[Chem. Pharm. Bull. 30(10)3580—3600(1982)]

Studies on Antidiabetic Agents. II.[1] Synthesis of 5-[4-(1-Methylcyclohexylmethoxy)-benzyl]thiazolidine-2,4-dione (ADD-3878) and Its Derivatives

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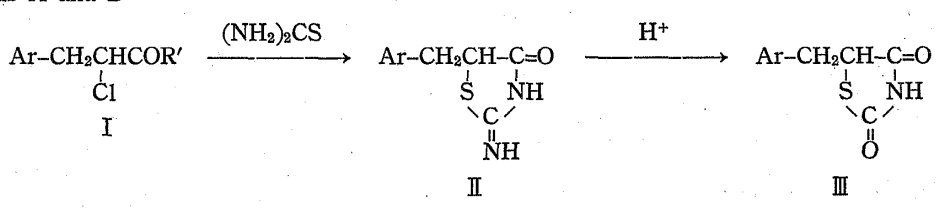
More than 100 5-substituted thiazolidine-2,4-diones were prepared and their hypoglycemic and hypolipidemic activities were evaluated with genetically obese and diabetic mice, yellow KK. The structure–activity relationship study showed that the 5-(4-oxybenzyl) moiety is essential for substantial activity. Among these compounds, 5-(4-cyclohexylmethoxy)benzylthiazolidine-2,4-dione (**47**), 5-[4-(1-methylcyclohexylmethoxy)benzyl]-thiazolidine-2,4-dione (**49**, ADD-3878) and 5-{4-[2-(3-pyridyl)ethoxy]benzyl}thiazolidine-2,4-dione (**59**) exhibited the most favorable properties in terms of activity and toxicity.

Keywords——5-benzylthiazolidine-2,4-dione; hypoglycemic activity; hypolipidemic activity; genetically obese and diabetic mice (yellow KK); structure–activity relationship

In the preceding paper,[1] we reported that 5-[4-(2-methyl-2-phenylpropoxy)benzyl]-thiazolidine-2,4-dione (**1**, AL-321), prepared from ethyl 2-chloro-3-[4-(2-methyl-2-phenylpropoxy)phenyl]propionate by reaction with thiourea followed by acid hydrolysis, had potent hypoglycemic and hypolipidemic activities. The present paper reports chemical modifications of the substituents at the 5-position of the thiazolidine ring in **1** and their effects on the pharmacological activities. 5-Benzylthiazolidine-2,4-diones bearing the 4-oxy group in the benzyl moiety, *i.e.*, **1**—**73**, were prepared to investigate the structure–activity relationships. The synthesis and activities of 5-(4-aminobenzyl)- and 5-(2-alkoxy-5-pyridylmethyl)thiazolidine-2,4-dione derivatives, *i.e.*, **74**—**83** and **92**—**101**, respectively, are also described.

Chemistry

Most of the thiazolidine-2,4-dione derivatives listed in Tables I—VII were prepared by the method shown in Chart 1. The reaction of 3-aryl-2-chloropropionic acids (I) with thiourea afforded the imino compounds (II), which either were (method A) or were not (method B) isolated, then subjected to acid hydrolysis to obtain the desired thiazolidine-2,4-diones (III).

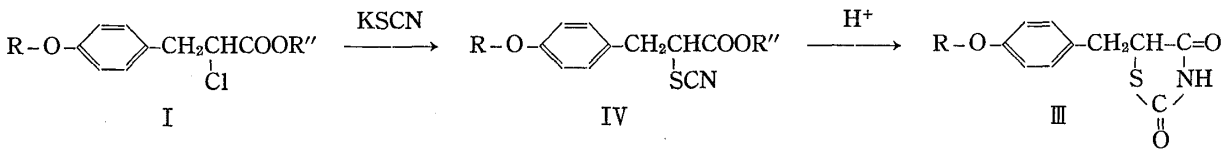


Ar = substituted phenyl, 2-alkoxy-5-pyridyl

Chart 1

Although the 3-aryl-2-chloropropionic acid derivatives (I) used in this reaction include esters, amides and sodium or ammonium salts as well as the free acids, the methyl or ethyl esters were mainly used in this study. Compounds III were also prepared by the methods shown in Chart 2 (methods C and D).[1,2]

method C



method D

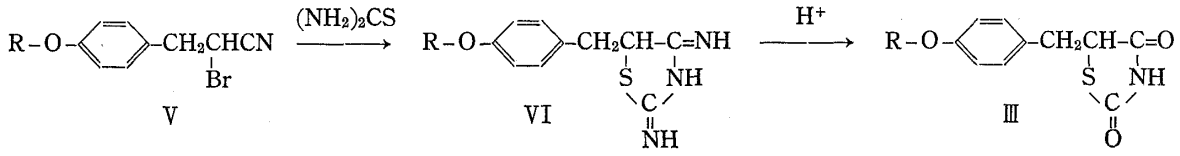
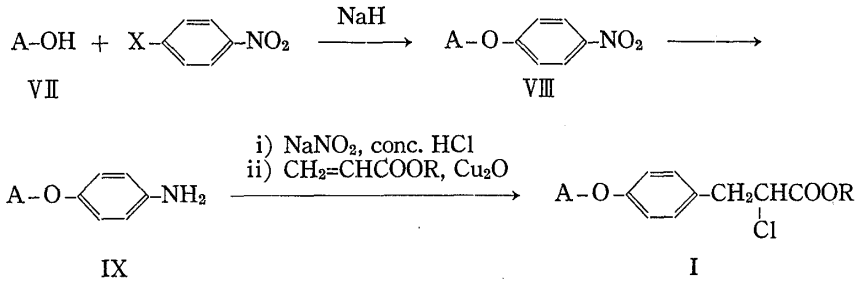
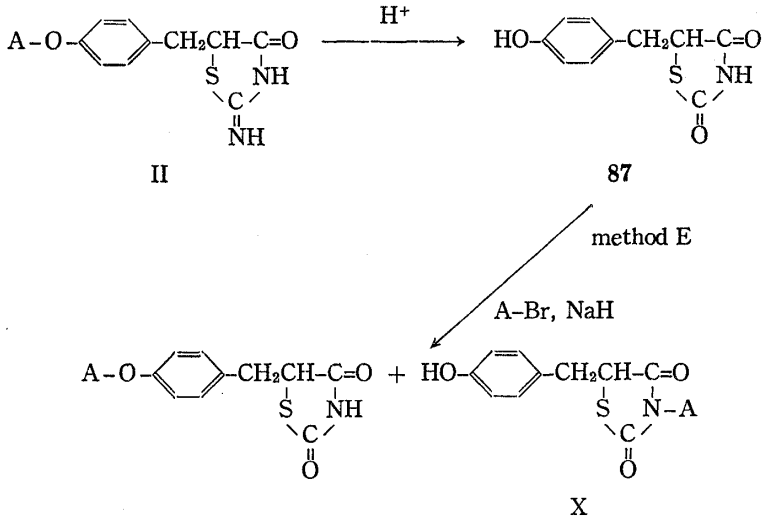


Chart 2



X=Cl, F R=Me, Et

Chart 3



41: A=geranyl **42**: A=phytyl

Chart 4

The starting compounds (I) with 4-oxy substituents were prepared by the general process shown in Chart 3, which includes the Meerwein arylation reaction (*i.e.*, IX→I), as described previously.[1,3]

As shown in Chart 4, acid hydrolysis of the imino compound (II) bearing a geranyloxy or phytyloxy group resulted in concomitant cleavage of the ether linkage to yield a phenolic compound **87** (Table VI). Compounds **41** and **42** (Table III) were therefore prepared by *O*-alkylation of **87** (method E). In this method, the *N*-alkylated compound (X) was isolated as a by-product (Chart 4).

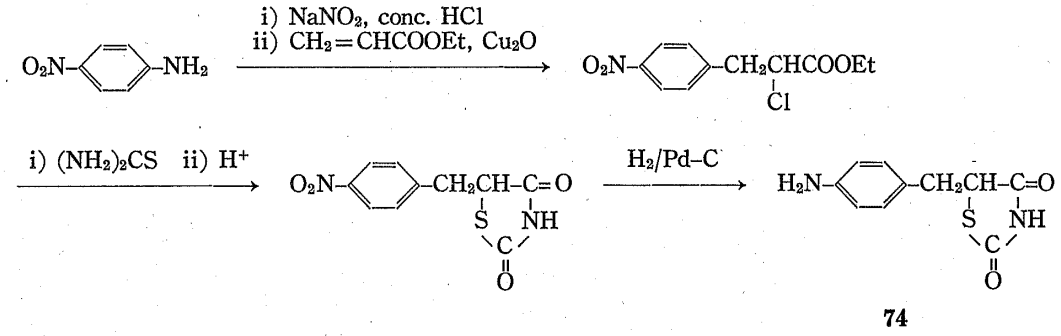


Chart 5

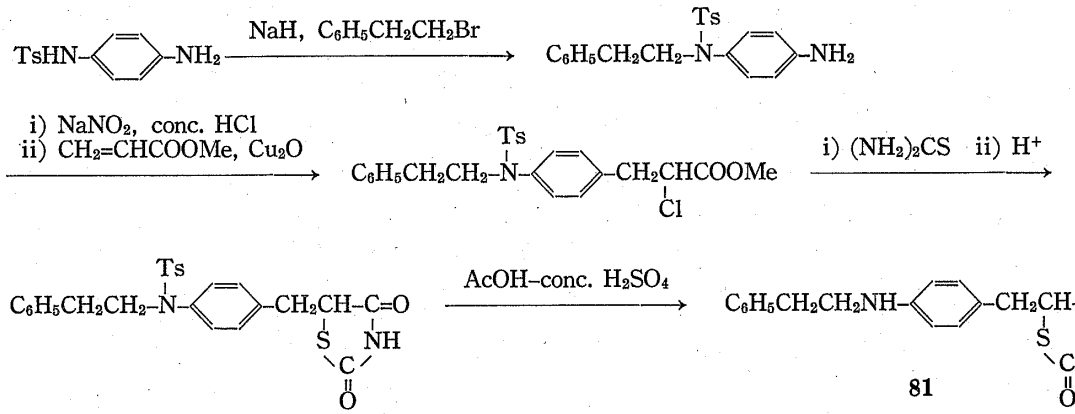


Chart 6

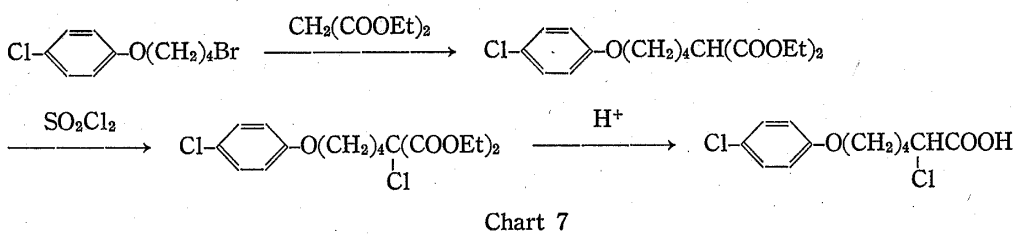


Chart 7

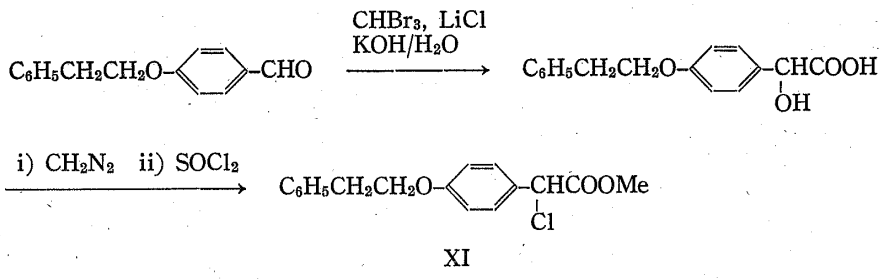
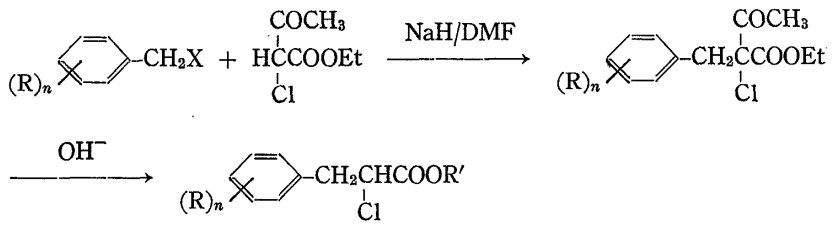


Chart 8

Compound **64** (Table IV) was prepared by concomitant hydrolysis of the 2-imino group on the thiazolidine ring and the *N*-benzoyl group on the pyrrolidine ring of the corresponding imino compound (II) (method F).

A series of compounds listed in Table V (except **81**) was prepared from **74**, which was derived starting from *p*-nitroaniline as shown in Chart 5.

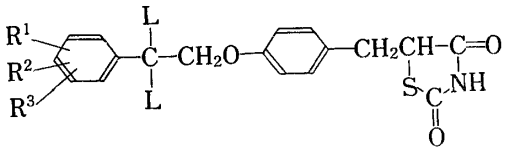
Appropriate acylation of **74** gave the corresponding 5-(4-acylaminobenzyl)thiazolidine-2,4-diones (**76**, **77** and **82**). Reaction of **74** with *p*-toluenesulfonyl chloride, ethoxycarbonylmethylisocyanate and bis(2-chloroethyl)amine afforded **75**, **80** and **83**, respectively. Conden-



$(R)_n$=4-$(CH_3)_3CCO$-, 3,4-$(CH_3O)_2$-, 2,4,5-$(C_2H_5O)_3$-
R′=H, Et
X=Cl, Br

Chart 9

TABLE I. Physical and Biological Properties of Thiazolidine -2,4-dione Derivativaties



No.	L	R^1	R^2	R^3	Method[a]	Yield[b] (%)	mp (°C)	Recrystn. solvent[c]	Formula[d]	Hypoglycemic activity[e]	Plasma triglyceride-lowering activity[e]
1 (AL-321)	CH_3	H	H	H	A	88.7	110—111	Et–W	$C_{20}H_{21}NO_3S$	3	3
					B	80.8					
					C	72.5					
					D	70.4					
2	CH_3	4-CH_3	H	H	B	86.3	110—111	E–H	$C_{21}H_{23}NO_3S$	2	2
3	CH_3	2-CH_3O	H	H	B	77.8	116—117	E–H	$C_{21}H_{23}NO_4S$	3	2
4	CH_3	3-CH_3O	H	H	B	81.4	68—69	E–H	$C_{21}H_{23}NO_4S$	3	2
5	CH_3	4-CH_3O	H	H	B	58.1	107—108	E–H	$C_{21}H_{23}NO_4S$	1	2
6	CH_3	4-C_2H_5	H	H	B	63.7	104—105	E–H	$C_{22}H_{25}NO_3S$	3	1
7	CH_3	4-C_2H_5O	H	H	B	81.7	92—93	E–H	$C_{22}H_{25}NO_4S$	3	3
8	CH_3	4-OH	H	H	B	67.2	157—158	E	$C_{20}H_{21}NO_4S$	1	3
9	CH_3	3-CH_3O	4-CH_3O	H	B	69.4	106—107	E–H	$C_{22}H_{25}NO_5S$	1[f]	1[f]
10	H	H	H	H	B	69.2	93—94	B–L	$C_{18}H_{17}NO_3S$	3	4
11	H	4-CH_3	H	H	B	77.8	130—131	EA–H	$C_{19}H_{19}NO_3S$	3	2
12	H	2-CH_3O	H	H	B	59.3	72—73	A–H	$C_{19}H_{19}NO_4S$	3	4
13	H	4-CH_3O	H	H	B	71.0	104—105	EA–H	$C_{19}H_{19}NO_4S$	3	3
14	H	4-C_2H_5	H	H	B	78.5	87—88	E–H	$C_{20}H_{21}NO_3S$	3	2
15	H	4-C_2H_5O	H	H	B	79.5	102—103	EA–H	$C_{20}H_{21}NO_3S$	3	4
16	H	4-Cl	H	H	B	87.7	148—149	EA	$C_{18}H_{16}ClNO_3S$	3	3
17	H	2-CH_3O	4-CH_3	H	B	78.9	92—93	EA–H	$C_{20}H_{21}NO_4S$	3	1
18	H	3-CH_3O	4-CH_3O	H	B	70.0	110—111	EA–H	$C_{20}H_{21}NO_5S$	3	4
19	H	3-CH_3O	4-CH_3O	5-CH_3O	B	43.8	109—110	EA–H	$C_{21}H_{23}NO_6S$	3	2
20	H	3,4-OCH_2O-		H	B	73.1	132—133	EA–H	$C_{19}H_{17}NO_5S$	3	3

a) See "Experimental".
b) Overall yield from the corresponding 2-iminothiazolidin-4-one (II) (method A), 2-chloro-3-arylpropionic acid (I) (method B), 3-aryl-2-thiocyanatopropionate (IV) (method C) or 2-bromo-3-arylpropionitrile (V) (method D).
c) A=acetone, B=C_6H_6, C=$CHCl_3$, Cy=cyclohexane, Et=EtOH, H=hexane, IPE=isopropyl ether, L=ligroin, M=MeOH, PE=petroleum ether, Pr=propanol, 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.
e) Maximum reductions in blood glucose and plasma triglyceride levels at the dosage of 0.1% (w/w) in the diet were calculated as percentage with respect to the control value; 70—89% reduction=4, 50—69% reduction=3, 30—49% reduction=2, 10—29% reduction=1, less than 9% reduction=0.
f) The dosage 0.02% (w/w).

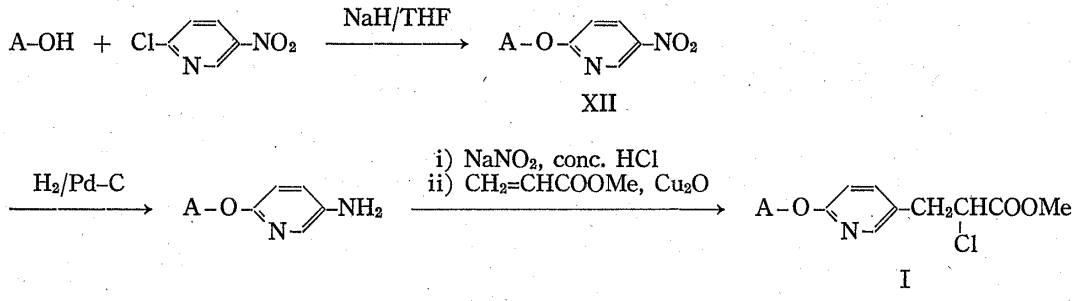
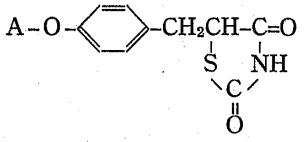
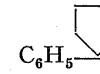


Chart 10

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



No.	A	Method[a]	Yield[b] (%)	mp (°C)	Recrystn. solvent[c]	Formula[d]	Hypoglycemic activity[e]	Plasma triglyceride-lowering activity[e]
21	C_6H_5–	B	23.4	118—119	B–H	$C_{16}H_{13}NO_3S$	1	1
10	$C_6H_5CH_2CH_2$–						3	4
22	$C_6H_5CH_2CH_2CH_2$–	B	48.9	79—80	EA–Cy	$C_{19}H_{19}NO_3S$	2	1
		C	75.6					
23	$C_6H_5CH_2CH_2CH_2CH_2$–	B	38.4	82—83	EA–Cy	$C_{20}H_{21}NO_3S$	2	1
24	$C_6H_5CH(CH_3)CH_2$–	B	78.5	Oil[f]	—	$C_{19}H_{19}NO_3S$	3	2
25	$C_6H_5CH_2CH(CH_3)$–	B	76.7	84—85	E–H	$C_{19}H_{19}NO_3S$	3	3
1	$C_6H_5(CH_3)_2CH_2$– (AL-321)						3	3
26	$C_6H_5CH_2C(CH_3)_2CH_2$–	B	85.8	107—108	EA–H	$C_{21}H_{23}NO_3S$	3	2
		C	71.1					
27	$(C_6H_5)_2CHCH_2$–	B	77.0	162—163	Et	$C_{24}H_{22}NO_3S$	1	1
28	$(C_6H_5)_2C(CH_3)CH_2$–	B	80.8	Oil[f]	—	$C_{25}H_{24}NO_3S$	2	3
29		B	51.0	136—137	B–L	$C_{22}H_{23}NO_3S$	3	1
30	3-Cl–C_6H_4–	B	44.6	89—90	EA–H	$C_{16}H_{12}ClNO_3S$	2	1
31	4-Cl–$C_6H_4CH_2$–	B	64.7	135—136	B–Cy	$C_{17}H_{14}ClNO_3S$	2	2
32	2-Cl–C_6H_4–CH_2–	B	33.0	85—86	B–H	$C_{17}H_{14}ClNO_3S$	3	2
33	3,4-$(OCH_3)_2$–$C_6H_3CH_2$–	B	44.0	176—177	C	$C_{19}H_{19}NO_5S$	1	1

a—*e*) See the corresponding footnotes in Table I.
f) Purified by column chromatography.

sation of **74** with *N*-protected ω-aminoalkanoic acids by the mixed anhydride method followed by deprotection yielded **78** and **79** (see "Experimental"). Compound **81** was prepared by the method illustrated in Chart 6.

2-Chloro-6-(4-chlorophenoxy)hexanoic acid required for the preparation of **84** was prepared by the method illustrated in Chart 7.

Methyl 2-chloro-2-(4-phenethyloxyphenyl)acetate (XI) required for the preparation of **85** (Table VI) was obtained from the corresponding aldehyde as shown in Chart 8.[4]

The starting 3-aryl-2-chloropropionic acids (I) for the preparations of **86** to **88** and **89** to **91** were obtained by the above-mentioned Meerwein arylation reaction of the corresponding aniline derivatives and the method shown in Chart 9, respectively.

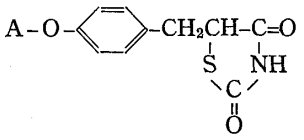
A series of 5-(2-substituted-5-pyridylmethyl)thiazolidine-2,4-dione derivatives (**92**—**101**)

listed in Table VII was prepared by method B, and the starting 3-(2-alkoxy-5-pyridyl)-2-chloropropionic acids (I) were prepared according to the route shown in Chart 10 using 2-chloro-5-nitropyridine.

Biological Method

Genetically obese and diabetic mice, yellow KK[5] (male, 9 weeks old), were used. After prefeeding on a laboratory chow (CE-2, CLEA Japan) for 3 d, they were allocated to experimental groups of five mice each, so that the average blood glucose of each group was the same. The test compounds at 0.1% or 0.02% concentration, were mixed thoroughly with the powdered

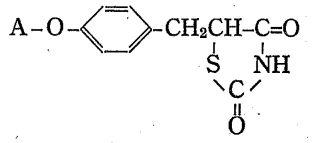
TABLE III. Physical and Biological Properties of Thiazolidine-2,4-dione Derivatives

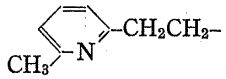
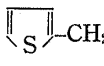
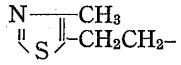
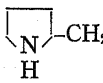
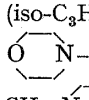
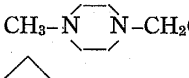


No.	A	Method[a]	Yield[b] (%)	mp (°C)	Recrystn. solvent[c]	Formula[d]	Hypoglycemic activity[e]	Plasma triglyceride-lowering activity[e]
34	$CH_3(CH_2)_4CH_2-$	B	53.3	55—56	EA–H	$C_{16}H_{21}NO_3S$	1	1
35	$(CH_3)_2CHCH_2-$	B	64.0	91—92	EA–H	$C_{14}H_{17}NO_3S$	1	1
36	$(CH_3)_3CCH_2-$	B	62.0	101—102	E–H	$C_{16}H_{21}NO_3S$	2	3
		C	73.5					
37	$CH_3CH_2C(CH_3)_2CH_2-$	B	76.9	128—129	IPE	$C_{16}H_{21}NO_3S$	3	1
38	$CH_3(CH_2)_2C(CH_3)_2CH_2-$	B	66.7	103—104	E–H	$C_{17}H_{23}NO_3S$	2	2
39	$CH_3(CH_2)_3C(CH_3)_2CH_2-$	B	72.6	102—103	Cy	$C_{18}H_{25}NO_3S$	3	2
40	$CH_3(CH_2)_4C(CH_3)_2CH_2-$	B	65.2	101—102	Cy	$C_{19}H_{27}NO_3S$	2	2
41	Geranyl-	E	50.0[f]	55—56	Cy–H	$C_{20}H_{25}NO_3S$	1	0
42	Phytyl-	E	40.9[f]	31—33	H	$C_{30}H_{47}NO_3S$	0	1
43	$CH_2=CH-CH_2C(CH_3)_2CH_2-$	B	73.6	99—100	Cy	$C_{17}H_{21}NO_3S$	2	0
44	Geranyl-$C(CH_3)_2CH_2-$	B	78.4	Oil[g]	—	$C_{24}H_{33}NO_3S$	1	0
45		B	55.4	86—87	E–H	$C_{14}H_{15}NO_3S$	3	1
46		A	89.0	140—141	Et–W	$C_{16}H_{19}NO_3S$	1[h]	1[h]
		D	77.5					
47		A	87.3	120—121	Pr	$C_{17}H_{21}NO_3S$	2	3
48		B	67.1	82—83	Cy	$C_{18}H_{23}NO_3S$	2	2
49	 (ADD-3878)	A	88.3	130—131	Et	$C_{18}H_{23}NO_3S$	3	2
		B	57.3					
		C	70.3					
		D	80.0					
50		A	78.5	88—89	H	$C_{19}H_{25}NO_3S$	2	1
51		A	90.4	Oil[g]	—	$C_{20}H_{27}NO_3S$	3	2
52		A	89.2	137—138	B–L	$C_{17}H_{21}NO_3S$	3	2
53	Isobornyl-	A	68.5	153—154	Et–W	$C_{20}H_{25}NO_3S$	2	2
54	Bornyl-	A	71.3	144—145	L	$C_{20}H_{25}NO_3S$	2	1
55	*l*-Menthyl	A	87.4	87—88	H	$C_{20}H_{27}NO_3S$	1	1

a—*e*) See the corresponding footnotes in Table I.
f) Yield from **87**.
g) Purified by column chromatography.
h) The dosage 0.02% (w/w).

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



No.	A	Method[a]	Yield[b] (%)	mp (°C)	Recrystn. solvent[c]	Formula[d]	Hypoglycemic activity[e]	Plasma triglyceride-lowering activity[e]
56		B	55.6	183—184	C–M	$C_{16}H_{14}N_2O_3S$	3	3
57		B	38.4	209—210	DMF–W	$C_{17}H_{16}N_2O_3S$	3	2
58		B	42.7	103—104	EA–H	$C_{18}H_{18}N_2O_3S \cdot 1/2H_2O$	3	4
59		B	51.6	175—176	C–M	$C_{17}H_{16}N_2O_3S$	3[g]	2[g]
60		B	77.8	176—177	C–M	$C_{18}H_{18}N_2O_3S$	3	2
61		B	54.3	73—74	E–H	$C_{16}H_{15}NO_3S_2$	3	2
62		B	28.5	63—64	E–H	$C_{16}H_{15}NO_4S$	2	2
63		B	45.0	193—194	Et	$C_{16}H_{16}N_2O_3S_2$	3	3
64		F	33.3[f]	163—164	E–A	$C_{15}H_{18}N_2O_3S \cdot HCl$	1	1
65	$(CH_3)_2CHNH-CH_2CH_2-$	B	42.9	229—231	M–E	$C_{15}H_{20}N_2O_3S \cdot HCl$	1	1
66	$(CH_3)_3CNH-CH_2CH_2-$	B	52.9	260—261	Et	$C_{16}H_{22}N_2O_3S \cdot HCl$	1	1
67	$(C_2H_5)_2N-CH_2CH_2-$	B	64.3	151—152	A–E	$C_{16}H_{22}N_2O_3S \cdot HCl$	2	1
68	$(C_3H_7)_2N-CH_2CH_2-$	B	61.5	124—125	E	$C_{18}H_{26}N_2O_3S$	2	1
69	$(iso\text{-}C_3H_7)_2N-CH_2CH_2-$	B	65.2	134—135	Et	$C_{18}H_{26}N_2O_3S$	1[g]	2[g]
70		A	92.7	188—189	DMF–W	$C_{16}H_{20}N_2O_4S$	3[g]	2[g]
71		B	31.3	215—217	Et–W	$C_{17}H_{23}N_3O_3S \cdot 2HCl \cdot 1/2H_2O$	1	1
72		B	16.2	232—234	M	$C_{16}H_{20}N_2O_3S \cdot HCl$	3	3
73		B	80.3	244—245	M	$C_{17}H_{22}N_2O_3S \cdot HCl$	3	4

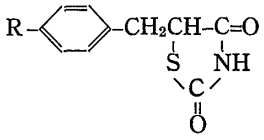
a—*e*) See the corresponding footnotes in Table I.

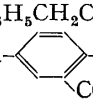
f) Overall yield from methyl 3-[4-(1-benzoyl-2-pyrrolidinylmethoxy)phenyl]-2-chloropropionate (Table X).

g) The dosage 0.02% (w/w).

CE-2 diet. The mice were fed the experimental diet and water *ad libitum* for 4 d. Blood samples were taken from orbital vein. Blood glucose and plasma triglyceride were determined by the glucose oxidase method[6] and the method of Fletcher,[7] respectively. The maximum decreases of blood glucose and plasma triglyceride levels were calculated as percentage change from the control value.

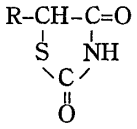
TABLE V. Physical and Biological Properties of Thiazolidine-2,4-dione Derivatives

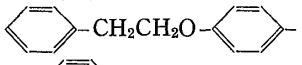
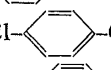
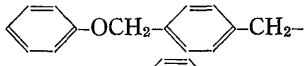


No.	R	Yield[a] (%)	mp (°C)	Recrystn. solvent[b]	Formula[c]	Hypoglycemic activity[d]	Plasma triglyceride lowering activity[d]
74	H_2N–	88.6[e]	162—163	M	$C_{10}H_{10}N_2O_2S$	2	1
75	CH_3–  –SO_2NH–	95.6	224—225	M	$C_{17}H_{16}N_2O_4S_2$	2	1
76	CH_3CH_2CONH–	55.8	140—141	EA	$C_{13}H_{14}N_2O_3S$	2	1
77	 –CONH–	30.6	271—272	DMF–W	$C_{16}H_{13}N_3O_3S$	1	1
78	$H_2NCH_2CH_2CONH$–	44.6	242—243	M	$C_{13}H_{15}N_3O_3S \cdot HBr$	0	0
79	$H_2N(CH_2)_5CONH$–	47.9	216—218	DMF–E	$C_{16}H_{21}N_3O_3S$	0	0
80	$C_2H_5OCOCH_2NHCONH$–	30.7	161—162	Et	$C_{15}H_{17}N_3O_5S$	0	0
81	$C_6H_5CH_2CH_2NH$–	63.4	156—157	A	$C_{18}H_{18}N_2O_2S \cdot HCl$	1	1
82	Cl–  –OCH_3  –CONH–	48.4	221—222	M	$C_{18}H_{15}ClN_2O_4S$	1	0
83		6.2	221—223	M	$C_{14}H_{17}N_3O_2S \cdot 1/2H_2O$	0	0

a) Yield from **74**.
b—*d*) See footnotes *c*), *d*) and *e*) in Table I, respectively.
e) Yield from 5-(4-nitrobenzyl)thiazolidine-2,4-dione.

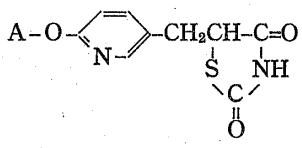
TABLE VI. Physical and Biological Properties of Thiazolidine-2,4-dione Derivatives

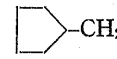
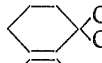
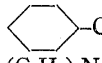
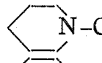
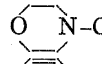
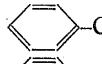
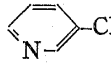
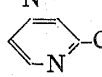


No.	R	Method[a]	Yield[b] (%)	mp (°C)	Recrystn. solvent[c]	Formula[d]	Hypoglycemic activity[e]	Plasma triglyceride-lowering activity[e]
84	Cl–  –$O(CH_2)_4$–		66.7[f]	79—80	EA–H	$C_{13}H_{14}ClNO_3S$	1	0
85			55.6[g]	118—119	EA–H	$C_{17}H_{15}NO_3S$	0	0
86	Cl–  –CH_2–	B	39.0	110—111	B–H	$C_{10}H_8ClNO_2S$	0	0
87	HO–  –CH_2–	B	60.7	159—160	EA–H	$C_{10}H_9NO_3S$	0	0
88		B	47.5	133—134	EA–H	$C_{17}H_{15}NO_3S$	1	2
89	$(CH_3)_3CCO$–  –CH_2–	B	64.6	173—174	Et	$C_{15}H_{17}NO_3S$	2	0
90	CH_3O–  –CH_2– 	B	80.4	162—164	M	$C_{12}H_{13}NO_4S$	1	1
91		B	81.4	104—105	EA–H	$C_{16}H_{21}NO_5S$	0	0

a—*e*) See the corresponding footnotes in Table I.
f) Yield from 2-chloro-6-(4-chlorophenoxy)hexanoic acid.
g) Yield from methyl 2-chloro-2-(4-phenethyloxyphenyl)acetate (XI).

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



No.	A	Yield[a] (%)	mp (°C)	Recrystn. solvent[b]	Formula[c]	Hypoglycemic activity[d]	Plasma triglyceride-lowering activity[d]
92		45.1	147—148	Et	$C_{15}H_{18}N_2O_3S \cdot HCl$	1[e]	1[e]
93		25.7	124—125	Et	$C_{15}H_{18}N_2O_3S$	1[e]	1[e]
94		47.3	141—142	Et	$C_{17}H_{22}N_2O_3S \cdot HCl$	3	2
95		42.2	86—87	E–PE	$C_{17}H_{22}N_2O_3S$	2	1
96	$(C_4H_9)_2N-CH_2CH_2-$	59.8	100—101	EA–H	$C_{19}H_{29}N_3O_3S$	1	1
97		29.6	161—162	Et	$C_{16}H_{21}N_3O_3S$	1[e]	1[e]
98		41.0	202—203	C–M	$C_{15}H_{19}N_3O_4S$	1	1
99		36.8	75—77	EA–L	$C_{17}H_{16}N_2O_3S$	3	4
100		54.5	165—166	M	$C_{16}H_{15}N_3O_3S$	3	2
101		4.4	167—168	Et	$C_{16}H_{15}N_3O_3S$	3[e]	3[e]

a) Yield from the corresponding methyl 3-(2-alkoxy-5-pyridyl)-2-chloropropionate. Prepared by method B.
b—*d*) See footnotes *c*), *d*) or *e*) in Table I, respectively.
e) The dosage 0.02% (w/w).

Results and Discussion

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

Since compound **1** (AL-321) was first found to possess potent hypoglycemic and hypolipidemic activities,[1] various compounds having modified phenethyl moieties, as shown in Table I, have been synthesized. All the compounds, especially **12**, **15** and **18**, had pronounced hypoglycemic and hypolipidemic activities. Although slight potentiation of the biological activity was noted when the methyl groups on the side chain of **1** were removed (**1** *vs.* **10**), introduction of substituent(s) on the benzene ring of the phenethyl moiety did not alter the activities (**1** *vs.* **2**—**9**, **10** *vs.* **11**—**20**).

Variation of the distance between the two benzene rings as listed in Table II indicated that the two-carbon unit was the most effective for eliciting the activity (**1**, **10**, **24**, **25**>**21**, **23**, **26**; **16**>**31**; **18**>**33**).

Among the compounds listed in Tables I and II, compounds **10**, **12**, **15**, **18** and **25** showed more potent activities than **1**, but these compounds caused considerable increases in relative liver weight and liver lipid at high dose levels or on chronic administration. As this undesirable effect may have been a consequence of the existence of two benzene rings in the molecule, we replaced one of them with other moieties.

First, the phenethyl group of **10** was replaced by various alkyl groups. Such compounds, listed in Table III, exhibited good activities with reduced side effects. In particular, **49** (ADD-3878) showed a pronounced hypoglycemic effect and extremely low toxicity, though

its triglyceride lowering effect was not prominent. Compound **49** (ADD-3878) might therefore have potential utility as an antidiabetic drug. Compound **52** was as effective as but more toxic than **49** (ADD-3878). Compound **47** also showed good activities with low toxicity.

A series of compounds bearing less lipophilic groups (*i.e.*, pyridylalkyl, aminoalkyl, *etc.*) instead of aralkyl or alkyl groups was next investigated. Although compounds **56**, **57**, **58**, **59** and **63** in Table IV showed potent activities, they, especially **57** and **58**, caused considerable increases in body weight and brown fat weight. Compound **70**, **72** and **73** also exhibited potent activities, but had some side effects.

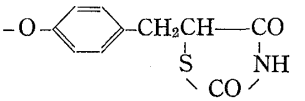
Besides these compounds, those listed in Tables V and VI were also prepared, but they exhibited no valuable activities. The fact that compounds **85** and **88** were completely or nearly inactive suggests that the partial structure  is the essential structural feature for both glucose- and triglyceride-lowering activities.

Table VII lists compounds having a pyridine ring instead of the benzene ring in the 4-oxybenzyl group. These compounds, except **99** and **101**, had weaker activities than the corresponding 4-oxybenzyl derivatives.

Conclusion

In a search for antidiabetic agents, we prepared a series of compounds related to thiazolidine-2,4-dione derivatives and evaluated their potential hypoglycemic and hypolipidemic activities in genetically obese and diabetic mice, yellow KK. Compounds **47**, **49** (ADD-3878) and **59** exhibited the most favorable profiles in terms of activity and toxicity. These compounds may be valuable for the treatment of maturity-onset diabetes and/or hyperlipidemia which involves obesity.

Experimental

Melting points were determined on Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were taken on a Hitachi IR-215 spectrophotometer. 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 coupling constants (J) are given in Hz. The following abbreviations are used; s=singlet, br s=broad singlet, d=doublet, t=triplet, q=quartet, m=multiplet.

Nitro Compounds VIII and XII

Typical examples are given to illustrate the general procedure.

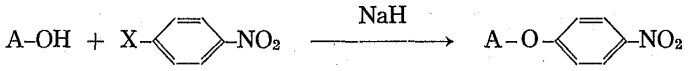
4-[2-(3-Methoxyphenyl)-2-methylpropoxy]nitrobenzene——A stirred mixture of 2-(3-methoxyphenyl)-2-methyl-1-propanol (10.9 g), *p*-chloronitrobenzene (9.5 g) and dimethylsulfoxide (DMSO) (100 ml) was treated portionwise with 50% NaH in oil (3.2 g) at 40°C. The mixture was stirred at 70°C for 30 min, poured into H_2O, acidified with 2 N HCl and extracted with Et_2O. The usual work-up gave crystals (12.7 g, 70.2%). Recrystallization from MeOH gave colorless prisms, mp 69—70°C. IR ν_{max}^{Nujol} cm^{-1}: 1585, 1345. NMR δ: 1.43 (6H, s), 3.78 (3H, s), 4.00 (2H, s), 6.6—7.0 (3H, m), 6.83 (2H, d, J=9), 8.17 (2H, d, J=9). *Anal.* Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.66; H, 6.37; N, 4.56.

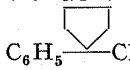
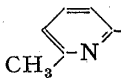
4-[2-(2-Pyridyl)ethoxy]nitrobenzene——A stirred and ice-cooled solution of 2-(2-pyridyl)ethanol (25.0 g) and *p*-fluoronitrobenzene (28.6 g) in dimethylformamide (DMF) (300 ml) was treated portionwise with 50% NaH in oil (10 g). The mixture was stirred with ice-cooling for 1 h and diluted with H_2O. The crystalline solid was filtered off and recrystallized from MeOH to give light yellow prisms (29.0 g, 58.5%), mp 74—75°C. IR ν_{max}^{Nujol} cm^{-1}: 1500, 1335. NMR δ: 3.27 (2H, t, J=7), 4.50 (2H, t, J=7), 6.90 (2H, d, J=9), 7.0—7.8 (3H, m), 8.13 (2H, d, J=9), 8.50 (1H, m). *Anal.* Calcd for $C_{13}H_{12}N_2O_3$: C, 63.92; H, 4.95; N, 11.47. Found: C, 64.14; H, 4.92; N, 11.38.

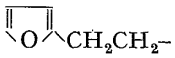
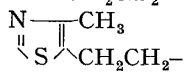
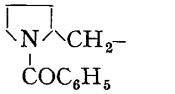
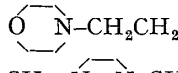
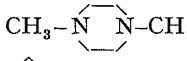
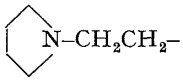
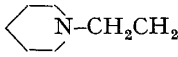
The 4-alkoxynitrobenzenes (VIII) listed in Table VIII were similarly prepared. The unlisted compounds were reported in preceding papers.[3]

2-(2-Morpholinoethoxy)-5-nitropyridine——A stirred and ice-cooled solution of 2-chloro-5-nitropyridine (15.9 g) and 2-morpholinoethanol (13.1 g) in anhydrous tetrahydrofuran (THF) (200 ml) was treated portionwise with 60% NaH in oil (4.4 g). The mixture was stirred with ice-cooling for 1 h, diluted with H_2O (1 l) and extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated to give

TABLE VIII. Nitro Compounds (VIII)

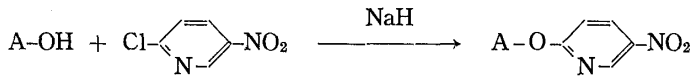


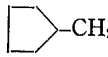
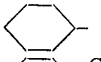
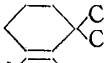
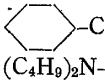
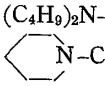
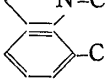
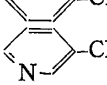
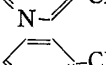
A	X	Yield (%)	mp (°C)	Recrystn. solvent[a]	Formula[b]
4-CH_3O–$C_6H_4C(CH_3)_2CH_2$–	Cl	80.6	78—79	M	$C_{17}H_{19}NO_4$
4-C_2H_5–$C_6H_4C(CH_3)_2CH_2$–	Cl	32.4	66—67	M	$C_{18}H_{21}NO_3$
4-C_2H_5O–$C_6H_4C(CH_3)_2CH_2$–	Cl	70.3	59—60	M	$C_{18}H_{21}NO_4$
4-$C_6H_5CH_2O$–$C_6H_4C(CH_3)_2CH_2$–	Cl	83.1	120—121	M	$C_{23}H_{23}NO_4$
3,4-$(CH_3O)_2$–$C_6H_3C(CH_3)_2CH_2$–	Cl	60.4	62—64	M	$C_{18}H_{21}NO_5$
4-CH_3–$C_6H_4CH_2CH_2$–	Cl	35.3	Oil	—	$C_{15}H_{15}NO_3$
2-CH_3O–$C_6H_4CH_2CH_2$–	Cl	58.9	91—92	M	$C_{15}H_{15}NO_4$
4-CH_3O–$C_6H_4CH_2CH_2$–	Cl	72.3	56—57	M	$C_{15}H_{15}NO_4$
4-C_2H_5–$C_6H_4CH_2CH_2$–	Cl	62.0	Oil	—	$C_{16}H_{17}NO_3$
4-C_2H_5O–$C_6H_4CH_2CH_2$–	F	77.9	85—87	M	$C_{16}H_{17}NO_4$
4-Cl–$C_6H_4CH_2CH_2$–	F	68.0	87—88	M	$C_{14}H_{12}ClNO_3$
2-CH_3O–, 4-CH_3–$C_6H_3CH_2CH_2$–	F	79.2	60—61	M	$C_{16}H_{17}NO_4$
3,4-$(CH_3O)_2$–$C_6H_3CH_2CH_2$–	Cl	55.9	93—94	M	$C_{16}H_{17}NO_5$
3,4,5-$(CH_3O)_3$–C_6H_2–CH_2CH_2–	F	60.4	109—110	M	$C_{17}H_{19}NO_6$
3,4-(–OCH_2O–)–$C_6H_3CH_2CH_2$–	F	52.9	79—80	M	$C_{15}H_{13}NO_5$
$(C_6H_5)_2CHCH_2$–	F	80.0	132—133	Et	$C_{20}H_{17}NO_3$
$(C_6H_5)_2C(CH_3)CH_2$–	Cl	76.1	115—116	M	$C_{21}H_{19}NO_3$
	Cl	51.3	99—100	Et	$C_{18}H_{19}NO_3$
$CH_3CH_2C(CH_3)_2CH_2$–	Cl	56.0	Oil	—	$C_{12}H_{17}NO_3$
$CH_3(CH_2)_3C(CH_3)_2CH_2$–	Cl	73.9	Oil	—	$C_{14}H_{21}NO_3$
$CH_3(CH_2)_4C(CH_3)_2CH_2$–	Cl	57.9	Oil	—	$C_{15}H_{23}NO_3$
Geranyl-	Cl	86.5	Oil	—	$C_{16}H_{21}NO_3$
Phytyl-	F	79.5	Oil	—	$C_{26}H_{43}NO_3$
CH_2=CH–$CH_2C(CH_3)_2CH_2$–	Cl	74.2	Oil	—	$C_{13}H_{17}NO_3$
Geranyl-$C(CH_3)_2CH_2$–	Cl	61.2	Oil	—	$C_{20}H_{29}NO_3$
	F	78.1	Oil	—	$C_{10}H_{11}NO_3$
	F	75.0	Oil	—	$C_{12}H_{15}NO_3$
	F	75.5	77—78	M	$C_{13}H_{17}NO_3$
	Cl	62.0	67—68	M	$C_{14}H_{19}NO_3$
	Cl	86.9	59—60	Et–W	$C_{14}H_{19}NO_3$
	F	89.0	Oil	—	$C_{15}H_{21}NO_3$
	Cl	73.1	Oil	—	$C_{16}H_{23}NO_3$
	Cl	63.0	47—48	M	$C_{13}H_{17}NO_3$
Isobornyl-	Cl	78.5	109—110	M	$C_{16}H_{21}NO_3$
Bornyl-	Cl	78.8	107—108	M	$C_{16}H_{21}NO_3$
l-Menthyl-	Cl	80.3	64—65	M	$C_{16}H_{23}NO_3$
	Cl	62.9	135—136	M	$C_{12}H_{10}N_2O_3$
	F	70.9	61—62	M	$C_{14}H_{14}N_2O_3$
	F	75.0	104—105	M	$C_{13}H_{12}N_2O_3$
	F	75.7	86—87	M	$C_{14}H_{14}N_2O_3$
	F	67.2	63—64	M	$C_{12}H_{11}NO_3S$

A	X	Yield (%)	mp (°C)	Recrystn. solvent[a]	Formula[b]
	F	57.2	52—54	M	$C_{12}H_{11}NO_4$
	F	85.6	92—93	M	$C_{12}H_{12}N_2O_3S$
	F	68.2	Oil	—	$C_{18}H_{18}N_2O_4$
$(CH_3)_2CHNH-CH_2CH_2-$	F	72.1	215—216	M–E	$C_{11}H_{16}N_2O_3 \cdot HCl$
$(CH_3)_3CNH-CH_2CH_2-$	F	74.5	243—244	M–E	$C_{12}H_{18}N_2O_3 \cdot HCl$
$(C_2H_5)_2N-CH_2CH_2-$	Cl	61.6	162—163	M–E	$C_{12}H_{18}N_2O_3 \cdot HCl$
$(C_3H_7)_2N-CH_2CH_2-$	Cl	71.0	Oil	—	$C_{14}H_{22}N_2O_3$
$(iso\text{-}C_3H_7)_2N-CH_2CH_2-$	Cl	67.2	Oil	—	$C_{14}H_{22}N_2O_3$
	F	82.4	82—83	EA–H	$C_{12}H_{16}N_2O_3$
	Cl	69.1	201—202	Et–W	$C_{13}H_{19}N_3O_3 \cdot HCl \cdot 2H_2O$
	Cl	53.3	195—196	Et–E	$C_{12}H_{16}N_2O_3 \cdot HCl$
	Cl	68.6	210—211	M–E	$C_{13}H_{18}N_2O_3 \cdot HCl$

a) E=Et_2O, EA=AcOEt, Et=EtOH, M=MeOH, W=H_2O.
b) All compounds were analyzed for C, H and N; analytical results obtained for these elements were within ±0.4% of calculated values. Oily compounds were purified by column chromatography and used for the subsequent reactions.

TABLE IX. Nitro Compounds (XII)



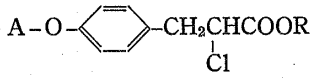
A	Yield (%)	mp (°C)	Recrystn. solvent[a]	Formula[b]
	55.8	61—62	M	$C_{11}H_{14}N_2O_3$
	57.7	Oil	—	$C_{11}H_{14}N_2O_3$
	42.2	38—39	E–H	$C_{13}H_{18}N_2O_3$
	59.9	68—69	M	$C_{13}H_{18}N_2O_3$
$(C_4H_9)_2N-CH_2CH_2-$	52.1	Oil	—	$C_{15}H_{25}N_3O_3$
	31.0	71—72	M	$C_{12}H_{17}N_3O_3$
	75.0	72—73	Et	$C_{13}H_{12}N_2O_3$
	73.5	56—57	E–H	$C_{12}H_{11}N_3O_3$
	87.7	116—117	M	$C_{12}H_{11}N_3O_3$

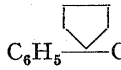
a, *b*) See the corresponding footnotes in Table VIII.

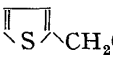
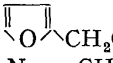
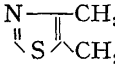
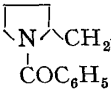
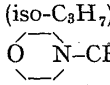
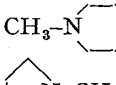
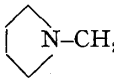
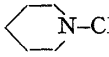
crystals (20.0 g, 79.1%). Recrystallization from EtOH gave light yellow prisms, mp 77—78°C. IR ν_{max}^{Nujol} cm^{-1}: 1575, 1345. NMR δ: 2.60 (4H, t, J=5), 3.76 (4H, t, J=5), 4.64 (2H, t, J=6), 6.92 (1H, d, J=9), 8.41 (1H, q, J=9 and 3), 9.12 (1H, d, J=3). *Anal.* Calcd for $C_{11}H_{15}N_3O_4$: C, 52.17; H, 5.97; N, 16.59. Found: C, 52.14; H, 5.92; N, 16.47.

The 2-alkoxy-5-nitropyridines (XII) listed in Table IX were similarly prepared.

Table X. 3-Aryl-2-chloropropionic Acids (I)



A	R	Yield[a] (%)	Formula[b]
3-CH_3O–$C_6H_4C(CH_3)_2CH_2$–	Me	54.0	$C_{21}H_{25}ClO_4$
4-CH_3O–$C_6H_4C(CH_3)_2CH_2$–	Me	49.0	$C_{21}H_{25}ClO_4$
4-C_2H_5–$C_6H_4C(CH_3)_2CH_2$–	Me	66.7	$C_{21}H_{27}ClO_3$
4-C_2H_5O–$C_6H_4C(CH_3)_2CH_2$–	Me	49.7	$C_{22}H_{27}ClO_4$
4-HO–$C_6H_4C(CH_3)_2CH_2$–	Et	46.0	$C_{20}H_{23}ClO_4$
3,4-$(CH_3O)_2$–$C_6H_3C(CH_3)_2CH_2$–	Me	50.0	$C_{22}H_{27}ClO_5$
4-CH_3–$C_6H_4CH_2CH_2$–	Et	40.7	$C_{20}H_{23}ClO_3$
2-CH_3O–$C_6H_4CH_2CH_2$–	Me	41.4	$C_{19}H_{21}ClO_4$
4-CH_3O–$C_6H_4CH_2CH_2$–	Me	47.0	$C_{19}H_{21}ClO_4$
4-C_2H_5–$C_6H_4CH_2CH_2$–	Me	64.9	$C_{20}H_{23}ClO_3$
4-C_2H_5O–$C_6H_4CH_2CH_2$–	Me	51.7	$C_{20}H_{23}ClO_4$
4-Cl–$C_6H_4CH_2CH_2$–	Me	35.1	$C_{18}H_{18}Cl_2O_3$
2-CH_3O–, 4-CH_3–$C_6H_3CH_2CH_2$–	Me	68.9	$C_{20}H_{23}ClO_4$
3,4-$(CH_3O)_2$–$C_6H_3CH_2CH_2$–	Me	46.7	$C_{20}H_{23}ClO_5$
3,4,5-$(CH_3O)_3$–C_6H_2–CH_2CH_2–	Me	64.0	$C_{21}H_{25}ClO_6$
3,4-(–OCH_2O–)–$C_6H_3CH_2CH_2$–	Me	66.7	$C_{19}H_{19}ClO_5$
$(C_6H_5)_2CHCH_2$–	Et	67.5	$C_{24}H_{23}ClO_3$
$(C_6H_5)_2C(CH_3)CH_2$–	Et	78.0	$C_{25}H_{25}ClO_3$
	Et	78.5	$C_{22}H_{25}ClO_3$
$CH_3CH_2C(CH_3)_2CH_2$–	Et	63.3	$C_{17}H_{25}ClO_3$
$CH_3(CH_2)_3C(CH_3)_2CH_2$–	Me	60.9	$C_{18}H_{27}ClO_3$
$CH_3(CH_2)_4C(CH_3)_2CH_2$–	Et	64.1	$C_{20}H_{31}ClO_3$
Geranyl-	Et	52.8	$C_{21}H_{29}ClO_3$
Phytyl-	Et	69.3	$C_{31}H_{51}ClO_3$
CH_2=CH–$CH_2C(CH_3)_2CH_2$–	Et	58.0	$C_{18}H_{25}ClO_3$
Geranyl-$C(CH_3)_2CH_2$–	Et	52.8	$C_{25}H_{37}ClO_3$
	Me	54.0	$C_{14}H_{17}ClO_3$
	Me	77.1	$C_{16}H_{21}ClO_3$
	Me	75.4	$C_{17}H_{23}ClO_3$
	Me	78.5	$C_{18}H_{25}ClO_3$
	Me	73.2	$C_{19}H_{27}ClO_3$
	Et	76.7	$C_{21}H_{31}ClO_3$
	Me	78.1	$C_{16}H_{21}ClO_3$
Isobornyl-	Me	75.0	$C_{20}H_{27}ClO_3$
Bornyl-	Me	74.3	$C_{20}H_{27}ClO_3$
l-Menthyl-	Me	78.8	$C_{20}H_{29}ClO_3$
	Me	54.3	$C_{16}H_{16}ClNO_3$
	Me	41.2	$C_{17}H_{18}ClNO_3$
	Me	30.1	$C_{18}H_{20}ClNO_3$
	Me	51.3	$C_{17}H_{18}ClNO_3$
	Me	43.6	$C_{18}H_{20}ClNO_3$

A	R	Yield[a] (%)	Formula[b]
	Me	72.7	$C_{16}H_{17}ClO_3S$
	Me	65.4	$C_{16}H_{17}ClO_4$
	Me	67.0	$C_{16}H_{18}ClNO_3S$
	Me	65.1	$C_{22}H_{24}ClNO_4$
$(CH_3)_2CHNH-CH_2CH_2-$	Me	37.8	$C_{15}H_{22}ClNO_3$
$(CH_3)_3CNH-CH_2CH_2-$	Me	48.3	$C_{16}H_{24}ClNO_3$
$(C_2H_5)_2N-CH_2CH_2-$	Me	53.0	$C_{16}H_{24}ClNO_3$
$(C_3H_7)_2N-CH_2CH_2-$	Me	53.5	$C_{18}H_{83}ClNO_3$
$(iso\text{-}C_3H_7)_2N-CH_2CH_2-$	Me	33.8	$C_{18}H_{28}ClNO_3$
	Me	45.1	$C_{16}H_{22}ClNO_4$
	Me	31.6	$C_{17}H_{25}ClN_2O_3$
	Me	48.1	$C_{16}H_{22}ClNO_3$
	Me	52.7	$C_{17}H_{24}ClNO_3$

a) Overall yield from the corresponding nitro compound (VIII).
b) All compounds were oily products and were purified by column chromatography on silica gel.

3-Aryl-2-chloropropionic Acids (I)

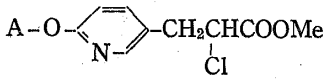
Typical examples are given to illustrate the general procedure.

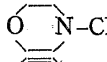
Methyl 2-Chloro-3-[4-(1-methylcyclohexylmethoxy)phenyl]propionate——A mixture of 4-(1-methylcyclohexylmethoxy)nitrobenzene (60.2 g), 10% Pd-C (3.0 g) and MeOH (400 ml) was hydrogenated at room temperature and atmospheric pressure. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residual oil was dissolved in acetone (500 ml). To this stirred and ice-cooled solution, conc. HCl (60 ml) and a solution of $NaNO_2$ (18.2 g) in H_2O (40 ml) were added dropwise below 5°C. The whole was stirred at 5°C for 30 min, then methyl acrylate (124 g) was added thereto and the temperature was raised to 35°C. Cu_2O (0.8 g) was added to the mixture in small portions with vigorous stirring. After N_2 gas evolution had ceased, the reaction mixture was concentrated *in vacuo*, diluted with H_2O and extracted with Et_2O. The usual work-up gave a crude oil, which was purified by column chromatography on silica gel (700 g) using Et_2O–hexane (1: 10, v/v) as an eluent to give a pure oil (61.0 g, 77.8%). IR ν_{max}^{neat} cm^{-1}: 1745. NMR (C_6D_6) δ: 1.0 (3H, s), 1.39 (10H, br s), 2.97 (1H, q, J=14 and 7), 3.17 (1H, q, J=14 and 7), 3.24 (3H, s), 3.45 (2H, s), 4.30 (1H, t, J=7), 6.75 (2H, d, J=9), 6.95 (2H, d, J=9). The ester was converted to the corresponding acid by the usual alkaline hydrolysis in quantitative yield, mp 104—105°C (from hexane). IR ν_{max}^{Nujol} cm^{-1}: 1710. NMR δ: 1.0 (3H, s), 1.43 (10H, br s), 3.05 (1H, q, J=14 and 7), 3.31 (1H, q, J=14 and 7), 3.60 (2H, s), 4.39 (1H, t, J=7), 6.81 (2H, d, J=9), 7.10 (2H, d, J=9), 10.56 (1H, br s). *Anal.* Calcd for $C_{17}H_{23}ClO_3$: C, 65.69; H, 7.46. Found: C, 65.60; H, 7.30.

The 3-(4-alkoxyphenyl)-2-chloropropionates listed in Table X were similarly prepared. The unlisted compounds were reported in preceding papers.[3]

Methyl 2-Chloro-3-{2-[2-(3-pyridyl)ethoxy]-5-pyridyl}propionate——A mixture of 5-nitro-2-[2-(3-pyridyl)ethoxy]pyridine (15.0 g), 10% Pd–C (2.0 g) and MeOH (150 ml) was hydrogenated at room temperature and atmospheric pressure. After removal of the catalyst by filtration, acetone (100 ml) was added to the filtrate. To this stirred and ice-cooled solution, conc. HCl (25 ml) and a solution of $NaNO_2$ (4.6 g) in H_2O (10 ml) were added dropwise below 5°C. The mixture was stirred at 5°C for 30 min and methyl acrylate (35 g) was added thereto. The temperature was raised to 35°C and Cu_2O (1.0 g) was added to the mixture in small portions with vigorous stirring. After N_2 gas evolution had ceased, the reaction mixture was concentrated *in vacuo*, diluted with H_2O, neutralized with conc. NH_4OH and extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated. The residual oil was chromatographed on silica gel (150 g) using Et_2O–hexane–Et_3N (25: 25: 1, v/v) as an eluent to give a pure oil (6.5 g, 33.2%). IR ν_{max}^{neat} cm^{-1}: 1735. NMR δ: 3.08 (2H, t, J=7), 3.0—3.5 (2H, m), 3.73 (3H, s), 4.43 (1H, t, J=7), 4.57 (2H, t, J=7), 6.73 (1H, d, J=8), 7.2—7.8 (3H, m), 8.02 (1H, d, J=2), 8.5—8.7 (2H, m).

Table XI. Methyl 3-(2-Alkoxy-5-pyridyl)-2-chloropropionates (I)



A	Yield[a] (%)	Formula[b]
	60.2	$C_{15}H_{20}ClNO_3$
	41.2	$C_{15}H_{20}ClNO_3$
	38.7	$C_{17}H_{24}ClNO_3$
	63.9	$C_{17}H_{24}ClNO_3$
$(C_4H_9)_2N-CH_2CH_2-$	19.6	$C_{19}H_{31}ClN_2O_3$
	53.3	$C_{16}H_{23}ClN_2O_3$
	58.6	$C_{15}H_{21}ClN_2O_4$
	74.6	$C_{18}H_{18}ClNO_3$
	21.5	$C_{16}H_{17}ClN_2O_3$

a, *b*) See the corresponding footnotes in Table X.

The 3-(2-alkoxy-5-pyridyl)-2-chloropropionates listed in Table XI were similarly prepared.

Thiazolidine-2,4-diones (III)

Typical examples are given to illustrate the general procedure.

Method A——5-[4-(1-Methylcyclohexylmethoxy)benzyl]thiazolidine-2,4-dione (**49**, ADD-3878): A mixture of 2-imino-5-[4-(1-methylcyclohexylmethoxy)benzyl]thiazolidin-4-one (6.0 g), 2 N HCl (10 ml) and 2-methoxyethanol (40 ml) was refluxed for 6 h, cooled and diluted with H_2O to give crystals of **49**. Recrystallization from 85% EtOH gave colorless plates (5.3 g, 88.3%), mp 130—131°C. IR ν_{max}^{Nujol} cm^{-1}: 3160, 3050, 1750, 1685. NMR δ: 1.03 (3H, s), 1.47 (10H, br s), 3.08 (1H, q, J=14 and 9), 3.48 (1H, q, J=14 and 4), 3.67 (2H, s), 4.56 (1H, q, J=9 and 4), 6.92 (2H, d, J=9), 7.23 (2H, d, J=9), 9.12 (1H, br s). *Anal.* Calcd for $C_{18}H_{23}NO_3S$: C, 64.84; H, 6.95; N, 4.20. Found: C, 64.78; H, 6.88; N, 4.10.

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

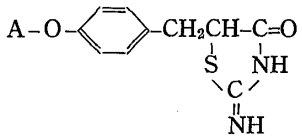
2-Imino-5-[4-(1-methylcyclohexylmethoxy)benzyl]thiazolidin-4-one: A mixture of methyl 2-chloro-3-[4-(1-methylcyclohexylmethoxy)phenyl]propionate (13.2 g), thiourea (5.0 g), NaOAc (3.3 g) and 2-methoxyethanol (80 ml) was stirred at 100°C for 10 h and concentrated *in vacuo*. H_2O (50 ml)–hexane (50 ml) was added to the residue and the insoluble solid was filtered off (10.8 g, 80.4%). Recrystallization from EtOH gave colorless prisms, mp 262—264°C (dec.). IR ν_{max}^{Nujol} cm^{-1}: 3220, 1685. NMR (d_6-DMSO) δ: 0.96 (3H, s), 1.40 (10H, br s), 2.79 (1H, q, J=14 and 9), 3.28 (1H, q, J=14 and 4), 3.62 (2H, s), 4.48 (1H, q, J=9 and 4), 6.82 (2H, d, J=9), 7.12 (2H, d, J=9), 8.65 (1H, br s), 8.85 (1H, br s). *Anal.* Calcd for $C_{18}H_{24}N_2O_2S$: C, 65.03; H, 7.28; N, 8.43. Found: C, 64.92; H, 7.31; N, 8.27.

The 2-iminothiazolidin-4-ones (II) listed in Table XII were similarly prepared.

Method B——5-{4-[2-(2-Methoxy-4-methylphenyl)ethoxy]benzyl}thiazolidine-2,4-dione (**17**): A mixture of methyl 2-chloro-3-{4-[2-(2-methoxy-4-methylphenyl)ethoxy]phenyl}propionate (13.0 g), thiourea (5.5 g) and sulfolane (150 ml) was stirred at 120°C for 10 h, then 2 N HCl (50 ml) was added thereto. The mixture was stirred at 100°C for 8 h, cooled, diluted with H_2O and extracted with Et_2O. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated to give **17** as crystals (10.5 g, 78.9%). Recrystallization from AcOEt–hexane gave colorless prisms, mp 92—93°C. IR ν_{max}^{Nujol} cm^{-1}: 3180, 1750, 1690. NMR δ: 2.34 (3H, s), 3.02 (1H, q, J=14 and 9), 3.05 (2H, t, J=7), 3.47 (1H, q, J=14 and 4), 3.80 (3H, s), 4.12 (2H, t, J=7), 4.45 (1H, q, J=9 and 4), 6.6—7.4 (7H, m), 9.15 (1H, br s). *Anal.* Calcd for $C_{20}H_{21}NO_4S$: C, 64.68; H, 5.70; N, 3.77. Found: C, 64.55; H, 5.59; N, 3.81.

Method C——5-[4-(1-Methylcyclohexylmethoxy)benzyl]thiazolidine-2,4-dione (**49**, ADD-3878): A mixture of methyl 3-[4-(1-methylcyclohexylmethoxy)phenyl]-2-thiocyanatopropionate (2.0 g), 6 N HCl (20 ml) and EtOH (20 ml) was refluxed for 50 h, cooled, diluted with H_2O and extracted with Et_2O. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated to give **49** as crystals (1.35 g, 70.3%). Recrystallization from 85% EtOH gave colorless plates, mp 130—131°C. This sample was identical with an authentic sample of **49** prepared by method A.

Table XII. 2-Iminothiazolidin-4-ones (II)



A	Yield[a] (%)	mp (°C)	Recrystn. solvent[c]	Formula[d]
Geranyl-	54.9	189—190	A	$C_{20}H_{26}N_2O_2S$
Phytyl-	62.0	173—174	A	$C_{30}H_{48}N_2O_2S$
	66.7	260—261[b]	Et	$C_{16}H_{20}N_2O_2S$
	78.0	253—254[b]	Et	$C_{17}H_{22}N_2O_2S$
	74.1	237—238[b]	Et	$C_{19}H_{26}N_2O_2S$
	73.0	233—234[b]	Et	$C_{20}H_{28}N_2O_2S$
	75.6	259—260[b]	Et	$C_{17}H_{22}N_2O_2S$
Isobornyl-	79.5	263—264[b]	Et	$C_{20}H_{26}N_2O_2S$
Bornyl-	86.6	259—269[b]	Et	$C_{20}H_{26}N_2O_2S$
l-Menthyl-	75.1	218—220[b]	Et	$C_{20}H_{28}N_2O_2S$
	50.0	191—192	EA–M	$C_{16}H_{21}N_3O_3S$

a) Yield from the corresponding 3-aryl-2-chloropropionic acid (I).
b) Dec.
c) A=acetone, EA=AcOEt, Et=EtOH, M=MeOH.
d) All compounds were analyzed for C, H and N; analytical results obtained for these elements were within 0.4% of calculated values.

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

Methyl 3-[4-(1-Methylcyclohexylmethoxy)phenyl]-2-thiocyanatopropionate: A mixture of methyl 2-chloro-3-[4-(1-methylcyclohexylmethoxy)phenyl]propionate (3.25 g), potassium thiocyanate (1.46 g) and DMSO (35 ml) was stirred at 100°C for 2 h, poured into H_2O and extracted with Et_2O. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated to give crystals (3.18 g, 91.6%). Recrystallization from hexane gave colorless needles, mp 54—55°C. IR ν_{max}^{Nujol} cm^{-1}: 2140, 1730. NMR δ: 1.00 (3H, s), 1.43 (10H, br s), 3.11 (1H, q, J=14 and 7), 3.38 (1H, q, J=14 and 7), 3.62 (2H, s), 3.78 (3H, s), 3.94 (1H, t, J=7), 6.85 (2H, d, J=9), 7.13 (2H, d, J=9). *Anal.* Calcd for $C_{19}H_{25}NO_3S$: C, 65.69; H, 7.25; N, 4.03. Found: C, 65.74; H, 7.47; N, 4.16.

The following compounds were similarly prepared.

Ethyl 3-[4-(2-Methyl-2-phenylpropoxy)phenyl]-2-thiocyanatopropionate: Oil. Yield 90.6%. IR ν_{max}^{neat} cm^{-1}: 2145, 1735. NMR δ: 1.20 (3H, t, J=7), 1.43 (6H, s), 3.13 (1H, q, J=14 and 7), 3.22 (1H, q, J=14 and 7), 3.83 (1H, t, J=7), 3.86 (2H, s), 4.13 (2H, q, J=7), 6.68 (2H, d, J=9), 7.00 (2H, d, J=9), 7.2—7.5 (5H, m).

Ethyl 3-[4-(2,2-Dimethylpropoxy)phenyl]-2-thiocyanatopropionate: Oil. Yield 82.4%. IR ν_{max}^{neat} cm^{-1}: 2145, 1735. NMR δ: 1.03 (9H, s), 1.26 (3H, t, J=7), 3.18 (1H, q, J=14 and 7), 3.25 (1H, q, J=14 and 7), 3.56 (2H, s), 3.92 (1H, t, J=7), 4.21 (2H, q, J=7), 6.82 (2H, d, J=9), 7.12 (2H, d, J=9).

Ethyl 3-[4-(2,2-Dimethyl-3-phenylpropoxy)phenyl]-2-thiocyanatopropionate: Oil. Yield 80.0%. IR ν_{max}^{neat} cm^{-1}: 2145, 1735. NMR δ: 1.0 (6H, s), 1.23 (3H, t, J=7), 2.67 (2H, s), 3.16 (1H, q, J=14 and 7), 3.26 (1H, q, J=14 and 7), 3.47 (2H, s), 3.88 (1H, t, J=7), 4.17 (2H, q, J=7), 6.77 (2H, d, J=9), 7.06 (2H, d, J=9), 7.10 (5H, br s).

Ethyl 3-[4-(3-Phenylpropoxy)phenyl]-2-thiocyanatopropionate: Oil. Yield 85.1%. IR ν_{max}^{neat} cm^{-1}: 2145, 1735. NMR δ: 1.21 (3H, t, J=7), 1.9—2.4 (2H, m), 2.76 (2H, t, J=7), 3.14 (1H, q, J=14 and 7), 3.21 (1H, q, J=14 and 7), 3.86 (2H, t, J=7), 3.90 (1H, t, J=7), 4.14 (2H, q, J=7), 6.74 (2H, d, J=9), 7.04 (2H, d, J=9), 7.12 (5H, s).

Method D——5-[4-(1-Methylcyclohexylmethoxy)benzyl]thiazolidine-2,4-dione (**49**, ADD-3878): A mixture of 2-bromo-3-[4-(1-methylcyclohexylmethoxy)phenyl]propionitrile (2.5 g), thiourea (0.85 g) and sulfolane (20 ml) was stirred at 110°C for 2 h, then 2 N HCl (20 ml) was added thereto. The mixture was refluxed for 8 h, cooled, diluted with H_2O and extracted with Et_2O. The usual work-up gave **49** (2.0 g, 80.0%), mp 130—131°C (from 85% EtOH). This sample was identical with an authentic sample of **49**

prepared by method A.

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

2-Bromo-3-[4-(1-methylcyclohexylmethoxy)phenyl]propionitrile: A mixture of 4-(1-methylcyclohexylmethoxy)nitrobenzene (6.0 g), 10% Pd-C (0.5 g) and MeOH (60 ml) was hydrogenated at room temperature and atmospheric pressure. The catalyst was filtered off and the filtrate was concentrated. The residual oil was dissolved in acetone (60 ml). To this stirred and ice-cooled solution, 47% HBr (12.5 g) and a solution of $NaNO_2$ (1.82 g) in H_2O (4 ml) were added dropwise below 5°C. The mixture was stirred at 5°C for 30 min, then acrylonitrile (7.6 g) was added thereto and the temperature was raised to 35°. Cu_2O (0.3 g) was added to the mixture in small portions with vigorous stirring. After N_2 gas evolution had ceased, the reaction mixture was concentrated, diluted with H_2O and extracted with Et_2O. The usual work-up gave a crude oil, which was purified by column chromatography on silica gel (80 g) using Et_2O–hexane (1: 10, v/v) as an eluent to give a pure oil (3.9 g, 48.1%). IR ν_{max}^{neat} cm^{-1}: 2230. NMR δ: 1.02 (3H, s), 1.43 (10H, br s), 3.23 (2H, d, J=7), 3.60 (2H, s), 4.27 (1H, t, J=7), 6.78 (2H, d, J=9), 7.10 (2H, d, J=9).

The following compound was similarly prepared.

2-Bromo-3-(4-cyclohexyloxy)phenylpropionitrile: Oil. Yield 42.9%. IR ν_{max}^{neat} cm^{-1}: 2230. NMR δ: 1.2—2.2 (10H, br s), 3.15 (2H, d, J=7), 4.30 (1H, m), 4.32 (1H, t, J=7), 6.84 (2H, d, J=9), 7.14 (2H, d, J=9).

Method E——5-(4-Geranyloxybenzyl)thiazolidine-2,4-dione (**41**) and 3-Geranyl-5-(4-hydroxybenzyl)-thiazolidine-2,4-dione (X, A=geranyl): A mixture of **87** (1.12 g), 50% NaH in oil (0.48 g) and DMSO (10 ml) was stirred at room temperature for 15 min and a solution of geranyl bromide (1.08 g) in DMSO (2 ml) was added thereto. The mixture was stirred at room temperature for 30 min, poured into H_2O, acidified with 2 N HCl and extracted with Et_2O. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated. The residual oil was chromatographed on silica gel (30 g) with cyclohexane–AcOEt (4: 1, v/v). The first part of the eluate gave X (A=geranyl) (0.45 g, 25.0%), mp 83—84°C (from cyclohexane). IR ν_{max}^{Nujol} cm^{-1}: 3400—3200, 1740, 1660. NMR δ: 1.63 (3H, s), 1.68 (3H, s), 1.73 (3H, s), 2.0 (4H, m), 3.00 (1H, q, J=14 and 9), 3.43 (1H, q, J=14 and 4), 4.13 (2H, d, J=7), 4.37 (1H, q, J=9 and 4), 5.02 (1H, m), 5.87 (1H, m), 6.72 (2H, d, J=9), 7.03 (2H, d, J=9). *Anal.* Calcd for $C_{20}H_{25}NO_3S$: C, 66.82; H, 7.09; N, 3.90. Found: C, 66.51; H, 7.01; N, 3.81. The following part of the eluate gave **41** (0.9 g, 50.0%), mp 55—56°C (from cyclohexane–hexane). IR ν_{max}^{Nujol} cm^{-1}: 3200, 1760, 1680. NMR δ: 1.60 (3H, s), 1.67 (3H, s), 1.70 (3H, s), 2.1 (4H, m), 3.00 (1H, q, J=14 and 9), 3.43 (1H, q, J=14 and 4), 4.46 (1H, q, J=9 and 4), 4.51 (2H, d, J=7), 5.08 (1H, m), 5.28 (1H, t, J=7), 6.80 (2H, d, J=9), 7.10 (2H, d, J=9), 8.93 (1H, br s). *Anal.* Calcd for $C_{20}H_{25}NO_3S$: C, 66.82; H, 7.09; N, 3.90. Found: C, 66.78; H, 6.81; N, 3.63.

The following compounds were similarly prepared.

5-(4-Phytyloxybenzyl)thiazolidine-2,4-dione (**42**): mp 31—33°C (from hexane). Yield 40.9%. IR ν_{max}^{Nujol} cm^{-1}: 3220, 1760, 1710. NMR δ: 0.8—0.9 (12H, br s), 1.1—2.3 (24H, m), 3.07 (1H, q, J=14 and 9), 3.50 (1H, q, J=14 and 4), 4.44 (1H, q, J=9 and 4), 4.47 (2H, d, J=7), 5.43 (1H, t, J=7), 6.80 (2H, q, J=9), 7.11 (2H, d, J=9), 8.50 (1H, br s). *Anal.* Calcd for $C_{30}H_{47}NO_3S$: C, 71.81; H, 9.44; N, 2.79. Found: C, 72.10; H, 9.56; N, 2.68.

5-(4-Hydroxybenzyl)-3-phytylthiazolidine-2,4-dione (X, A=phytyl): Oil. Yield 21.3%. IR ν_{max}^{neat} cm^{-1}: 3300—3200, 1740, 1670. NMR δ: 0.85—0.95 (12H, br s), 1.15—2.3 (24H, m), 3.10 (1H, q, J=14 and 9), 3.47 (1H, q, J=14 and 4), 4.60 (1H, q, J=9 and 4), 4.65 (2H, d, J=7), 5.45 (1H, t, J=7), 6.81 (2H, d, J=9), 7.15 (2H, d, J=9).

Method F——5-[4-(2-Pyrrolidinylmethoxy)benzyl]thiazolidine-2,4-dione Hydrochloride (**64**·HCl): A mixture of methyl 3-[4-(1-benzoyl-2-pyrrolidinylmethoxy)phenyl]-2-chloropropionate (6.4 g), thiourea (1.8 g) and BuOH (40 ml) was stirred at 110°C for 12 h and concentrated *in vacuo*. The residue was extracted with $CHCl_3$, and the extract was washed with H_2O, dried ($MgSO_4$) and concentrated. The residue was dissolved in AcOH (40 ml) and conc. HCl (40 ml). The mixture was refluxed for 32 h, cooled, diluted with H_2O and extracted with AcOEt. The aqueous layer was concentrated *in vacuo* and $CHCl_3$ (30 ml)–MeOH (5 ml) was added to the residue. The insoluble solid was filtered off and the filtrate was concentrated to leave a crystalline residue. Recrystallization from EtOH gave colorless prisms (1.8 g, 33.3%), mp 162—164°C. IR ν_{max}^{Nujol} cm^{-1}: 3350, 2700—2400, 1740, 1690. NMR (d_6-DMSO) δ: 1.7—2.3 (4H, m), 2.8—4.0 (5H, m), 4.17 (2H, d, J=6), 4.82 (1H, q, J=9 and 4), 6.90 (2H, d, J=9), 7.18 (2H, d, J=9), 10.2 (3H, br). *Anal.* Calcd for $C_{15}H_{18}N_2O_3S$·HCl: C, 52.55; H, 5.59; N, 8.17. Found: C, 52.66; H, 5.86; N, 7.77.

5-(4-Aminobenzyl)thiazolidine-2,4-dione (**74**): A mixture of 5-(4-nitrobenzyl)thiazolidine-2,4-dione (10.0 g), 10% Pd-C (10.0 g) and MeOH (150 ml)–AcOEt (150 ml) was hydrogenated at room temperature and atmospheric pressure. After removal of the catalyst by filtration, the filtrate was concentrated *in vacuo* to give crystals of **74** (7.8 g, 88.6%). Recrystallization from MeOH gave light yellow prisms, mp 162—163°C. IR ν_{max}^{Nujol} cm^{-1}: 3360, 3300, 2650 (br), 1735, 1690. NMR (d_6-DMSO) δ: 2.85 (1H, q, J=14 and 8), 3.23 (1H, q, J=14 and 4), 4.73 (1H, q, J=8 and 4), 6.48 (2H, d, J=9), 6.88 (2H, d, J=9), 7.0—7.6 (3H, br). *Anal.* Calcd for $C_{10}H_{10}N_2O_2S$: C, 54.05; H, 4.54; N, 12.01. Found: C, 54.02; H, 4.48; N, 12.78.

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

Ethyl 2-Chloro-3-(4-nitrophenyl)propionate: Conc. HCl (25 ml) and a solution of $NaNO_2$ (7.8 g) in H_2O (15 ml) were added dropwise to a stirred and ice-cooled solution of *p*-nitroaniline (13.8 g) in acetone (150 ml) below 5°C. The whole was stirred at 5°C for 30 min, then ethyl acrylate (60 g) was added thereto and the

temperature was raised to 10°C. Cu_2O (0.1 g) was added to the mixture in small portions with vigorous stirring. After N_2 gas evolution had ceased, the reaction mixture was concentrated *in vacuo*, diluted with H_2O and extracted with Et_2O. The usual work-up gave an oily residue, which was purified by column chromatography on silica gel (150 g) using Et_2O–hexane (1: 10), v/v) as an eluent to give the title compound as an oil (16.5 g, 64.0%). IR ν_{max}^{neat} cm^{-1}: 1735, 1520, 1345. NMR δ: 1.23 (3H, t, J=7), 3.28 (1H, q, J= 14 and 7), 3.35 (1H, q, J=14 and 7), 4.15 (2H, q, J=7), 4.40 (1H, q, J=7), 7.38 (2H, d, J=9), 8.07 (2H, d, J=9).

5-(4-Nitrobenzyl)thiazolidine-2,4-dione: A mixture of ethyl 2-chloro-3-(4-nitrophenyl)propionate (13.0 g), thiourea (7.6 g) and sulfolane (120 ml) was stirred at 120°C for 5 h and 2 N HCl (80 ml) was added thereto. The mixture was stirred at 100°C for 15 h, cooled and diluted with H_2O to give crystals. Recrystallization from MeOH gave colorless rods (9.0 g, 71.4%), mp 186—187°C. IR ν_{max}^{Nujol} cm^{-1}: 3250, 1750, 1695, 1345. NMR (d_6-DMSO) δ: 3.23 (1H, q, J=14 and 9), 3.57 (1H, q, J=14 and 4), 4.85 (1H, q, J=9 and 4), 7.45 (2H, d, J=9), 8.05 (2H, d, J=9), 11.9 (1H, br s). *Anal.* Calcd for $C_{10}H_8N_2O_4S$: C, 47.62; H, 3.20; N, 11.11. Found: C, 47.59; H, 3.31; N, 11.30.

5-[4-(*p*-Toluenesulfonylamino)benzyl]thiazolidine-2,4-dione (**75**): Reaction of **74** (4.0 g) and *p*-toluenesulfonyl chloride (3.8 g) gave the title compound (6.5 g, 95.6%), mp 224—225°C (from MeOH). IR ν_{max}^{Nujol} cm^{-1}: 3230, 1745, 1660. NMR (d_6-DMSO) δ: 2.32 (3H, s), 2.97 (1H, q, J=14 and 9), 3.28 (1H, q, J=14 and 4), 4.79 (1H, q, J=9 and 4), 7.07 (4H, s), 7.32 (2H, d, J=9), 7.62 (2H, d, J=9), 10.13 (1H, s), 12.0 (1H, br s). *Anal.* Calcd for $C_{17}H_{16}N_2O_4S_2$: C, 54.26; H, 4.29; N, 7.44. Found: C, 54.18; H, 4.18; N, 7.32.

5-(4-Propionylaminobenzyl)thiazolidine-2,4-dione (**76**): Reaction of **74** (2.2 g) and propionyl chloride (1.0 ml) gave the title compound (1.55 g, 55.8%), mp 140—141°C (from AcOEt). IR ν_{max}^{Nujol} cm^{-1}: 3330, 1750, 1690, 1655. NMR (d_6-DMSO) δ: 1.10 (3H, t, J=7), 2.30 (2H, q, J=7), 3.00 (1H, q, J=14 and 9), 3.38 (1H, q, J=14 and 4), 4.82 (1H, q, J=9 and 4), 7.12 (2H, d, J=9), 7.52 (2H, d, J=9). *Anal.* Calcd for $C_{13}H_{14}N_2O_3S$: C, 56.11; H, 5.07; N, 10.07. Found: C, 55.79; H, 5.12; N, 9.83.

5-(4-Nicotinoylaminobenzyl)thiazolidine-2,4-dione (**77**): Reaction of **74** (2.2 g) and nicotinoyl chloride [prepared from sodium nicotinate (1.74 g) and phosphorus oxychloride (0.97 g) according to the method of Rossels *et al.*[8]] gave the title compound (1.0 g, 30.6%), mp 271—272°C (from DMF–H_2O). IR ν_{max}^{Nujol} cm^{-1}: 3380, 1740, 1690, 1670. NMR (d_6-DMSO) δ: 3.08 (1H, q, J=14 and 8), 3.38 (1H, q, J=14 and 5), 4.88 (1H, q, J=8 and 5), 7.27 (2H, d, J=9), 7.4—7.7 (1H, m), 7.75 (2H, d, J=9), 8.32 (1H, d, J=7), 8.8 (1H, m), 9.1 (1H, m), 10.42 (1H, br s), 11.9 (1H, br s). *Anal.* Calcd for $C_{16}H_{13}N_3O_3S$: C, 58.71; H, 4.00; N, 12.84. Found: C, 58.39; H, 4.01; N, 12.94.

5-[4-(3-Aminopropionylamino)benzyl]thiazolidine-2,4-dione Hydrobromide (**78**·HBr): A mixture of 5-[4-(3-benzyloxycarbonylaminopropionylamino)benzyl]thiazolidine-2,4-dione (1.9 g) and 25% HBr in AcOH (w/w, 20 ml) was stirred at room temperature for 30 min and diluted with Et_2O (100 ml). The crystalline precipitate was filtered off and recrystallized from MeOH to give **78**·HBr (1.02 g, 61.4%), mp 242—243°C. IR ν_{max}^{Nujol} cm^{-1}: 3300, 2700—2300, 1750, 1690, 1660. NMR (d_6-DMSO) δ: 2.72 (2H, t, J=7), 2.9—3.5 (4H, m), 4.83 (1H, q, J=7 and 4), 7.16 (2H, d, J=9), 7.56 (2H, d, J=9), 7.8 (3H, br s), 10.17 (1H, s). *Anal.* Calcd for $C_{13}H_{15}N_3O_3S$·HBr: C, 41.72; H, 4.31; N, 11.23. Found: C, 41.25; H, 4.33; N, 11.16.

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

5-[4-(3-Benzyloxycarbonylaminopropionylamino)benzyl]thiazolidine-2,4-dione: Et_3N (1.4 ml) and ethyl chloroformate (0.96 ml) were added dropwise to a stirred and ice-cooled solution of *N*-benzyloxycarbonyl-β-alanine (1.1 g). The mixture was stirred with ice-cooling for 15 min, and a solution of **74** (2.22 g) and Et_3N (1.4 ml) in CH_2Cl_2 (10 ml) was added dropwise thereto at −10°C. The reaction mixture was stirred at room temperature overnight, concentrated *in vacuo*, diluted with 2 N HCl (50 ml) and extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$), and concentrated to leave an oil, which was treated with Et_2O to give the title compound (3.1 g, 72.6%) as a powder. Crystallization from EtOH–Et_2O gave colorless prisms, mp 139—141°C. IR ν_{max}^{Nujol} cm^{-1}: 3300, 1750, 1720, 1680. NMR (d_6-DMSO) δ: 2.4—2.7 (2H, m), 3.0—3.6 (4H, m), 4.90 (1H, q, J=8 and 5), 5.03 (2H, s), 7.1—7.6 (9H, m), 7.2 (1H, br s), 9.8 (1H, br s), 11.8 (1H, br s). *Anal.* Calcd for $C_{21}H_{21}N_3O_5S$: C, 59.00; H, 4.95; N, 9.83. Found: C, 58.82; H, 4.96; N, 9.65.

5-[4-(6-Aminohexanoylamino)benzyl]thiazolidine-2,4-dione (**79**): A mixture of 5-[4-(6-*tert*-butoxycarbonylaminohexanoylamino)benzyl]thiazolidine-2,4-dione (2.6 g) and 25% HBr in AcOH (w/w, 20 ml) was stirred at room temperature for 30 min then concentrated. The residue was charged on a column packed with Amberlite IRC-400 (AcO^-) (25 ml) and eluted with 70% MeOH (v/v). The solvent was evaporated off to give **79** as crystals (0.76 g, 47.9%), mp 216—218°C (from DMF–Et_2O). IR ν_{max}^{Nujol} cm^{-1}: 3500, 3300, 3150, 1670. NMR (d_6-DMSO) δ: 1.1—1.9 (6H, m), 2.2—3.4 (6H, m), 4.77 (1H, m), 7.1—7.7 (4H, m), 7.6 (2H, m), 9.8 (1H, br s), 11.8 (1H, br s). *Anal.* Calcd for $C_{16}H_{21}N_3O_3S$: C, 56.29; H, 6.20; N, 12.31. Found: C, 56.50; H, 6.46; N, 12.29.

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

5-[4-(6-*tert*-Butoxycarbonylaminohexanoylamino)benzyl]thiazolidine-2,4-dione: Et_3N (1.4 ml) and ethyl chloroformate (0.96 ml) were added dropwise to a stirred and ice-cooled solution of 6-*tert*-butoxycarbonylaminohexanoic acid (2.15 g) in CH_2Cl_2 (10 ml). The mixture was stirred with ice-cooling for 15 min and a solution of **74** (2.2 g) and Et_3N (1.4 ml) in CH_2Cl_2 (10 ml) was added dropwise thereto at −10°C. The reaction mixture was stirred at −10°C for 30 min and at room temperature for 1 h, concentrated *in vacuo*, neutralized

with 10% (w/w) citric acid aq. solution and extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated to leave the title compound as a crude oil (4.0 g, quant.). IR ν_{max}^{neat} cm^{-1}: 3350, 3130, 1760, 1710, 1680. NMR (d_6-DMSO) δ: 1.2—1.7 (6H, m), 1.35 (9H, s), 2.1—2.5 (2H, m), 2.8—3.5 (4H, m), 4.80 (1H, q, J=8 and 5), 6.53 (1H, br s), 7.1—7.6 (4H, m), 9.75 (1H, br s), 11.93 (1H, br s). The crude oil was used for the subsequent reaction without purification.

5-(4-Ethoxycarbonylmethylcarbamoylaminobenzyl)thiazolidine-2,4-dione (**80**): A solution of ethoxycarbonylmethylisocyanate (0.65 g) in THF (5 ml) was added dropwise to a stirred and ice-cooled solution of **74** (1.1 g) in THF (10 ml). The mixture was stirred at 0°C for 1 h and at room temperature for 10 h, poured into H_2O and extracted with AcOEt. The usual work-up gave crystals of **80** (0.55 g, 30.7%). Recrystallization from EtOH gave colorless prisms, mp 161—162°C. IR ν_{max}^{Nujol} cm^{-1}: 3330, 3170, 1750, 1690. NMR δ: 1.28 (3H, t, J=7), 3.01 (1H, q, J=14 and 8), 3.43 (1H, q, J=14 and 4), 3.97 (2H, d, J=5), 4.18 (2H, q, J=7), 4.53 (1H, q, J=8 and 4), 6.37 (1H, t, J=5), 7.08 (2H, d, J=9), 7.38 (2H, d, J=9), 8.5 (1H, br s), 11.8 (1H, br s). *Anal.* Calcd for $C_{15}H_{17}N_3O_5S$: C, 51.27; H, 4.88; N, 11.96. Found: C, 51.12; H, 4.83; N, 11.77.

5-(4-Phenethylaminobenzyl)thiazolidine-2,4-dione Hydrochloride (**81**·HCl): A mixture of 5-{4-[*N*-phenethyl-*N*-(*p*-toluenesulfonyl)amino]benzyl}thiazolidine-2,4-dione (3.5 g), conc. H_2SO_4 (15 ml) and AcOH (15 ml) was stirred at 100°C for 1 h, cooled, neutralized with sat. aq. $NaHCO_3$ and extracted with AcOEt The extract was washed with H_2O, dried ($MgSO_4$) and concentrated. The oily residue was treated with a solution of HCl in Et_2O (3.54 mmol/g, 10 ml) to give crystals of **81**·HCl (1.7 g, 63.4%). Recrystallization from acetone gave colorless rods, mp 156—157°C. IR ν_{max}^{Nujol} cm^{-1}: 3300—2200, 1750, 1690. NMR (d_6-DMSO) δ: 2.8—3.6 (6H, m), 4.86 (1H, q, J=8 and 4), 7.25 (5H, s), 7.28 (2H, d, J=9), 7.40 (2H, d, J=9), 8.1—8.7 (2H, br), 12.0 (1H, br). *Anal.* Calcd for $C_{18}H_{18}N_2O_2S$: C, 59.58; H, 5.28; N, 7.72. Found: C, 59.88; H, 5.36; N, 7.65.

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

4-[*N*-Phenethyl-*N*-(*p*-toluenesulfonyl)amino]aniline: A mixture of 4-(*p*-toluenesulfonylamino)aniline[9] (13.1 g), 50% NaH in oil (2.64 g) and DMF (150 ml) was stirred at room temperature for 30 min, then phenethyl bromide (11.1 g) was added thereto. The mixture was stirred at 70°C for 2 h, poured into H_2O and extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated to leave an oil, which was chromatographed on silica gel (100 g). Elution with $CHCl_3$ gave crystals of the title compound (13.6 g, 74.6%), mp 105—106°C (from MeOH). IR ν_{max}^{Nujol} cm^{-1}: 3470, 3370, 1335, 1155. NMR δ: 2.43 (3H, s), 2.85 (2H, t, J=7), 3.7—4.0 (4H, m), 6.63 (2H, d, J=9), 6.90 (2H, d, J=9), 7.2—7.8 (9H, m). *Anal.* Calcd for $C_{21}H_{22}N_2O_2S$: C, 68.83; H, 6.05; N, 7.65. Found: C, 69.04; H, 6.00; N, 7.74.

Methyl 2-Chloro-3-{4-[*N*-phenethyl-*N*-(*p*-toluenesulfonyl)amino]phenyl}propionate: Conc.HCl (8.7 ml) and a solution of $NaNO_2$ (2.64 g) in H_2O (10 ml) were added dropwise to a stirred and ice-cooled solution of 4-[*N*-phenethyl-*N*-(*p*-toluenesulfonyl)amino]aniline (12.7 g) in acetone (150 ml)–MeOH (100 ml) below 5°C. The mixture was stirred at 5°C for 15 min and methyl acrylate (18.0 g) was added thereto. The temperature was raised to 35°C and Cu_2O (0.5 g) was added portionwise to the mixture with vigorous stirring. After N_2 gas evolution had ceased, the mixture was concentrated *in vacuo*, diluted with H_2O and extracted with Et_2O. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (200 g) with cyclohexane–AcOEt (8: 1, v/v) to give a pure oil (9.8 g, 59.8%). IR ν_{max}^{neat} cm^{-1}: 1750, 1350, 1160. NMR δ: 2.38 (3H, s), 2.6—3.0 (2H, m), 3.1—3.6 (2H, m), 3.73 (3H, s), 3.7—4.0 (2H, m), 4.40 (1H, q, J=9 and 4), 6.9—7.7 (13H, m).

5-{4-[*N*-Phenethyl-*N*-(*p*-toluenesulfonyl)amino]benzyl}thiazolidine-2,4-dione: A mixture of 2-chloro-3-{4-[*N*-phenethyl-*N*-(*p*-toluenesulfonyl)amino]phenyl}propionate (9.5 g), thiourea (3.1 g) and sulfolane (100 ml) was stirred at 110°C for 16 h, then 1 N HCl (40 ml) was added. The mixture was refluxed for 8 h, cooled, diluted with H_2O and extracted with Et_2O. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (100 g) with cyclohexane–AcOEt (3: 1, v/v) to give the title compound as an oil (6.5 g, 67.7%). IR ν_{max}^{neat} cm^{-1}: 3210, 1755, 1705, 1340, 1155. NMR δ: 2.40 (3H, s), 2.6—4.1 (6H, m), 4.53 (1H, q, J=9 and 4), 7.0—7.7 (13H, m), 9.5 (1H, br s).

5-[4-(5-Chloro-2-methoxybenzoylamino)benzyl]thiazolidine-2,4-dione (**82**): A mixture of 5-chloro-2-methoxybenzoic acid (1.51 g), thionyl chloride (1.73 ml) and C_6H_6 (20 ml) was refluxed for 1 h, then concentrated *in vacuo* to leave an oil. The oil was dissolved in DMF (10 ml) and the solution was added to a solution of **74** (1.8 g) in DMF (10 ml). The mixture was stirred at room temperature for 30 min, diluted with H_2O and extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated to give crystals of **82** (1.55 g, 48.4%). Recrystallization from MeOH gave colorless prisms, mp 221—222°C. IR ν_{max}^{Nujol} cm^{-1}: 3320, 3100, 1740, 1685, 1640. NMR (d_6-DMSO) δ: 3.08 (1H, q, J=14 and 8), 3.40 (1H, q, J=14 and 4), 4.85 (1H, q, J=8 and 4), 7.0—7.8 (7H, m), 10.25 (1H, s), 12.1 (1H, br s). *Anal.* Calcd for $C_{18}H_{15}ClN_2O_4S$: C, 55.32; H, 3.87; N, 7.17. Found: C, 55.20; H, 3.81; N, 7.26.

5-(4-Piperazinylbenzyl)thiazolidine-2,4-dione Hemihydrate (**83**·1/2H_2O): A mixture of **74** (2.64 g), bis(2-chloroethyl)amine hydrochloride (2.5 g) and MeOH (15 ml) was refluxed for 25 h. After removal of the solvent, the residue was partitioned between $CHCl_3$ and sat. aq. $NaHCO_3$. The $CHCl_3$ layer was separated, washed with H_2O, dried ($MgSO_4$) and concentrated. The oily residue was chromatographed on silica gel (100 g) using $CHCl_3$–MeOH (9: 1, v/v) as an eluent to give crystals of **83**. Recrystallization from MeOH gave colorless prisms (0.22 g, 6.2%), mp 221—223°C. IR ν_{max}^{KBr} cm^{-1}: 1690. NMR (d_6-DMSO) δ: 2.7—3.4

(10H, m), 4.57 (1H, q, J=9 and 4), 6.83 (2H, d, J=9), 7.10 (2H, d, J=9), 9.0 (1H, br), 12.0 (1H, br). *Anal.* Calcd for $C_{14}H_{17}N_3O_2S \cdot 1/2H_2O$: C, 55.98; H, 6.04; N, 13.99. Found: C, 56.11; H, 5.79; N, 14.02.

Diethyl 4-(4-Chlorophenoxy)butylmalonate: Diethyl malonate (7.7 g) and a solution of 4-(4-chlorophenoxy)butyl bromide[10] (11.5 g) in EtOH (80 ml) were added dropwise to a stirred solution of Na (1.1 g) in EtOH (80 ml) at room temperature. The mixture was refluxed for 3 h, cooled, diluted with H_2O and extracted with Et_2O. The usual work-up gave an oily residue which was chromatographed on silica gel (150 g). Elution with Et_2O–hexane (1: 2, v/v) gave a pure oil (11.8 g, 78.7%). IR ν_{max}^{neat} cm^{-1}: 1745, 1725. NMR δ: 1.25 (6H, t, J=7), 1.5—2.2 (4H, m), 3.33 (1H, t, J=7), 3.88 (2H, t, J=7), 4.15 (4H, q, J=7), 6.68 (2H, d, J=9), 7.10 (2H, d, J=9).

Diethyl α-Chloro-α-[4-(4-chlorophenoxy)butyl]malonate: A mixture of diethyl 4-(4-chlorophenoxy)-butylmalonate (10.0 g) and sulfuryl chloride (5.9 g) was heated at 70°C for 1 h, then concentrated. The residue was dissolved in Et_2O (200 ml). The solution was successively washed with H_2O, sat. aq. $NaHCO_3$ and H_2O, dried ($MgSO_4$) and concentrated to give crystals (8.9 g, 81.7%). Recrystallization from hexane gave colorless rods, mp 51—52°C. IR ν_{max}^{Nujol} cm^{-1}: 1740. NMR δ: 1.27 (6H, t, J=7), 1.4—2.0 (4H, m), 2.29 (2H, t, J=7), 3.91 (2H, t, J=6), 4.26 (4H, q, J=7), 6.78 (2H, d, J=9), 7.22 (2H, d, J=9). *Anal.* Calcd for $C_{17}H_{22}Cl_2O_5$: C, 54.12; H, 5.88. Found: C, 54.29; H, 5.89.

2-Chloro-6-(4-chlorophenoxy)hexanoic Acid: A mixture of diethyl α-chloro-α-[4-(4-chlorophenoxy)butyl]-malonate (3.77 g), AcOH (15 ml) and 6 N HCl (15 ml) was refluxed for 20 h, cooled, diluted with H_2O and extracted with C_6H_6. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated to give crystals (1.62 g, 58.5%). Recrystallization from cyclohexane gave colorless plates, mp 86—87°C. IR ν_{max}^{Nujol} cm^{-1}: 1720. NMR δ: 1.4—2.3 (6H, m), 3.91 (2H, t, J=6), 4.33 (1H, t, J=7), 6.78 (2H, d, J=9), 7.22 (2H, d, J=9), 10.54 (1H, s). *Anal.* Calcd for $C_{12}H_{14}Cl_2O_3$: C, 52.01; H, 5.09. Found: C, 52.08; H, 5.03.

5-[4-(4-Chlorophenoxy)butyl]thiazolidine-2,4-dione (**84**): A mixture of 2-chloro-6-(4-chlorophenoxy)-hexanoic acid (2.8 g), thiourea (1.1 g) and 2-methoxyethanol (20 ml) was stirred at 110°C for 3 h, then 2 N HCl (20 ml) was added thereto. The mixture was refluxed for 8 h, cooled, diluted with H_2O and extracted with AcOEt. The usual work-up gave **84** as crystals (2.0 g, 66.7%). Recrystallization from AcOEt–hexane gave colorless prisms, mp 79—80°C. IR ν_{max}^{Nujol} cm^{-1}: 3160, 1745, 1690. NMR δ: 1.6—2.6 (6H, m), 3.92 (2H, t, J=7), 4.30 (1H, t, J=7), 6.75 (2H, d, J=9), 7.21 (2H, d, J=9), 8.70 (1H, br s). *Anal.* Calcd for $C_{13}H_{14}ClNO_3S$: C, 52.09; H, 4.71; N, 4.67. Found: C, 52.11; H, 4.85; N, 4.80.

2-Hydroxy-2-(4-phenethyloxyphenyl)acetic Acid: $CHBr_3$ (12.6 g) was added to a stirred and ice-cooled mixture of 4-phenethyloxybenzaldehyde[11] (11.3 g), LiCl (4.2 g), KOH (11.2 g), H_2O (50 ml) and dioxane (50 ml). The mixture was stirred at 5°C for 25 h then at 35°C for 25 h, acidified with 2 N HCl and extracted with Et_2O. The usual work-up gave crystals of the title compound (9.8 g, 72.1%). Recrystallization from AcOEt–hexane gave colorless needles, mp 136—137°C. IR ν_{max}^{Nujol} cm^{-1}: 3450, 1745, 1715. NMR δ: 3.07 (2H, t, J=7), 4.0 (1H, br s), 4.15 (2H, t, J=7), 5.16 (1H, s), 6.87 (2H, d, J=9), 7.28 (5H, s), 7.35 (2H, d, J=9). *Anal.* Calcd for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.74; H, 5.96.

Methyl 2-Hydroxy-2-(4-phenethyloxyphenyl)acetate: Reaction of 2-hydroxy-2-(4-phenethyloxyphenyl)-acetic acid (2.7 g) and a solution of CH_2N_2 in Et_2O gave the title compound as an oil (2.8 g, quant.). IR ν_{max}^{neat} cm^{-1}: 3500, 1735. NMR δ: 3.10 (2H, t, J=7), 3.42 (1H, d, J=5), 3.73 (3H, s), 4.20 (2H, t, J=7), 5.15 (1H, d, J=5), 6.8—7.4 (9H, m).

Methyl 2-Chloro-2-(4-phenethyloxyphenyl)acetate (XI): Thionyl chloride (0.22 ml) and pyridine (0.23 ml) were added to a solution of methyl 2-hydroxy-2-(4-phenethyloxyphenyl)acetate (0.8 g) in C_6H_6 (10 ml). The mixture was stirred at room temperature for 1 h and at 50°C for 30 min, then concentrated *in vacuo*. The residue was diluted with H_2O and extracted with Et_2O. The usual work-up gave an oily residue, which was chromatographed on silica gel (20 g). Elution with cyclohexane–AcOEt (9: 1, v/v) gave XI as an oil (0.56 g, 66.0%). IR ν_{max}^{neat} cm^{-1}: 1755. NMR δ: 3.08 (2H, t, J=6), 3.75 (3H, s), 4.18 (2H, t, J=6), 5.35 (1H, s), 6.7—7.5 (9H, m).

5-(4-Phenethyloxyphenyl)thiazolidine-2,4-dione (**85**): A mixture of XI (0.56 g), thiourea (0.28 g) and sulfolane (3 ml) was stirred at 110°C for 6 h, then 2 N HCl (3 ml) was added thereto. The mixture was stirred at 100°C for 15 h, diluted with H_2O and extracted with Et_2O. The usual work-up gave crystals of **85** (0.32 g, 55.6%). Recrystallization from EtOH gave colorless prisms, mp 121—122°C. IR ν_{max}^{KBr} cm^{-1}: 3190, 1755, 1725, 1685. NMR δ: 3.10 (2H, t, J=7), 4.20 (2H, t, J=7), 5.33 (1H, s), 6.97 (2H, d, J=9), 7.37 (2H, d, J=9), 7.39 (5H, s), 9.0 (1H, br s). *Anal.* Calcd for $C_{17}H_{15}NO_3S$: C, 65.16; H, 4.82; N, 4.47. Found: C, 65.06; H, 4.80; N, 4.60.

Ethyl 2-Chloro-3-(4-pivaloylphenyl)propionate: A solution of ethyl 2-chloroacetoacetate[12] (1.6 g) in DMF (40 ml) was treated with 50% NaH in oil (0.48 g) and the mixture was stirred at room temperature for 30 min. 4-Pivaloylbenzyl bromide[13] (2.1 g) was added to the mixture. The whole was stirred at 70°C for 2 h, poured into ice-H_2O, acidified with 2 N HCl and extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated. The residue was dissolved in EtOH (20 ml), and $Ba(OH)_2 \cdot 8H_2O$ (1.2 g) was added to the stirred and ice-cooled solution. After being stirred for 20 min, the mixture was poured into ice-H_2O and extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (40 g) using cyclohexane–iso-Pr_2O (4: 1, v/v) as an eluent to give the title compound (1.16 g, 48.3%) as a pure oil. IR ν_{max}^{neat} cm^{-1}: 1740, 1670. NMR

δ: 1.23 (3H, t, J=7), 1.32 (9H, s), 3.10 (1H, q, J=14 and 7), 3.40 (1H, q, J=14 and 7), 4.13 (2H, q, J=7), 4.33 (1H, t, J=7), 7.20 (2H, d, J=9), 7.65 (2H, d, J=9).

Ethyl 2-Chloro-3-(3,4-dimethoxyphenyl)propionate: Reaction of 3,4-dimethoxybenzyl chloride[14] (22.5 g) and 2-chloroacetoacetate[12] (19.8 g) gave the title compound as an oil (12.7 g, 38.8%). IR ν_{max}^{neat} cm^{-1}: 1740. NMR δ: 1.21 (3H, t, J=7), 3.00 (1H, q, J=14 and 7), 3.30 (1H, q, J=14 and 7), 3.75 (6H, s), 4.15 (2H, q, J=7), 4.27 (1H, t, J=7), 6.66 (3H, s).

2-Chloro-3-(2,4,5-triethoxyphenyl)propionic Acid: The condensation of 2-chloroacetoacetate[12] (4.13 g) with 2,4,5-triethoxybenzyl chloride (6.5 g) followed by treatment with 2 N KOH (30 ml) gave the title compound as crystals (5.5 g, 69.9%), mp 98—99°C (from AcOEt–hexane). IR ν_{max}^{Nujol} cm^{-1}: 1725. NMR δ: 1.37 (3H, t, J=7), 1.40 (3H, t, J=7), 1.42 (3H, t, J=7), 3.08 (1H, q, J=14 and 7), 3.38 (1H, q, J=14 and 7), 3.8—4.4 (6H, m), 4.63 (1H, t, J=7), 6.52 (1H, s), 6.78 (1H, s), 10.66 (1H, s). *Anal.* Calcd for $C_{15}H_{21}ClO_5$: C, 56.87; H, 6.68. Found: C, 56.98; H, 6.70.

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