Note

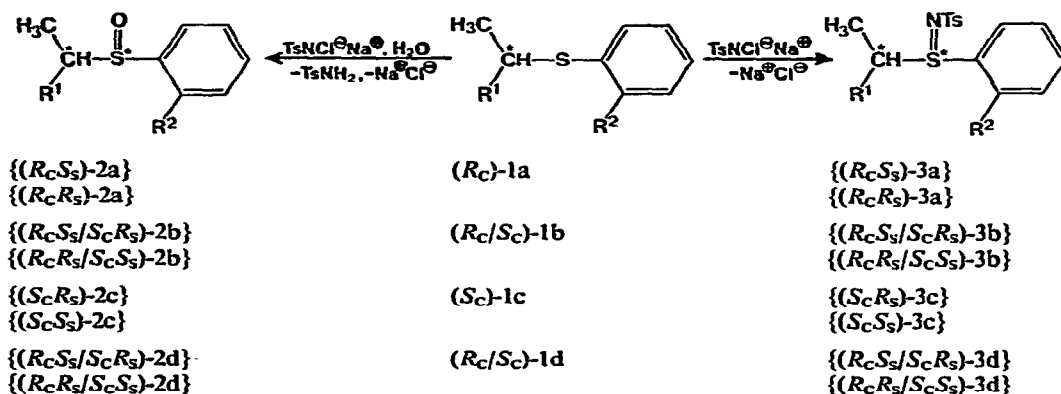## High-performance liquid chromatography of diastereomeric sulphoxides and sulphilimines

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When sulphides are treated with N-chloroarenesulphonamides (*e.g.* chloramine-T) in solvents containing water, sulphilimines with equimolecular mixtures of sulphoxides and sulphonamides are formed[1]. The distribution of sulphilimine and sulphoxide products can be measured by polarography[2]. Recently the stereochemistry of the reaction has been studied[3] by the use of chiral alkyl aryl sulphides (1a–d) and TsNCl⁻Na⁺ as reactants, producing unequal amounts of diastereomers (or diastereomeric racemates) of both sulphoxides (2a–d) and sulphilimines (3a–d). The compounds examined are shown in Scheme 1, together with configuration symbols for chiral carbon (R_C and S_C) and sulphur (R_S and S_S) centres.

{($R_C S_S$)-2a}	(R_C)-1a	{($R_C S_S$)-3a}
{($R_C R_S$)-2a}		{($R_C R_S$)-3a}
{($R_C S_S$/$S_C R_S$)-2b}	(R_C/S_C)-1b	{($R_C S_S$/$S_C R_S$)-3b}
{($R_C R_S$/$S_C S_S$)-2b}		{($R_C R_S$/$S_C S_S$)-3b}
{($S_C R_S$)-2c}	(S_C)-1c	{($S_C R_S$)-3c}
{($S_C S_S$)-2c}		{($S_C S_S$)-3c}
{($R_C S_S$/$S_C R_S$)-2d}	(R_C/S_C)-1d	{($R_C S_S$/$S_C R_S$)-3d}
{($R_C R_S$/$S_C S_S$)-2d}		{($R_C R_S$/$S_C S_S$)-3d}

Scheme 1. a: $R^1 = C_6H_{13}$, $R^2 = H$; b: $R^1 = C_2H_5$, $R^2 = H$; c: $R^1 = C_6H_{13}$, $R^2 = CO_2H$; d: $R^1 = C_2H_5$, $R^2 = CO_2H$.

Different pathways have been suggested for the product-controlling steps of the reaction. The diastereomeric product distributions can be readily measured by high-performance liquid chromatography (HPLC). This communication describes an HPLC procedure used for the separation and quantitative determination of diastereomeric sulphoxides and sulphilimines utilizing silica as column packing material. Our results seem to provide a contribution to the HPLC analyses of organic sulphur compounds[4–6], as well as to those of diastereomers[7].

EXPERIMENTAL

Equipment
Chromatographic separations were performed on a laboratory assembled instrument of which the principal components were a reciprocating piston pump (Type 1515; Orlita, Giessen, G.F.R.) and a variable-wavelength photometer fitted to a 10-μl flow-cell (Model 212; Cecil, Cambridge, Great Britain). Column effluents were monitored at 254 nm. Columns, 250 × 4 mm I.D., were of internally polished stainless steel. Injection, by 5-μl microsyringe, was made centrally through a septum into a bed of glass beads placed on top of the column packing.

Packing materials
Hypersil (Shandon Southern Products, Runcorn, Great Britain) and Chromsfer-Sil (Labor-MIM, Budapest, Hungary) silicas with spherical particles (*ca.* 6 and 9 μm, respectively) were used as packing materials. Columns were packed either by the balance density method[8] (Hypersil) or by the slurry method[9] (Chromsfer-Sil). In the latter case freshly distilled cyclohexanol was used to prepare slurries containing 10% (w/w) of silica. The slurry was homogenized in an ultrasonic bath for 10 min. The packing was carried out in the conventional way, the slurry being pressurized to 280 bar with the aid of a Haskel pump (MCP 71; Haskel Burbank, CA, U.S.A.). The flushing solvents were methanol (250 ml), acetone (150 ml), acetone–cyclohexane (150 ml) and diethyl ether (250 ml).

Other conditions
All solvents used were of p.a. quality. Samples were dissolved in small amounts of methanol then diluted with diethyl ether to tenfold volume (*c* = 2 mg/ml). Injection aliquots were 5 μl. Various mixtures of diethyl ether, pentane, methanol and acetic acid were used as mobile phase. Using the isocratic method, the chromatograph was operated at ambient temperature; flow-rates were between 0.8 and 1.2 ml/min. Peaks were recorded on a chart recorder (Type OH-814/1; Radelkis, Budapest, Hungary), and the areas under them were calculated using Simpson's rule.

Materials
Diastereomers (or diastereomeric racemates) of the alkyl aryl sulphoxides (2a–d) and those of the S-alkyl-S-aryl-N-[(4-methylphenyl)sulphonyl]-sulphilimines (3a–d) were prepared from the corresponding alkyl aryl sulphides (1a–d) (Scheme 1), and the configurations at sulphur were determined either by optical rotatory dispersion/circular dichroism measurements or by stereospecific reactions[3]. Diastereomeric product distributions for both sulphoxides and sulphilimines were measured in the crude products obtained by the conversion of sulphides with chloramine-T[3].

RESULTS AND DISCUSSION

Experimental data on chromatographic separations, including capacity factors (*k'*), separation factors (*α*) and resolution values obtained for sulphoxide and sulphilimine diastereomers, are summarized in Table I. Figs. 1–4 show typical chromatograms. Sulphides and diastereomeric sulphoxide and sulphilimine products of analo-

TABLE I

SEPARATION OF DIASTEREOMERIC SULPHOXIDES (2a–d) AND SULPHILIMINES (3a–d)

Chromatographic conditions as in Experimental section.

	Sulphoxide				Sulphilimine			TsNH$_2$,	Pack-ing***	Eluent (v/v)$^{\$}$
	k' $(R_cS_s)^*$	k' $(R_cR_s)^*$	α^{**}		k' $(R_cS_s)^*$	k' $(R_cR_s)^*$	α^{**}	k'		
2a	0.38	0.53	1.38	3a	0.42	0.59	1.41		Ch	E
2a	0.47	0.61	1.29	3a	0.66	0.89	1.36		Ch	E–P (90:10)
2a	0.49	0.67	1.36	3a	0.88	1.27	1.46	0.36	Ch	E–P (80:20)
			(1.97)				(2.72)			
2a	0.69	0.98	1.40	3a	1.43	2.00	1.40	0.45	Hy	E–M (99.5:0.5)
			(3.44)				(2.90)			
	k' $(R_cS_s/ S_cR_s)^*$	k' $(R_cR_s/ S_cS_s)^*$			k' $(R_cS_s/ S_cR_s)^*$	k' $(R_cR_s/ S_cS_s)^*$				
2b	0.63	0.82	1.31	3b	0.87	1.09	1.26		Ch	E–M (98:2)
2b	0.84	1.24	1.47	3b	1.11	1.63	1.47		Ch	E
2b	0.95	1.39	1.46	3b	1.39	2.02	1.46		Ch	E–P (95:5)
2b	1.03	1.51	1.47	3b	1.65	2.46	1.49		Ch	E–P (90:10)
2b	1.07	1.57	1.47	3b	1.85	2.68	1.45	0.46	Ch	E–P (85:15)
			(3.45)				(3.59)			
2b	0.72	1.04	1.45	3b	1.37	1.92	1.41	0.27	Hy	E–M (98:2)
			(4.50)				(3.85)			
	k' $(S_cR_s)^*$	k' $(S_cS_s)^*$			k' $(S_cR_s)^*$	k' $(S_cS_s)^*$				
2c	0.63	0.81	1.28	3c	1.53	1.71	1.12		Ch	E–P–A (67.5:30:2.5)
2c	0.74	0.98	1.32	3c	2.02	2.27	1.12		Ch	E–P–A (57.5:40:2.5)
2c	0.98	1.36	1.38	3c	3.34	3.89	1.16	0.70	Ch	E–P–A (47.5:50:2.5)
			(1.82)				(1.32)			
	k' $(R_cS_s/ S_cR_s)^*$	k' $(R_cR_s/ S_cS_s)^*$			k' $(R_cS_s/ S_cR_s)^*$	k' $(R_cR_s/ S_cS_s)^*$				
2d	0.12	0.12	1.00	3d	0.20	0.20	1.00		Ch	E–M–A (88:10:2)
2d	0.39	0.46	1.17	3d	0.62	0.76	1.22		Ch	E–M–A (97:2.5:0.5)
2d	0.86	1.03	1.19	3d	1.33	1.63	1.23		Ch	E–P–A (83:15:2)
2d	0.87	1.07	1.23	3d	1.98	2.46	1.24	0.48	Ch	E–P–A (77:20:3)
			(1.00)				(1.40)			

* The symbols indicate the configuration of the chiral centres in the diastereomer.

** Resolution values are given in parentheses.

*** Column packing materials: Ch = Chromsfer-Sil; Hy = Hypersil.

$^{\$}$ Solvents used for elution: A = acetic acid; E = diethyl ether; M = methanol; P = pentane.

gous constitution as well as p-toluenesulphonamide show selective sorption on silica adsorbents, owing to the different polarities of the sulphur compounds examined.

Under isocratic conditions optimum analysis time (maximum 15 min) and resolutions were achieved with the instrumentation described in the Experimental section and with the eluents listed in Table I. Theoretical plate numbers of the
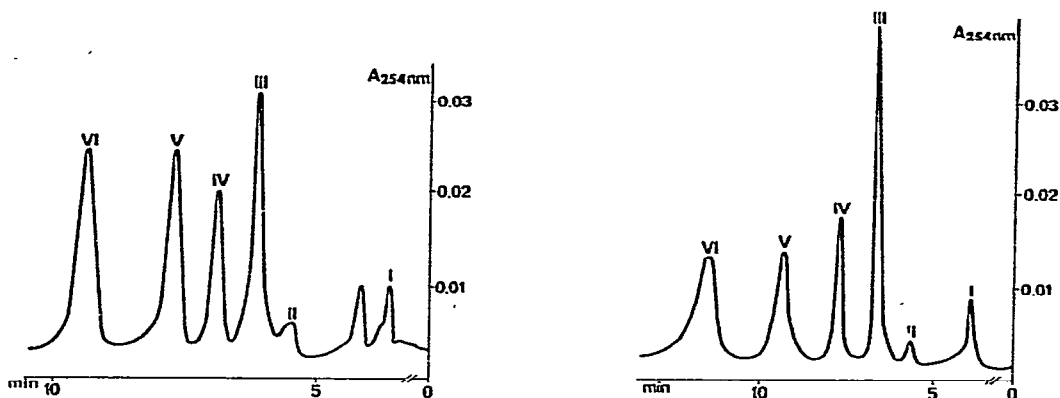
Fig. 1. Chromatogram of crude product obtained[3] in the reaction of (R_C)-$(-)$-1a with $TsNCl^-Na^+$ in ethanol. Packing, Chromsfer-Sil; eluent, diethyl ether–pentane (80:20, v/v). Chromatographic conditions as in Experimental. Peaks: I = 1a; II = $TsNH_2$; III = (R_CS_S)-2a; IV = (R_CR_S)-2a; V = (R_CS_S)-3a; VI = (R_CR_S)-3a. Ratio of molar absorptivities at 254 nm: $TsNH_2$:2a:3a = 0.091: 1.62:1. Evaluated product distributions: 2a:3a = 28:72; III:IV = 59:41; V:VI = 41:59.

Fig. 2. Chromatogram of crude product obtained[3] in the reaction of (R_C)-$(-)$-1a with $TsNCl^-Na^+$ in ethanol–water (50:50). Packing, Hypersil; eluent, diethyl ether–methanol (99.5:0.5, v/v). Chromatographic conditions as in Experimental. Peaks: I = 1a; II = $TsNH_2$; III = (R_CS_S)-2a; IV = (R_CR_S)-2a; V = (R_CS_S)-3a; VI = (R_CR_S)-3a. Ratio of molar absorptivities at 254 nm: $TsNH_2$:2a:3a = 0.091:1.62:1. Evaluated product distributions: 2a:3a = 42:58; III:IV = 64:36; V:VI = 40:60.
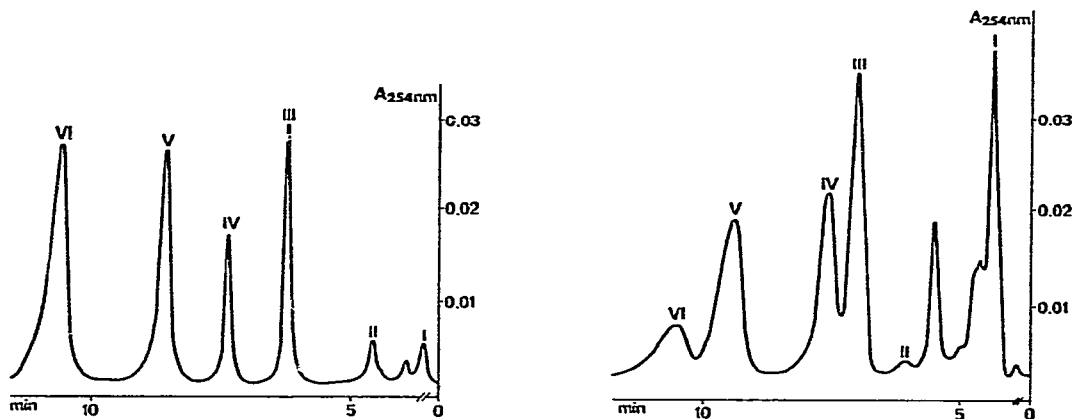

Fig. 3. Chromatogram of crude product obtained[3] in the reaction of (R_C/S_C)-1b with $TsNCl^-Na^+$ in ethanol–water (50:50). Packing, Hypersil; eluent, diethyl ether–methanol (98:2, v/v). Chromatographic conditions as in Experimental. Peaks: I = 1b; II = $TsNH_2$; III = (R_CS_S/S_CR_S)-2b; IV = (R_CR_S/S_CS_S)-2b; V = (R_CS_S/S_CR_S)-3b; VI = (R_CR_S/S_CS_S)-3b. Ratio of molar absorptivities at 254 nm: $TsNH_2$:2b:3b = 0.082:1.37:1. Evaluated product distributions: 2b:3b = 20:80; III:IV = 58:42; V:VI = 40:60.

Fig. 4. Chromatogram of crude product obtained[3] in the reaction of (R_C/S_C)-1d with $TsNCl^-Na^+$ in dioxane. Packing, Chromsfer-Sil; eluent, diethyl ether–pentane–acetic acid (77:20:3, v/v/v). Chromatographic conditions as in Experimental. Peaks: I = 1d; II = $TsNH_2$; III = (R_CS_S/S_CR_S)-2d; IV = (R_CR_S/S_CS_S)-2d; V = (R_CS_S/S_CR_S)-3d; VI = (R_CR_S/S_CS_S)-3d. Ratio of molar absorptivities at 254 nm: $TsNH_2$:2d:3d = 0.069:0.87:1. Evaluated product distributions: 2d:3d = 70:30; III:IV = 60:40; V:VI = 74:26.

columns packed with Chromsfer-Sil and Hypersil were *ca.* 4000 and 8000, respectively. Baseline separations required for quantitative analysis were obtained without difficulty ($\alpha = 1.2$–1.5; resolution $= 1.3$–4.5).

The optimization of eluent composition for Chromsfer-Sil packing material is shown in Table I. The values of k' increased with increasing concentration of pentane in the mobile phase. On the other hand, k' and α values decreased when a small amount of methanol was added to the ether eluent. For Chromsfer-Sil packing material a slightly polar diethyl ether–pentane mixture, and for Hypersil a more polar system containing diethyl ether and a few percent of methanol, were found to be appropriate eluents.

In order to counteract the undesirable effect of the dissociable COOH group, small amounts of acetic acid were added to the eluents used for the chromatography of carboxy substituted compounds. This change in the composition of the solvent resulted in a favourable reduction of band tailing. Though 2-butyl derivatives were eluted somewhat slower than 2-octyl analogues, only a slight alteration in eluent composition was required to attain optimum conditions.

Table I and Figs. 1–4 indicate that the examined compounds are eluted in the following order: sulphide*, sulphonamide, sulphoxide diastereomers, sulphilimine diastereomers. Both sulphoxide and sulphilimine diastereomers (diastereomeric racemates) with R_CS_S/S_CR_S configurations are eluted faster than those of R_CR_S/S_CS_S configurations.

Quantitative data for the diastereomeric product distribution (see details in ref. 3) can be obtained by evaluating the chromatograms. In the cases of the separations illustrated in Figs. 1–4, the corresponding numerical values are given in the figure legends (standard deviation $\pm 2\%$).

ACKNOWLEDGEMENT

REFERENCES

1 T. L. Gilchrist and C. J. Moody, *Chem. Rev.*, 77 (1977) 409; and refs. cited therein.
2 F. Ruff and Á. Kucsman, *J. Chem. Soc., Perkin Trans. II*, (1975) 509.
3 F. Ruff, G. Szabó, J. Vajda, I. Kövesdi and Á Kucsman, *Tetrahedron*, 36 (1980) 1631.
4 F. M. Rabel, *Anal. Chem.*, 45 (1973) 957.
5 P. H. Cobb and G. T. Hill, *J. Chromatogr.*, 123 (1976) 444.
6 W. H. Pirkle and D. W. House, *J. Org. Chem.*, 44 (1979) 1957.
7 T. Tamegai, M. Ohmae, K. Kawabe and M. Tomoeda, *J. Liquid Chromatogr.*, 2 (1979) 1229; and refs. cited therein.
8 J. H. Knox and J. F. Parcher, *Anal. Chem.*, 41 (1969) 1599.
9 G. Vigh, E. Gémes and J. Inczédy, *J. Chromatogr.*, 147 (1978) 59.

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* Under the given conditions sulphides are not retained on silica adsorbents, and appear, together with the solvent, as the first peak in the chromatograms.