Reaction of 3-Phenylglycidic Esters. Part 2.[1]† Stereo- and Regio-selectivity in the Oxirane Ring Opening of Methyl *trans*-3-(4-Methoxyphenyl)glycidate with Various Thiophenols and the Effects of Solvent and Temperature

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The effects of the solvent and temperature on the reaction of the *trans*-glycidate (**1**) with various substituted thiophenols (**2**) in the presence or absence of a catalyst have been investigated. The temperature had a surprisingly large effect on the stereochemistry of the oxirane ring-opening of (**1**). At room temperature, the *erythro*-isomer (**4**) (*trans*-opening product) was obtained as a major product in the absence of catalyst, while the *cis*-opening product (**3**) (*threo*-isomer) was produced predominantly at higher temperature. On the other hand, in a dipolar aprotic solvent, the regioisomer (**5**) was formed, the yield increasing with the electron-donating ability of the substituents on (**2**). The formation of compound (**5**) may involve single-electron transfer as a key step.

The reactions of epoxides have been widely explored from both the synthetic and the biochemical aspects.[2,3] However, the mechanism of oxirane ring-opening has not been elucidated fully, especially in terms of the stereochemistry.

In an earlier paper,[1] we reported the highly stereoselective opening of the oxirane ring of methyl 3-(4-methoxyphenyl)-glycidate (**1**) with 2-nitrothiophenol (**2a**) which was achieved by the use of appropriate catalysts; for example, tin compounds effected the stereospecific *cis*-opening, while $MgCl_2$ and $CaCl_2$ brought about the *trans*-opening.

During the course of this work, we noticed that the reaction of compound (**1**) with 2-nitrothiophenol (**2a**) at room temperature in the absence of catalyst gave predominantly the *trans*-opening product (**4a**). This greatly contrasts with the predominant formation of the *cis*-opening product (**3a**) at higher temperatures in the absence of catalyst.[1] We have examined more closely the effect of temperature and solvent on the reaction of compound (**1**) with 2-nitrothiophenol (**2a**), and have investigated its reaction with other thiophenols (**2b**—**e**) under various conditions.

Results and Discussion

The reaction of the thiophenols (**2a**—**e**) with the glycidate (**1**) (Scheme 1) was examined in different solvents at various temperatures in the presence or absence of catalysts, and the results are summarized in Table 2. The *threo*- and *erythro*-α-hydroxy esters (**3**) and (**4**) and the regioisomer (**5**) were separated by column and preparative thin layer chromatography (t.l.c.). The planar structures of the α-hydroxy esters (**3b**—**d**) and (**4b**—**d**) were deduced by comparing their spectral data with those of the known 2-nitro derivatives (**3a**) and (**4a**). The mass spectra of compounds (**3**) and (**4**) showed the characteristic fragment ion peaks of $[M - CH(OH)CO_2Me]$ and $[M - CH(C_6H_4OMe)CH(OH)CO_2Me]$, which differ distinctly from those of the regioisomer (**5**) (see below). The stereochemistry of the esters (**3**) and (**4**) was deduced on the basis of the n.m.r. spectra of their corresponding 2-acetoxy derivatives (**6**) and (**7**). In an earlier paper,[1] we reported that the methyl signal of the acetoxy group of the *threo*-isomer (**6a**) appeared at higher field (δ2.12) than that of the *erythro* counterpart (**7a**) (δ2.20) and this difference was used to estimate the ratio of the mixture of (**6a**) and (**7a**). In addition, similar differences were observed for all the isomers (**6**) and (**7**) (Table 1) and they were therefore assigned *threo* and *erythro* configurations, respectively. This assignment was further confirmed by the completely stereoselective formation of the *erythro*-isomers (**4b**—**d**) in the $NaHCO_3$-catalysed reaction (Table 2, entry 15) *via trans*-opening of the epoxide ring by thiolate anion;[1,4b] in addition, the stereochemistry of the *threo*-isomer (**3b**) was established finally by an *X*-ray crystallographic analysis (Figures 1 and 2). The structures of the 2-amino derivatives (**3e**) and (**4e**) have been reported previously.[4]

Table 1. N.m.r. chemical shifts of the acetyl protons of the *threo*- and *erythro*-2-acetoxy derivatives (**6**) and (**7**) ($CDCl_3$, 100 MHz)

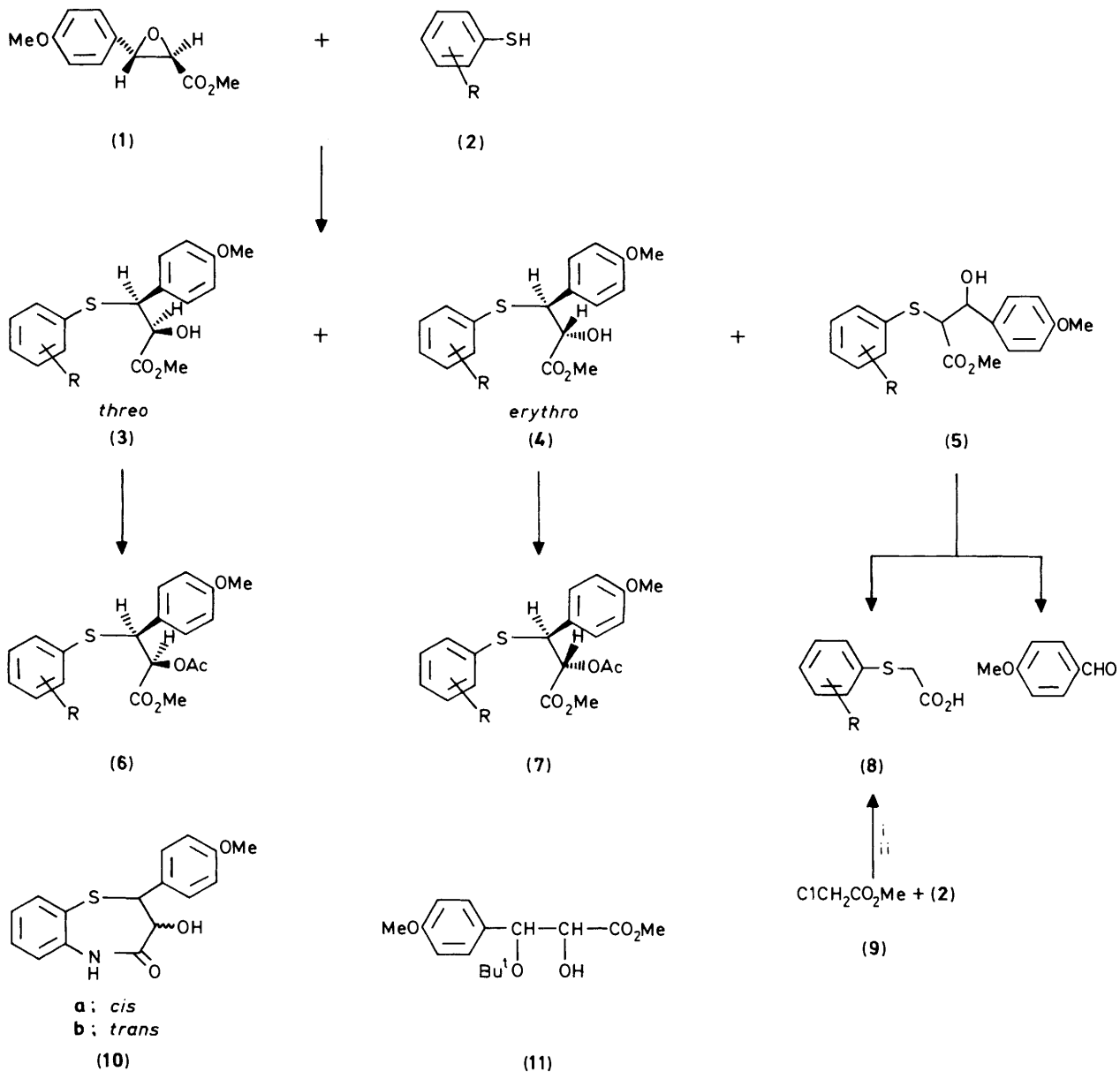
R	(6)	(7)
2-NO_2	2.12 (s)	2.20 (s)
4-NO_2	2.09 (s)	2.16 (s)
H	2.09 (s)	2.15 (s)
4-OMe	2.16 (s)	2.20 (s)

The *threo*/*erythro* ratios of the mixtures of isomers (**3a**) and (**4a**), and (**3b**) and (**4b**), which were not separable by t.l.c., were estimated on the basis of the n.m.r. spectra of their 2-acetoxy derivatives.[1] The ratio of the 2-amino derivatives (**3e**) and (**4e**) was determined by converting them into the *cis*- and *trans*-lactams (**10a**) and (**10b**).[1,4b]

The structure of the regioisomer (**5**), which was formed by attack of the thiol group on the α-position of the glycidate (**1**), was confirmed as follows. In the mass spectra, the molecular ion of compound (**5**) was identical with that of the regioisomer (**3**) or (**4**); however, the base peak was invariably the characteristic retro-aldol fragment ion $[M - CH(OH)C_6H_4OMe]$. The n.m.r. and i.r. data are compatible with structure (**5**). On treatment with dilute aqueous NaOH at room temperature, compound (**5**) readily underwent retro-aldol condensation, giving *p*-anisaldehyde and the arylthioacetic acid (**8**).[5] The latter product was identified by comparison with an authentic sample prepared by condensation of the thiophenol (**2**) with methyl chloroacetate (**9**).[6-8]

The relative proportions of *threo*- and *erythro*-isomers (**3**) and (**4**), and the regioisomers (**5**) from the reaction of the glycidate

† Part of this study was presented at the 42nd Symposium on Synthetic Organic Chemistry (Japan), Tokyo, November, 1982.



a; R = 2-NO_2
b; R = 4-NO_2
c; R = H
d; R = 4-MeO
e; R = 2-NH_2

Scheme 1. *Reagents:* i, NaOMe, benzene; ii, 5% NaOH

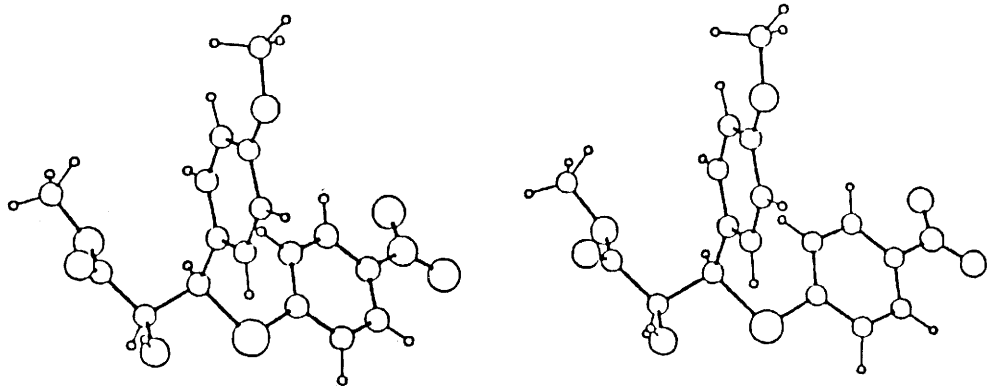


Figure 1. Stereoview of the structure of the *threo*-compound (**3b**)

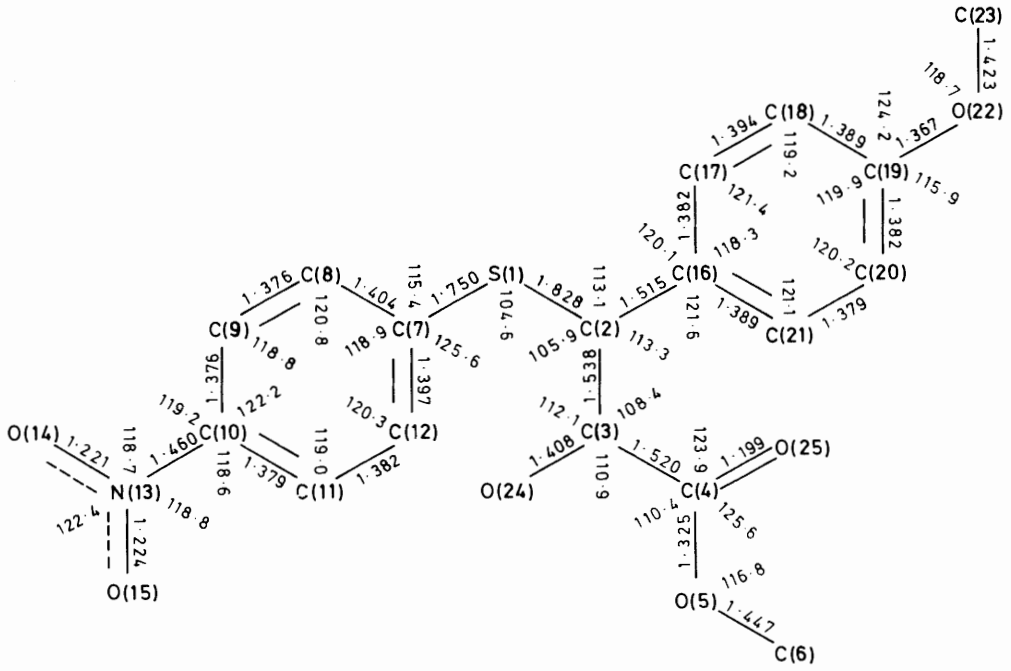


Figure 2. *threo*-Compound (**3b**), showing the crystallographic numbering scheme and the bond lengths (Å) and angles (°). The standard deviations in the bond lengths and angles range from 0.004 to 0.006 Å and from 0.3 to 0.5° respectively

(**1**) with the thiophenols (**2a—e**) varied greatly with temperature, solvent, catalyst, and the electronic nature of the substituent of (**2**).

Effect of Temperature.—Varying the temperature had a surprisingly large effect on the stereochemistry of the oxirane ring-opening of the glycidate (**1**). As the reaction temperature is increased, the ratio of *threo*- to *erythro*-isomers [(**3**):(**4**)] formed increased markedly, regardless of the nature of the substituent on the thiophenol (**2**). Thus, in the absence of a catalyst, the *erythro*-isomer (**4**) (*trans*-opening product) was obtained as the major product at room temperature, while the *threo*-isomer (**3**) (*cis*-opening product) was produced predominantly at higher temperatures. The *erythro*-ester (**4a**) was recovered unchanged when heated in MeCN with or without 2-nitrothiophenol (**2a**); this result rules out the possible epimerization of the initially formed (**4**) to the *threo*-isomer (**3**) at higher temperatures. Similar temperature effects have been observed in the acid-catalysed solvolysis of aryl-substituted oxiranes by Battistini *et al*,[9] where the ratios of *cis*- to *trans*-diol increased with increasing temperature;* they also attempted to use relative activation parameters to assign a transition state structure for the reaction. The effect of temperature on the *cis*- to *trans*-opening ratio in our case was much more dramatic.

Effect of the Substituent on the Thiophenols (**2**).—Generally, the total yield of the α-hydroxy esters (**3**) and (**4**) was higher from thiophenols with electron-withdrawing substituents. The order roughly parallels the order of acidity of the substituted thiophenols: 4-NO_2 > 2-NO_2 > H > 4-MeO.† The same is true for the ratios of (**3**) to (**4**). 4-Nitrothiophenol (**2b**) generally gave better results than the 2-nitro derivative (**2a**) both in yield and in stereoselectivity, indicating that no neighbouring group participation was involved in the reaction. The presence of electron-donating groups gave the regioisomer (**5**) in dipolar aprotic solvents (see below).

Effect of Catalysts.—The presence of $SnCl_2$ affected both the reactivity of the thiophenols (**2**) and stereoselectivity of the reaction (predominant *cis* opening), and its effect increases with the acidity of the thiophenol. The presence of BF_3·Et_2O greatly accelerates the reaction of all the thiophenols except for the 2-amino derivative (**2e**), but its effect on the stereoselectivity was not significant. Lewis acids had no effect in the reaction of compound (**2e**).

$MgCl_2$, which was expected to result in the *trans*-opening products (**4**),[1] only affected the reactions of the acidic thiophenols (**2a**) and (**2b**). This result suggests that the catalytic effect of $MgCl_2$ does not involve activation of the glycidate (**1**).

Effect of Solvent.—In a dipolar aprotic solvent such as hexamethylphosphoramide (HMPA) or dimethylformamide (DMF), the regioisomer (**5**) was formed significantly. The reaction in HMPA was fast and afforded (**5**) as the major product, together with the *erythro*-α-hydroxy ester (**4**); the *threo*-isomer (**3**) was not formed. The yield of the regioisomer (**5**) increased with increasing electron-donating ability of the substituents (4-NO_2 < 2-NO_2 < H < 4-MeO). Thus, compounds (**5c**) and (**5d**) were formed, even in MeCN.

Thiophenol is known to undergo ready oxidation with molecular oxygen, and this oxidation is facilitated by electron release from the substituents on the aromatic ring. This suggests that a thiol group can act as an electron donor. When *m*-dinitrobenzene, a strong electron acceptor,[12] was added to the reaction mixture of thiophenol (**2c**) with the glycidate (**1**) in MeCN, the formation of compound (**5c**) was markedly inhibited. Similarly, the addition of azoisobutyronitrile (AIBN), a radical initiator,[13] to the reaction of thiophenol (**2c**) with the glycidate (**1**) in toluene resulted in no formation of (**5c**) (Table 3).

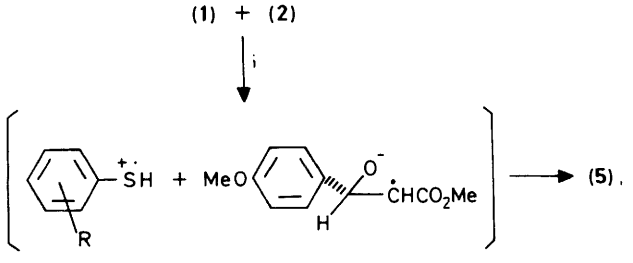
* See also refs. 10 and 11.

† 4-$NO_2C_6H_4SH$ (pK_a 6.42), 2-$NO_2C_6H_4SH$ (7.46), PhSH (9.32), 2-$NH_2C_6H_4SH$ (9.02), and 4-$MeOC_6H_4SH$ (9.76) in 95:5 (v/v) EtOH–H_2O at 20 °C; see M. R. Crampton, 'The Chemistry of the Thiol Group' Part 1, ed. S. Patai, John Wiley and Sons, London, 1974, p. 402, and refs. therein.

Table 2.

				Product yield (%) [*threo*/*erythro* ratio (3)/(4)][b]									
				2-NO_2		4-NO_2		H		4-OMe		2-NH_2	
Entry	Solvent	Catalyst	Reaction temp. (°C)	Time (h)	(3a) and (4a)[a] (5a)	Time (h)	(3b) and (4b)[a] (5b)	Time (h)	(3c) and (4c)[a] (5c)	Time (h)	(3d) and (4d)[a] (5d)	Time (h)	(3e) and (4e)[a] (5e)
1	Toluene		22	48	32.7 (0.33)	72	65.3 (1.0)	72	11.7 (0.50)	72	12.6 (0.22)	72	23.4 (0.12)
2	Toluene		60	48	41.6 (2.1)	72	67.9 (5.0)	72	44.6 (3.75)	72	33.2 (1.89)	72	77.0 (*threo*)
3	Toluene		Reflux	22	40.0 (3.0)								
4	Toluene	$SnCl_2$	22	18	80.0 (14.5)	0.1	85.8 (21.3)	72	31.7 (4.3)	18	33.3 (3.0)	72	28.8 (1.33)
5	Toluene	$MgCl_2$	22	16	65.0 (*erythro*)	16	66.0 (*erythro*)	72	16.9 (0.44)	18	6.2 (0.33)	18	15.6 (0.19)
6	Toluene	BF_3·Et_2O	22	0.1	78.5 (3.0)	0.1	87.7 (1.0)	0.1	86.9 (1.24)	0.1	100 (1.1)	1	*f*
7	Benzene		Reflux	46	61.9 (6.0)								
8	Dioxane		22	48	46.2 (0.25)	72	38.2 (2.7)	72	54.8 (1.83)	72	14.5 (1.3)	72	17.4 (1.3)
9	Dioxane		60	48	40.0 (2.6)	72	52.9 (7.0)	72	21.5 (1.81)	72	26.2 (1.4)	72	39.4 (12.3)
10	HMPA		22	6.5	13.5 (*erythro*) 19.9	4	17.7 (*erythro*) 18.7	4	4.3 (*erythro*) 73.9	2	3.2 (*erythro*) 89.9		
11	DMF		22	21	23.8 (1.0) 9.0								
12	MeCN		22	72	37.2 (0.33)			72	10.7 (0.56) 6.0	72	3.7 (0.3) 1.4		
13	MeCN		50—60	72	84.6 (3.0)			72	23.5 (1.72) 30.4	72	4.5 (1.31) 15.5		
14	MeCN		Reflux	27	70.0 (7.8)								
15	MeCN	$NaHCO_3$	60	18	80.0[c] (*erythro*)	24	55.5 (*erythro*)	24	18.5 (*erythro*)	24	7.7 (*erythro*)	72	40.0[g] (*erythro*)
16	Bu^{t}OH		22	18	43.4[d] (2.0)								
17	Bu^{t}OH		50	19	28.3[e] (1.7)								

[a] Total yield of *threo*- and *erythro*-esters (3) and (4). [b] In the case of the 4-NO_2 and 2-NO_2 derivatives, the ratio of (3)/(4) was calculated on the basis of the sum of isolated yields of (3) and (4) and the ratio of the remaining mixture obtained from the mother-liquor. The latter was estimated by comparison of the intensity of Ac peaks of the 2-acetoxy compounds (6) and (7) in the n.m.r. spectrum by means of a calibration curve and was reliable in the range of 1:4—4:1. [c] Reaction in EtOH solution at room temperature. [d] Methyl 2-hydroxy-3-(4-methoxyphenyl)-3-(t-butoxy)propionate (11) (25%) was obtained. [e] (11) was obtained in 14.2% yield. [f] (3e) and (4e) were not obtained. [g] Reaction in benzene or EtOH solution at room temperature.



Scheme 2. i, Single electron transfer.

Therefore, the formation of the regioisomer (5) may involve single-electron transfer from the thiol group to the glycidate (1) as a key step. According to Shapiro *et al.*, electrochemical reduction of an α,β-epoxy ketone system proceeds *via* fission of the α-C–O bond of the oxirane ring.[14] In the photofragmentation of α,β-epoxy ketones, α-C–O bond cleavage generally predominates over β-C–O bond cleavage.[15] On this basis, we propose a possible pathway (Scheme 2) for the formation of the regioisomer (5). The fact that the more electron-rich thiophenols give higher proportions of (5) appears to support this mechanistic proposal.

When Bu^{t}OH was used as the solvent, solvolysis of the epoxide was accompanied by attack of the thiol group to give the 2-hydroxy-3-(t-butoxy) ester (11).*

Thus, the regio- and stereo-chemical course of the reaction of the glycidate (1) with the thiophenols (2) is affected by the choice of temperature, solvent, and catalyst; this is important in view of the usefulness of glycidate esters in organic synthesis.

Experimental

All reactions were carried out under argon. I.r. spectra were taken on Hitachi IR-215 or FX-6200 FTIR spectrometers

* The solvolysis of the glycidate (1) with Bu^{t}OH under the same conditions in the absence of 2-nitrothiophenol was not observed, even in the presence of catalyst (BF_3·Et_2O).

Table 3. The reaction of the glycidate (**1**) with the thiophenols (**2**) at 60 °C in MeCN or toluene

Solvent	Additive	Total yield of (**3c**) and (**4c**) (%)	Ratio (**3c**)/(**4c**)	Yield of (**5c**) (%)
MeCN		23.5	1.72	30.4
MeCN	*m*-Dinitrobenzene (1.5 equiv.)	50.1	1.84	4.9
MeCN	*m*-Dinitrobenzene (3.0 equiv.)	64.0	1.37	0.9
Toluene		44.6	3.75	
Toluene	AIBN (0.1 equiv.)	42.6		

Table 4. Mass spectral data of methyl *threo*- and *erythro*-3-arylthio-2-hydroxy-3-(4-methoxyphenyl)propionates (**3**) and (**4**) and methyl 2-arylthio-3-hydroxy-3-(4-methoxyphenyl)propionate (**5**)

R	(**3**)	(**4**)	(**5**)
2-NO_2	363 (M^+), 274[a] 209, 149, 121	363 (M^+), 274[a] 209, 149, 121	363 (M^+), 240, 227[b], 209, 136
4-NO_2	363 (M^+), 274[a] 209, 149, 121	363 (M^+), 227[a] 209, 149, 121	363 (M^+), 345, 227[b], 136
H	318 (M^+), 229[a] 209, 149, 121	318 (M^+), 229[a] 209, 149, 121	300, 182[b,c]
4-MeO	348 (M^+), 259[a] 209, 149, 121	348 (M^+), 259[a] 209, 149, 121	348 (M^+), 330, 212[b], 153

[a] Base peak, $[M - CH(OH)CO_2Me]^+$. [b] Base peak, $[M - CH(OH)C_6H_4OMe]^+$. [c] M^+ was not seen.

(Analect Instruments). N.m.r. spectra were recorded on a JEOL PMX-60 or FX-100S spectrometer. Chemical shifts are given in δ from tetramethylsilane as internal standard. Mass spectra were recorded on a Hitachi RMU-60 spectrometer. Preparative t.l.c. was carried out on Kieselgel PF_{254} (Merck), and Kieselgel 60 (230—400 mesh) (Merck) was used for flash column chromatography. The following abbreviations are used for n.m.r. assignments; s = singlet, d = doublet, dd = double doublet, t = triplet, and m = multiplet. The rest of the i.r. and n.m.r. data are available as a Supplementary Publication * (SUP No. 56076, 6pp.)

2-Nitrothiophenol was prepared from bis(2-nitrophenyl) disulphide by Chrzaszczewska's method.[16] All the thiophenols were used without further purification.

Reaction of Methyl trans-3-(4-*Methoxyphenyl*)*glycidate* (**1**) *with Various Substituted Thiophenols* (**2**) (*Table* 1).—The following examples are representative.

(*a*) *Reaction with 2-nitrothiophenol* (**2a**) *in HMPA.* The glycidate (**1**) (1.6 g, 7.68 mmol) and then (**2a**) (1.0 g, 6.44 mmol) were added successively to HMPA (10 ml). The reaction mixture became red immediately after the addition of (**2a**).

After stirring at room temperature for 6.5 h, the reaction mixture was poured into ice–water and extracted with AcOEt. The extracts were washed with water, dried, and evaporated. The residual oil was separated by flash column chromatography (eluted with benzene–AcOEt, 20:1). The first fraction gave bis-(2-nitrophenyl) disulphide (270 mg, 27%). From the second fraction, the *erythro*-nitro ester (**4a**) (315 mg, 13.5%), m.p. 135—136.5 °C, was obtained. From the third fraction, the regioisomer (**5a**) (465 mg, 19.9%) was obtained as an oil; the spectral data are given in the Supplementary Publication.

(*b*) *Reaction with* 4-*nitrothiophenol* (**2b**) *in the presence of a catalytic amount of* BF_3–Et_2O. BF_3–Et_2O (0.05 ml) was added to a mixture of compound (**2b**) (1.0 g, 6.44 mmol) and the glycidate (**1**) (1.6 g, 7.68 mmol) in toluene (10 ml) under ice-cooling. The thiol (**2b**) was consumed within 5 min under these conditions. The reaction mixture was separated by flash column chromatography (eluted with C_6H_6–AcOEt, 20:1). After the removal of bis(4-nitrophenyl) disulphide (195 mg, 19.5%) as the first fraction, a mixture of the *threo*- and *erythro*-nitro esters (**3b**) and (**4b**) (2.055 g, 87.7%; yellow oil) was obtained from the second fraction. The ratio of (**3b**)/(**4b**) was 1.0, determined by comparison of the intensity of the Ac signals of the corresponding acetoxy derivatives (**6b**) and (**7b**), prepared by acetylation of the mixture of (**3b**) and (**4b**) according to the method in our previous report (see ref. 1).

The pure threo-*isomer* (**3b**) was prepared by recrystallization (from EtOH) of the crude product obtained from the reaction of compound (**1**) with (**2b**) in the presence of $SnCl_2$ (Table 2, entry 4), m.p. 119—121 °C (EtOH) (Found: C, 56.3; H, 4.7; N, 3.9; S, 8.9. $C_{17}H_{17}O_6NS$ requires C, 56.19; H, 4.72; N, 3.86; S, 8.82%).

The pure erythro-*isomer* (**4b**) was prepared by the reaction of compound (**1**) with (**2b**) in the presence of $MgCl_2$ (Table 2, entry 5), m.p. 112—114 °C (from EtOH) (Found; C, 56.2; H, 4.7; N, 3.9; S, 8.6. $C_{17}H_{17}O_6NS$ requires C, 56.19; H, 4.72; N, 3.86; S, 8.82%).

(*c*) *Reaction with thiophenol* (**2c**) in MeCN *without a catalyst.* A mixture of thiophenol (**2c**) (1.0 g, 9.1 mmol), the glycidate (**1**) (1.89 g, 9.08 mmol), and MeCN (10 ml) was stirred at 60 °C for 3 days and the reaction mixture was separated by flash column chromatography (eluted with C_6H_6–AcOEt, 20:1). The first fraction gave diphenyl disulphide (390 mg, 39%). The second fraction gave a mixture of the *threo*- and *erythro*-esters (**3c**) and (**4c**) (680 mg, 23.5%) which was separated by preparative t.l.c. (developed ten times with n-hexane–AcOEt, 5:1) to give the threo-*isomer* (**3c**) from the faster running material, m.p. 56—58 °C (Pr^i_2O–n-hexane) (389 mg) (Found: C, 64.1; H, 5.7; S, 10.1. $C_{17}H_{18}O_4S$ requires C, 64.13; H, 5.70; S, 10.07%) and the erythro-*isomer* (**4c**) (226 mg) as an oil from the slower running component. The *threo*/*erythro* ratio (**3c**)/(**4c**) was 1.72. From the third fraction, the regioisomer (**5c**) (880 mg, 30.4%) was obtained as an oil.

(*d*) *Reaction with* 4-*methoxythiophenol* (**2d**) *in* MeCN *at* 60 °C *without a catalyst.* A solution of compound (**2d**) (800 mg, 5.71 mmol) and the glycidate (**1**) (1.3 g, 6.24 mmol) in MeCN (10 ml) was heated at 60 °C for 3 days. After removal of MeCN under reduced pressure, the residual mixture was separated by flash column chromatography (eluted with C_6H_6–AcOEt, 15:1). The first fraction gave bis(4-methoxyphenyl) disulphide (640 mg, 80%). From the second fraction, a mixture of the *threo*- and *erythro*-esters (**3d**) and (**4d**) (135 mg, 4.5%) was obtained as an oil, and from the third fraction the *regioisomer* (**5d**) (307 mg, 15.5%), m.p. 64—66 °C (from Pr^i_2O) (Found; C, 62.1; H, 5.8; S,

* For details of the Supplementary Publications Scheme see Instructions for Authors (1985), in *J. Chem. Soc., Perkin Trans. 1*, 1985, Issue 1.

9.4. $C_{18}H_{20}O_5S$ requires C, 62.05; H, 5.79; S, 9.20%) was obtained. The mixture of (**3d**) and (**4d**) was separated by preparative t.l.c. (developed five times with n-hexane–AcOEt, 3.5:1), the faster running component giving the *threo-isomer* (**3d**) (51 mg, 2.6%), m.p. 70—72 °C (from Pr^i_2O–n-hexane) (Found: C, 62.05; H, 5.7; S, 9.3. $C_{18}H_{20}O_5S$ requires C, 62.05; H, 5.79; S, 9.20%) and the slower running material the *erythro*-isomer (**4d**) (39 mg, 2.0%).

(*e*) *Reaction with 2-aminothiophenol* (**2e**) *in the presence of* $SnCl_2$. A mixture of (**2e**) (1.0 g, 7.99 mmol), the glycidate (**1**) (1.6 g, 7.68 mmol), $SnCl_2$ (100 mg), and toluene (10 ml) was stirred at room temperature for 72 h. The reaction mixture was concentrated under reduced pressure at room temperature and the residue was separated by flash column chromatography (eluted with C_6H_6–AcOEt, 5:1) to give a mixture of the *threo*- and *erythro*-amino esters (**3e**) and (**4e**) (760 mg, 28.8%) as an oil. The mixture was converted into the corresponding mixture of the *cis*- and *trans*-lactams (**10**) by the method described in our earlier paper.[4] The *cis*- and *trans*-isomers of 2,3-dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one (**10a**) and (**10b**) (160 and 120 mg, respectively) were separated by preparative t.l.c. (developed with C_6H_6–AcOEt, 4:1). Thus, the *threo*/*erythro* ratio of the amino esters (**3e**)/(**4e**) was 1.33.

(*f*) *Reaction with compound* (**2a**) *in* Bu^tOH *in the absence of catalyst.* A mixture of the glycidate (**1**) (1.6 g, 7.68 mmol) and 2-nitrothiophenol (**2a**) (1.0 g, 6.44 mmol) in Bu^tOH (10 ml) was heated at 50 °C for 19 h and the reaction mixture was concentrated under reduced pressure. The residual gum was dissolved in hot EtOH and allowed to stand at room temperature. The precipitated yellow needles were collected and washed with Pr^i_2O to give the *threo*-nitro ester (**3a**) (330 mg), m.p. 152—156 °C. The mother-liquor was concentrated and the residue was separated by flash column chromatography (eluted with C_6H_6–AcOEt, 20:1) and then by preparative t.l.c. (developed with n-hexane–AcOEt, 1:1). The faster running component on preparative t.l.c. was a mixture (1:1) of threo- and erythro-*methyl* 2-*hydroxy*-3-(4-*methoxyphenyl*)-3-(*t-butoxy*)-*propionates* (**11**) (308 mg, 14.2%), m.p. 88—93 °C (from Pr^i_2O–hexane) (Found: C, 63.9; H, 7.9. $C_{15}H_{22}O_5$ requires C, 63.81; H, 7.90%), $\nu_{max.}$(Nujol) 3 510, 3 420, 1 730, 1 710, and 1 610 cm^{-1}; *m*/*z* 193 [base peak, *M* − CH(OH)CO_2Me]; δ_H ($CDCl_3$; 60 MHz) 1.10 and 1.15 (ds, 9 H), 3.70 (s, $\frac{3}{2}$ H, OMe), 3.76 (s, $\frac{3}{2}$ H, OMe), 3.81 (s, 3 H, OMe), 2.74 (d, $\frac{1}{2}$ H, *J* 7 Hz, OH), 2.97 (d, $\frac{1}{2}$ H, *J* 9 Hz, OH), 4.12 (dd, $\frac{1}{2}$ H, *J* 3 and 9 Hz, 2-H), 4.29 (dd, $\frac{1}{2}$ H, *J* 5 and 7 Hz, 2-H), 4.77 (d, $\frac{1}{2}$ H, *J* 5 Hz, 3-H), 4.83 (d, $\frac{1}{2}$ H, *J* 3 Hz, 3-H), and 6.80—7.45 (4 H, m, aryl H). A mixture of the *threo*- and *erythro*-nitro esters (**3a**) and (**4a**) (332 mg, total yield 28.3%) was obtained from the slower running component. The ratio (**3a**)/(**4a**) of this mixture was 0.36 which was determined by comparison of the intensity of the Ac signals of the corresponding acetoxy derivatives (**6a**) and (**7a**) prepared by acetylation of the mixture according to our previous report (see ref. 1). Accordingly, the *threo*/*erythro* ratio of the whole nitro ester (**3a**)/(**4a**) was 1.7.

The other results are summarized in Table 2.

Reaction of Compound (**1**) *with Thiophenol* (**2c**) *in the Presence of* m-*Dinitrobenzene in* MeCN.—To a solution of (**2c**) (795 mg, 7.23 mmol) and compound (**1**) (1.65 g, 7.95 mmol) in MeCN (10 ml), *m*-dinitrobenzene (3.64 g, 21.7 mmol) was added at 60 °C and the reaction mixture was stirred at 60 °C for 3 days. After removal of the solvent under reduced pressure, the residual oil was separated by flash column chromatography. Thiophenol (**2c**) (starting material) and *m*-dinitrobenzene were eluted first with benzene–AcOEt (15:1), then a mixture of the *threo*- and *erythro*-esters (**3c**) and (**4c**) was obtained (1.47 g, 64.0%) as an oil from the second fraction. The ratio of *threo*/*erythro* [(**3c**)/(**4c**)], determined by separation of (**3c**) and (**4c**) by preparative t.l.c., was 1.37. From the final fraction, only a trace (20 mg, 0.9%) of the regioisomer (**5c**) was obtained.

Reaction of Compound (**1**) with *Thiophenol* (**2c**) *in the Presence of AIBN in Toluene.*—AIBN (130 mg, 0.79 mmol) was added to a solution of thiophenol (**2c**) (868 mg, 7.9 mmol) and the glycidate (**1**) (1.65 g, 7.9 mmol) in toluene (10 ml) at 60 °C and the reaction mixture was stirred at 60 °C for 3 days. After work-up in the usual manner, a mixture of the *threo*- and *erythro*-esters (**3c**) and (**4c**) was obtained (1.069 g, 42.6%). No regioisomer (**5c**) was obtained in this reaction.

Treatment of Compound (**5a**) *with Dilute* NaOH.—Compound (**5a**) (400 mg) was stirred in 5% aq. NaOH (1 ml) and EtOH (1 ml) at room temperature for 2 h. After evaporation of EtOH under reduced pressure, the residue was extracted with Et_2O. The extracts were washed with water, dried (Na_2SO_4), and evaporated to give anisaldehyde (120 mg). The aqueous layer was acidified with dilute HCl and extracted with EtOAc. The extracts were washed with water, dried (Na_2SO_4), and evaporated to give 2-(2-nitrophenylthio)acetic acid (**8a**) (190 mg), m.p. 104 °C (after recrystallization from water), identical with an authentic sample[6] prepared by condensation of methyl chloroacetate (**9**) with 2-nitrothiophenol (**2a**) in the presence of

Table 5. Atomic parameters for compound (**3b**)

Atom	*x*	*y*	*z*
S(1)	0.935 12	0.699 50	0.119 96
O(5)	0.509 99	0.740 98	−0.189 86
C(10)	1.265 35	0.511 75	−0.245 09
C(17)	0.946 67	0.798 51	−0.336 76
C(2)	0.824 51	0.735 62	−0.042 27
C(19)	1.156 39	0.929 17	−0.323 70
C(16)	0.945 76	0.802 69	−0.141 27
C(21)	1.053 82	0.870 83	−0.038 88
C(20)	1.157 00	0.933 71	−0.128 34
C(12)	1.068 20	0.605 19	−0.235 81
O(24)	0.698 70	0.825 59	0.250 35
C(7)	1.065 56	0.630 28	−0.034 86
O(14)	1.335 21	0.413 76	−0.522 25
C(9)	1.269 85	0.536 82	−0.048 17
C(3)	0.656 98	0.765 26	0.082 29
C(8)	1.171 38	0.596 54	0.056 51
N(13)	1.364 53	0.446 31	−0.356 45
C(11)	1.168 15	0.545 62	−0.341 19
O(15)	1.475 33	0.426 78	−0.280 93
C(6)	0.440 19	0.767 45	−0.335 81
O(25)	0.547 53	0.873 03	−0.011 50
O(22)	1.262 04	0.994 69	−0.399 19
C(18)	1.051 23	0.861 17	−0.429 92
C(4)	0.564 28	0.800 66	−0.042 28
C(23)	1.280 41	0.990 00	−0.602 84
H(17)	0.874 30	0.753 57	−0.411 70
H(3)	0.566 42	0.719 02	0.147 32
H(18)	1.044 34	0.858 62	−0.565 57
H(21)	1.046 14	0.876 28	0.103 23
H(11)	1.175 95	0.526 63	−0.484 12
H(12)	1.001 59	0.629 57	−0.295 48
H(20)	1.243 93	0.979 00	−0.058 96
H(23A)	1.148 81	0.985 09	−0.633 69
H(9)	1.343 30	0.513 28	0.015 90
H(8)	1.152 55	0.611 83	0.209 20
H(6A)	0.419 85	0.720 91	−0.445 88
H(6B)	0.549 72	0.797 53	−0.413 90
H(2)	0.777 54	0.685 65	−0.140 88
H(23B)	1.324 88	0.945 40	−0.667 63
H(23C)	1.386 40	1.030 35	−0.645 17
H(6C)	0.324 25	0.781 95	−0.290 35
H(24)	0.696 91	0.866 62	0.236 83

NaOMe in benzene solution to give methyl 2-nitrophenylthioacetate followed by hydrolysis with 5% NaOH.

Similarly, compounds (**5b**) and (**5c**) were converted into (**8b**), m.p. 152—154.5 °C, and (**8c**), m.p. 62—65 °C, respectively, both identical with authentic samples.[7,8]

X-*Ray Crystallographic Analysis of Compound* (**3b**).—Crystal data. $C_{17}H_{17}NO_6S$, M = 363.39, triclinic, a = 7.728 1(6), b = 16.574 0(15), c = 7.152 2(5) Å, α = 103.623(8), β = 79.640(7), γ = 102.544(9)°, U = 861.0(1) Å^3, D_c = 1.402 g cm^{-3}, Z = 2, $F(000)$ = 380, Space group $P\bar{1}$.

Crystallographic Measurements and Structure Analysis.—The intensities and cell dimensions were obtained from a Rigaku four-circle diffractometer (AFC-V) by an $2\theta - \omega$ scan with graphite-monochromated Cu-K_α radiation. Of 2 943 reflections, measured to a maximum 2θ of 130°, 2 351 had $I > 2.67\ \sigma(I)$ and were considered observed. The data were corrected for the Lorentz-polarization factor, but not for absorption. The structure was solved by the direct method using MULTAN and refined by the block-diagonal least-squares procedure. R was reduced to 5.8% after several cycles of least-squares calculation assuming anisotropic thermal parameters for the non-hydrogen atoms and isotropic ones for the hydrogen atoms. The function minimized in the refinement was $\Sigma w(|F_o| - |F_c|)^2$ where $\sqrt{w} = (2\ F_{min.} + |F_o| + 2|F_o|^2/F_{max.})^{-1}$. The bond lengths and angles and the numbering system (non-systematic) used in the crystallographic analysis are illustrated in Figure 2. Thermal parameters and full bond lengths and angles are available as a Supplementary Publication (SUP. No. 56076, 6 pp.).* Atomic co-ordinates are given in Table 5. Structure factors are available from the editorial office on request.

* See footnote, p. 425.

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