(14) S. C. Abrahams and E. T. Keve, *Acta Crystallogr., Sect. A*, **27**, 157 (1971).
(15) L. Pauling, "The Nature of the Chemical Bond", 3d ed, Cornell University Press, Ithaca, N.Y., 1960.
(16) R. J. Steer, S. F. Watkins, and P. Woodward, *J. Chem. Soc. C*, 403 (1970).
(17) E. L. Eliel, "Stereochemistry of Carbon Compounds", McGraw-Hill, New York, N.Y., 1962, p 250.

Synthesis of Monoesters of Aryl- (or alkyl-) phosphonic Acids of Selected Arenols. A Study of the Effect of Dimethylformamide on the Preparation of 2-Naphthylphenylphosphonic Acid via Proton and Phosphorus-31 Nuclear Magnetic Resonance Analysis[1]

William Ronald Purdum[2a] and Kenneth Darrell Berlin*

Department of Chemistry, Oklahoma State University, Stillwater, Oklahoma 74074

Susan J. Kelly[2b] and Larry G. Butler*

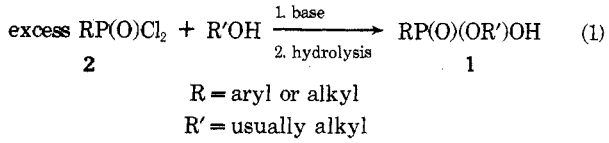
Department of Biochemistry, Purdue University, West Lafayette, Indiana 47907

Received September 8, 1975

The general synthesis of aryl- (or alkyl-) phosphonate monoesters of selected arenols has been accomplished in good yield by reaction of the substituted phosphonic dichloride with the arenol in pyridine solvent. Careful hydrolysis of the reaction mixture gave the phosphonate monoester which was isolated as the ammonium salt from acetone–ether (1:2). A comprehensive study of the preparation of 2-naphthyl phenylphosphonate revealed that the yield was enhanced by premixing of the phosphonic dichloride with dimethylformamide in pyridine prior to the addition of the arenol in pyridine. The influence of dimethylformamide on the reaction path has been studied by ^1H NMR and ^{31}P NMR analysis.

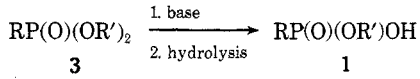
It has recently been shown that monoesters of phosphonic acids **1** are good substrates for certain phosphodiesterase enzymes which are widely distributed in nature.[3] Phosphonate monoesters have several advantages over conventional substrates, usually complex nucleotide phosphodiesters, or the simple diester, bis(4-nitrophenyl)phosphate, for assaying these enzymes.[4] For example, phosphonate monoesters readily and conveniently distinguish[4] between 5′-nucleotide phosphodiesterases and other phosphodiesterases.[5] In light of the elevated levels of 5′-nucleotide phosphodiesterase activity in fast-growing rat hepatomas[6] and the suggested diagnostic value of 5′-nucleotide phosphodiesterase isoenzyme patterns in the sera of human hepatic cancer patients,[7,8] considerable interest in phosphonate monoesters as enzyme substrates for diagnostic and analytical purposes can be expected. We have thus investigated the preparation of these compounds.

The preparation of phosphonate monoesters **1** has normally been accomplished via (a) reaction of an excess of an appropriate phosphonic dichloride **2** with an aliphatic alcohol (thus minimizing diester formation)[9] and subsequent hydrolysis to the phosphonate monoester or (b) by the synthesis of the aliphatic phosphonate diester **3** by known methods[10] followed by a controlled basic hydrolysis to the monoacid ester **1** (2).[11] These procedures, although affording good yields, have been primarily limited to the preparation of monoacid esters derived from aliphatic alcohols and not arenols.



(1)

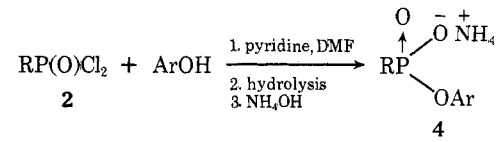
R = aryl or alkyl
R′ = usually alkyl



(2)

R = aryl, alkyl
R′ = alkyl

The scarcity of good methods for phosphonate monoesters of arenols is likely the result of the known low reactivity of the oxygen atom of the arenol with respect to a weak electrophilic center such as the phosphorus atom of a phosphonic dichloride. However, we have synthesized several phosphonate monoesters in good yield (isolated as the ammonium salts **4**), via the reaction in pyridine solvent of a selected phosphonic dichloride with a suitable arenol. The results of 11 such syntheses are listed in Table I. An observation that dimethylformamide (DMF) greatly influenced the reaction prompted us to make a careful study of the process with one case. As can be noted from Table II, the influence of dimethylformamide on the yield of the overall reaction (eq 3) (R = C_6H_5; Ar = 2-$HOC_{10}H_7$) is dramatic. Without DMF, the variation in the yield of monoester is considerable and, as expected, is very dependent upon the concentration of both the phosphonic dichloride and the arenol. Owing to the expense and difficulty in obtaining



(3)

R = C_6H_5, C_6H_{11}, C_3H_7, CH_3, $ClCH_2$
Ar = 2-$HOC_{10}H_7$, 4-$O_2NC_6H_4$

most of the initial phosphonic dichlorides, maintenance of their concentrations at a minimum level during the synthesis is economically desirable. For example, the yield of isolated monoester **4** (R = C_6H_5; Ar = 2-$C_{10}H_7$) decreases with decreasing concentration of phenylphosphonic dichloride and increasing concentration of 2-naphthol. This result is

Table I. Summary of Synthesis of Phosphonate Monoesters $RP(O)(OAr)ONH_4$

R	Ar	Molecular formula	Separation technique[a]	Yield, %[b]	R_f[e]	Ir,[f] ν cm^{-1} P→O	Anal. % Found (calcd) C	H	P
C_6H_5	p-$O_2NC_6H_4$	$C_{12}H_{13}N_2O_5P$	C_6H_6	20,[c,d] 58	0.73	1185 (1053)	48.78 (48.64)	4.70 (4.42)	10.69 (10.57)
C_6H_5	2-$C_{10}H_7$	$C_{16}H_{16}NO_3P\cdot\frac{1}{2}H_2O$	C_6H_6	72,[c] 78	0.75	1215 (1057)	62.46 (61.93)	5.63 (5.48)	10.49 (10.29)
c-C_6H_{11}	p-$O_2NC_6H_4$	$C_{12}H_{19}N_2O_5P$	C_6H_6	53	0.80	1190 (1060)	47.95 (47.68)	6.40 (6.29)	10.00 (10.26)
n-C_3H_7	p-$O_2NC_6H_4$	$C_9H_{15}N_2O_5P$	$HCCl_3$	53	0.74	1171 (1054)	41.23 (41.22)	5.90 (5.73)	12.09 (11.83)
n-C_3H_7	2-$C_{10}H_7$	$C_{13}H_{18}NO_3P$	C_6H_6	59	0.75	1165 (1055)	58.16 (58.43)	6.99 (6.74)	11.30 (11.61)
2-C_3H_7	p-$O_2NC_6H_4$	$C_9H_{15}N_2O_5P\cdot\frac{1}{2}H_2O$	$HCCl_3$	51	0.75	1175 (1060)	39.33 (39.85)	6.14 (5.90)	11.41 (11.83)
2-C_3H_7	2-$C_{10}H_7$	$C_{13}H_{18}NO_3P$	C_6H_6	60	0.76	1154 (1058)	58.33 (58.43)	6.66 (6.74)	11.21 (11.61)
$ClCH_2$	p-$O_2NC_6H_4$	$C_7H_{10}ClN_2O_5P$	$HCCl_3$	40	0.62	1213 (1065)	31.05 (31.28)	3.84 (3.72)	11.31 (11.54)
$ClCH_2$	2-$C_{10}H_7$	$C_{11}H_{13}ClNO_3P$	C_6H_6	44	0.68	1200 (1064)	48.41 (48.26)	4.85 (4.75)	11.30 (11.33)
CH_3	p-$O_2NC_6H_4$	$C_7H_{11}N_2O_5P$	$HCCl_3$	43	0.59	1220 (1067)	35.94 (35.90)	4.95 (4.70)	13.21 (13.25)
CH_3	2-$C_{10}H_7$	$C_{11}H_{14}NO_3P$	C_6H_6	64	0.63	1160 (1061)	51.06 (51.36)	6.12 (6.30)	11.82 (12.10)

[a] C_6H_6 refers to benzene extraction and $HCCl_3$ to chloroform extraction of water layer. [b] Percentage calculated on basis of limiting component. All compounds were chromatographically pure. The ratio of arenol:dichloride was 1:1 with the one exception in *c* below; solvent was pyridine (no DMF present). [c] Ratio of arenol:dichloride was 1:3 but acid not added to maximize extraction into benzene. Ester isolated in acid rather than in salt form by recrystallization from boiling water after removal of benzene in vacuo.[4] [d] An analysis was also performed on the free acid obtained as described in footnote *c*. Anal. Calcd for $C_{12}H_{10}NO_5P$: C, 51.62; H, 3.61; N, 5.01; P, 11.09; mol wt, 279.1. Found: C, 51.42; H, 3.62; N, 4.91; P, 11.00; mol wt, 280. [e] On ascending paper chromatography using 2-propanol–H_2O–NH_4OH (80:20:0.2). [f] The ir spectra show the top band for the asymmetric stretch while the lower band is the symmetric stretch; for a review of the ir frequencies of a few members of this family, see L. G. Thomas, "Interpretation of the Infrared Spectra of Organophosphorus Compounds", Heyden, London, 1974, Chapter 15.

expected if the amount of diester formed correspondingly increases. However, attempts to isolate appreciable amounts of diester from this reaction solution even with large excesses of 2-naphthol have been difficult (the presence of diester **5** in the reaction mixture in good yield was confirmed spectrally) because of the general work-up procedure to obtain **4**; solubility properties of 2-naphthol and the diester **5** are very similar. The important observation to be made in viewing the data of Table II is that the addition of 1 equiv of DMF [with respect to $C_6H_5P(O)Cl_2$] to the reaction mixture afforded a twofold increase in the amount of phosphonate monoester, **4** (R = C_6H_5; Ar = 2-$C_{10}H_7$) formed even with a *large excess* of the arenol. It is worthy of mention that excess 2-naphthol was easier to remove in the work-up than $C_6H_5P(O)(OH)_2$ which formed when excess $C_6H_5P(O)Cl_2$ was present prior to hydrolysis.

In all cases utilizing DMF, the phenylphosphonic dichloride and DMF are premixed in pyridine before being added to 2-naphthol in pyridine. This premixing is an important consideration when it is noted that the combination of phenylphosphonic dichloride–DMF is very similar to a typical Vilsmeier reagent: DMF–phosphorus oxychloride. Thus, premixing could lead to formation of a complex with a different reactivity (with respect to 2-naphthol) than the noncomplexed phosphonic dichloride. In order to test this hypothesis and to gain some insight regarding the intermediates present, the course of the reaction of phenylphosphonic dichloride with 2-naphthol was followed via ^{31}P nuclear magnetic resonance, with and without added DMF; see Table III.

Before the addition of DMF or 2-naphthol, the ^{31}P resonance of phenylphosphonic dichloride **2** (R = C_6H_5) in pyridine was observed at −34.3 ppm[12] (relative to H_3PO_4) along with a very minor second resonance at −18.8 ppm

Table II. Effect of Concentration of Phenylphosphonic Dichloride, 2-Naphthol, and Added Dimethylformamide on the Yield of 2-Naphthyl Phenylphosphonate[a]

$C_6H_5P(O)Cl_2$ rel concn	2-$HOC_{10}H_7$ rel concn	DMF rel concn	Yield of monoester,[b] %
3	1		94.9
2	1		82.3
1	1		78.6
1	2		49.9
1	3		42.6
1	3	1	80.5
1	3	2	85.6

[a] Taken in part from the Ph.D. Thesis of S. J. Kelly, Purdue University, 1974. [b] Yields are uncorrected for any water of hydration and are for the ammonium salt of the monoester, calculated on basis of the limiting reactant, $C_6H_5P(O)Cl_2$ or 2-$C_{10}H_7OH$.

(sample A). This high-field ^{31}P resonance was observed in all of the initial spectra and may be tentatively attributed to slow complexation of pyridine with **2** (R = C_6H_5). The concentration of this "complex" slowly increased with time. Although the presence of phenylphosphonic acid is unfavorable under our anhydrous conditions, its ^{31}P resonance has been observed, for example, at −17.5 ppm in acetone.[13] However, in the present study the ^{31}P resonance of phenylphosphonic acid (as the dipyridinium salt) was observed only at −10.2 ppm in pyridine in very good agreement with the reported values of −10.8 ($2NH_4^+$ salt)[14a] and −10.9 ppm [$2(CH_3)_4N^+$ salt][14b] for other ammonium salts. The presence of phenylphosphonic acid can also be eliminated from consideration since the resonance of −18.7 ppm was observed to disappear slowly upon the addition of 2-naphthol or DMF. Phenylphosphonic acid would not be expect-

Table III. ^{31}P Resonances Observed in the Reaction of Phenylphosphonic Dichloride with 2-Naphthol in Pyridine[a]

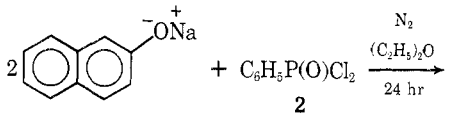
Sample[b]	Time[c]	^{31}P resonance position, ppm	Rel abundance, %
A		−34.3	97.8
		−18.8	2.2
B	t_0 + 10 min	−12.1	57.1
		−9.5	29.6
		−6.1	13.3
B	t_0 + 12 h	−12.1	64.9
		−9.5	35.1
C	t_0	−34.3	7.6
		−18.7	13.2
		−1.5	62.0
		+0.12	17.2
C	t_0 + 10 min	−1.5	66.4
		+1.0	33.6
D	t_0 + 10 min	−12.0	20.3
		−9.3	72.5
		−6.4	7.2
D	t_0 + 12 h	−12.0	20.2
		−9.2	79.8

[a] The ^{31}P resonances are relative to H_3PO_4 as 0.00 ppm. [b] A, 3 g (0.015 mol) of $C_6H_5P(O)Cl_2$ dissolved in 5 ml of pyridine; B, a 5-ml aliquot of 3.9 g (0.02 mol) of $C_6H_5P(O)Cl_2$ + 11.5 g (0.08 mol) of 2-$C_{10}H_7OH$ in 35 ml of pyridine; C, 3 g (0.015 mol) of $C_6H_5P(O)Cl_2$ and 1.1 g (0.015 mol) of DMF in 5 ml of pyridine; D, a 5-ml aliquot of 3.9 g (0.02 mol) of $C_6H_5P(O)Cl_2$ + 1.5 g (0.02 mol) of DMF + 11.5 g (0.08 mol) of 2-$C_{10}H_7OH$ in 35 ml of pyridine. [c] The time t_0 in all cases is within 3 min of the time of mixing.

ed to react with either of these reagents under the conditions of the overall synthesis.

The addition of phenylphosphonic dichloride in pyridine to 4 equiv of 2-naphthol also in pyridine caused a complete disappearance of resonances at −34.3 and −18.8 ppm with appearance of three new resonances at −12.1, −9.5, and −6.1 ppm (sample B) within 10 min of mixing. After 12 min at room temperature, only the ^{31}P resonances at −12.1 (64.9%) and −9.5 (35.1%) ppm were observed, and the relative abundance of these two resonances did not fluctuate appreciably with extended times. The addition of 1 equiv of DMF to **2** (R = C_6H_5) in pyridine (no 2-naphthol present) immediately afforded the appearance of four ^{31}P resonances (C, Table III). After 10 min, the two ^{31}P resonances (−34.3 and −18.7 ppm) attributable to **2** (R = C_6H_5) dissolved in pyridine disappeared. The two remaining resonances (−1.5 and +1.10 ppm), thus, could be due to complexation of DMF with **2** (R = C_6H_5). However, the addition of a solution of **2** (R = C_6H_5) and DMF in pyridine to 4 equiv of 2-naphthol also in pyridine (D, Table III) afforded only the same three ^{31}P resonances (−12.0, −9.3, and −6.4 ppm) observed without the presence of DMF (B, Table III). After 12 h, again only two resonances [−12.0 (20.2%) and −9.2 ppm (79.8%)] remained. Therefore, with or without DMF, intermediates similar in configuration (electronic and steric) about phosphorus are apparently present prior to hydrolysis. However, the relative abundance of these intermediates is drastically different (from Table III): (a) −12.1 (64.9%, B, no DMF) and −12.0 ppm (20.2%, D, DMF); (b) −9.5 (35.1%, B, no DMF) and −9.2 ppm (79.8%, D, DMF). Thus, the presence of DMF increased the concentration of an intermediate (that which had a signal at −9.2 ppm) which apparently led to monoester formation upon hydrolysis (based on the results obtained in Table II with and without DMF and with an excess of 2-naphthol).

Since the presence or absence of the diester di-2-naphthyl phenylphosphonate (**5**) must also be determined in these reaction mixtures, it was necessary to synthesize an authentic sample. Diester **5** was obtained by a modification of a synthetic procedure normally used for dialkyl phosphonates (eq 4).[11a] The sodium salt of 2-naphthol was



treated with phenylphosphonic dichloride in diethyl ether and upon isolation afforded the diester **5** (30.1%). The ^{31}P resonance of pure diester **5** was determined to be −11.34 ppm in the mixed solvent $DCCl_3$–pyridine. With added DMF before the addition of diester, the ratio of relative abundance of the resonances at −11.7 ppm to that at −9.0 ppm was 0.52. If the diester **5** was present as the low-field resonance (−11.7 ppm), addition of an authentic sample of **5** to this mixture should increase the −11.7-ppm resonance with an overall decrease in the abundance of the −9.0-ppm resonance relative to the −11.7-ppm resonance. The addition of 250 mg of **5** *did increase* the −11.7-ppm resonance, and the ratio of the relative abundance (−11.7 to −9.0 ppm signals) increased slightly to 0.62. Without DMF, the addition of 250 mg of **5** to sample G caused the expected increase in the ratio of relative abundance (−11.4 ppm resonance to the −9.0-ppm resonance) from 1.25 to 1.54. With these observations, the diester **5** was spectrally confirmed to be present in both cases (with and without DMF) and was a major contributor to the low-field resonance. Thus, the signals at −11.34, −11.7, or 12.0 (Table III) are due to **5** predominantly but vary in chemical shift because of shielding changes created by dilution and solute effects.

Before postulating potential reaction paths for phosphonate monoester and diester formation, the dependence of the ^{31}P resonances should be examined as a function of added pyridine or DMF in a noncomplexing solvent ($DCCl_3$ for this system, Table IV). The ^{31}P resonance of −34.3 ppm [phenylphosphonic dichloride (**2**) (R = C_6H_5)] in $DCCl_3$ (without pyridine and DMF) was in agreement with earlier literature reports.[12] The addition of DMF to this solution

Table IV. ^{31}P Resonances as a Function of Presence of Dimethylformamide and Pyridine[a]

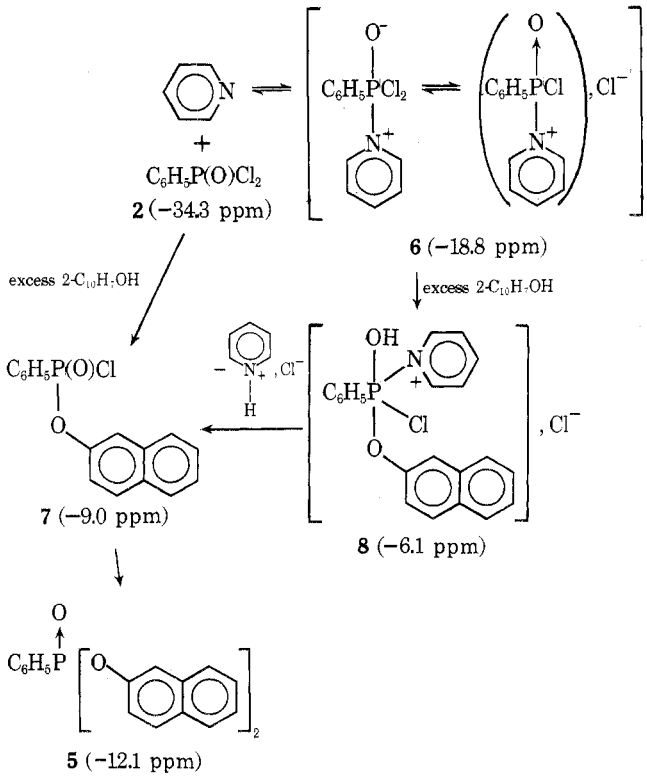
Sample[b]	Time, h	Solvent	^{31}P resonance position, ppm	Rel abundance, %
$C_6H_5P(O)Cl_2$–DMF		$DCCl_3$	−34.3	90.7
			−18.5	9.3
$C_6H_5P(O)Cl_2$–DMF	3	$DCCl_3$	−34.4	50.5
			−18.5	21.8
			−0.8	15.1
			+0.8	12.5
$C_6H_5P(O)Cl_2$–DMF	12	$DCCl_3$	−34.5	48.3
			−18.7	21.4
			−1.0	14.8
			+0.6	15.5
$C_6H_5P(O)Cl_2$–DMF		$DCCl_3$–pyridine	−34.2	51.5
			−18.5	17.3
			−1.0	19.2
			+0.7	12.0
$C_6H_5P(O)Cl_2$–DMF	12	$DCCl_3$–pyridine	−1.1	66.7
			+0.8	33.3

[a] ^{31}P resonances are relative to H_3PO_4 as 0.0 ppm. [b] ^{31}P resonances of only $C_6H_5P(O)Cl_2$ in $DCCl_3$ was −34.3 ppm.

caused the immediate appearance of a second ^{31}P resonance at −18.5 ppm (Table IV). After 12 h at room temperature, four resonances were observed (−34.5, −18.7, −1.0, and +0.6 ppm) similar in position to those observed with sample C of Table III. Upon the addition of **2** (R = C_6H_5) and DMF to the mixed solvent system, $DCCl_3$ and pyridine, these four resonances appeared immediately and in approximately the same relative abundance as those which were present without the added pyridine but only after 12 h (Table IV). However, after maintaining the mixture of **2** (R = C_6H_5), DMF, and pyridine in $DCCl_3$ for 12 h at room temperature, only the two high-field resonances (−0.1 and +0.8 ppm) remained. Thus, the presence of pyridine facilitated complexation of **2** (R = C_6H_5) with DMF. The presence of the resonance at −18.5 ppm [previously discussed and assigned solely to the complex of **2** (R = C_6H_5) with pyridine] may also be composed of a signal from the initial adduct of **2** (R = C_6H_5) with DMF and without pyridine. As was observed, the concentration of this adduct would be expected to increase upon mixing and then decrease with extended time as the initial concentration of **2** (R = C_6H_5) decreased.

With the observed positions and relative abundances (as a function of time) for the various ^{31}P resonances of Tables III and IV *without the added DMF*, a tentative path for mono- and diester formation can be formulated (Scheme I). The initial step could involve incomplete formation of adduct **6** from reaction of **2** (R = C_6H_5) and pyridine which provides two observed resonances, −34.3 and −18.8 ppm, respectively. The excess 2-naphthol may then react with noncomplexed **2** (R = C_6H_5) yielding, initially, the monoester acid chloride **7** which is subsequently converted to the diester **5**. If the reaction of 2-naphthol were to occur with the adduct **6**, the new complex **8** formed might be expected to shift to higher field position owing to the changes in electronic charge and configuration about phosphorus.[15]

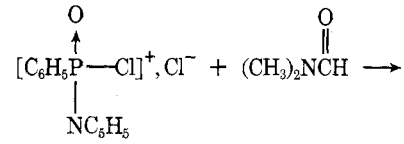
Scheme I[a]

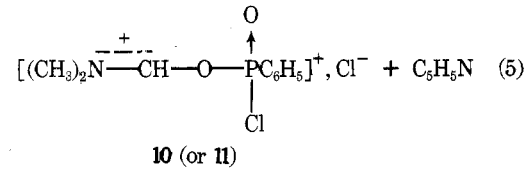


[a] Tentative ^{31}P resonance positions are indicated in parentheses.

Collapse of this complex **8** could afford more of the monoester acid chloride **7** which could then also form more of the diester **5**. The fact that at least four separate ^{31}P resonances appeared at one time, initially, would indicate that the reaction kinetics are quite complex.

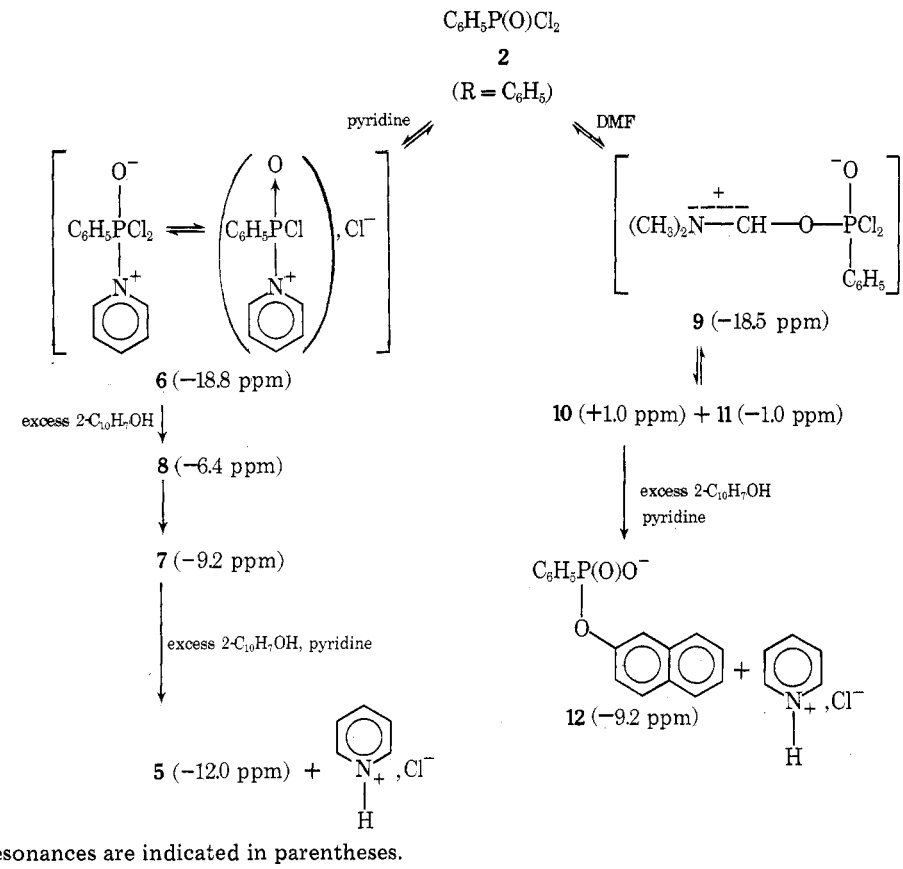
In the presence of 1 equiv of DMF, a slightly different reaction path may be postulated (Scheme II). Complexation of **2** (R = C_6H_5) with pyridine as in Scheme I to again afford **6** is expected owing to the very large excess of pyridine. This intermediate **6** could then react with the excess 2-naphthol to yield **8** which could subsequently be converted to the monoester acid chloride **7** and the diester **5**. However, the increase in the relative abundance for the ^{31}P resonance at −9.3 ppm vs. the diester resonance at low field may be explained by complexation of **2** (R = C_6H_5) with dimethylformamide. This initial complex **9** may fortuitously resonate at the same position as the pyridinium salt **6**. Rapid conversion of **9**, via **10** or **11**, to the monoester acid salt **12** (a new product), which may resonate at the same position as the monoester acid chloride **7**, is not unreasonable. The presence of **12** would hinder further conversion to the diester and thus increase the yield of monoester upon hydrolysis. Without the excess 2-naphthol the conversion of **2** (R = C_6H_5) to **10** and **11** was observed with the appearance of two high-field ^{31}P resonances (~+1 and ~−1.0 ppm assigned to **10** and **11**, respectively). In this regard, the initial pyridine complex **6** in the absence of 2-naphthol may also be converted to the dimethylformamide complex **9** (or **10** or **11**) which might be pictured as a simple displacement of pyridine (eq 5).[16] Of course **10** must be considered a tentative structure. The transformation involving **2** (R = C_6H_5) and DMF into the complexes **9** and **10** (or **11**) is in good agreement with what has been previously reported for the complexes formed between the Vilsmeier reagents, DMF–$POCl_3$.[17]





A ^1H NMR study of the mixture of **2** (R = C_6H_5), DMF, and pyridine in $DCCl_3$ also supported the existence of two structures **10** and **11** but no appreciable amount of **9**. The addition of DMF to **2** (R = C_6H_5) in $DCCl_3$ caused a downfield shift in the resonance of the aldehydic proton (δ 8.01 to 8.11) but only slightly shifted signals for the cis–trans methyl groups of the $(CH_3)_2N$ moiety in **10** (or **11**). Also a very minor difference in separation between the two ^1H resonances [shift 0.3 ppm and $\Delta\delta$ (change in separation between CH_3 resonances) 0.02 ppm] was observed. This system remained constant for at least 72 h at room temperature. However, the addition of pyridine had a dramatic effect. Upon mixing, only a negligible shift in the resonances of the aldehydic protons and the methyl protons was observed. After 12 h, however, two resonances of equal intensity appeared downfield (δ 10.57 and 10.51) for the aldehydic proton plus a broad resonance for the methyl groups of a complex at δ 3.06. These resonances are in addition to those present earlier. Extensive ^{31}P heteroatom decoupling of ^1H of these mixtures indicated that the downfield aldehydic proton resonances were *not* covalently bound

Scheme II[a]



[a] Tentative ^{31}P resonances are indicated in parentheses.

through carbon and oxygen to phosphorus. Thus, ion pairs may be formed which may be the structure of **11**. Such structures have been reported for Vilsmeier complexes formed between DMF and $OPCl_3$.[17]

In summary, a good preparative method has been developed for monophosphonates of the type $RP(O)(OR')ONH_4$. Chemical and NMR evidence is presented which strongly suggest that a Vilsmeier type complex is involved when the arenol and phosphonic dichloride are allowed to react in the presence of pyridine and DMF.

Experimental Section

General Data. Melting points were obtained with a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 521 grating infrared spectrophotometer as KBr pellets. ^1H NMR and ^{31}P NMR spectra were obtained with a XL-100(15) Varian spectrometer in the solvents indicated (pyridine, $DCCl_3$). Mass spectral analysis was performed on a CEC Model 21 HR unit.

Starting Materials. Phenylphosphonic dichloride was distilled under reduced pressure utilizing the center fraction for all experiments, bp 100–102 °C (4.0 mm). Dimethylformamide was distilled from NaH directly before use. All other phosphonic dichlorides were obtained from Speciality Organics Inc., Irwindale, Calif., and were used without purification. Pyridine was distilled from anhydrous K_2CO_3 also directly before use. Commercially available 2-naphthol was recrystallized (95% C_2H_5OH–H_2O) and dried in vacuo, mp 121–122 °C.

Ammonium 2-Naphthyl Phenylphosphonate (4, R = C_6H_5; Ar = 2-$C_{10}H_7$). A. Without Dimethylformamide. A solution of 7.5 g (0.052 mol) of 2-naphthol in 20 ml of anhydrous pyridine was treated (dropwise) with 1.78 (0.009 mol) of phenylphosphonic dichloride with formation of a light reddish-brown color. This solution was stirred at room temperature for 4 h. Removal of the solvent in vacuo afforded a viscous oil which was dissolved in benzene and extracted with 75 ml of aqueous HCl (8 N). The aqueous layer was then reextracted (2 × 100 ml) with benzene. Evaporation of the organic extracts in vacuo yielded a white semisolid material. This solid was dissolved in acetone (25 ml), the solution of which was warmed and treated dropwise with 1 ml of concentrated NH_4OH (0.015 mol) over a 5-min period and then ether (50 ml) was added. After standing at room temperature for 24 h, the precipitated ammonium salt of 2-naphthylphenylphosphonic acid (4) was collected and dried at 35° in vacuo for 24 h: yield 1.3 g (48%); mp 183–185 °C; ir[18] (KBr) ν 3400–2075 (broad, NH_4^+ salt), 1620 and 1600 (aromatic), 1255, 1215, 1139, 1057, 1032, 968, 920, 861, 823, 748, 720, 698, and 644 cm^{-1}; mass spectrum (70 eV) *m/e* 284 ($M^+ - NH_3$); ^1H NMR ($DCCl_3$) δ 7.14–7.98 (m, $C_{10}H_7$ and C_6H_5, 12 H), 8.40–9.40 (broad, NH_4^+).

B. With Dimethylformamide. A solution of 7.5 g (0.052 mol) of 2-naphthol in 20 ml of anhydrous pyridine was treated (dropwise) with a dark red colored mixture of 1.78 g (0.009 mol) of phenylphosphonic dichloride and 0.66 g (0.009 mol) of DMF in 15 ml of pyridine. The resulting dark red solution was stirred at room temperature for 4 h. Removal of the solvent in vacuo afforded a viscous oil which was dissolved in benzene and extracted with 75 ml of aqueous HCl (8 N). The aqueous layer was then reextracted (2 × 100 ml) with benzene. Evaporation of the organic extracts in vacuo yielded a white solid. This solid was dissolved in acetone (25 ml) and treated with 1 ml of concentrated NH_4OH (0.015 mol) in the usual manner and then ether (50 ml) was added. After standing at room temperature for 24 h, the precipitated ammonium salt of the monoester was collected and dried in vacuo at 35 °C for 24 h, 2.2 g (81.2%), mp 182–184 °C. The sample was identical in all respects with that previously identified.

Di(2-naphthyl) Phenylphosphonate (5). This diaryl ester was prepared by an adaptation of a literature procedure for dialkyl phosphonates.[11a] A slurry of 2.3 g (55.6% in mineral oil, 0.053 mol) of NaH in 75 ml of anhydrous ether at room temperature was treated (dropwise) with 7.6 g (0.053 mol) of 2-naphthol in 50 ml of ether, and the resulting mixture was stirred at room temperature for 1 h. Treatment of this sodium aryloxide–ether mixture with 4.9 g (0.025 mol) of phenylphosphonic dichloride in 50 ml of ether afforded a clear solution. After addition, this solution was boiled (24 h), cooled to room temperature, and hydrolyzed (25 ml of saturated NH_4Cl solution) to remove unreacted aryloxide. The layers were separated and the aqueous layer was extracted (2 × 50 ml) with ether. The dried ($MgSO_4$) organic extracts were evaporated in

vacuo to give a white solid. Recrystallization of this solid from C_6H_6–C_6H_{12} (1:3) afforded 3.1 g (30.1%) of the diester **5**: mp 129–131 °C; ir[18] (KBr) ν 1620, 1592 (aromatic), 1260, 1238, 1205, 1150, 1115, 1027, 963, 937, 885, 862, 849, 815, 752, 739, 696, and 640 cm^{-1}; ^1H NMR ($DCCl_3$) δ 7.06–7.84 (m, 2 $C_{10}H_7$ and C_6H_5, 17 H), 8.05 (m, C_6H_5 2 H); ^{31}P NMR ($DCCl_3$ + pyridine) −11.34 ppm relative to 85% H_3PO_4; mass spectrum (70 eV) *m/e* 410 (M^+). Peak matching for $C_{26}H_{19}O_3P$: 410.107175. Found: 410.128523. The ester is insoluble in H_2O and was recovered unchanged after being stirred in 8 N HCl for 3 h.

Registry No.—**2** (R = C_6H_5), 824-72-6; **2** (R = c-C_6H_4), 1005-22-7; **2** (R = n-C_3H_7), 4708-04-7; **2** (R = 2-C_3H_7), 1498-46-0; **2** (R = $ClCH_2$), 1983-26-2; **2** (R = CH_3), 676-97-1; **4** (R = C_6H_5; Ar = p-$O_2NC_6H_4$), 57885-61-7; **4** (R = C_6H_5; Ar = 2-$C_{10}H_7$), 57885-62-8; **4** (R = c-C_6H_4; Ar = p-$O_2NC_6H_4$), 57885-63-9; **4** (R = n-C_3H_7, Ar = p-$O_2NC_6H_4$), 57885-64-0; **4** (R = n C_3H_7, Ar = 2-$C_{10}H_7$), 57885-65-1; **4** (R = C_6H_5; Ar = p-$O_2NC_6H_4$) free acid, 57072-35-2; **4** (R = 2-C_3H_7; Ar = p-$O_2NC_6H_4$), 57885-66-2; **4** (R = 2-C_3H_7; Ar = 2-$C_{10}H_7$), 57885-67-3; **4** (R = $ClCH_2$; Ar = p-$O_2NC_6H_4$), 57885-68-4; **4** (R = $ClCH_2$; Ar = 2-$C_{10}H_7$), 57885-69-5; **4** (R = CH_3; Ar = p-$O_2NC_6H_4$), 57885-70-8; **4** (R = CH_3; Ar = 2-$C_{10}H_7$), 57885-71-9; **5**, 57885-72-0; dimethylformamide, 68-12-2; p-nitrophenol, 100-02-7; 2-naphthol, 135-19-3.

References and Notes

(1) Journal paper no. 5976 of the Agriculture Experiment Station, Purdue University. This work was supported in part by National Institutes of Health Training Grant GM 1195 from the National Institute of General Medical Sciences and the USPHS, Grant CA 10367-06 (to K.D.B.) from the National Institute of Cancer. We (K.D.B.) also acknowledge the National Science Foundation grant to purchase the XL-100(15) NMR unit, Grant NSF GP-17641. L.G.B. is a recipient of a Research Career Development Award (GM 46404) from the U.S. Public Health Service.

(2) (a) Research Associate in Chemistry, 1973–1975; (b) Research Associate in Biochemistry, 1974–1975.

(3) S. J. Kelly and L. G. Butler, *Biochem. Biophys. Res. Commun.*, **68**, 316 (1975).

(4) S. J. Kelly, D. E. Dardinger, and L. G. Butler, *Biochemistry*, **14**, 4983 (1975).

(5) W. E. Razzell, *Experientia*, **23**, 321 (1961).

(6) K. C. Tsou, H. P. Morris, K. W. Lo, and J. J. Muscato, *Cancer Res.*, **34**, 1295 (1974).

(7) K. C. Tsou, S. Ledis, and M. G. McCoy, *Cancer Res.*, **33**, 2215 (1973).

(8) K. C. Tsou, M. G. McCoy, H. T. Enterline, R. Herberman, and H. Wahner, *J. Natl. Cancer Inst.*, **51**, 2005 (1973).

(9) (a) A. Michaelis and K. Kammerer, *Ber.*, **8**, 1307 (1875); (b) L. Keay, *Can. J. Chem.*, **43**, 2637 (1965), and references cited therein.

(10) For a brief discussion on the synthesis of phosphonates, see G. M. Kosolapoff, "Organophosphorus Compounds", Wiley, New York, N.Y., 1950, Chapter 7, and references cited therein. Diesters may also be prepared by a variety of methods analogous to the synthesis of phosphate triesters; see E. Cherbuliez, "Organic Phosphorus Compounds", Vol. 6, G. M. Kosolapoff and L. Maier, Ed., Wiley-Interscience, New York, N.Y., 1973, Chapter 15.

(11) (a) H. Cristol, M. Levy, and C. Marty, *J. Organomet. Chem.*, **12**, 459 (1968); (b) E. J. Behrman et al., *J. Org. Chem.*, **35**, 3063 (1970); (c) R. Rabinowitz, *J. Am. Chem. Soc.*, **82**, 4564 (1960).

(12) This value is in good agreement with those previously reported for the ^{31}P NMR of the pure liquid; see V. Mark et al., *Top. Phosphorus Chem.*, **5**, 227 (1967), and references cited therein.

(13) J. R. Van Wazer, C. F. Callis, J. N. Shoolery, and R. C. Jones, *J. Am. Chem. Soc.*, **78**, 5715 (1956).

(14) (a) Obtained in water; see M. L. Nielsen, J. V. Pustinger, Jr., and J. Strobel, *J. Chem. Eng. Data*, **9**, 167 (1964). (b) Obtained in water; see J. G. Riess, J. R. Van Wazer, and J. H. Letcher, *J. Phys. Chem.*, **71**, 1925 (1967).

(15) For a brief discussion on the effects of charge (generally negligible), electronegativity of other atoms, and configurational changes on the ^{31}P resonance of phosphorus moieties, see ref 12.

(16) The conversion of **6** to **10** in the absence of 2-$C_{10}H_7OH$ is necessitated by the appearance of only the two ^{31}P resonances, −1.0 and +1.0 ppm (sample C, Table III) after 10 min mixing. These same resonances are also present in the absence of both pyridine and 2-$C_{10}H_7OH$; see Table IV.

(17) The interaction of DMF and $POCl_3$ has been extensively investigated by nuclear magnetic resonance in the last decade. A few of the conclusions are (1) that the major cationic formylating specie has the tentative structure $(CH_3)_2NCHCl^+$ with the anion being either $^-O_2PCl_2$ or Cl^-; (2) extensive heteronuclear decoupling experiments on ^1H have shown that there is no P–OCH covalent structure to the intermediate cation. For more detailed discussion, see (a) G. J. Martin and S. Poignant, *J. Chem. Soc., Perkin Trans. 2*, 642 (1974); (b) S. Alummi et al., *ibid.*, 2070 (1972); (c) G. J. Martin and S. Poignant, *ibid.*, 1964 (1972); (d) G. J. Martin, S. Poignant, M. L. Filleux, and M. T. Quemeneur, *Tetrahedron Lett.*, 5061 (1970); (e) G. Martin and M. Martin, *Bull. Soc. Chim. Fr.*, 1637 (1963), and references cited therein.

(18) Owing to the complexity of the infrared spectra, detailed interpretations were not attempted.

A One-Step Synthesis of Epoxyphosphonates

Bleecker Springs and Paul Haake*

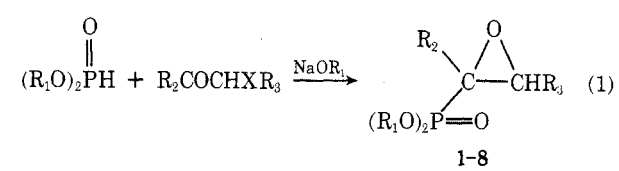
Department of Chemistry, Wesleyan University, Middletown, Connecticut 06457

Received November 3, 1975

Owing to the recent interest in epoxyphosphonates generated by the newly discovered antibiotic fosfomycin, we have synthesized some epoxyphosphonates, $(R_1O)_2P(O)\overline{CR_2\text{–}O\text{–}CHR_3}$, by a facile one-step procedure. Our synthesis proceeds by the reaction of a stoichiometric amount of a dialkyl phosphonate, an α-halo ketone, and sodium alkoxide; the yields include (R_1, R_2, R_3, % yield) CH_3, CH_3, H, 84; C_2H_5, CH_3, H, 83; CH_3, $(CH_3)_3C$, H, 87. In addition, for the reaction with $R_1 = CH_3$, $R_2 = CH_3$, and $R_3 = H$, we have NMR evidence, a doublet at τ 8.5 (J_{PCCH} = 15 Hz), which indicates that the reaction proceeds via a phosphonate halohydrin intermediate (eq 6).

The novel structure of the newly discovered antibiotic fosfomycin [**1**, (−)-(1*R*,2*S*)-1,2-epoxypropylphosphonic acid] has generated interest in epoxyphosphonates.[1,2] Previous studies on epoxyphosphonates have been concerned primarily with either their potential as synthetic intermediates[3] or the mechanism of the reaction of dialkyl phosphonates, $(RO)_2P(O)H$, with α-halo ketones.[4] The discovery of fosfomycin and its mode of action as an analogue of phosphoenol pyruvate in its inhibition of the enzyme pyruval transferase has given epoxyphosphonates biochemical significance.[5]

We have synthesized epoxyphosphonates **2**–**8** by a facile, one-step procedure by the action of sodium alkoxide on a dialkyl phosphonate and an α-halo ketone (eq 1). In addition, we have NMR evidence concerning the mechanism of this reaction.



(1)

1–**8**

Experimental Section

We used the following instruments: Varian A-60 for NMR spectra, tetramethylsilane as internal standard; Perkin-Elmer 137 for infrared spectra; Hitachi RMU-6L for mass spectra. Analyses were determined by Spang Microanalytical Laboratory, Ann Arbor, Mich.

Materials. Chloroacetone and 2-chloro-4,4-dimethyl-3-pentanone were prepared by treating acetone and ethyl *tert*-butyl ketone, respectively, with sulfuryl chloride.[6,7] Chlorocyclohexanone and 1-chloro-3,3-dimethyl-2-butanone were prepared by the reaction