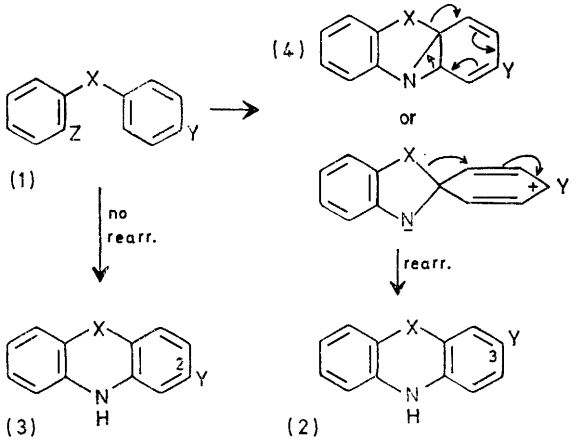
Nitrene-induced Cyclisations Accompanied by Rearrangement in Thermolyses of Aryl 2-Azidophenyl Sulphones: a Note on Quantitative High-speed Liquid Chromatographic Analysis of Substituted Phenothiazine 5,5-Dioxides

By **J. I. G. Cadogan,* John N. Done, George Lunn,** and (in part) **Peter K. K. Lim,** Department of Chemistry, University of Edinburgh, West Mains Road, Edinburgh EH9 3JJ

Thermolysis in decalin or triethyl phosphate at 192 °C of a series of aryl 2-azidophenyl sulphones (2-$N_3C_6H_4{\cdot}SO_2{\cdot}C_6H_4R$; R = 2-Cl, 3-Cl, 4-Cl, 2-Me, 3-Me, 4-Me, 2-OMe, 3-OMe, 4-OMe, 4-Bu^t, 2-CF_3, 3-CF_3, 4-CF_3, or 2,6-Cl_2), characterised as the 2-triphenylphosphoranylideneamino-derivatives, have been studied and the products analysed quantitatively by high-speed liquid chromatography. The reactions gave small amounts of 2-aminophenyl aryl sulphones (0—30%), and phenothiazine 5,5-dioxides (25—90%) which were mixtures of rearranged and unrearranged isomers, *e.g.* 2-azidophenyl 3-methylphenyl sulphone in decalin gave a mixture of methylphenothiazine 5,5-dioxides in the following proportions: 1- (62%), 2- (10%), 3- (20%), and 4- (8%). Consideration of the rearrangement ratio in each case points to cyclisation *via* an electrophilic nitrene, the position of attack being influenced mainly by the electronic character of the substituent, although proximity effects cannot be excluded. In most cases there was no significant difference between rearrangement ratios in decalin and in triethyl phosphate so, in this system, in general, there is no reason to invoke formation of and reaction *via* the species $ArN{-}O{-}P(OEt)_3$ in the latter case.

The reaction of 4-chlorophenyl 2-nitrophenyl sulphone with triethyl phosphite in boiling cumene gave no chlorophenothiazine dioxides; an intractable tar was obtained.

CYCLISATIONS accompanied by rearrangements involving nitrenes, nitrene precursors, or nitrene-related species of the type shown in Scheme 1 are now well established.[1]



SCHEME 1 (Z = N_3 or NO_2)

Rearrangement is particularly prevalent in cases involving bridgehead sulphur in thermolysis of aryl 2-azidophenyl sulphides (1; X = S, Z = N_3)[2] or the deoxygenation of aryl 2-nitrophenyl sulphides (1; X = S, Z = NO_2) by triethyl phosphite,[2a,b] both of which proceed with rearrangement to give phenothiazines (2; X = S). *o*-Aroylarylnitrenes (1; X = CO, Z = N) produced *via* thermolysis of 2,1-benzisoxazoles also undergo cyclisation with rearrangement to give acridones (2; X = CO)[3a] but in certain cases products corresponding to direct insertion [*e.g.* (3; X = CO)] also arise.[3a,b] In theory this could be a function of the reduced electron density on the receptor ring arising from the presence of the electron-withdrawing carbonyl group and/or its reduced migratory aptitude. It was therefore of interest to examine the effect of the related bridgehead sulphonyl group in this connection through thermolyses of aryl 2-azidophenyl sulphones (1; X = SO_2, Z = N_3), which are more readily available than the corresponding 2,1-benzisoxazoles. We expected that phenothiazine 5,5-dioxides produced both with and without rearrangement, *e.g.* (2 and 3; X = SO_2), would result and, hopefully, the ratio of rearranged to unrearranged products would provide information on the nature of the reaction through substituent effects. Further, for a given range of substituents the rearrangement ratio could provide information on the nature of the reactive intermediate produced under different conditions. In particular this could provide a test of the suggestion of Holliman and his co-workers[4] that whereas thermolyses of azides in decalin proceed *via* attack of nitrenes, those in triethyl phosphate involve the formation and subsequent reaction of the species $(EtO)_3\overset{+}{P}{-}O{-}\bar{N}Ar$, also previously postulated as an intermediate in the deoxygenation of nitro-compounds by triethyl phosphite.[5] If this were the case thermolysis of 2-azidophenyl aryl sulphones in triethyl phosphate might be expected to give a rearrangement ratio different from that produced in the decalin experiments.

At the outset of the investigation it was known only that thermolysis of 2-azidophenyl phenyl sulphone (1; X = SO_2, Z = N_3, Y = H) gave phenothiazine 5,5-dioxide (3; X = SO_2, Y = H) in unspecified yield.[6] Substituent effects had not been studied. We therefore

[1] J. I. G. Cadogan, *Accounts Chem. Res.*, 1972, **5**, 303.

[2] (*a*) J. I. G. Cadogan, S. Kulik, and M. J. Todd, *Chem. Comm.*, 1968, 736; (*b*) J. I. G. Cadogan, S. Kulik, C. Thomson, and M. J. Todd, *J. Chem. Soc.* (*C*), 1970, 2437; (*c*) M. Messer and D. Farge, *Bull. Soc. chim. France*, 1968, 2832.

[3] (*a*) R. Kwok and P. Pranc, *J. Org. Chem.*, 1968, **32**, 2880; (*b*) R. Y. Ning, W. Y. Cheau, and L. H. Sternbach, *J. Heterocyclic Chem.*, 1974, **11**, 125.

[4] P. K. Brooke, R. B. Herbert, and F. G. Holliman, *Tetrahedron Letters*, 1973, 761.

[5] J. I. G. Cadogan and S. Kulik, *J. Chem. Soc.* (*C*), 1971, 2621.

[6] P. A. S. Smith, B. B. Brown, R. K. Putney, and R. F. Reinisch, *J. Amer. Chem. Soc.*, 1953, **75**, 6335.

investigated thermolyses in decalin and in triethyl phosphate of a series of 2-, 3-, and 4-substituted 2-azidophenyl phenyl sulphones (1; X = SO_2, Z = N_3) and examined the products both by isolation and, quantitatively, by high-speed liquid chromatography (h.s.l.c.).

TABLE 1

Aryl 2-nitrophenyl sulphides

2-NO_2·C_6H_4·S·C_6H_4R

R	Yield (%)	M.p. (°C)	Analyses (%) * C	H	N
3-OMe	87	121—122	59.7	4.4	5.1
			59.8	4.2	5.4
2-CF_3	71	94—95	52.3	2.7	4.4
			52.2	2.7	4.7
3-CF_3	74	86—87	51.9	2.7	4.4
			52.2	2.7	4.7
4-CF_3	57	81—82	51.9	2.7	4.4
			52.2	2.7	4.7

* Upper row ' Found '; lower row ' Required '.

EXPERIMENTAL

Preparation of Materials.—*Aryl 2-nitroaryl sulphides* were prepared by Galt and Loudon's method.[7] Most had been described previously and all had the correct characteristics.[5,7-9] New compounds are summarised in Table 1.

Aryl 2-nitrophenyl sulphones (Table 2) were prepared by oxidation of the corresponding sulphides either (i) with hydrogen peroxide (30% w/v) in acetic acid at 100 °C for 3h, or (ii) with *m*-chloroperbenzoic acid (2 mol. equiv.) in boiling methylene chloride for 8h, the latter being particularly suitable for 2-substituted derivatives. *2-Nitrophenyl 2-pyridyl sulphone* N-*oxide* decomposed slowly over a range of temperature (Found: C, 47.6; H, 2.8; N, 10.0. $C_{11}H_8NO_5S$ requires C, 47.1; H, 2.9; N, 10.0%).

2-Aminophenyl aryl sulphones (Table 3) were prepared by reduction of the corresponding nitro-compounds with iron powder in ethanol in the presence of hydrochloric acid as catalyst.[5]

Aryl 2-azidophenyl sulphones (Table 4) were prepared in *ca.* 80—90% yields from the corresponding amines by diazotisation and treatment with sodium azide, and purified by chromatography on alumina. Not all were stable enough to await analysis so they were characterised as the corresponding 2-triphenylphosphoranylideneamino-derivatives, formed from the azide and triphenylphosphine at 0 °C in dry ether and recrystallised from hexane–dichloromethane (Table 5).

Phenothiazines, all known compounds, were prepared mainly by reduction of the corresponding 2-nitrophenyl aryl sulphides [2b] with triethyl phosphite or by addition of sulphur to diarylamines. All had characteristics in accord with literature values, and were shown to be isomerically pure by h.s.l.c.

Phenothiazine 5,5-dioxides (Table 6) were prepared by reactions of the phenothiazines with *m*-chloroperbenzoic acid (85%; 2.5 equiv.) in boiling dry dichloromethane for 24 h. When cool the solution was diluted with more solvent and *m*-chlorobenzoic acid and unchanged peroxy-acid were removed by washing with dilute alkali and dilute aqueous sodium sulphite. The products were purified by sublimation, the isomeric purity being confirmed by h.s.l.c.

High-speed Liquid Chromatography.—Homogenised mix-

TABLE 2

Aryl 2-nitrophenyl sulphones

2-NO_2·C_6H_4·SO_2·C_6H_4·R

R	Yield (%)	M.p. (°C)	Lit. m.p. (°C)	Ref.	Method	Analyses (%) * C	H	N
2-Me	45	146	144—145	8	(i)			
3-Me	77	114—115	118—119	9	(i)			
4-Me	82	155—157	156—157	*a*	(i)			
2-OMe	84	120—121			(ii)	53.4	3.8	4.4
						53.2	3.8	4.8
3-OMe	90	92.5—93.5			(i)	53.5	3.9	4.5
						53.2	3.8	4.8
4-OMe		149—150	149.5	*b*	(i)			
2-Cl	82	154—155	152	*b*	(ii)			
3-Cl		132—134	131—132	9	(i)			
4-Cl	95	140—141	137—138	*b*	(i)	48.2	2.7	4.6
						48.4	2.7	4.7
2-CF_3	46	146—147			(ii)	47.45	2.5	4.0
						47.1	2.4	4.2
3-CF_3	64	98—99			(ii)	47.2	2.5	3.8
						47.1	2.4	4.2
4-CF_3	52	122—123			(ii)	46.7	2.4	4.1
						47.1	2.4	4.2
2,6-Cl_2	93	171—172			(ii)	43.4	2.1	4.2
						43.7	2.2	3.9
2,6-$(OMe)_2$	72	216—217			(ii)	51.7	4.1	4.15
						52.0	4.05	4.3
2,4,6-Me_3	85	138—139			(i)	58.8	4.8	4.2
						59.0	4.9	4.6
4-Bu^t	92	129—130			(i)	60.4	5.2	4.3
						60.2	5.3	4.4

* For new compounds: upper row ' Found '; lower row ' Required '.

[a] Ger.P. 562 824 (*Chem. Abs.*, 1933, **27**, 998). [b] H. Landers, U.S.P. 1 936 721 (*Chem. Abs.*, 1934, **28**, 1049).

[7] R. H. B. Galt and J. D. Loudon, *J. Chem. Soc.*, 1959, 885.
[8] H. Gilman and H. S. Broadbent, *J. Amer. Chem. Soc.*, 1947, **69**, 2053.
[9] R. Passerini, *Boll. sci. Fac. Chim. ind. Bologna*, 1951, **9**, 1.

tures of products from thermolyses of aryl 2-azidophenyl sulphones were analysed by h.s.l.c., with a modified Du Pont 820 liquid chromatograph and 0.5 cm diameter polished stainless steel columns [10] slurry packed with Spherisorb alumina (Phase Separations Ltd.). The detector was a Du Pont 410 fixed-wavelength (254 nm) u.v. spectrophotometer fitted with an 8 μl flow cell. This was connected to a chart recorder and an Autolab 6300 integrator. A known amount of an inert internal standard was added to each reaction mixture and the area of each peak determined.

TABLE 3

Aryl 2-aminophenyl sulphones

$2\text{-}NH_2\cdot C_6H_4\cdot SO_2\cdot C_6H_4R$

R	Yield (%)	M.p. (°C)	Analyses (%) * C	H	N
2-Me	87	119—120	63.45	5.4	5.7
			63.2	5.3	5.7
3-Me	79	126	62.9	5.3	5.5
			63.2	5.3	5.7
4-Me †	67	119			
2-OMe		184—185	59.1	5.0	5.15
			59.3	5.0	5.3
3-OMe	84	107	59.4	5.2	5.2
			59.3	5.0	5.3
4-OMe		149—150	58.9	4.9	5.1
			59.3	5.0	5.3
2-Cl	62	176—177	53.85	3.8	5.1
			53.8	3.8	5.2
3-Cl		106.5—107.5	53.9	3.7	5.1
			53.8	3.8	5.2
4-Cl	48	134—135	54.1	3.8	5.5
			53.8	3.8	5.2
$2\text{-}CF_3$	70	113—114	51.7	3.3	4.6
			51.8	3.35	4.65
$3\text{-}CF_3$	82	60—62	52.2	3.4	4.6
			51.8	3.35	4.65
$4\text{-}CF_3$	96	147—148	51.7	3.4	4.65
			51.8	3.35	4.65
$2,6\text{-}Cl_2$	39	201—202	48.1	3.25	4.5
			47.7	3.1	4.6
$2,6\text{-}(OMe)_2$	87	158.5—159.5	57.2	5.3	4.6
			57.3	5.15	4.8
$2,4,6\text{-}Me_3$	84	153—154	66.0	6.1	5.2
			65.5	6.2	5.2
2-Pyridyl ‡	42	113—114	56.7	4.5	11.7
			56.4	4.3	12.0
2-Pyridyl *N*-oxide ‡	1.8	178—179	53.1	4.2	10.9
			52.8	4.0	11.2
4-Bu^t	86	107—108	66.8	6.5	5.2
			66.4	6.6	4.8

* For new compounds: upper row 'Found'; lower row 'Required'. † Lit.,[1] m.p. 120—121° (J. Halberkann, *Ber.*, 1922, **55**, 3074). ‡ Reduction of 2-nitrophenyl 2-pyridyl sulphone *N*-oxide gave both 2-aminophenyl 2-pyridyl sulphone and its *N*-oxide, separated by chromatography on alumina.

Thus the ratio of the area of each peak to the area of the internal standard peak was found and a calibration factor (determined by running a mixture containing a known weight of each component under identical conditions) was used to obtain the ratio of the weight of each component to the weight of the added standard. Thus the amount of each component of the mixture was determined.

Identification of components. Retention times are not very satisfactory for peak identification because the activity of the column changes with time;[11] to counteract this, capacity ratios (k') are used which relate the speed with which a solute moves through the column to that with which a non-adsorbed solute (*e.g.* pentane) moves. The latter gives rise to the so-called 'unretained peak,' familiar as the 'air' peak in g.l.c. The k' value of a peak is related

[10] J. H. Knox, *Chem. and Ind.*, 1975, 29.

[11] (*a*) J. J. Kirkland and L. R. Snyder, 'Introduction to Modern Liquid Chromatography,' Wiley, New York, 1974; (*b*) L. R. Snyder, 'Principles of Adsorption Chromatography,' Dekker, New York, 1968.

TABLE 4

Aryl 2-azidophenyl sulphones

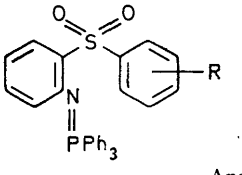
$2\text{-}N_3C_6H_4\cdot SO_2\cdot C_6H_4R$

R	M.p. (°C)	Analyses (%) * C	H	N
2-Me	168	58.0	4.6	14.3
		57.1	4.1	15.4
3-Me	143—144	57.2	4.2	15.3
		57.1	4.1	15.4
4-Me	110—111	56.9	4.3	15.2
		57.1	4.1	15.4
2-OMe	172—173	55.1	4.45	13.25
		54.0	3.8	14.5
3-OMe	121—122	54.3	3.95	13.9
		54.0	3.8	14.5
4-OMe	92—94	54.6	4.1	14.3
		54.0	3.8	14.5
2-Cl	163—164	49.3	2.9	14.2
		49.1	2.75	14.3
3-Cl	137—139	49.4	2.9	14.0
		49.1	2.75	14.3
4-Cl	108—110	49.0	2.8	13.6
		49.1	2.75	14.3
$2\text{-}CF_3$	106—109	49.5	2.7	12.8
		47.7	2.5	12.8
$3\text{-}CF_3$	95—96	47.9	2.4	12.7
		47.7	2.5	12.8
$4\text{-}CF_3$	111—112	48.0	2.6	12.35
		47.7	2.5	12.8
$2,6\text{-}Cl_2$	174—175	45.2	2.5	11.85
		43.9	2.15	12.8
$2,6\text{-}(OMe)_2$	147—148	53.0	4.4	12.3
		52.7	4.1	13.2
$2,4,6\text{-}Me_3$	175—176	59.9	4.8	14.6
		59.8	5.0	14.0
2-Pyridyl	170—171	50.7	3.1	21.8
		50.8	3.1	21.5
4-Bu^t	122—123°	60.9	5.3	13.6
		61.0	5.4	13.3

* For new compounds: upper row 'Found'; lower row 'Required'.

TABLE 5

Aryl 2-(triphenylphosphoranylideneamino)phenyl sulphones



R	Yield (%)	M.p. (°C)	Analyses (%) * C	H	N
2-Me	78	225—226	73.3	5.3	3.2
			73.35	5.2	2.8
2-OMe	41	248—249	70.7	5.1	2.9
			71.1	5.0	2.7
3-OMe	37	208—209	70.8	5.1	2.8
			71.1	5.0	2.7
$2\text{-}CF_3$	41	186	65.9	4.2	2.55
			66.3	4.1	2.5
$2,6\text{-}Cl_2$	39	243—244	63.9	4.0	2.6
			64.1	3.9	2.5
$2,6\text{-}(OMe)_2$	50	221—223	68.9	5.1	2.6
			69.4	5.1	2.5

* For new compounds: upper row 'Found'; lower row 'Required'

to the equilibrium established in the column for each component, and is defined as follows:

$$k' = \frac{\text{quantity of solute in stationary phase}}{\text{quantity of solute in mobile phase}}$$

However, it is more convenient to use the derived equation relating k' to retention volumes or, if the flow is constant, retention times. Thus:[11]

$$k' = \frac{\text{retention volume of peak} - \text{retention volume of unretained peak}}{\text{retention volume of unretained peak}}$$

$$= \frac{\text{retention time of peak} - \text{retention time of unretained peak}}{\text{retention time of unretained peak}}$$

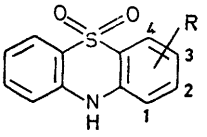
This compensates for long-term variations in flow rate.

Components were identified by comparison of k' for each peak in the mixture with k' for a pure component. It was also necessary to compensate for changes in the activity of the column (and hence in the values of k') with time. To overcome this, $k'(1)$ at time t_1 and $k'(2)$ at time t_2 for the internal standard were noted. Corrected k' values for each component at time t_2 could then be obtained by multiplication of $k'(2)$(component) by the factor $k'(1)\ k'(2)$(marker).

Solvents and markers. The mobile phase was hexane, with various amounts of modifying, more polar, components added. Hexane was purified by passage through a silica column which removed water and u.v.-absorbing impurities. Ethyl acetate was AnalaR grade having a water content limit of 0.05%, and water (0.6% w/v) was added before use. Dioxan was purified according to the method of Vogel [12] then distilled from lithium aluminium hydride. Water (0.6% v/v) was added before use. Water was added because it has been found empirically [11b] that this enables retention times to be stabilised. A small amount of water blocks the most active sites on the alumina whereas the absence of water leads to very poor resolution. On the other hand too much water leads to deactivation of the column and very short retention times. In practice 0.6% v/v water content is found to give good results. For most analyses a 10 cm column slurry packed with Spherisorb A7.5Y alumina was used.

TABLE 6

Phenothiazine 5,5-dioxides



R	Yield (%)	M.p. (°C)	Lit. M.p. (°C)	Ref.	Analyses (%) * C	H	N
1-Me	67	251			63.7	4.6	5.6
					63.65	4.5	5.7
2-Me	10	274—275			63.55	4.6	5.55
					63.65	4.5	5.7
3-Me	12	284—285			63.4	4.5	5.5
					63.65	4.5	5.7
4-Me	48	267—268			63.5	4.35	5.6
					63.65	4.5	5.7
1-OMe	71	208—210			60.05	4.3	5.4
					59.8	4.2	5.4
2-OMe	35	223—224			59.9	4.3	5.05
					59.8	4.2	5.4
3-OMe	60	234—236			59.95	4.4	5.3
					59.8	4.2	5.4
4-OMe	13	>316			59.7	4.4	5.2
					59.8	4.2	5.4
1-Cl		211—212			54.5	3.0	5.2
					54.2	3.0	5.3
2-Cl	78	275	276—277	*a*	54.4	2.94	5.56
					54.2	3.0	5.3
3-Cl	69	293	295—297	*b*			
4-Cl		284—286	283—284	*c*			
1-CF_3	89	194—196			52.1	2.8	4.5
					52.2	2.7	4.7
2-CF_3	56	274—276	268—270	*d*			
3-CF_3	30	315—317			52.4	3.45	4.1
					52.2	2.7	4.7
4-CF_3	22	275—278	275—276	*e*			
2-Bu^t		226—227			66.6	5.9	4.7
					66.85	6.0	4.9
3-Bu^t		229—230			66.6	5.9	4.75
					66.85	6.0	4.9
H	93	264—265	257—259	*e*			

* For new compounds: upper row ' Found '; lower row ' Required '.

[a] A. Wunderlich and A. Stark, *Pharmazie*, 1920, **20**, 8. [b] H. L. Yale, *J. Amer. Chem. Soc.*, 1955, **77**, 2270. [c] H. Kano and M. Fujimoto, *Pharm. Bull. (Japan)*, 1946, **5**, 389. [d] H. L. Yale, F. Sowinski, and J. Bernstein, *J. Amer. Chem. Soc.*, 1957, **79**, 4375. [e] A. Bernthsen, *Ber.*, 1906, **39**, 1804.

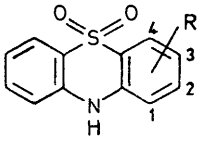
[12] A. I. Vogel, ' Practical Organic Chemistry,' 3rd edn., Longman, London, 1959.

Methylphenothiazine 5,5-dioxides and the corresponding amines were determined by using hexane–ethyl acetate (75 : 25). Products from the decomposition of 2-azidophenyl 2- and 3-methylphenyl sulphones were analysed by using *p*-nitroaniline (*k'* 4.40) as standard. Products from the decomposition of 2-azidophenyl 4-methylphenyl sulphone were analysed by using *m*-nitroaniline (*k'* 1.93) as standard. Methoxyphenothiazine 5,5-dioxides (standard 2-chlorophenothiazine 5,5-dioxide, *k* 3.17) and 2- and 3-t-butylphenothiazine 5,5-dioxides (standard *p*-nitroacetanilide, *k'* 2.50) were determined by using hexane–ethyl acetate (65 : 35), as were most of the chlorophenothiazine 5,5-dioxides and their associated amines (standard *p*-nitroaniline, *k'* 2.50). However, 1-chlorophenothiazine 5,5-dioxide and 2-aminophenyl 2-chlorophenyl sulphone were determined by using hexane–dioxan (75 : 25) (standard *p*-nitroaniline, *k'* 6.76), and while 1-chlorophenothiazine 5,5-dioxide and 2-aminophenyl 3-chlorophenyl sulphone obtained from the decomposition of 2-azidophenyl 3-chlorophenyl sulphone in decalin were determined by using hexane–ethyl acetate (75 : 25) (standard *p*-nitroaniline, *k'* 4.40). Products obtained from the decomposition of 2-azidophenyl 2,6-dichlorophenyl sulphone were analysed using a 15 cm column slurry packed with Spherisorb A5Y alumina. The mobile phase was hexane–ethyl acetate (65 : 35) and the standard was *p*-nitroaniline (*k'* 2.50). Trifluoromethylphenothiazine 5,5-dioxides and their associated amines were determined by using the same system but the standard was *m*-nitroacetanilide (*k'* 2.96). In order to separate 1-trifluoromethylphenothiazine 5,5-dioxide and 2-aminophenyl 3-trifluoromethylphenyl sulphone, hexane–ethyl acetate (85 : 15) was used as the mobile phase.

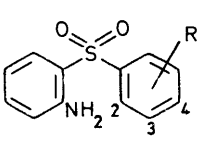
Relevant *k'* values are given in Table 7.

TABLE 7

H.s.l.c. analysis of phenothiazine 5,5-dioxides and 2-aminophenyl aryl sulphones: *k'* values



R	1-	2-	3-	4-	H
Me	7.13	10.84	10.30	8.65	
OMe	4.22	10.46	6.26	18.20	
Cl	1.34	3.12	6.40	9.95	6.75
CF_3	0.54	1.39	3.88	6.44	
Bu^t		3.30	4.30		



R	2-	3-	4-
Me	1.52	1.64	1.73
OMe	2.45	1.34	1.76
Cl	1.41	0.91	0.80
CF_3	0.96	0.58	0.48
Bu^t			0.82
2,6-Cl_2	1.16		

Thermolysis of Aryl 2-Azidophenyl Sulphones—(i) *In decalin.* The aryl 2-azidophenyl sulphone (0.3 g) was added in portions over 30 min under nitrogen to stirred decalin (25 ml) maintained at 150—160 °C. The mixture was then boiled under reflux (192 °C) under nitrogen with stirring for 4h. The decalin was evaporated off under reduced pressure and the residue chromatographed on deactivated alumina (elution with methanol) to give the mixed phenothiazine 5,5-dioxides. Control experiments established that all phenothiazine 5,5-dioxides were recovered by this method. The eluate was made up to a standard volume and a known amount of the internal standard was added. An aliquot portion was evaporated and the residue dissolved in the appropriate mobile phase. In some cases the residue from the evaporation of the decalin was not chromatographed but simply analysed as it was, after addition of the internal standard. The results are summarised in Table 8, in which the proportion of each isomer is shown as a percentage of the total yield of phenothiazine 5,5-dioxide.

Control experiments were carried out to establish the extent, if any, of decomposition of each isomeric phenothiazine 5,5-dioxide under the conditions of thermolysis of the parent azides and resulting work-up. The results given in Table 8 are corrected for any such decomposition which occurred. We estimate the accuracies of the isomer ratios to be *ca.* ±5%.

Thermolysis of 2-azidophenyl 2-pyridyl sulphone and 2-azidophenyl 2,6-dimethoxyphenyl sulphone in decalin and in triethyl phosphate and the thermolysis of 2-azidophenyl 2,4,6-trimethylphenyl sulphone in decalin gave no identifiable products. Similarly the deoxygenation of 4-chlorophenyl 2-nitrophenyl sulphone by triethyl phosphite in boiling cumene gave no identifiable products. H.s.l.c. showed that neither 2- nor 3-chlorophenothiazine 5,5-dioxide was present.

(ii) *In triethyl phosphate.* A solution of the azide in triethyl phosphate (12 mg ml^{-1}) was placed in a vessel surrounded by a bath of decalin. This bath was slowly heated over 30 min until the decalin was boiling and the azide solution was then stirred, under nitrogen, at the b.p. of decalin (192 °C) for 4h. The mixture was worked up as (i) and the results are summarised in Table 8, corrected, *via* control experiments, for loss due to any decomposition of the resulting phenothiazine 5,5-dioxides.

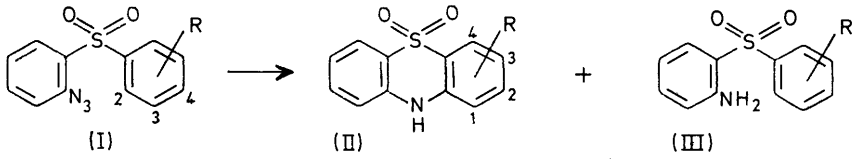
DISCUSSION

The results of thermal decompositions in decalin and in triethyl phosphate of 2-azidophenyl 2-, 3-, and 4-methylphenyl sulphones and each of the isomeric chloro-, methoxy-, and trifluoromethyl analogues together with the 4-t-butyl- and 2,6-dichloro-derivatives are summarised in Table 8. In each case substituted phenothiazine 5,5-dioxides were obtained in 25—90% yields together with smaller (0—30%) amounts of the corresponding 2-aminophenyl aryl sulphides. The products were identified by comparison with authentic materials synthesised by oxidation of the known phenothiazines or by reduction of the corresponding aryl 2-nitrophenyl sulphides. Thermolyses of the corresponding 2-pyridyl, 2,6-dimethoxyphenyl, and 2,4,6-trimethylphenyl azidosulphones gave no identifiable products.

As to quantitative analysis of the mixtures of isomeric phenothiazine 5,5-dioxides, their involatile nature

TABLE 8

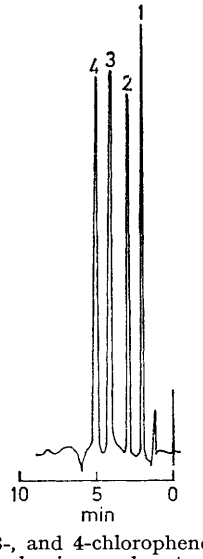
H.s.l.c. analyses of the products of thermolysis of 2-$N_3C_6H_4{\cdot}SO_2{\cdot}C_6H_4R$ in $(EtO)_3PO$ or decalin at 192 °C



R in (I)	Solvent *	(II) Yield (%)	Isomer ratios (%) of (II) 1-R	2-R	3-R	4-R	(III) (%)	Accountance (%)
2-Me	D	33	64			36	6	39
	P	54	77			23	2	56
3-Me	D	54	62	10	20	8	11	65
	P	84	55	17	16	12	3	87
4-Me	D	54		70	30		10	64
	P	68		57	43		6	74
2-OMe †	D	30	100			0	0	31
	P	33	98			2	2	36
3-OMe	D	56	41	3	53	3	12	68
	P	79	48	10	25	17	8	87
4-OMe	D	47		27	73		12	59
	P	82		25	75		3	85
2-Cl †	D	63	94			6	7	91
	P	40	100			Trace	2	48
3-Cl	D	62	32	8	56	4	20	82
	P	62	8	9	81	2	4	66
4-Cl	D	30		59	41		20	50
	P	44		32	68		9	53
2-CF_3	D	26	77			23	9	35
	P	34	84			16	3	37
3-CF_3	D	49	25	23	26	26	21	70
	P	22	45	14	29	12	4	26
4-CF_3	D	28		84	16		30	58
	P	21		77	23		26	47
4-Bu^t ‡	D	50		58	42		23	73
	P	67		43	57		10	77
2,6-Cl_2	D	29	100			0	0	29
	P	14	100			0	0	14
2,6-Cl_2 §	D	23	96			4	6	29
	P	12	99			1	0	12

* D, decalin; P, $(EtO)_3PO$. † Phenothiazine 5,5-dioxide was formed: 2-OMe gave 1% (D and P); 2-Cl gave 21% (D) or 6% (P). ‡ Uncorrected results. 2- and 3-t-Butylphenothiazine 5,5-dioxides were separated and isolated by preparative-scale h.s.l.c. The 3-isomer was identified by comparison with an authentic sample, and the 2-isomer by n.m.r. and elemental analysis. § At 152 °C.

rendered g.l.c. useless and only an unacceptably crude estimate could be obtained by n.m.r. or i.r. spectroscopy.



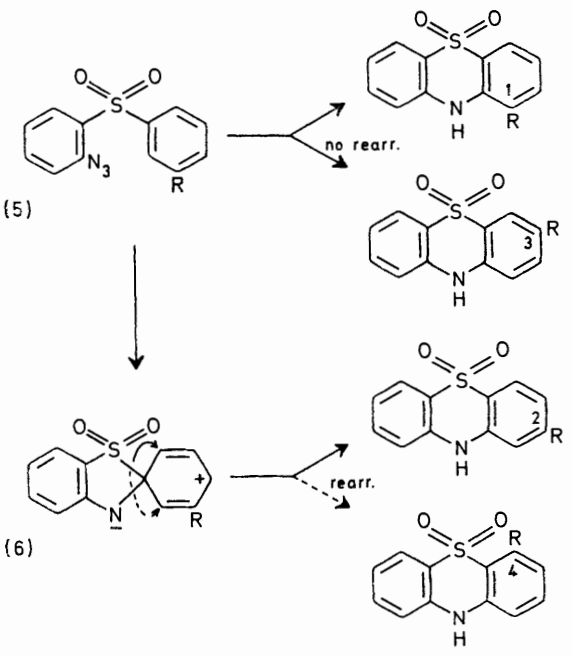
Separation of 1-, 2-, 3-, and 4-chlorophenothiazine 5,5-dioxides on 8μ Spherisorb alumina; eluant 1 : 1 hexane–dioxan; column 115 × 5 mm; u.v. detector

Very good results were obtained by h.s.l.c., however, including, for example, the resolution of the four monochlorophenothiazine 5,5-dioxides (Figure). The accuracy of the isomer ratios, determined by h.s.l.c., is ±2%, but the overall accuracy of the results given in Table 8 is diminished to ±5%, of each value, because the values incorporate a correction factor, established from control experiments, necessary because it was observed that the first formed phenothiazine 5,5-dioxides slowly decomposed under the reaction conditions.

Decompositions in Decalin.—All decompositions proceeded smoothly at 192 °C over 4 h, *i.e.* at about the normal rate of thermolysis of azides to nitrenes and, as will be seen, our results are consistent with cyclisation involving electrophilic attack by a nitrene, to give various phenothiazine 5,5-dioxides. In accord with this is the formation of smaller amounts of amines, produced by hydrogen abstraction.

With respect first to thermolyses of 2-azidophenyl 3-substituted phenyl sulphones (5) (Scheme 2), in theory, all four isomeric monosubstituted phenothiazine 5,5-dioxides could result, the 2- and 4-isomers by rearrangement *via* 1,2-SO_2-shift of a first formed spirodiene

intermediate (6),* and the 1- and 3-isomers by direct insertion into the free *ortho*-positions in the receptor ring. Thus, in this case, the key step leading to rearrangement products is attack by the electrophilic



SCHEME 2

nitrene at the 1′-position, *i.e. meta* to the 3-substituent R, whereas that for products formed without rearrangement is attack *ortho* or *para* to the 3-substituent R. Thus, on the reasonable assumption that the electronic effects of the sulphonyl group at the relevant positions will be comparable, it should follow that those groups which direct *ortho*/*para* in electrophilic aromatic substitution, such as Me, MeO, and Cl, should lead to phenothiazine 5,5-dioxides largely without rearrangement, whereas the *meta*-directing group CF_3 should cause more rearrangement. The results (Table 9) are in accord with this prediction.

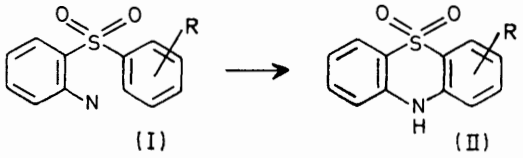
Similar qualitative conclusions can be drawn from cyclisations of 2-nitrenophenyl 4-substituted phenyl sulphones, the possible reaction pathways being outlined in Scheme 1 (X = SO_2, Z = N). The key step leading to the rearrangement product [the 3-substituted phenothiazine dioxide (2)] is attack by the electrophilic nitrene *para* to the substituent Y, whereas the 2-substituted phenothiazine dioxide (3) would arise by attack *meta* to the substituent. In accord with this, the *meta*-directing CF_3 group leads to only 16% rearrangement, whereas the *ortho*/*para*-directing Me, Bu^t, MeO, and Cl groups lead to higher proportions of rearrangement product (Table 9).

* The reactions may also be depicted in terms of the more strained azanorcaradiene species (4) (Scheme 1; X = SO_2). We adhere to (6) for simplicity of discussion for there is no direct evidence for either form and the main argument is unaffected in either event.

However, such a rationalisation of substituent effects can be of only qualitative value. It would be unsound, for example, to ignore proximity effects in this intramolecular reaction. Although crystal data on the phenothiazine dioxide system are not available it can be estimated from Toussaint's crystal data on 4,4′-dibromodiphenyl sulphone,[13] if we assume a C–N bond

TABLE 9

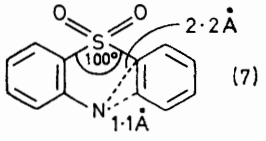
Rearrangement during cyclisation of aryl 2-nitrenophenyl sulphones



R in (I)	Rearrangement (%) in (II) * D	P
2-OMe	100	98
2-Me	64	77
2-Cl	94	100
2-CF_3	77	84
3-OMe	6	27
3-Me	18	29
3-Cl	12	11
3-CF_3	49	26
4-OMe	73	75
4-Me	30	43
4-Bu^t	42	57
4-Cl	41	68
4-CF_3	16	23
2,6-Cl_2	96	99

* D, in decalin; P, in $(EtO)_3PO$.

distance in 2-nitrenophenyl phenyl sulphone (7) equal to that in phenothiazine (1.4 Å), that the nitrene centre is only 1.1 Å distant from the *ortho*-positions in the receptor ring (*i.e.* positions leading to products without rearrangement). On the other hand the corresponding distance to the 1′-position (leading to rearrangement products) is

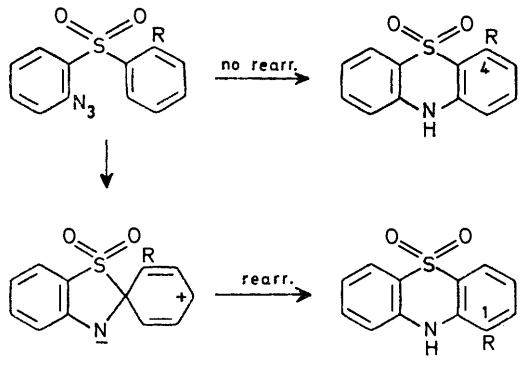


2.2 Å. These are minimum distances based on assumption of a planarity which is impossible as a result of the presence of the *ortho*-hydrogen atom; nevertheless it is evident that reaction leading to products without rearrangement is not likely to be hampered on steric grounds, to say the least.

The products from thermolysis of 2-azidophenyl 2-substituted phenyl sulphones (Scheme 3) are mainly those arising from rearrangement (1-substituted phenothiazine dioxides) (Table 9), but the sterically crowded reaction site renders comparison with the 3- and 4-substituted analogues difficult. From similar arguments, *ortho*/*para*-directing groups would be expected to favour

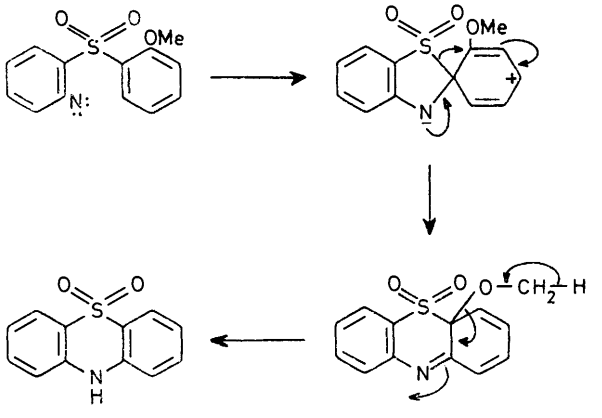
[13] J. Toussaint, *Bull. Soc. chim. belges*, 1945, **54**, 319.

rearrangement products as observed, but the *meta*-directing CF_3 group also gives mainly rearrangement product (77%). In this connection the statistical effect of only one free *ortho*-position (leading to non-rearrangement) may lead to greater attack at the 1′-position.



SCHEME 3

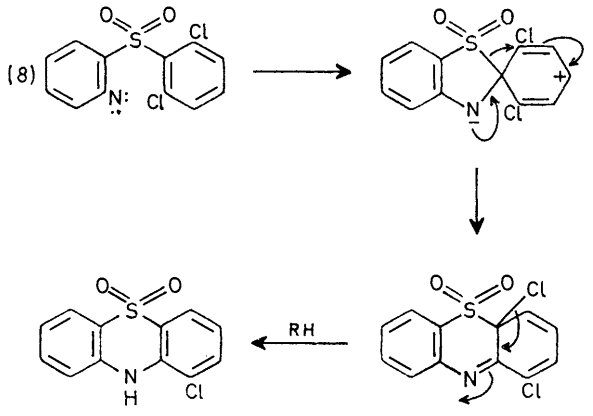
Reactions of 2-methoxyphenyl and 2-chlorophenyl azido-sulphones is also complicated by demethoxylation and dechlorination to give phenothiazine 5,5-dioxide, presumably as shown in Scheme 4, which recalls demethoxylation and dechlorination of related methoxyphenyl- and chlorophenyl-2-nitrenophenyl sulphides.[5]



SCHEME 4

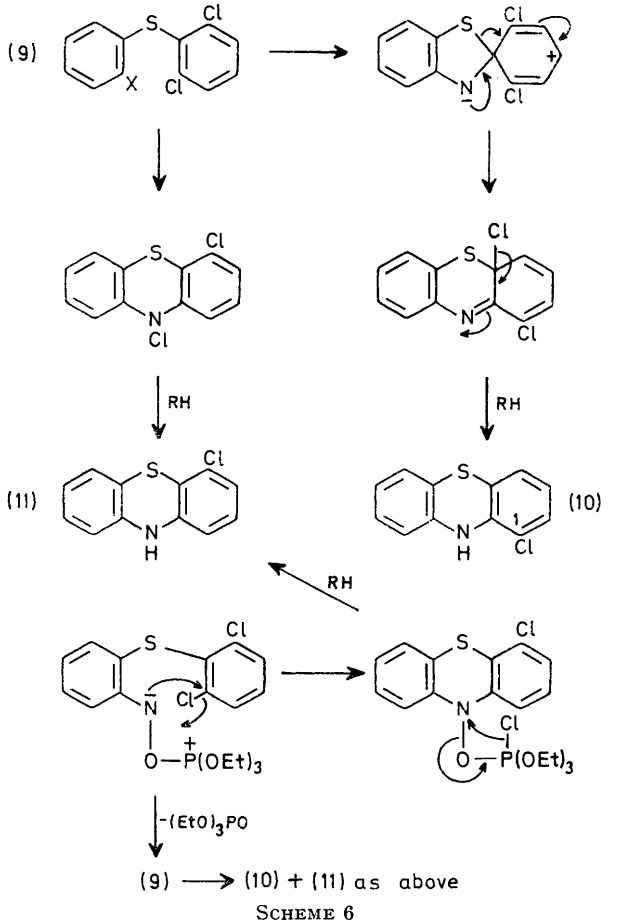
Thermolysis of 2-azidophenyl 2,6-dichlorophenyl sulphone (8) gave almost exclusively 1-chlorophenothiazine 5,5-dioxide, with a small amount of the 4-isomer. This corresponds to almost exclusive rearrangement (Table 9, Scheme 5), presumably because the bulky *ortho*-chloro-atoms block direct attack of the nitrene at the *ortho*-positions.

Decompositions in Triethyl Phosphate.—The rationale of these experiments is as follows: Cadogan and Kulik [5] explained the observations that whereas thermolysis of 2-azidophenyl 2,6-dichlorophenyl sulphide *via* the nitrene (9; X = N) gave 1-chlorophenothiazine (10) (40%) and the 4-isomer (11) (5%), deoxygenation of the corresponding nitro-compound (9; X = NO_2) by triethyl phosphite gave, in addition to the 1-isomer (35%), a higher yield of the 4-isomer (45%). These workers



SCHEME 5

attributed this difference to the intermediacy of a nitrenoid species $ArN\text{–}O\text{–}\overset{+}{P}(OEt)_3$ (12) in the latter reaction (Scheme 6). Holliman and his co-workers [4]



SCHEME 6

confirmed these results and went on to make a suggestion which, if correct, is of considerable mechanistic signifi-

cance, *viz.* that the same nitrenoid species (12) could arise *via* attack of the nitrene on triethyl phosphate:

$$ArN_3 \longrightarrow ArN \xrightarrow{(EtO)_3PO} Ar\tilde{N}-O-\overset{+}{P}(OEt)_3$$

In qualitative accord with this they showed that thermolysis of 2-azidophenyl 2,6-dichlorophenyl sulphide in triethyl phosphate gave 1-chloro- (44%) and 4-chlorophenothiazine (23%).

If this explanation is correct it might therefore be expected that thermolysis of 2-azidophenyl phenyl sulphones in triethyl phosphate would similarly proceed *via* the species $Ar\tilde{N}-O-\overset{+}{P}(OEt)_3$ which, being markedly different from nitrenes produced on thermolysis in decalin, would give different ratios of rearranged products. Tables 8 and 9 summarise the results and show that in general such differences are small and in most cases are within the experimental error. We conclude therefore that the phenomenon observed by Holliman does not extend in general to the diaryl sulphone system, even in what, from the foregoing, might be expected to be the most favourable case, that of 2-azidophenyl 2,6-dichlorophenyl sulphone, where the close proximity of the $\tilde{N}-O-\overset{+}{P}(OEt)_3$ group might have been expected to lead to direct substitution of an *ortho*-chlorine atom without rearrangement to give 4-chlorophenothiazine 5,5-dioxide, by analogy with the corresponding sulphide (Scheme 6). Nevertheless, in a few cases there are differences which remain to be explained (Table 9), in this way or another. Finally, the reaction of triethyl phosphite in boiling cumene with 2-nitrophenyl 4-chlorophenyl sulphone gave no chlorophenothiazine dioxides, which are stable under these conditions. Tarry products, so far intractable, were obtained.

We thank the S.R.C. and the Carnegie Trust for the Universities of Scotland for support. We also thank Miss E. Ramage, who carried out preliminary experiments on the cyclisation of 2-azidophenyl 4-chlorophenyl sulphone, and Dr. G. Abbot for help with the preparation of some standard compounds.

[6/106 *Received*, 16*th January*, 1976]