Stereochemistry of α-Halogeno-sulphoxides. Part III.[1] Absolute Stereochemistry of α-Chlorination and α-Bromination of Benzyl Methyl Sulphoxide

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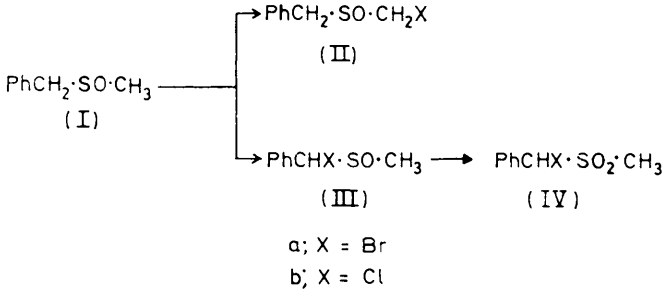
α-Chlorination and α-bromination of benzyl methyl sulphoxide by electrophilic halogenating agents in pyridine afford mixtures of benzyl halogenomethyl sulphoxide and α-halogenobenzyl methyl sulphoxide. The reactions at the methyl and at the benzylic carbon atoms proceed with retention and inversion of configuration at the sulphur atom, respectively. Only one of the two possible α-halogenobenzyl methyl sulphoxides is obtained. In the case of the (*S*)-sulphoxide the reaction involves selective replacement of the *pro-S* benzylic hydrogen atom and occurs with retention of configuration at carbon.

α-HALOGENATION of optically active sulphoxides has been shown to occur either with retention or with inversion at the chiral sulphur atom, depending on the nature of the sulphoxide and the reaction conditions.[1,2] We have now found that in benzyl methyl sulphoxide (I) both stereochemical processes at sulphur can take place at the same time, since each of the two processes is selectively involved in halogenation at one of two different carbon atoms.

RESULTS

Benzyl methyl sulphoxide (I) has two possible reaction sites: the methyl and the benzylic carbon atoms. Bromination of the (−)-(*S*)-isomer † (100% optically pure) with bromine in pyridine at −40° gave benzyl bromomethyl sulphoxide [(−)-(IIa)] and α-bromobenzyl methyl sulphoxide [(−)-(IIIa)], in the molar ratio 3 : 2. Reduction of (−)-(IIa) and (−)-(IIIa) with zinc dust in methanol afforded (−)-(*S*)-(I), 83% optically pure, and (+)-(*R*)-(I), 48% optically pure, respectively. Since reduction does not involve the chiral sulphinyl centre, bromination at the methyl and



benzylic groups must have occurred with 91% retention and 74% inversion at sulphur, respectively.‡

Chlorination of (−)-(*S*)-(I) with (dichloroiodo)benzene in pyridine [3] gave a mixture of benzyl chloromethyl sulphoxide [(−)-(IIb)] and α-chlorobenzyl methyl

† Ambiguity can arise from the fact that the sign of optical rotation of a benzylic sulphoxide may be affected by the solvent: *e.g.* the rotation of (*S*)-(I) is positive in ethanol but negative in chloroform. In the present paper all the signs of specific rotations refer to solutions in chloroform.

‡ These are minimum values, since an acid-catalysed partial racemization of the sulphinyl group may accompany or follow reduction.

[1] Part II, P. Calzavara, M. Cinquini, S. Colonna, R. Fornasier, and F. Montanari, *J. Amer. Chem. Soc.*, 1973, **95**, 7431.

[2] (*a*) M. Cinquini, S. Colonna, and F. Montanari, *Chem. Comm.*, 1970, 1441; (*b*) M. Cinquini, S. Colonna, R. Fornasier, and F. Montanari, *J.C.S. Perkin I*, 1972, 1886.

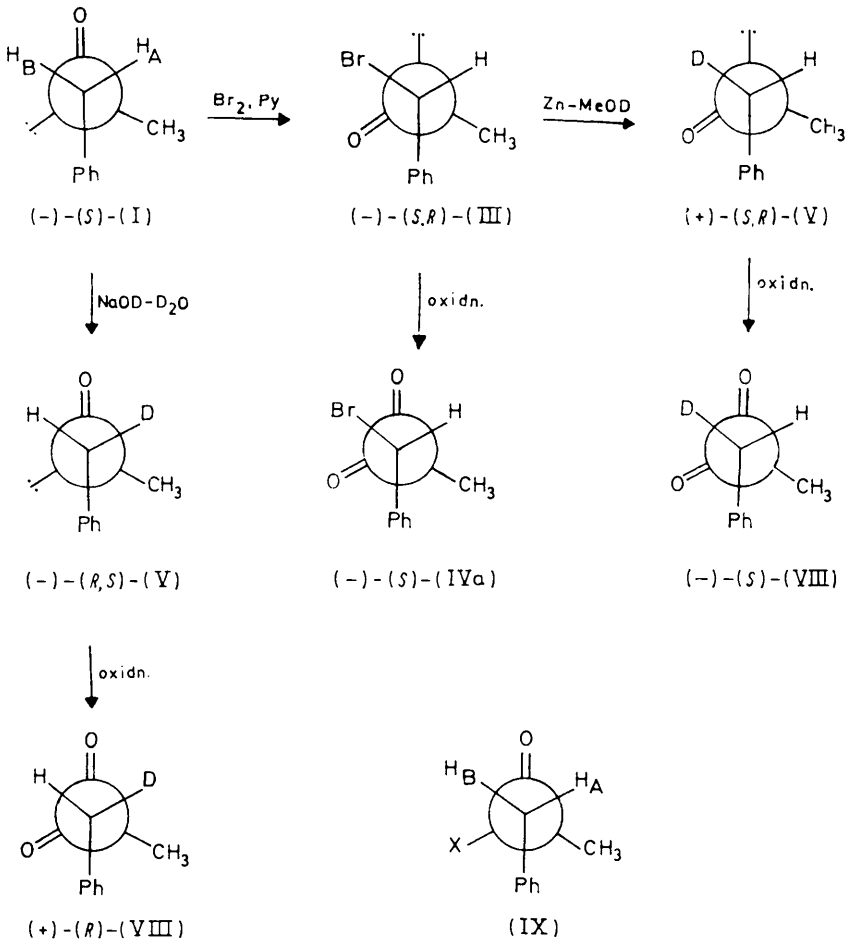
[3] M. Cinquini, S. Colonna, and F. Montanari, *Chem. Comm.*, 1969, 607.

sulphoxide [(+)-(IIIb)] in about 1 : 1 molar ratio. On the basis of their c.d. curves, the same configuration at the sulphinyl group can be assigned to compounds (−)-(IIa) and (−)-(IIb) and to compounds (−)-(IIIa) and (+)-(IIIb). Compounds (−)-(IIa) and (−)-(IIb) indeed show a negative sign, whereas (−)-(IIIa) and (+)-(IIIb) show a positive sign for the Cotton effect centred at 236—246 nm in ethanol, and attributed [4] to the n–π^* transition of the SO group. Chlorination and bromination of benzyl methyl sulphoxide thus follow the same stereochemical paths with respect to the configuration at the sulphur atom.

Starting sulphoxide		α-Halogenobenzyl sulphoxide (% yield)		Halogenomethyl sulphoxide (% yield)	
$PhCH_2{\cdot}SO{\cdot}CH_3$	(I)	$PhCClH{\cdot}SO{\cdot}CH_3$ [c]	(30)	$PhCH_2{\cdot}SO{\cdot}CH_2Cl$	(32)
$PhCHD{\cdot}SO{\cdot}CH_3$ [a]	(V)	$PhCClD{\cdot}SO{\cdot}CH_3$ [c]	(30)	$PhCHD{\cdot}SO{\cdot}CH_2Cl$	(32)
$PhCD_2{\cdot}SO{\cdot}CH_3$	(VI)	$PhCClD{\cdot}SO{\cdot}CH_3$ [c]	(8)	$PhCD_2{\cdot}SO{\cdot}CH_2Cl$	(54)
$PhCDH{\cdot}SO{\cdot}CH_3$ [b]	(VII)	$PhCClH{\cdot}SO{\cdot}CH_3$ [c]	(8)	$PhCDH{\cdot}SO{\cdot}CH_2Cl$	(54)
$PhCHD{\cdot}SO{\cdot}CH_3$ [a]	(V)	$PhCBrD{\cdot}SO{\cdot}CH_3$ [c]	(29)	$PhCHD{\cdot}SO{\cdot}CH_2Br$	(44)

[a] (*RS,SR*); from benzyl methyl sulphoxide *via* H/D exchange. [b] (*RR,SS*); from αα-dideuteriobenzyl methyl sulphoxide *via* D/H exchange. [c] (*SR,RS*).

Oxidation of (−)-(IIIa) and (+)-(IIIb) afforded the corresponding sulphones (−)-(IVa and b), thus indicating that asymmetric induction at the α-carbon atom is involved in the halogenation. Halogenation of



SCHEME

compound (I) at the benzylic carbon atom affords only one of the two possible diastereoisomeric α-halogenosulphoxides; [5] thus, as in the halogenation of ethyl *p*-tolyl sulphoxide,[2] the stereochemistry at carbon seems to be closely related to that at sulphur. This

[4] (*a*) K. K. Andersen, W. Gaffield, N. E. Papanikolaou, 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, *J. Amer. Chem. Soc.*, 1965, **87**, 1958; (*c*) M. Cinquini, S. Colonna, I. Moretti, and G. Torre, *Tetrahedron Letters*, 1970, 2773.

[5] M. Cinquini and S. Colonna, *J.C.S. Perkin I*, 1972, 1883.

relationship has been investigated by the use of deuteriated species.[3]

Halogenation of the diastereoisomeric (*RS,SR*)-(V) and (*RR,SS*)-(VII) α-deuteriobenzyl methyl sulphoxides, obtained *via* stereospecific H/D and D/H exchange from benzyl methyl (I) and αα-dideuteriobenzyl methyl sulphoxide (VI),[6] respectively, involved replacement of the hydrogen or deuterium atom diastereotopic to that preferentially exchanged in basic medium (see Table).* In (−)-(*S*)-(I) the *pro-R* hydrogen atom H_A was more rapidly exchanged in $NaOD–D_2O$, and the *pro-S* hydrogen atom H_B was selectively substituted by the halogen atom (see Scheme).

Reduction of α-bromobenzyl methyl sulphoxide (IIIa), $[\alpha]_D^{20}$ −17° (in $CHCl_3$), with zinc dust and methan[^{2}H]ol yielded α-deuteriobenzyl methyl sulphoxide (V), $[\alpha]_D^{20}$ +26·3° (in $CHCl_3$), which was oxidized to the corresponding α-deuterio-sulphone (VIII), $[\alpha]_D^{20}$ −1·16° ($CHCl_3$), whose absolute configuration is *S*.[6] The ^{1}H n.m.r. spectrum of (+)-(V) is identical with that of the enantiomeric monodeuteriated species (−)-(V) obtained by H/D exchange from (−)-(*S*)-(I) in $NaOD–D_2O$, which on oxidation gives [8] the sulphone (+)-(*R*)-(VIII). The *S,R*-configuration is thus attributed to (+)-(V); therefore bromination of (−)-(*S*)-(I) to give (−)-(IIIa), which involves replacement of the *pro-S* hydrogen atom, and the reduction of (−)-(IIIa) to (+)-(V) must proceed with overall retention at the α-carbon centre.

As already found for methyl *p*-tolyl sulphoxide,[2] halogenation of ^{18}O-enriched sulphoxide (I) by (dichloroiodo)benzene in aqueous pyridine proceeded with complete retention of the isotopic content.

It has been shown previously [1] that α-halogenation of alkyl aryl sulphoxides usually proceeds with inversion at sulphur and inversion at carbon, and that reduction of the corresponding α-bromo-sulphoxides with zinc and methanol also occurs with inversion at carbon. Nevertheless it was not possible to extrapolate these results to the case of benzyl methyl sulphoxide, since it has been established that the course of reductive dehalogenation of bromo-sulphoxides and bromo-sulphones strongly depends on the nature of the substrate.[1,9]

However, *X*-ray analysis, by the anomalous scattering technique, of the bromo-sulphone (IVa), $[\alpha]_D^{20}$ −110° (in $CHCl_3$), proved it to have the *S*-absolute configuration.[10] The bromo-sulphoxide (IIIa) therefore has the *S,R*-absolute configuration, and halogenation of (I) as well as reduction of (IIIa) must proceed with retention of configuration at carbon. Since the stereochemical behaviour at sulphur is the same in both chlorination and bromination and since the same diastereotopic hydrogen atom is substituted by the halogen in both cases, it seems likely that the stereochemical behaviour at carbon is also the same and thus that the bromo-sulphone (−)-(IVa) and the chloro-sulphone (−)-(IVb) have the same absolute configuration.

In the case of benzyl methyl sulphoxide the prevailing stereochemical process in halogenation at the benzylic carbon atom thus involves inversion at sulphur and retention at carbon. Since only one of the two possible diastereoisomeric α-halogeno-benzyl sulphoxides is formed, the partial racemization which accompanies inversion at sulphur must derive from a competitive stereochemical process involving retention at sulphur and inversion at carbon.

DISCUSSION

Two aspects of the present work are noteworthy. First, the halogeno-sulphoxides (IIa and b) and (IIIa and b) are formed in similar amounts, although the kinetic acidities of the two benzylic hydrogen atoms in (I) are $4·6 \times 10^2$ and $6·3 \times 10^3$ times that of the methyl protons,[6] and in spite of the primary isotope effect involved in halogenation at the benzylic carbon atom. The ratio between the yields of the isomers (II) and (III) seems therefore to be mainly a result of the relative energies of different reactions occurring through a common halogeno-oxosulphonium salt intermediate (IX). Such salts, as mentioned previously,[1,2b,7] are thought to be the usual intermediates in electrophilic halogenations of sulphoxides.

The second notable feature is the stereochemical course of the reactions. Halogenation at the methyl carbon atom occurs with predominant retention at sulphur, as in the case of methyl aryl sulphoxides, and therefore probably according to the same mechanism.[1,2b]

Halogenation at the benzylic carbon atom is more complex, because it involves a prochiral centre. As in the case of alkyl aryl sulphoxides, a change in the stereochemical process at sulphur is accompanied by a change in the concomitant stereochemical process at the α-carbon atom. However, the stereochemical correlation between sulphur and carbon is different: one finds retention–retention and inversion–inversion in alkyl aryl sulphoxides,[2] and inversion–retention and retention–inversion in the case of benzyl methyl sulphoxide.

Changes in stereochemical processes at sulphur and/or at carbon, caused even by small variations in structure and in reaction conditions, are known in reactions

* The molar ratio (about 1 : 1) of chlorobenzyl and chloromethyl sulphoxides obtained from the monodeuteriated species (V) is identical with that observed for the non-deuteriated species. The molar ratio of the products derived from the diastereoisomeric monodeuteriated species (VII) and from the dideuteriated species (VI), on the other hand, is 1 : 7. A primary kinetic isotope effect, of about 6, is thus operating; this value is similar to that kinetically measured (5·5) in the chlorination of methyl aryl sulphoxides.[7]

[6] A. Rauk, E. Buncel, R. Y. Moir, and S. Wolfe, *J. Amer. Chem. Soc.*, 1965, **87**, 5498.
[7] M. Cinquini, S. Colonna, and D. Landini, *J.C.S. Perkin II*, 1972, 296.
[8] J. E. Baldwin, R. E. Hackler, and R. M. Scott, *Chem. Comm.*, 1969, 1415.
[9] F. G. Bordwell, E. Doomer, and W. R. Corfield, *J. Amer. Chem. Soc.*, 1970, **92**, 2581.
[10] G. D. Andreetti, G. Bocelli, and P. Sgarabotto, *Cryst. Struct. Comm.*, 1973, 519.

involving α-sulphinyl carbanions;[1,11,12] these observations are in contrast with the high stereospecificity often met with in the same reactions,[1,11] particularly in α-halogenations.* A possible rationalisation of this contradiction can be envisaged, in agreement with Nishio's recent conclusions[11a] and with the theoretical work by Wolfe,[14] in terms of the following postulates: (i) the barrier to pyramidal inversion of α-sulphinyl carbanions is relatively low; (ii) their configurations and those of the reaction products depend on the preferred conformations of the systems, so that the carbanion, according to the conformational situation, can maintain or suffer inversion of the initial configuration; and (iii) the sulphinyl group is unusual with respect to other chiral groups in carrying ligands which are very different from each other in their stereoelectronic properties (lone pair, oxygen, and only two alkyl or aryl groups). From this arises the high conformational preference of sulphoxides and of some related functional groups, and this explains why, more than in other chiral systems, the conformational equilibrium can change dramatically according to the nature of the substrate and the reaction medium.

If the foregoing argument is accepted, it should be possible to include in a more general context the mechanisms previously proposed [1] to explain the stereochemistry of halogenation of alkyl aryl sulphoxides, as well as similar mechanisms which could be proposed for benzyl methyl sulphoxide. Nevertheless, a detailed discussion of the latter mechanisms would require a knowledge of the factors which decide the stereoselectivity of substitution of benzylic hydrogen atoms by halogen, and of those which in sulphoxides and in halogeno-oxosulphonium salts determine retention or inversion of the configurations of α-carbanions

EXPERIMENTAL

Optically Active α-Halogeno-sulphoxides.—α-Halogenation [with (dichloroiodo)benzene or bromine in pyridine] of (−)-(*S*)-benzyl methyl sulphoxide {$[\alpha]_D^{20}$ +96° (in EtOH); −55° (in $CHCl_3$)},[15] carried out as previously described,[5] gave a mixture of halogenomethyl and α-halogenobenzyl derivatives, which were separated by column chromatography [silica; ether–light petroleum (1 : 1 v/v)]. α-Chlorobenzyl methyl sulphoxide (IIIb) had m.p. 50—51°, $[\alpha]_D^{20}$ −27·9° (in EtOH) and +10·8° (in $CHCl_3$). Benzyl chloromethyl sulphoxide (IIb) had m.p. 54—55°, $[\alpha]_D^{20}$ +36° (in EtOH) and −23° (in $CHCl_3$). C.d. curves of the two chloro-derivatives in ethanol and in iso-octane are reported elsewhere.[4c] α-Bromobenzyl methyl sulphoxide (IIIa) had m.p. 66—68°, $[\alpha]_D^{20}$ −17° (in $CHCl_3$); the c.d. spectra showed a positive Cotton effect centred at 246—248 nm and a negative effect centred at 221—223 nm in ethanol, and two positive Cotton effects centred at 253—255 and 222—224 nm in iso-octane. Benzyl bromomethyl sulphoxide (IIa) had m.p. 74—75°, $[\alpha]_D^{20}$ −28·7° (in $CHCl_3$); the c.d. spectra showed a negative and a positive Cotton effect centred at 240—242 and 218—220 nm, respectively, in ethanol, and at 255—257 and 225—227 nm, respectively, in iso-octane. The c.d. spectra of the bromo-derivatives (−)-(IIa) and (−)-(IIIa) parallel those [4c] of the chloro-derivatives (−)-(IIb) and (+)-(IIIb).

Optically Active α-Halogeno-sulphones.—The α-halogeno-sulphoxides (IIIa and b) (0·01 mol) in dichloromethane (30 ml) were oxidized with a slight excess of *m*-chloroperbenzoic acid at 0 °C for 24 h. Work-up afforded the corresponding sulphones (IVa and b) which were purified by column chromatography [silica; ether–light petroleum (1 : 1 v/v)] and/or by crystallization; yields 90—100%. α-Chlorobenzyl methyl sulphone (IVb) had m.p. 111—112°, $[\alpha]_D^{20}$ −17·1° (in $CHCl_3$). Crude α-bromobenzyl methyl sulphone (IVa) had m.p. 98—102°, $[\alpha]_D^{20}$ −43° (in $CHCl_3$); after column chromatography and crystallization from methanol it had m.p. 129—130°, $[\alpha]_D^{20}$ −110°, $CHCl_3$. *X*-Ray analysis proved it to have the *S*-absolute configuration.[10]

Reduction of the α-Bromo-sulphoxides (IIa) *and* (IIIa).—Zinc dust (10 mmol) was added to a solution of bromomethyl benzyl sulphoxide (IIa) ($[\alpha]_D^{20}$ −28·7° in $CHCl_3$) (2 mmol) in methanol (10 ml) in the presence of a few drops of concentrated sulphuric acid. The mixture was stirred for 10 min at room temperature, diluted with chloroform, filtered, and washed with aqueous sodium carbonate. Evaporation and column chromatography (silica; chloroform) afforded the (*S*)-sulphoxide (−)-(*S*)-(I), $[\alpha]_D^{20}$ −45·6° (in $CHCl_3$), 83% optically pure, in 60% yield.

Reduction of α-bromobenzyl methyl sulphoxide (IIIa) ($[\alpha]_D^{20}$ −17° in $CHCl_3$) with zinc and methan[^{2}H]ol in the presence of sulphuric acid under the conditions just described afforded (*S*,*R*)-α-deuteriobenzyl methyl sulphoxide (V), $[\alpha]_D^{20}$ +26·3° (in $CHCl_3$) (48% optically pure), in 50% yield. The ^{1}H n.m.r. spectrum of (+)-(V) in D_2O was identical with that of the deuterio-sulphoxide (−)-(V) obtained by H/D exchange of (I) in NaOD–D_2O. It has been shown [16] that there is almost no variation of the optical rotation of (I) associated with H/D exchange.

Oxidation of the Sulphoxide (+)-(V) *to* (−)-α-*Deuteriobenzyl Methyl Sulphone* (VIII).—Oxidation of (*S*,*R*)-α-deuteriobenzyl methyl sulphoxide (V) ($[\alpha]_D^{20}$ +26·3° in $CHCl_3$) by a slight excess of *m*-chloroperbenzoic acid in methylene chloride afforded a quantitative yield of the corresponding (*S*)-sulphone (VIII), which was purified by repeated column chromatography [silica; ether–light petroleum (1 : 1 v/v)]. It had m.p. 126—127°, $[\alpha]_D^{20}$ −1·16°, $[\alpha]_{345}^{20}$ −3·36° (*c* 3 in $CHCl_3$). This is the enantiomer of the (+)-(*R*)-sulphone (VIII), m.p. 127·5—128°, $[\alpha]_D^{25}$ +0·83° (*c* 4 in $CHCl_3$), obtained [7] by oxidation of (−)-(*R*,*S*)-(V).

* The stereochemistry of reductive dehalogenation of bromobenzyl sulphoxides (retention) discussed in this paper and the opposite behaviour (inversion) met with in bromoalkyl sulphoxides [1] are analogous to the stereochemistry of reductive dehalogenation of bromobenzyl [9] and bromoalkyl sulphones,[1] respectively. Nevertheless it is difficult at present to proceed beyond a formal analogy, since it has not been established whether these reductions follow an ionic mechanism, or whether they are homolytic, like similar reductive dehalogenations.[13]

[11] (*a*) K. Nishihata and M. Nishio, *J.C.S. Perkin II*, 1972, 1730; (*b*) T. Durst, R. Viau, and M. R. McClory, *J. Amer. Chem. Soc.*, 1971, **93**, 3077.
[12] T. Durst, R. R. Fraser, M. R. McClory, R. B. Swingle, R. Viau, and Y. Y. Wigfield, *Canad. J. Chem.*, 1970, **48**, 2148.
[13] E. Ghera, D. H. Perry, and S. Shona, *J.C.S. Chem. Comm.*, 1973, 858.
[14] A. Rauk, S. Wolfe, and I. G. Csizmadia, *Canad. J. Chem.*, 1969, **47**, 113.
[15] M. Axelrod, P. Bickart, J. Jacobus, M. M. Green, and K. Mislow, *J. Amer. Chem. Soc.*, 1968, **90**, 4835.
[16] S. Wolfe and A. Rauk, *Chem. Comm.*, 1966, 778.

α-Chlorination of ^{18}O-*Enriched Benzyl Methyl Sulphoxide* (I).—The ^{18}O-enriched sulphoxide (I), isotopic content 10% in ^{18}O by mass spectrometry, was prepared by oxidation of the corresponding sulphide with (dichloroiodo)-benzene and pyridine in the presence of ^{18}O-enriched water.[17] α-Halogenation of ^{18}O-enriched (I) by (dichloroiodo)benzene in pyridine in the presence of isotopically normal water afforded a mixture of ^{18}O-enriched α-chlorobenzyl methyl (IIIb) and chloromethyl benzyl sulphoxide (IIb), separated as already described. Both compounds were 10% isotopically enriched in ^{18}O (mass spectrometry).

α-Halogenation of the Diastereoisomeric α-Deuteriobenzyl Methyl Sulphoxides (V) *and* (VII) *and of the αα-Dideuteriobenzyl Methyl Sulphoxide* (VI).—The sulphoxides (*RS,SR*)-(V), (*RR,SS*)-(VII), and (VI) were prepared according to Wolfe's procedure [6] *via* stereoselective H/D and D/H exchange from benzyl methyl sulphoxide (I), and halogenated as already described. Yields of α-halogeno-sulphoxides are given in the Table. The deuterium contents of starting materials and products were measured by ^{1}H n.m.r. The results (Table) were consistent within experimental error.

We are indebted to Professor K. K. Andersen (Durham, New Hampshire) for o.r.d. measurements on the (—)-(*S*)-sulphone (VIII), and to Professor G. Gottarelli (Bologna) for c.d. spectra of the bromo-sulphoxides (IIa) and (IIIa).

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[17] G. Barbieri, M. Cinquini, S. Colonna, and F. Montanari, *J. Chem. Soc.* (*C*), 1968, 659.