Hydroxy-group Participation in the Chlorination of Thian 1-Oxides

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Chlorination of 4-hydroxythian 1-oxides with hydroxy- and *S*-oxide groups *cis* to each other gives 4-chloro-sulphones. The reaction proceeds *via* a cyclic alkoxyoxosulphonium ion formed by nucleophilic displacement of chlorine by the 4-hydroxy-group in an initially formed chloro-oxosulphonium ion in which the *S*-oxide group is axial. The equatorial chlorine atom is displaced with inversion at sulphur. Nucleophilic attack by chloride ion at C-4 of the cyclic alkoxyoxosulphonium ion with inversion at C-4 causes ring opening with transfer of the C-4 oxygen atom to sulphur. Chlorination of a thian 1-oxide containing a 4-chloro- or a 4-tosyloxy-group, or a 4-hydroxy-group *trans* to the *S*-oxide group, proceeds without participation to give the α-chloro-sulphoxide.

THE mechanism of α-chlorination of sulphoxides was controversial until recently. The natural analogy between ketones and sulphoxides led initially to the assumption that abstraction of the proton α to the sulphoxide group is the first step.[1] Another mechanism, involving a chloro-oxosulphonium ion formed by attack of a positive chlorine species on sulphur, was shown later to be more likely.[2,3] Much confusion existed about the transformation of the initially formed chloro-oxo-sulphonium ion into the α-chloro-sulphoxide product,[4-6] but recent studies on the chlorination of thian 1-oxides [7-9] seem to have resolved this problem.

The observation [2,3] that β-, γ-, and δ-chloroalkyl sulphones are formed by chlorination of the corresponding hydroxyalkyl sulphoxides was explained as occurring by ring opening of a cyclic alkoxyoxosulphonium ion intermediate with inversion at the oxygen-bearing carbon atom. However, no data are available on the steric course of the reaction at sulphur.

As a continuation of our studies on the chlorination of thian 1-oxides and to investigate the stereochemistry of cyclic alkoxyoxosulphonium ions, we have investigated the chlorination of 4-hydroxythian 1-oxides and related compounds.

RESULTS

The chlorinations were performed in dichloromethane with an excess of chlorine and pyridine as described previously,[7] unless otherwise indicated.

Chlorination of *cis*-4-hydroxy-*cis*,*cis*-2,6-diphenylthian 1-oxide (1) [10] gave a mixture of the sulphones (2)—(4) in yields of 29, 29, and 5%, respectively. In some runs no ketone (4) was detected. With t-butyl hypochlorite in pyridine [11] as chlorinating agent the sulphones (2) and (3) were obtained in 19 and 55% yields, respectively, whereas sulphuryl chloride and calcium oxide [12] gave (2) only, in 60% yield. In contrast, chlorinations of the corresponding acetate (5), ketone (6),[10] and the isomeric sulphoxide (7) [10] resulted in complex mixtures.

[1] G. Tsuchihashi and S. Iriuchijima, *Bull. Chem. Soc. Japan*, 1970, **43**, 2271.
[2] T. Durst and K. C. Tin, *Canad. J. Chem.*, 1971, **49**, 2374.
1973, **51**, 1704.
[3] T. Durst, K. C. Tin, and M. J. V. Marcil, *Canad. J. Chem.*, 1973, **51**, 1704.
[4] M. Cinquini, S. Colonna, and F. Montanari, *Chem. Comm.*, 1969, 607.
[5] G. Tsuchihashi, K. Ogura, S. Iriuchijima, and S. Tomisawa, *Synthesis*, 1971, 89.
[6] (*a*) M. Cinquini and S. Colonna, *J.C.S. Perkin I*, 1972, 1883; (*b*) P. Calzavara, M. Cinquini, S. Colonna, R. Fornasier, and F. Montanari, *J. Amer. Chem. Soc.*, 1973, **95**, 7431.
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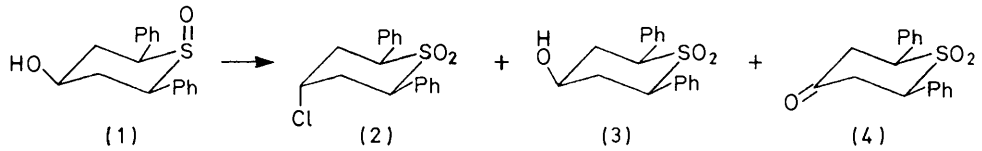
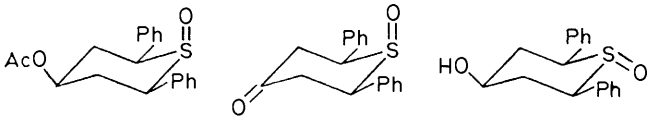
[9] S. Iriuchijima, M. Ishibashi, and G. Tsuchihashi, *Bull. Chem. Soc. Japan*, 1973, **46**, 921.
[10] J. Klein and H. Stoller, *Tetrahedron*, in the press.
[11] S. Iriuchijima and G. Tsuchihashi, *Tetrahedron Letters*, 1969, 5259.
[12] K. C. Tin and T. Durst, *Tetrahedron Letters*, 1970, 4643.

Chlorination of *cis*-4-hydroxythian 1-oxide (8) [10,13] gave the dichloro-sulphone (9). However, with 1 mol. equiv. of sulphuryl chloride and calcium oxide, the oxidation of *cis,cis*-2,6-diphenylthian-4-ol [14] with peroxide. The oxo-sulphone (4),[15] the dichloro-sulphone (9),[9] and the monochloro-sulphone (10) [16] are known



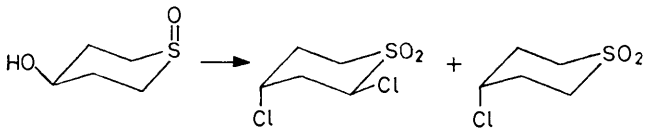
(1) (2) (3) (4)

monochloro-sulphone (10) was obtained. Chlorination of the corresponding tosylate (11a) [13] and chloride (11b) [13] gave the dichloro-sulphoxides (12a and b),



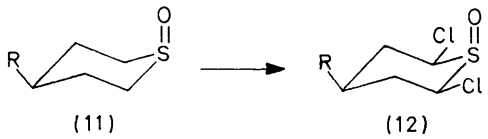
(5) (6) (7)

respectively. The *trans*-4-hydroxythian 1-oxide (13) [10,13] gave a mixture of the chloro-sulphoxides (14) and (15).



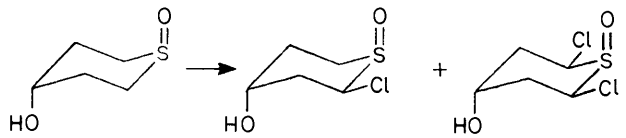
(8) (9) (10)

The structures of the chlorination products were established primarily from spectral data. In some compounds and were prepared by the reported procedures for comparison purposes. The dichlorohydroxythian 1-oxide (15) was converted into the known [7] acetate. The axial configuration of the sulphoxide



(11) (12)

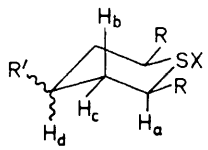
a; R = OTs a; R = OTs
b; R = Cl b; R = Cl



(13) (14) (15)

groups in compounds (5), (12a), (12b), and (15) was established by the appearance of the n.m.r. signals due to the β-axial protons at lower field than those of the

N.m.r. data for some substituted thians



		δ [a]					J/Hz			
Compd.	Solvent	H_a	H_b	H_c	H_d [$W_{\frac{1}{2}}$/Hz]	H_R	J_{ab} = J_{bc}	J_{ac}	J_{bd}	J_{cd}
(2)	$CDCl_3$	4·75 [b]	3·11 (sx) [c]	2·51 (sx)	4·69 [b] [—] [b]	7·29 (s)	13·5	3	3	3
(3)	CD_3CN	4·47 (q)	2·60 (q)	2·33 (m)	4·15 (sp) [c] [15]	7·43 (s)	12	3	12	5
(4)	CD_3CN	4·77 (q)	3·63 (t)	2·80 (d) [d]		7·33 (s)	14	3		
(5)	CF_3CO_2H	4·35 (d) [d]	2·86 (q)	2·34 (d) [d]	5·37 (m) [20]	7·37 (s)	12	*b*	12	*b*
(12a)	C_5H_5N [e]	5·25 (q)	2·65 (q)	2·42 (sx)	4·96 (sp) [15]		12	4	12	5
(12b)	$CDCl_3$	4·67 (q)	2·70 (q)	2·5 [b]	3·92 (sp) [18]		12	4	12	5
(15)	$CDCl_3$ [e]	4·97 (q)	2·37 (sx)	2·12 (sx)	4·18 (m) [9]		13	4	2	4

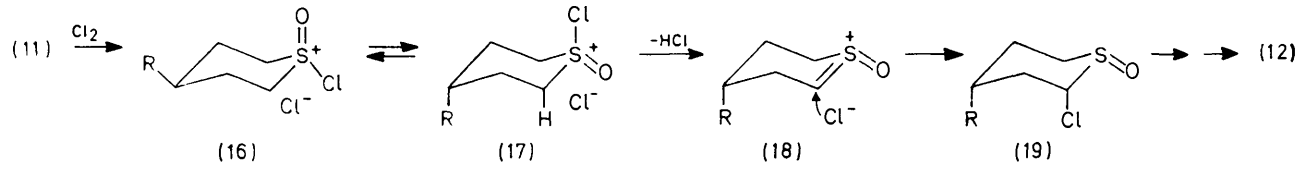
[a] Standard tetramethylsilane. [b] Multiplicity uncertain owing to overlap of peaks. [c] sx = sextet; sp = septet. [d] Broad. [e] Temp. 50°. In this case hexamethyldisiloxan was used as internal standard.

cases the products were synthesized by alternative routes. Thus, the hydroxy-sulphone (3) was prepared together with a small amount of the sulphoxide (7) by β-equatorial protons [7,17,18] (Table). The axial configuration of S=O in (14) is inferred from the known [7] mechanism of the reaction.

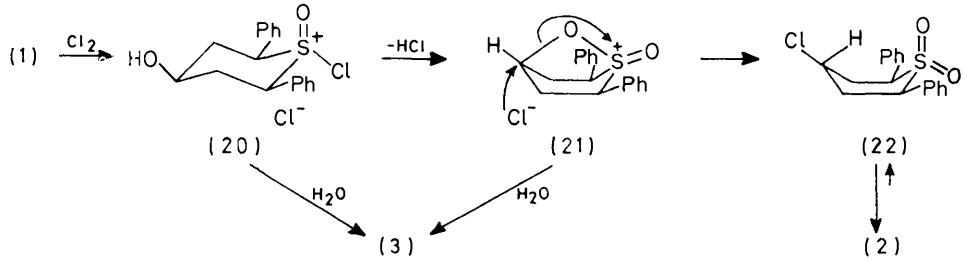
[13] J. C. Martin and J. J. Uebel, *J. Amer. Chem. Soc.*, 1964, **86**, 2936.
[14] C. A. R. Baxter and D. A. Whiting, *J. Chem. Soc.* (*C*), 1968, 1174.
[15] F. Arndt, P. Nachtwey, and J. Pusch, *Ber.*, 1925, **58**, 1633.
[16] H. Remane, R. Borsdorf, and A. Zschunke, *Z. Chem.*, 1971, 427.
[17] B. J. Hutchinson, K. K. Andersen, and A. R. Katritzky, *J. Amer. Chem. Soc.*, 1969, **91**, 3839.
[18] A. B. Foster, T. D. Inch, M. H. Qadir, and J. M. Webber, *Chem. Comm.*, 1968, 1086.

DISCUSSION

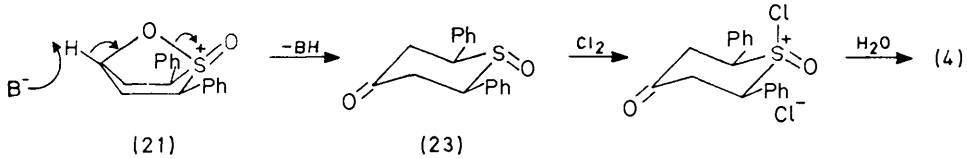
The chlorination of thian 1-oxides containing small 4-substituents such as *cis*-tosyloxy (12a), *cis*-chloro (12b), or *trans*-hydroxy (13) follows the normal course encountered previously;[7] the substituent stabilizes one conformation only slightly relative to the other. Thus (Scheme 1) chlorination of (11) gives the chloro-oxosulphonium ion [(16) ⇌ (17)] and a *trans*-diaxial elimination of HCl, which can proceed only through oxidation of the 4-hydroxy-group of (3) by the excess of chlorine and pyridine. Oxidation of secondary alcohols to ketones by iodobenzene dichloride and pyridine has recently been demonstrated.[19] An alternative explanation is shown in Scheme 3. Abstraction of the C-4 proton in the alkoxyoxosulphonium ion (21) by chloride anion or some other base gives the 4-oxo-sulphoxide (23) which, after chlorination and reaction with water present as an impurity, leads to (4). The larger amount



SCHEME 1



SCHEME 2



SCHEME 3

(17), leads to the 'inverted ylide'[7] intermediate (18). Axial addition of chloride ion to the α-carbon atom of (18), giving the α-chloro-sulphoxide (19), followed by a repetition of this sequence with (19), leads to the products (12). Similar considerations with (13) account for the formation of the products (14) and (15).

Those compounds with a *cis*-4-hydroxy-group react differently. Thus (Scheme 2) chlorination of (1) results in the chloro-oxosulphonium ion (20) in which the *S*-oxide group is axial and the chlorine atom is equatorial and *trans* to the 4-hydroxy-group. Intramolecular elimination of HCl with inversion at sulphur then takes place to give the cyclic alkoxyoxosulphonium ion (21). Nucleophilic attack by chloride anion at C-4 with inversion of configuration results in the sulphone (22) which is the boat conformation of (2). The intermediates (20) and (21) may be attacked by water, either as an impurity or in the hydrolysis step at the end of the reaction, to give the hydroxy-sulphone (3). The formation of sulphones during the chlorination of sulphoxides has been observed.[2] The ketone (4) may result from the of (3) obtained in the reaction of (1) with t-butyl hypochlorite relative to that in the reaction with chlorine or sulphuryl chloride can be explained by the attack of the t-butoxide counterion, formed in the first step of the reaction, on the intermediate chloro-oxosulphonium ion.

In the case of the sulphoxide (7), in which the hydroxy-group cannot participate in the chlorination reaction because of the unsuitable *trans*-configuration of the *S*-oxide group, and in the case of compounds (5) and (6), which have no hydroxy-groups, chlorination results in complex mixtures, perhaps containing C–S cleavage products. Such cleavage during the halogenation of benzyl sulphoxides has been reported.[20,21]

The chlorination of the *cis*-hydroxy-sulphoxide (8) proceeds partly according to the normal mechanism and partly with participation of the hydroxy-group. Thus (Scheme 4) chlorination results in the pair of chloro-oxosulphonium ions (24) ⇌ (25). The former is suitably disposed for intramolecular elimination of HCl to form the cyclic alkoxy-oxosulphonium ion (26), analogous to

[19] J. Wicha, A. Zarecki, and M. Kocor, *Tetrahedron Letters*, 1973, 3635.

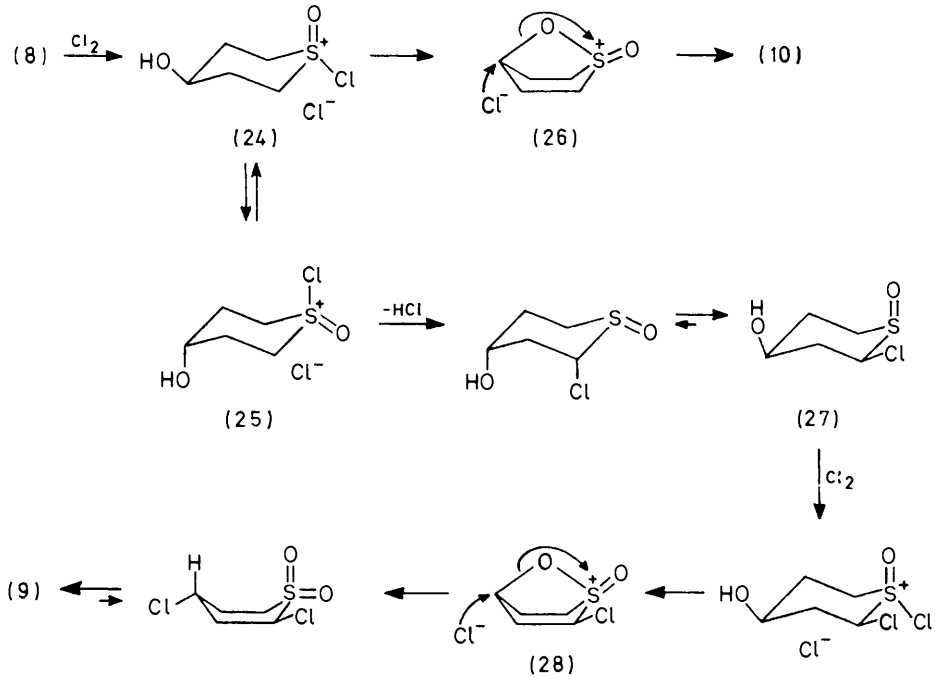
[20] F. Jung and T. Durst, *J.C.S. Chem. Comm.*, 1973, 4.

[21] C. Y. Meyers and G. J. McCollum, *Tetrahedron Letters*, 1973, 289.

(20) and (21) of Scheme 2, and the reaction proceeds according to Scheme 2 to give the 4-chloro-sulphone (10). On the other hand the isomeric chloro-oxosulphonium ion (25) is suitably disposed for *trans*-diaxial elimination of HCl as in Scheme 1. After the elimination–addition sequence of this mechanism, the α-chloro-sulphoxide (27) results. Further chlorination leads to the cyclic alkoxyoxosulphonium ion (28), which is attacked by chloride ion at C-4 to give the dichlorosulphone (9).

EXPERIMENTAL

General methods and chlorination procedures were as reported previously [7] unless otherwise indicated. In addition, preparative t.l.c. was performed on 0·75 mm × 20 cm² layers of fluorescent silica gel (Merck GF 254).



SCHEME 4

Bands were located under u.v. light or by exposure to iodine vapour. Products were extracted from the plates with MeOH–$CHCl_3$ (1 : 1).

Chlorination of cis-4-*Hydroxy*-cis,cis-2,6-*diphenylthian* 1-*Oxide* (1).[10]—(a) *With chlorine–pyridine.* The sulphoxide (1) (702 mg, 2·4 mmol) gave a crude product (840 mg) which was separated into three fractions by t.l.c. on eight plates ($CHCl_3$). The uppermost band gave 4-*chloro*-trans,trans-2,6-*diphenylthian* 1,1-*dioxide* (2) (208 mg, 29%), m.p. 190—191° (from CH_2Cl_2–Et_2O), $\nu_{max.}$ 1135 and 1320 cm^{-1} (SO_2) (Found: C, 63·5; H, 5·25; Cl, 11·25; S, 10·0. $C_{17}H_{17}ClSO_2$ requires C, 63·65; H, 5·35; Cl, 11·05; S, 10·0%). The middle band gave 4-oxo-*cis*-2,6-diphenylthian 1,1-dioxide (4) (36 mg, 5%), m.p. 239—240° (from $CHCl_3$–Et_2O), $\nu_{max.}$ 1130 and 1330 (SO_2), and 1730 cm^{-1} (C=O) (lit.,[16] m.p. 235°), identical (i.r. and n.m.r. spectra and mixed m.p.) with a sample prepared by the literature [15] procedure. The lowest band gave 4-*hydroxy*-cis,cis-2,6-*diphenylthian* 1,1-*dioxide* (3) (220 mg, 29%), m.p. 243—244° ($CHCl_3$), $\nu_{max.}$ 1128 (SO_2) and 3540 cm^{-1} (OH) (Found: C, 67·8; H, 6·0; S, 10·85. $C_{17}H_{18}SO_3$ requires C, 67·5; H, 6·00; S, 10·6%).

(b) *With t-butyl hypochlorite–pyridine.* The sulphoxide (1) (143 mg, 0·5 mmol) gave a crude product (160 mg), which, after t.l.c., yielded the sulphones (2) (29 mg, 19%) and (3) (83 mg, 55%).

(c) *With sulphuryl chloride–calcium oxide.* The sulphoxide (1) (143 mg, 0·5 mmol) gave a crude product (178 mg) which, after t.l.c., yielded the sulphone (2) (96 mg, 60%), starting material (1 mg), and (3) (1 mg).

4-*Hydroxy*-cis,cis-2,6-*diphenylthian* 1,1-*Dioxide* (3).—To a slurry of *cis,cis*-2,6-diphenylthian-4-ol [14] (270 mg, 1 mmol) in glacial acetic acid (5 ml) was added aqueous 30% hydrogen peroxide (620 mg, 6 mmol). A clear solution was formed after several minutes and stirring was continued for 40 h. Water was then added and the resulting precipitate was filtered off, washed with water, and air-dried to give a white solid (275 mg), m.p. 228—235°. T.l.c. on three plates [$CHCl_3$–MeCN (9 : 1)] gave two fractions. The upper band yielded the sulphone (3) (195 mg), m.p. 243—244°, identical (i.r. and n.m.r. spectra and mixed m.p.) with the product obtained above. The lower band yielded *trans*-4-hydroxy-*trans,trans*-2,6-diphenylthian 1-oxide (7) (31 mg), m.p. 240—241°, identical with an authentic [10] sample.

Chlorination of cis-4-*Hydroxythian* 1-*Oxide* (8).—(a) *With chlorine–pyridine.* The sulphoxide (8) (268 mg, 2 mmol) gave a crude product (292 mg) which crystallized from CH_2Cl_2–Et_2O to give *trans*-2,4-dichlorothian 1,1-dioxide (9) (112 mg, 28%), m.p. 128—130° (130—131° after recrystallization) (lit.,[9] m.p. 131·5—132°), identical (i.r. and n.m.r. spectra and mixed m.p.) with a sample prepared by the literature [9] procedure.

(b) *With sulphuryl chloride–calcium oxide.* Treatment of the sulphoxide (8) (134 mg, 1 mmol) for 45 min with sulphuryl chloride (0·07 ml, 0·9 mmol) gave a crude product

(102 mg). Recrystallization from CH_2Cl_2–Et_2O yielded 4-chlorothian 1,1-dioxide (10) (61 mg, 37%), m.p. 129—131° (lit.,[16] 132—133°), identical (i.r. and n.m.r. spectra and mixed m.p.) with a sample prepared by the literature [16] procedure.

cis,cis-2,6-*Dichloro*-cis-4-*tosyloxythian* 1-*Oxide* (12a).—Chlorination of *cis*-4-tosyloxythian 1-oxide (11a) [11] (288 mg, 1 mmol) with chlorine–pyridine gave a crude product (389 mg). Several recrystallizations from $CHCl_3$–CCl_4 gave the *dichloro-sulphoxide* (12a), m.p. 199—201°, $\nu_{max.}$ 1065 cm^{-1} (S=O) (Found: C, 40·1; H, 4·0; Cl, 19·55; S, 18·15. $C_{12}H_{14}Cl_2O_4S_2$ requires C, 40·35; H, 3·95; Cl, 19·85; S, 17·95%).

cis,cis,cis-2,4,6-*Trichlorothian* 1-*Oxide* (12b).—Chlorination of *cis*-4-chlorothian 1-oxide (11b) [11] (228 mg, 1·5 mmol) with chlorine–pyridine gave a crude product (320 mg). Several recrystallizations from CH_2Cl_2–Et_2O gave the *trichloro-sulphoxide* (12b) (73 mg, 22%), m.p. 148—150°, $\nu_{max.}$ 1070 cm^{-1} (S=O) (Found: C, 27·3; H, 2·95; Cl, 47·6; S, 14·15. $C_5H_7Cl_3OS$ requires C, 27·1; H, 3·2; Cl, 48·0; S, 14·45%).

Chlorination of trans-4-*Hydroxythian* 1-*Oxide* (13).—Chlorination of the sulphoxide (13) [11] (236 mg, 1·8 mmol) with chlorine–pyridine gave an oily product (279 mg) which was separated into two fractions by t.l.c. on three plates [C_6H_6–MeOH (9 : 1)]. The lower band gave cis,cis-2,6-*dichloro*-trans-4-*hydroxythian* 1-*oxide* (15) (97 mg, 27%), m.p. 123—125° (from CH_2Cl_2–ether–petroleum), $\nu_{max.}$ 1015 (S=O) and 3420 cm^{-1} (OH) (Found: C, 29·65; H, 3·9; Cl, 34·55; S, 16·25. $C_5H_8Cl_2O_3S$ requires C, 29·55; H, 3·95; Cl, 34·9; S, 15·8%). The upper band gave *cis*-2-chloro-*trans*-4-hydroxythian 1-oxide (14) as an oil (68 mg, 22%), $\nu_{max.}$ (film) 1055 (S=O) and 3410 cm^{-1} (OH), δ 5·56 (1H, q, *J* 3 and 12 Hz, 2-H), 4·28 (1H, quint, *J* 3 Hz, $W_{\frac{1}{2}}$ 9 Hz, 4-H), and 2·84—2·12 (6H, m).

cis-4-*Acetoxy*-cis,cis-2,6-*diphenylthian* 1-*Oxide* (5).—A solution of *cis*-4-hydroxy-*cis*,*cis*-2,6-diphenylthian 1-oxide (1) (1·0 g, 3·5 mmol) in pyridine (15 ml) and acetic anhydride (5 ml) was stirred at room temperature overnight during which time a precipitate formed. Water was then added and the precipitate was filtered off, air-dried, and recrystallized from $CHCl_3$ to give the *acetate* (5) (820 mg, 72%), purified by t.l.c. [$CHCl_3$–MeOH (50 : 1)]; m.p. 261—263° (decomp.), $\nu_{max.}$ 1038 (S=O) and 1739 cm^{-1} (ester) (Found: C, 69·25; H, 5·95; S, 9·65. $C_{19}H_{20}SO_3$ requires C, 69·5; H, 6·15; S, 9·75%).

trans-4-*Acetoxy*-cis,cis-2,6-*dichlorothian* 1-*Oxide*.—This compound was similarly prepared (67%) by acetylation of *trans*-4-hydroxy-*cis*,*cis*-2,6-dichlorothian 1-oxide (15); it had m.p. 190—191° (lit.,[7] 190·5—191·5°) and was identical (i.r. and n.m.r. spectra and mixed m.p.) with a sample prepared by the literature [7] procedure.

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