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Studies on Antidiabetic Agents. I. Synthesis of 5-[4-(2-Methyl-2-phenylpropoxy)-benzyl]thiazolidine-2,4-dione (AL-321) and Related Compounds

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A series of compounds bearing the 4-(2-methyl-2-phenylpropoxy)benzyl moiety was prepared and their hypoglycemic and hypolipidemic activities were evaluated with genetically obese and diabetic mice, yellow KK. Among these compounds, 5-[4-(2-methyl-2-phenylpropoxy)benzyl]thiazolidine-2,4-dione (**18**, AL-321) was found to prossess hypoglycemic and hypolipidemic activities higher than or comparable to those of ethyl 2-chloro-3-[4-(2-methyl-2-phenylpropoxy)phenyl]propionate (**1a**). The acidic thiazolidine-2,4-dione ring appeared to be essential for the activities.

Keywords——hypoglycemic activity; hypolipidemic activity; 5-[4-(2-methyl-2-phenylpropoxy)benzyl]thiazolidine-2,4-dione; genetically obese and diabetic mice (yellow KK); structure–activity relationship

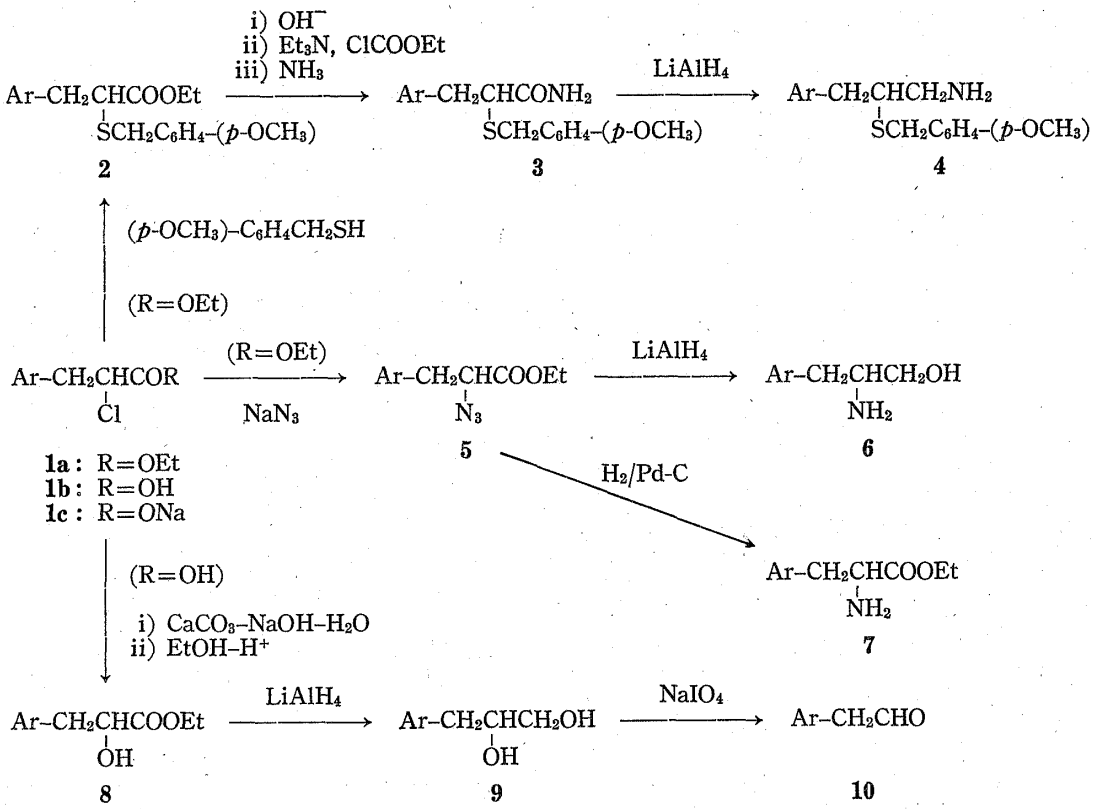
During the course of our search for novel hypolipidemic agents, we found that ethyl 2-chloro-3-[4-(2-methyl-2-phenylpropoxy)phenyl]propionate[1] (**1a**, AL-294) was effective against hyperglycemia and hyperlipidemia in genetically obese and diabetic mice, yellow KK,[2] which develop glucose and lipid dismetabolism associated with severe insulin resistance. We thus continued chemical modification studies of **1a** to seek compounds with better activity. This paper describes the structure–activity relationships of a variety of compounds bearing the 4-(2-methyl-2-phenylpropoxy)benzyl moiety, which seemed to be the most promising functional group in terms of activity and toxicity, as we have reported previously.[1c]

Chemistry

All compounds possessing the 4-(2-methyl-2-phenylpropoxy)benzyl moiety listed in Table I were prepared starting from **1a** or its derivatives (**1b**, **c**) by initial displacement of the active chlorine atom by other nucleophiles. The synthetic scheme for the preparation of some intermediate compounds (**2**—**10**) is shown in Chart 1.

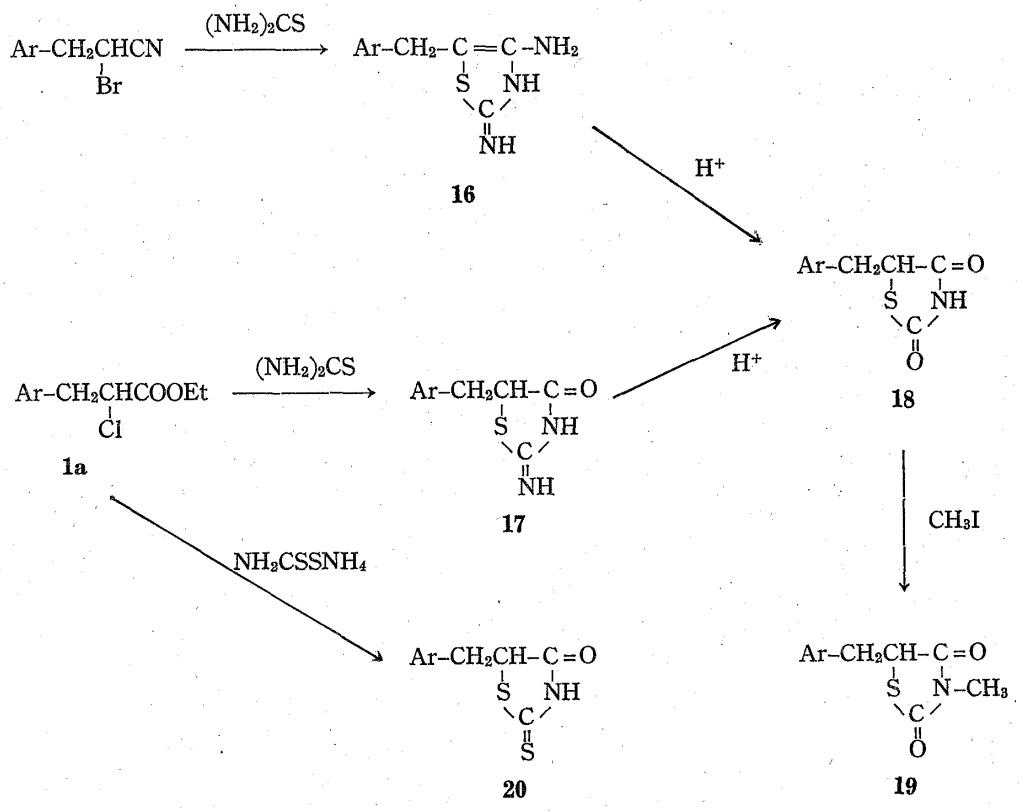
The 2-mercapto ester (**11**) was prepared by treatment of **2** with mercury(II) trifluoroacetate according to the method of Fujino *et al.*[3] Other 2-mercapto analogues (**12**—**15**) were obtained from **1a** or **1b** by reaction with the corresponding thiol derivatives as described in the experimental section. Thiazoline and thiazolidine derivatives (**16**—**20**) were prepared by means of the sequence shown in Chart 2.[4] The reaction of **1a** with thiourea and ammonium dithiocarbamate afforded **17** and **20**, respectively. In an analogous fashion, 4-amino-2-imino-Δ^4-thiazoline (or its tautomer) (**16**) was prepared from 2-bromo-3-[4-(2-methyl-2-phenylpropoxy)-phenyl]propionitrile by reaction with thiourea. Acid hydrolysis of **16** and **17** afforded the thiazolidine-2,4-dione (**18**), which yielded the *N*-methylated compound (**19**) on methylation.

Compounds **21** and **23** were prepared by treatment of **4** with mercury(II) trifluoroacetate followed by cyclization with formaldehyde and phosgene, respectively. The preparation of **24** was based on the method of Crawhall *et al.*[5] starting from the aminoalcohol (**6**). The reaction of **10** with 2-mercaptoethylamine gave **22**. The oxazolidine-2,4-dione (**25**) and the imidazolidine-2,4-dione (**26**) were prepared by the usual method from the 2-hydroxy ester (**8**) and the 2-amino ester (**7**), respectively (see "Experimental"). The thiazine derivatives **27**, **28** and **29** were prepared starting from **1a** as shown in Chart 3.



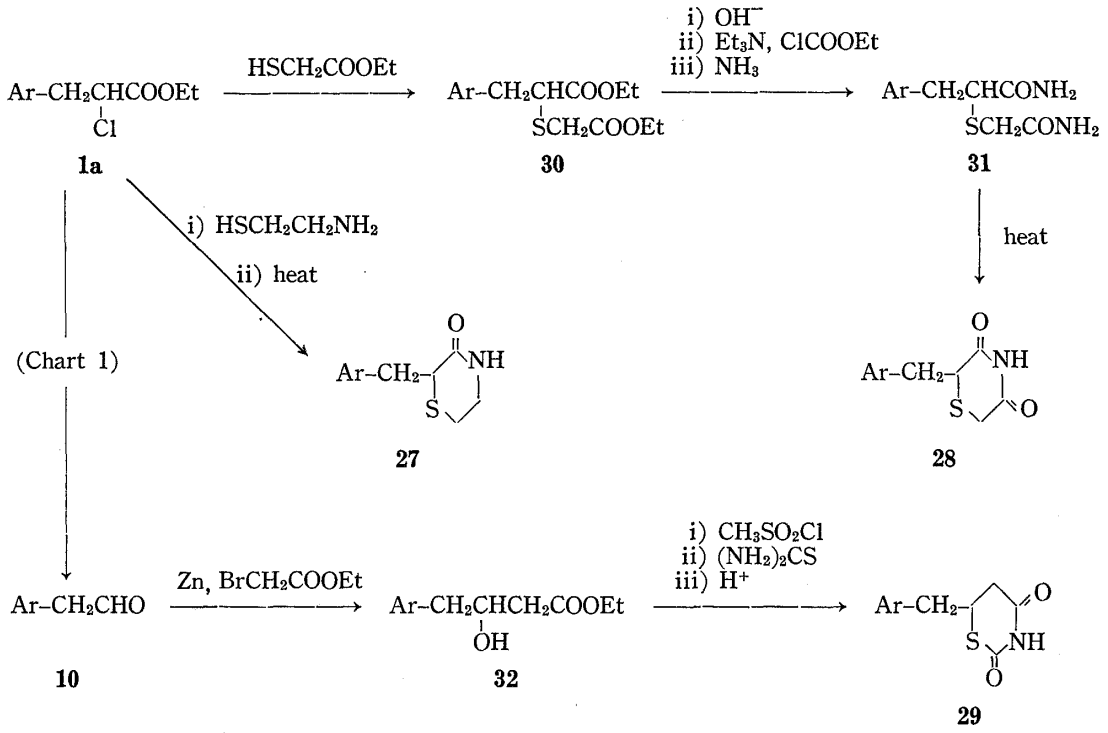
Ar=4-(2-methyl-2-phenylpropoxy)phenyl

Chart 1



Ar=4-(2-methyl-2-phenylpropoxy)phenyl

Chart 2



Ar=4-(2-methyl-2-phenylpropoxy)phenyl

Chart 3

Biological Method

Genetically obese and diabetic mice, yellow KK[2] (male, 9 weeks old), were used. After prefeeding on a powdered 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% concentration, were mixed thoroughly with the powdered CE-2 diet. The mice were fed the experimental diet and water *ad libitum* for 4 d. Blood samples were taken from the orbital vein. Blood glucose and plasma triglyceride levels 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.

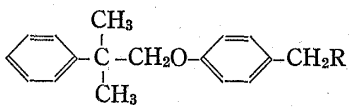
Results and Discussion

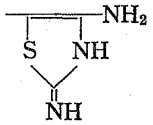
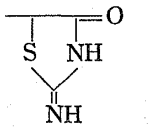
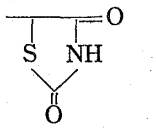
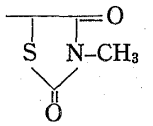
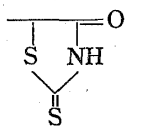
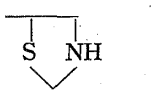
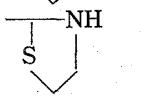
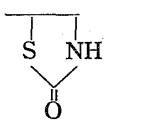
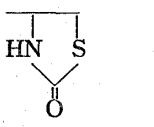
The structures, physical constants and biological data of the prepared compounds possessing the 4-(2-methyl-2-phenylpropoxy)benzyl moiety are shown in Table I.

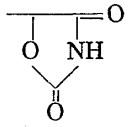
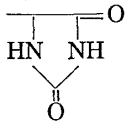
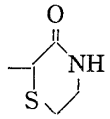
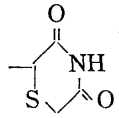
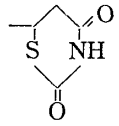
Our previous study[1b] on a series of 2-chloro-3-arylpropionic acids showed that substitution of the 2-chlorine atom with a hydroxy, a methoxy or an amino group as well as a hydrogen atom reduced the activities. The 2-mercapto analogues (**11**—**15**) prepared in this work also showed weaker activity than the parent compound **1a** (AL-294) indicating that substitution with a thiol moiety does not offer a potentiating effect. These results led us to study 5- or 6-membered heterocyclic compounds which can be derived from **1a**—**1c** and contain the 4-(2-methyl-2-phenylpropoxy)benzyl group.

Among the thiazolidine analogues (**16**—**24**); 5-[4-(2-methyl-2-phenylpropoxy)benzyl]-thiazolidine-2,4-dione (**18**, AL-321) showed more potent hypoglycemic activity than **1a**, though its hypolipidemic activity was slightly weaker than that of **1a**. The analogues of **18** bearing

Table I. Biological Properties of Compounds bearing the 4-(2-Methyl-2-phenylpropoxy)benzyl Moiety



No.	R	Activity[a]	
		Hypoglycemic activity	Plasma triglyceride-lowering activity
1a	$-CH(Cl)COOEt$ (AL-294)	2	4
11	$-CH(SH)COOEt$	2	0
12	$-CH(SCH_3)COOH$	1	0
13	$-CH(SCOCH_3)COOEt$	1	0
14[b]	$-CH(SCH_2CH(NH_2)COOH)COOH$	1	0
15[c]	$-CH(SCH_2CH_2NH_2)COOEt$	1	0
16[d]		0	0
17		2	1
18	 (AL-321)	3	3
19		0	0
20		2	0
21[e]		1	0
22		0	0
23		1	1
24		0	0

No.	R	Activity[a]	
		Hypoglycemic activity	Plasma triglyceride-lowering activity
25		1	1
26		0	0
27		0	0
28		0	0
29		0	1

a) Maximum reductions in blood glucose and plasma triglyceride levels at the dosage of 0.1% (w/w) in the diet were calculated as percentages 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.
b) Hemihydrate.
c) Hydrogen oxalate hemihydrate.
d) Monohydrate.
e) Hydrogen oxalate.

a modified thiazolidine-2,4-dione ring, *i.e.*, 2-imino (**17**), 2,4-diimino (tautomeric form of **16**) and 2-thioxo (**20**), showed considerably lower activities than **18**. *N*-Methylation completely removed the activities (see **19**). The other thiazolidine analogues lacking one or two oxo moieties (**21**, **22**, **23**, **24**) were also only slightly active or inactive. These observations with thiazolidine analogues suggest that the weak acidity of the thiazolidine-2,4-dione ring is important for the activities. The considerable retention of the activities in the 2-thioxothiazolidin-4-one (**20**) and the 2-iminothiazolidin-4-one (**17**) is thought to be due to the weak acidity of the rhodanine ring and the ease of hydrolysis to the thiazolidine-2,4-dione (**18**) in the animal body, respectively. However, the oxa (**25**), aza (**26**), and homo (**28** and **29**) analogues were only slightly active or inactive, though they have some acidity.

We concluded from this study that the thiazolidine-2,4-dione ring and its acidity are important factors affecting the activities. Various carboxylic acid derivatives which have fairly strong acidity and a large lipophilic group in the molecules are often adopted as antihyperlipidemic agents, *e.g.*, HCG-004,[8] nafenopin,[9] halofenate[10] and U-22105.[11] As the tetrazole moiety is a carboxylic acid substitute in nicotinic acid and several other hypolipidemic acids,[12–14] thiazolidine-2,4-dione is also expected to show a similar effect, possibly as an acetic acid substitute.

Conclusion

In a search for antihyperlipidemic agents, we prepared a series of compounds possessing the 4-(2-methyl-2-phenylpropoxy)benzyl moiety and evaluated their hypoglycemic and hypolipidemic activities in genetically obese and diabetic mice, yellow KK. Compound **18** (AL-321),

5-[4-(2-methyl-2-phenylpropoxy)benzyl]thiazolidine-2,4-dione, showed particularly potent hypoglycemic activity. Investigations are continuing on compounds possessing a thiazolidien-2,4-dione ring to develop a new antidiabetic agent.

Experimental

Melting points were determined on a 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 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.

Ethyl 2-(4-Methoxybenzylthio)-3-[4-(2-methyl-2-phenylpropoxy)phenyl]propionate (2)——Solutions of *p*-methoxybenzyl hydrosulfide (1.54 g) in dimethylformamide (DMF) (5 ml) and of **1a** (3.6 g) in DMF (10 ml) were added dropwise to a solution of Na (0.23 g) in EtOH (10 ml) at room temperature in that order. The mixture was stirred at room temperature for 10 min, poured into H_2O and extracted with Et_2O. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated to give **2** as an oil (4.8 g, quant.). IR ν_{max}^{neat} cm^{-1}: 1725. NMR δ: 1.19 (3H, t, J=7), 1.43 (6H, s), 2.8—3.6 (3H, m), 3.78 (5H, s), 3.94 (2H, s), 4.15 (2H, q, J=7), 6.7—7.7 (13H, m).

2-(4-Methoxybenzylthio)-3-[4-(2-methyl-2-phenylpropoxy)phenyl]propionamide (3)——A mixture of **2** (27.0 g), 2 N KOH (40 ml) and EtOH (150 ml) was refluxed for 10 min, cooled, diluted with H_2O, acidified with conc. HCl and extracted with Et_2O. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated to leave an oil (25.5 g). The oil was dissolved in tetrahydrofuran (THF) (200 ml). To this stirred and ice-salt-cooled solution, Et_3N (7.8 ml) and ethyl chloroformate (5.4 ml) were added in that order. The mixture was stirred for 15 min and a solution of NH_3 in EtOH (20%, w/w, 50 ml) was added thereto. The reaction mixture was stirred at room temperature for 10 min, poured into H_2O and extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated to give crystals of **3** (19.5 g, 76.5%). Recrystallization from AcOEt–hexane gave colorless rods, mp 86—87°C. IR ν_{max}^{Nujol} cm^{-1}: 3380, 3180, 1645. NMR δ: 1.47 (6H, s), 2.8—3.6 (3H, m), 3.65 (2H, s), 3.76 (3H, s), 3.90 (2H, s), 6.20 (2H, br s), 6.7—7.7 (13H, m). *Anal.* Calcd for $C_{27}H_{31}NO_3S$: C, 72.14; H, 6.95; N, 3.12. Found: C, 71.92; H, 6.99; N, 3.15.

1-Amino-2-(4-methoxybenzylthio)-3-[4-(2-methyl-2-phenylpropoxy)phenyl]propane Hydrogen Oxalate Hemihydrate [4·(COOH)$_2$·1/2H$_2$O]——A solution of **3** (12.0 g) in Et_2O (100 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (3.0 g) in Et_2O (100 ml) at room temperature. The mixture was refluxed for 2 h and the usual work-up gave the free base of **4** as an oil. The oil was dissolved in EtOH (5 ml) and a solution of oxalic acid (4.0 g) in EtOH (5 ml) was added thereto. The solution was treated with Et_2O (100 ml) to give crystals (8.5 g, 59.4%). Recrystallization from MeOH gave colorless prisms, mp 132—133°C. NMR (d_6-DMSO) δ: 1.39 (6H, s), 2.6—3.4 (5H, m), 3.67 (2H, s), 3.70 (3H, s), 3.97 (2H, s), 6.6—7.6 (13H, m), 7.85 (5H, br). *Anal.* Calcd for $C_{27}H_{33}NO_2S \cdot C_2H_2O_4 \cdot 1/2H_2O$: C, 65.15; H, 6.79; N, 2.62. Found: C, 65.18; H, 6.76; N, 2.59.

Ethyl 2-Azido-3-[4-(2-methyl-2-phenylpropoxy)phenyl]propionate (5)——A mixture of **1a** (0.72 g), NaN_3 (0.2 g), H_2O (0.5 ml) and DMSO (6 ml) was stirred at 95°C for 10 min, poured into H_2O and extracted with Et_2O. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated to give crystals (0.62 g, 84.4%). Recrystallization from EtOH gave colorless prisms, mp 65—66°C. IR ν_{max}^{Nujol} cm^{-1}: 2120, 1735. NMR δ: 1.37 (3H, t, J=7), 1.44 (6H, s), 2.8—3.4 (2H, m), 3.9—4.2 (1H, m), 3.90 (2H, s), 4.18 (2H, q, J=7), 6.72 (2H, d, J=9), 7.03 (2H, d, J=9), 7.1—7.5 (5H, m). *Anal.* Calcd for $C_{21}H_{25}N_3O_3$: C, 68.64; H, 6.86; N, 11.44. Found: C, 68.66; H, 6.80; N, 11.35.

2-Amino-3-[4-(2-methyl-2-phenylpropoxy)phenyl]-1-propanol Oxalate [6·1/2 (COOH)$_2$]——A solution of **5** (14.7 g) in Et_2O (100 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (3.0 g) in Et_2O (300 ml) at room temperature. The mixture was stirred at room temperature for 1 h and the usual work-up gave **6** as an oil (12.0 g, quant.). The oil was treated with a solution of oxalic acid (2.0 g) in EtOH (4 ml) to give the salt (11.2 g, 81.2%), mp 187—189°C (from MeOH–Et_2O). IR ν_{max}^{KBr} cm^{-1}: 3500—2500, 1575. NMR (d_6-DMSO) δ: 1.37 (6H, s), 2.8—3.7 (5H, m), 3.91 (2H, s), 6.77 (2H, d, J=9), 7.07 (2H, d, J=9), 7.2—7.5 (5H, m). *Anal.* Calcd for $C_{19}H_{25}NO_2 \cdot 1/2C_2H_2O_4$: C, 70.56; H, 7.61; N, 3.92. Found: C, 70.27; H, 7.67; N, 3.77.

Ethyl 2-Amino-3-[4-(2-methyl-2-phenylpropoxy)phenyl]propionate (7)——A mixture of **5** (2.0 g), 10% Pd-C (0.2 g) and EtOH (20 ml) was hydrogenated at room temperature and atmospheric pressure. After removal of the catalyst by filtration, the filtrate was concentrated to give **7** as an oil (1.85 g, quant.). IR ν_{max}^{neat} cm^{-1}: 3370, 1730. NMR δ: 1.23 (3H, t, J=7), 1.43 (6H, s), 1.66 (2H, br s), 2.7—3.2 (2H, m), 3.5—3.8 (1H, m), 3.96 (2H, s), 4.22 (2H, q, J=7), 6.87 (2H, d, J=9), 7.18 (2H, d, J=9), 7.2—7.7 (5H, m).

Ethyl 2-Hydroxy-3-[4-(2-methyl-2-phenylpropoxy)phenyl]propionate (8)——A mixture of **1b**[1c] (20.0 g), $CaCO_3$ (5.6 g), NaOH (2.4 g) and H_2O (100 ml) was stirred under reflux for 24 h, cooled, acidified with 6 N HCl and extracted with Et_2O. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated. The

residual oil was dissolved in EtOH (200 ml)–conc. H_2SO_4 (1 ml). The mixture was refluxed for 3 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 an oily residue. Purification by column chromatography on silica gel (200 g) using cyclohexane–AcOEt (10: 1, v/v) as an eluent gave crystals of **8** (11.8 g, 62.4%). Recrystallization from hexane gave colorless prisms, mp 52—53°C. IR ν_{max}^{Nujol} cm^{-1}: 3550, 1730. NMR δ: 1.27 (3H, t, $J=7$), 1.45 (6H, s), 2.77 (1H, d, $J=6$), 2.7—3.4 (2H, m), 3.93 (2H, s), 4.07 (2H, q, $J=7$), 4.40 (1H, m), 6.82 (2H, d, $J=9$), 7.15 (2H, d, $J=9$), 7.40—7.60 (5H, m). *Anal.* Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65. Found: C, 73.86; H, 7.81.

1,2-Dihydroxy-3-[4-(2-methyl-2-phenylpropoxy)phenyl]propane (9)——A solution of **8** (5.5 g) in Et_2O (20 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (0.8 g) in Et_2O (30 ml). The mixture was stirred at room temperature for 30 min and the usual work-up gave **9** as an oil (4.2 g, 87.5%). IR ν_{max}^{neat} cm^{-1}: 3350. NMR δ: 1.45 (6H, s), 2.70 (2H, d, $J=6$), 2.73 (2H, br s), 3.4—3.9 (3H, m), 3.95 (2H, s), 6.82 (2H, d, $J=9$), 7.13 (2H, d, $J=9$), 7.3—7.6 (5H, m).

4-(2-Methyl-2-phenylpropoxy)phenylacetaldehyde (10)——$NaIO_4$ (3.6 g) was added to a stirred solution of **9** (4.2 g) in 80% MeOH (50 ml), and the mixture was stirred at room temperature for 20 min. The insoluble solid was filtered off and the filtrate was diluted with H_2O. The usual work-up gave **10** as a crude oil. Purification by column chromatography on silica gel (60 g) using Et_2O–hexane (1: 2, v/v) as an eluent gave a pure oil (2.7 g, 72.2%). IR ν_{max}^{neat} cm^{-1}: 1720. NMR δ: 1.45 (6H, s), 3.58 (2H, d, $J=2$), 3.93 (2H, s), 6.86 (2H, d, $J=9$), 7.12 (2H, d, $J=9$), 7.3—7.7 (5H, m), 9.80 (1H, t, $J=2$).

Ethyl 2-Mercapto-3-[4-(2-methyl-2-phenylpropoxy)phenyl]propionate (11)——Mercuric trifluoroacetate (5.0 g) was added to a stirred solution of **2** (4.8 g) in 80% AcOH (30 ml), and the mixture was stirred at room temperature for 15 h. After treatment with H_2S gas for 15 min, the insoluble solid was filtered off. The filtrate was diluted with H_2O and extracted with Et_2O. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated to leave an oily residue, which was chromatographed on silica gel (40 g). Elution with cyclohexane–iso-Pr_2O (9: 1, v/v) gave **11** as an oil (2.34 g, 65.3%). IR ν_{max}^{neat} cm^{-1}: 1730. NMR δ: 1.18 (3H, t, $J=7$), 1.40 (6H, s), 2.03 (1H, d, $J=9$), 2.6—3.7 (3H, m), 3.87 (2H, s), 4.08 (2H, q, $J=7$), 6.73 (2H, d, $J=9$), 7.04 (2H, d, $J=9$), 7.27 (5H, s). *Anal.* Calcd for $C_{21}H_{26}O_3S$: C, 70.36; H, 7.31. Found: C, 70.64; H, 7.31.

3-[4-(2-Methyl-2-phenylpropoxy)phenyl]-2-methylthiopropionic Acid (12)——A solution of **1c**[1] (1.77 g) in DMF (4 ml) was treated with aq. $NaSCH_3$ solution (25%, w/w, 4 ml). The mixture was stirred at 80°C for 16 h, diluted with H_2O, acidified with 2 N HCl and extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated to leave an oily residue, which was chromatographed on silica gel (50 g). Elution with $CHCl_3$–MeOH (15: 1, v/v) gave **12** as an oil (1.32 g, 77.0%). IR ν_{max}^{neat} cm^{-1}: 3500—2500, 1700. NMR δ: 1.43 (6H, s), 2.03 (3H, s), 2.8—3.5 (3H, m), 3.93 (2H, s), 6.83 (2H, d, $J=9$), 7.18 (2H, d, $J=9$), 7.2—7.6 (5H, m), 10.3 (1H, br s). *Anal.* Calcd for $C_{20}H_{24}O_3S$: C, 69.74; H, 7.02. Found: C, 69.76; H, 7.06.

Ethyl 2-Acetylthio-3-[4-(2-methyl-2-phenylpropoxy)phenyl]propionate (13)——A mixture of **1a** (1.8 g), thiolacetic acid (0.9 g), K_2CO_3 (1.66 g) and DMF (8 ml) was stirred at room temperature for 2 h, diluted with H_2O and extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated. The residual oil was purified by column chromatography on silica gel (30 g) using cyclohexane–iso-Pr_2O (4: 1 v/v) as an eluent to give **13** as an oil (1.0 g, 50.0%). IR ν_{max}^{neat} cm^{-1}: 1735, 1700. NMR δ: 1.13 (3H, t, $J=7$), 1.40 (6H, s), 2.23 (3H, s), 2.82 (1H, q, $J=14$ and 7), 3.33 (1H, q, $J=14$ and 7), 3.90 (2H, s), 4.16 (2H, q, $J=7$), 4.44 (1H, t, $J=7$), 6.7—7.5 (9H, m). *Anal.* Calcd for $C_{23}H_{28}O_4S$: C, 68.34; H, 7.03. Found: C, 68.57; H, 7.05.

2-(2-Amino-2-carboxyethylthio)-3-[4-(2-methyl-2-phenylpropoxy)phenyl]propionic Acid Hemihydrate ($14 \cdot 1/2H_2O$)——A mixture of **1a** (0.84 g), cysteine hydrochloride monohydrate (0.40 g), K_2CO_3 (0.69 g) and DMF (5 ml)–H_2O (3 ml) was stirred at room temperature for 2 h and at 70°C for 5 h. After cooling, the mixture was poured into ice-H_2O, acidified with 2 N HCl and extracted with AcOEt. The AcOEt layer was extracted with sat. aq. $NaHCO_3$. The aqueous layer was neutralized with 1 N HCl and extracted with Et_2O. The aqueous layer was acidified to pH 4 with 1 N HCl. The precipitate was filtered off to yield **15** (0.38 g, 38.7%), mp 166—167°C (from EtOH). IR ν_{max}^{KBr} cm^{-1}: 3450, 1700, 1610. NMR (d_6-DMSO) δ: 1.52 (6H, s), 2.9 (4H, m), 3.6 (2H, m), 3.93 (2H, s), 6.7—7.5 (13H, m). *Anal.* Calcd for $C_{22}H_{27}NO_5S \cdot 1/2H_2O$: C, 61.95; H, 6.62; N, 3.28. Found: C, 62.27; H, 6.34; N, 3.04.

Ethyl 2-(2-Aminoethylthio)-3-[4-(2-methyl-2-phenylpropoxy)phenyl]propionate Hydrogen Oxalate Hemihydrate [$15 \cdot (COOH)_2 \cdot 1/2H_2O$]——A mixture of **1a** (7.2 g), 2-mercaptoethylamine (6.2 g) and EtOH (80 ml) was refluxed for 2 h, cooled and concentrated *in vacuo*. The residue was diluted with H_2O and extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated to leave an oil. The oil was dissolved in Et_2O (30 ml) and a solution of oxalic acid (2.0 g) in EtOH (5 ml) was added thereto to yield crystals (6.5 g, 65.0%), mp 78—81°C (from EtOH–H_2O). IR ν_{max}^{Nujol} cm^{-1}: 3300, 1735, 1670, 1620. NMR (d_6-DMSO) δ: 1.15 (3H, t, $J=7$), 1.36 (6H, s), 2.9 (6H, broad), 3.67 (1H, t, $J=7$), 4.00 (2H, s), 4.05 (2H, q, $J=7$), 6.75 (2H, q, $J=9$), 7.15 (2H, d, $J=9$), 7.0—7.6 (5H, m), 7.9 (6H, broad). *Anal.* Calcd for $C_{23}H_{31}NO_3S \cdot C_2H_2O_4 \cdot 1/2H_2O$: C, 59.98; H, 6.85; N, 2.80. Found: C, 59.72; H, 6.99; N, 2.84.

4-Amino-2-imino-5-[4-(2-methyl-2-phenylpropoxy)benzyl]-Δ^4-thiazoline Monohydrate ($16 \cdot H_2O$)——A mixture of 2-bromo-3-[4-(2-methyl-2-phenylpropoxy)phenyl]propionitrile (3.6 g) and thiourea (0.9 g) was heated at 120°C for 1 h and cooled. AcOEt (15 ml) and sat. aq. $NaHCO_3$ (50 ml) were added to the reaction

mixture. After being stirred for 15 min, the mixture was allowed to stand for 5 h. The resulting crystalline solid was filtered off to give **16**·H_2O (1.9 g, 51.7%). Recrystallization from MeOH gave colorless needles, mp 183—185°C. IR ν_{max}^{Nujol} cm^{-1}: 3350, 3260, 3150, 1645. NMR (d_6-DMSO) δ: 1.37 (6H, s), 3.00 (2H, s), 3.93 (2H, s), 6.72 (2H, d, J=9), 6.75 (1H, s), 7.12 (2H, d, J=9), 7.1—7.5 (5H, m), 8.20 (2H, br), 9.63 (1H, s). *Anal.* Calcd for $C_{20}H_{23}N_3OS \cdot H_2O$: C, 64.66; H, 6.78; N, 11.31. Found: C, 64.42; H, 6.59; N, 11.24.

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

2-Bromo-3-[4-(2-methyl-2-phenylpropoxy)phenyl]propionitrile——A mixture of 4-(2-methyl-2-phenylpropoxy)nitrobenzene[1c] (15.0 g), 10% Pd-C (1.0 g) and MeOH (150 ml) was hydrogenated at room temperature and atmospheric pressure. After removal of the catalyst by filtration, the filtrate was concentrated *in vacuo*. The residue was dissolved in acetone (150 ml). To this stirred and ice-salt-cooled solution, 47% HBr (28.6 g) and a solution of $NaNO_2$ (4.2 g) in H_2O (15 ml) were added dropwise below 5°C. The mixture was stirred at 5°C for 20 min and acrylonitrile (17.6 g) was added thereto. The temperature was raised to 35°C and powdered Cu_2O (0.5 g) was added to the mixture in small portions 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 residual oil was purified by column chromatography on silica gel (200 g) using Et_2O–hexane (1: 6, v/v) to give a pure oil (12.8 g, 64.6%). IR ν_{max}^{neat} cm^{-1}: 2220. NMR δ: 1.40 (6H, s), 3.10 (2H, d, J=7), 3.83 (2H, s), 4.15 (1H, t, J=7), 6.66 (2H, d, J=9), 6.98 (2H, d, J=9), 7.0—7.5 (5H, m).

2-Imino-5-[4-(2-methyl-2-phenylpropoxy)benzyl]thiazolidin-4-one (**17**)——A mixture of **1a** (1.08 g), thiourea (0.23 g), NaOAc (0.25 g) and EtOH (5 ml) was stirred under reflux for 16 h, cooled and diluted with H_2O. The precipitate was filtered off and recrystallized from EtOH–acetone to give colorless prisms (0.8 g, 75.0%), mp 210—212°C. IR ν_{max}^{nujol} cm^{-1}: 3230, 1670. NMR (d_6-DMSO) δ: 1.38 (6H, s), 2.85 (1H, q, J=14 and 10), 3.25 (1H, q, J=14 and 4), 3.98 (2H, s), 4.63 (1H, q, J=10 and 4), 6.80 (2H, d, J=9), 7.15 (2H, d, J=9), 7.3—7.6 (5H, m), 8.80 (1H, br s), 9.00 (1H, br s). *Anal.* Calcd for $C_{20}H_{22}N_2O_2S$: C, 67.77; H, 6.27; N, 7.90. Found: C, 67.56; H, 6.37; N, 7.59.

5-[4-(2-Methyl-2-phenylpropoxy)benzyl]thiazolidine-2,4-dione (**18**, **AL-321**)——a) A mixture of **17** (0.3 g), 6 N HCl (2 ml) and sulfolane (2 ml) was stirred at 110°C for 5 h and diluted with H_2O. The precipitate was filtered off and recrystallized from 80% EtOH to give **18** (0.25 g, 83.3%) as colorless plates, mp 110—111°C. IR ν_{max}^{Nujol} cm^{-1}: 3170, 1755, 1680. NMR δ: 1.43 (6H, s), 3.02 (1H, q, J=14 and 9), 3.48 (1H, q, J=14 and 4), 3.95 (2H, s), 4.50 (1H, q, J=9 and 4), 6.80 (2H, d, J=9), 7.10 (2H, d, J=9), 7.2—7.5 (5H, m), 11.0 (1H, br s). *Anal.* Calcd for $C_{20}H_{21}NO_3S$: C, 67.58; H, 5.95; N, 3.94. Found: C, 67.70; H, 5.87; N, 3.71.

b) A mixture of **16**·H_2O (1.0 g), 2 N HCl (10 ml) and EtOH (10 ml) was refluxed for 15 h and diluted with H_2O. The precipitate was filtered off and recrystallized from 80% EtOH to give **18** (0.78 g, 82.0%), mp 110—111°C.

3-Methyl-5-[4-(2-methyl-2-phenylpropoxy)benzyl]thiazolidine-2,4-dione (**19**)——A mixture of **18** (1.78 g), K_2CO_3 (0.4 g), CH_3I (0.9 ml) and DMF (5 ml) was stirred at 40°C for 2 h, diluted with H_2O and extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated *in vacuo* to leave an oily residue, which was chromatographed on silica gel (20 g). Elution with cyclohexane–AcOEt (9: 1, v/v) gave **19** as an oil. IR ν_{max}^{neat} cm^{-1}: 1750, 1690. NMR δ: 1.43 (6H, s), 3.00 (1H, q, J=14 and 9), 3.03 (3H, s), 3.48 (1H, q, J=14 and 4), 3.92 (2H, s), 4.40 (1H, q, J=9 and 4), 6.76 (2H, d, J=9), 7.07 (2H, d, J=9), 7.2—7.6 (5H, m).

5-[4-(2-Methyl-2-phenylpropoxy)benzyl]rhodanine (**20**)——A mixture of **1a** (3.5 g), Na_2CO_3 (0.6 g), ammonium dithiocarbamate (2.0 g), H_2O (10 ml) and EtOH (10 ml) was stirred at 0°C for 30 min then at room temperature for 24 h. Conc HCl (10 ml) was added thereto and the mixture was refluxed for 4 h. After cooling, the reaction mixture was poured into H_2O and extracted with AcOEt. The usual work-up gave **20** as crystals (1.1 g, 58.0%). Recrystallization from AcOEt–hexane gave pale yellow plates, mp 95—96°C. IR ν_{max}^{Nujol} cm^{-1}: 3170, 1720. NMR δ: 1.43 (6H, s), 3.05 (1H, q, J=14 and 9), 3.50 (1H, q, J=14 and 4), 3.95 (2H, s), 4.58 (1H, q, J=9 and 4), 6.90 (2H, d, J=9), 7.20 (2H, d, J=9), 7.3—7.7 (5H, m), 9.70 (1H, br s). *Anal.* Calcd for $C_{20}H_{21}NO_2S_2$: C, 64.66; H, 5.70; N, 3.77. Found: C, 64.87; H, 5.58; N, 3.76.

5-[4-(2-Methyl-2-phenylpropoxy)benzyl]thiazolidine Hydrogen Oxalate [**21**·$(COOH)_2$]——A mixture of **4**·$(COOH)_2 \cdot 1/2H_2O$ (2.3 g), mercuric trifluoroacetate (2.8 g) and 80% AcOH (20 ml) was stirred at room temperature for 16 h. After treatment with H_2S gas for 10 min, the insoluble solid was filtered off. The filtrate was concentrated *in vacuo* to give an oil. The oil was dissolved in THF (10 ml)–MeOH (10 ml). Formalin (1.0 ml) and AcOH (0.6 ml) were added to the solution. The mixture was stirred at room temperature for 10 min, diluted with 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 (50 g). Elution with cyclohexane–AcOEt (4: 1, v/v) gave **21** as an oil. NMR δ: 1.45 (6H, s), 2.6—3.7 (7H, m), 3.96 (2H, s), 6.73 (2H, d, J=9), 7.07 (2H, d, J=9), 7.2—7.6 (5H, m). The free base was dissolved in Et_2O (20 ml) and treated with a solution of oxalic acid (0.3 g) in EtOH (1 ml) to give crystals of the salt. Recrystallization from AcOEt gave colorless prisms (0.27 g, 15.0%), mp 127—131°C. *Anal.* Calcd for $C_{20}H_{25}NOS \cdot C_2H_2O_4$: C, 63.28; H, 6.52; N, 3.36. Found: C, 63.29; H, 6.51; N, 3.37.

2-[4-(2-Methyl-2-phenylpropoxy)benzyl]thiazolidine (**22**)——A mixture of **10** (0.67 g), 2-mercaptoethylamine (0.39 g), AcOH (0.2 ml) and THF (5 ml)–MeOH (5 ml) was refluxed for 5 min, diluted with H_2O and

extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated. The residue was treated with iso-Pr_2O to give crystals (0.6 g, 73.3%). Recrystallization from iso-Pr_2O gave colorless prisms, mp 78—79°C. IR ν_{max}^{Nujol} cm^{-1}: 3305. NMR δ: 1.45 (6H, s), 2.7—3.6 (6H, m), 3.94 (2H, s), 4.70 (1H, t, $J=6$), 6.80 (2H, d, $J=9$), 7.20 (2H, d, $J=9$), 7.2—7.6 (5H, m). *Anal.* Calcd for $C_{20}H_{25}NOS$: C, 73.35; H, 7.69; N, 4.28. Found: C, 73.34; H, 7.96; N, 4.10.

5-[4-(2-Methyl-2-phenylpropoxy)benzyl]thiazolidin-2-one (23)——A mixture of **4**·$(COOH)_2$·$1/2H_2O$ (2.3 g), mercuric trifluoroacetate (2.8 g) and 80% AcOH (20 ml) was stirred at room temperature for 16 h. After treatment with H_2S gas for 10 min, the insoluble solid was filtered off. The filtrate was concentrated *in vacuo* to leave an oily residue. The residue was diluted with H_2O and extracted with Et_2O. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated to leave an oil. The oil was dissolved in C_6H_6 (20 ml). To this stirred and ice-cooled solution were added Et_3N (1.46 ml) and a solution of phosgene in toluene (20%, w/w, 2.6 g). The mixture was stirred at room temperature for 30 min then poured into conc NH_4OH (20 ml). The organic layer was separated, washed with H_2O, dried ($MgSO_4$) and concentrated to leave an oily residue, which was chromatographed on silica gel (30 g). Elution with C_6H_6–acetone (10: 1, v/v) gave **23** as crystals (0.83 g, 56.5%). Recrystallization from AcOEt–hexane gave colorless prisms, mp 103—104°C. IR ν_{max}^{Nujol} cm^{-1}: 3250, 1670. NMR (d_6-DMSO) δ: 1.37 (6H, s), 2.8—3.6 (4H, m), 3.8—4.2 (1H, m), 3.94 (2H, s), 6.76 (2H, d, $J=9$), 7.10 (2H, d, $J=9$), 7.1—7.6 (5H, m), 7.87 (1H, br s). *Anal.* Calcd for $C_{20}H_{23}NO_2S$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.30; H, 6.84; N, 4.30.

4-[4-(2-Methyl-2-phenylpropoxy)benzyl]thiazolidin-2-one (24)——A stirred suspension of 2-amino-3-[4-(2-methyl-2-phenylpropoxy)phenyl]propyl methyl dithiolcarbonate hydrochloride (2.0 g) in EtOH (40 ml) was treated with 1 N NaOH (14.1 ml). After being stirred at room temperature for 10 min, the mixture was acidified with 2 N HCl, diluted with H_2O and extracted with Et_2O. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated to give crystals (1.15 g, 71.9%). Recrystallization from MeOH gave colorless prisms, mp 123—124°C. IR ν_{max}^{Nujol} cm^{-1}: 3170, 1670. NMR δ: 1.45 (6H, s), 2.85 (2H, d, $J=7$), 3.0—3.6 (2H, m), 3.90 (2H, s), 4.0 (1H, m), 6.30 (1H, br s), 6.80 (2H, d, $J=9$), 7.08 (2H, d, $J=9$), 7.2—7.7 (5H, m). *Anal.* Calcd for $C_{20}H_{23}NO_2S$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.12; H, 6.81; N, 4.00.

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

2-(*N*-Dithiocarbomethoxy)-3-[4-(2-methyl-2-phenylpropoxy)phenyl]propan-1-ol——Et_3N (1.67 ml) and CS_2 (0.72 ml) were added in that order to a stirred and ice-cooled solution of **6** (3.6 g) in pyridine (80 ml). Stirring was continued with ice-cooling for 1 h, then CH_3I (0.82 ml) was added. The mixture was allowed to stand in an ice box overnight, then poured into H_2O and extracted with Et_2O. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated *in vacuo* to leave an oil, which was chromatographed on silica gel (80 g). Elution with Et_2O–hexane (1: 1, v/v) gave a pure oil (4.2 g, 89.9%). IR ν_{max}^{neat} cm^{-1}: 3330—3200, 1510, 1245. NMR δ: 1.45 (6H, s), 2.12 (1H, br s), 2.60 (3H, s), 2.8—3.1 (2H, m), 3.66 (2H, d, $J=6$), 3.90 (2H, s), 4.6—4.8 (1H, m), 6.82 (2H, d, $J=9$), 7.15 (2H, d, $J=9$), 7.3—7.6 (5H, m). *Anal.* Calcd for $C_{21}H_{27}NO_2S_2$: C, 64.76; H, 6.99; N, 3.60. Found: C, 64.69; H, 6.92; N, 3.50.

4-(2-Methyl-2-phenylpropoxy)benzyl-2-methylthio-Δ^2-thiazoline——A solution of 2-(*N*-dithiocarbomethoxy)-3-[4-(2-methyl-2-phenylpropoxy)phenyl]propan-1-ol (3.7 g) in Et_2O (30 ml) was added dropwise to thionyl chloride (30 ml) with ice-cooling. The mixture was stirred for 1 h, poured into ice-H_2O 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 (70 g) using Et_2O–hexane (1: 10, v/v) as an eluent to give a pure oil (2.0 g, 56.7%). NMR δ: 1.45 (6H, s), 2.46 (3H, s), 2.7—3.5 (4H, m), 3.90 (2H, s), 4.3—4.8 (1H, m), 6.78 (2H, d, $J=9$), 7.12 (2H, d, $J=9$), 7.3—7.6 (5H, m). *Anal.* Calcd for $C_{21}H_{25}NOS_2$: C, 67.90; H, 6.78; N, 3.77. Found: C, 67.83; H, 6.85; N, 3.56.

2-Amino-3-[4-(2-methyl-2-phenylpropoxy)phenyl]propyl Methyl Dithiolcarbonate Hydrochloride——A mixture of 4-(2-methyl-2-phenylpropoxy)benzyl-2-methylthio-Δ^2-thiazoline (2.0 g), 6 N HCl (25 ml) and EtOH (25 ml) was refluxed for 12 h and concentrated *in vacuo* to a half of the original volume. The crystals formed were filtered off and recrystallized from EtOH to give colorless prisms (1.5 g, 65.2%). IR ν_{max}^{Nujol} cm^{-1}: 3400, 3200—2300, 1635. NMR (d_6-DMSO) δ: 1.39 (6H, s), 2.42 (3H, s), 2.6—3.6 (5H, m), 3.95 (2H, s), 6.82 (2H, d, $J=9$); 7.13 (2H, d, $J=9$), 7.2—7.5 (5H, m), 8.43 (3H, br s). *Anal.* Calcd for $C_{21}H_{27}NO_2S_2$·HCl: C, 59.20; H, 6.62; N, 3.29. Found: C, 59.47; H, 6.70; N, 3.25.

5-[4-(2-Methyl-2-phenylpropoxy)benzyl]oxazolidine-2,4-dione (25)——A mixture of **8** (1.26 g), urea (0.4 g), a solution of $NaOCH_3$ (0.28 g) in MeOH (1 ml) and EtOH (10 ml) was stirred at room temperature for 1 h and refluxed for 4 h. After cooling, the mixture was concentrated to leave an oily residue. The residue was acidified with 2 N HCl 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 $CHCl_3$–MeOH (20: 1, v/v) as an eluent to give crystals (0.92 g, 74.0%). Recrystallization from EtOH gave colorless prisms, mp 87—88°C. IR ν_{max}^{Nujol} cm^{-1}: 3420, 3230, 1820, 1750, 1720. NMR δ: 1.43 (6H, s), 3.15 (2H, q, $J=5$ and 2), 3.92 (2H, s), 5.00 (1H, t, $J=5$), 6.80 (2H, d, $J=9$), 7.15 (2H, d, $J=9$), 7.2—7.5 (5H, m), 8.80 (1H, br s). *Anal.* Calcd for $C_{20}H_{21}NO_4$: C, 70.28; H, 6.24; N, 4.13. Found: C, 69.99; H, 6.24; N, 3.78.

5-[4-(2-Methyl-2-phenylpropoxy)benzyl]imidazolidine-2,4-dione (26)——Ethyl chlorocarbonate (0.6 ml) was added to a stirred and ice-cooled solution of **7** (2.0 g) in CH_2Cl_2 (20 ml). After being stirred for 10 min,

the mixture was washed with H_2O and dried ($MgSO_4$). The solvent was evaporated off to leave an oil, which was dissolved in saturated methanolic ammonia (30 ml). The mixture was heated at 100°C for 6 h in a sealed tube. After removal of the solvent, MeOH (10 ml) and 4 N KOH (5 ml) were added to the crystalline residue. The mixture was refluxed for 1 h and concentrated *in vacuo*. The residue was acidified with 2 N HCl to give crystals (1.1 g, 55.5%). Recrystallization from MeOH gave colorless needles, mp 160—161°C. IR ν_{max}^{Nujol} cm^{-1}: 3230, 1700. NMR δ: 1.55 (6H, s), 2.6—3.4 (2H, m), 4.03 (2H, s), 4.35 (1H, q, J=9 and 4), 6.10 (1H, br s), 6.95 (2H, d, J=9), 7.10 (2H, d, J=9), 7.4—7.8 (5H, m), 8.65 (1H, br s). *Anal.* Calcd for $C_{20}H_{22}N_2O_3S$: C, 70.98; H, 6.55; N, 8.28. Found: C, 71.31; H, 6.75; N, 8.33.

2-[4-(2-Methyl-2-phenylpropoxy)phenyl]-perhydro-1,4-thiazin-3-one (27)——The oily free base obtained from **15**·$(COOH)_2$·$1/2H_2O$ (1.5 g) in the usual way was heated at 120°C for 2.5 h, cooled and treated with iso-Pr_2O to give crystals (0.9 g, 84.9%). Recrystallization from iso-Pr_2O gave colorless needles, mp 109—110°C. IR ν_{max}^{Nujol} cm^{-1}: 3330, 3300, 1675, 1625. NMR δ: 1.55 (6H, s), 2.6—3.9 (7H, m), 4.00 (2H, s), 6.90 (2H, d, J=9), 7.30 (2H, d, J=9), 7.3—7.8 (5H, m). *Anal.* Calcd for $C_{21}H_{25}NO_2S$: C, 70.95; H, 7.09; N, 3.94. Found: C, 70.81; H, 7.11; N, 3.89.

2-[4-(2-Methyl-2-phenylpropoxy)benzyl]-perhydro-1,4-thiazine-3,5-dione (28)——**31** (3.5 g) was heated at 200°C for 1.5 h. After cooling, the dark brown oil was chromatographed on silica gel (90 g). Elution with cyclohexane–AcOEt (4: 1, v/v) gave **28** as crystals (0.43 g, 13.4%). Recrystallization from Et_2O–hexane gave colorless needles, mp 110—111°C. IR ν_{max}^{Nujol} cm^{-1}: 3190, 3090, 1715, 1680. NMR δ: 1.42 (6H, s), 2.90 (1H, q, J=14 and 8), 3.30 (2H, s), 3.4—3.7 (2H, m), 3.86 (2H, s), 6.76 (2H, d, J=9), 7.08 (2H, d, J=9), 7.2—7.5 (5H, m), 8.10 (1H, br s). *Anal.* Calcd for $C_{21}H_{23}NO_3S$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.55; H, 6.27; N, 3.70.

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

Ethyl 2-Ethoxycarbonylmethylthio-3-[4-(2-methyl-2-phenylpropoxy)phenyl]propionate (30)——Ethyl thioglycolate (1.83 g) and **1a** (5.0 g) were added to a solution of Na (0.36 g) in EtOH (40 ml). The mixture was stirred at room temperature 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 leave an oil. Purification by column chromatography on silica gel (100 g) using cyclohexane–iso-Pr_2O (10: 1, v/v) as an eluent gave **30** as an oil (4.8 g, 77.4%). IR ν_{max}^{neat} cm^{-1}: 1730. NMR δ: 1.20 (3H, t, J=7), 1.23 (3H, t, J=7), 1.40 (6H, s), 2.8—3.8 (5H, m), 3.83 (2H, s), 4.03 (2H, q, J=7), 6.68 (2H, d, J=9), 7.00 (2H, d, J=9), 7.1—7.5 (5H, m). *Anal.* Calcd for $C_{25}H_{32}O_5S$: C, 67.55; H, 7.26. Found: C, 67.51; H, 7.33.

2-Carbamoylmethylthio-3-[4-(2-methyl-2-phenylpropoxy)phenyl]propionamide (31)——The diester **30** (3.3 g) was saponified to give an oily diacid in the usual way. The oil (2.9 g) was dissolved in THF (50 ml), then Et_3N (2.48 ml) and ethyl chloroformate (1.71 ml) were added to the stirred and ice-cooled solution. After stirring at 0°C for 15 min, a solution of NH_3 in EtOH (20%, w/w, 5 ml) was added to the mixture. The reaction mixture was stirred at 5°C for 15 min and the usual work-up gave crystals of **31** (0.55 g, 19.2%). Recrystallization from MeOH gave colorless prisms, mp 128—129°C. IR ν_{max}^{Nujol} cm^{-1}: 3370, 3180, 1655. NMR (d_6-DMSO) δ: 1.38 (6H, s), 2.8 (2H, m), 3.15 (2H, s), 3.45 (1H, q, J=9 and 6), 3.90 (2H, s), 6.72 (2H, d, J=9), 7.03 (2H, d, J=9), 6.7—7.5 (9H, m). *Anal.* Calcd for $C_{21}H_{26}N_2O_3S$: C, 65.27; H, 6.78; N, 7.25. Found: C, 65.51; H, 6.68; N, 7.10.

6-[4-(2-Methyl-2-phenylpropoxy)benzyl]-perhydro-1,3-thiazine-2,4-dione (29)——Methanesulfonyl chloride (0.56 ml) was added to a stirred and ice-cooled solution of **32** (2.15 g) in pyridine (10 ml). The mixture was stirred at room temperature for 1 h, poured into H_2O and extracted with Et_2O. The usual work-up gave an oily methanesulfonate. The oil was dissolved in sulfolane (10 ml) and thiourea (0.7 g) was added to the solution. The mixture was stirred at 110°C for 3 h and 6 N HCl (4 ml) was added thereto. The mixture was heated at 100°C for 16 h, cooled, diluted with H_2O and extracted with Et_2O. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated to leave an oil, which was purified by column chromatography on silica gel (30 g). Elution with $CHCl_3$–MeOH (99: 1, v/v) gave **29** as crystals (0.27 g, 12.0%). Recrystallization from AcOEt–hexane gave colorless prisms, mp 95—96°C. IR ν_{max}^{Nujol} cm^{-1}: 3150, 1730. NMR δ: 1.43 (6H, s), 2.73 (1H, q, J=16 and 9), 2.88 (2H, d, J=6), 2.90 (1H, q, J=16 and 5), 3.53 (1H, m), 3.90 (2H, s), 6.77 (2H, d, J=9), 7.01 (2H, d, J=9), 7.15—7.50 (5H, m), 8.30 (1H, br s). *Anal.* Calcd for $C_{21}H_{23}NO_3S$: C, 68.28; H, 6.27; N, 3.79. Found: C, 67.92; H, 6.14; N, 3.60.

Ethyl 3-Hydroxy-4-[4-(2-methyl-2-phenylpropoxy)phenyl]butylate (32)——A solution of **10** (9.8 g) and ethyl bromoacetate (18.4 g) in toluene (40 ml) was added dropwise to a stirred suspension of Zn powder (7.2 g) in toluene (40 ml) under reflux. The mixture was refluxed for 1 h and cooled, then 12 N H_2SO_4 (30 ml) was added dropwise and the organic layer was separated, washed with H_2O, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (150 g) using cyclohexane–AcOEt (6: 1, v/v) as an eluent to give **32** as an oil (4.1 g, 31.5%). IR ν_{max}^{neat} cm^{-1}: 3500, 1730. NMR δ: 1.23 (3H, t, J=7), 1.43 (6H, s), 2.2—2.9 (5H, m), 3.90 (2H, s), 4.17 (2H, q, J=7), 4.0—4.3 (1H, m), 6.73 (2H, d, J=9), 7.08 (2H, d, J=9), 7.2—7.6 (5H, m).

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