#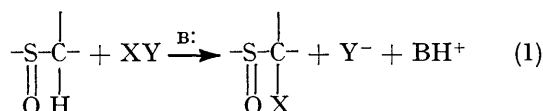 Stereochemistry of α-Halogeno-sulphoxides. Part I. Inversion of Chirality at the Sulphinyl Sulphur Atom in a Reaction not involving the Breaking of the Sulphinyl Bonds at the Chiral Sulphur Atom

By **M. Cinquini, S. Colonna, R. Fornasier,** and **F. Montanari,**[*] C.N.R. Centro di studio sulla sintesi e stereochimica di speciali sistemi organici, Istituto di Chimica Industriale dell'Università, Via Saldini 50, 20133 Milano, Italy

Conversion of optically active aryl methyl sulphoxides into the corresponding chloro- and bromo-methyl sulphoxides by (dichloroiodo)benzene, N-chlorobenzotriazole, or bromine, in the presence of pyridine and of silver(I) nitrate, is accompanied by inversion of configuration at the sulphur atom. In the absence of silver ions, halogenation proceeds with retention of configuration. Neither of the two processes involves substitution of the groups initially bonded to the chiral centre. The possible mechanisms are discussed.

α-HALOGENO-SULPHOXIDES can be easily prepared from dialkyl and alkyl aryl sulphoxides with at least one α-proton by reaction with (dichloroiodo)benzene [1] or with several other halogenating agents,[1-10] generally in the presence of organic or inorganic bases [equation (1)]. Bases avoid Pummerer-type rearrangements,[11] which give α-halogeno-sulphides and are catalysed by the hydrogen halides formed in the reaction.

$$-\overset{|}{\underset{\underset{H}{\overset{\|}{O}}}{S}}\overset{|}{C}- + XY \xrightarrow{\text{B:}} -\overset{|}{\underset{\underset{X}{\overset{\|}{O}}}{S}}\overset{|}{C}- + Y^- + BH^+ \qquad (1)$$

α-Halogeno-sulphoxides, practically unknown until a few years ago,[12] are relatively inert towards nucleophilic reagents.[1d,e,2,3,12e,13-16] Especially noteworthy are the stereochemical aspects of some of the methods of α-

halogenation [1c-e,3,5-7] which involve both the sulphur and α-carbon atoms. The present work deals with the retention and inversion of configuration at the sulphinyl sulphur atom, which, depending on the conditions of the reaction, accompany halogenation of aryl methyl sulphoxides.

RESULTS

(+)-(R)-Methyl p-tolyl sulphoxide (I) was halogenated with (dichloroiodo)benzene,[1] N-chlorobenzotriazole,[1g] or bromine [5] in the presence of pyridine. Since it seemed likely that the halide ions formed in the reaction could catalyse a partial racemisation of the sulphinyl group,[17] to prevent this, the reactions were repeated in the presence of an excess of silver(I) nitrate. The result was totally unexpected: not only were the specific rotations of chloro- and bromo-methyl p-tolyl sulphoxides (II) and (III) higher, but they were also opposite

[1] (a) M. Cinquini and S. Colonna, preceding paper; (b) G. Barbieri, M. Cinquini, S. Colonna, and F. Montanari, *J. Chem. Soc. (C)*, 1968, 659; (c) M. Cinquini, S. Colonna, and F. Montanari, *Chem. Comm.*, 1969, 607; (d) *ibid.*, 1970, 1441; (e) M. Cinquini, S. Colonna, and D. Iarossi, *Boll. sci. Fac. chim. ind. Bologna*, 1969, **27**, 197; (f) M. Cinquini, S. Colonna, U. Folli, and F. Montanari, *ibid.*, p. 203; (g) M. Cinquini and S. Colonna, *Synthesis*, 1972, in the press.

[2] M. Hojo and Z. Yoshida, *J. Amer. Chem. Soc.*, 1968, **90**, 4496.

[3] R. N. Loeppky and D. C. Chang, *Tetrahedron Letters*, 1968, 5415.

[4] S. Iriuchijima and G. Tsuchihashi, *Tetrahedron Letters*, 1969, 5259.

[5] M. Cinquini and S. Colonna, *Boll. sci. Fac. chim. ind. Bologna*, 1969, **27**, 201.

[6] G. Tsuchihashi and S. Iriuchijima, *Bull. Chem. Soc. Japan*, 1970, **43**, 2271.

[7] S. Iriuchijima and G. Tsuchihashi, *Synthesis*, 1970, 588.

[8] K. C. Tin and T. Durst, *Tetrahedron Letters*, 1970, 4643.

[9] G. Tsuchihashi, K. Ogura, S. Iriuchijima, and S. Tomisawa, *Synthesis*, 1971, 89.

[10] G. Tsuchihashi and K. Ogura, *Bull. Chem. Soc. Japan*, 1971, **44**, 1726.

[11] (a) T. Durst in ' Advances in Organic Chemistry,' eds. E. C. Taylor and H. Wynberg, Wiley, New York, 1969, vol. 6, p. 356; (b) G. A. Russell and G. J. Mikol in ' Mechanisms of Molecular Migrations,' ed. B. S. Thyagarajan, Interscience, New York, vol. 1, p. 157.

[12] (a) H. Böhme, H. Fischer, and R. Frank, *Annalen*, 1949, **54**, 563; (b) H. Böhme and H. Fischer, *Ber.*, 1942, **75B**, 1310; (c) D. L. Tuleen and R. M. White, *J. Tenn. Acad. Sci.*, 1967, **42**, 111; (d) E. Ayca, *Rev. Fac. Sci. Univ. Istanbul Ser. C.*, 1957, **22**, 371; (e) F. G. Bordwell and W. T. Branner, jun., *J. Amer. Chem. Soc.*, 1964, **86**, 4645; (f) G. A. Russell and G. S. Mikol, *ibid.*, 1966, **88**, 5498.

[13] Unpublished results from this laboratory.

[14] T. Durst, *J. Amer. Chem. Soc.*, 1969, **91**, 1034.

[15] T. Durst and K. C. Tin, *Tetrahedron Letters*, 1970, 2369.

[16] K. Ogura and G. Tsuchihashi, *Chem. Comm.*, 1970, 1689.

[17] (a) K. Mislow, T. Simmons, J. T. Melillo, and A. L. Ternay, jun., *J. Amer. Chem. Soc.*, 1964, **86**, 1452; (b) D. Landini, G. Modena, F. Montanari, and G. Scorrano, *ibid.*, 1970, **92**, 7168.

in sign (see Table). This means that one of the two reactions, either in the presence or in the absence of

α-Halogenation of methyl *p*-tolyl sulphoxide [a]

Halogenating agent	$[\alpha]_D^{25}(°)$ [b]	Halogenomethyl sulphoxides, (II) and (III)		
		Optical purity (%)	Yield (%)	
PhICl$_2$	+92	43 [d]	75	
PhICl$_2$–AgNO$_3$	−106	49 [d]	55	
NCBTA [c]	+104	48 [d]	77	
NCBTA [c]–AgNO$_3$	−134	62 [d]	50	
Br$_2$	+153	73 [e]	86	
Br$_2$–AgNO$_3$	−196	98 [e]	84	

[a] $[\alpha]_D^{25}$ +144° (acetone). [b] In acetone. [c] NCBTA, *N*-chlorobenzotriazole. [d] Minimum values based on the correlation between the chloro- and bromo-derivatives (II) and (III) *via* reaction with sodium *p*-toluenethiolate. [e] Minimum values based on the reduction (III) ——► (I).

silver ions, must proceed with inversion of configuration at the sulphur atom. When the (−)-halogeno-sulph-

$$p\text{-MeC}_6\text{H}_4\cdot\text{SO}\cdot\text{CH}_2\text{X}$$
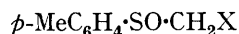
(I) X = H   (IV) X = OMe
(II) X = Cl   (V) X = S·C$_6$H$_4$Me-*p*
(III) X = Br

oxides (II) and (III) were treated with sodium methoxide and with sodium toluene-*p*-thiolate in methanol, (−)-methoxymethyl *p*-tolyl sulphoxide (IV), and (−)-*p*-tolyl *p*-tolylthiomethyl sulphoxide (V), respectively, were obtained in both cases. Reduction of the halogeno-sulphoxides with zinc and methanol afforded the (−)-(S)-sulphoxide (I). The (−)-compounds (I)—(III) show Cotton effects of the same sign, centred at 240—250 nm in ethanol and attributed to the n–π^* transition of the SO group.[18,19] Since reduction and nucleophilic substitutions of the α-halogen atom do not involve the carbon–sulphur bonds, compounds (I)—(III), having the same sign of specific rotation, must have the same absolute configuration. Halogenations of methyl *p*-tolyl sulphoxide (I) in the presence of silver(ɪ) nitrate therefore must be accompanied by inversion of configuration at the sulphur atom.

Bromination with Br$_2$–AgNO$_3$, and chlorination with PhICl$_2$–AgNO$_3$ and *N*-chlorobenzotriazole–AgNO$_3$ proceed with at least 99, 74, and 81% inversion, respectively, whereas in the absence of silver(ɪ) nitrate, halogenations proceed with 86, 71, and 74% retention.*

The sulphoxide (I) and halogeno-sulphoxides (II) and (III) were recovered without any loss of optical activity from a solution in pyridine containing silver(ɪ) nitrate. Water has no effect on the stereochemistry, with and without silver(ɪ) nitrate, and in both cases chlorination of ^{18}O-enriched sulphoxide (I) proceeds with complete retention of the isotopic content. As carbon–sulphur bonds are unlikely to be involved in the reaction, the two stereochemical processes both proceed seemingly

* % Inversion or retention = $\frac{1}{2}$(100 + % optical purity).

[18] (a) K. K. Andersen, W. Gaffield, N. E. Papanikolau, J. W. Foley, and R. I. Perkins, *J. Amer. Chem. Soc.*, 1964, **86**, 5637; (b) K. Mislow, M. M. Green, P. Laur, J. T. Melillo, T. Simmons, and A. L. Ternay, jun., *ibid.*, 1965, **87**, 1958.
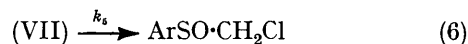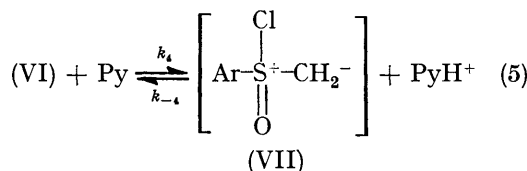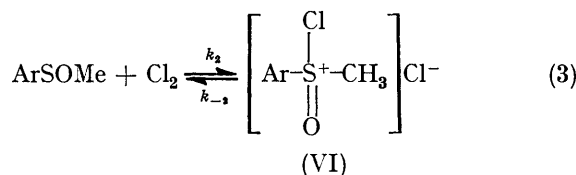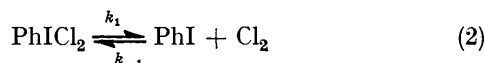
without any substitution of ligands at the chiral centre. Conversion of (+)-(R)-methyl *p*-tolyl sulphoxide (I) into the (−)-(S)-enantiomer *via* the (−)-(S)-bromosulphoxide (III), bromination of (−)-(S)-sulphoxide (I) to the (+)-(R)-compound (III), and reduction of this to (+)-(R)-sulphoxide (I) constitute a Walden cycle at the sulphur atom (Scheme 1).
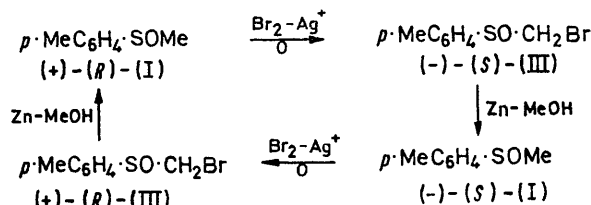
SCHEME 1

DISCUSSION

On the basis of kinetic data, the mechanism formulated in equations (2)—(4) was proposed [20] for the chlorination of aryl methyl sulphoxides by (dichloroiodo)benzene and pyridine. The reaction should proceed *via* electrophilic attack by chlorine at the sulphinyl group to give a chloro-oxosulphonium salt (VI), abstraction of an α-proton, and migration of the chlorine atom to the α-carbon.

$$\text{PhICl}_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{PhI} + \text{Cl}_2 \qquad (2)$$

$$(3)$$

$$(VI) + Py \xrightarrow{k_3} \text{ArSO·CH}_2\text{Cl} \qquad (4)$$

$$(5)$$

$$(VII) \xrightarrow{k_5} \text{ArSO·CH}_2\text{Cl} \qquad (6)$$

As (dichloroiodo)benzene acts only as a controlled source of chlorine, this mechanism can be extended reasonably to other electrophilic halogenating agents, which act in similar conditions and follow an analogous stereochemical pattern. The relevant primary isotope effect, $k_H/k_D = 5.5$, and the absence of H–D exchange with the solvent, found in the case of substrates for which step (4) is rate-determining,[20] seem to indicate that abstraction of proton and migration of chlorine occur in

[19] M. Cinquini, S. Colonna, I. Moretti, and G. Torre, *Tetrahedron Letters*, 1970, 2773.
[20] M. Cinquini, S. Colonna, and D. Landini, *J.C.S. Perkin II*, 1972, 296.

a concerted process. Alternatively, a two-step process [21] can be envisaged: formation of an intermediate ylide (VII), whose conversion in the final product is much faster than its reprotonation $(k_5 \gg k_{-4})$ [equations (5) and (6)]. The kinetic data also indicate that electrophilic attack by halogen should occur at the sulphur rather than at the oxygen atom,[20] to give a chloro-oxosulphonium salt (VI) instead of an O-chlorosulphoxonium salt (VIII).

(VIII)
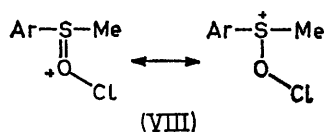
This is in agreement with the result of the chlorination of hydroxy-sulphoxides with sulphuryl chloride [22] and with the retention of the sulphinyl oxygen atom found in the halogenation of (I) in the presence of water. O-Alkylsulphoxonium salts, structurally analogous to (VIII), readily undergo nucleophilic attack at sulphur by hydroxylic solvents, with displacement of oxygen; [23] displacement also occurs when, in case of neighbouring-group participation, only a partial positive charge at sulphur arises.[24]

A simple 1,2-migration of a halogenonium ion from sulphur to carbon via (IX) (Scheme 2) is in agreement with the retention of configuration at sulphur which accompanies halogenation in the absence of metal ions.

SCHEME 2
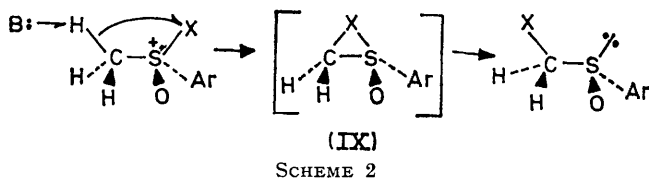
The role played by silver ions in causing inversion at sulphur is more difficult to account for, since the halogen atom, the lone pair, and the oxygen atom are each potentially able to bond the metal ion. It can be tentatively assumed that the latter, by co-ordination with the halogen or other ligands of sulphur, polarises a negative charge on this atom, catalysing a migration of the halogen as anion in a pseudo-ylide (XI) (Scheme 3).

The mechanism formulated in Scheme 3 presupposes that, according to the principle of least motion,[25] in the pseudo-ylide (XI) the sulphur–oxygen and sulphur–carbon bonds assume first an equatorial conformation in a trigonal bipyramid [26] around sulphur, then determine inversion of chirality at sulphur in the structural rearrangement which accompanies the halogen migration.

Although this mechanism involves a polarisation of charge opposite to that normally found in phosphorus- and sulphur-ylides,[27] it seems to be in agreement with

SCHEME 3

the stereochemical processes at carbon which are met with when the α-carbon is a chiral or prochiral centre,[13] and which appear to be strictly related to the stereochemical processes at sulphur.[14]

To the best of our knowledge, conversion of $(+)$-(R)-methyl p-tolyl sulphoxide (I) into the $(-)$-(S)-halogenomethyl sulphoxides (II) and (III) is the first example of a reaction in which inversion of chirality does not involve substitution of the original ligands, but is effected by the attachment and subsequent displacement of the new ligand at the chiral centre.

EXPERIMENTAL

Optically Active Halogenomethyl p-*Tolyl Sulphoxides* (II) *and* (III).—α-Halogenation of $(+)$-(R)-methyl p-tolyl sulphoxide (I), $[\alpha]_D^{25}$ $+144°$ (c 1 in acetone) {lit.,[18b] $[\alpha]_D^{25}$ $+145\cdot5°$ (acetone)} with (dichloroiodo)benzene,[1a] N-chlorobenzotriazole,[1g] or bromine,[5] in the presence or absence of metal ions, was carried out as described elsewhere. Specific rotations and yields of (II) and (III) are reported in the Table. *Chloromethyl* p-*tolyl sulphoxide*, $[\alpha]_D^{25}$ $-134°$ (c 1 in acetone), had m.p. 63—64° (Found: C, 50·85; H, 4·75. C_8H_9ClOS requires C, 50·9; H, 4·8%), o.r.d. in 95% ethanol at 25°, $[\phi]_{254}$ $-14,700°$ tr, $[\phi]_{245}$ 0°, $[\phi]_{220}$ $+33,200°$. *Bromomethyl* p-*tolyl sulphoxide*, $[\alpha]_D^{25}$ $-196°$ (c 1 in acetone), had m.p. 86—87° (Found: C, 40·95; H, 4·0. C_8H_9BrOS requires C, 41·25; H, 3·9%), o.r.d. in 95% ethanol at 25°, $[\phi]_{260}$ $-34,400°$ tr, $[\phi]_{246}$ 0°, $[\phi]_{223}$ $+68,600°$. α-Chlorination by (dichloroiodo)benzene in the presence of water (5 mol per mol of sulphoxide) gave no variation either in yield or specific rotation. When the reaction was repeated in the presence and absence of silver ions with ^{18}O-enriched sulphoxide (I) (isotopic content 10%), the α-chlorosulphoxide (II) had an isotopic content of 9·5 and 9·8%, respectively. The isotopic content was determined by mass spectroscopy on an RMU Hitachi 6D spectrometer.

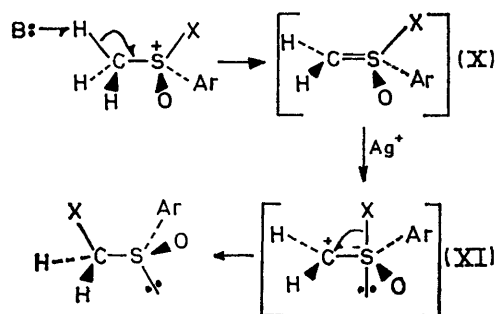*Reduction of* α-*Halogeno-sulphoxides* (II) *and* (III) *with*

[21] (a) F. G. Bordwell, *Accounts Chem. Res.*, 1970, **3**, 281; (b) J. F. Bunnett in ' Survey of the Progress of Chemistry,' ed. A. F. Scott, Academic Press, New York, 1969, vol. 5, p. 53.
[22] T. Durst and K. C. Tin, *Canad. J. Chem.*, 1971, **49**, 2374.
[23] C. R. Johnson and D. McCants, jun., *J. Amer. Chem. Soc.*, 1965, **87**, 5405.
[24] (a) H. Hogeveen, G. Maccagnani, and F. Montanari, *J. Chem. Soc.* (C), 1966, 1585; (b) M. Cinquini, S. Colonna, and F. Montanari, *J. Chem. Soc.* (C), 1967, 1213; (c) *ibid.*, 1970, 572.

[25] J. Hine, (a) *J. Org. Chem.*, 1966, **31**, 1236; (b) *J. Amer. Chem. Soc.*, 1966, **88**, 5525.
[26] (a) E. L. Muetterties, *Quart. Rev.*, 1966, **20**, 245; (b) K. Mislow, *Accounts Chem. Res.*, 1970, **3**, 321; and references therein.
[27] (a) A. W. Johnson, ' Ylid Chemistry,' Academic Press, New York, 1966; (b) R. F. Hudson, *Chem. in Britain*, 1971, **7**, 287, and references therein.

Zinc.—Zinc dust (10 mmol) was added to a solution of bromo-sulphoxide (III), $[\alpha]_D^{25}$ $-196°$ (c 1 in acetone) (2 mmol) in methanol (10 ml) in the presence of a few drops of concentrated sulphuric acid. The mixture was heated under reflux for 1 h, diluted with chloroform, filtered, and washed with aqueous sodium carbonate. Evaporation afforded the $(-)$-(S)-sulphoxide (I) which was purified from minor quantities of the corresponding sulphide and of unchanged starting material by column chromatography [silica; ether–light petroleum (1 : 1)] to give the sulphoxide (I) (70%), $[\alpha]_D^{25}$ $-142°$ (c 1 in acetone).

Reduction of the chloro-sulphoxide (II), $[\alpha]_D^{25}$ $-134°$ (c 1 in acetone), is slower and leads to greater quantities of the corresponding sulphide. A 25% yield of $(-)$-sulphoxide (I), $[\alpha]_D^{25}$ $-72°$ (c 1 in acetone) was obtained after heating under reflux for 3 h.

Nucleophilic Substitutions of α-Halogeno-sulphoxides.— (a) Optically active chloromethyl *p*-tolyl sulphoxide (II), $[\alpha]_D^{25}$ $-134°$ (c 1 in acetone) and bromomethyl *p*-tolyl sulphoxide (III), $[\alpha]_D^{25}$ $-196°$ (c 1 in acetone) were treated with sodium methoxide as described for the optically inactive compounds.[1a] Optically active *methoxymethyl* p-*tolyl sulphoxide* (IV) was obtained, $[\alpha]_D^{25}$ $-135°$, m.p. 37—38°, and $[\alpha]_D^{25}$ $-274°$ (c 1 in acetone), m.p. 40° (from the chloro- and bromo-derivative, respectively) (Found: C, 58·6; H, 6·5. $C_9H_{12}O_2S$ requires C, 58·7; H, 6·55%).

(b) The bromo-sulphoxide (III), $[\alpha]_D^{25}$ $-196°$ (c 1 in acetone) (0·92 g, 4 mmol) was added to a solution of sodium *p*-toluenethiolate (0·58 g, 4 mmol) in methanol (15 ml). The mixture was heated under reflux under nitrogen for 3 h, then poured into water, and extracted with chloroform. Evaporation and purification by column chromatography [silica; ether–light petroleum (1 : 1)] gave p-*tolyl* p-*tolylthiomethyl sulphoxide* (V), m.p. 73—74°, $[\alpha]_D^{25}$ $-77°$ (c 1 in acetone) (Found: C, 65·5; H, 5·65. $C_{15}H_{16}OS_2$ requires C, 65·2; H, 5·8%). Similarly chloromethyl *p*-tolyl sulphoxide (II), $[\alpha]_D^{25}$ $-134°$ (c 1 in acetone), afforded after 24 h the sulphoxide (V) (70%), $[\alpha]_D^{25}$ $-49°$ (c 1 in acetone).