Alkaline Hydrolysis of Aryl Phosphoramidates and their Cyclic Analogues

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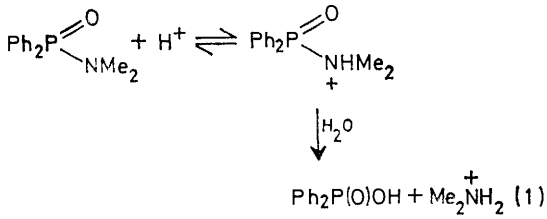
The products of alkaline hydrolysis of the title compounds have been determined and their rates of formation measured. While the acyclic compounds react slowly to give products derived exclusively from loss of phenolate ion, the cyclic compounds react *ca.* 10^4 times faster to give more complex mixtures of products. In the case of *N*-alkyl derivatives, small amounts of cyclic P–N and P–O bond cleavage are observed in addition to cleavage of the P–O aryl bond, whereas in the case of the *N*-aryl derivatives, loss of phenolate ion is accompanied by significant amounts of cyclic P–O cleavage, with no detectable P–N bond cleavage. These results are interpreted in terms of trigonal bipyramidal intermediates, which in the case of the *N*-methyl cyclic compounds may undergo protonation at nitrogen, even in the basic medium employed in their formation.

AMINO-DERIVATIVES of phosphoric acid have been widely investigated in recent years, mainly from two points of view. First, the hydrolysis of phosphoramidic acids has been studied in detail in relation to the mode of action of phosphorocreatine.[1] Secondly the high reactivity in alkaline media of phosphoramidates, phos-

[1] G. W. Allen and P. Haake, *J. Amer. Chem. Soc.*, 1973, **95**, 8080.

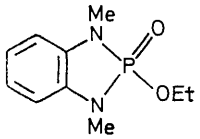
phoramidic halides, and similar molecules derived from primary amines has received considerable attention [2] following the original suggestion of Westheimer [3] that intermediate amidate anions and imides are involved. This *E*lcB type of mechanism, which is still a matter of some controversy, has been discussed in detail recently by Hamer [4] and by Williams.[5] We are not concerned with this problem at this time, as we have studied only *N*-disubstituted phosphoramidates.

These are rapidly hydrolysed in acidic solution by process (1) which probably involves protonation on nitrogen as suggested by the investigations of Haake [6]



but are comparatively unreactive in alkaline solution. This is attributed to the combined effect of electron release from the lone pair on nitrogen, and steric hindrance.[7] Moreover the anionic amino-group is highly basic and hence is usually regarded as a very poor leaving group. In view of this low alkaline reactivity little quantitative work has been reported on the hydrolysis of neutral phosphoramidates.

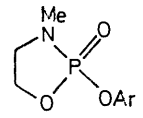
The research reported here is concerned with the alkaline hydrolysis of cyclic phosphoramidates with a labile phenoxy-group in the exocyclic position. The influence of nitrogen in a five-membered ring of a phosphorus heterocycle has not been widely investigated, although Dennis and Westheimer [8a] report an enhanced reactivity of a 2-alkoxy-2-oxo-1,3,2-diazaphospholidine (I) comparable with that found for ethylene phosphate.



(I)

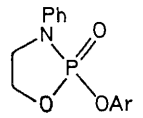
This suggests that the ring is under considerable strain, leading to the reported fission of the P–N bonds in *alkaline* solution.[8b] Products arising from P–N cleavage in the reaction of 2-methyl- and of 2-methoxy-2-oxo-1,3,2-oxazaphospholans with methoxide ion have also been reported recently by Inch and his co-workers.[9]

The main object of the present work is to investigate the influence of stereo-electronic control on the rate of displacement in alkaline solution of a labile exocyclic group from the phosphorus atom constrained in a five-membered ring. This is a general problem and hence is relevant to similar studies already reported on other systems.[10] We have therefore determined the products of alkaline hydrolysis of the compounds (II)—(V), and measured their rates of formation.



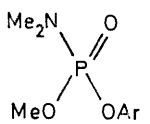
(II)

a; Ar = 4-MeC_6H_4
b; Ar = Ph
c; Ar = 4-$NO_2C_6H_4$
d; Ar = 3-$NO_2C_6H_4$
e; Ar = 4-$MeOC_6H_4$



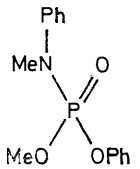
(III)

a; Ar = 4-$MeOC_6H_4$
b; Ar = Ph
c; Ar = 4-NO_2-C_6H_4



(IV)

a; Ar = 4-MeC_6H_4
b; Ar = Ph
c; Ar = 4-$NO_2C_6H_4$
d; Ar = 3-$NO_2C_6H_4$



(V)

RESULTS

Product Analyses.—Analyses of the reaction mixtures from kinetic experiments after $\geqslant$10 half-lives, by u.v.-visible spectrophotometry, showed the release of 100 $\pm$ 1% 4-nitrophenol from the *N*-methyl- and *N*-phenyl-nitrophenyl derivatives (IIc) and (IIIc), but only 91 and 69% phenol release from the corresponding phenyl esters (IIb) and (IIIb).

A full analysis of reaction products was achieved using noise-decoupled ^{31}P pulse Fourier transform n.m.r. spectroscopy. Reaction mixtures (*ca.* 0.5M in 50% aqueous dioxan) were examined immediately after mixing. Although complex mixtures of products, formed in secondary reactions, were observed if the reaction mixtures were allowed to stand for extended periods (>12 h), the freshly prepared solutions were stable for periods well in excess of the time required for spectral analysis. The results of these experiments are summarised in Table 1. Good agreement between the two methods was observed.

Kinetics.—Pseudo-first-order rate constants were obtained by following changes in the intensity of the appropriate band in the u.v. spectrum in the conventional manner.

[2] E. W. Crunden and R. F. Hudson, *J. Chem. Soc.*, 1962, 3591; P. S. Traylor and F. H. Westheimer, *J. Amer. Chem. Soc.*, 1965, **87**, 553; A. F. Gerrard and N. K. Hamer, *J. Chem. Soc.* (*B*), 1968, 539; 1969, 369; I. Oney and M. Caplow, *J. Amer. Chem. Soc.*, 1967, **89**, 6972; D. B. Coult and M. Green, *J. Chem. Soc.*, 1964, 5478.

[3] F. H. Westheimer, Chem. Soc. Special Publication, 1957, No. 8, p. 180.

[4] N. K. Hamer and R. D. Tach, *J.C.S. Perkin II*, 1974, 1184.

[5] A. Williams and K. T. Douglas, *J.C.S. Perkin II*, 1972, 1454; 1973, 318.

[6] T. Koizumi and P. Haake, *J. Amer. Chem. Soc.*, 1973, **95**, 8073.

[7] R. F. Hudson, 'Structure and Mechanism in Organophosphorus Chemistry,' Academic Press, New York, 1965, ch. 8.

[8] (*a*) E. A. Dennis and F. H. Westheimer, *J. Amer. Chem. Soc.*, 1966, **88**, 3431; (*b*) D. H. Williams, Ph.D. Thesis, Harvard University, 1970.

[9] D. B. Cooper, J. M. Harrison, and T. D. Inch, *Tetrahedron Letters*, 1974, 2697.

[10] F. H. Westheimer, *Accounts Chem. Res.*, 1968, **1**, 70.

Low concentrations of the substrate (*ca.* 10^{-4}M) and an excess of sodium hydroxide in the 0.01—0.2M concentration range were used. The reactions were all shown to be strictly second order (Table 2) by variation of the concentration of hydroxide ion.

TABLE 1

Product analyses of reactions of phosphoramidates with hydroxide ion in 50% dioxan–water

	Position and extent (%) of bond fission		
Compound	P–OAr	P–O	P–N
(IIb)	91,[a] 92 [b]	4 [b]	5 [b]
(IIc)	98 [a]		
(IId)	99 [a]		
(IIIa)	73,[b] 72 [a]	27 [b]	
(IIIb)	71,[b] 69 [a]	29 [b]	
(IIIc)	100, 98		
(IVb)	100 [a]		
(V)	100 [a]		

[a] U.v.–visible spectrophotometry. [b] ^{31}P Fourier transform n.m.r.

TABLE 2

Kinetic data for hydrolysis of phosphoramidates (II)—(V) in aqueous sodium hydroxide solution

Compound	[OH$^-$]/M	k_2 (25 °C)/ l mol^{-1} s^{-1}	k_2 (55 °C)/ l mol^{-1} s^{-1}
(IIa)	0.02—0.20	1.11×10^{-1}	5.75×10^{-1}
(IIb)	0.01—0.50	1.24×10^{-1}	6.84×10^{-1}
(IIc)	0.01—0.10	7.24×10^{-1}	3.20
(IId)	0.01—0.20	5.29×10^{-1}	2.99
(IIe)	0.01—0.20	1.06×10^{-1}	6.15×10^{-1}
(IIIa)	0.01—0.15	2.30×10^{-1}	1.40
(IIIb)	0.01—0.20	3.50×10^{-1}	1.46
(IIIc)	0.005—0.05	2.65	8.34
(IVa)	0.075—0.20	1.82×10^{-6}	4.79×10^{-5}
(IVb)	0.01—0.20	6.85×10^{-6}	6.79×10^{-5}
(IVc)	0.02—0.20	1.17×10^{-4}	1.60×10^{-3}
(IVd)	0.05—0.20	6.61×10^{-5}	8.35×10^{-4}
(V)	0.40—1.0	1.91×10^{-5}	2.15×10^{-4}

The cyclic esters were found to be more reactive than their acyclic analogues by factors of the order of 10^4. Rate constants were obtained at several temperatures (Table 3) so

TABLE 3

Arrhenius parameters for the alkaline hydrolysis of phosphoramidates (II)—(V)

Compound	[OH$^-$]/M	Temp. (°C)	E_a/ kcal mol^{-1}	ΔS/ cal mol^{-1} K^{-1}
(IIa)	0.02—0.05	25.6—55.5	10.8 ± 0.4	-28.9 ± 1.1
(IIb)	0.01	25.6—56.2	11.2 ± 0.1	-27.0 ± 0.5
(IIc)	0.01	25.2—57.6	9.7 ± 0.3	-28.5 ± 0.9
(IId)	0.01—0.05	25.5—46.2	10.7 ± 0.3	-25.8 ± 0.9
(IIe)	0.01	25.8—55.1	11.7 ± 0.1	
(IIIa)	0.01	26.8—63.9	10.1 ± 0.4	-38.1 ± 1.2
(IIIb)	0.01	25.0—63.2	9.9 ± 0.2	-39.2 ± 0.7
(IIIc)	0.005	25.0—63.2	9.4 ± 0.5	-38.1 ± 1.5
(IVa)	0.20	75.2—95.7	18.9 ± 1.2	-23.5 ± 3.2
(IVb)	0.10	55.6—97.1	14.8 ± 0.6	-34.5 ± 1.0
(IVc)	0.20	37.9—68.2	16.4 ± 0.7	-23.6 ± 1.3
(IVd)	0.20	45.9—74.0	16.5 ± 0.4	-24.4 ± 1.0
(V)	1.00	25.0—64.7	16.9 ± 0.6	-25.4 ± 1.8

that extrapolation or interpolation to a common temperature could be made, and Table 4 includes values of the ratios of the second-order rate constants for pairs of cyclic and acyclic esters (k_c/k_a).

[11] See, for example, F. Ramirez, *Accounts Chem. Res.*, 1968, **1**, 168; J. A. Howard, D. R. Russell, and S. Trippett, *J.C.S. Chem. Comm.*, 1973, 856 and references cited therein.

A study of the effect of substituents on the k_c/k_a ratio was made for the esters (II) and (IV) and k_c/k_a found to increase regularly with electron release in the phenol. From the values of the Arrhenius parameters the differences in enthalpy of activation, $\Delta\Delta H^{\ddagger}$, between cyclic and acyclic esters were obtained (Table 4). Despite the relatively large errors involved in the value of these, it can be seen that the

TABLE 4

Arrhenius parameter differences and rate ratios for the alkaline hydrolysis of phosphoramidates (II)—(V)

Compound	Pair $\Delta\Delta G$/ kcal mol^{-1}	$\Delta\Delta H$/ kcal mol^{-1}	k_c/k_a (25°)	k_c/k_a (55°)
(IIc)–(IVc)	5.3	6.6	6.2×10^3	2.0×10^3
(IId)–(IVd)	5.5	5.8	8.0×10^3	3.6×10^3
(IIb)–(IVb)	6.0	4.2	1.8×10^4	1.0×10^4
(IIa)–(IVa)	6.6	6.9	6.1×10^4	1.2×10^4
(IIIb)–(V)	6.0	7.0	1.8×10^4	0.7×10^4

major part of the rate changes on passing from cyclic to acyclic molecules is due to the change in $\Delta H^{\ddagger}$, and the average value is close to the thermochemical value of the strain energy found by Westheimer for methyl ethylene phosphate using heat of hydrolysis data.

DISCUSSION

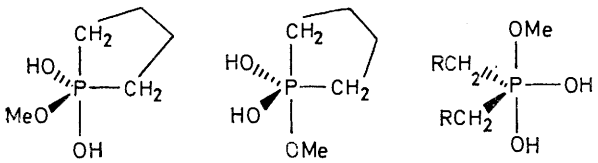
In order to explain these kinetic and analytical data we shall adopt the hypotheses advanced by Westheimer [10] to explain the products of hydrolysis of cyclic phosphonates and phosphates, in terms of the fluctional behaviour of postulated five-co-ordinate intermediates. According to this approach, the more electronegative groups, which include incoming and leaving groups occupy the apical positions of an assumed bipyramidal structure in which the strain in the original ester is released by the ring adopting an apical–equatorial configuration. This release of strain (*ca.* 5—6 kcal mol^{-1}) accounts for the abnormally high reactivity of the cyclic esters.

This elegant interpretation is supported by *X*-ray structural investigations of oxyphosphoranes [11] and by studies of the temperature-dependence of the n.m.r. spectra of these and related molecules.[12] Thus in certain cases, particularly in the phosphetan system, direct estimates of the ' apicophilicity ', *i.e.* the tendency of a particular group to occupy an apical position, can be obtained.[12] In general this tendency follows the electronegativity of the group, although other factors, in particular non-bonded repulsions and π-bonding, modify the effect. Thus according to the experimentally determined order, $F > Cl > RO \gg R_2N \simeq R_3C > Ph$, the more electronegative phenyl group is less apicophilic than an alkyl group, which itself is similar to the more electronegative amino-group.

This order may well depend on the structure of the pentacovalent intermediate, but in the absence of data for anions, we shall use this as a guideline for pseudorotational behaviour of such reaction intermediates. In view of the comparable apicophilicity of the alkyl and

[12] S. A. Bone, S. Trippett, and P. J. Whittle, *J.C.S. Perkin I*, 1974, 2125; S. A. Bone, S. Trippett, M. W. White, and P. J. Whittle, *Tetrahedron Letters*, 1974, 1795 and references therein.

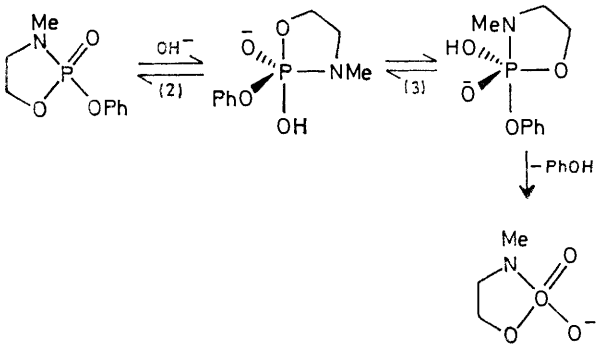
amino-groups, hydrolysis of cyclic phosphoramidates should follow the same course as cyclic phosphonate esters. One of the early successes of Westheimer's



(VI) (VII) (VIII)

hypotheses was the explanation of the low reactivity of cyclic phosphinate esters.[10] Release of ring strain in the phosphorane leads to a structure (VI) in which a carbon atom is apical. This is a high energy structure compared with the intermediate formed by the acyclic ester (VIII). Pseudorotation of (VI) leads to structure (VII) (of comparably high energy) from which the methoxy-group is released.

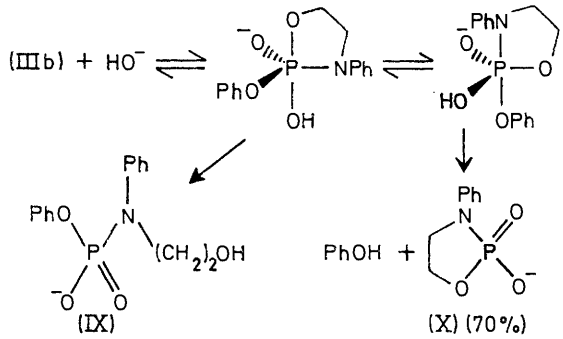
Thus the decrease in energy produced by the release of ring strain is opposed by the increased electronic energy caused by the unfavourable apical disposition of the carbon atom. Consequently the rates of hydrolysis of cyclic and acyclic phosphinates are comparable as the result of a combination of these compensatory effects.



Similarly in the hydrolysis of cyclic phosphoramidates, the phenolate ion can be released only after pseudorotation of the initially formed intermediate which places the amino-group in the unfavourable apical position. This leads to the formation of a high energy species, and consequently the enhanced reactivity due to the release of strain in step (2) should be considerably reduced. This is however not the case, and the high values of k_c/k_a show that some other factor must be involved.

Moreover hydrolysis of (IIb) in strong alkali leads to 5% P–N fission, although no P–N fission is observed for the *N*-phenyl compound (IIIb). Significantly less phenol is released from the *N*-phenyl compound, and consequently an increased yield of open chain acid (IX) formed by exclusive P–O fission is obtained. These results can be explained in the following way. Pseudorotation produces the second intermediate with apical PhO and PhN groups, the former having a high, the latter a lower, apicophilicity. The net result is the formation of comparable yields of cyclic and open chain acids.

The remaining question therefore is why should the NMe compound give a significantly higher yield of phenol and an appreciable yield (5%) of the acid formed by P–N fission? The reasonable inference is that the more basic and less apicophilic nitrogen atom is rendered more apicophilic and labile by protonation involving specific or general acid catalysis by a water molecule, of a kind known to be important in the alkaline hydrolysis of carboxylic acid amides. The site of protonation of course is unknown, but Haake [6] has shown that the nitrogen atom of phosphinamides is protonated in preference to the oxygen atom. In the present case the

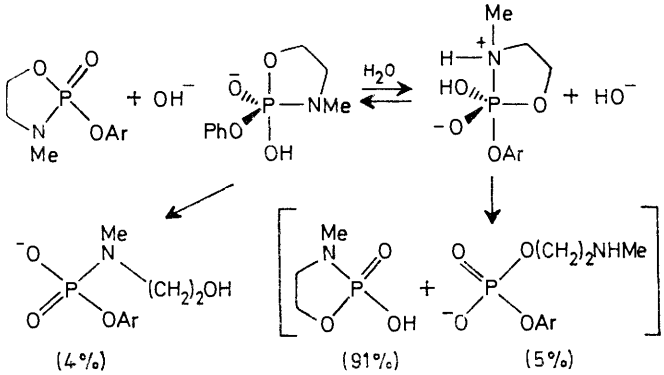


(IX) (X) (70%)

ionised oxygen atom may be protonated preferentially, but according to the explanation given the zwitterion is the kinetically important species. We are presently investigating this interesting possibility in greater detail.

This explanation requires the phenolate ion to leave with retention of configuration, and this has been found [13] for the reaction of methoxide ion in methanol with 3,4-dimethyl-2-oxo-2-phenoxy-5-phenyl-1,3,2-oxazaphospholan derived from ephidrine.

The above reaction mechanism is relevant to intramolecular catalysis of 2-aminoethyl esters related to serine. Thus Wilson and Turnbull [14] noted the formation of a trace of 2-aminoethyl phenyl phosphate in addition to 2-aminoethyl phosphate in the hydrolysis of



(4%) (91%) (5%)

2-aminoethyl diphenyl phosphate. A mechanism involving the intermediate formation of 2-oxo-2-phenoxy-1,3,2-oxazaphospholan was postulated.

[13] T. D. Inch, personal communication.
[14] G. J. Durant, J. H. Turnbull, and W. Wilson, *Chem. and Ind.*, 1958, 157.

It remains to discuss the reason why no P–N fission is observed in the hydrolysis of the acyclic ester (within the limits of the u.v. analytical method), and the influence of the ring constraint on the reaction mechanism. The reaction path for the formation of phenol can best be described in terms of potential energy profiles (Figure 1).

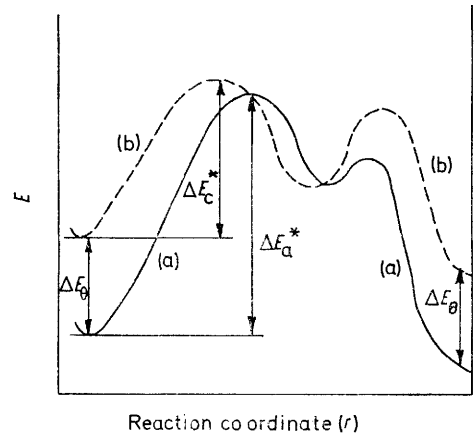


FIGURE 1 Energy profiles for alkaline hydrolysis of (a) acyclic and (b) cyclic phosphoramidates

On the assumption that phenoxide ion is a better leaving group than hydroxide ion, the potential energy profile for the acyclic ester is given by curve (a) in terms of the reaction co-ordinate, *r*. If all strain is released in the cyclic phosphorane its energy is approximately the same as that of the acyclic oxyphosphorane (although small differences in non-bonded interactions will modify the energy to some extent). The ground-state energy of the cyclic ester will be higher by ΔE_θ as shown in Figure 1, curve (b). This leads to a higher transition state energy, but a resultant activation energy ΔE_c^* smaller than the value ΔE_a^* for the acyclic ester. Similarly the cyclic acid produced is at a higher energy than the open-chain ester coming from the acyclic compound (by *ca.* ΔE_θ), and hence the energy barrier for the release of phenol is somewhat greater (Figure 1).

There are two consequences of these energy changes. First the cyclic pentacovalent intermediate is in a greater potential well than the acyclic intermediate, hence its lifetime is greater. This allows secondary processes, *e.g.* proton transfer, pseudorotation, to occur with the formation of the mixture of products described earlier.†

We have represented the reaction of the acyclic species in terms of a five-co-ordinate intermediate. This is still a matter of some controversy, although Haake [15] has recently presented direct kinetic evidence for such an intermediate in the alkaline hydrolysis of phosphinate esters.

† For the sake of simplicity we have not included protonation and pseudo-rotation barriers in Figure 1, and these should be taken into account in the interpretation of the rate ratios given in Table 4. Their omission from Figure 1, however, does not change the present argument.

‡ A similar value, 0.75, was obtained for the corresponding *N*-phenyl cyclic series (III) (see Figure 2).

§ This value was calculated by A. Williams from data of D. F. Heath: see ref. 5.

Secondly the displacement of the potential energy profiles (Figure 1) leads to the conclusion that the transition state of the first step, *i.e.* the rate-determining process, is formed at an earlier stage for the cyclic compound than for its acyclic analogue. This conclusion is supported by the effect of substitution in the leaving group as shown by the Hammett plots (Figure 2). The value of 1.56 for the acyclic esters (IV) is significantly greater than the value of 0.80 found for the cyclic analogues (II).‡ Moreover the corresponding Brönsted values are 0.52 and 0.29 for acyclic and cyclic compounds respectively. The former value is close to that of 0.4 found for the alkaline hydrolysis of dialkyl phenyl phosphates.§

We come to the general conclusion therefore that the incorporation of phosphorus in a five-membered ring modifies the transition state and intermediate appreciably, so that the reaction may take a completely different course. We have already described a striking example of stereoelectronic control in the acylation of phosphoramidites.[16] The influence of ring strain on the position of bond fission is particularly interesting, and we are investigating further the nature of the incipient protonation on nitrogen which may be responsible for the remarkably easy P–N cleavage in alkaline media.

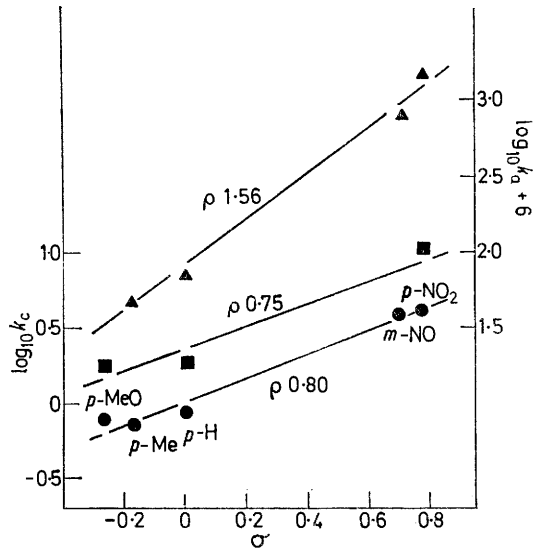


FIGURE 2 Hammett data for phosphoramidates at 55 °C: ▲, series (IV), acyclic; ■, series (III), cyclic; ●, series (II), cyclic

EXPERIMENTAL

M.p.s are uncorrected. N.m.r. spectra were obtained using Perkin-Elmer R-10 (^{1}H) and JEOL PS100 (^{1}H, ^{31}P) instruments. The latter was used in the continuous wave mode to obtain ^{1}H spectra, which are all reported as p.p.m. downfield from internal tetramethylsilane, and in the pulsed Fourier transform mode to obtain ^{31}P spectra. In most cases ^{31}P spectra were recorded both with and without the use of noise-modulated proton decoupling, and in all cases a sufficient number of free induction decay signals were accumulated to give good signal-to-noise ratios. ^{31}P Shifts

[15] R. D. Cook, C. E. Diebert, W. Schwarz, P. C. Turley, and P. Haake, *J. Amer. Chem. Soc.*, 1973, **95**, 8088.

[16] C. Brown and R. F. Hudson, *Tetrahedron Letters*, 1971, 3192.

are reported in p.p.m. from external 85% H_3PO_4, downfield shifts being designated as negative.

Preparation of 2-*Aryloxy*-3-*methyl*-2-*oxo*-1,3,2-*oxazaphospholan* (II).—These cyclic phosphoramidates were prepared by a general route applied here to the unsubstituted phenyl ester. A solution of phenyl phosphorodichloridate * (21.1 g, 0.10 mol) in benzene (60 ml) was added dropwise over 1 h to a solution of *N*-methylethanolamine (7.51 g, 0.10 mol) and triethylamine (20.20 g, 0.20 mol) in benzene (150 ml) with rapid stirring. Stirring was continued for 3 h after addition was complete and then the precipitated triethylamine hydrochloride was filtered off at the pump. The solvent was evaporated and the resulting oil was distilled under reduced pressure to give 3-methyl-2-oxo-2-phenoxy-1,3,2-oxazaphospholan [17] (7.79 g, 36.6 mmol, 37%).

TABLE 5

Data for the cyclic amidates (II) and (III)

Compound	Yield (%)	M.p. (°C) or b.p. (°C) [*p*/mmHg]	Analysis Found (%) C	H	N	Calc. (%) C	H	N
(IIa)	35	154—160 [0.02]	52.7	6.4	6.0	52.9	6.2	6.2
(IIb)	37	152—154 [0.02]	50.2	5.8	6.4	50.7	5.6	6.6
(IIc)	27 [a]	91—92	41.7	4.5	10.7	41.9	4.3	10.9
(IId)	58 [a]	92—93	41.7	4.4	10.5	41.9	4.3	10.9
(IIe)	10	182—184 [0.02]	49.3	5.7	5.6	49.4	5.8	5.8
(IIIa)	85 [b]	68—70	59.2	5.4	4.7	59.0	5.3	4.6
(IIIb)	45 [b]	64—66	61.1	5.1	5.1	61.3	5.1	5.0
(IIIc)	4 [b]	143—145	52.5	4.1	8.8	52.3	4.3	8.6

[a] Crude solid recrystallised from CCl_4. [b] Recrystallised from CCl_4–hexane.

Table 5 gives yields, physical properties, and analytical data for this and other derivatives similarly obtained. N.m.r. data for these esters are given in Table 6.

Preparation of 2-*Aryloxy*-2-*oxo*-3-*phenyl*-1,3,2-*oxazaphospholans* (III).—These esters were prepared from *N*-phenylethanolamine and the corresponding phosphorodichloridate in toluene in the presence of triethylamine in a similar manner. They were characterised by elemental analysis and by ^1H and ^{31}P n.m.r. spectroscopy (Tables 5 and 6).

Preparation of O-*Aryl* O′-*Methyl* NN-*Dimethylphosphoramidates* (IV).—The mixed phosphoramidates were prepared by a general route outlined below for the phenyl ester. However, due to the nature of reactions involved, stepwise replacement of chloride by oxygen and nitrogen ligands, pure products were not obtained. G.l.c. and n.m.r. analysis of the products obtained by distillation showed the presence of aryl dimethyl phosphates and/or *O*-aryl *NNN′N′*-tetramethylphosphorodiamidates as impurities which could not be removed by repeated fractionation. Attempts at separation by preparative g.l.c. (Pye 105; 4 m column; 15% SE30 on Chromosorb W, 200%) were unsuccessful due to decomposition of the compounds on the column. The impurities were shown not to interfere with the reactions observed kinetically (see below). The relative ratios of the three compounds obtained were determined by n.m.r. and/or g.l.c.

Phenyl phosphorodichloridate (21.10 g, 0.10 mol) dissolved in benzene (10 ml) was heated under reflux, and methanol (3.20 g, 0.10 mol) dissolved in benzene (30 ml) was added dropwise over 0.5 h. The mixture was then stirred and boiled for 2 h with a slow stream of nitrogen passing over the solution to blow off hydrogen chloride. The rate of nitrogen inflow was then increased and the remaining hydrogen chloride removed (0.5 h). The solution was then cooled in ice–water and a solution of dimethylamine (9.00 g, 0.20 mol) in benzene (60 ml) was added over 1 h with stirring. Stirring was continued whilst the mixture was allowed to attain room temperature (2 h). The precipitated dimethylamine hydrochloride was then filtered off and the solvent removed by evaporation. The resulting oil was distilled under reduced pressure to give a clear liquid (12.36 g), b.p. 104—105° at 0.1 mmHg, which was shown by g.l.c. and n.m.r. to consist of *O*-phenyl *O′*-methyl *NN*-dimethylphosphoramidate (88%), phenyl dimethyl phosphate (10%), and phenyl *NNN′N′*-tetramethyl phosphorodiamidate (2%). Attempts to improve the purity of the product by washing the crude material with dilute sodium hydrogen carbonate, a procedure which was successful in the case of the *N*-phenyl compound (V), served to eliminate the diamidate, but did not significantly reduce the amount of aryl dimethyl phosphate.

TABLE 6

N.m.r. data

Compound	^1H [a] NCH_3	NCH_2	OCH_2	NC_6H_5	AOr	^{31}P [b]
(IIa)	2.68(d)	3.20(m)	4.14(m)		7.08(m) [ArCH_3 2.19(s)]	
(IIb)	2.69(d)	3.15(m)	4.10(m)		7.27(m)	−15.5
(IIc)	2.84(d)	3.43(m)	4.40(m)		7.87(AA′BB′)	−21.5
(IIe)	2.78(d)	3.20(m)	4.15(m)		7.04(AA′BB′) [ArOCH_3 3.78(s)]	
(IIIa)		3.80(m)	4.30(m)	8.00—6.80(m) [ArOCH_3 3.80(s)]		−9.9
(IIIb)		3.52(m)	4.32(m)	7.30		−9.0
(IIIc)		3.90(m)	4.55(m)	8.30 + 7.30 (d + m)		−8.2

[a] Relative to internal tetramethylsilane. [b] Relative to external H_3PO_4.

Preparation of O-*Phenyl* O′-*Methyl* N-*Methyl*-N-*phenylphosphoramidate* (V).—Phenyl phosphorodichloridate (10.6 g) in benzene was treated with a solution of *N*-methylaniline (5.3 g) and triethylamine (5.1 g) in benzene at room temperature. After 2 h the precipitated amine hydrochloride was filtered off and the filtrate treated, without further purification,

* The phosphorodichloridates were prepared from $P(O)Cl_3$ and the appropriate phenol in good yield, and all had satisfactory analytical and/or spectroscopic data.

[17] J. Devillers, F. Mathis, and J. Navech, *Compt. rend.*, 1968, **267C**, 849.

with a solution of methanol (1.6 g) and triethylamine (5.1 g) in benzene again at room temperature. After the precipitated amine hydrochloride had been removed by filtration, the benzene solution was washed successively with dilute sodium hydrogen carbonate solution and water, then dried ($MgSO_4$). The benzene was then removed under reduced pressure and the residue distilled to give the *product* in 25% yield overall, b.p. 195—198° at 0.05 mmHg (Found C, 60.7; H, 5.8; N, 5.0. $C_{14}H_{16}NO_3P$ requires C, 60.65; H, 5.8; N, 5.05%), $\delta(CCl_4)$ 3.25 (3 H, d, J_{PH} 10 Hz), 3.81 (3 H, d, J_{PH} 11 Hz), and 7.3 (10 H, m).

Products.—In all cases, the concentration of phenol released in the first stage of the reaction was determined by u.v. spectroscopy from the intensity of absorption of the major peak compared with the absorption given by standard solutions.

The product composition was determined in each case by ^{31}P n.m.r. spectroscopy, under kinetic control, since the initial products underwent further hydrolysis.

In a typical analysis 0.1—0.2 g of compound was dissolved in 1 : 1 dioxan–D_2O (total 1.5 ml) and the normal and proton decoupled spectra recorded. The solution was then divided into two equal portions. Portion (i) was treated with 4N-NaOD (with the addition of further dioxan–D_2O if necessary) to make the resultant solution *ca.* 0.5N in NaOD, and the spectra recorded immediately. Portion (ii) was acidified with a few drops of concentrated hydrochloric acid and the spectra taken in a similar manner.

(a) 3-*Methyl*-2-*oxo*-2-*phenoxy*-1,3,2-*oxazaphospholan*. On treatment with alkali the initial absorption (−15.48 p.p.m.) was immediately replaced by a major absorption at −23.7 p.p.m. (92%) corresponding to the cyclic acid (91% determined from phenol released) and two minor absorptions at +4.8 (5%) and −6.0 p.p.m. (4%).

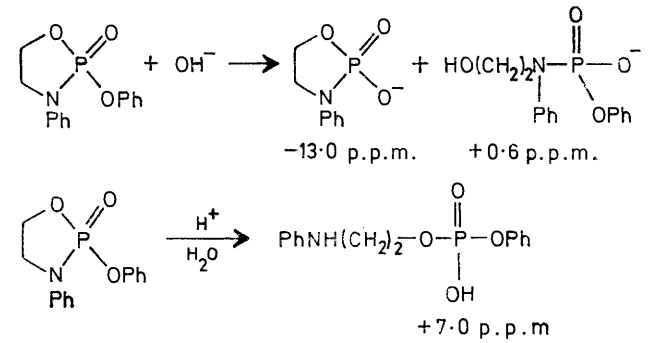
These were assigned to the open chain acids, phenyl 2-*N*-methylaminoethyl phosphate (formed by P–N fission) and *O*-phenyl *N*-methyl-*N*-(2-hydroxyethyl)phosphoramidate (formed by P–O fission) respectively.

These assignments were made by comparison with a large number of models where the phosphate shift is always downfield compared with the shift for the comparable phosphoramidate. For example, compare $(EtO)_2P(O)NHEt$ (δ_P −10.7 p.p.m.) with $(EtO)_3P(O)$ (δ_P +1.0 p.p.m.), and (MeO)(PhO)P(O)N(Me)Ph (δ_P −8.3 p.p.m.) and $(MeO)_2P(O)$-OPh (δ_P +4.1 p.p.m.). Ionisation in addition causes small downfield shifts, for example $(EtO)_2P(O)PH$ has δ_P +1.3 p.p.m., while the corresponding anion has δ_P −3.8 p.p.m.

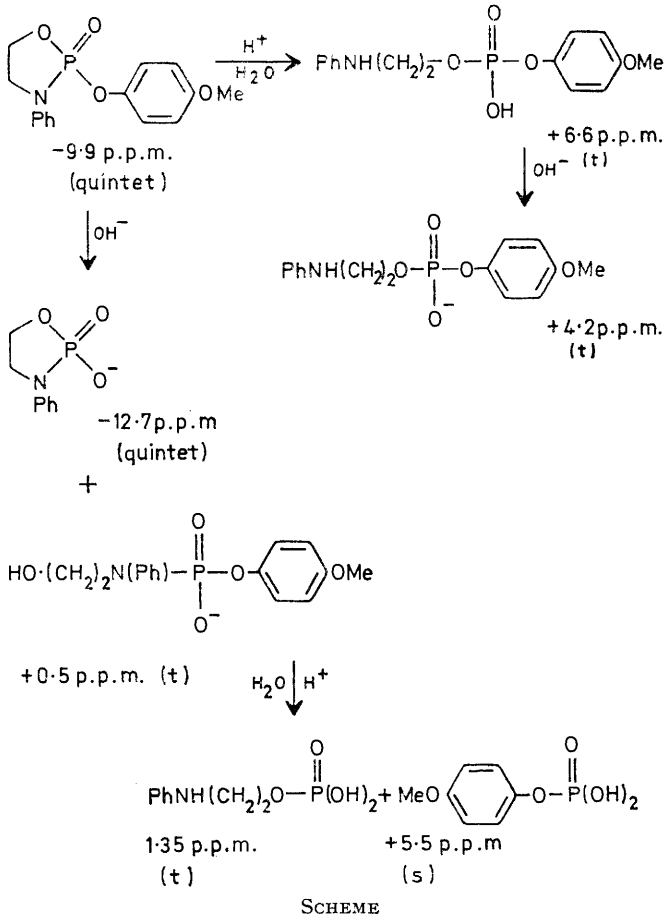
(b) 2-*Oxo*-2-*phenoxy*-3-*phenyl*-1,3,2-*oxazaphospholan*. The initial absorption at −9.0 p.p.m. was completely replaced in alkaline solution by a major peak at −13.0 p.p.m. (71%, *cf.* 69% obtained by release of phenol) attributed to the cyclic acid and a minor peak (29%) at +0.6 p.p.m. attributed to the 2-hydroxyethylphosphoramidate (formed by P–O fission). In acid solution, a single peak at +7.0 p.p.m. corresponding to the phosphate ester (P–N fission) was observed.

(c) 2-p-*Methoxyphenoxy*-2-*oxo*-3-*phenyl*-1,3,2-*oxazaphospholan*. In alkaline solution, the initial absorption at −9.9 p.p.m. was replaced by a major peak at −12.7 p.p.m. (73%, *cf.* 72% phenol released) corresponding to the cyclic acid, and a minor peak (27%) at +0.5 p.p.m. On treatment with acid these peaks were replaced by others at 1.35 and +5.5 p.p.m. respectively.

In acid solution the original ester gave a single product as shown by the absorption at +6.6 p.p.m., which on treatment with alkali was immediately converted to a single absorption at +4.2 p.p.m. These observations which are



in complete agreement with unique P–O fission in the alkaline reaction, and P–N fission in acid, are interpreted in the Scheme.



SCHEME

Kinetics of Alkaline Hydrolysis.—A solution (*ca.* 0.2M) of the cyclic ester in dioxan (10 ml) was prepared, and 10 μl added to sodium hydroxide solution (3 ml) of known concentration held in the temperature controlled cuvette in the u.v. spectrometer (SP 800). The disappearance of the ester and appearance of phenoxide ion were followed spectrophotometrically by changes in the intensity of absorption in the usual manner. Phenoxide ion was followed at 256, *p*-nitrophenoxide at 400, *p*-methoxyphenoxide at 312,

p-methylphenoxide at 289, and *m*-nitrophenoxide at 400 nm. The pseudo-first-order rate constants were obtained for various initial concentrations of sodium hydroxide (0.01—0.2M), and the second-order rate constants at 25° found by the appropriate computer program. The results given in the Tables show the reactions to be strictly of the first order.

As the hydrolysis of the acyclic ester was found to be very slow, higher concentrations of base (0.1—0.2N) were used in the temperature range 40—100°. Solutions of known concentrations were heated in Teflon bombs in a thermostat and at known times samples (3 ml) were removed and analysed over the 370—500 nm range. Pseudo-first-order constants were calculated only in those experiments where clear isosbestic points were observed. This procedure was possible for the impure samples of the *NN*-dimethylphosphoramidates, since the impurities were shown to hydrolyse either very rapidly or very slowly compared with the mixed ester.

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