Reaction of 3-Phenylglycidic Esters. Part 1.† Stereoselective Opening of the Oxirane Ring of *trans*-3-Phenylglycidic Esters with 2-Nitrothiophenols and the Effect of Various Catalysts Thereon

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In the reaction of 2-nitrothiophenol (**2**) with *trans*-3-phenylglycidic esters carrying various substituents on the benzene ring, both reactivity and stereoselectivity of the oxirane ring-opening of the glycidates were markedly influenced by the electronic nature of the substituents. The presence of electron-donating groups was favourable for both reactivity and the preferential formation of *cis*-opening products, while the reverse was true for electron-withdrawing groups. As a result of our investigation on the catalytic effect of various Lewis acids in the reaction of the 4-methoxy derivative (**1**) with (**2**), tin compounds were found to be effective catalysts for *cis*-opening and readily produced the *threo*-nitro ester (**3a**), a key intermediate for the synthesis of diltiazem (**5**).

Isolation of the crystalline complex (adduct A) from the reaction of (**2**) with $SnCl_4$ and its efficient catalytic activity similar to that of $SnCl_4$ suggest that the transition state involves co-ordination of tin derivatives both with (**2**) and the epoxy oxygen of (**1**) to cause highly specific *cis*-opening.

The synthetic value of stereoselective ring-opening of oxiranes with nucleophiles is well recognized. Recently, Posner and Rogers[1] reported a useful method of *trans*-opening of oxirane rings. However, there have been only a few examples of an efficient method of *cis*-opening. Furthermore, information on the stereochemistry of the ring-opening of glycidic esters has been scarce.[2,3] Our prior work [2a,b] has shown that the reaction of the *trans*-3-(4-methoxyphenyl)glycidic ester (**1**) with 2-nitrothiophenol (**2**) mainly gave the *threo*-nitro ester (**3a**), the *cis*-opening product resulting from attack of the thiol group from the side of the oxirane ring, after prolonged heating in CH_3CN. Compound (**3a**) served as a key intermediate for the synthesis of diltiazem (**5**), a potent coronary vasodilating agent.[2d,e,4]

However, this procedure suffers from flaws such as low yield, insufficient stereoselectivity, and too long a reaction time, which have been major obstacles in the synthesis of diltiazem. The reaction of (**1**) and (**2**) in the presence of a catalytic amount of $NaHCO_3$, on the other hand, readily gave the undesired *erythro*-isomer (**3b**), the *trans*-opening product resulting from S_N2-type attack of thiolate anion.[2b] These reactions are shown in Scheme 1.

In the present study, we examined the effect of various catalysts on the reaction of (**1**) with (**2**) in order to obtain the *threo*-ester (**3a**) more easily with greater stereoselectivity. The effect of various substituents on the benzene ring of (**1**) on this reaction was also examined.

Results and Discussion

1. *The Effect of Substituents on the Benzene Ring of* trans-3-*Phenylglycidic Esters.*—The reaction of 2-nitrothiophenol (**2**) with *trans*-3-phenylglycidic esters (**1**) and (**6**)—(**10**) carrying various substituents on the benzene ring was examined in CH_3CN at 50 °C (Scheme 2) and the results are summarized in Table 1. The stereochemistry and the ratio of the isomeric nitro-esters formed were determined by converting them into the corresponding *cis*- and *trans*-lactams.‡ In the case of the 4-methoxy derivatives (**3a** and **b**) the *threo*/*erythro* ratio could be estimated more easily by comparison of the intensity of methyl signals of the $OCOCH_3$ groups of the corresponding acetoxy derivatives (**18a** and **b**) in the n.m.r. spectrum (100 MHz) (at δ 2.12 and 2.20 for the *threo*- and *erythro*-isomer, respectively), and the ratio thus obtained was in good accord with that determined *via* the *cis*- and *trans*-lactams (**4a** and **b**).

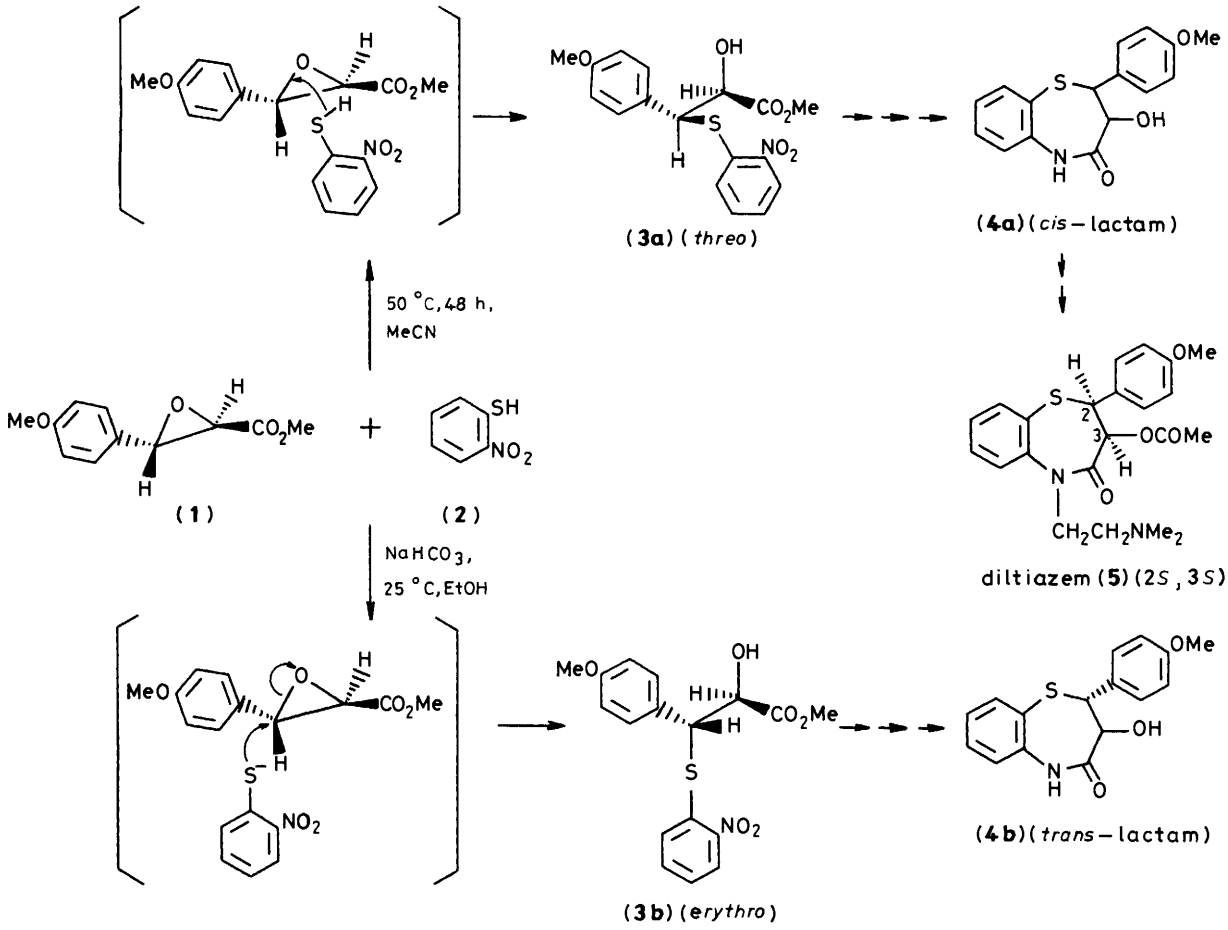
Both the reactivity and stereochemistry of ring-opening of these glycidates were markedly influenced by the electronic nature of their substituents. Thus, in the case of glycidates with electron-withdrawing substituents [(**9**) and (**10**)] or without a substituent (**8**), no reaction was observed under these conditions. The ester (**7**) with a 4-methyl substituent scarcely reacted, and the *cis*/*trans* ratio of the oxirane ring-opening reaction (*threo*/*erythro* ratio of the product) was *ca.* 1. On the other hand, the 4-methoxy analogue (**1**) reacted more smoothly, and gave the *cis*-opening product more selectively (*cis*/*trans* ratio 3). Therefore, in the case of the glycidates carrying electron-donating substituents, both the reactivity and the *cis*/*trans* ratio of oxirane ring opening tend to increase with an increase in the electron-donating ability of the substituent in the following order: $CH_3 < CH_3O < (CH_3O)_2$; in other words, with increasing carbocationic character of the benzylic carbon in the transition state. A similar substituent effect on the stereochemistry of the ring-opening of various 1-arylcyclohexene oxides has been reported by Battistini and co-workers.[5]

2. *Effect of Catalysts.*—Like the previous result with the 4-methoxy derivative (**1**),[2b] the $NaHCO_3$-catalysed reaction of various ring-substituted glycidates proceeded smoothly to give the *erythro*-isomers except for (**10**) (Table 2). The 4-nitro derivative (**10**) gave a low yield of a mixture of *threo*- and *erythro*-isomers together with the mercaptoacetic acid derivatives [(**25**) and (**26**)] resulting from attack of the thiol group on the α-position of the glycidate.

Our prior work has shown that the reaction of unsubstituted 3-phenylglycidic ester with (**2**) in the presence of BF_3·Et_2O gave a low yield of the *trans*-opening product.[2b] On the other hand, similar reaction of the 4-methoxy analogue (**1**) with (**2**) was found to proceed very rapidly and gave the *cis*-opening product [*threo*-ester (**3a**)] as the major product. However, the

† Part of this work was presented at the 1st French–Japanese Symposium on Medicinal and Fine Chemistry, Lake Biwa, Japan, May 1981 and at the 42nd Symposium on the Synthetic Organic Chemistry (Japan), Tokyo, November 1982.

‡ It is known that the *threo*- and *erythro*-nitro esters could be converted into the corresponding *cis*- and *trans*-lactams, respectively, without any epimerization under the reaction conditions described in the Experimental section (see refs. 2*a*, *b*, and *d*).



Scheme 1.

Table 1. Reaction of 2-nitrothiophenol (**2**) with the 3-phenylglycidates (**1**) and (**6**)—(**10**)

3-Arylglycidate		2-Nitrothiophenol	Reaction	Isolated yield (%)	*threo/erythro* Ratio of the
R^1	R^2	X	conditions	of *threo*-nitro ester	whole product
(**1**) 4-MeO	Me	H	50 °C, 2 d	(**3a**) 56	3.0[a] (2.95)[b]
(**6**) 3,4-$(MeO)_2$	Et	H	50 °C, 2 d	(**11a**) 65[c]	
(**7**) 4-Me	Me	H	reflux, 20 h	(**12**) 21 (mixture)	1.2[b]
(**8**) H	Me	H	50 °C, 2 d	*d*	
(**9**) 4-Cl	Me	H	50 °C, 5 d	*d*	
(**10**) 4-NO_2	Me	H	50 °C, 4 d	*d*	
(**1**) 4-MeO	Me	Cl	30 °C, 5 d	(**16a**) 40	
(**8**) H	Me	Cl	55 °C, 6 d	(**17b**) 3.6 (*erythro*)	
(**9**) 4-Cl	Me	Cl	55 °C, 2 d	*d*	
(**10**) 4-NO_2	Me	Cl	55 °C, 6 d	*d*	

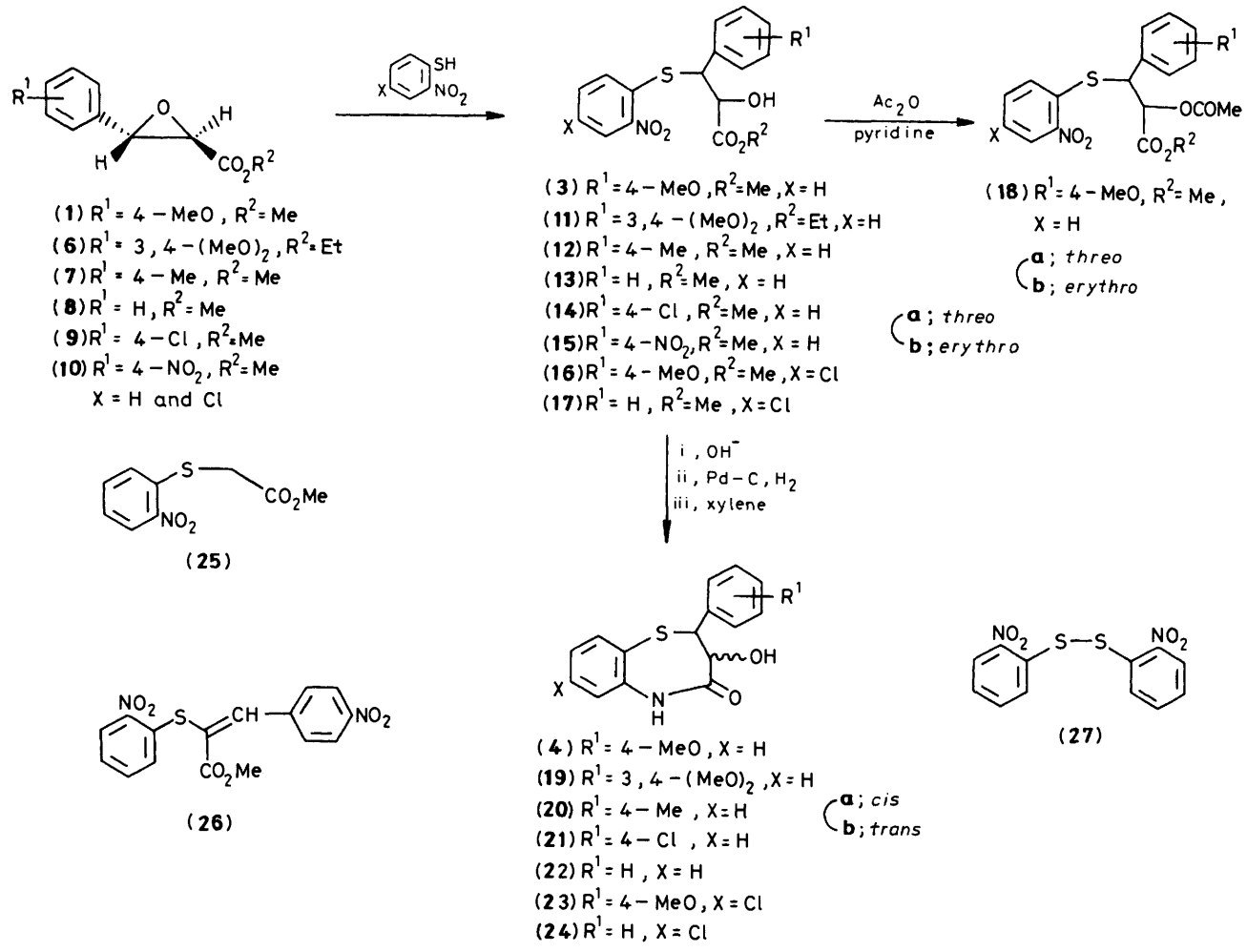
[a] The *threo/erythro* ratio was determined by comparison of the intensity of the $COCH_3$ peak of the 3-acetoxy compounds (**18**) in the n.m.r. spectrum (δ 2.12 and 2.20 for the *threo*- and *erythro*-isomers, respectively). [b] This ratio was determined from the *cis/trans* ratio of the corresponding lactams (**20**) (see Experimental section). [c] See ref. 2*a*. [d] The nitro ester was not obtained.

stereoselectivity (*threo/erythro* ratio of the whole product 4.2) was still unsatisfactory. The results of the BF_3·Et_2O-catalysed reaction of various ring-substituted glycidates with (**2**) are summarized in Table 3. The unfavourable effect of the presence electron-withdrawing substituents on both the reactivity and the *threo/erythro* ratio was still observed under these conditions.

Encouraged by the promising catalytic effect of BF_3·Et_2O on the reaction of the 4-methoxy derivative (**1**), we examined a wide variety of Lewis acids as well as Brønsted acids as a catalyst in this reaction to obtain better stereoselectivity (Table 4).

The *threo/erythro* ratio was calculated on the basis of the sum of the isolated yields of (**3a**) and (**3b**) and the *threo/erythro* ratio of the remaining mixture obtained from the mother liquor. The latter was estimated by comparison of the intensity of the $COCH_3$ peaks of the 3-acetoxy compounds (**18a** and **b**) in the n.m.r. spectrum.

Brønsted acids such as sulphuric acid and 70% aqueous perchloric acid were effective in acceleration of the reaction, but the *threo/erythro* ratio of the product was not improved. Zinc chloride behaved similarly. Surprisingly, $MgCl_2$ and $CaCl_2$ readily gave the *trans*-opening product. Since these chlorides,



Scheme 2.

Table 2. Reaction of 3-arylglycidates with 2-nitrothiophenol (**2**) in the presence of catalytic amounts of $NaHCO_3$

3-Arylglycidate R^1	R^2	2-Nitrothiophenol X	Reaction conditions	Isolated yield (%) of nitro ester
(**1**) 4-MeO	Me	H	EtOH, room temp., 18 h	80 (*erythro*) (**3b**)
(**8**) H	Me	H	EtOH, reflux, 2 h	55.6 (*erythro*) (**13b**)
(**9**) 4-Cl	Me	H	MeOH, reflux, 18 h	51.4 (*erythro*) (**14b**)[a]
(**10**) 4-NO_2	Me	H	MeOH, reflux, 5 h	17.9 (mixture) (**15**)[b]
(**1**) 4-MeO	Me	Cl	EtOH, reflux, 2 h	50.5 (*erythro*) (**16b**)

[a] Compound (**25**) was obtained as a minor product (4.5%). [b] A mixture of diastereoisomers. The *threo*/*erythro* ratio was not determined. Compounds (**25**) and (**26**) were obtained in yields of 9.5 and 19.2%, respectively.

Table 3. Reaction of 3-arylglycidates with 2-nitrothiophenol (**2**) in the presence of catalytic amounts of $BF_3 \cdot Et_2O$

3-Arylglycidate R^1	R^2	Reaction conditions	Total yield (%) of *threo* and *erythro* nitro esters	*threo*/*erythro* Ratio
(**1**) 4-MeO	Me	Et_2O, 16—20 °C, 20 min	69.2 (**3**)	4.2
(**8**) H	Me	Et_2O, 16—20 °C, 22 h	35.7 (**13**)	0.68
(**9**) 4-Cl	Me	dioxane, 50 °C, 3 d	11.0[a] (**14b**)	*erythro* only
(**10**) 4-NO_2	Me	dioxane, 50 °C, 3 d	12.2[b] (**15**)	*c*

[a] Bis(2-nitrophenyl) disulphide (**27**) was obtained in 84.5% yield. [b] Bis(2-nitrophenyl) disulphide (**27**) was obtained in 87% yield and the glycidate (**10**) was recovered in 86.3%. [c] A mixture of diastereoisomers. The *threo*/*erythro* ratio was not determined.

Table 4. Reaction of methyl 3-(4-methoxyphenyl)glycidate (**1**) with 2-nitrothiophenol (**2**) in the presence of catalytic amounts of various Lewis acids*

Entry	Catalyst	Solvent	Reaction conditions: temp. (°C)	Reaction conditions: time (h)	Product (isolated yield): *threo* (**3a**) (%)	Product (isolated yield): *erythro* (**3b**) (%)	*threo*/*erythro* Ratio[a] (whole product)
1		CH_3CN	50	48	56		3.0
2	Conc.H_2SO_4	dioxane	10	0.15	43	15	
3	$HClO_4$	dioxane	10	0.15	48	18	
4	BF_3·Et_2O	Et_2O	15	0.3	51	12	4.2
5	$ZnCl_2$	dioxane	15	1	50	25	
6	$MgCl_2$	dioxane	25	40		65	
7	$CaCl_2$	dioxane	25	40		63	
8	$SnCl_4$	dioxane	25	18	69		6.7
9	$SnBr_4$	dioxane	25	20	63		
10	SnI_4	dioxane	25	22	63		
11	$SnCl_2$	dioxane	25	21	69		12.5
12	SnI_2	dioxane	25	17	68		
13	SnF_2	dioxane	25	22	72		
14	$Sn(OCOC_7H_{15})_2$	dioxane	25	19	74 (82)[b]		9.3
15	$Sn(OCOC_7H_{15})_4$	dioxane	25	19	50		
16	$Sn(OCOC_{17}H_{35})_2$	dioxane	25 + 50	18 + 2	73		

* $TiCl_4$, $TiCl_3$, $FeCl_2$, $FeCl_3$, $AlCl_3$, CuCl, $CuCl_2$, $CdCl_2$, $NiCl_2$, $SbCl_3$, $SbCl_5$, $BiCl_3$, $PbCl_2$, TlCl, CsCl, $SnSO_4$, SnO, SnO_2, SnS, $Sn(OCOC_{11}H_{23})_2$, $Sn(OCOC_{15}H_{31})_2$, $Sn(OCOCO_2)$, $(Bu_3Sn)_2O$, and $(Bu_3Sn)_2S$ were ineffective.

[a] The *threo*/*erythro* ratio was calculated based on the sum of the isolated yields of (**3a**) and (**3b**) and the *threo*/*erythro* ratio of the remaining mixture obtained from the mother liquor. The latter was estimated by comparison of the intensity of $COCH_3$ peaks of the 3-acetoxy compounds (**18a** and **b**) in the n.m.r. spectrum by means of a calibration curve, and was reliable over the range of 1:4—4:1. [b] Corrected yield based on the purity of (**2**) which was determined by titration.

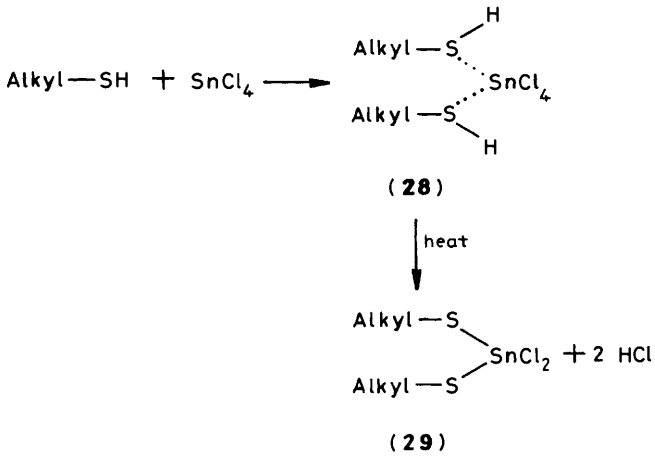
Table 5. Reaction of less reactive glycidates with 2-nitrothiophenol (**2**) in the presence of tin(II) 2-ethylhexanoate

	Glycidate R^1	Glycidate R^2	Reaction conditions	Yield of nitro ester (%)	*threo*/*erythro* Ratio
(**7**)	4-Me	Me	80—90 °C, 16 h, dioxane	17.3 (**12**)	4.0
(**8**)	H	Me	80—90 °C, 10 h, dioxane	4.9 (**13**)	1.7

which are available commercially, are known to be contaminated by a small amount of their respective hydroxides, we examined the catalytic effect of $Mg(OH)_2$ and $Ca(OH)_2$. However, these hydroxides showed only a small effect compared with their chlorides and produced the *erythro*-isomer much more slowly (see Experimental section). Therefore, the results obtained with $MgCl_2$ and $CaCl_2$ appear to be due to their own effect, but their precise role in the reaction is not clear.

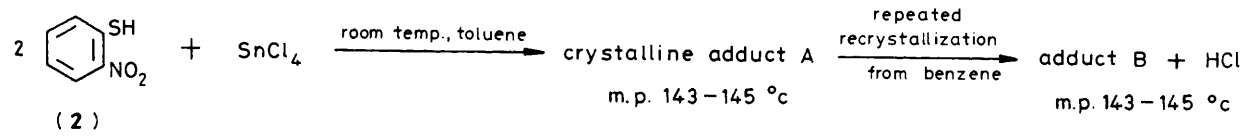
Finally, $SnCl_4$ was found to exhibit good catalytic activity with a much improved yield of the *cis*-opening product. Both stannous [tin(II)] and stannic [tin(IV)] halides were effective regardless of the nature of the halogen groups. Some carboxylates of tin (stannous 2-ethylhexanoate, stannic 2-ethylhexanoate, and stannous stearate) were also effective catalysts. Other Lewis acids listed in Table 4 had no catalytic effect. The reaction of less reactive glycidates in the presence of stannous 2-ethylhexanoate proceeded in poor yield, though the improved *threo*/*erythro* ratio (compared with the absence of catalyst) was observed in the case of the 4-methyl derivative (**7**) (Table 5).

3. *Isolation of Adducts of* $SnCl_4$ *with 2-Nitrothiophenol* (**2**).— We attempted to clarify the unique role of tin compounds in effecting the highly stereospecific *cis*-opening of (**1**) with (**2**). Douek and Spickett[6] have shown that $SnCl_4$ forms crystalline

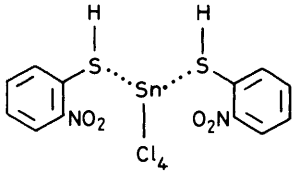


Scheme 3.

adducts with alkyl thiols. These hexaco-ordinated complexes (**28**) were reported to be thermally and hydrolytically unstable. Above room temperature, they readily decomposed to dichloro(dithiolate)tin complexes (**29**) with evolution of HCl (Scheme 3). The complex (**28**) was easily hydrolysed by moisture and decomposed with time even in the absence of air.



Scheme 4.



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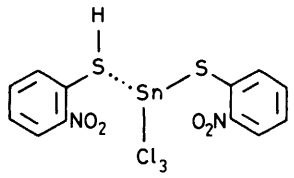

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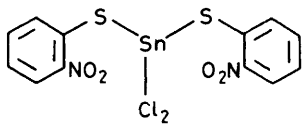

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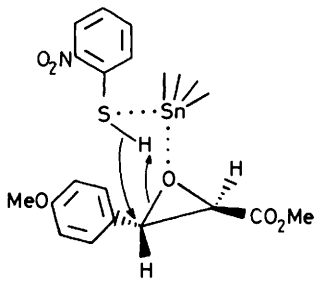

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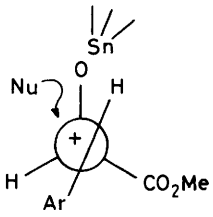

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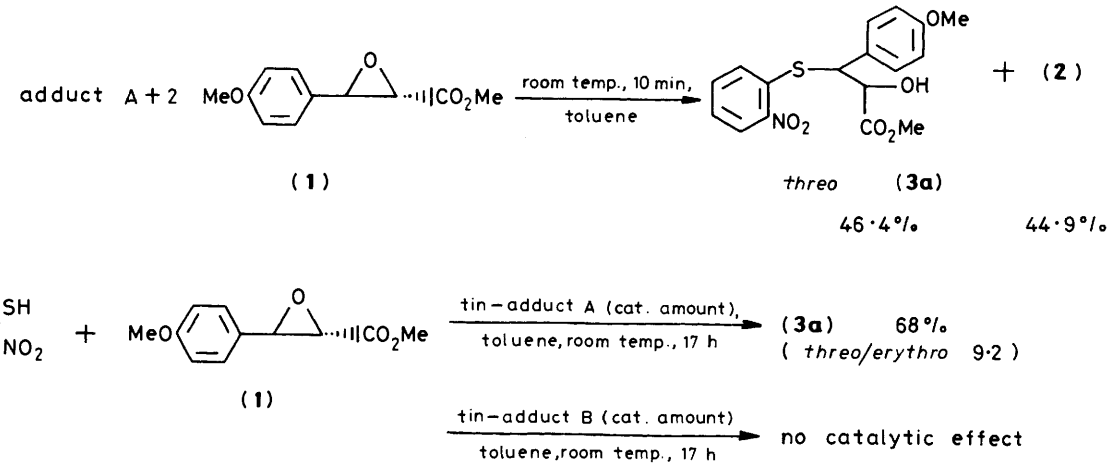
When 2-nitrothiophenol (**2**) was allowed to react with $SnCl_4$ in a 2:1 molar ratio in toluene at room temperature, a yellow crystalline adduct was obtained. The instability of this adduct* to moisture and heat led to difficulties in purification and in both spectral and elemental analyses. Quick and careful recrystallization of the crude adduct from dry benzene† gave yellow crystals of m.p. 143—145 °C (adduct A, Scheme 4), whose elemental analysis and mass spectral data (see Experimental section) appear to indicate that this adduct is a mixture of tin-adducts [(**30**), (**31**), and (**32**)], in which (**31**) seems to be predominant.

addition, the reaction of adduct A with two equivalents of (**1**) in benzene at room temperature proceeded exceedingly fast and gave the *threo*-ester (**3a**) in 46.4% yield within 10 min. The low yield appears to suggest that only the co-ordinated thiol group in adduct A is utilized in the reaction. On the other hand, repeated recrystallization of adduct A from dry benzene‡ gave the thermally more stable adduct B, to which structure (**32**) was assigned on the basis of its elemental analysis. Adduct B differed markedly from adduct A in its reactivity and showed no catalytic activity. The above results suggest that the catalytically active species in the $SnCl_4$-catalysed reaction of (**1**) with (**2**) are the tin–2-nitrothiophenol complexes [(**30**) and/or (**31**)]. Therefore, the thiol group co-ordinated with tin may play an important role, while an ionically linked thiol group may not.



Scheme 5.

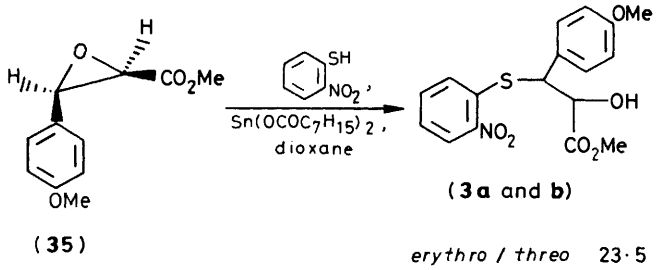
At any rate, addition of a catalytic amount of this adduct A to the mixture of (**1**) and (**2**) in toluene at room temperature readily gave a 68% yield of the *threo*-ester (**3a**) with a good *threo*/*erythro* ratio of the whole product (9.2) (see Scheme 5). Thus, the catalytic effectiveness of adduct A was quite similar to that of $SnCl_4$ in both stereoselectivity and reactivity. In

In conclusion, it appears likely that the balanced co-ordination of tin with both 2-nitrothiophenol and the oxygen atom of the oxirane ring of (**1**) leads to the formation of a plausible intermediate (**33**). This intermediate would provide suitable geometry in the reactants for selective *cis*-opening as well as electronic activation of the oxirane ring in the transition

* Douek and Spickett reported[6] that the $SnCl_4$-adduct of thiophenol was too unstable for them to record its spectra.

† Evolution of HCl was observed during recrystallization.

state and lead to ready and highly stereoselective formation of the *threo*-ester (**3a**).



Scheme 6.

The tin-catalysed reaction of the *cis*-glycidate (**35**) corresponding to (**1**) with (**2**) was also highly stereospecific and gave the *erythro*-isomer (**3b**), the *cis*-opening product (*erythro*/*threo* ratio 23.5) (Scheme 6).

This result ruled out another possible mechanistic explanation of the reaction, which involves formation of the benzylic carbonium ion (**34**) followed by stereoselective attack of nucleophile.* If this is the case, the *threo*-isomer (**3a**) would be obtained from either the *trans*- or *cis*-glycidate [(**1**) and (**35**)].

Experimental

All reactions were carried out under argon. I.r. spectra were taken on a Hitachi IR-215 spectrophotometer. N.m.r. spectra were recorded on JEOL PMX-60 or FX-100S instrument. Chemical shifts are given as δ values from tetramethylsilane as internal standard. Mass spectra were recorded on a Hitachi RMU-6D spectrometer. Preparative t.l.c. was carried out on Kieselgel GF_{254} (Merck). Kieselgel 60 (230—400 mesh) (Merck) was used for flash column chromatography.

2-Nitrothiophenol (**2**) was prepared by Chrzaszczewska's procedure[7] and used without further purification, since it was unstable in air. The yields quoted in the Tables were calculated based on crude (**2**) without correction, unless otherwise noted.

Reaction of trans-3-*Arylglycidic Esters with* 2-*Nitrothiophenols without Catalyst* (*Table* 1).—(*a*) *The reaction of methyl* trans-3-(p-*tolyl*)*glycidate* (**7**). A mixture of the glycidate (**7**) (1.3 g, 6.77 mmol) and 2-nitrothiophenol (**2**) (1.0 g, 6.45 mmol) in CH_3CN (5 ml) was heated under reflux for 20 h. The reaction mixture was concentrated and the residue was separated by flash column chromatography. A mixture of methyl *threo*- and *erythro*-2-hydroxy-3-(2-nitrophenylthio)-3-(*p*-tolyl)propionate (**12**) (480 mg; m.p. 95—118 °C) was obtained from the eluate with C_6H_6–AcOEt (20:1).

The mixture of nitro esters was converted into a mixture of the corresponding *cis*- and *trans*-lactams (**20a** and **b**) as follows.

The mixture of nitro esters (**12**) (3.07 g) was hydrolysed in a stirred mixture of 5% aqueous NaOH (10 ml) and EtOH (10 ml) at room temperature for 1 h. The reaction mixture was acidified with 10% HCl and extracted with EtOAc. The extracts were washed with water, dried, and evaporated to give a crude mixture of *threo*- and *erythro*-nitro carboxylic acids (2.7 g).

A solution of this crude mixture of nitro carboxylic acids in 10% NaOH (2 ml) and water (50 ml) was hydrogenated overnight in the presence of 10% Pd–C (1 g) under ordinary pressure and temperature. After removal of Pd–C by filtration, the filtrate was acidified (pH 4) with AcOH and the precipitated crystals were extracted with AcOEt. The extracts were washed with water, dried, and evaporated to give a mixture of *threo*- and *erythro*-amino carboxylic acids (2.5 g).

The mixture of amino carboxylic acids was heated in xylene (20 ml) under reflux for 20 h. After removal of xylene, the residual solid was separated by preparative t.l.c. [developed with $CHCl_3$–EtOH (10:1)]. *cis*-2,3-Dihydro-3-hydroxy-2-(*p*-tolyl)-1,5-benzothiazepin-4(5*H*)-one (**20a**) (850 mg; m.p. 194—198 °C) was obtained from the faster moving band. This was shown to be identical with an authentic sample,[2b] $\nu_{max.}$(Nujol) 3 350, 3 200, 3 100, 1 680, and 1 640 cm^{-1}; *m*/*z* 285 (M^+), 256 (100%), 164, 134, and 105; $\delta_H(CDCl_3$; 60 MHz), 2.30 (3 H, s, CH_3), 2.95 (1 H, d, *J* 9 Hz, OH), 4.47 (1 H, dd, *J* 6.5 and 9 Hz, 3-H), 5.07 (1 H, d, *J* 6.5 Hz, 2-H), and 7.0—7.8 (8 H, m, ArH).

The trans-*isomer* (**20b**) (700 mg; m.p. 215—217 °C) was obtained from the slower moving band (Found: C, 67.1; H, 5.2; N, 4.9; S, 11.2. $C_{16}H_{15}NO_2S$ requires C, 67.34; H, 5.30; N, 4.91; S, 11.23%), $\nu_{max.}$(Nujol) 3 500, 3 160, 3 030, and 1 670 cm^{-1}; *m*/*z* 285 (M^+), 256 (100%), 164, 134, and 105; δ_H[$(CD_3)_2SO$; 100 MHz] 2.27 (3 H, s, CH_3), 4.09 (1 H, dd, *J* 8 and 11 Hz, 3-H), 4.34 (1 H, d, *J* 11 Hz, 2-H), 5.28 (1 H, d, *J* 8 Hz, OH), and 7.0—7.6 (8 H, m, ArH).

(*b*) *The reaction of methyl* trans-3-(4-*methoxyphenyl*)*glycidate* (**1**). A mixture of the glycidate (**1**) (3.2 g, 15.4 mmol) and 2-nitrothiophenol (**2**) (2.0 g, 12.9 mmol) in CH_3CN (20 ml) was stirred at 50 °C for 48 h. After removal of the solvent under reduced pressure the residue was dissolved in a mixture of EtOH (10 ml) and Pr^i_2O (10 ml) and kept at room temperature. The precipitated yellow needles were filtered off and washed with Pr^i_2O to give the *threo*-nitro ester (**3a**) (2.39 g, 56%), m.p. 152—156 °C which was identical with an authentic sample of methyl *threo*-2-hydroxy-3-(4-methoxyphenyl)-3-(2-nitrophenylthio)propionate.[2b]

The filtrate was evaporated and the residue was separated by flash column chromatography. Elution with AcOEt–benzene (1:8) gave a mixture of the *threo*- and *erythro*-nitro esters (**3a** and **b**) (1.215 g, 25.7%) as a yellow oil.

A small portion of the epimeric nitro esters (**3a** and **b**) was acetylated by being heated with acetic anhydride and pyridine for 2 h on a boiling water bath. Ac_2O, AcOH, and pyridine were evaporated off completely under reduced pressure. The intensity of the methyl signals of the $OCOCH_3$ group of the resulting mixture of the *threo*- and *erythro*-2-acetoxy derivatives (**18a** and **b**) was measured by n.m.r. spectrometry. The ratio of *threo*- to *erythro*-nitro esters was 3.0.

Authentic samples of the *threo*- and *erythro*-2-acetoxy derivatives (**18a** and **b**) were prepared by acetylation of the corresponding authentic nitro esters (**3a** and **b**) and showed the following signals in their n.m.r. spectrum ($CDCl_3$; 100 MHz).

threo-Isomer [(**18a**), yellow oil] δ_H 2.12 (3 H, s, $COCH_3$), 3.65 (3 H, s, CO_2CH_3), 3.80 (3 H, s, $C_6H_4OCH_3$), 4.88 (1 H, d, *J* 6 Hz, 3-H), 5.40 (1 H, d, *J* 6 Hz, 2-H), and 6.78—8.10 (8 H, m, ArH).

erythro-Isomer [(**18b**), yellow oil] δ_H 2.20 (3 H, s, $COCH_3$), 3.65 (3 H, s, CO_2CH_3), 3.80 (3 H, s, $C_6H_4OCH_3$), 4.95 (1 H, d, *J* 5 Hz, 3-H), 5.51 (1 H, d, *J* 5 Hz, 2-H), and 6.78—8.10 (8 H, m, ArH).

Another portion of the nitro esters (**3a** and **b**) (3.85 g) was converted into the *cis*- and *trans*-lactam (**4a** and **b**) in the same manner as described for (**20**). The ratio (**4a**)/(**4b**) (1.65 g and 0.56 g, respectively) was 2.95.

(*c*) *The reaction of methyl* trans-3-*phenylglycidate* (**8**). When a mixture of the glycidate (**8**) (1.13 g, 6.34 mmol) and 4-chloro-2-nitrothiophenol (1.0 g, 5.28 mmol) in CH_3CN (10 ml) was stirred at 50 °C for 5 d, the *erythro*-nitro ester (**17b**) (70 mg, 3.6%), m.p. 131—132.5 °C was obtained after work-up as described above, $\nu_{max.}$(Nujol) 3 100, 1 710, 1 340, 1 250, and 1 100 cm^{-1}; *m*/*z* 367 (M^+) and 278 [M – $CH(OH)CO_2Me$]; $\delta_H(CDCl_3$; 60 MHz) 3.76 (3 H, s, OCH_3), 3.29 (1 H, brs, OH), and 4.50—4.76 (2 H, m, 2- and 3-H).

* We thank a referee for this suggestion.

This *erythro*-nitro ester (**17b**) was converted into the *trans*-lactam (**24b**) by the usual method; the product was identical with an authentic sample.[2b]

Reaction of trans-3-*Arylglycidic Esters with Nitrothiophenol* (**2**) *in the Presence of* $NaHCO_3$ (*Table* 2).—(*a*) *The reaction of methyl* trans-3-(4-*methoxyphenyl*)*glycidate* (**1**). To a mixture of 2-nitrothiophenol (**2**) (9.8 g, 63.2 mmol) and $NaHCO_3$ (100 mg) in EtOH (110 ml) was added the glycidate (**1**) (13.8 g, 66.3 mmol). The reaction mixture was stirred at room temperature overnight. The precipitated yellow crystals were filtered off and recrystallized from EtOH to afford the known [2b] *erythro*-nitro ester (**3b**), m.p. 135—136.5 °C (1.83 g, 80.0%) as yellow needles.

(*b*) *The reaction of methyl* trans-3-(4-*chlorophenyl*)*glycidate* (**9**). Similarly, the glycidate (**9**) (2.3 g, 10.8 mmol) was allowed to react with 2-nitrothiophenol (**2**) (1.68 g, 10.8 mmol) in absolute MeOH (20 ml) in the presence of $NaHCO_3$ (150 mg) under reflux overnight. The crude product was separated by flash column chromatography. Evaporation of the first eluate [eluant $CHCl_3$–hexane (3:1)] gave a mixture of the 2-nitrothiophenol (**2**), the glycidate (**9**), and *p*-chlorobenzaldehyde. Methyl (2-nitrophenylthio)acetate (**25**)[2b] was obtained from the second eluate. From the third eluate the erythro-*nitro ester* (**14b**) (1.69 g, 51·4%) was obtained as yellow needles, m.p. 129.5—132 °C (from EtOH) (Found: C, 52.25; H, 3.7; N, 3.8; S, 8.7; Cl, 9.9. $C_{16}H_{14}ClNO_5$ requires C, 52.25; H, 3.84; N, 3.81; S, 8.71; Cl, 9.93%); $\nu_{max.}$(Nujol) 3 475, 1 740, 1 590, 1 565, 1 515, and 1 335 cm^{-1}; *m/z* 367 (M^+) and 278 [M – $CH(OH)CO_2Me$]; δ_H($CDCl_3$; 60 MHz) 3.73 (3 H, s, OCH_3), 3.00 (1 H, d, *J* 6 Hz, OH), 4.75—4.85 (2 H, m, 2- and 3-H) [changed to 4.77 and 4.82 (2 H, AB system, *J* 4 Hz) on treatment with D_2O], 7.1—7.5 (7 H, m, ArH), and 8.01 (1 H, dd, *J* 7 and 3 Hz, ArH).

The trans-*lactam* (**21b**), m.p. 213—214.5 °C (from benzene) obtained from the *erythro*-nitro ester (**14b**) in 54.3% overall yield had the following spectral data (Found: C, 59.0; H, 3.8; N, 4.4; S, 10.7; Cl, 11.7. $C_{15}H_{12}ClNO_2S$ requires C, 58.92; H, 3.96; N, 4.58; S, 10.48; Cl, 11.59%); $\nu_{max.}$(Nujol) 3 470, 3 190, 3 100, 3 050, 1 670, 1 580, and 1 570 cm^{-1}; *m/z* 305, and 307 (M^+) and 276 and 278 [M – $CH(OH)CO_2Me$]; δ_H[$(CD_3)_2SO$; 100 MHz] 4.09 (1 H, dd, *J* 8 and 11 Hz, 3-H), 4.43 (1 H, d, *J* 11 Hz, 2-H), 5.38 (1 H, d, *J* 8 Hz, OH), 7.14 and 7.48 (4 H, AB system, *J* 8 Hz, C_6H_4Cl), and 7.1—7.4 (4 H, m, ArH).

(*c*) *The reaction of methyl* trans-3-(4-*nitrophenyl*)*glycidate* (**10**). Similar reaction of the glycidate (**10**)[8] gave the following compounds after separation by flash column chromatography: a mixture of the threo- and erythro-*nitro ester* (**15a** and **b**), 17.9% yield, m.p. 143.5—145 °C* after recrystallization from EtOH (Found: C, 50.6; H, 4.3; N, 7.2. $C_{16}H_{14}N_2O_7S$ requires C, 50.79; H, 3.73; N, 7.40%); $\nu_{max.}$(Nujol) 3 500, 3 110, 3 080, 1 730, 1 590, 1 510, and 1 340 cm^{-1}; *m/z* 378 (M^+) and 289 [M – $CH(OH)CO_2Me$]; δ_H($CDCl_3$; 60 MHz) 3.44 (1 H, d, *J* 5 Hz, OH), 3.79 (3 H, s, OCH_3), 4.60 (1 H, dd, *J* 5 and 3 Hz, 2-H), 4.85 (1 H, d, *J* 3 Hz, 3-H), 7.68 and 8.14 (4 H, AB system, *J* 8 Hz, $C_6H_4NO_2$-*p*), and 7.0—8.2 (4 H, m, ArH); methyl (2-nitrophenylthio)acetate (**25**), 9.5%; and *methyl* p-*nitro*-α-(2-*nitrophenylthio*)*cinnamate* (**26**), 19.2%, m.p. 187—189.5 °C (from $CHCl_3$) (Found: C, 52.9; H, 3.2; N, 7.7; S, 9.0. $C_{16}H_{12}N_2O_6S$ requires C, 52.33; H, 3.36; N, 7.77; S, 8.90%); $\nu_{max.}$(Nujol) 1 710, 1 605, 1 590, 1 565, 1 520, 1 350, and 1 330 cm^{-1}; *m/z* 360 (M^+) and 332; δ_H($CDCl_3$, 60 MHz) 3.69 (3 H, s, OCH_3), 7.90 and 8.22 (4 H, AB system, *J* 8 Hz, $C_6H_4NO_2$-*p*), 8.31 (1 H, s, β-H), and 7.1—8.4 (4 H, m, ArH).

Reaction in the Presence of BF_3·Et_2O (*Table* 3).—In a typical procedure, BF_3·Et_2O (0.1 ml) in absolute Et_2O (5 ml) was added to a solution of 2-nitrothiophenol (**2**) (2.0 g, 12.9 mmol) in absolute Et_2O (15 ml) at 10 °C during 5 min, and then the glycidate (**8**) (2.76 g, 15.5 mmol) was added to the ice-cooled mixture. The reaction mixture was stirred at room temperature for 22 h and separated by flash column chromatography after removal of Et_2O under reduced pressure. The mixture of the *threo*- and *erythro*-nitro ester (**13a** and **b**) (1.535 g, 35.7%) thus obtained was treated with Pr^i_2O to afford the *erythro*-isomer (**13b**)[2b] (425 mg, 9.9%), m.p. 124—127.5 °C (from EtOH). The mixture of the *threo*- and *erythro*-nitro ester obtained from the mother liquor was converted into a mixture of the corresponding *cis*- and *trans*-lactam (**22a** and **b**) in the usual manner. The *cis*/*trans* ratio of the lactams obtained was 1.31. Accordingly, the *threo*/*erythro* ratio of the whole product (**13**) was 0.68.

The other results obtained in the presence of BF_3·Et_2O are summarized in Table 3.

Reaction of Methyl trans-3-(4-*Methoxyphenyl*)*glycidate* (**1**) *with* 2-*Nitrothiophenol* (**2**) *in the Presence of Various Catalysts* (*General Procedure*) (*Tables* 4 *and* 5).—An appropriate catalyst (100 mg or 0.1 ml) was added to a solution of 2-nitrothiophenol (**2**) (2.0 g, 12.9 mmol) in dioxane (10 ml) at 10 °C and then a solution of the glycidate (**1**) (3.2 g, 15.4 mmol) in dioxane (10 ml) was added to the mixture at 10 °C during a period of 5 min. The reaction mixture was stirred under the conditions shown in Table 4 or 5. The reaction was monitored by t.l.c. After completion of the reaction, the solvent was removed under reduced pressure and the residue was treated with Pr^i_2O–EtOH (1:1; 20 ml). The precipitated yellow crystals were collected. In entries 1, 8, 11, and 14 in Table 4, the mother liquor was evaporated and the residue was separated by flash column chromatography. The nitro esters obtained from flash column chromatography were acetylated with Ac_2O–pyridine and the *threo*/*erythro* ratio was determined by n.m.r. spectrometry.

Reaction of the Glycidate (**1**) *with* 2-*Nitrothiophenol* (**2**) *in the Presence of* $Mg(OH)_2$, MgCl(OH), *or* $Ca(OH)_2$.—Reaction of the glycidate (**1**) with 2-nitrothiophenol (**2**) was carried out in the presence of a catalytic amount of $Mg(OH)_2$, MgCl(OH), or $Ca(OH)_2$ under the same conditions as described for the reaction in the presence of $CaCl_2$ or $MgCl_2$ (at room temperature for 40 h). As shown by t.l.c., the reaction catalysed by $Mg(OH)_2$ and $Ca(OH)_2$ was very slow and gave the *erythro*-nitro ester (**3b**) in 23.5 and 44.4% yield, respectively, while in the case of Mg(OH)Cl, the *erythro*-isomer (**3b**) was obtained in 66.2% yield.

Adducts of 2-*Nitrothiophenol* (**2**) *with* $SnCl_4$.—A solution of $SnCl_4$ (25 g, 96.0 mmol) in absolute benzene (50 ml) was added to a solution of 2-nitrothiophenol (**2**) (33.0 g, 213 mmol) in absolute benzene (230 ml) at 10 °C. The reaction mixture was stirred at room temperature for 1 h. The precipitated amorphous product (7.5 g) was removed by filtration. The filtrate was evaporated under reduced pressure below room temperature and n-hexane–benzene (1:3) (100 ml) was added to the residual yellow gum. The precipitated yellow crystals (15.6 g), m.p. 142—145 °C (decomp.), were collected on a filter. The crude adduct (10 g) was rapidly recrystallized from dry benzene under dry argon below 50 °C† to give the *adduct A* (5.6 g), m.p. 143—145 °C as yellow needles (Found: C, 27.1; H, 1.7; N, 5.3; S, 12.1; Cl, 15.4; Sn, 23.5. $C_{12}H_9Cl_3N_2O_4S_2Sn$ (**31**) requires C, 26.97; H, 1.70; N, 5.24; S, 12.00; Cl, 19.90; Sn, 22.21%); $\nu_{max.}$(Nujol) 2 530vw, 2 350vw, 1 580, 1 560, 1 510, 1 335, 1 160,

* The stereochemistry of this compound was not determined.

† The mother liquor was strongly acidic.

‡ 2-Nitrothiophenol (**2**) showed the following spectral data: $\nu_{max.}$(Nujol) 2 520, 1 590, 1 560, 1 500, 1 450, 1 330, 1 300, 1 115, 1 060, 1 040, 980, 855, 783, 730, and 655 cm^{-1}; δ_H($CDCl_3$) 4.02 (1 H, s, SH), 7.1—7.5 (3 H, m, ArH), 8.16 (1 H, dd, *J* 7 and 2 Hz, 3-H).

1 140, 1 120, 960, 860, 780, 730, and 650 cm $^{-1}$; ‡ *m/z* (M^+ not seen), 496 [(*o*-$NO_2C_6H_4S)_2SnCl_2]^+$, 379 (*o*-$NO_2C_6H_4SSnCl_3)^+$, 260 ($SnCl_4^+$), 225 ($SnCl_3^+$), and 155 (*o*-$NO_2C_6H_4SH$); δ_H($CDCl_3$; 60 MHz) 4.05 (1 H, s, SH), 7.40—8.1 (7 H, m), 8.29 (1 H, br d, *J* 7 Hz).*

When the adduct A was repeatedly recrystallized from dry benzene more than three times,† it rearranged to the adduct B as yellow pillars, m.p. 143—145 °C. The i.r. and n.m.r. spectra of the *adduct B* were similar to those of the adduct A, although the i.r. spectrum had no absorption around 2 530—2 300 cm $^{-1}$ [Found: C, 28.8; H, 1.6; N, 5.8; S, 12.5; Cl, 14.8; Sn, 23.2. $C_{12}H_8Cl_2N_2O_4S_2Sn$ (**32**) requires C, 28.95; H, 1.62; N, 5.63; S, 12.88; Cl, 14.24; Sn, 23.84%].

Reaction of the Adduct A with Methyl trans-3-(4-*Methoxyphenyl)glycidate* (**1**).—The glycidate (**1**) (1.17 g, 5.62 mmol) was added to a solution of the adduct A [1.5 g, 2.8 mmol based on the structure (**31**)] in dry benzene (10 ml). After being stirred for 10 min, the reaction mixture was separated by flash column chromatography [elution with benzene–AcOEt (20:1)]. 2-Nitrothiophenol (**2**) [390 mg, 44.9% based on moles of 2-nitrothiophenol in compound (**31**)] was recovered from the first eluate. From the second eluate, the *threo*-nitro ester (**3a**) (1.083 g, 46.4%), m.p. 154—157 °C, was obtained.

Reaction of the Glycidate (**1**) *with* 2-*Nitrothiophenol* (**2**) *in the Presence of a Catalytic Amount of the Adduct A.*—The adduct A (60 mg) was added to a solution of (**2**) (2.0 g, 12.9 mmol) in toluene (20 ml), and then the glycidate (**1**) (3.2 g, 15.4 mmol) was added. After being stirred at room temperature for 17 h, the reaction mixture was concentrated under reduced pressure at room temperature and treated with Pr^i_2O–EtOH (1 : 1, 20 ml) to give the *threo*-nitro ester (**3a**) (3.18 g, 67.9%), m.p. 156—158 °C. When the mother liquor was concentrated and the residue was separated by flash column chromatography, an additional amount of the nitro ester (**3a** and **b**) (880 mg, 18.8%) was obtained as an oil. The *threo/erythro* ratio of this oil was 1.2 which was determined by the n.m.r. spectrum of the corresponding 2-acetoxy nitro ester (**18**). Accordingly, the *threo/erythro* ratio of the whole product was 9.2.

Reaction of the Glycidate (**1**) *with* 2-*Nitrothiophenol* (**2**) *in the Presence of a Catalytic Amount of the Adduct B.*—When the reaction of the glycidate (**1**) (1.6 g, 7.69 mmol) with 2-nitrothiophenol (**2**) (1.0 g, 6.45 mmol) in toluene (10 ml) was carried out in the presence of a catalytic amount of the adduct B (30 mg) at room temperature, the reaction proceeded very slowly. After being stirred for 20 h, the reaction mixture was worked up in the same manner as described for the reaction of the adduct A. The *erythro*-nitro ester (**3b**) (675 mg, 28.8%), m.p. 135—137 °C, was obtained. This result was very similar to that in the reaction at room temperature without a catalyst.

The reaction of the adduct B (100 mg, 0.2 mmol) with the glycidate (**1**) (120 mg, 0.6 mmol) in dioxane (1 ml) at room temperature was also quite slow. After 3 d, the *threo*-nitro ester (**3a**) (73 mg, 50% based on moles of 2-nitrothiophenol in the adduct B) was isolated.

Methyl cis-3-(4-*Methoxyphenyl)glycidate* (**34**).—A solution of anisaldehyde (40.86 g, 0.30 mol) and methyl chloroacetate (32.56 g, 0.30 mol) in hexamethylphosphoric triamide (HMPA) (250 ml) was added to a suspension of NaH (11.5 g, 0.30 mol; 63% dispersion in mineral oil) in HMPA (250 ml) at 20 ± 2 °C during a period of 1.5 h. After being stirred at room temperature overnight, the reaction mixture was poured into ice–water and extracted with benzene. The extracts were washed with water, dried, and evaporated. The residual oil (56.0 g) was distilled to give an oil, b.p. 145—153 °C/0.6 mmHg (41.4 g, 66.3%).

The *cis/trans* ratio of this oil was 1/1.1 which was determined by n.m.r. spectrometry [Me proton of CO_2Me of the *cis*-glycidate (**34**) appears at δ 3.45 (s), while those of $MeOC_6H_4$ of the *cis*- and *trans*-glycidates and of CO_2Me of the *trans*-isomer (**1**) are at 3.70].

The oil was dissolved in Pr^i_2O (22 ml) and the solution was kept in the refrigerator. The precipitated *trans*-isomer (**1**), m.p. 66—68 °C (16.25 g, 26%) was filtered off. The *cis*-rich residue obtained from the mother liquor was distilled twice to give the pure *cis*-glycidate (**34**) (10.7 g, 17.1%), b.p. 137—138 °C/0.7 mmHg; δ_H(100 MHz; CCl_4) 3.45 (3 H, s, CO_2CH_3), 3.70 (3 H, s, $CH_3OC_6H_4$), 3.58 and 4.02 (2 H, dd, *J* 4.5 Hz, 2- and 3-H), and 6.74 and 7.20 (4 H, dd, *J* 9 Hz, ArH); $\nu_{max.}$(liquid) 1 750 cm $^{-1}$.

Reaction of the cis-*Glycidate* (**34**) *with* (**2**) *in the Presence of a Catalytic Amount of Stannous* 2-*Ethylhexanoate.*—$Sn(OCOC_7H_{15})_2$ (0.04 ml) and then the *cis*-glycidate (**34**) (1.0 g, 4.80 mmol) were added to a solution of (**2**) (750 mg, 4.83 mmol) in dioxane (4 ml) at room temperature and the mixture was stirred at room temperature for 18 h (it was found that the reaction was almost complete within 1 h, when the reaction was monitored by t.l.c.). After removal of the solvent under reduced pressure, the residue was treated with EtOH–Pr^i_2O to give the *erythro*-nitro ester (**3b**) (1.17 g), m.p. 135—136.5 °C.

The mother liquor was evaporated and the residual oil was separated by preparative t.l.c. to give a mixture of the *threo*- and *erythro*-nitro esters (**3a**) and (**3b**) (300 mg, total yield 83.3%); the *erythro/threo* ratio of the mixture was 4:1, as determined by n.m.r. spectrometry. Accordingly the *erythro/threo* ratio of the whole product was 23.5.

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* The 2EtSH·$SnCl_4$ complex prepared by Douek's method [6] showed the following fragment ions; *m/z* 320 (EtSH–$SnCl_4^+$), 286 (EtS–$SnCl_3^+$), 260 ($SnCl_4^+$), 251 (EtS–$SnCl_2^+$), 225 ($SnCl_3^+$), 190 ($SnCl_2^+$), and 155 ($SnCl^+$).