Stereochemistry of α-Halogeno-sulphoxides. Part IV.[1] Halogenation of Thian 1-Oxides

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Chlorination of *trans*- and *cis*-4-*p*-chlorophenylthian 1-oxide [(I) and (II)] affords as main product 2*ax*-chloro-4*eq*-*p*-chlorophenylthian 1*eq*-oxide (IIIa), together with minor amounts of 2*eq*-chloro-4*eq*-*p*-chlorophenylthian 1*ax*-oxide (IVa). Bromination of (I) gives a similar mixture of the bromo-sulphoxides (IIIb) and (IVb). In the presence of silver nitrate the main products from the *trans*-substrate (I) are the 1*ax*-oxides (IV) and the only products from the *cis*-substrate (II) are the 1*eq*-oxides (III). The reactions in the absence and in the presence of silver ions seem to be subject to predominant thermodynamic and kinetic control, respectively.

In the α-halogenation of sulphoxides [1-3] a strict relationship between the stereochemical processes at sulphur and at carbon is always encountered, the nature of which depends on the structural features of the substrate. In particular, in alkyl aryl sulphoxides retention and inversion of configuration at sulphur are accompanied by retention and inversion at carbon, respectively, but in benzyl methyl sulphoxide and in the corresponding deuteriated species retention and inversion at sulphur are accompanied by inversion and retention at carbon, respectively.[1,3] Even small variations in structure and in reaction conditions can give rise to changes in the stereochemistry at sulphur and/or at carbon; nevertheless the reaction retains in most cases its high stereospecificity. This has been explained [1] on the basis of the 'unique' characteristics of α-sulphinyl carbanions, whose stereochemical fate probably depends on the orientation of the carbanion system with respect to the sulphinyl group.[4-6]

Although some hypotheses can be made about the favoured conformations of sulphoxides in the ground state, it is more difficult to anticipate the conformation of transition states leading to α-sulphinyl carbanions, particularly in view of the discrepancies between theoretical calculations on model systems [4] and experimental results on base-catalysed H/D exchange reactions.[5-10] For this reason, and in order to evaluate the importance of conformational effects on the stereochemistry of α-halogenation of sulphoxides, we have studied systems with a low degree of conformational freedom, namely the diastereoisomeric *trans*- and *cis*-4-*p*-chlorophenylthian 1-oxides, (I) and (II).[11] Results reported recently by Marquet and Tsuchihashi on the

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[2] M. Cinquini, S. Colonna, R. Fornasier, and F. Montanari, *J.C.S. Perkin I*, 1972, 1886.
[3] P. Calzavara, M. Cinquini, S. Colonna, R. Fornasier, and F. Montanari, *J. Amer. Chem. Soc.*, 1973, **95**, 7431, and references therein.
[4] S. Wolfe, A. Rauk, and I. G. Csizmadia, *Canad. J. Chem.*, 1969, **47**, 113.
[5] R. R. Fraser, F. J. Schuber, and Y. Y. Wigfield, *J. Amer. Chem. Soc.*, 1972, **94**, 8795.
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[7] B. J. Hutchinson, K. K. Andersen, and A. R. Katritzky, *J. Amer. Chem. Soc.*, 1969, **91**, 3839.
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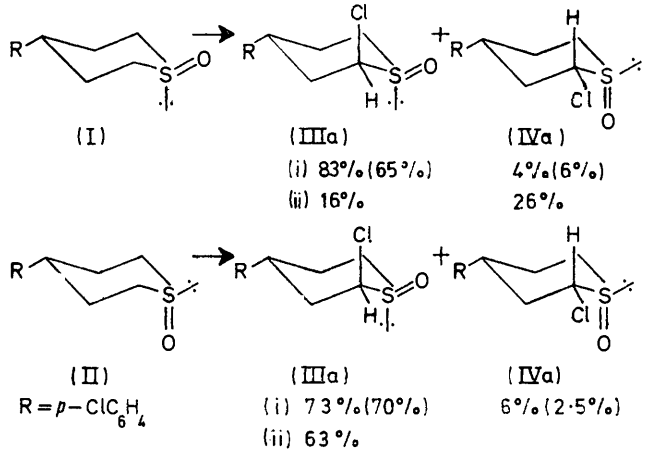
[10] (*a*) T. Durst, R. Viau, and M. R. McClory, *J. Amer. Chem. Soc.*, 1971, **93**, 3077; (*b*) T. Durst, R. R. Fraser, M. R. McClory, R. B. Swingle, R. Viau, and Y. Y. Wigfield, *Canad. J. Chem.*, 1970, **48**, 2148.
[11] Preliminary communication, M. Cinquini, S. Colonna, U. Folli, and F. Montanari, *Boll. sci. Fac. Chim. ind. Bologna*, 1969, **27**, 203.

α-halogenation of similar thian 1-oxides [12,13] are comparable to those obtained in the present work.

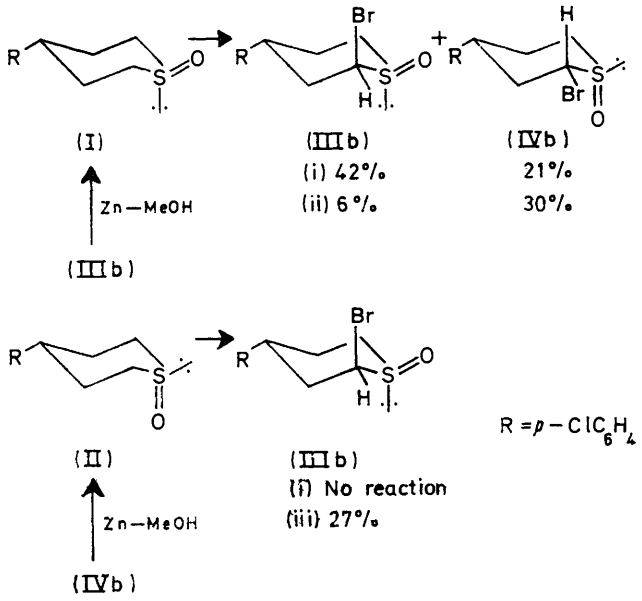
RESULTS

The *trans*- and *cis*-4-*p*-chlorophenylthian 1-oxides, (I) and (II), were obtained by oxidation of the corresponding sulphide with (dichloroiodo)benzene in aqueous pyridine,[14] and with t-butyl hypochlorite in methanol at −40°.[15] The *cis*-isomer (II) was also obtained *via* alkylation of the *trans*-sulphoxide (I) with triethyloxonium tetrafluoroborate followed by alkaline hydrolysis.[16] α-Halogenations were carried out, as described elsewhere, with (dichloroiodo)benzene,[17] *N*-chlorobenzotriazole,[18] and bromine [17] in pyridine, in the presence and in the absence of silver nitrate. The results are reported in Schemes 1 and 2.



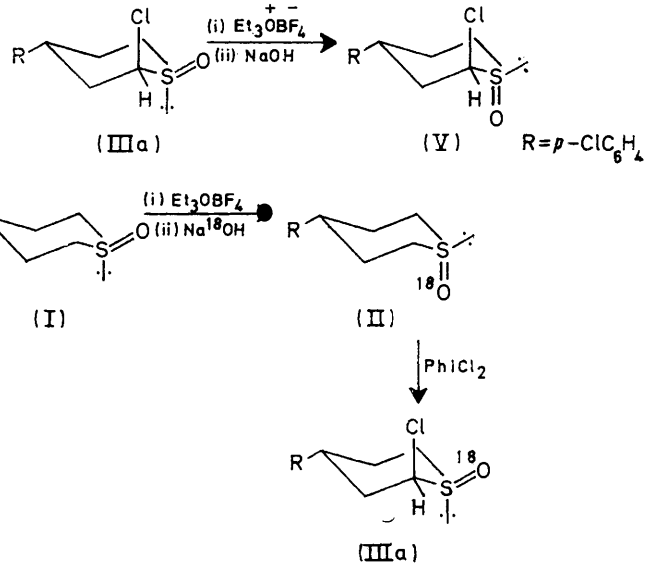
SCHEME 1 (i) $PhICl_2$, C_5H_5N, 24 h, 25° (in parentheses: *N*-chlorobenzotriazole, C_5H_5N, 4 h, 25°); (ii) $PhICl_2$, $AgNO_3$, C_5H_5N, 1 h, −40°

The only products of the reaction, obtained in various ratios, were the 4-*p*-chlorophenyl-2-halogenothian 1-oxides (IIIa and b) and (IVa and b). The configurations of the sulphinyl groups in the bromo-derivatives (IIIb) and (IVb) were established by reduction with zinc and methanol [1-3] to the corresponding sulphoxides (I) and (II). The configurations at the halogenated carbon atoms in (IIIa and b) and (IVa and b) and at the sulphinyl groups in the chloro-derivatives (IIIa) and (IVa) were deduced from 100 MHz ^1H n.m.r. data, with the aid of the shift reagent $Eu(dpm)_3$ (see Experimental section). Further evidence of configuration was obtained by conversion of (IIIa), *via* reaction with triethyloxonium tetrafluoroborate and subsequent hydrolysis, into the epimeric chloro-sulphoxide (V) with the inverse configuration at sulphur. Compound (V) differs from (IVa), thus indicating that (IIIa) and (IVa) have opposite configurations both at sulphur and at carbon. As previously found with other substrates,[1,3] chlorination of the *cis*-thian 1-oxide (II) [and thus probably



SCHEME 2 (i) Br_2, C_5H_5N, 6 days, 25°; (ii) Br_2, $AgNO_3$, C_5H_5N, 15 h, 25°; (iii) Br_2, $AgNO_3$, C_5H_5N, 5 days, 25°

that of the *trans*-isomer (I) and bromination of both (I) and (II)] does not involve breaking of the sulphur–oxygen bond. Indeed the conversion of an ^{18}O-enriched



sample of (II) gave compound (IIIa) with the same isotopic content.

[12] S. Bory, R. Lett, B. Moreau, and A. Marquet, *Compt. rend.*, 1973, **276***C*, 1323.
[13] (*a*) S. Iriuchijima, M. Ishibashi, and G. Tsuchihashi, *Bull. Chem. Soc. Japan*, 1973, **46**, 921; (*b*) S. Iriuchijima and G. Tsuchihashi, *ibid.*, p. 929.
[14] G. Barbieri, M. Cinquini, S. Colonna, and F. Montanari, *J. Chem. Soc.* (*C*), 1968, 659.
[15] C. R. Johnson and D. McCants, jun., *J. Amer. Chem. Soc.*, 1965, **87**, 1109.
[16] (*a*) C. R. Johnson, *J. Amer. Chem. Soc.*, 1963, **85**, 1020; (*b*) C. R. Johnson and D. McCants, jun., *ibid.*, 1965, **87**, 5404.
[17] M. Cinquini and S. Colonna, *J.C.S. Perkin I*, 1972, 1883.
[18] M. Cinquini and S. Colonna, *Synthesis*, 1972, 259.

Chlorination of the *trans*-thian 1-oxide (I) with (dichloroiodo)benzene and with *N*-chlorobenzotriazole (Scheme 1) afforded mainly (IIIa), with retention of configuration at sulphur and introduction of the chlorine into the axial position (*cis* with respect to both the sulphinyl oxygen atom and the aryl group). The minor product (IVa) has an axial sulphinyl oxygen atom and an equatorial chloro-substituent, *i.e.* configuration is inverted at both centres with respect to (IIIa). Bromination of (I) is much slower than chlorination and led to a 2 : 1 mixture of bromo-sulphoxides (IIIb) and (IVb), the configurations of which are identical with those of (IIIa) and (IVa), respectively (Scheme 2).

Chlorination of the *cis*-isomer (II) with either of the two reagents gave a mixture similar to that obtained from (I); with bromine no reaction occurred.

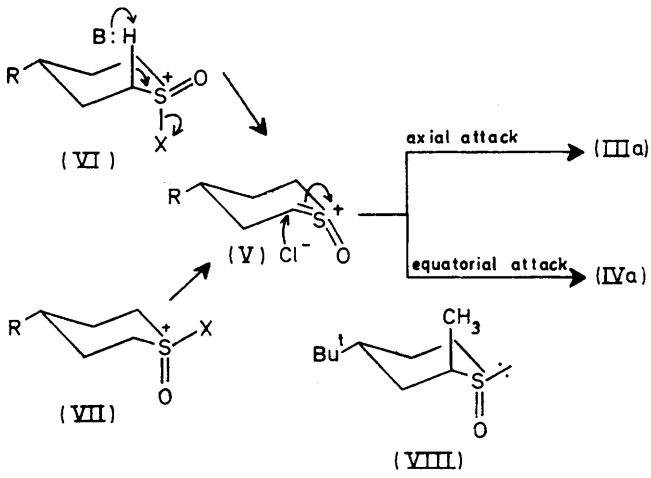
In the presence of silver nitrate all the reactions were faster: the *trans*-sulphoxide (I) still afforded a mixture of stereoisomers [(IIIa) and (IVa) or (IIIb) and (IVb)] but in every case the ratio between the isomers was substantially different from that obtained in the absence of silver nitrate. Indeed (IVa) and (IVb), of inverted configuration at sulphur and with an equatorial halogeno-substituent, were the main products under these conditions. The *cis*-isomer (II) afforded only one product, the chloro-derivative (IIIa) or (in low yield) the analogous bromo-derivative (IIIb).

In contrast with the behaviour of conformationally free substrates, halogenation of the thians (I) and (II) in the absence of catalysis by silver ions thus seems largely subject to thermodynamic control. Whatever the configuration of the starting sulphoxide and the nature of the halogen, compounds (IIIa and b) are in fact the main products. The isomers (IVa and b) seem on the contrary to be the result of prevailing kinetic control of the halogenation of the *trans*-sulphoxide (I).

DISCUSSION

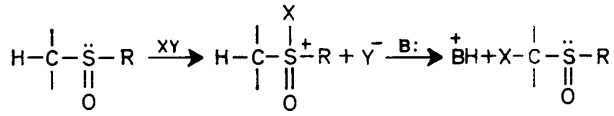
The results of the uncatalysed reaction tally with those obtained by Marquet and Tsuchihashi for the analogous 4-phenyl-, 4-chloro-, and 4-t-butyl-thian 1-oxides.[12,13] Since the diastereoisomeric α-halogeno-sulphoxides formed were characterized by a *trans*-diaxial or a *trans*-diequatorial arrangement of the halogen with respect to the sulphinyl lone pair, Marquet [12] and Tsuchihashi [13] proposed an elimination–addition mechanism, involving the ylide (V) (Scheme 3).

Elimination in the halogeno-oxosulphonium salts (VII) could occur either through a boat conformation, which would allow a *trans*-diaxial arrangement of halogen atom and proton, or after isomerization to the epimeric salt (VI). The elimination–addition mechanism is supported by the occurrence of preferential halogenation of 2-methylthian 1-oxide (VIII) at the more substituted α-carbon atom,[12] but it cannot account for the stereospecificity of halogenation met with in acylic systems, and in particular for the high optical purity of the products derived from optically active sulphoxides.[1-3] On the other hand, it seems reasonable that a single fundamental mechanism should be operating in the reactions of all the substrates. We previously proposed,[1-3] in agreement with kinetic data,[19] that formation of an intermediate halogeno-oxosulphonium salt



SCHEME 3

(IX) is followed by a base-promoted proton abstraction and by a concerted migration of halogen to the α-carbon atom (Scheme 4).



SCHEME 4

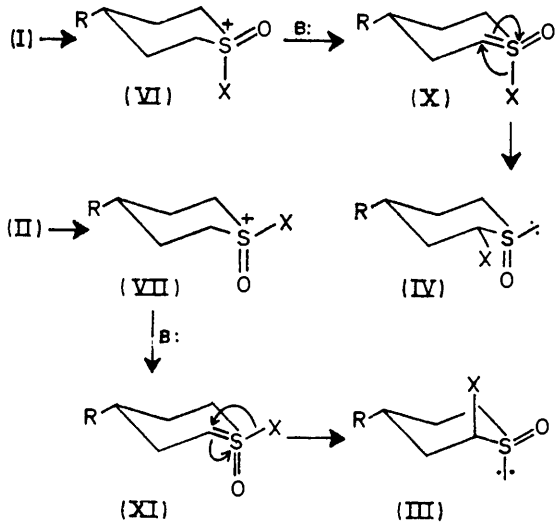
The stereochemistry of the second step depends on the nature of the substrate and the reaction conditions. It is in fact determined by the conformational equilibrium of (IX) in the transition state, by whether the halogen migrates as cation or anion, and by the ability of an incipient carbanion to maintain or invert its configuration.

The experimental results imply that a loss of conformational freedom makes the stereochemistry of these reactions more complex. In conformationally free substrates, such as alkyl aryl sulphoxides, proton abstraction and halogen migration are synchronous or highly concerted.[1-3,19] This does not necessarily apply to thian 1-oxides. Small variations in bond angles in rigid systems have been found by Fraser [5] to cause relevant differences in the rates of formation of α-sulphinyl carbanions from apparently similar pairs of diastereotopic protons. Furthermore, Wolfe's [4] and Nishio's [6] results, as well as our work on benzylic sulphoxides,[1] seem to indicate that the configurations of α-sulphinyl carbanions and of the reaction products are influenced only by the preferred conformation of the system. Small structural variations, together with a

[19] M. Cinquini, S. Colonna, and D. Landini, *J.C.S. Perkin II*, 1972, 296.

restricted conformational freedom could therefore, in thian 1-oxides, dramatically influence both the abstraction of an axial or equatorial proton, and retention or inversion of configuration. Conformationally fixed sulphoxides appear indeed to be less reactive than open-chain systems.

From all this one may deduce the occurrence, in cyclic systems, of a less concerted mechanism, possibly involving the ylides (X) and (XI) (Scheme 5). A fast



SCHEME 5

rearrangement, as experimentally found in the silver catalysed reactions, should lead to the halogeno-sulphoxides (IV) and (III) from the two ylides, respectively, if one assumes a minimum of molecular reorganization. The rearrangement may occur through intimate ion pairs, leading in the case of a non-catalysed reaction to an equilibration of the ylides (X) and (XI), and thus to thermodynamic control.* Such a mechanism, although not substantially different from that proposed by Marquet and Tsuchihashi, can be seen as a borderline case of the more general mechanism of halogenation of sulphoxides already proposed by us.†

EXPERIMENTAL

4-p-*Chlorophenylthian* 1-*Oxides* [(I) *and* (II)].—These were obtained by oxidation of the corresponding thian with (dichloroiodo)benzene in aqueous pyridine [14] and with t-butyl hypochlorite in methanol at −40°,[15] respectively. An alternative synthesis of the *cis*-isomer (II) (60% yield) involved inversion of the *trans*-isomer (I) *via* alkylation with triethyloxonium tetrafluoroborate, followed by hydrolysis with dilute aqueous sodium hydroxide.[16]

cis-4-p-*Chlorophenylthian* 1-[^{18}O]*Oxide*.—Inversion of the *trans*-isomer (I) was carried out in the presence of Na^{18}OH (10% ^{18}O) to give the *cis*-sulphoxide, m.p. 167—168°, 10% ^{18}O (mass spectrometry).

Chlorination of 4-p-*Chlorophenylthian* 1-*Oxides* (I) *and* (II).—Chlorination with an equimolecular amount of (dichloroiodo)benzene in aqueous pyridine was carried out as previously described.[17] Treatment of the *cis*-isomer for 24 h gave 2ax-*chloro*-4eq-p-*chlorophenylthian* 1eq-*oxide* (IIIa) (73%), m.p. 123—125° (decomp.) (Found: C, 50·2; H, 4·65. $C_{11}H_{12}Cl_2OS$ requires C, 50·2; H, 4·6%), together with 2eq-*chloro*-4eq-p-*chlorophenylthian* 1ax-*oxide* (IVa) (6%), m.p. 155—157° (decomp.) (Found: C, 50·25; H, 4·7%). The two compounds were separated by column chromatography on silica with ethyl acetate as eluant. Under the same conditions the *trans*-isomer (II) afforded a mixture of (IIIa) (83%) and (IVa) (4%).

In the presence of silver nitrate, chlorination of (I) afforded, after 1 h at −40°, compounds (IIIa) (16%) and (IVa) (26%); under the same conditions compound (II) only gave (IIIa), in 63% yield.

With *N*-chlorobenzotriazole as halogenating agent and a reaction time of 4 h a mixture of (IIIa) (65%) and (IVa) (6%) was obtained from the *trans*-sulphoxide (I). From the *cis*-isomer (II), the yields of (IIIa) and (IVa) were 70 and 2·5%, respectively.

^{1}H *N.m.r. Spectra*.—Spectra were recorded on a Varian A 60 and/or a JEOL 100 MHz instrument with $CDCl_3$ as solvent, and Me_4Si as internal standard. The equatorial configuration of the chlorine atom in (IVa) was shown by the presence of an axial H_α ($J_{ax,ax}$ 11, $J_{ax,eq}$ 4 Hz). In the isomer (IIIa) axial configuration of the chlorine atom was shown by the absence of axial–axial coupling and the observation of $J_{ax,eq}$ (2·5) and $J_{eq,eq}$ (2·3 Hz). The configurations of the sulphinyl groups in (IIIa) and (IVa) were established by running the spectra in the presence of $Eu(dpm)_3$. In compound (IVa) the strong deshielding of the two β-axial protons indicated the SO group to be axial (signals for all the protons were identified by double-resonance experiments). In the isomer (IIIa) all the protons are strongly shielded, in agreement with an equatorial configuration of the SO group.‡

In the case of the bromo-sulphoxide (IVb), the equatorial configuration of the halogen atom was established on the basis of the values of $J_{ax,ax}$ (12) and $J_{ax,eq}$ (4 Hz) (for H_α). The axial configuration of the bromine atom in compound (IIIb) is in agreement with the values of $J_{ax,eq}$ (3) and $J_{eq,eq}$ (3 Hz).

Bromination of the Diastereoisomeric Thian 1-*Oxides* (I) *and* (II).—This was carried out with bromine in pyridine in the presence of silver nitrate, as previously described.[17] After 15 h at room temperature, the *trans*-isomer (I) gave 2eq-*bromo*-4eq-p-*chlorophenylthian* 1ax-*oxide* (IVb) (30%), m.p. 159—160° (decomp.) (Found: C, 42·9; H, 4·05. $C_{11}H_{12}BrClOS$ requires C, 42·95; H, 3·95%), together with 2ax-*bromo*-4eq-p-*chlorophenylthian* 1eq-*oxide* (IIIb) (6%), m.p. 139—140° (decomp.) (Found: C, 43·1; H, 4·05%). The two compounds were separated by column chromatography on silica with diethyl ether as eluant.

Under the same conditions, after 5 days at room temperature, the *cis*-isomer (II) afforded (IIIb) (27%) as the only product.

In the absence of silver nitrate a mixture of (IIIb) (42%) and (IVb) (21%) was obtained after 6 days at room temperature from the *trans*-isomer (I). The *cis*-isomer (II) did

* Equilibration *via* halogen exchange in (VI) and (VII) is also possible.

† *Added in proof:* α-Halogenation of thian 1-oxides has recently been studied by Klein.[20]

‡ We thank Miss A. Marquet (Paris) for the ^{1}H n.m.r. data obtained in the presence of $Eu(dpm)_3$.

[20] J. Klein and H. Stollar, *J. Amer. Chem. Soc.*, 1973, **95**, 7437.

not react, even when longer reaction times (12 days) were employed.

Inversion of the Chloro-sulphoxide (IIIa).—This was carried out according to Johnson's method [16] to give a 50% yield of 2ax-*chloro*-4eq-p-*chlorophenylthian* 1ax-*oxide* (V), m.p. 66—67° (decomp.) (from light petroleum–cyclohexane, 2 : 1) (Found: C, 50·25; H, 4·55. $C_{11}H_{12}Cl_2OS$ requires C, 50·2; H, 4·6%).

Reduction of the Bromo-sulphoxides (IIIb) *and* (IVb).—This was effected with zinc dust in methanol in the presence of a few drops of concentrated sulphuric acid at room temperature for 30 min. Work-up as previously described [3] afforded the sulphoxides (I) (40%) and (II) (30%), respectively, together with unchanged material which was separated by column chromatography on silica (eluant chloroform–methanol, 9 : 1).

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