

Method N——5-(4-Aminophenyl)thiazolidine-2,4-dione (**20**): A mixture of **19** (5.0 g), 10% Pd–C (50% wet, 8.0 g) and MeOH (150 ml) was hydrogenated at room temperature and atmospheric pressure. The catalyst was filtered off and the filtrate was concentrated *in vacuo* to give crystals (2.5 g, 56.8%). Recrystallization from MeOH gave colorless prisms, mp 206—207°C. IR ν_{max}^{Nujol} cm^{-1}: 3475, 3370, 3150, 1735, 1670. NMR (d_6-DMSO) δ: 5.47 (1H, s), 6.47 (2H, d, J=9), 6.95 (2H, d, J=9), 6.5—8.2 (3H, br). *Anal.* Calcd for $C_9H_8N_2O_2S$: C, 51.92; H, 3.87; N, 13.46. Found: C, 52.11; H, 3.90; N, 13.38.

Method O——5-(4-Acetamidophenyl)thiazolidine-2,4-dione (**21**): A mixture of **20** (0.5 g), Ac_2O (0.3 ml) and pyridine (10 ml) was allowed to stand at room temperature overnight, diluted with H_2O, dried ($MgSO_4$) and concentrated *in vacuo* to give crystals (0.47 g, 78.3%). Recrystallization from MeOH gave colorless rods, mp 225—226°C. IR ν_{max}^{Nujol} cm^{-1}: 3300, 3170, 3030, 1745, 1685, 1660. NMR (d_6-DMSO) δ: 2.0 (3H, s),

5.62 (1H, s), 7.17 (2H, d, $J=9$), 7.42 (2H, d, $J=9$), 9.83 (1H, br s), 12.0 (1H, br s). *Anal.* Calcd for $C_{11}H_{10}N_2O_3S$: C, 52.80; H, 4.03; N, 11.20. Found: C, 52.85; H, 4.09; N, 11.01.

5-(3,4-Diacetoxyphenyl)thiazolidine-2,4-dione (**39**): Similar acetylation of **38** gave **39** in 82.9% yield. mp 134—135°C (from AcOEt–hexane). IR ν_{max}^{Nujol} cm^{-1}: 3180, 3070, 1760, 1720, 1700. NMR δ: 2.27 (6H, s), 5.23 (1H, s), 7.35 (3H, m), 8.7 (1H, br s). *Anal.* Calcd for $C_{13}H_{11}NO_6S$: C ,50.48; H, 3.58; N, 4.53. Found: C, 50.44; H, 3.54; N, 4.54.

5-(4-Acetoxy-3-ethoxyphenyl)thiazolidine-2,4-dione (**40**): Similar acetylation of **48** gave **40** in 84.7% yield. mp 120—121°C (from AcOEt–hexane). IR ν_{max}^{Nujol} cm^{-1}: 3170, 3070, 1750, 1730, 1710. NMR δ: 1.48 (3H, t, $J=7$), 2.30 (3H, s), 4.17 (2H, q, $J=7$), 5.40 (1H, s), 7.3 (3H, m), 9.10 (1H, br s). *Anal.* Calcd for $C_{13}H_{13}NO_5S$: C, 52.87; H, 4.44; N, 4.74. Found: C, 52.89; H, 4.49; N, 4.94.

Method P——5-(4-Carboxyphenyl)thiazolidine-2,4-dione (**22**): A mixture of 5-(4-ethoxycarbonylphenyl)thiazolidine-2,4-dione (1.7 g) and 2 N NaOH (20 ml) was stirred at 60°C for 1 h, cooled, acidified with 2 N HCl and extracted with AcOEt. The usual work-up gave **22** as crystals (0.98 g, 65.8%). Recrystallization from MeOH–Et_2O gave colorless prisms, mp 252—253°C (dec.). IR ν_{max}^{Nujol} cm^{-1}: 3300—3000, 1740, 1710. NMR (d_6-DMSO) δ: 5.47 (1H, s), 7.40 (2H, d, $J=9$), 7.93 (2H, d, $J=9$). *Anal.* Calcd for $C_{10}H_7NO_4S$: C, 50.63; H, 2.97; N, 5.90. Found: C, 50.57; H, 2.97; N, 5.75.

The starting material used for this method was prepared as follows:

2-Chloro-2-(4-ethoxycarbonylphenyl)acetonitrile: AcOH (10.4 g) and a solution of NaCN (6.4 g) in H_2O (20 ml) were added to a stirred and ice-cooled solution of 4-ethoxycarbonylbenzaldehyde (15.5 g) in EtOH (200 ml). After being stirred for 1 h with ice-cooling, the mixture was poured into H_2O and extracted with Et_2O. The usual work-up gave 2-(4-ethoxycarbonylphenyl)-2-hydroxyacetonitrile (18.4 g) as a crude oil. IR ν_{max}^{neat} cm^{-1}: 3420. NMR δ: 1.33 (3H, t, $J=7$), 4.32 (2H, q, $J=7$), 4.70 (1H, br s), 5.53 (1H, s), 7.45 (2H, d, $J=9$), 7.93 (2H, d, $J=9$). The oil was dissolved in $CHCl_3$ (50 ml) and thionyl chloride (15 ml) was added thereto. The mixture was refluxed for 1 h and concentrated *in vacuo*. The residue was extracted with Et_2O. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated to give the title compound (17.4 g) as a crude oil. IR ν_{max}^{neat} cm^{-1}: 1715. NMR δ: 1.40 (3H, t, $J=7$), 4.47 (2H, q, $J=7$), 5.67 (1H, s), 7.58 (2H, d, $J=9$), 8.08 (2H, d, $J=9$).

5-(4-Ethoxycarbonylphenyl)thiazolidine-2,4-dione: A mixture of 2-chloro-2-(4-ethoxycarbonylphenyl)-acetonitrile (17.4 g), thiourea (7.6 g) and EtOH (100 ml) was refluxed for 1 h, then 6 N HCl (100 ml) was added thereto. The mixture was refluxed for 20 h, cooled, diluted with H_2O and extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated to leave an oil. Purification by column chromatography on silica gel (200 g) using AcOEt–hexane (1: 3, v/v) as an eluent gave crystals (7.5 g, 36.2%). Recrystallization from Et_2O gave colorless prisms, mp 103—104°C. IR ν_{max}^{Nujol} cm^{-1}: 3170, 1750, 1710, 1690. NMR δ: 1.37 (3H, t, $J=7$), 4.40 (2H, q, $J=7$), 5.40 (1H, s), 7.49 (2H, d, $J=9$), 8.11 (2H, d, $J=9$), 9.33 (1H, br s). *Anal.* Calcd for $C_{12}H_{11}NO_4S$: C, 54.33; H, 4.12; N, 5.32. Found: C, 54.38; H, 4.17; N, 5.43.

Method Q——5-(4-Hydroxyphenyl)thiazolidine-2,4-dione (**23**): Boron tribromide (1 ml) was added to a stirred solution of **24** (0.71 g) in $CHCl_3$ (30 ml), and the mixture was stirred at room temperature for 30 min, then refluxed for 1 h. After cooling, the mixture was poured into H_2O and extracted with $CHCl_3$. The usual work-up gave crystals. Recrystallization from MeOH gave colorless prisms of **23** (0.35 g, 56.0%), mp 239—240°C. IR ν_{max}^{Nujol} cm^{-1}: 3340, 3210, 1710, 1670. NMR (d_6-DMSO) δ: 5.73 (1H, s), 6.90 (2H, d, $J=9$), 7.35 (2H, d, $J=9$), 9.70 (1H, br s), 11.90 (1H, br s). *Anal.* Calcd for $C_9H_7NO_3S$: C, 51.67; H, 3.37; N, 6.69. Found: C, 51.91; H, 3.30; N, 6.74.

5-(3,4-Dihydroxyphenyl)thiazolidine-2,4-dione (**38**): Compound **38** was similarly prepared by reaction of **48** with boron tribromide. mp 186—187°C (dec.) (from AcOEt–hexane). Yield 72.2%. IR ν_{max}^{Nujol} cm^{-1}: 3450, 3400, 3100, 3050, 1730, 1690. NMR (d_6-DMSO) δ: 5.67 (1H, s), 6.8 (3H, m), 9.17 (3H, br). *Anal.* Calcd for $C_9H_7NO_4S$: C, 48.00; H, 3.13; N, 6.22. Found: C, 47.77; H, 3.15; N, 6.11.

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