The Reactivity of Organophosphorus Compounds. Part XXVIII.[1] Fast, Neighbouring Group-induced Rearrangement during Alkaline Hydrolysis of α-Hydroxyimino-*p*-nitrobenzyl Phosphates, Phosphonates, and Phosphinates

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A kinetic and product study of the fast, anchimerically assisted, alkaline hydrolysis of the 1 :1 adducts of *p*-nitrobenzonitrile oxide and various phosphorus acids has been carried out. The adducts were alkyl α-hydroxyimino-*p*-nitrobenzyl alkylphosphonates (II; R^1 = Me, R^2 = Me, Et, Pr, Pr^i, Bu^{t}CH$_2$, or Bu^{t}CHMe) and (II; R^1 = Et, Bu^t, or Ph, R^2 = Et), diethyl α-hydroxyimino-*p*-nitrobenzyl phosphate (II; R^1 = EtO, R^2 = Et), α-hydroxyimino-*p*-nitrobenzyl diethyl- and dihexyl-phosphinate (II; R^1 = R^2O = Et, hexyl), and the α-hydroxyimino-*p*-nitrobenzyl esters of 1-hydroxy-2,2,3,4,4-pentamethyl- and -2,2,3-trimethylphosphacyclobutan-1-ones [(VII) and (VIII); X = C(:NOH)·C$_6$H$_4$NO$_2$(-*p*)], and the corresponding esters of 1-hydroxy-3,4-dimethyl- and -3-methylphospholen oxides [(IX) and (X)]. In each case at pH 7—9, it is suggested that hydrolysis proceeds *via* intramolecular attack by the oximinate function on phosphorus to give a pentacovalent intermediate and hence a phosphonylated benzohydroxamic acid, which *via* fission and a subsequent Lössen rearrangement gives *p*-nitroaniline and the parent phosphorus acid. These intramolecular reactions are noteworthy, not only in view of their rapidity, but also because they are not subject to steric hindrance at phosphorus, in marked contrast to bimolecular, intermolecular attack by nucleophiles. Corresponding reactions of ethyl α-hydroxyimino-*p*-chlorobenzyl methylphosphonate are also reported.

In Part XXVII [1] the preparation of novel α-hydroxyimino-*p*-nitrobenzyl alkylphosphonates (II; R^1 = Me, R^2 = Me, Et, Pr, Pr^i, Bu^{t}CH$_2$, or Bu^{t}CHMe), (II; R^1 = Et, Bu^t, or Ph, R^2 = Et), and phosphates (II; R^1 = EtO, R^2 = Et) by reaction of the corresponding phosphorus acids (I) with *p*-nitrobenzonitrile oxide (Ar = *p*-NO$_2$C$_6$H$_4$) was described. These adducts were

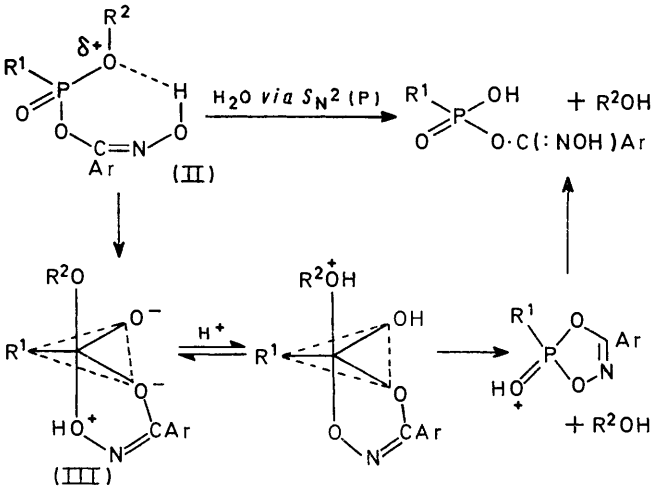
$$R^2O\cdot(R^1)P(:O)OH + ArC\equiv\overset{+}{N}\text{–}\bar{O} \longrightarrow R^2O\cdot(R^1)P(:O)\cdot O\cdot C(:NOH)Ar$$

(I) (II)

shown to undergo very fast, anchimerically assisted P–O fission at pH 2—3·5 in dilute aqueous dioxan, *ca.* 10^7 faster than corresponding hydrolyses of simple esters which undergo alkyl–oxygen fission under similar conditions, involving a novel participation of the proton of the hydroxyimino-group in (II) *via* either of the routes indicated in Scheme 1. In accord with this the adduct [Et$_2$P(O)·O·C(:NOH)Ar] from diethylphosphinic acid [Et$_2$P(O)OH] and the *O*-methylated adduct, α-methoxyimino-*p*-nitrobenzyl neopentyl methylphosphonate [Bu^{t}CH$_2$O(Me)P(O)OC(:NOMe)Ar], were stable in acid solution.

[1] Part XXVII, J. I. G. Cadogan, J. A. Challis, and D. T. Eastlick, *J. Chem. Soc.* (*B*), 1971, 1988.

We now report the results of kinetic and product studies on reactions of the above compounds in alkaline solution (pH 7—9), together with those of the adducts



Scheme 1

with *p*-nitrobenzonitrile oxide of dihexylphosphinic acid [(C$_6$H$_{13}$)$_2$P(O)OH], 1-hydroxy-2,2,3-trimethylphosphacyclobutan-1-one {(VIII; X = H); adduct: [VIII; X = O·C(:NOH)·C$_6$H$_4$NO$_2$(-*p*)]}, 1-hydroxy-2,2,3,4,4-

pentamethylphosphacyclobutan-1-one {(VII; X = H); adduct: [VII; X = O·C(:NOH)·$C_6H_4NO_2$(-*p*)]}, 1-hydroxy-3,4-dimethyl-3-phospholen oxide {(IX; X = H); adduct: [IX; X = O·C(:NOH)·$C_6H_4NO_2$(-*p*)]}, 1-hydroxy-3-methyl-2-phospholen oxide {(X; X = H); adduct: [X; X = O·C(:NOH)·$C_6H_4NO_2$(-*p*)]}. Also reported are reactions of ethyl α-hydroxyimino-*p*-chlorobenzyl methylphosphonate (II; Ar = *p*-ClC_6H_4, R^2 = Et, R^1 = Me). As will be seen, fast, anchimerically assisted rearrangements followed by hydrolyses again occurred, but which gave products completely different from the corresponding reactions at low pH.

TABLE 1

Rate constants for hydrolysis of $R^1R^2P(O)OC(:NOH)$-$C_6H_4NO_2$(-*p*) at 25·0°

Compound	R^1	R^2	pH and rate constant ($10k_1$/min^{-1})			
1	MeO	Me	pH	7·95	8·42	9·07
			$10k_1$	1·10	1·05	1·03
2	EtO	Me	pH	8·00	8·60	9·09
			$10k_1$	0·90	0·88	0·82
3	PrO	Me	pH	7·98	8·48	8·95
			$10k_1$	0·74	0·72	0·67
4	Pr^{i}O	Me	pH	8·09	8·48	9·10
			$10k_1$	0·45	0·47	0·44
5	Bu^{t}CH$_2$O	Me	pH	8·03	8·50	9·05
			$10k_1$	0·60	0·61	0·59
6	Bu^{t}CHMeO	Me	pH	8·00	8·48	8·95
			$10k_1$	0·41	0·40	0·41
7*‡	EtO	EtO	pH	7·91	8·48	8·98
			$10k_1$	0·25	0·27	0·30
8	EtO	Et	pH	7·98	8·48	9·04
			$10k_1$	0·78	0·66	0·67
9†	Et	Et	pH	7·87	8·47	8·98
			$10k_1$	0·096	0·064	0·042
10	EtO	Bu^t	pH	8·04	8·47	9·08
			$10k_1$	0·65	0·59	0·57
11	EtO	Ph	pH	7·97	8·48	8·97
			$10k_1$	3·70	4·42	4·79
13*	see Table 2		pH	7·95	8·45	9·08
			$10k_1$	0·59	0·54	0·47
14	see Table 2		pH	8·05	8·45	9·30
			$10k_1$	0·36	0·39	0·37
15	see Table 2		pH	7·98	8·53	9·09
			$10k_1$	0·17	0·14	0·14
16	see Table 2		pH	7·98	8·48	9·13
			$10k_1$	0·34	0·29	0·27

* At 0·00°. † 4% ethanol–dioxan (see text). ‡ Extrapolated value of k_1 at 25° and pH 8·48 = 0·91 min^{-1}.

TABLE 2

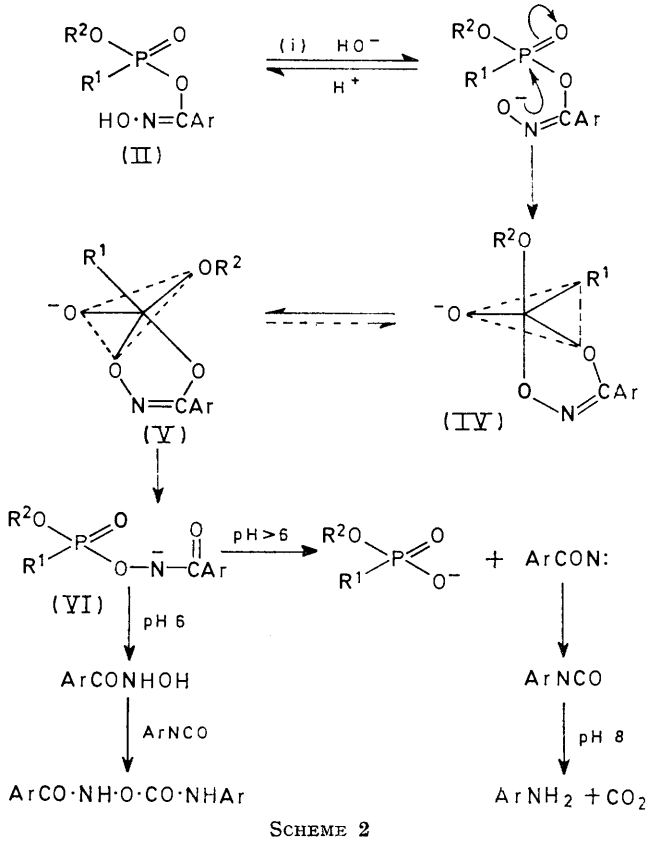
Preparation of 1 : 1 adducts of *p*-nitrobenzonitrile oxide and hydrogen phosphinates

Compound	1 : 1 Adduct*	Analysis (%)† C	H	N	Yield (%)	M.p. (°C)
12	$Hex_2P(O)X$	57·2	7·9	7·3	73	97—99
		57·3	7·8	7·0		
13	(VII)	52·8	6·0	8·1	78	125
		52·9	6·2	8·2		
14	(VIII)	49·8	5·3	9·2	13	118—120
		49·9	5·5	9·0		
15	(IX)	50·0	4·7	8·9	44	127
		50·0	4·9	9·0		
16	(IX)	48·8	4·1		36	118—120
		48·7	4·4			

Compound	τ Values
12	1·74 (4H, q, ArH), 8·35 (4H, d, PCH_2), 8·6—9·1 (26H, m)
13	1·92 (4H, q, ArH), 8·0—9·1 (16H, m)
15	1·92 (4H, q, ArH), 7·3, 7·92, 8·22, 8·7 (10H, m)
16	1·73 (4H, q, ArH), 8·59 (6H, s, CMe_2)

* X = OC(*p*-$NO_2C_6H_4$):NOH † New compounds: top row 'Found,' bottom row 'Required.'

*Alkaline Hydrolysis of α-Hydroxyimino-*p*-nitrobenzyl Esters of Phosphorus Acids.*—(i) *Products.* In all cases studied (see Tables 1 and 2) rearrangement and hydrolysis proceeded at pH 7—9 by P–O fission to give ultimately, and quantitatively, *p*-nitroaniline and the corresponding phosphorus acid, *e.g.* $R^2O·(R^1)P(:O)·O·C(:NOH)Ar \longrightarrow R^2O·(R^1)P(:O)OH + ArNH_2 + CO_2$. This, together with evidence given below, suggests reaction as described in Scheme 2, whereby the hydroxyiminate anion undergoes intramolecular attack at phosphorus to give the pentacovalent species (IV) which, after the necessary pseudorotation to (V), leads to the phosphonylated benzohydroxamate (VI) which rapidly loses the phosphorus acid anion to create an electron deficient nitrogen atom. The resulting species then, by a Lössen rearrangement, gives *p*-nitrophenyl isocyanate and hence, at pH 8—9, *p*-nitroaniline. This proposal is further supported by the following observations. (*a*) Samuel and Silver [2] have shown that phosphoryl

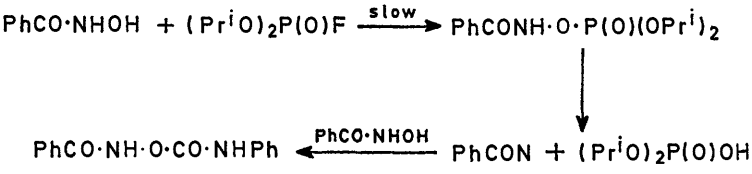


SCHEME 2

hydroxamates formed from phosphorofluoridates and benzohydroxamic acid undergo fast rearrangement at pH 6 to give isocyanate which is trapped by unchanged benzohydroxamic acid to give a carbamate (Scheme 3). (*b*) In our case, reaction of the propyl methylphosphonate adduct (II; R^2 = Pr, R^1 = Me) in the presence of

[2] D. Samuel and B. L. Silver, *J. Amer. Chem. Soc.*, 1963, **85**, 1197.

cyclohexylamine gave *N*-cyclohexyl-*N'*-(*p*-nitrophenyl) urea [reaction (1)]. (*c*) The *O*-methylated neopentyl methylphosphonate adduct [$Bu^tCH_2O{\cdot}(Me)P(:O){\cdot}O{\cdot}C(:NOMe)Ar$], which cannot form an hydroxyiminate anion, was stable in alkali, under these conditions.



SCHEME 3

We discount alternative modes of reaction involving either attack by water on phosphorus with expulsion of

$$(PrO)MeP(:O){\cdot}O{\cdot}C(:NOH)Ar \xrightarrow[\text{Scheme 2}]{via} ArNCO \xrightarrow{C_6H_{11}NH_2} ArNH{\cdot}CO{\cdot}NHC_6H_{11} \quad (1)$$

p-nitrobenzohydroxamic acid or attack by water on the *p*-nitrobenzylic carbon atom with resulting PO–acyl fission and formation of *p*-nitrobenzohydroxamic acid because *p*-nitrobenzohydroxamic acid or its transformation products were not formed (but see the case of the *p*-chloro-analogue at lower pH, below).

acyclic alkyl alkylphosphonate adducts (II) are almost constant over the pH range 8—9, falling only very slightly at pH 9. The rates are also very similar to one another, there being only a factor of 2·5 between the fastest and the slowest. The form of the kinetics followed a rapid deprotonation of the hydroxyimino-group with a slower first-order decomposition to yield the phosphorus acid anion and *p*-nitroaniline.

If Scheme 2 is operating, as we suggest, the independence of the rates on pH in the range 8—9 implies an unusually low pK_a for the α-hydroxyimino-*p*-nitrobenzyl esters studied (*p*-nitrobenzaldoxime, for example, has pK_a 10). Our experimental results support this fully: α-hydroxyimino-4-nitrobenzyl dicyclohexylphosphinate (I; $R^1 = R^2O = C_6H_{11}$), where direct measurement could be achieved because hydrolysis during titration in the acid region cannot occur,[1] was found to have pK_a 5·6 in aqueous ethanol (50% w/v). The pK_a

TABLE 3

Rate constants and Arrhenius parameters for hydrolysis of $R^1R^2P(O)OC(:NOH)C_6H_4NO_2(-p)$ at pH 8·45 in the temperature range 0—39° *

Compounds (see Tables 1 and 2)		Temp. (°C) and rate constants ($100k_1$/min^{-1})						E_{act}/kJ mol^{-1} (± 5%)	$\Delta S^{\ddagger}$/J mol^{-1} K^{-1} (± 1)
1	Temp.	25·0	18·3	13·9	0·00			81·5	−7·8
	$100k_1$	10·5	4·36	1·99	0·38				
3	Temp.	25·0	19·9	13·9	7·5			88·0	−3·2
	$100k_1$	7·20	4·05	1·70	0·69				
		7·20	4·10		0·66				
7	Temp.	15·8	12·1	5·0	3·1			92·6	+7·3
	$100k_1$	28·2	16·9	5·8	3·10				
		27·4	16·5	5·6	3·00				
8	Temp.	25·0	20·1	13·2	5·7	0·00		78·0	−11·4
	$100k_1$	6·5	3·50	1·26	0·60	0·28			
		6·4	3·44	1·27	0·54	0·28			
9	Temp.	39·0	35·1	29·5	25·0			78·0	−16·2
	$100k_1$	2·40	1·72	0·93	0·55				
			1·62		0·60				
10	Temp.	30·7	25·0	20·3	14·7			93·0	+0·5
	$100k_1$	12·0	6·1	3·20	1·60				
		12·1	6·0	3·25	1·65				
13	Temp.	31·4	25·0	20·2	13·4	8·2		81·7	−8·8
	$100k_1$	10·4	5·40	2·81	1·32	0·62			
		10·8	5·40	2·86	1·29	0·64			
14	Temp.	25·0	18·5	18·1	11·7	8·4	2·1	86·5	−4·7
	$100k_1$	3·66	1·56	1·53	0·73	0·39	0·23		

* Very satisfactory straight line plots were obtained.

(ii) *Kinetic results and discussion.* The kinetic results of the alkaline hydrolysis of the α-hydroxyimino-*p*-nitrobenzyl esters of phosphorus acids in 2% aqueous dioxan or ethanol are summarised in Tables 1 and 3. The results of these experiments support the proposed Scheme 2 and also allow further refinements to be made.

(iia) *Acyclic adducts.* The rates of reaction of the in water would not be expected to differ greatly from this value, since Bell [3] has shown that the change in pK_a in going from water to ethanol for a series of carboxylic acids does not change by more than 0·7 units. In the case of the corresponding phosphonates and

[3] R. P. Bell, 'The proton in Chemistry,' Cornell Univ. Press, Ithaca, 1959, p. 44.

phosphates direct measurement by titration is, of course, impossible as a result of the very rapid hydrolysis of the product in acid solution.[1] Indirectly the pK_a of these esters can be determined from hydrolysis data in acid solution. At 0° for ethyl α-hydroxyimino-*p*-nitrobenzyl methylphosphonate (II; $R^1 = Me$, $R^2 = Et$, $Ar = p\text{-}NO_2C_6H_4$) the calculated pK_a is 4·5.

In further support of Scheme 2, the reactions are very fast ($t_{\frac{1}{2}}$ *ca.* 9 min at 25°), indicating their anchimeric nature, while the observed relative rates of hydrolysis

TABLE 4

Relative rates of hydrolysis of adducts

Adduct	Relative rate
$(EtO)_2P(O)\cdot O\cdot C(:NOH)Ar$	140
$EtO\cdot(Et)P(O)\cdot O\cdot C(:NOH)Ar$	10
$Et_2P(O)\cdot O\cdot C(:NOH)Ar$	1

(Table 4) of the diethyl phosphate, ethyl ethylphosphonate, and diethylphosphinate-adducts (II; $R^2 = Et$, $R^1 = EtO$; $R^2 = Et$, $R^1 = Et$; and $R^1 = R^2O = Et$), can be explained on the basis of the intermediacy of a pentacovalent intermediate (V) for the following reasons. Thus, the initially formed pentacovalent intermediate (IV) is formed with an alkoxy-group in the apical position and an alkyl group in an equatorial position, in accordance with the preference rules for pseudorotation.[4,5] It is then necessary for this initial form (IV) to undergo pseudorotation, so as to allow the benzyl–oxygen bond to break from the preferred apical position.

The pseudorotated form (V) is the one that is most likely to be formed if the preference rules are obeyed.[4-6] The pentaco-ordinate intermediate (V) will be more readily formed from the diethyl phosphate adduct (II; $R^2 = Et$; $R^1 = EtO$) than from either the ethyl ethylphosphonate adduct (II; $R^2 = R^1 = Et$) or the diethylphosphinate adduct (II; $R^2O = R^1 = Et$), because the apical group R^1 is alkoxy rather than alkyl. It has been shown [6] that the formation of the pentaco-ordinate intermediate in which one of the apical groups is alkyl, is inhibited. Further, the formation of the initial pentaco-ordinate intermediate is inhibited for the diethylphosphinate adduct (IV; $R^2O = R^1 = Et$) because of the apical ethyl group, whereas for the other two adducts the initial apical group is the preferred ethoxy. All this is in accord with the results given in Table 4.

It is noteworthy that the rates of alkaline hydrolysis of the alkyl alkylphosphonate adducts (II) are very similar and are almost independent of steric factors. Thus the *P*-t-butyl adduct (II; $R^2 = Et$, $R^1 = Bu^t$) hydrolyses at almost the same rate as the *P*-ethyl analogue (II; $R^2 = R^1 = Et$). This is to be compared with the behaviour observed in the alkaline hydrolysis of the simple di-isopropyl methyl- and di-isopropyl t-butyl-phosphonates where strong steric hindrance causes a large rate decrease (500 : 1).[7] Thus attack by the particularly well positioned neighbouring hydroxyiminate anion is not subject to the steric factors implicit in apical bimolecular attack by an external nucleophile. Indeed, inspection of models suggest that such intramolecular attack is not purely apical.

The activation energies (Table 3) for the hydrolysis of the adducts (II) are similar in magnitude but rather higher (78—93 kJ mol^{-1}) than those of bimolecular alkaline hydrolysis of simple phosphorus esters (34—77 kJ mol^{-1}).[8]

Although the differences are small the activation energy is greatest for substituents which are capable of increasing the electronic charge at phosphorus, either inductively (II; $R^2 = Et$, $R^1 = Bu^t$) or mesomerically (II; $R^2 = Et$, $R^1 = EtO$). The activation energy also increases with increasing alkyl substitution in the ester group. Similar trends have been reported in the literature for alkaline hydrolyses, proceeding by attack on phosphorus, of other phosphorus compounds.[1,9] This lends support to the proposed attack of the hydroxyiminate anion on the phosphorus centre in the initial formation of the cyclic intermediate.

The small, in general negative, values of the activation entropies (Table 3) show that there is an increase in the order of the transition state which can be associated with the proposed cyclic transition state. The hydroxyiminate function would be expected not to show a great loss in its degrees of freedom in forming the transition state, since the configuration of the C=N bond holds the anion in a position that is favourable for attack in a five-membered transition state leading to the intermediate.

These results are therefore accommodated by Scheme 2 amplified as follows: the protonation–deprotonation step (i) is fast; the attack by the neighbouring hydroxyiminate anion is not sterically hindered; the breakdown of the phosphonylated hydroxamate is known to be fast [3] as is the hydration of the isocyanate (Experimental section); and the relative rates of reaction of the diethyl phosphate, ethyl ethylphosphonate, and diethylphosphinate-adducts can be accommodated by current theories of pseudo-rotation. This is in accord with the comparatively small $\Delta S^{\ddagger}$ values, the insensitivity of the rates to steric factors, electronegatively factors being dominant, and also with the greater rate of reaction of the ethyl phenylphosphonate adduct (II; $R^2 = Et$, $R^1 = Ph$), compared with the methyl methylphosphonate adduct where the high electronegativity of phenyl, approaching that of ethoxy, becomes more important than steric factors so that the formation of (V) becomes less inhibited than that of the alkyl alkylphosphonates.

(iib) *Cyclic adducts.* The results of hydrolyses of a series of adducts of cyclic phosphinates (Tables 1 and 3) are also in accord with the above mechanism. That the rates of hydrolysis of the adducts (VII)—(X) (Table 5)

[4] D. B. Boyd, *J. Amer. Chem. Soc.*, 1969, **91**, 1200.
[5] F. H. Westheimer, *Accounts Chem. Res.*, 1968, **1**, 70; I. Ugi and F. Ramirez, *Chem. Brit.*, 1972, **8**, 207.
[6] D. S. Frank and D. A. Usher, *J. Amer. Chem. Soc.*, 1967, **89**, 6360.
[7] R. F. Hudson and L. Keay, *J. Chem. Soc.*, 1956, 2463.
[8] J. R. Cox and O. B. Ramsay, *Chem. Rev.*, 1964, **64**, 317.
[9] (*a*) G. Aksnes and J. Songstod, *Acta Chem. Scand.*, 1965, **19**, 893; (*b*) R. F. Hudson and L. Keay, *J. Chem. Soc.*, 1960, 1859.

are more rapid than that of the acyclic diethylphosphinate adduct (II; $R^1 = R^2O = Et$) is as expected following the relief of strain in forming the initial pentacovalent intermediate analogous to (IV). The rates of rearrangement of the cyclic five-membered adducts (Tables 1, 3, and 4) are intermediate between that of the acyclic adduct and the cyclic four-membered adducts, thus reflecting the increased strain inherent in the latter. This order of reactivity of the cyclophosphinate adducts parallels the behaviour previously recorded [10] for alkaline hydrolysis of simple alkyl cyclophosphinates, four-membered cyclic derivatives being more easily hydrolysed than the five-membered analogues.

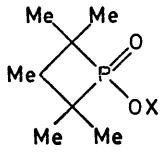
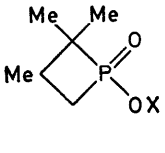
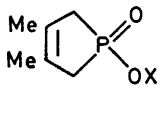
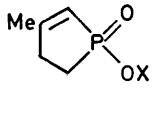
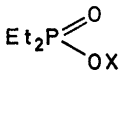
(the hydroxyiminate group) in the former leading to a discrete pentacovalent intermediate (V).

Previously Reported Reactions relevant to the Alkaline Hydrolysis of the Adducts (II).—Adducts of benzonitrile oxide and carboxylic acids have been described,[11,12] but in some cases,[12,13] instead of the initial adduct, products of rearrangement, *e.g.* (XI), analogous to the phosphonylated hydroxamic acids reported as intermediates in this paper, were isolated (Scheme 4).

A closer analogy is provided by Gaudiano *et al.*[14] who obtained Δ^2-1,2,5-oxazaphosph(v)olines (XII) from 2-oximinophosphonium salts (XIII), in high yield (Scheme 4). The ease of formation of the former compound in

TABLE 5

Rates of alkaline hydrolysis of cyclic phosphinate adducts relative to α-hydroxyimino-*p*-nitrobenzyl diethylphosphinate

Adduct	 (VII)	 (VIII)	 (IX)	 (X)	
Relative rate	8·5	6·1	2·2	4·5	1

X = ·C(:NOH)·$C_6H_4NO_2$(*p*)

There is a major difference, however, between the alkaline hydrolysis of our four-membered cyclic phosphinate adducts [(VII) and (VIII); X = C(:NOH)·Ar] and that of the simple analogous methyl esters [(VII) and (VIII); X = Me] (Table 6) studied by Hawes and

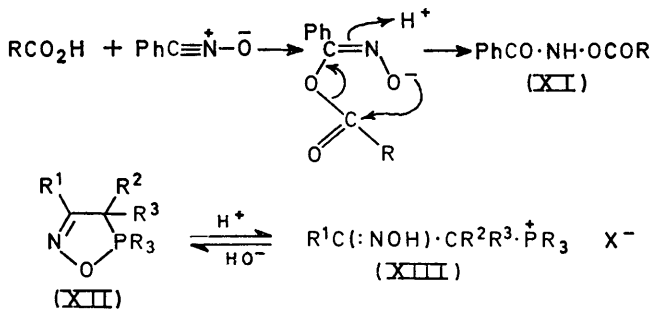
TABLE 6

Relative rates of hydroylsis of esters (VII) and (VIII) of 1-hydroxyphosphacyclobutan-1-ones

X	Relative rates (VII) : (VIII)
Me	1 : *ca* 4 × 10^3
C(:NOH)·$C_6H_4NO_2$(-*p*)	1 : 0·7

Trippett.[10] These workers attributed their observed faster rate of hydrolysis (by a factor of 4 × 10^3) of the trimethyl derivative (VIII; X = Me), compared with the pentamethyl analogue (VII; X = Me), to steric hindrance, in the latter case, of the attacking nucleophile. No such retardation by steric hindrance was observed in the corresponding α-hydroxyimino-*p*-nitrobenzyl esters, however (Table 6). Rather, the pentamethyl derivative was hydrolysed slightly faster than the less hindered trimethyl derivative. This is in accord with the insensitivity of the acyclic α-hydroxyimino-analogues towards steric effects and with the mechanism (Scheme 2) discussed above. The essential difference between this mechanism and that applying in Hawes and Trippett's case lies in the anchimeric participation of the nucleophile

this case suggests that the deprotonated hydroxyiminate anion is well positioned in the molecule easily to complete the five-membered ring. By analogy, the deprotonated hydroxyiminate anion is equally well situated for the



SCHEME 4

formation of the initial pentaco-ordinate intermediate (V) (Scheme 2) in the adducts (II) described in this paper.

Less mechanistically similar examples of anchimeric attack by neighbouring hydroxyiminate on phosphorus have been provided by the case of accelerated hydrolysis of *p*-nitrophenyl phenacyl methylphosphonate oxime [15] and by the conversion of 1,2-naphthoquinone 1-oxime 2-(*OO'*-diphenyl)phosphorohydrazone in boiling, dilute aqueous potassium carbonate solution to 1*H*-naphtho-[2,1-*d*]triazole in 89% yield.[16]

*Hydrolysis of Ethyl α-Hydroxyimino-*p*-chlorobenzyl*

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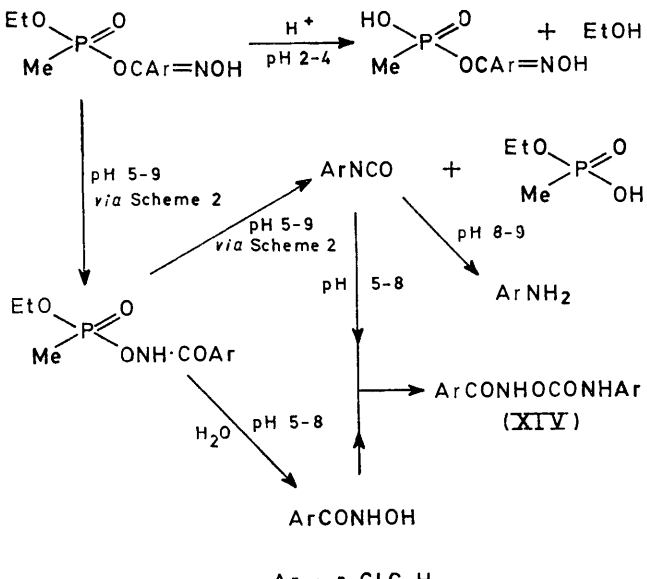
Methylphosphonate.—At pH 2—4 and 9—10 this compound behaved as expected giving hydrogen α-hydroxyimino-*p*-chlorobenzyl methylphosphonate and ethanol in the first case [1] and *p*-chloroaniline at the higher pH. It is of interest in the present context mainly, however, because at around neutral pH 5—8 *O*-p-chlorophenylcarbamoyl *p*-chlorobenzohydroxamate (XIV) was formed. This indicates a duality of mechanism in this intermediate pH range, *i.e.* reaction as in Scheme 2 to give *p*-chloroaniline *via* *p*-chlorophenylisocyanate together with competing hydrolysis of the intermediate phosphonylated benzohydroxic acid to give *p*-chlorobenzohydroxamic acid, which reacts with *p*-chlorophenyl isocyanate, some of which is unchanged at this pH, to give the observed product (Scheme 5).



SCHEME 5

EXPERIMENTAL

1-Hydroxy-2,2,3,4,4-pentamethylphosphacyclobutan-1-one.—This was obtained by the *in situ* hydrolysis of the chloride obtained from 2,4,4-trimethylpent-2-ene, anhydrous aluminium chloride, and redistilled phosphorus trichloride according to McBride's method. After crystallisation from light petroleum (b.p. 60—80°), the anhydrous acid, m.p. 71—72° (lit.,[17] 71°), was obtained by drying it above the m.p. over phosphorus pentoxide under high vacuum.

1-Hydroxy-2,2,3-trimethylphosphacyclobutan-1-one.— This was prepared analogously by substituting 2,3-dimethylbut-1-ene as the olefin substrate. No attempt was made to isolate the acid chloride and after decomposition of the intermediate, the oil was boiled with water (250 ml) for 75 min. During this time a white amorphous solid (22·7 g), m.p. >240°, formed, which was filtered off, but not further characterised. On removal of water, the oil was dried and the acid obtained by distillation from glass-wool in a side-arm receiver at a block temperature of 210° at 0·05 mmHg. The acid, a faintly coloured oil which darkened on standing, was characterised as its *cyclohexylamine salt*, m.p. 184—185° (Found: C, 57·7; H, 10·4; N, 5·9. $C_{12}H_{26}NO_2P$ requires C, 58·3; H, 10·6; N, 5·7%).

1-Hydroxy-3,4-dimethyl-3-phospholen Oxide.—This was prepared by adaptation of the method of Hunger.[18] Phosphorus tribromide (103 g, 0·38 mol) was added dropwise (3—4 h) with stirring, to 2,3-dimethylbutadiene (35·2 g, 0·43 mol) in dry light petroleum (b.p. 40—60°) (500 ml) at a temperature between −15 and −10°. The solution was maintained at −10° for 1 h, and then kept for 5 days at room temperature. The hygroscopic solid which precipitated was immediately dissolved in methylene chloride (1 l) and was esterified by the dropwise addition (1 h), with vigorous stirring at −10°, of a mixture of methanol and triethylamine (1·5 mol, based on 100% yield of phosphorane) dissolved in methylene chloride (100 ml). The solution was warmed to room temperature with stirring (2 h), solvents were removed under reduced pressure, and the base hydrochloride was filtered from a benzene solution. The methyl ester (21·8 g, 0·14 mol, 57%) was obtained by distillation, b.p. 66—76° at 0·05 mmHg, n_D^{20} 1·4878 (lit.,[19] 131° at 10 mmHg, *n* 1·4892).

The corresponding acid, which was not further purified, was obtained by hydrolysis of the methyl ester in boiling hydrochloric acid (1 : 1) for 12 h. It is generally agreed that the double bond does not migrate to the 2-position when it is substituted by two methyl groups in the 3- and 4-positions. Quin and his co-workers [20] have demonstrated the stability of the related 1,3,4-trimethyl-3-phospholen oxide in boiling hydrochloric acid (3N). No change was detected after 18 h and there was only slight reaction to yield two products after 72 h. The isomers are separable by g.l.c.

1-Hydroxy-3-methyl-2-phospholen Oxide.—The methyl ester, b.p. 72—75° at 0·05 mmHg, n_D^{25} 1·4902 (lit.,[20] b.p. 79° at 0·04 mmHg) was prepared from isoprene by the method of Quin *et al.*[20]

The position of the double bond was found to lie in the 2-position by n.m.r. and i.r. spectroscopy. The n.m.r. spectrum of a 20% solution ($CDCl_3$) showed τ 4·08 (1H, d, C=C–H, *J* 24 Hz), 6·32 (3H, d, $POCH_3$, J_{POCH_3} 11 Hz), and 7·2—8·3 (7H, m, CH_2 and CMe_3). The i.r. spectrum (liquid film showed prominent peaks at $\nu_{max.}$ 1610 (C=C, s), 1220 (P=O, s), 1040 (P–O–Me, s), 925 (m), 885 (m), and 800 (s) cm^{-1}.

Quin and his co-workers [20] reported the part-spectrum of the methyl ester and gave the position of the vinyl proton doublet as τ 3·7 (*J* 24 Hz). They also reported that the i.r. frequency of C=C was generally lower and more intense for the 2- than the 3-isomer. The frequency observed above is in good agreement with the value observed for the related 1,3-dimethyl-2-phospholen oxide.

The acid was obtained by hydrolysis of the ester in boiling hydrochloric acid (1 : 1) for 4 h. After removal of water under reduced pressure, the acid was dried and distilled (block temperature 230—260° at 0·12 mmHg) to yield a yellow oil, which partly solidified on standing. The i.r. spectrum (liquid film) showed peaks characteristic of an acid, $\nu_{max.}$ 2700 and 2280br (POH), 1600 (C=C), and 1180 and 1160 (PO_2^-) cm^{-1}.

Dihexylphosphinic Acid.—This was prepared by adaptation of Silver's method for phosphinamides.[21] Bromine (3·20 g,

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[21] H. Silver, *J. Chem. Soc.* (*C*), 1967, 1326.

20 mmol) in carbon tetrachloride (10 ml) was added dropwise to a stirred solution of dihexylphosphine oxide (4·35 g, 20 mmol) in carbon tetrachloride (50 ml). The mixture was allowed to react overnight at room temperature. Shaking with a solution of sodium carbonate (6·45 g, 100 mmol) in water (10 ml), acidification with sulphuric acid (2N), washing with water (3 × 50 ml), and drying ($MgSO_4$) of the carbon tetrachloride solution gave dihexylphosphinic acid on evaporation of solvent. Recrystallisation from light petroleum (b.p. 60—80°) containing animal charcoal yielded pure product (2·7 g, 58%), m.p. 75·5—77·0°, equivalent weight 240 (Calc. for $C_{12}H_{27}O_2P$: 234). Williams and Hamilton [22] gave m.p. 77·0—78·5°.

*Preparation of α-Hydroxyimino-*p*-nitrobenzyl Phosphylates.*—These were prepared, as described in the previous Part,[1] from *p*-nitrobenzonitrile oxide and the corresponding hydrogen phosphylate. Compounds 1—11 (for structures see Table 1) were as described previously.[1] Details of compounds 12—16 are given in Table 2.

*Reaction of α-Hydroxyimino-*p*-nitrobenzyl Propyl Methylphosphonate with Cyclohexylamine.*—Cyclohexylamine (25 ml) was added to the phosphonate (0·3 g) in dioxan (5 ml). After 11 h at room temperature, the solvents were removed at room temperature under reduced pressure. The addition of light petroleum (b.p. 40—60°) to the residue dissolved in the smallest volume of dioxan precipitated a light yellow solid (0·15 g). A further quantity of the solid (22 mg; identified by its i.r. spectrum) was obtained by elution with ether of the residue absorbed on alumina. The solid was identified as N-*cyclohexyl*-N′-(p-*nitrophenyl*)*urea* (79%) by comparison of its i.r. spectrum to that of an authentic sample prepared from cyclohexylamine and *p*-nitrophenyl isocyanate. The compounds had identical R_F values (alumina, ether solvent, iodine detection, R_F 0·36), m.p. and mixed m.p. 196°, resolidification and second m.p. 236° (Found: C, 59·7; H, 6·3. $C_{13}H_{17}N_3O_3$ requires C, 59·3; H, 6·5%).

*Hydrolysis of α-Hydroxyimino-*p*-nitrobenzyl Phosphylates at* pH >5.—(a) *Products.* In general the solutions were bright yellow and had u.v. spectra showing absorptions with $\lambda_{max.}$ 380—382 nm ($\lambda_{max.}$ for *p*-nitroaniline 382 nm). The solutions, when run on t.l.c. plates (silica or alumina coated, ether developer, chromogenic detection by iodine vapour or *p*-dimethylaminobenzaldehyde, R_F values *ca.* 0·5), showed only one spot, which was identical with that of *p*-nitroaniline.

α-Hydroxyimino-*p*-nitrobenzyl propyl methylphosphonate (0·41 g, 1·41 mmol) was decomposed in 98% aqueous dioxan buffer, pH 9·2, at room temperature for 6 h. The solvents were removed under reduced pressure and the residue extracted with chloroform and ethyl methyl ketone to leave a white, water-soluble solid, m.p. >260°, which was the salt component of the buffer. The organic extract was chromatographed on alumina, and *p*-nitroaniline (0·18 g, 93%), m.p. 147° and mixed m.p. 149°, was eluted with 50% ether–ethyl acetate.

No pinacolyl alcohol could be detected by g.l.c. after α-hydroxyimino-*p*-nitrobenzyl pinacolyl methylphosphonate was allowed to decompose in aqueous dioxan buffer, pH 9·20, and *p*-nitroaniline was again recovered in 83% yield.

In representative cases (compounds 7—11, 13, 15) the adducts were hydrolysed as follows and *p*-nitroaniline quantitatively estimated by u.v. spectroscopy. Thus, a known quantity of compound was dissolved in dioxan (2 ml) and a portion (1 ml) was introduced by a pipette into the titration vessel of the Radiometer assembly containing sodium chloride solution (25 ml, 0·1M) and allowed to react for 10 half-lives at pH 8·43. The volumes of titrant added were recorded. The optical density of the hydrolysate was determined on a sample made by withdrawing 1 ml of the solution and diluting with water (×25). All the compounds showed only the absorption at 382 nm after 10 half-lives. The absorption at 268 nm in the starting material had completely disappeared. The estimated yields of *p*-nitroaniline were in the region 90—92%.

(b) *Kinetics.* The kinetics of alkaline hydrolysis were measured by means of a Radiometer automatic titration assembly as described previously.[1] Rate data are recorded in Table 1 and Arrhenius parameters in Table 3.

Reaction of p-*Nitrophenyl Isocyanate in Aqueous Alkaline Solution.*—*p*-Nitrophenyl isocyanate (0·04 mmol) in dioxan (0·5 ml) was added to the Radiometer titration cell at pH 8·48 and 25°. Rapid uptake of sodium hydroxide solution occurred, which was completed in 2 min to give a yellow solution, $\lambda_{max.}$ 385 nm ($\lambda_{max.}$ for *p*-nitroaniline 382 nm). The rate of addition of sodium hydroxide was limited by the rate of operation of the automatic burette and it is thus considered that *p*-nitrophenyl isocyanate reacts instantaneously to form *p*-nitroaniline under the reaction conditions.

*Reaction of α-Methoxyimino-*p*-nitrobenzyl Neopentyl Methylphosphonate in Alkaline Solution.*—The reaction was examined by u.v. spectroscopy. A drop of the phosphylate [1] in 5% dioxan–water with sodium hydroxide solution (2M) gave no absorption in the region 350—400 nm ($\lambda_{max.}$ for *p*-nitroaniline 382 nm) after 105 min, which corresponds to 10 half-lives of reaction for hydrolysis of the free oxime. A more concentrated solution (×15) similarly gave no orange colouration with *p*-dimethylaminobenzaldehyde.

*Preparation and Hydrolysis of Ethyl α-Hydroxyimino-*p*-chlorobenzyl Methylphosphonate.*—(a) *Preparation.* 4-Chlorobenzohydroxamoyl chloride (4·8 g) in dry ether (150 ml) was treated with triethylamine (5·2 ml) in dry ether (15 ml) at 0°. Removal of the hydrochloride and evaporation gave *p*-chlorobenzonitrile oxide, m.p. 82°, which was used immediately, as a result of its instability. Reaction with ethyl hydrogen methylphosphonate in dry dioxan in the previously described manner [1] gave ethyl α-hydroxyimino-*p*-chlorobenzyl methylphosphonate, m.p. 79° (correct i.r. and ^1H n.m.r. spectra [1]), which was rapidly hydrolysed in water to give the corresponding hydrogen α-hydroxyimino-*p*-chlorobenzyl methylphosphonate, m.p. 158°.

(b) *Hydrolysis.* The kinetics in the range pH 3—10·9 were measured as previously described [1] for the *p*-nitrobenzyl analogue, and followed the same general form. At 0° in the pH range 3·00—4·77, 10^2k_1 = 2·82—2·94 min^{-1}, and in the pH range 8·9—10·9, 10^2k_1 = 4·19—4·20 min^{-1}. In the latter range, *p*-chloroaniline was formed. In the former hydrogen α-hydroxyimino-*p*-chlorobenzyl methylphosphonate and ethanol was formed. In the intermediate pH range both types of hydrolysis were evident, thus *p*-chloroaniline was detected from pH 6—8·91 and *O*-*p*-chlorophenylcarbamoyl *p*-chlorobenzohydroxamate, identical with an authentic specimen, m.p. 250°, synthesised from *p*-chlorophenyl isocyanate and *p*-chlorobenzohydroxamic acid, was isolated from hydrolyses carried out in the pH range 5·4—7·95.

[3/419 *Received*, 23*rd February*, 1973]

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