

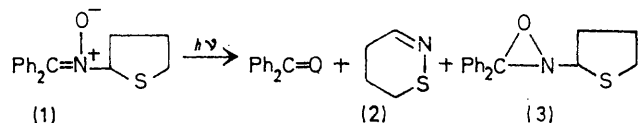
A Thermal Reaction of 2-(Thiolan-2-yl)oxaziridines and Related Compounds. Evidence for Neighbouring Group Participation in the Displacement of Oxygen by Sulphur at Nitrogen

By Wynford M. Leyshon and David A. Wilson,* University College, Cathays Park, Cardiff CF1 1XL

3,3-Diphenyl-2-(thiolan-2-yl)oxaziridine decomposes thermally by a first-order reaction, forming benzophenone and 5,6-dihydro-4*H*-1,2-thiazine. The entropy of activation (average ΔS^\ddagger -16 cal K^{-1} mol $^{-1}$), solvent effects, and other results point to a mechanism involving rate-determining intramolecular attack by sulphur on the nitrogen of the oxaziridine ring. Other sulphur-containing oxaziridines behave in like manner.

IN our report of the photochemical reactions of sulphur-containing cyclic nitrones,¹ we described the reaction of the nitron (1) to give benzophenone, 5,6-dihydro-4*H*-1,2-thiazine (2), and the oxaziridine (3). It was also reported there that the oxaziridine product (3) itself underwent a thermal reaction to form benzophenone and the reduced thiazine (2). We now describe our kinetic study of this reaction, and those of related oxaziridines.

The crystalline oxaziridine reacted cleanly, when dissolved in a variety of solvents, to give only the two products indicated. No others were detected by g.l.c., and the good kinetic results also argue for only one reaction taking place. Rates of reaction were followed by



measuring the increase with time in u.v. absorption at 250 nm of samples taken directly from the heated stock solutions. This absorption was mainly due to the benzophenone (ϵ ca. 18 000) but contained a contribution from the reduced thiazine (ϵ ca. 2 800 at 250 nm). This technique was limited to solvents sufficiently transparent at this wavelength in 1 mm cells. An attempt was made to follow the reaction by estimation of unchanged oxaziridine, using its reaction with potassium iodide in propanol-acetic acid.² The method gave inconsistent results because the oxaziridine, as it later transpired, decomposed rapidly, by the mechanism that we wished to study, in solvents of such polarity. The rate constants for reaction were determined in a number of solvents over a range of temperatures. These results, and the derived energies and entropies of activation, are recorded in Table 1.

The effect of solvent on the rate of reaction was clearly demonstrated by measuring, or extrapolating, the rate constants at 60 °C for a wider range of solvents. These are recorded in Table 2. Two features are evident. As solvent polarity increases, as measured by dielectric constant, so does the rate of reaction. However, the protic solvents, alcohols, increase the rate by an additional factor, readily seen in a plot of log (relative rate) against dielectric constant, shown in Figure 1. A plot of log (relative rate) against the Winstein-Grunwald *Y* values³

for the alcohol solvents gives a straight line, slope $m = 0.52$ (Figure 2).

TABLE 1

Kinetic results for reaction of the oxaziridine (3)

Solvent	$10^6 k/s^{-1}$ ^a	Temp. (°C)	$E_a/kcal$ mol $^{-1}$ ^b	$\Delta S^\ddagger/cal$ K $^{-1}$ mol $^{-1}$ ^b (60 °C)			
Dodecane	5.4	83.4	21.6 ± 0.8	-19.7 ± 2.2			
	11	91.7					
	23	101.2					
	54	109.5					
	66	115.6					
	93	121.1					
	Bis-(2-methoxyethyl) ether	3.2			63.3	23.0 ± 0.5	-13.0 ± 1.3
9.2		73.6					
9.6		75.1					
20		81.7					
24		84.9					
61		95.0					
87		98.9					
100		101.3					
Hexanenitrile		3.3	55.4	21.5 ± 0.5	-15.9 ± 1.4		
		7.5	62.8				
	19	74.3					
	43	82.9					
	91	92.0					
Ethanol ^c	19	31.4	18.7 ± 1	-16.5 ± 3			
	51	41.3					
	120	51.4					
Methanol	1.3	0.0	18.7 ± 0.6	-14.6 ± 2.1			
	7.9	16.0					
	24	27.0					
	51	33.0					
	140	42.0					

^a Rate constants quoted are the average of two or more determinations within 10% of each other. ^b Estimated standard deviations given. ^c Errors quoted in this solvent are greater than computed e.s.d.s to allow for the small temperature range that it was possible to study.

TABLE 2

Rate constants at 60° for reaction of the oxaziridine (3)

Solvent	Dielectric constant (25 °C)	$10^6 k_{60}/s^{-1}$ ^a	$k_{60}^{rel.}$	$\log k_{60}^{rel.} Y^b$
1, Dodecane	2.0	6.8	1	0
2, Bis-(2-methoxyethyl) ether	7.2	25	3.7	0.57
3, Hexanenitrile	17.3	55	8.1	0.91
4, Acetonitrile	37.5	170	25	1.40
5, <i>t</i> -Butyl alcohol	12.5	610	90	$1.95-3.26$
6, Propan-2-ol	19.9	1 000	147	$2.17-2.73$
7, Ethanol	24.6	3 200	470	$2.67-2.03$
8, Methanol	32.7	6 400	940	$2.97-1.09$

^a See Table 1. ^b Ref. 3.

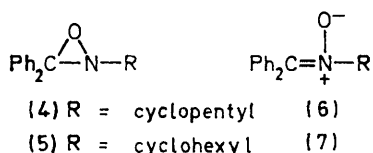
The sulphur atom of the thiolanyl ring is a necessary structural feature for this reaction to take place. The carbocyclic oxaziridines (4) and (5) rearrange thermally

¹ W. M. Leyshon and D. A. Wilson, preceding paper.

² S. Siggia, 'Quantitative Organic Analysis via Functional Groups,' Wiley, New York, 1949, p. 100.

³ E. Grunwald and S. Winstein, *J. Amer. Chem. Soc.*, 1948, **70**, 846.

to their isomeric nitrones (6) and (7).⁴ This instructive comparison, demonstrating the role of sulphur, is shown in Table 3.



The evidence so far presented leads to the mechanism shown in the Scheme. The observed products, the substantial negative entropy of activation resulting from a

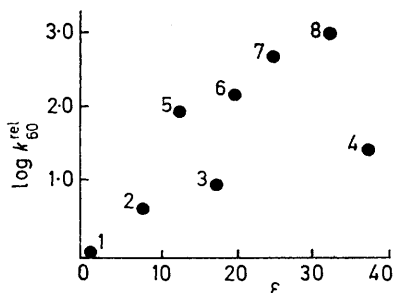


FIGURE 1 $\log k_{60}^{\text{rel}}$ against dielectric constant (Σ) for reaction of the oxaziridine (3). Solvents are numbered as in Table 2.

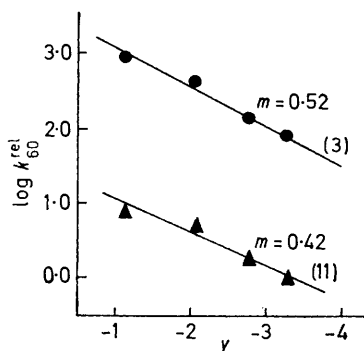


FIGURE 2 $\log k_{60}^{\text{rel}}$ against Winstein-Grunwald Y values for reactions of the oxaziridines (3) and (11). The two series of rate constants are given relative to different rate constants (see Tables 2 and 5)

TABLE 3
Half-lives for thermal reactions of oxaziridines

Oxaziridine	$t_{1/2}$ at 111 °C	Products	Solvent
(3)	5.2 min	$\text{Ph}_2\text{C}=\text{O} + \text{Thio-imine (2)}$	Bis-(2-methoxyethyl) ether
(11)	11.5 min	$\text{Ph}_2\text{C}=\text{O} + \text{Thio-imine (13)}$	
(4)	96 h	Nitrone (6)	[² H ₆]-benzene
(5)	55 h	Nitrone (7)	

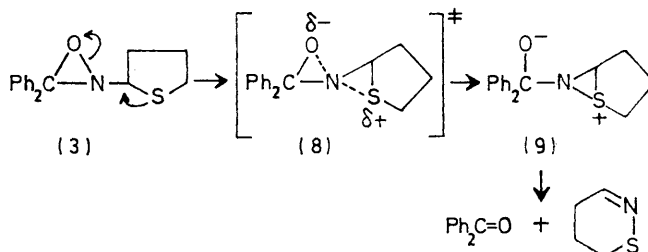
transition state (8) more ordered than the reactant, the role of solvent in stabilising a transition state more polar than reactant, and the role of sulphur are all explained by this mechanism with the first step being rate-determining.

⁴ W. M. Leyshon and D. A. Wilson, *J.C.S. Perkin I*, 1975, 1920.

⁵ S. Winstein, E. Grunwald, and H. W. Jones, *J. Amer. Chem. Soc.*, 1951, **73**, 2700.

⁶ A. Streitwieser, 'Solvolytic Displacement Reactions,' McGraw-Hill, New York, 1962, p. 109; B. Capon, *Quart. Rev.*, 1964, **18**, 45; K. D. Gunderman, *Angew. Chem. Internat. Edn.*, 1963, **2**, 674; S. Ikegami, T. Asai, K. Tsuneoka, S. Matsumura, and S. Akaboshi, *Tetrahedron*, 1974, **30**, 2087.

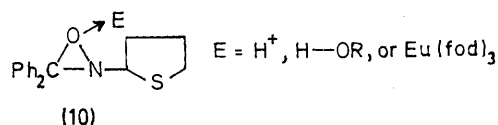
The Winstein-Grunwald correlation ($m = 0.52$) is similar to that found⁵ for the solvolyses of *trans*-2-bromo- and *trans*-2-methoxycyclohexyl bromomethane-sulphonates ($m = 0.70$ and 0.49) where neighbouring



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group participation by bromine or oxygen in a three-membered ring obtains. The analogy between these reactions and the one now described should not be pressed too far, for on the one hand a bromine or oxygen nucleophile attacks an electrophilic carbon, and on the other a sulphur nucleophile attacks an electrophilic nitrogen, but the parallel in solvent effect is striking.

We also find that the reaction of oxaziridine (3) in acetic acid is too fast to be measured, in that reaction is substantially complete at room temperature by the time the compound has dissolved and the u.v. spectrum has been taken. Additionally, when the oxaziridine (3) in deuteriochloroform was treated with the shift reagent $\text{Eu}(\text{fod})_3$ (0.2 mol. equiv.), the same reaction was complete in 10 min at 33 °C. Electrophilic catalysis shown in (10) makes the nitrogen more readily attacked by the nucleophilic sulphur by weakening the O-N bond.



The ability of sulphur to participate in displacement reactions involving three-membered rings is well documented,⁶ but there are no conclusive examples of the thiaziridinium species such as we visualise as an intermediate (9) in this reaction. However, thiaziridines have been proposed as intermediates in a few reactions.^{7,8} Intermolecular reaction of sulphur nucleophiles with oxaziridines has been suggested⁷ to proceed by way of attack at the ring carbon. Whilst intermolecular nucleophilic attack by sulphur on nitrogen with displacement of halogen is known,⁹ displacement of an oxygen leaving group has only recently been reported,¹⁰ in the reactions of 2,4-dinitrophenoxamine with sulphides and thiols, again intermolecular reactions.

The oxaziridines (11) and (12) react to give the thio-imines (13) and (14) and benzophenone,¹ in clean first-order reactions in a manner entirely analogous to that of

⁷ D. St. C. Black and K. G. Watson, *Austral. J. Chem.*, 1973, **26**, 2159.

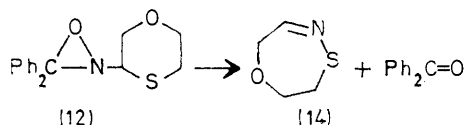
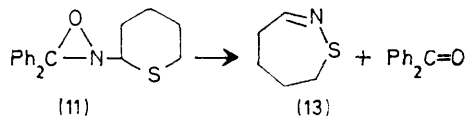
⁸ M. Komatsu, Y. Ohshiro, K. Yasuda, S. Ichijima, and T. Agawa, *J. Org. Chem.*, 1974, **39**, 957.

⁹ E. Vilsmaier and W. Sprügel, *Tetrahedron Letters*, 1972, 625.

C. R. Johnson, C. C. Bacon, and W. D. Kingsbury, *ibid.*, p. 501.

¹⁰ S. Oae and F. Yamamoto, *Tetrahedron Letters*, 1973, 5143.

the oxaziridine (3). The kinetic results for these compounds are given in Tables 4 and 5. A plot of log (relative rate) for oxaziridine (11) against the Winstein-Grunwald Y values for the alcohol solvents, gives a



straight line, slope $m = 0.42$ (Figure 2). In all the solvents used, the thiolanyloxaziridine (3) reacted faster than the thiacyclohexyloxaziridine (11), but only by a relatively small factor.

The product-forming step or steps remain a matter for speculation, but conrotatory ring opening, followed by

TABLE 4

Kinetic results for reaction of the oxaziridines (11) and (12)

	$10^3 k/s^{-1}$ ^a	Temp. (°C)	$E_a/kcal\ mol^{-1}$ ^b	$\Delta S^\ddagger/cal\ K^{-1}\ mol^{-1}$ ^b (60 °C)
(11) in bis-(2-methoxyethyl) ether	3.8	70.2	20.7 ± 0.6	-20.5 ± 1.7
	11	80.0		
	22	91.0		
	47	100.0		
	100	111.0		
(11) in propan-2-ol	4.0	40.1	19.2 ± 0.4	-19.6 ± 1.1
	10	50.2		
	26	60.1		
	67	71.0		
	130	80.0		
(12) in bis-(2-methoxyethyl) ether	1.3	71.2	24.6 ± 0.6	-11.4 ± 1.6
	6.0	83.7		
	11	91.0		
	28	101.4		
	51	109.2		
	90	115.6		
	130	121.3		

^{a, b} See Table 1.

TABLE 5

Rate constants at 60 °C for reaction of the oxaziridine (11)

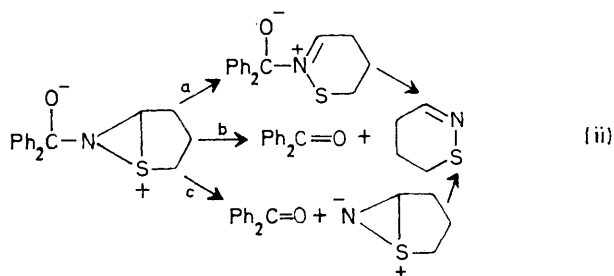
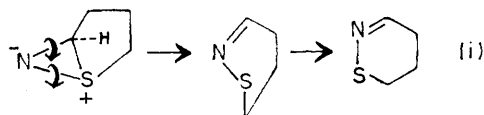
Solvent	$10^3 k_{60}/s^{-1}$ ^a	$k_{60}^{rel.}$	$\log k_{60}^{rel.}$	$\frac{k_{60}\ \text{for}\ (3)}{k_{60}\ \text{for}\ (11)}$
2, Bis-(2-methoxyethyl) ether	1.7			1.5
4, Acetonitrile	4.0			4.3
5, t-Butyl alcohol	13	1.0	0	4.7
6, Propan-2-ol	26	2.0	0.30	3.8
7, Ethanol	64	4.9	0.69	5.0
8, Methanol	120	9.2	0.96	5.3

^a See Table 1.

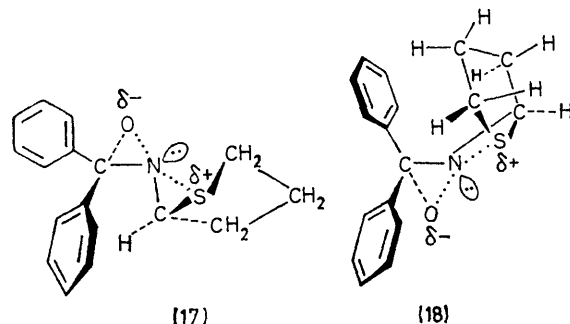
rotation about the N-S bond, or inversion at sulphur [see (i)], should be allowed. This step could precede fission of the C-N bond (iia), be concerted with it (iib), or follow it (iic). In any event, precedent exists for the ring-opening step,¹¹ and for ring opening in a molecule in which a similar change of stereochemistry is needed to give an unstrained product.¹²

¹¹ R. B. Woodward and R. Hoffmann, 'The Conservation of Orbital Symmetry,' Academic Press, New York, 1970, p. 57.

A further point that deserves some discussion is the stereochemistry of the reactant. Inversion at the nitrogen of oxaziridines is slow (ΔG^\ddagger 31.6 kcal mol⁻¹ for 2-isopropyl-3,3-diphenyloxaziridine) and is not significantly solvent-dependent.¹³ Compound (3) should therefore exist as a pair of racemic diastereoisomers [(*RR*) + (*SS*) and (*RS*) + (*SR*)], with chiral centres at N and C-2'. The oxaziridines which we have isolated have given all



appearances of being pure compounds (racemates). Indeed, the clean first-order kinetics observed argues for only one reacting species being involved. Molecular models indicate that while there is little difference in energies to be expected between the oxaziridine diastereoisomers, in the transition state (8) very marked differences would be manifest. The (*RS*)- [or (*SR*)]-isomer would give a transition state (17), while the (*RR*)- [or (*SS*)]-isomer would give transition state (18). In the latter very severe crowding would exist between hydrogens on C-3' and C-4' of the thiolanyl ring and one of the phenyl rings. We think such an arrangement to be unlikely in a reaction that proceeds so readily, even at 0 °C in some solvents. On this basis only, we believe the oxaziridine in these experiments to be the (*RS*) + (*SR*) racemate.



EXPERIMENTAL

The starting materials and products have been described elsewhere.^{1,4}

Kinetic Method.—The oxaziridine (1.2–1.8 mg) was dissolved in the solvent (10 ml) (purified by standard methods)

¹² Ref. 11, p. 51; W. J. Theuer and J. A. Moore, *Chem. Comm.*, 1965, 468.

¹³ J. Bjørge and D. R. Boyd, *J.C.S. Perkin II*, 1973, 1575.

and the solution was placed in a thermostatically controlled oil-bath (± 0.1 °C). Samples were removed at intervals and placed immediately in 1 mm silica cells, and the u.v. absorption was measured. Reactions were followed for two half-lives, and infinity readings were obtained after ten half-lives, or a shorter time at a higher temperature, when optical densities corresponded to $100 \pm 10\%$ reaction. Rate constants were obtained graphically from plots of $\log(O.D._\infty - O.D._t)$ against time. The constants recorded in the Tables are the averages of two or more determinations, agreeing within $\pm 10\%$. Rate constants in bis-(2-methoxyethyl) ether were also measured with the addition of limited amounts of water (up to 50 μ l in 10 ml), but no detectable alteration of rate was observed. By using the experimental

rate constants, rather than the averages listed in the Tables, the Arrhenius activation energies and entropies of activation were calculated for unimolecular reactions in solution,¹⁴ using a computer program that also gave estimated standard deviations.

We thank Dr. M. J. E. Hewlins for help with the computing, and for his original suggestions concerning this mechanism. We also thank the S.R.C. for an award (to W. M. L.) under the C.A.P.S. scheme, in collaboration with Allen and Hanbury Research Ltd.

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¹⁴ A. A. Frost and R. G. Pearson, 'Kinetics and Mechanism,' Wiley, New York, 2nd edn., 1961, p. 98.
