The Mechanisms of the Conversion of Thiophosphoryl Compounds into their Phosphoryl Analogues by Photochemically Excited 3-Methylpyridazine 2-Oxide and by 2-Methyl-3-*p*-nitrophenyloxaziridine; a Comparison

Alan G. Rowley * and John R. F. Steedman
Department of Chemistry, University of Edinburgh, West Mains Road, Edinburgh EH9 3JJ

Reactions of tri-*p*-substituted triarylphosphine sulphides with 3-methylpyridazine 2-oxide, under photolysis, and with 2-methyl-3-*p*-nitrophenyloxaziridine both give the corresponding phosphine oxides. A detailed study and comparison of the two reactions shows that they are mechanistically quite distinct and that it is unlikely that the active oxygenating species generated by photolysis of the *N*-oxide, which attacks the phosphine sulphides, is an oxaziridine. The evidence presented suggests that this species may in fact be ' oxene '.

One of the most satisfactory models for the oxygen atom transfer reactions carried out by the mono-oxygenase enzymes in biological systems is the photolysis of aza-heteroaromatic *N*-oxides. A range of reactions typical of the enzyme system [1-7] *e.g.* epoxidation, aromatic and aliphatic hydroxylations, and *S*-oxidation can be accomplished with this model. Aromatic hydroxylation by this system is accompanied by an NIH shift,[4] an important criterion in assessing the validity of any model for mono-oxygenases.

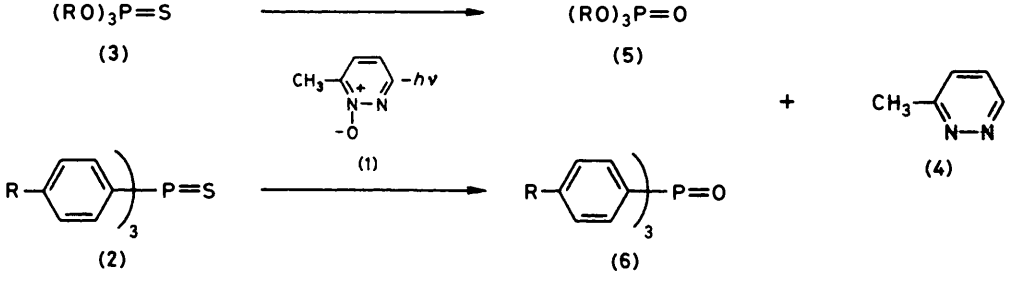
The mammalian hepatic mono-oxygenases are also believed [1,2] to be responsible for the conversion of thiophosphoryl compounds into their phosphoryl analogues. This reaction is of vital importance since, whereas many phosphoryl esters are active acetylcholinesterase inhibitors, the corresponding thiophosphoryl analogues have no *in vitro* anticholinesterase activity and owe their *in vivo* action to metabolic conversion into the phosphoryl analogues.

We have made a preliminary report [8] that this reaction *too* can be modelled by photolysis of 3-methylpyridazine 2-oxide (1) in the presence of triarylphosphine sulphides (2) and of some triesters (3) of phosphorothionic acid (Scheme 1). We now report this work in full and attempt to throw some light on the mechanism of this reaction and on the mechanism of oxygenation by photolysis of heterocyclic *N*-oxides in general.

The nature of the active oxygenating species generated on photolysis of aza-heteroaromatic *N*-oxides is not definitely established. It is generally assumed that the first stage in the reaction is the formation of an oxaziridine and Boyd and his co-workers [7] have recently presented convincing evidence that it is this oxaziridine itself which reacts directly with sulphides when the reaction is used to model *S*-oxidation. In the case of aromatic and aliphatic oxidation, however, it has been recently shown [9] that the photochemical decomposition of aza-heteroaromatic *N*-oxides is unperturbed by the presence, or absence, of an oxygen acceptor and this has been adduced as evidence for the intermediacy, in this reaction, of a free six-electron oxygen species, ' oxene '. It is, of course, entirely possible that the oxaziridine is a precursor to the ' oxene ' but the discussion centres around the question of the nature of the active oxygenating species which actually *attacks* the substrate.

Results and Discussion

Many of the studies of aromatic hydroxylation by photolysis of heteroaromatic *N*-oxides [4,6] have employed pyridine *N*-oxide. The yields of phenolic products from these reactions are low, even when the aromatic is the solvent, and when the substrate is present as a solution the yields are reduced further.[4] Since many of our proposed substrates were solids we were constrained to work with solutions and, as we had suspected, photolysis of a mixture of pyridine *N*-oxide and *OOO*-triethyl phosphorothionate in methylene dichloride solution under a wide variety of conditions gave complete recovery of the thiophosphoryl starting material and only traces (<3%) of pyridine, although the *N*-oxide was completely decomposed, largely to a polymer previously shown to be a poly(acrylonitrile).[10] Replacement of pyridine *N*-oxide by its boron trifluoride adduct gave no improvement even though this is known, in some instances, to be advantageous in oxygen transfer reactions.[11] Photolysis of 3-methylpyridazine 2-oxide in the presence of benzene is reported [5] to give high yields of phenol even when the benzene is present as a dilute solution and we found similarly that this *N*-oxide could be used as an oxygen source in the conversion of methylene dichloride solutions of a variety of trisubstituted triphenylphosphine sulphides and triesters of phosphorothionic acid into their phosphoryl analogues. The reactions were all



Scheme 1.

Table 1. Photolysis of (1) (1.25 mmol) in the presence of (p-$RC_6H_4)_3P{=}S$ (2) in methylene dichloride (100 cm^3)

		Yields (%)	
R	[(2)]/mM	(4)	(6)
Me	25	45	10
	5	35	31
MeO	25	43	9
	5	35	38
H	25	45	7
	5	35	29
Cl	25	38	12
	5	30	35
CO_2Me	25	43	18
	5	35	33

Table 2. Photolysis of (1) (1.25 mmol) in the presence of $(RO)_3P{=}S$ (3) (25mM) in methylene dichloride (100 cm^3)

	Yields (%)	
R	(4)	(5)
Me	43	27
Et	38	22
Ph	43	32

Table 3. Photolysis of (1) (1.25 mmol) in the presence of triphenylphosphine sulphide (2; R = H) in methylene dichloride (100 cm^3)

	Yields (%)		Yield (mmol)
[(2)]/mM	(4)	(6; R = H)	(6; R = H)
50	44	4.3	0.22
25	45	7	0.18
5	35	29	0.15
0.5	34	62	0.03
0	35		

carried out until the N-oxide was completely consumed but in all cases there was unchanged thiophosphoryl compound present at the end of the reaction.

The results are shown in Tables 1 and 2, and their most striking feature is that the yield of 3-methylpyridazine produced is little affected by the nature of the substrate or its concentration. In the specific case of the reaction between 3-methylpyridazine 2-oxide and triphenylphosphine sulphide we investigated the effect of a greater variation in concentration of the substrate and these results, which confirm those of Tables 1 and 2, are shown in Table 3. In addition we investigated the time course of the formation of 3-methylpyridazine in the presence and absence of a triarylphosphine sulphide. The results, shown in the Figure, show quite clearly that the presence or absence of the oxygen acceptor has no effect on the rate of the reaction.

These results all point strongly to the fact that any direct reaction between photoexcited N-oxide or a rearrangement product, such as an oxaziridine, and the thiophosphoryl substrate is most unlikely and could be regarded as circumstantial evidence for the intermediacy of oxene as the active oxygenating species.

Table 3 shows the yields of triphenylphosphine oxide obtained on photolysis of a fixed amount of 3-methylpyridazine 2-oxide in the presence of varying concentrations of triphenyl phosphine sulphide. The variation in the absolute yield of the oxide is only small, changing by less than a factor of two over a ten-fold change in phosphine sulphide concentration, *i.e.* from 50 to 5mM. The penultimate entry in Table 3 shows the result of reduction of the concentration of the oxygen trap by a further factor of ten into a region where the amount of triphenylphosphine sulphide available must be limiting the oxide yield. Although now the absolute yield of triphenylphosphine oxide has, of course, dropped, all the available sulphide was now consumed. This shows that the active oxygenating species is a relatively long-lived entity, able to react with its substrate even when the latter is present at very low concentration. Attempts made by other workers to observe the postulated oxaziridine or similar intermediate in flash photolysis of some pyridazine N-oxides have met with failure but it has been possible from these experiments to estimate that such a species, if it is an intermediate, must have a lifetime of <20 ns before unimolecular decomposition.[12] Oxene on the other hand has clearly no unimolecular reactions open to it and there is no reason, therefore, why, although very reactive, it should not be relatively stable. The lifetimes of the isoelectronic methylene and nitrene are of the order of milliseconds.[13] We therefore feel that our results, which show that the active oxygenating species is a long-lived entity which is free of the parent heterocycle, are well explained in terms of oxene as the intermediate and are not consistent with the active oxygenating species being an oxaziridine or photochemically excited N-oxide.

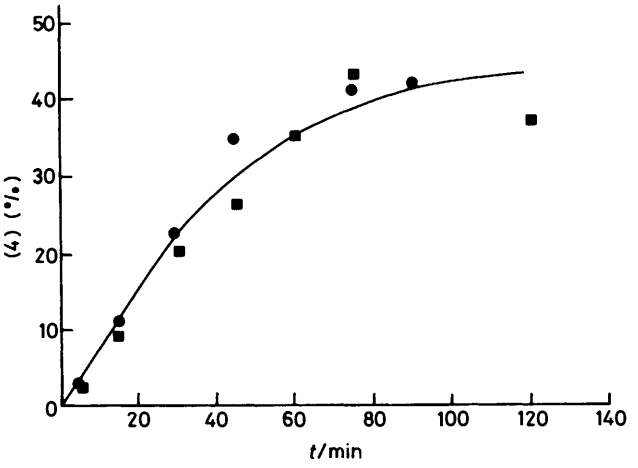


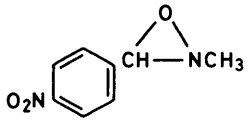
Figure. Yield (%) of (4) as a function of time in the presence of (■) and absence of (●) (2; R = Cl)

A closer scrutiny of the yields of 3-methylpyridazine obtained on reaction of the trisubstituted triphenylphosphine sulphides at different concentrations (see Tables 1 and 3) reveals that there may, however, be a complication to this picture.

When the concentrations of the phosphine sulphides are ≥25mM then the yield of 3-methylpyridazine is generally, within experimental error, 45%. A reduction of the phosphine sulphide concentration to 5mM causes a drop in yield of the parent pyridazine into the region of 35%, but further reductions in phosphine sulphide concentration have no additional effect. This suggests that there *is* a small proportion of the yield of 3-methylpyridazine which is dependent on the oxygen acceptor concentration and is an indication that there may, in fact, be a dual mechanism for oxygen transfer to triaryl phosphine sulphides although this trap-concentration-dependent component of the mechanism is a minor pathway. This minor pathway appears to involve direct interaction of the substrate with photochemically excited N-oxide, or with an intermediate such as an oxaziridine. Interestingly, increasing the concentration of triphenylphosphine sulphide to 50mM did

Table 4. Photolysis of 3-methylpyridazine 2-oxide (1) in the presence of competing triarylphosphine sulphides (2a and b) (equimolar)

(2a)	(2b)	Ratio of products (6a) : (6b)
R = Me	R = MeO	0.91
R = MeO	R = H	1.08
R = Cl	R = H	1.07
R = MeO	R = Cl	1.15



(7)

not increase the 3-methylpyridazine yield significantly above 45%, indicating that trapping of the oxygenating species on the minor mechanistic pathway is optimum at 25mM concentration of trap and confirming that this alternative pathway is, indeed, a minor one.

All the known reactions of the active oxygenating species generated on photolysis of *N*-oxide *e.g.* sulphoxidation, aromatic and aliphatic hydroxylation and epoxidation, would suggest that it is electrophilic and it would seem reasonable that attack on the thiophosphoryl group would similarly be electrophilic. The phosphorus–sulphur double bond of triarylphosphine sulphides is polarised with negative charge at sulphur and the dipole moment increases with electron-supplying substituents in the benzene ring.[14] As would be expected, therefore, the nucleophilic centre of phosphine sulphides, and indeed of thiophosphoryl species in general, is the sulphur and its nucleophilicity is enhanced by electron supply and reduced by electron withdrawal.[15]

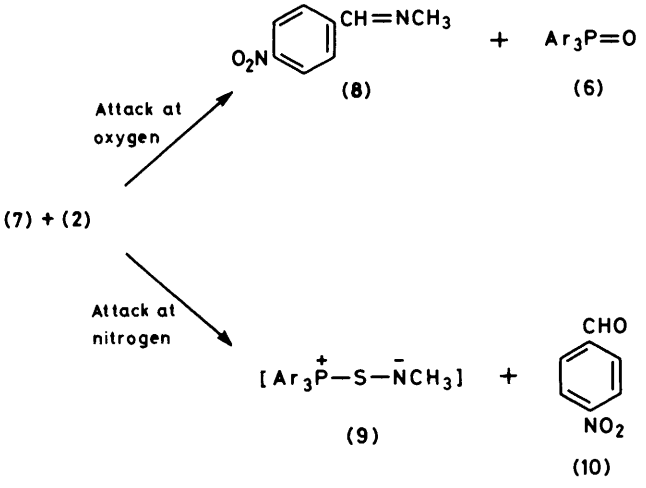
Since in all the reactions shown in Table 1 the triarylphosphine sulphide is not fully consumed the yields of trisubstituted triphenylphosphine oxides, for any given concentration of trap, potentially give an indication of the relative reactivities of the differently substituted phosphine sulphides with the oxygenating species. No pronounced electronic effect is apparent. We were able to confirm this directly by carrying out competition experiments where two differently substituted triarylphosphine sulphides, present in equimolar amounts, competed for the oxygenating species generated by photolysis of 3-methylpyridazine 2-oxide. The results are shown in Table 4 and confirm that, within experimental error, the ratio of phosphine oxides produced is essentially determined by the ratio of the amounts of phosphine sulphides originally present and thus that there is no pronounced electronic effect on the reaction.

This observation of the absence of a substituent effect in the triarylphosphine sulphides on photochemical reaction with 3-methylpyridazine 2-oxide suggests that either the oxygenating species is not a strong electrophile or that, if it is electrophilic, that its reactivity with thiophosphoryl species is very high and hence it is non-selective. An effect of this type is well known in carbene chemistry where it has been shown that the more electrophilic a carbene becomes the less selectivity it shows when reacting with alkenes of differing electron richness.[16]

In view of the already noted general electrophilic character of the oxygenating species generated on photolysis of heteroaromatic *N*-oxides we feel that the explanation of the lack of

Table 5. Reactions of (7) with $(p\text{-}RC_6H_4)_3P{=}S$ (2) in $CDCl_3$ at 40° over 72 h

	Yield (%)				
			Unchanged	Unchanged	
R	(8)	(10)	(7)	(2)	(6)
Me	53	31	10		98
MeO	60	31	5		93
H	45	31	8	22	73
Ph	29	19	44	30	68
Cl	25	20	54	56	34
CO_2Me	27	27	45	67	34



Scheme 2.

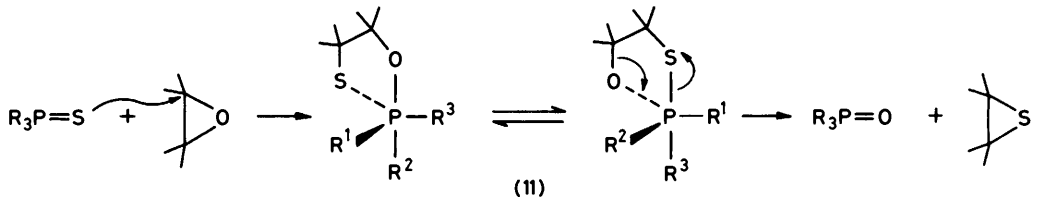
substituent effect in terms of a highly reactive electrophile is the more plausible.

Oxene, which is of course electron deficient, could easily fit the role of a highly reactive electrophile as regards attack at thiophosphoryl species but since nothing was known about the reactivity of oxaziridines in this context we could not exclude them entirely without an investigation of the reactions of oxaziridines with thiophosphoryl compounds. We chose to study the reactions of the stable 2-methyl-3-*p*-nitrophenyloxaziridine (7) with triarylphosphine sulphides.

Oxaziridines are known to be mild oxidising agents, converting triphenylphosphine into its oxide, for example,[17] and the reaction appears to involve direct nucleophilic attack at the oxaziridine oxygen in contrast to the apparently similar reaction of oxiranes where nucleophilic attack at *carbon*[18] is the first step. The general topic of nucleophilic attack on oxaziridines has recently been thoroughly investigated[19] and it has been shown that the main site for nucleophilic attack is the oxygen although some reaction at the nitrogen also occurs. The carbon seems to be totally unreactive with nucleophiles.

The results of our studies on the reactions of (7) with a series of trisubstituted triphenylphosphine sulphides are shown in Table 5, and an outline scheme for the reaction, based on the general mechanism proposed for nucleophilic attack on oxaziridines,[19] is shown in Scheme 2.

Attack of the phosphine sulphide sulphur at the oxaziridine oxygen yields the corresponding phosphine oxide (6), *p*-nitrobenzylidenemethylamine (8), and elemental sulphur, which we were able to detect qualitatively in all our reactions. Attack of the phosphine sulphide at the oxaziridine nitrogen

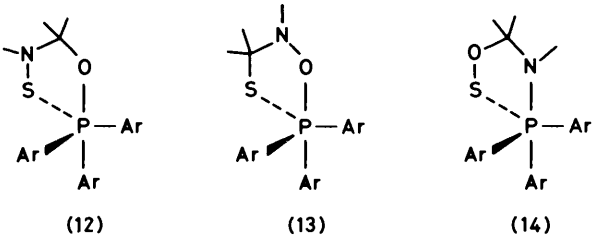


(11)

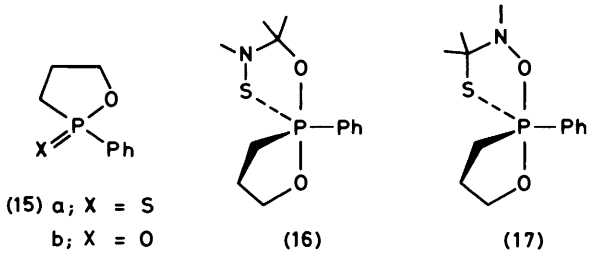
Scheme 3.

Table 6. Second-order rate constants at 313 K for the reaction of (7) with $(p\text{-}RC_6H_4)_3P{=}S$

R	$10^{-4}k$/l mol^{-1} s^{-1}
MeO	4.36 ± 0.25
Me	1.18 ± 0.12
H	1.06 ± 0.08
Cl	0.158 ± 0.008



(12) (13) (14)



(15) a; X = S
b; X = O

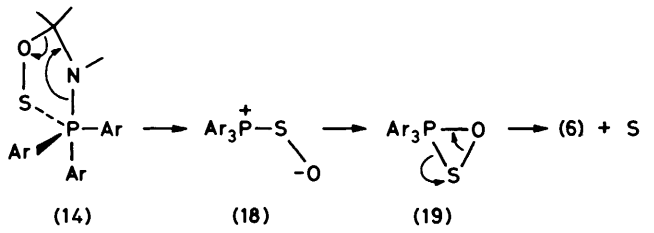
(16) (17)

is responsible for the formation of *p*-nitrobenzaldehyde (10). The intermediate (9) is only speculative but it is the direct 1,3-dipolar analogue of the stable ylides [19] known to be formed by attack of more conventional nucleophiles on oxaziridine nitrogens. A ^{31}P n.m.r. study of the reaction products showed the presence of no phosphorus-containing species other than (2) and (6), and it would therefore seem reasonable that (9), or some similar intermediate on the route to the benzaldehyde (10), decomposes so as to regenerate (2). Control experiments ruled out completely the possibility that (10) was being formed either by direct decomposition of (7) or by hydrolysis of (8) under the reaction conditions.

The results in Table 5 show a clear indication that there is a marked substituent effect on the reaction of (7) with (2). Electron-supplying substituents in the phosphine sulphide enhance the reaction and electron withdrawal retards it. We studied this more precisely by following the rate of consumption of the triarylphosphine sulphides by ^{31}P n.m.r. The results are shown in Table 6. The second-order rate constants in Table 6 correlate poorly with both σ and σ$^+$ ($|r|$ for σ$^+$ 0.88, ρ −1.31 : $|r|$ for σ 0.90, ρ −3.14) but the general trend indicates that reaction of the oxaziridine (7) shows all the normal characteristics of a process involving electrophilic attack, by the oxaziridine on the triarylphosphine sulphide, in sharp contrast to the photochemical reaction of 3-methylpyridazine 2-oxide with the same substrates, and is evidence against the active oxygenating agent in the latter reaction being an oxaziridine. Some caution is, of course, necessary in comparing the putative properties of reactive intermediates with the behaviour of stable analogues but if an oxaziridine is the active intermediate in oxygenation by *N*-oxide photolysis it must be much more reactive with phosphine sulphides than is (7) so as to negate the substituent effect.

The mechanism of the reaction of oxaziridines with triarylphosphine sulphides can, in theory, involve nucleophilic attack of the sulphur at any of the three members of the oxaziridine ring. The analogous reaction of thiophosphoryl compounds with epoxides has been investigated and the mechanism shown in Scheme 3, where attack is at the epoxide carbon and the first-formed cyclic intermediate (11) pseudorotates before cleavage of the P–S bond, has been suggested and substantiated.[20] The pseudorotation is essential if Westheimer's extended principle [21] requiring apical attack and apical leaving in reactions *via* P^V intermediates is to be upheld and to explain the observed stereochemistry of the reaction which goes with retention of configuration at phosphorus.

The three possible intermediates in our reaction, analogous to (11), are (12)—(14), derived by attack of the sulphur of the phosphine sulphide, at the oxaziridine nitrogen, carbon, and oxygen, respectively. Only (12) and (13) can lead directly to the product phosphine oxide in the sense that only they have a phosphorus–oxygen bond, but to do so they must pseudorotate to bring the sulphur into an apical position before the P–S bond can break.[22] We argued that if the reaction were carried out with the cyclic species 2-thiono-2-phenyl-1,2-oxaphospholane (15a) then the spirocyclic intermediates (16) and (17), the equivalents to (12) and (13), would, by analogy with similar systems, be very slow to pseudorotate and indeed would probably be conformationally quite rigid.[23] This situation arises because any pseudorotation would require one of the five-membered rings to occupy the strained diequatorial positions [21] in the trigonal bipyramid and in addition apicophilic oxygens would become equatorial.[24] The energy barrier associated with such a process in analogous systems has been shown by measurement [25,26] and calculation [25] to be typically between 60 and 80 kJ mol^{-1} and so any similar pseudorotation of (16) or (17) would presumably require the surmounting of a comparable energy barrier. This, therefore, seemed to be a system in which, if the reaction were occurring *via* intermediates of this type, we might see a very slow reaction, or indeed get no reaction at all. If reaction did occur, however, it seemed likely that intermediates such as (16) and (17) might be sufficiently long lived to be observed by ^{31}P n.m.r. In the event the reaction of (15a) with (7) proceeded as smoothly and rapidly as the reaction with the triarylphosphine sulphides to give the oxygenated derivative (15b) (69%) and we observed no intermediate P^V species by ^{31}P n.m.r. We, therefore, regard it as highly unlikely that either (12) or (13) are intermediates in the reaction of oxaziridines with phosphine sulphides to give phosphine oxides.



Scheme 4.

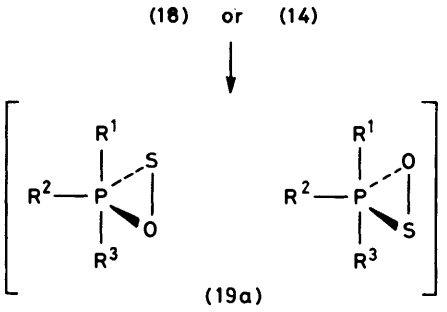
Intermediate (14), which arises from attack of sulphur at the oxaziridine oxygen and which precedent [19] would suggest to be the most likely species to form, cannot, of course, give the phosphine oxide directly but can undergo extrusion of imine (Scheme 4) to give the 1,3-dipolar intermediate (18) which could lead to the strained cyclic isomer (19) and thence to the observed products. No pseudorotation of (14) is required for this process and so the reaction would be expected to be equally facile with (15a).

We have no evidence that (14) is a *required* precursor to (18) and indeed it seems equally likely that (18) may form directly by nucleophilic attack of the sulphur at an oxaziridine oxygen without active participation by phosphorus. It would seem probable, therefore, that the reaction of oxaziridines with phosphine sulphides is typical [19] in the sense that the main site of attack is the oxaziridine oxygen. We completed the study by photolysing 3-methylpyridazine 2-oxide in the presence of (15a); again (15b) (33%) formed smoothly and rapidly and no intermediates were observed by ^{31}P n.m.r. and so in this sense the *N*-oxide photolysis is not differentiated from the reactions of (7) with phosphine sulphides. This is not surprising, in that the formation of an intermediate such as (18) is entirely feasible by attack of oxene or a photochemically modified *N*-oxide at the phosphine sulphide sulphur without participation of phosphorus.

We have finally studied the reaction of both 3-methylpyridazine 2-oxide and (7) with the chiral (*S*)-methylphenyl-n-propylphosphine sulphide (20). A mechanism *via* (18) and (19) would be expected to lead to retention of configuration at phosphorus since the oxygen must approach from the same side as the sulphur leaves.

Reaction of 2-methyl-3-*p*-nitrophenyloxaziridine (7) with (20) proceeded smoothly. The expected product phosphine oxide was shown, by measuring its optical rotation, to be formed with at least 92% retention of configuration at phosphorus. In contrast the same reaction carried out by photolysis of 3-methylpyridazine 2-oxide showed considerable loss of optical activity indicating only 57% retention of configuration at phosphorus. Again we have a clear distinction between the reaction of a phosphine sulphide with an oxaziridine and with an aza-aromatic *N*-oxide under photolysis and a strong indication that the main active oxygenating species in the latter reaction is not an oxaziridine. We have no definite explanation of the lack of stereochemical control in the *N*-oxide photolysis.

We thank a referee for the suggestion embodied in Scheme 5, whereby the intermediate (19a) is formed with trigonal bipyramidal geometry and the three-membered ring diequatorial. Such geometry, which would be extremely strained, is expected to be only transient but can provide an explanation for loss of stereochemical control, since the formation of (19a) from a species such as (18) might lead to both enantiomers. On the other hand the formation of (19a) *via* an intermediate such as (14) collapsing directly, rather than as shown in Scheme 4, might reasonably be stereospecific. Hence the difference in stereochemistry between the



Scheme 5.

N-oxide photolyses and the oxaziridine reactions could be explained if only the former involve the dipolar species (18) and the photolyses, at least, involve (19a).

In conclusion we feel that we have presented sufficient evidence to show that it is extremely unlikely that the active oxygenating species which participates in the photochemical reaction of 3-methylpyridazine 2-oxide with triarylphosphine sulphides is an oxaziridine and that its properties are largely consistent with the expected properties of the electroneutral, electron-deficient oxene.

Experimental

M.p.s, which are uncorrected, were determined in capillary tubes. ^1H N.m.r. spectra were determined either on a Varian EM360 or a HA100 spectrometer. ^{31}P N.m.r. spectra were obtained using a JEOL FX60 spectrometer. Chemical shifts are measured relative to external 85% phosphoric acid and are positive to high frequency. Mass spectra were obtained on an AEI MS902 spectrometer and g.c.–m.s. was on a VG Micromass 12 spectrometer coupled *via* a jet separator to a Pye 104 chromatograph. G.l.c. was on Pye 104 and 204 instruments with flame ionisation detectors and using glass columns 1.5 m × 4 mm i.d. Compounds were identified by comparison of retention times and mass spectra with those of authentic samples.

H.p.l.c. was carried out on a reversed-phase system using 25 cm × 5 mm i.d. stainless steel columns packed with 6 μm octadecyl silica (ODS) by the method of Knox.[27] The solvent system was methanol (79%)–water. The chromatograph used twin Altex 110A pumps operating at *ca.* 800 lb in^{-2} and the flow rate was 1 cm^3 min^{-1}. The detector was a Cecil CE12 U.V. detector operating at 254 nm. Optical rotations were measured on a Perkin-Elmer 141 polarimeter in a 100 mm path length cell using the sodium D line.

Preparation of Thiophosphoryl and Phosphoryl Compounds.—Trimethyl phosphorothionate was prepared by reaction of thiophosphoryl chloride with sodium methoxide [28] in methanol and had b.p. 75—82° at 5 mmHg (lit.,[28] 75° at 3 mmHg) and δ_P +72.5 p.p.m. Triethyl phosphorothionate from reaction of triethylphosphite with sulphur [29] had b.p. 80—82° at 6 mmHg (lit.,[29] 95.5° at 12 mmHg); δ_P +67.5 p.p.m. Triphenyl phosphorothionate was prepared by the method of Gottlieb [30] from triphenyl phosphite and thiophosphoryl chloride and had m.p. 51—53° (lit.,[31] 53°) and δ_P +53.1 p.p.m.

Trimethyl, triethyl, and triphenyl phosphates were all commercially available and purified by recrystallisation or distillation before use.

Triarylphosphine sulphides and the corresponding oxides, where not commercially available, were all prepared by standard routes (see Tables 7 and 8), the starting phosphines required either being commercially available or prepared by

Table 7. Triarylphosphine oxides (p-$RC_6H_4)_3P{=}O$

R	M.p. (°)	δ_P ($CDCl_3$) (p.p.m.)	Lit. m.p. (°)	Refs.
Me	141—143	+29.1	142—143	32, 33
MeO	143—144	+28.5	142—143	32, 34
Cl	168—172	+27.3	172—173	35
CO_2Me	118—119	+27.0	118—120	36

Table 8. Triarylphosphine sulphides (p-$RC_6H_4)_3P{=}S$

R	M.p. (°)	δ_P ($CDCl_3$) (p.p.m.)	Lit. m.p. (°)	Refs.
Me	183—185	+42.3	185—186	32, 33
MeO	109—110	+40.7	109—110	32, 33
Cl	150—151	+41.3	152—153	32, 37
CO_2Me	172—175	+40.8	178—179	36

reaction of the appropriate *p*-substituted phenylmagnesium bromide with phosphorus trichloride.

3-Methylpyridazine 2-oxide was prepared by oxidation of 3-methylpyridazine with hydrogen peroxide in glacial acetic acid. The resulting mixture of 1- and 2-oxides was chromatographed on alumina and the pure 2-oxide eluted with benzene [38] had m.p. 82—83° (lit.,[39] 85—86°).

Pyridine *N*-oxide was commercially available and its boron trifluoride adduct was prepared as described by Sammes and his co-workers [11] and had m.p. 95—96° (lit.,[11] 97°).

2-Methyl-3-p-*nitrophenyloxaziridine* was prepared by oxidation of *p*-nitrobenzylidenemethylamine (1.8 g, 0.011 mol) with *m*-chloroperbenzoic acid (85%) (2.3 g, 0.0113 mol) in methylene dichloride (50 cm^3) at 0°, and after chromatography on alumina (1 : 1 petroleum–ether) and recrystallisation from ether–petroleum had m.p. 82—83° (yield 1.3 g) (Found: C, 53.6; H, 4.4; N, 15.4. $C_8H_8N_2O_3$ requires C, 53.3; H, 4.5; N, 15.4%), δ_H ($CDCl_3$) 3.92 (3 H, s, CH_3), 4.56 (1 H, s, CH–N), 7.56 and 8.18 (4 H, AB, *J* 9 Hz, *o*-, *m*-ArH).

2-Phenyl-1,2-oxaphospholane was prepared as described by Grayson and Farley [40] by cyclisation of 3-hydroxypropylphenylphosphine in the presence of diphenyl disulphide and purified by bulb-to-bulb distillation at 110° at 0.5 mmHg (lit.,[40] 112° at 0.5 mmHg). It was converted into 2-thiono-2-phenyl-1,2-oxaphospholane (15a) by reaction with sulphur in chloroform [40] and into 2-phenyl-1,2-oxaphospholane 2-oxide (15b) by oxidation with hydrogen peroxide in acetone at 0°, b.p. 125—130° at 0.1 mmHg (lit.,[40] 142° at 0.2 mmHg).

(*S*)-*P*-Menthyl methylphenylphosphinate was prepared as described by Korpiun *et al.*[41] and had m.p. 78—79° (lit.,[41] 79—80°) and $[\alpha]_D^{24}$ −88.7° (benzene) (lit.,[41] $[\alpha]_D$ −94°). It was treated with n-propylmagnesium bromide [42] to give (*R*)-methylphenyl-n-propylphosphine oxide which was deoxygenated by treatment with hexachlorodisilane and treated with sulphur, all as described by Zon *et al.*,[42] to obtain (*S*)-methylphenyl-n-propylphosphine sulphide which, after purification by recrystallisation from hexane, had m.p. 77—80° (Found: C, 60.4; H, 7.8. Calc. for $C_{10}H_{15}PS$: C, 60.6; H, 7.6%), δ_P ($CDCl_3$) +39.2 p.p.m. ($[\alpha]_D^{23}$ −15.7°, methanol) (lit.,[42] $[\alpha]_D$ −22° for 100% optical purity). Our material was 71% optically pure on the basis of its specific rotation.

Photolysis of 3-Methylpyridazine 2-Oxide in the Presence of Thiophosphoryl Compounds.—The *N*-oxide (normally 0.14 g, 1.25 mmol) and the thiophosphoryl compound were dissolved in dry methylene dichloride (100 cm^3) and the solution purged with dry nitrogen for 0.5 h before irradiation with an Applied Photophysics (125 W) medium-pressure mercury lamp contained in a Pyrex, water-cooled, immersion well. The reaction was continued until examination by t.l.c. showed that all the *N*-oxide was consumed, typically 5 h. After removal of the solvent the residue was examined quantitatively by g.l.c. for 3-methylpyridazine (10% Carbowax 20M + 2% KOH on 100—120 mesh Celite; 150°; with biphenyl as internal standard) and by h.p.l.c. (*m*-terphenyl as internal standard) for unchanged thiophosphoryl compounds and the phosphoryl products. The g.l.c. identifications were confirmed by g.c.–m.s. and the presence of, and relative amounts of, the thiophosphoryl and phosphoryl compounds confirmed by ^{31}P n.m.r. Control experiments to establish the stability of the products, and each starting material when present alone under the reaction conditions, were carried out similarly. The rate of formation of 3-methylpyridazine in the presence and absence of tris-*p*-chlorophenylphosphine sulphide was carried out in the same manner with samples (*ca.* 5 μl) being withdrawn at *ca.* 20 min intervals for g.l.c. analysis. In the experiments shown in Table 4 0.25 mmol of each of the triarylphosphine sulphides and 1.25 mmol of 3-methylpyridazine 2-oxide were photolysed for 5 h in dry methylene dichloride (100 cm^3) under nitrogen as already described. The absolute yields of the product triarylphosphine oxides were determined by h.p.l.c. as already described and their relative yields confirmed by ^{31}P n.m.r.

Reaction of 3-methylpyridazine 2-oxide (0.25 mmol) with 2-thiono-2-phenyl-1,2-oxaphospholane (0.2 mmol) in deuteriochloroform (0.5 cm^3) was carried out in an n.m.r. tube attached to the side of the Pyrex, water-cooled, immersion well containing the photolysis lamp. Reaction was continued over 4 h with periodic examination of the sample by ^{31}P n.m.r. for intermediates. Only the starting material and the oxygenated derivative (15b) were observed. The yields of products were determined by g.l.c. and h.p.l.c. as described above and a sample of (15b) isolated by preparative t.l.c. had a mass spectrum identical to that of an authentic sample.

Reaction of 2-Methyl-3-p-*nitrophenyloxaziridine* (7) *with Triarylphosphine Sulphides.*—This was carried out in deuteriochloroform to permit direct monitoring by n.m.r. The phosphine sulphide (0.05 g) and a 2 molar excess of (7) in $CDCl_3$ (0.5 cm^3) contained in an n.m.r. tube were surrounded by boiling methylene dichloride for 72 h. The mixture was analysed by g.l.c. (3% OV1 on 100—120 mesh silanised Chromosorb W; 150°; with biphenyl as internal standard) for *p*-nitrobenzaldehyde and *p*-nitrobenzylidenemethylamine and by h.p.l.c. (with *m*-terphenyl as internal standard) for triarylphosphine oxide. All the products were confirmed by ^1H n.m.r. and ^{31}P n.m.r. as appropriate. Control experiments performed in the same manner showed that all the products and each starting material, when present alone, were stable under the reaction conditions.

The kinetic measurements required to derive the second-order rate constants shown in Table 6 were obtained by direct monitoring of the ^{31}P n.m.r. spectrum of a reaction mixture containing equimolar amounts (0.13 mmol) of phosphine sulphides and the oxaziridine in deuteriochloroform (0.5 cm^3) at 40°. A standard stacking and analysis program recorded a spectrum every 32 or 47 min. A capillary of triethyl phosphate served as internal standard and the concentrations of the

triarylphosphine sulphides and oxides were obtained from the spectra, using peak areas.

Standard mixtures of the phosphine oxides and sulphides subjected to the same procedure returned concentrations with ±3% of the expected values.

The reaction of 2-thiono-2-phenyl-1,2-oxaphospholane (0.2 mmol) with 2-methyl-3-*p*-nitrophenyloxaziridine (0.2 mmol) in $CDCl_3$ (0.5 cm^3) was also carried out in the ^{31}P n.m.r. probe at 40° with continuous monitoring for intermediates. Only the starting material and 2-phenyl-1,2-oxaphospholane 2-oxide, δ_P ($CDCl_3$) +57.6 p.p.m., were observed. Yields of products were measured by h.p.l.c. and g.l.c. as described for the triarylphosphine sulphides above and in addition (15b) was isolated by preparative t.l.c. and its mass spectrum shown to be identical with that of an authentic sample.

Stereochemical Studies.—(*S*)-Methyl(phenyl)-n-propylphosphine sulphide (1 mmol) and 2-methyl-3-*p*-nitrophenyloxaziridine (1.5 mmol) in methylene dichloride (20 cm^3) were heated at the reflux temperature until t.l.c. showed the reaction to be complete (72 h). After removal of solvent the residue was chromatographed on alumina and a mixture of *p*-nitrobenzaldehyde and *p*-nitrobenzylidenemethylamine (0.15 g in total) eluted with petroleum–ether (1 : 1). Elution with ether gave an oil which was further purified by preparative t.l.c. to give (*S*)-methyl(phenyl)-n-propylphosphine oxide (0.075 g, 41%) with $[\alpha]_D^{23}$ −12.8° (methanol). The material was identical (^{31}P and ^1H n.m.r., i.r., t.l.c., one spot) with an authentic sample. On the basis of the reported specific rotations [41-43] for product and starting materials the reaction proceeds with, at most, 8% net inversion.

Photolysis of 3-methylpyridazine 2-oxide (2.5 mmol) in the presence of (*S*)-methyl(phenyl)-n-propylphosphine sulphide in methylene dichloride (100 cm^3) was carried out by the standard method already described. After removal of solvent the residue was chromatographed on alumina. Elution with petroleum–ether (3 : 2) gave unchanged phosphine sulphide (0.11 g, 55%) and 3-methylpyridazine (0.075 g, 32%). Further elution with ether gave methyl(phenyl)-n-propylphosphine oxide (36%) identical by t.l.c. (one spot), ^1H and ^{31}P n.m.r., i.r. with an authentic sample, and $[\alpha]_D^{23}$ −6.1° (methanol). The reaction proceeds with at most 43% net inversion.[41-43]

Control experiments confirmed that (*S*)-methyl(phenyl)-n-propylphosphine oxide and the starting sulphide were stable and retained their stereochemical integrity under the reaction conditions.

Acknowledgements

We thank S.E.R.C. for a studentship for J. R. F. S.

References

1 W. M. Diggle and J. C. Gage, *Biochem. J.*, 1951, **49**, 491.
2 K. A. Ptashne, R. M. Wolcott, and R. A. Neal, *J. Pharmacol. Exp. Ther.*, 1971, **179**, 381 and references therein.
3 G. A. Hamilton, 'Molecular Mechanisms of Oxygen Activation,' Academic Press, New York, 1974.
4 D. M. Jerina, D. R. Boyd, and J. W. Daly, *Tetrahedron Lett.*, 1970, 457.
5 H. Igeta, T. Tsuchiya, M. Yamada, and H. Arai, *Chem. Pharm. Bull. (Tokyo)*, 1968, **16**, 767.
6 J. Strieth, B. Donner, and G. Sigwalt, *Chem. Commun.*, 1967, 979.
7 M. N. Akhtar, D. R. Boyd, J. D. Neill, and D. M. Jerina, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1693.
8 A. G. Rowley and J. F. R. Steedman, *Chem. Ind. (London)*, 1981, 365.
9 Y. Ogawa, S. Iwasaki, and S. Okuda, *Tetrahedron Lett.*, 1981, **22**, 2277.
10 O. Buchardt, J. J. Christensen, C. Lohse, J. J. Turner, and I. R. Dunkin, *J. Chem. Soc., Chem. Commun.*, 1977, 837.
11 P. G. Sammes, G. Serra-Errante, and A. C. Tinker, *J. Chem. Soc., Perkin Trans. 1*, 1978, 853.
12 A. Lablache-Combier in 'Photochemistry of Heterocyclic Compounds,' ed. O. Buchardt, Wiley, New York, 1976, p. 224.
13 O. W. Lwowski, 'Nitrenes,' Wiley, New York, 1970; R. A. Moss and M. Jones, 'Carbenes,' Wiley, New York, 1975, p. 218.
14 S. B. Bulgarevich, L. V. Goncharova, O. A. Osipov, V. V. Hesarev, and A. A. Schvets, *J. Gen. Chem. USSR*, 1978, **48**, 1219.
15 H. Teichmann and G. Hilgetad, *Angew. Chem., Int. Ed. Engl.*, 1967, **6**, 1013.
16 P. S. Skell and M. S. Cholod, *J. Am. Chem. Soc.*, 1969, **91**, 7131.
17 L. Horner and E. Jurgens, *Chem. Ber.*, 1957, **90**, 2184.
18 C. B. Scott, *J. Org. Chem.*, 1957, **22**, 1118.
19 Y. Hatta and M. Watanabe, *J. Org. Chem.*, 1981, **46**, 610.
20 T. H. Chan and J. R. Finkenbine, *J. Am. Chem. Soc.*, 1972, **94**, 2880.
21 F. H. Westheimer, *Acc. Chem. Res.*, 1968, **1**, 70.
22 For analysis of a similar system see K. Mislow, *Acc. Chem. Res.*, 1970, **3**, 321.
23 F. Ramirez, *Acc. Chem. Res.*, 1968, **1**, 168; F. Ramirez, J. F. Pilot, O. P. Madan, and C. P. Smith, *J. Am. Chem. Soc.*, 1968, **90**, 1275; K. E. DeBruin, K. Naumann, G. Zon, and K. Mislow, *ibid.*, 1969, **91**, 7031.
24 R. K. Oram and S. Trippett, *J. Chem. Soc., Perkin Trans. 1*, 1973, 1300.
25 S. A. Bone, S. Trippett, M. W. White, and P. J. Whittle, *Tetrahedron Lett.*, 1974, 1795.
26 J. Brierley, S. Trippett, and M. W. White, *J. Chem. Soc., Perkin Trans. 1*, 1977, 273.
27 J. H. Knox, 'High Performance Liquid Chromatography,' Edinburgh University Press, Edinburgh, 1980, p. 151.
28 W. G. Emmett and H. O. Jones, *J. Chem. Soc.*, 1911, **99**, 713.
29 W. Strecher and R. Spitalter, *Ber.*, 1926, **59**, 1754.
30 H. Gottlieb, *J. Am. Chem. Soc.*, 1932, **54**, 748.
31 'Dictionary of Organic Compounds,' Eyre and Spottiswoode, London, 1965.
32 F. G. Mann and E. G. Chaplin, *J. Chem. Soc.*, 1937, 527.
33 A. Michaelis, *Liebig's Ann. Chem.*, 1901, **315**, 43.
34 V. Balaih and P. Subbarayan, *J. Org. Chem.*, 1960, **25**, 1833.
35 L. Maier, *Helv. Chim. Acta*, 1964, **47**, 120.
36 G. P. Schiemenz and H.-U. Siebeneick, *Chem. Ber.*, 1969, **102**, 1883.
37 G. P. Schiemenz, *Chem. Ber.*, 1966, **99**, 504.
38 T. Nakagome, *Yakugaku Zasshi*, 1962, **82**, 249.
39 M. Ogata and H. Kano, *Chem. Pharm. Bull. (Tokyo)*, 1963, **11**, 29.
40 M. Grayson and C. E. Farley, *Chem. Commun.*, 1967, 830.
41 O. Korpiun, R. A. Lewis, J. Chickos, and K. Mislow, *J. Am. Chem. Soc.*, 1968, **90**, 4842.
42 G. Zon, K. E. DeBruin, K. Naumann, and K. Mislow, *J. Am. Chem. Soc.*, 1969, **91**, 7023.
43 J. P. Casey, R. A. Lewis, and K. Mislow, *J. Am. Chem. Soc.*, 1969, **91**, 2789.

Received 30*th September* 1982; *Paper* 2/1680