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STEREOCHEMISTRY OF SULPHILIMINE AND SULPHOXIDE FORMATIONS IN REACTIONS OF SULPHIDES WITH CHLORINATING AGENTS AND NUCLEOPHILES

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Abstract—The stereochemistry of sulphilimine and sulphoxide formations was studied in reactions of chiral alkyl aryl sulphides either with N-chloro toluenesulphonamides or with *t*-BuOCl followed by $TsNH^-Na^+$ both leading to unequal amounts of diastereomers of products. Configurations were determined by spectroscopic methods and stereospecific reactions, and diastereomeric product distributions were measured by hplc. Results are discussed and reaction pathways are suggested for the product-controlling steps. From sulphonium type intermediates sulphoxides are formed by hydrolysis with inversion, while sulphilimines with retention or inversion of configuration at sulphur depending on manner of attack by N-nucleophile. In reactions of *ortho*-carboxy-substituted sulphides both sulphilimines and sulphoxides are formed from cyclic acyloxysulphonium intermediates with inversion of configuration at sulphur.

Sulphilimines can be well prepared from sulphides with N-halogeno compounds or with halogenating agents and N-nucleophiles.[1] When these reactions are carried out in solvents containing water, different amounts of sulphoxides as by-products are also formed.[2] On the basis of kinetic measurements and product analysis we have proposed[2] a mechanism for the reaction of sulphides with sodium salts of N-chloro arenesulphonamides (*cf* Scheme 1).

Investigations on steric effect have shown[2b,c] that reaction rates are not markedly affected by the bulkiness of the alkyl group in sulphides, indicating a rate-controlling electrophilic Cl^+-addition to the S atom (eqn 2). On the other hand, the yields of sulphilimines (eqn 5) increase, while those of sulphoxides (eqn 6) decrease when the steric requirements of the alkyl substituent are greater, i.e. when the S_N2 type displacement on chlorosulphonium ion is more hindered. These observations clearly point to different stereochemical pathways of the product-controlling steps (5) and (6).

The present paper reports on the stereochemistry of the formation of sulphilimines and sulphoxides from chiral sulphides converted by either N-chloro toluenesulphonamides ($TsNCl^-Na^+$, $TsNCl_2$) or by *t*-BuOCl and $TsNH^-Na^+$. In the latter case the reactions involving Cl^+-addition and subsequent nucleophilic displacements were carried out separately. The stereochemistry of reactions occurring with neighbouring group participation is also discussed.

†In order to obtain higher yields, *ortho*-carboxy-substituted sulphilimines (**3c–3d**) were synthesized from the **1e** and **1f** methyl esters of the corresponding sulphides **1c** and **1d** (Experimental).

‡Details on the chiroptical properties of alkyl aryl sulphoxides and sulphilimines will be published elsewhere.[3]

RESULTS

Configurations of sulphoxide and sulphilimine diastereomers. Optically active 2-octyl phenyl and 2-octyl 2-carboxyphenyl sulphides, as well as racemic 2-butyl phenyl and 2-butyl 2-carboxyphenyl sulphides (**1a–1d**) were prepared and converted to sulphoxides (**2a–2d**) and sulphilimines (**3a–3d**) by known methods† (Scheme 2). Optically active sulphoxides and sulphilimines were found to be mixtures of two diastereomers, while the racemic products were mixtures of four diastereomers forming two enantiomeric pairs. One of either the diastereomers or of the racemates of each sulphoxide and sulphilimine were isolated by chromatography or crystallisation. In all cases the isolated (optically active or racemic) diastereomer eluted in hplc faster than the non-isolated diastereomer of the same compound. Configurations for the isolated sulphoxide and sulphilimine diastereomers were determined either from their ORD–CD‡ curves or by stereospecific reactions.

From the mixture of sulphoxide diastereomers **2a** prepared from the sulphide (R_c)-(−)-**1a**, the (R_cS_s)-(−)-**2a** diastereomer[4] was isolated and its configuration was checked by ORD measurements.[5] Since the ORD curves of optically active sulphinyl compounds were reported[5] not to be markedly influenced by an adjacent non-chromophoric chiral carbon centre, the analogy in ORD data found for the sulphilimine diastereomer (−)-**3a** (Table 1) prepared from the sulphide (R_c)-(−)-**1a**, and for the known (S_s)-(−)-S-methyl-S-(4-methylphenyl)-N-[(4-methylphenyl) sulphonyl]-sulphilimine[6] points to (R_cS_s) configuration of the former compound. The (S_cR_s) configuration can be assigned for the isolated *ortho*-carboxy-substituted (+)-**2c** sulphoxide and (+)-**3c** sulphilimine diastereomers prepared from the sulphide (S_c)-(+)-**1c**, because their CD spectra are analogous to those of (R_s) – (+) – (2-carboxyphenyl) methyl sulphoxide[7]

$$TsNHCl + H_2O \underset{}{\overset{K_a}{\rightleftharpoons}} TsNCl^- + H_3O^+ \quad (1)$$

$$TsNHCl + RArS \xrightarrow{slow} [RArSCl^+, TsNH^-] \quad (2)$$

$$TsNHCl + TsNCl^- \underset{fast}{\overset{slow}{\rightleftharpoons}} TsNCl_2 + TsNH^- \quad (3)$$

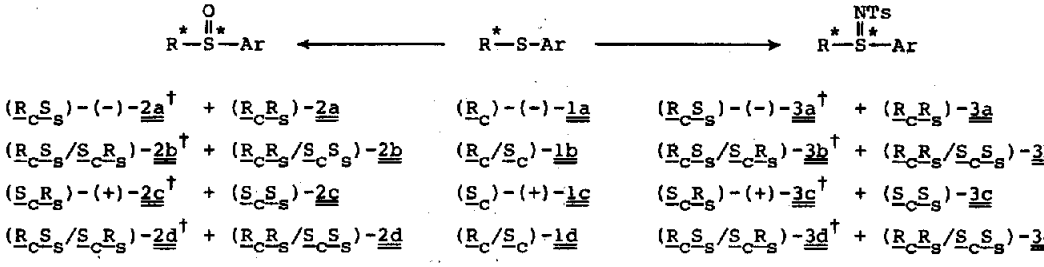
$$TsNCl_2 + RArS \xrightarrow{fast} [RArSCl^+, TsNCl^-] \quad (4)$$

$$[RArSCl^+, TsNQ^-] \xrightarrow{fast} \begin{cases} \xrightarrow{-Cl^-} RArS^+N(Q)Ts \xrightarrow[-QB^+]{B} RArSNTs & (5) \\ \xrightarrow[-HCl]{H_2O} RArSO + TsNHQ & (6) \end{cases}$$

intimate ion-pair

(Q = H or Cl)

Scheme 1.



(7)

a: R = 2-octyl, Ar = phenyl; b: R = 2-butyl, Ar = phenyl; c: R = 2-octyl Ar = 2-carboxyphenyl; d: R = 2-butyl, Ar = 2-carboxyphenyl

†Isolated diastereomers; eluted first in HPLC

Scheme 2.

(2g) and (R_s)-(+)-S-(2-carboxyphenyl)-S-methyl-N-[(4-methylphenyl)-sulphonyl]-sulphilimine[8] (3g) of known absolute configuration (Table 1). The anchimerically assisted, acid-catalysed hydrolysis of the sulphilimine (S_cR_s)-(+)-3c (eqn 8 in Scheme 3) can be expected to proceed with retention of configuration at sulphur (*cf* Ref. 8); therefore the formation of the sulphoxide (S_cR_s)-(+)-2c provides further evidence that these compounds are homochiral analogues.

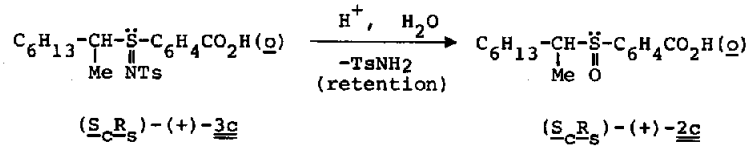
Relative configurations for the isolated enantiomeric pairs of the 2b sulphoxide and 3b sulphilimine were determined by correlating them with stereospecific reactions proceeding without inversion of configuration at sulphur.[6] Both compounds were converted to sulphoximine as shown in eqns (9) and (10). In these reactions, however, two different racemates of the sulphoximine 4b were obtained (NMR data in Experimental), indicating that the above mentioned enantiomeric pairs of the compounds 2b and 3b are homochiral analogues. The isolated enantiomeric pair of the *ortho*-carboxy-substituted sulphilimine 3d hydrolysed to that of the sulphoxide 2d, providing evidence for their homochirality (eqn 11). Absolute configurations for the enantiomeric pairs of the compounds 2b, 2d, 3b and 3d have also been provisionally assigned on the basis of the chromatographic behaviour similar to that of the optically active diastereomers of the analogous compounds 2a, 2c, 3a and 3c, respectively (*cf* Schemes 2 and 3).

Diastereomeric product distribution. The yields of the diastereomers of sulphoxide and sulphilimine products were measured in the reaction of the sulphides (R_c)-(−)-1a and racemic 1b with $TsNCl^-Na^+$ or $TsNCl_2$. In other experiments the same substrates were treated with *t*-BuOCl and subsequently with $TsNH^-Na^+$ in order to definitely separate the chlorination step from the attack of the N-nucleophile. In case of the *ortho*-carboxy-substituted sulphides (S_c)-(+)-1c and racemic 1d the products obtained with $TsNCl^-Na^+$ were investigated. The reactions were carried out in homogenous solutions varying the experimental conditions as given in Table 2. The diastereomeric product distributions were determined from the crude products by hplc on silica gel using ether-pentane eluents and detecting the UV absorption of the effluents. When eluents of appropriate composition were applied, a fair separation of all products ($TsNH_2$, sulphoxide and sulphilimine diastereomers) could be achieved; an example is shown in Fig. 1. The retention times and the ratio of the UV absorptions were determined for the isolated sulphoxide and sulphilimine diastereomers, as well as for their mixtures, and the yields were calculated from the areas of the corresponding peaks. Results are summarised in Table 2. The

Table 1. ORD and CD spectra of sulphilimines and sulphoxides

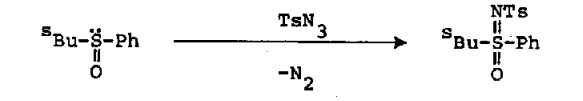
Compound		Concentration (g/l)[a]	λ/nm ([φ] or [θ])[b]							
($R_C S_S$)-(-)-3a	[ORD]	1 - 0.2	300	274 sh	269 sh	241 tr	230	218 pk	215[c]	
			(-8400)	(-16000)	(-18100)	(-44500)	(0)	(+37500)	(+30300)	
($S_C R_S$)-(+)-2c	[CD]	0.74	337	294 max	270 min	264 max	245 min	230 max	212 min	204[c]
			(0)	(+33600)	(+10400)	(+12900)	(-14400)	(+13200)	(-69500)	(0)
(R_S)-(+)-2g	[CD]	0.61	335	290 max	268 min	260 max	241 min	227.5 max	207 min	203[c]
			(0)	(+29300)	(+6700)	(+11500)	(-4200)	(+17300)	(-98200)	(0)
($S_C R_S$)-(+)-3c	[CD]	0.39	330	290 max	267 min	258 sh	235 max	217 min	205 max	202[c]
			(0)	(+25200)	(+4300)	(+11100)	(+53300)	(-12900)	(+73600)	(+44800)
(R_S)-(+)-3g	[CD]	0.47	325	288 max	266 min	257.5 sh	232.5 max	217.5 min	204 max	200[c]
			(0)	(+27300)	(+1200)	(+4900)	(+63700)	(+11800)	(+99700)	(+55800)

[a] In EtOH solvent. [b] sh: shoulder, pk: peak, tr: trough. [c] Last reading.



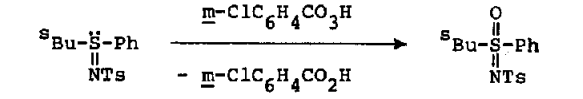
(8)

(S_CR_S)-(+)-**3c** (S_CR_S)-(+)-**2c**



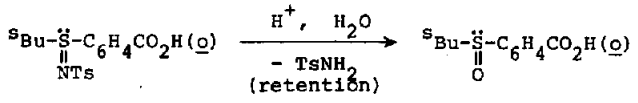
(9)

(R_CS_S/S_CR_S)-**2b** (R_CS_S/S_CR_S)-**4b**



(10)

(R_CS_S/S_CR_S)-**3b** (R_CR_S/S_CS_S)-**4b**



(11)

(R_CS_S/S_CR_S)-**3d** (R_CS_S/S_CR_S)-**2d**

Scheme 3.

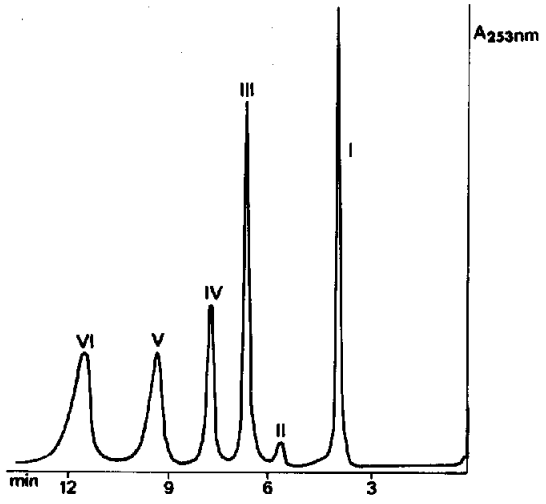


Fig. 1. Chromatogram of products formed in the reaction of (R_c)-(−)-2-octyl phenyl sulphide (**1a**) with $TsNCl^-Na^+ \cdot 2H_2O$ in 1:1 (v/v) EtOH–H_2O. Peaks: I: (R_c)-**1a**; II: $TsNH_2$; III: (R_cS_s)-**2a**; IV: (R_cR_s)-**2a**; V: (R_cS_s)-**3a**; VI: (R_cR_s)-**3a**.

overall yields for sulphilimines were found to be controlled by the N-nucleophile ($TsNH^-$, $TsNCl^-$, $TsNH_2$) and by the procedure used (*cf* Refs. 1 and 2). Stereoselectivities of about 20% were observed in the formation of diastereomeric sulphoxides and sulphilimines from the sulphides **1a** and **1b**. These values were practically independent of the solvents and of the starting concentrations of the reactants listed in Table 2, and showed only a slight increase, when the reaction was conducted at low temperature.

As to the conversion of the sulphides **1a** and **1b**, the main point is that the *predominant* diastereomers of the sulphoxides **2a** and **2b** and those of the sulphilimines **3a** and **3b** are *heterochiral* analogues at sulphur when the sulphides are treated with $TsNCl^-Na^+$ or $TsNCl_2$, while they are *homochiral* when the reaction of the same substrates are carried out in a two-stage procedure with *t*-BuOCl and $TsNH^-Na^+$. The anchimerically assisted conversions of the *ortho*-carboxy-substituted sulphides **1c** and **1d** with $TsNCl^-Na^+$ yield sulphoxide (**2c** and **2d**) and sulphilimine (**3c** and **3d**) products with *homochiral predominant* diastereomers. In this case, however, the stereoselectivity observed in the formation of sulphilimine diastereomers significantly exceeded that of sulphoxide diastereomers exhibiting a dependence on solvent, as well (Table 2).

DISCUSSION

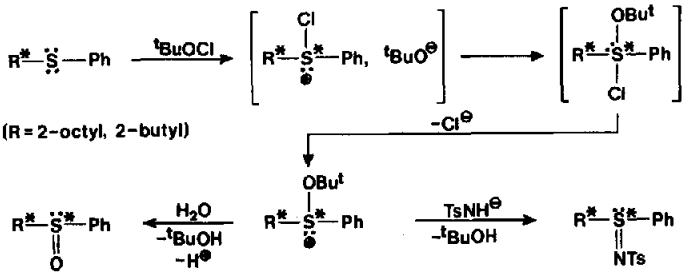
The above experimental data seem to provide a means to explain the stereochemistry of the product-controlling steps in the reaction of sulphides with chlorinating agents and nucleophiles resulting in the formation of sulphilimines and sulphoxides. The following interpretation of reaction pathways is based exclusively on the obser-

ved distribution of diastereomers of products obtained from chiral sulphides. Cram's open chain model is not applied here for predicting the predominant diastereomers, because it failed to give correct results in case of oxidations of chiral acyclic sulphides to sulphoxides.[9,10]

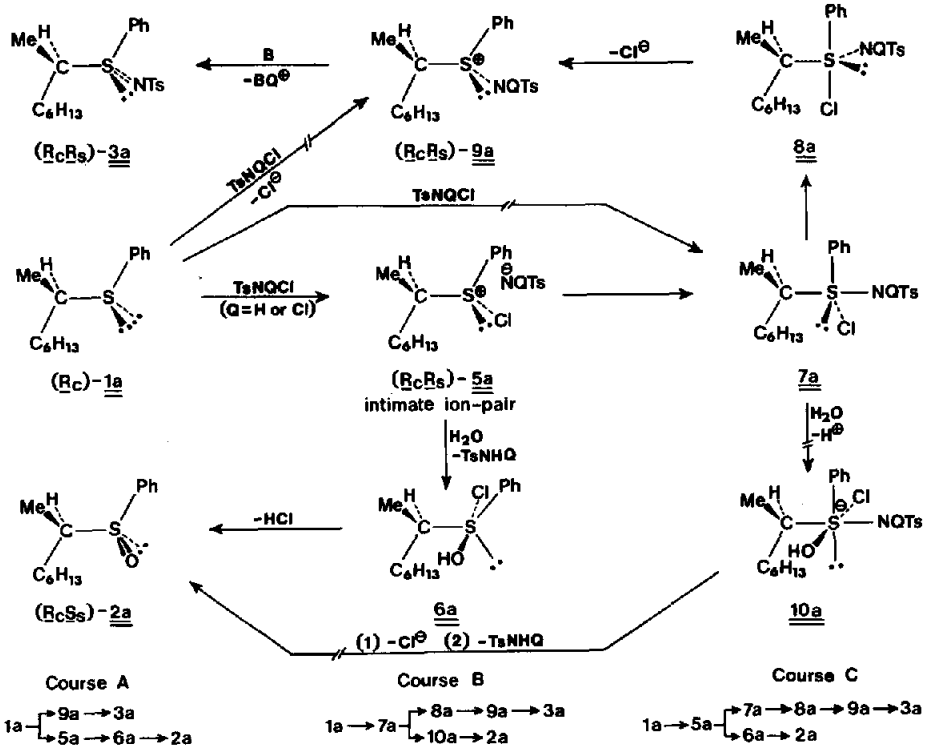
Reaction of chiral sulphides with t-BuOCl *and* $TsNH^-Na^+$. The stereochemistry of sulphilimine and sulphoxide formations in the reactions of the sulphides **1a** and **1b** with *t*-BuOCl chlorinating agent and subsequently with H_2O or $TsNH^-$ nucleophiles can be discussed on the basis of the mechanism proposed by Swern *et al.*[11] (Scheme 4). The first step, the asymmetric chlorination of chiral sulphides affords unequal amounts of the diastereomers of chlorosulphonium-*t*-butoxide ion-pairs. They are converted in the subsequent steps through *t*-butoxychlorosulphurane intermediates to *t*-butoxysulphonium ions from which sulphilimines and sulphoxides are formed in two parallel nucleophilic displacements. Since the attacks of both H_2O and $TsNH^-$ nucleophiles on alkoxysulphonium ions proceed with inversion of configuration at sulphur (*cf* Refs. 12, 13), the predominant diastereomers of the products are expectedly homochiral analogues, as observed experimentally.†

Reaction of chiral sulphides with $TsNCl^-Na^+$ *or* $TsNCl_2$. Three different reaction pathways (*cf* Ref. 1) can be envisaged for the interpretation of the observed stereochemistry of the reaction between sulphides (**1a**, **1b**) and N-chloro compounds ($TsNCl^-Na^+$, $TsNCl_2$). These are outlined in Scheme 5 for the conversion of the compound (R_c)-**1a** to the predominant diastereomers of the sulphoxide **2a** and sulphilimine **3a**. In course A the nucleophilic attack of sulphide on the nitrogen atom of

†The stereochemistry of a similar conversion of cyclic sulphides with either N-chlorosuccinimide or t-butyl hypochlorite and 4-chloroaniline was recently studied by Claus *et al.*[14] In these cases, however, the chlorinating agent and the nucleophile were not separately added to the sulphide, and the observed stereochemistry of sulphilimine formation was not explained by the intermediacy of a sulphonium cation attacked subsequently by the nucleophilic amine, but assuming a reaction between sulphides and N-chloroaniline intermediate.



Scheme 4.



Scheme 5.

Table 2. Diastereomeric sulphoxide and sulphilimine product distribution in the reaction of chiral sulphides with chlorinating agents and nucleophiles

Sulphide	Reaction[a] Reactant	Solvent	Diastereomeric product distribution (%)[b] Sulphoxide	Sulphilimine	Overall yield (%)[b] Sulphoxide	Sulphilimine
			$(R_C S_S) : (R_C R_S)$	$(R_C S_S) : (R_C R_S)$		
(R_C)-1a	$TsNCl^-Na^+.2H_2O$	50% EtOH-H_2O	66 : 34	41 : 59	29	71
		50% EtOH-H_2O (c)	64 : 36	40 : 60	42	58
		96% EtOH	59 : 41	40 : 60	16	84
		96% EtOH (c)	59 : 41	41 : 59	28	72
		MeOH	60 : 40	40 : 60	15	85
		MeOH (c)	62 : 38	40 : 60	19	81
		90% dioxan-H_2O	61 : 39	40 : 60	47	53
(R_C)-1a	$TsNCl_2$	CH_2Cl_2	57 : 43	40 : 60	94	6
		MeOH	60 : 40	41 : 59	91	9
(R_C)-1a	^tBuOCl + $TsNH^-Na^+$ (d)	$CHCl_2$ (e)	62 : 38	58 : 42	97	3
		MeOH (e)	64 : 36	61 : 39	88	12

			$(R_CS_S/S_CR_S):(R_CR_S/S_CS_S)$	$(R_CS_S/S_CR_S):(R_CR_S/S_CS_S)$		
(R_C/S_C)-1b	$TsNCl^-Na^+.2H_2O$	50% EtOH-H_2O	58 : 42	40 : 60	20	80
		96% EtOH	57 : 43	42 : 58	19	81
		MeOH	57 : 43	40 : 60	18	82
(R_C/S_C)-1b	$TsNCl_2$	$CHCl_2$	58 : 42	39 : 62	91	9
		MeOH	56 : 44	38 : 62	91	9
		MeOH (e)	59 : 41	38 : 62	91	9
(R_C/S_C)-1b	^tBuOCl / $TsNH^-Na^+$ (d)	CH_2Cl_2 (e)	61 : 39	56 : 44	91	9
		MeOH (e)	61 : 39	58 : 42	94	6
		MeOH	57 : 43	55 : 45	94	6
			$(S_CR_S):(S_CS_S)$	$(S_CR_S):(S_CS_S)$		
(S_C)-1c	$TsNCl^-Na^+.\frac{1}{2}H_2O$	MeOH	66 : 34	70 : 30	92	2
		CH_2Cl_2	68 : 32	67 : 33	90	10
		dioxan	66 : 34	80 : 20	81	19
			$(R_CS_S/S_CR_S):(R_CR_S/S_CS_S)$	$(R_CS_S/S_CR_S):(R_CR_S/S_CS_S)$		
(R_C/S_C)-1d	$TsNCl^-Na^+.\frac{1}{2}H_2O$	MeOH	62 : 38	71 : 29	97	3
		CH_2Cl_2	62 : 38	63 : 37	86	14
		dioxan	60 : 40	74 : 26	70	30

(a) Reactions were carried out with 10^{-2} mol/l starting concentrations of both reactants at t:20°, except in cases noted. (b) Standard deviation ±2%. (c) Starting concentrations of both reactants 10^{-3} mol/l. (d) Two-stage procedure (see text). (e) t:-78°.

N-chloro arenesulphonamides produces sulphilimine (**1a**→**9a**→**3a**), while the competitive chlorination of sulphide, followed by the hydrolysis of chlorosulphonium ion, affords sulphoxide (**1a**→**5a**→**6a**→**2a**). In course B the sulphurane intermediate formed by oxidative addition (**1a**→**7a**) either transforms into sulphilimine with loss of Cl^- and Q^+ (Q = H or Cl; **7a**→**8a**→**9a**→**3a**) or undergoes hydrolysis resulting in the formation of sulphoxide *via* octahedral sulphur anion intermediate (**7a**→**10a**→**2a**). In course C the rate-controlling step leads to chlorosulphonium-sulphonamidate intimate ion-pair (**1a**→**5a**) from which either sulphilimine is produced by nucleophilic substitution starting with rapid addition of sulphonamidate anion to the sulphonium centre (**5a**→**7a**→**8a**→**9a**→**3a**; retention of configuration at sulphur) or sulphoxide is formed, owing to the separation of the ion-pair followed by usual fast hydrolysis[15] (**5a**→**6a**→**2a**; inversion of configuration at sulphur).[12]

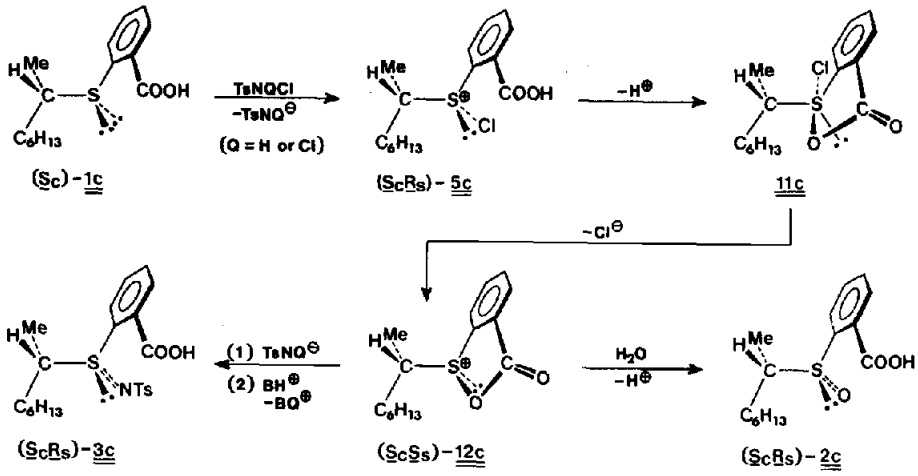
Although the observed diastereomeric distributions can be formally explained by any one of the discussed mechanisms, we believe that only course C is operative, because courses A and B are inconsistent with either the results of earlier kinetic measurements and product analyses,[2] or with the known stability of sulphilimines toward hydrolysis in practically neutral reaction media. The investigation of substituent and neighbouring group effects has shown[2b,d] that in the transition state considerable positive and negative charges are developed on the S and N atoms of the reactants, respectively. This is in accordance with the slow formation of an ion-pair intermediate (**5a**) in course C, but not with that of the intermediates **9a** and **7a** in courses A and B. In addition, earlier experiments have shown that sulphoxides and sulphilimines are formed from a common intermediate in parallel fast steps controlled by other factors than the rate-determining step.[2b] Again, if the reaction followed course A, a competitive formation of two intermediates (**5a**, **9a**) should be supposed, because the latter does not hydrolyse to sulphoxide in the reaction media, but produces sulphilimine with rapid deprotonation or Cl^+-transfer (*cf* pK_a and hydrolysis of sulphilimines,[16] as well as the chlorination potential of N-chloro compounds[17]). As to course B, the sulphoxide **2a** might be formed from the common intermediate **7a** only through the octahedral S anion **10a** (*cf* the mechanism of sulphurane hydrolysis).[18] It is obvious, however, that the sulphurane **7a** can transform much faster by loss of chloride ion than by the nucleophilic attack of water molecules on sulphurane. This is consistent with the observation that sulphilimines do not hydrolyse in the mixture even if chloride ions are present, indicating the equilibrium **7a** ⇌ **3a** to be completely shifted toward the formation of sulphilimine.

Nucleophilic substitutions at a sulphonium centre are known[12] to occur usually with inversion of configuration at sulphur, involving a sulphurane intermediate with both entering and leaving groups in apical positions (a,a). Such a reaction pathway is accepted for sulphoxide formation in course C (**5a**→**6a**→**2a**). Since the major diastereomers of the sulphoxide **2a** and sulphilimine **3a** are heterochiral at sulphur, the latter compound must be formed from the chlorosulphonium intermediate **5a** by nucleophilic displacement occurring with retention of configuration at sulphur. This unusual reaction may be assumed to start with the instant combination of the oppositely charged ions ($RArSCl^+$ and $TsNQ^-$) developing as an intimate ion-pair in the same solvent cage. If $TsNQ^-$ anion attacks the sulphonium centre on the nearest face of the sulphur tetrahedron, a sulphurane intermediate (**7a**) can be formed with apical-equatorial (a, e) arrangement of the entering and leaving groups. Sulphilimine is produced from the primary sulphurane by pseudorotation followed by loss of Cl^- and Q^+ (Q = H or Cl; **7a**→**8a**→**9a**→**3a**). Some support for this reaction pathway comes from the following facts. Ion-pair intermediates have been found to form sulphurane very rapidly even at low temperature.[19] Although the a, e positions for the entering and leaving groups are less favourable than the a, a ones, some reactions supposed to proceed through an intermediate of the former arrangement of substituents occur even at room temperature.[12] If sulphilimine is formed from the very reactive species **5a**, the transition state resembles the reactants **5a** much more closely than the sulphurane **7a**. Thus $TsNQ^-$ anion can approach the positive sulphonium centre from the side of the plane [Cl, Ph, lone-pair] which is less hindered than the plane [R, Ph, lone-pair], giving rise to a nucleophilic displacement with retention of configuration at sulphur.

The observed diastereomeric product distribution might also be accounted for by presuming a thermodynamically controlled equilibration of the diastereomers of the sulphoxides **2a–2b** and sulphilimines **3a–3b**, initiated by chloride ions formed during the reaction. For sulphoxides, however, such an equilibration has been ruled out, although in all cases the oxidation of acyclic chiral sulphides afforded the mixture of diastereomers with the thermodynamically more stable component being predominant.[9,10a] As to sulphilimines, a Cl^--catalysed equilibration would also be inconsistent with the experimental observations. Data in Table 2 show that the major diastereomers of the sulphilimine products **3a** or **3b** can have just opposite configurations at sulphur, depending on the method used for the transformation of the given sulphide.

Reaction of ortho-*carboxy-substituted chiral sulphides with* $TsNCl^-Na^+$. The conversion of the compound (S_c)-**1c** into the major diastereomers of the sulphoxide **2c** and sulphilimine **3c** is shown in Scheme 6 representing the stereochemistry of reactions of *o*-carboxyphenyl sulphides (**1c** and **1d**) with N-chloro sulphonamides. As it has been suggested in a preceding paper (Scheme 3 in Ref. 2*d*) the rate-controlling Cl^+-addition to *ortho*-carboxyphenyl sulphides (**1c**→**5c**) is followed by a very fast reaction resulting in the separation of the chlorosulphonium-sulphonamidate ion-pair and in the formation of a cyclic acyloxysulphonium ion *via* cyclic sulphurane intermediate (**5c**→**11c**→**12c**; inversion of configuration at sulphur). The subsequent nucleophilic attack of either the solvent water molecules or the $TsNQ^-$ nucleophile separated from the sulphonium ion occurs in both cases with the inversion of configuration at sulphur[8] (**12c**→**2c** + **3c**), giving rise to the formation of products in which the major diastereomers of sulphoxide and sulphilimine are homochiral analogues. To explain the higher stereoselectivity observed in sulphilimine formation (Table 2), it may be assumed that the bulky nucleophile $TsNQ^-$ exhibits a bigger difference in reactivity toward the diastereomers of cyclic acyloxysulphonium ions than water.

In order to obtain more information about the stereochemistry of the chlorination of sulphides, the study of the reaction of cyclic sulphides of rigid conformation is in progress in our laboratory.



Scheme 6.

EXPERIMENTAL†

S - (2 - Octyl) - S - phenyl - N - [(4 - methylphenyl)sulphonyl] - sulphilimine (**3a**). The mixture of sulphilimine diastereomers was prepared from the sulphide (R_c)-(−)-**1a**[4] and $TsNCl^-Na^+ \cdot 2H_2O$ as published in Ref. 20. The (R_cS_s) diastereomer was obtained by recrystallising (5 times) the mixture from EtOH; m.p. 106–7°, $[\alpha]_D^{25} = -238.5°$ ($c = 2$, MeOH).

2-Butyl phenyl sulphoxide (**2b**). The racemic **1b**[21] was oxidised to **2b**[22] with $NaIO_4$ (*cf* Ref. 23); yield 70%. To separate the two racemates formed, 2 g of the product was chromatographed in one run with ether eluent on a 2.5 by 100 cm column packed with Merck Kieselgel-60, 70–230 mesh silica gel. In four subsequent runs, 1.09 g of the first eluted sulphoxide (R_cS_s/S_cR_s)-**2b** was obtained from 4 g of the mixture of racemates, and its purity was checked by hplc and ^{13}C NMR spectroscopy. ^{13}C NMR ($CDCl_3$): δ 9.80, 11.54, 23.95 for (R_cS_s/S_cR_s)-**2b** and δ 10.85, 11.99, 21.77 for (R_cR_s/S_cS_s)-**2b**, assigned to $\underline{C}H_3$–CH_2, $\underline{C}H_3$–CH and $\underline{C}H_2$ groups, respectively.

S - (2 - Butyl) - S - phenyl - N - [(4 - methylphenyl) - sulphonyl] - sulphilimine (**3b**). The racemic **1b**[21] was converted (*cf* Ref. 24) by $TsNCl^-Na^+ \cdot 2H_2O$ into the mixture of the two **3b** sulphilimine racemates. After recrystallisation (4 times) from EtOH–Et_2O (1:1) the racemate (R_cS_s/S_cR_s)-**3b** was separated, m.p. 116–7°. ^1H NMR ($CDCl_3$): δ 1.12 (d, CH_3CH) for (R_cS_s/S_cR_s)-**3b**, and δ 1.08 (d, CH_3CH) for (R_cR_s/S_cS_s)-**3b**.

S - (2 - Butyl) - S - phenyl - N - [(4 - methylphenyl)sulphonyl] - sulphoximine (**4b**). (a) The sulphoxide **2b** (1.76 g, 10 mmol; mixture of two racemates) was treated (*cf* Ref. 25) with (4-methylphenyl)sulphonyl azide (9.86 g, 50 mmol) added to the mixture in 5 portions in 100 hr. The formed mixture of the two sulphoximine racemates was crystallised from MeOH; yield 1.05 g (30%), m.p. 103–4°. (Found: C, 58.2; H, 6.4; N, 4.3; S, 18.4. Calc. for $C_{17}H_{21}NO_3S_2$ [351.5]: C, 58.1; H, 6.0, N, 4.0; S, 18.2%). IR (KBr): ν_{SO_2}: 1320, 1153 cm^{-1}; ν_{OSN}: 1220, 1055 cm^{-1}.

Starting with the isolated sulphoxide racemate (R_cS_s/S_cR_s)-**2b**, the sulphoximine racemate (R_cS_s/S_cR_s)-**4b** was obtained; yield 33%, m.p. 120–1°. ^1H NMR ($CDCl_3$): δ 1.24 (d, CH_3CH), 0.97 (t, CH_3CH_2).

(b) The sulphilimine **3b** (1.01 g, 3 mmol; mixture of two racemates) was oxidised with 3-chloroperbenzoic acid (2.41 g, 15 mmol) for 120 hr (*cf* Ref. 6). The obtained product (0.295 g, 28%) was identical with that prepared from **2b** by method (a).

The oxidation of the isolated sulphilimine racemate (R_cS_s/S_cR_s)-**3b** afforded the sulphoximine racemate (R_cR_s/S_cS_s)-**4b**; yield 32%, m.p. 99–100°. ^1H NMR ($CDCl_3$): δ 1.34 (d, CH_3CH), 0.93 (t, CH_3CH_2).

†Absolute configurations of the sulfoxides **2b**, **2d** and sulphilimines **3d**, **3d** as well as sulphoximine **4b** are assigned provisionally (*vide supra*).

(S_c)-*Methyl 2-(2-octylthio)benzoate* (**1e**). Methyl thiosalicylate (33.6 g, 0.2 mol) was dissolved in a soln of NaOEt (0.2 mol; from 4.6 g of Na and 100 ml of abs EtOH), then (R_c)-(−)-2-octyl bromide (38.6 g, 0.2 mol; $[\alpha]_D^{25} = -35.4°$, neat, 1 dm) was dropwise added at 0°. The soln was allowed to warm up to room temp overnight. The NaBr was filtered off. After evaporation of the solvent, the residue was distilled *in vacuo*; yield 47 g (83.8%), b.p. 157–8°/0.5 mmHg, $[\alpha]_D^{25} = +8.80°$ (neat, 1 dm) $[\alpha]_D^{25} = +4.7°$ ($c = 2.8$ EtOH). (Found: C, 69.0; H, 8.5; S, 11.3. Calc. for $C_{16}H_{24}O_2S$ [280.4]: C, 68.5; H, 8.6; S, 11.4%).

(S_c)-2-*(2-Octylthio)benzoic acid* (**1c**). To the sulphide (S_c)-(+)-**1e** (2.8 g, 10 mmol) in EtOH (13.5 ml) was added NaOH (0.8 g, 20 mmol) dissolved in water (1.5 ml), and the soln was refluxed for 45 min. After evaporation of the solvent the residue was acidified with 2N H_2SO_4. Petroleum ether (5 ml) was added to the separated oily product and the racemic **1c** was filtered off; yield 0.23 g (9%), m.p. 74–6°. The filtrate was evaporated and the residue was distilled *in vacuo*; yield 1.90 g (71%), b.p. 150°/0.001 mmHg (temperature of the bath), $[\alpha]_D^{25} = +4.6$ ($c = 2.7$, EtOH). (Found: C, 67.3; H, 8.3; S, 11.8. Calc. for $C_{15}H_{22}O_2S$ [266.4]: C, 67.6; H, 8.3; S, 12.0%.)

S-(2-Octyl)-S-(2-methoxycarbonyl-phenyl)-N-[(4-methylphenyl)sulphonyl]-sulphilimine (**3e**). The sulphide (S_c)-(+)-**1e** (10.45 g, 37 mmol) and $TsNCl^-Na^+ \cdot 2H_2O$ (10.8 g, 41 mmol) were dissolved in MeOH (75 ml). The soln was boiled for 5 min then allowed to cool to room temp. After 5 hr water (25 ml) was added, the ppt was filtered off (the filtrate was used for preparation of **2c**) then crystallised from MeOH–H_2O (3:1), yielding the mixture of two sulphilimine diastereomers (8.14 g, 48.9%), m.p. 102–3°. (Found: C, 61.1; H, 7.1; N, 3.3; S, 14.7. Calc. for $C_{23}H_{31}NO_4S_2$ [449.6]: C, 61.4; H, 7.0; N, 3.1; S, 14.3%.) IR (KBr): ν_{CO}: 1713 cm^{-1}; ν_{SO_2}: 1288, 1142 cm^{-1}; ν_{SNS}: 958, 764 cm^{-1}

Recrystallising (6 times) the product from MeOH–H_2O (3:1), the (S_cR_s) diastereomer was obtained; m.p. 116–7°, $[\alpha]_D^{25} = +293°$ ($c = 0.3$, EtOH).

S - (2 - Octyl) - S - (2 - carboxyphenyl) - N - [(4 - methylphenyl)sulphonyl] - sulphilimine (**3c**). To **3e** (1 g, 2.2 mmol; mixture of two diastereomers) suspended in MeOH (10 ml) was added NaOH (0.2 g, 5 mmol) dissolved in water (2.5 ml). The mixture was stirred at room temp for 1 hr, then the solvent was evaporated. The residue was diluted with water and acidified with 2N H_2SO_4, the ppt was filtered off and recrystallised from MeOH–H_2O, to yield the mixture of two sulphilimine diastereomers (0.85 g, 87.8%), m.p. 100–1°. (Found: C, 60.5; H, 7.0; N, 3.0; S, 14.8. Calc. for $C_{22}H_{29}NO_4S_2$ [435.6]: C, 60.7; H, 6.7; N, 3.2; S, 14.7%.) IR (KBr): ν_{CO}: 1713 cm^{-1}; ν_{SO_2}: 1279, 1135 cm^{-1}; ν_{SNS}: 980, 762 cm^{-1}.

Starting with the isolated (S_cR_s)-**3e** diastereomer, the above hydrolysis afforded the sulphilimine (S_cR_s)-**3c**; yield 95%, m.p. 103–4°, $[\alpha]_D^{25} = +291°$ ($c = 0.26$, EtOH).

2-(2-Octylsulphinyl)benzoic acid (**2c**). The filtrate obtained in

the preparation of **3e** was evaporated, the residue was dissolved in MeOH (50 ml), then NaOH (1.6 g) in water (30 ml) was added. The mixture was stirred at room temp for 1 hr. After evaporation of MeOH the aqueous soln was acidified with 2N H_2SO_4 and the separated oily product was crystallised from EtOAc to give the mixture of two sulphoxide diastereomers (1.5 g, 16%), m.p. 134–5°. (Found: C, 64.1; H, 8.0; S, 11.2. Calc. for $C_{15}H_{22}O_3S$ [282.4]: C, 63.8; H, 7.9; S, 11.4%.) IR (KBr): ν_{CO}: 1704 cm^{-1}, ν_{SO}: 1015 cm^{-1}.

Recrystallising (3 times) the product from EtOAc, (S_cR_s)-**2e** could be separated, m.p. 148–9°, $[\alpha]_D^{25} = +194.5°$ ($c = 1$, EtOH).

2-(2-Butylthio)benzoic acid (**1d**). To a soln of thiosalicylic acid (23.1 g, 0.15 mol) and NaOH (12 g, 0.3 mol) in water (225 ml) was added *s*-BuBr (20.6 g, 0.15 mol) dissolved in EtOH (300 ml), and the mixture was refluxed for 2 hr under N_2. After evaporation of EtOH the aqueous soln was extracted with ether, then acidified with 2N H_2SO_4. The separated oily product was crystallised from petroleum ether; yield 21.4 g (67.7%), m.p. 50–1°. (Found: C, 63.0; H, 6.7; S, 15.0. Calc. for $C_{11}H_{14}O_2S$ [210.3]: C, 62.8; H, 6.7; S, 15.2%.)

2-(2-Butylsulphinyl)benzoic acid (**2d**). To a soln of racemic **1d** (14.7 g, 70 mmol) and $KHCO_3$ (7 g, 70 mmol) in water (70 ml) was added $TsNCl^-Na^+ \cdot 2H_2O$ (20.3 g, 77 mmol) dissolved in water (70 ml). The mixture was boiled for 5 min then cooled. $TsNH_2$ was filtered off, the filtrate was extracted with EtOAc then acidified with 2N H_2SO_4. The separated oily product was crystallised from EtOH–H_2O (2:3) yielding the mixture of two sulphoxide racemates (12.2 g, 77%), m.p. 134–5°. (Found: C, 58.2; H, 6.1; S, 14.4. Calc. for $C_{11}H_{14}O_3S$ [226.3]: C, 58.4; H, 6.3; S, 14.2%.) IR (KBr): ν_{CO}: 1697 cm^{-1}; ν_{SO}: 970 cm^{-1}.

After a repeated crystallisation from EtOH–H_2O (2:3), the racemate (R_cS_s/S_cR_s)-**2d** was obtained; m.p. 123–4. ^1H NMR ($CDCl_3$): δ 0.92 (d, CH_3CH), 1.17 (t, CH_3CH_2) for (R_cS_s/S_cR_s)-**2d** and δ 1.50 (d, CH_3CH), 0.77 (t, CH_3CH_2) for (R_cR_s/S_cS_s)-**2d**.

Methyl 2-(2-butylthio)benzoate (**1f**). Methyl thiosalicylate (47.1 g, 0.28 mol) was dissolved in a soln of NaOEt (0.28 mol; from 6.44 g of Na and 100 ml of abs EtOH) and subsequently *s*-BuBr (38.4 g, 0.28 mol) in EtOH (50 ml) was dropwise added. The soln was refluxed for 2 hr then cooled, and the NaBr was filtered off. After evaporation of the solvent the residue was distilled *in vacuo*; yield 31.3 g (50%), b.p. 148–9°/13 mmHg. (Found: C, 64.4; H, 7.0; S, 14.4. Calc. for $C_{12}H_{16}O_2S$ [224.3]: C, 64.3; H, 7.2; S, 14.3%.)

S - (2 - *Butyl*) - S - (2 - *methoxycarbonyl - phenyl*) - N - [(4 - *methylphenyl*)*sulphonyl*] - *sulphilimine* (**3f**). To racemic **1f** (22.4 g, 0.1 mol) was added $TsNCl^-Na^+ \cdot 2H_2O$ (29.0 g, 0.11 mol) in MeOH (300 ml), the soln was boiled for 5 min then poured into water. The ppt was filtered off and crystallised from EtOH yielding the mixture of two sulphilimine racemates (29 g, 73.7%), m.p. 104–5°. (Found: C, 58.1; H, 5.8; N, 3.6; S, 16.1. Calc. for $C_{19}H_{23}NO_4S_2$ [393.5]: C, 58.0; H, 5.9; N, 3.6; S, 16.3%.) IR (KBr): ν_{CO}: 1716 cm^{-1}; ν_{SO_2}: 1287, 1146 cm^{-1}; ν_{SNS}: 978, 960 cm^{-1}.

After crystallisation (3 times) from EtOH, the racemate (R_cS_s/S_cR_s)-**3f** was obtained, m.p. 116–7°. ^1H NMR ($CDCl_3$): δ 1.04 (d, CH_3CH), 0.98 (t, CH_3CH_2) for (R_cS_s/S_cR_s)-**3f** and δ 1.25 (d, CH_3CH), 0.77 (t, CH_3CH_2) for (R_cR_s/S_cS_s)-**3f**.

S - (2 - *Butyl*) - S - (2 - *carboxyphenyl*) - N - [(4 - *methylphenyl*)*sulphonyl*] - *sulphilimine* (**3d**). To **3f** (3.93 g, 10 mmol; mixture of two racemates) suspended in MeOH (30 ml) was added NaOH (0.8 g, 20 mmol) dissolved in water (8 ml), and the mixture was stirred at room temp for 1 hr. After evaporation of MeOH the aqueous soln was diluted with water and acidified with 2N H_2SO_4. The ppt was filtered off and crystallised from MeOH–H_2O yielding the mixture of two sulphilimine racemates (3.2 g, 84%), m.p. 120–4°. (Found: C, 56.6; H, 6.0; N, 3.4; S, 16.9. Calc. for $C_{18}H_{21}NO_4S_2$ [379.5]: C, 57.0; H, 5.6; N, 3.7; S, 16.9%.) IR (KBr): ν_{CO}: 1693 cm^{-1}; ν_{SO_2}: 1286, 1142 cm^{-1}; ν_{SNS}: 989, 763 cm^{-1}.

Starting with the isolated (R_cS_s/S_cR_s)-**3f** racemate, the above hydrolysis afforded the sulphilimine (R_cS_s/S_cR_s)-**3d**; yield 90%, m.p. 133–4°. ^1H NMR (DMSO): δ 0.90 (d, CH_3CH), 0.90 (t, CH_3CH_2) for (R_cS_s/S_cR_s)-**3d** and δ 1.14 (d, CH_3CH), 0.70 (t, CH_3CH_2) for (R_cR_s/S_cS_s)-**3d**.

Hydrolysis of the ortho-*carboxy-substituted sulphilimines* **3c** *and* **3d**. A suspension of sulphilimine (0.2 g) in MeOH (8 ml), water (2 ml) and $HClO_4$ aq (1.2 ml, 70%) was stirred at room temp for 3 weeks. Sulphilimine was slowly dissolved, and a homogeneous soln was obtained finally. To the soln was added NaOH aq (50%) enough to ensure pH 2, then MeOH was evaporated. From aqueous solns the hydrolysis products were extracted with CH_2Cl_2 and, after evaporation of the solvent, their composition was determined with hplc. When the mixture of the diastereomers of **3c** sulphilimine or that of the racemates of **3d** sulphilimine were submitted to hydrolysis, the formation of the mixture of both diastereomers of the **2c** sulphoxide and that of both racemates of **2d** sulphoxide, respectively, could be detected in addition to $TsNH_2$. The hydrolysis of the sulphilimines (S_cR_s)-**3c** and (R_cS_s/S_cR_s)-**3d** afforded the sulphoxides (S_cR_s)-**2c** and (R_cS_s/S_cR_s)-**2d**, respectively, together with $TsNH_2$.

Determination of diastereomeric sulphoxide and sulphilimine product distribution by hplc. Starting with 0.1 mmol of the reactants, reactions of sulphides with chlorinating agents and nucleophiles were carried out as given in Table 2. In case of the reaction of sulphides with *t*-BuOCl, the $TsNH^-Na^+$ nucleophile (dissolved in 1 ml of MeOH) was added 10 min after chlorination had started. To exclude atmospheric moisture, dried solvents were distilled onto the mixture of *ortho*-carboxy-substituted sulphides and $TsNCl^-Na^+ \cdot 1/2H_2O$, because the yields of sulphilimines were only in this case commensurable with those of sulphoxides (*cf* Ref. 2*d*). Solns were kept at the given temp for 5 hr then filtered, and the solvents were evaporated. The residues were dissolved in MeOH and diluted with tenfold amounts of ether for hplc.

Experimental conditions for hplc.† The chromatograph was a laboratory assembled instrument. Column: Chromsfer-Sil (Labor-MIM, Hungary); 9 μm particle size; 250 × 4 mm. Eluents (v/v): ether–pentane (80:20), ether–pentane (85:15), pentane–ether–acetic acid (50:47.5:2.5) and ether–pentane–acetic acid (77:20:3) were used for the chromatography of products obtained by the conversion of the sulphides **1a**, **1b**, **1c** and **1d**, respectively. Flow rate: 1 ml/min (maintained with an Orlita 1515 reciprocating piston pump). Injection: 5 μl of the solutions of products, $c = 2$ mg/ml. Detection: UV absorption of the column effluents were monitored at 253 nm (Cecil 212 variable wavelength ultraviolet monitor). Recording: peaks were recorded on a chart recorder (type: OH-814/1, Radelkis, Hungary) and areas under them were calculated with the application of Simpson's rule.

Spectra. IR, ^1H NMR, ^{13}C NMR, ORD and CD spectra were recorded on Zeiss UR-10, Varian A-60D, Varian XL-100, Zeiss REPM12 and Roussel Juan Dicrograph III instruments, respectively.

†Details on hplc of sulphilimines and sulphoxides studied will be published elsewhere.[26]

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