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One-Flask Phosphorylative Coupling of Two Alcohols by Means of Aryl Cyclic Enediol Phosphates. Phenoxide Ion Catalysis of Phosphorylations in Aprotic Solvents

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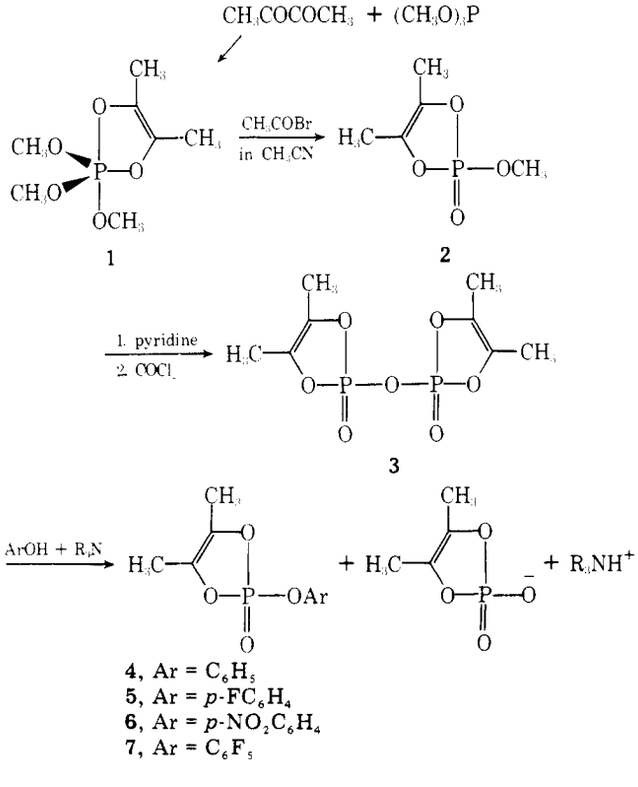
Aryl cyclic enediol phosphates, 2-*p*-nitrophenoxy- and 2-pentafluorophenoxy-4,5-dimethyl-1,3,2-dioxaphosphole 2-oxide, are efficient reagents for the *one-flask* conversion of two different alcohols, R^1OH and R^2OH, into dialky(1-methylacetonyl) phosphates, $(R^1O)(R^2O)P(O)OCH(CH_3)COCH_3$, which are readily hydrolyzed to unsymmetrical dialkyl phosphates, $(R^1O)(R^2O)P(O)(OH)$. The synthesis is made possible by the effective phenoxide ion catalysis of the phosphorylation of alcohols by alkyl cyclic enediol phosphates in aprotic solvents. Mechanisms which involve penta- and hexacoordinate phosphorus intermediates are suggested for the reactions. The phenoxide catalysis of the phosphorylations in aprotic solvents may have a bearing on enzymatic phosphorylations where the hydrophobic active site of the enzyme has tyrosine and lysine, arginine, or histidine residues.

This paper gives full details[2] of a new procedure to convert two different alcohols into a dialkyl(1-methylacetonyl) phosphate, $(R^1O)(R^2O)P(O)OCH(CH_3)COCH_3$, without isolation of intermediates ("one-flask" reaction), using as reagent an aryl cyclic enediol phosphate, 2-*p*-nitrophenoxy-4,5-dimethyl-1,3,2-dioxaphosphole 2-oxide (**6**), or its pentafluorophenyl analogue (**7**). The 1-methylacetonyl group can be easily removed from the triesters, and the procedure constitutes a two-stage synthesis of unsymmetrical phosphodiesters, $(R^1O)(R^2O)P(O)OH$, from the alcohols. The X=P(O)Ar[3] reagents, **6** and **7**, are made from the phenol and di(1,2-dimethylethenylene) pyrophosphate[4] (**3**), which is readily available from biacetyl and trimethyl phosphite via the oxyphosphorane[5] (**1**) and 2-methoxy-4,5-dimethyl-1,3,2-dioxaphosphole 2-oxide (**2**).



4, Ar = C_6H_5
5, Ar = p-FC_6H_4
6, Ar = p-$NO_2C_6H_4$
7, Ar = C_6F_5

A second "one-flask" synthesis of dialkyl(1-methylacetonyl) phosphates from two alcohols utilizes the pyrophosphate **3** as reagent.[6] These alternate procedures are desirable in view of the complexity of many biological phosphodiesters, e.g., the phospholipids of biological membranes and the polynucleotides. These substances, $(R^XO)(R^YO)P(O)OH$, are derived from two polyfunctional alcohol moieties, R^XOH and R^YOH, and can, in principle, be synthesized following the sequence $R^1OH = R^XOH$, $R^2OH = R^YOH$, or the sequence $R^1OH = R^YOH$, $R^2OH = R^XOH$, where R^1 and R^2 refer to the order in which the alcohols are phosphorylated. A choice of reagents widens the scope of these syntheses by making it possible to utilize different protective groups on the polyfunctional alcohols, and different phosphorylation sequences.[7]

Results

Preparation of 2-Aryloxy-4,5-dimethyl-1,3,2-dioxaphosphole 2-Oxides (4–7). Phenols react with the pyrophosphate **3** by displacement at phosphorus with ring retention.[4] It has now been found that tertiary amines, which are used to neutralize the acidic by-product of this reaction, X=P(O)OH, exert also a catalytic effect. The approximate half-time for the reaction of equimolar amounts of C_6H_5OH with **3**, in 0.2 M $CDCl_3$ (25°C), is reduced from 17 min to about 0.5 min upon addition of 1 molar equiv of pyridine; the reac-

Table I. Elemental Analyses and Spectral Data[a] of Aryl(1,2-dimethylethenylene) Phosphates, Dialkyl(1-methylacetonyl) Phosphates, and Dialkyl Phosphates

Compd	Substituents	Mp or bp, °C (mm)	Molecular formula	Calcd, %			Found, %			^{1}H NMR, τ, ppm (J, Hz)
	Ar		X=P(O)OAr[b]							CH_3C
4	C_6H_5	100 (0.1)[c]	[d]							8.20
5	p-FC_6H_4	105 (0.15)	$C_{10}H_{10}O_4PF$	49.2	4.1	12.7	49.4	4.3	12.5[e]	8.10
6	p-$NO_2C_6H_4$	102–104[f]	[d]							8.10 (0.6)
7	C_6F_5	54–56[g]	$C_{10}H_6O_4PF_5$	38.0	1.9	9.8	37.8	2.0	9.6[h]	7.98
	R^1; R^2		$(R^1O)(R^2O)P(O)OCH(CH_3)COCH_3$[i]							CH_3CO; CH_3CH[j]
15	$(CH_3)_3CCH_2$; $(CH_3)_2CHCH_2$	90 (0.1)	$C_{13}H_{27}O_5P$	53.1	9.3	10.5	53.2	9.4	10.5	7.75; 8.60 (7.0)
10	c-C_5H_9; $CH_2=C(CH_3)CH_2CH_2$	110 (0.1)	$C_{14}H_{25}O_5P$	55.2	8.3	10.2	55.1	8.3	10.1	7.75; 8.55 (7.0)
16	c-C_5H_9; $BrCH_2CH_2$	105 (0.1)	$C_{11}H_{20}O_5PBr$	38.5	5.9	9.0	38.7	5.9	9.0[k]	7.76; 8.53 (6.5)
13	c-C_6H_{11}; CH_3CH_2	95 (0.1)	$C_{12}H_{23}O_5P$	51.8	8.3	11.1	52.0	8.3	11.1	7.71; 8.53 (6.8)
11	$(CH_3CH_2)_2CH$; $(CH_3)_3CCH_2$	95 (0.15)	$C_{14}H_{29}O_5P$	54.5	9.5	10.1	54.3	9.6	9.9	7.74; 8.52 (6.9)
12	$(CH_3CH_2)_2CH$; $(CH_3CH_2)_2CH$	95 (0.15)	$C_{14}H_{29}O_5P$	54.5	9.5	10.1	54.3	9.3	10.0	7.75; 8.54 (6.9)
14	$[(CH_3)_2CH]_2CH$; $(CH_3)_2CHCH_2$	100 (0.15)	$C_{15}H_{31}O_5P$	55.9	9.7	9.6	55.9	9.8	9.6	7.65; 8.46 (7.0)
18	c-C_5H_9; C_6H_5		$C_{15}H_{21}O_5P$	57.7	6.8	9.9	57.7	6.9	10.1	7.78,[l] 8.47 (7.0) 7.82; 8.53 (7.0)
19	$[(CH_3)_2CH]_2CH$; C_6H_5		$C_{17}H_{27}O_5P$	58.2	8.2	9.4	58.3	8.1	9.2	7.78,[l] 8.52 (6.8) 7.90; 8.64 (6.8)
	R^1; R^2		$(R^1O)(R^2O)P(O)(OM)^m$							Main signals of R^1 and R^2
20a	$(CH_3)_3CCH_2$; $(CH_3)_2CHCH_2$	186–188[n]	$C_{21}H_{44}O_4PN$	62.2	10.9	7.6	62.0	10.9	7.7	6.50; 7.07; 8.35; 9.06; 9.13 (7.0)
21a	c-C_5H_9; $CH_2=C(CH_3)CH_2CH_2$	158–159[o]	$C_{22}H_{42}O_4PN$	63.6	10.2	7.5	63.4	10.2	7.6	5.30; 6.10 (7.0) 7.10; 7.70 (7.0); 8.28
22a	c-C_5H_9; $BrCH_2CH_2$	111–112[p]	$C_{13}H_{27}O_4PNBr$	41.9	7.3		43.2	7.6		5.37; 5.90; 6.50 (6.0); 8.35
23a	c-C_6H_{11}; CH_3CH_2	135–137[n]	$C_{20}H_{40}O_4PN$	61.7	10.4	8.0	61.7	10.4	7.8	5.95; 6.13 (7.2); 8.76 (7.2)
24a	$(CH_3CH_2)_2CH$; $(CH_3)_3CCH_2$	181–183[n]	$C_{22}H_{46}O_4PN$	63.0	11.1	7.4	62.9	11.1	7.2	5.95; 6.50 (4.8); 8.39 (7.3); 9.06; 9.11 (7.3)
25a	$(CH_3CH_2)_2CH$; $(CH_3CH_2)_2CH$	149–150[n]	$C_{22}H_{46}O_4PN$	63.0	11.1	7.4	62.9	11.0	7.4	5.94; 8.36 (7.3); 9.10 (7.3)
26a	$[(CH_3)_2CH]_2CH$; $(CH_3)_2CHCH_2$	155–156[n]	$C_{23}H_{48}O_4PN$	63.7	11.2	7.1	63.6	11.1	7.0	6.38 (6.3); 9.02 (6.8); 9.11 (6.3)

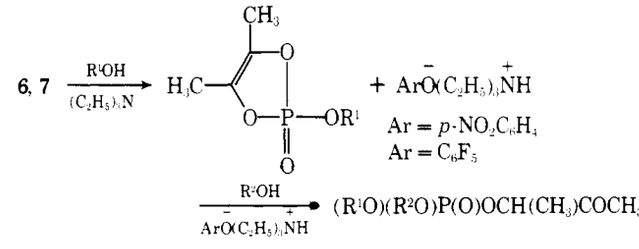
[a] NMR spectra in $CDCl_3$; ^{1}H shifts in parts per million vs. Me_4Si (τ 10), ^{31}P shifts in parts per million vs. H_3PO_4 = 0; coupling constants, J, in hertz. ^{1}H integrations agree with the proposed structures. [b] δ ^{31}P—6.2 (C_6H_5); —6.3 (p-FC_6H_4); —6.4 (p-$NO_2C_6H_4$); —8.0 ppm (C_6F_5). [c] Bath temperature in molecular distillation, in all cases. [d] Reference 4. [e] F: calcd, 7.8; found, 7.5. [f] From dichloromethane-hexane. [g] After molecular distillation at 75 °C (0.1 mm). [h] F: calcd, 30.0; found, 30.0. [i] δ ^{31}P of acyclic triesters, and of diesters and their salts, fall within 0 and +3.5 ppm. [j] Multiplet at τ 5.2–5.4 ppm due to methine ^{1}H of 1-methylacetonyl, and corresponding signals for R^1 and R^2 groups also present. [k] Br: calcd, 23.3; found, 23.0. [l] Two diastereomers are detectable. [m] M = $(C_6H_{11})_2NH_2^+$ in compounds **20a**, **21a**, **23a–26a**; M = $C_6H_{11}NH_3^+$ in **22a**. [n] From ethyl acetate. [o] The salt crystallized from ethyl acetate upon addition of the amine to the acid; recrystallized from cyclohexane. [p] Prepared in ether–hexane; recrystallized from cyclohexane.

tion is too fast to measure in the presence of triethylamine.

Two of the aryl cyclic triesters (**4**, **6**) have been described,[4] while compounds **5** and **7** are new; all have ^{31}P NMR shifts in the range −5 to −8 ppm. A small ($J \simeq 0.6$ Hz) long-range coupling, **H**–C–C–O–**P**, can be detected in the signal from the methyl groups.

One-Flask Phosphorylative Coupling of Two Alcohols. The p-nitrophenyl and the pentafluorophenyl cyclic phosphates, **6** and **7**, are excellent reagents for the conversion of two alcohols into a dialkyl(1-methylacetonyl) phosphate. The synthesis involves two steps, which are carried out in one laboratory operation according to the directions given in the Experimental Section.

The first step involves the reaction of the aryl cyclic triester, **6** or **7**, with alcohol R^1OH, and is carried out in the presence



of triethylamine. The reaction is autocatalytic, since the phenoxide ion that is generated as a by-product has a pronounced accelerating effect on the phosphorylation of the alcohol by the reagent, **6** or **7**, as shown below. The product of this step is an alkyl cyclic triester, X=P(O)OR^1, which results from a displacement at phosphorus with ring retention.

Table II. One-Flask Synthesis of Dialkyl(1-methylacetonyl) Phosphates from Alcohols R^1OH and R^2OH by Aryl(1,2-dimethylethenylene) Phosphates

Compd	R^1	R^2	Yield, %[a]
	$X=P(O)OC_6H_4NO_2$-*p*		
8	c-C_5H_9	$(CH_3)_2CHCH_2$	93[b]
9	c-C_5H_9	$C_6H_5CH_2$	91[b]
10	c-C_5H_9	$CH_2=C(CH_3)$-CH_2CH_2	93
11	$(CH_3CH_2)_2CH$	$(CH_3)_3CCH_2$	88[c]
12	$(CH_3CH_2)_2CH$	$(CH_3CH_2)_2CH$	90
13	c-C_6H_{11}	CH_3CH_2	90
14	$[(CH_3)_2CH]_2CH$	$(CH_3)_2CHCH_2$	90
	$X=P(O)OC_6F_5$		
15	$(CH_3)_3CCH_2$	$(CH_3)_2CHCH_2$	98
8	c-C_5H_9	$(CH_3)_2CHCH_2$	90[b]
16	c-C_5H_9	$BrCH_2CH_2$	97
17	(±)-3-*p*-Menthanyl	$C_6H_5CH_2$	95[b]

[a] Crude triester based on R^1OH; purity >98% according to ^1H NMR and the yield of diester after hydrolysis. [b] Triester first synthesized by another procedure; cf. ref 4, 6. [c] Yield after molecular distillation.

The second step is the reaction of the alkyl cyclic triester with alcohol R^2OH, and is also effectively catalyzed by phenoxide ion.[8] The product is the dialkyl(1-methylacetonyl) phosphate, which results from an attack at phosphorus with ring opening. Several examples of the synthesis are listed in Table II; the analytical data for the new compounds are summarized in Table I. The "first alcohols", R^1OH, in Table II range from relatively hindered primary alcohols to acyclic and alicyclic secondary alcohols. The "second alcohols", R^2OH, are mostly primary. Such combinations produce less than 2% of undesirable symmetrical dialkyl(1-methylacetonyl) phosphates.

The acyclic triesters, **8–17**, are converted into the unsymmetrical dialkyl phosphates by the procedures given in the Experimental Section. In these examples, less than 2% of alkyl(1-methylacetonyl) phosphates are generated during the hydrolysis. The new dialkyl phosphates are listed in Table I.

$$(R^1O)(R^2O)P(O)OCH(CH_3)COCH_3 \xrightarrow{H_2O} (R^1O)(R^2O)P(O)OH + HOCH(CH_3)COCH_3$$

The optimum experimental conditions for the acyclic triester synthesis were deduced from independent studies of the four sets of reactions shown in Tables III–VI. From these results it is concluded that alcohol R^1OH reacts much faster with the reagent $X=P(O)OAr$ than with the product $X=P(O)OR^1$, and, therefore, the symmetrical phosphates are not formed to any appreciable extent according to eq 1:

$$R^1OH + X=P(O)OR^1 \rightarrow (R^1O)_2P(O)OCH(CH_3)COCH_3 \quad (1)$$

Phenols, in particular those with electron-withdrawing substituents, are much less reactive than alcohols toward $X=P(O)OR^1$ and $X=P(O)OAr$, and, hence, aryl phosphates are not generated by reactions 2 and 3, under the conditions of the synthesis:

$$ArOH + X=P(O)OR^1 \rightarrow (R^1O)(ArO)P(O)OCH(CH_3)COCH_3 \quad (2)$$

$$ArOH + X=P(O)OAr \rightarrow (ArO)_2P(O)OCH(CH_3)COCH_3 \quad (3)$$

Table III. Half-Times of the Reaction of Alcohols with Aryl(1,2-dimethylethenylene) Phosphates in 0.2 M $CDCl_3$ at 25 °C:[a] $R^1OH + X=P(O)OAr \rightarrow X=P(O)OR^1 + ArOH$

R^1	Catalyst	$t_{1/2}$
	$X=P(O)OC_6F_5$	
$(CH_3)_2CHCH_2$	None	15 s
$(CH_3)_2CHCH_2$	$(C_2H_5)_3N$[b]	2 s
$(CH_3)_2CHCH_2$	$C_6F_5O^-(C_2H_5)_3NH^+$	2 s
c-C_5H_9	None	45 s
c-C_5H_9	$(C_2H_5)_3N$	2 s
c-C_5H_9	$C_6F_5O^-(C_2H_5)_3NH^+$	2 s
$[(CH_3)_2CH]_2CH$	None	2.5 h
$[(CH_3)_2CH]_2CH$	$(C_2H_5)_3N$	2 h
$[(CH_3)_2CH]_2CH$	$C_6F_5O^-(C_2H_5)_3NH^+$	2 h
$(CH_3)_3C$	None	2 h
$(CH_3)_3C$	$(C_2H_5)_3N$	1.75 h
$(CH_3)_3C$	$C_6F_5O^-(C_2H_5)_3NH^+$	1.75 h
	$X=P(O)OC_6H_4NO_2$-*p*	
$(CH_3)_2CHCH_2$	None	10 min
$(CH_3)_2CHCH_2$	$(C_2H_5)_3N$	30 s
$(CH_3)_2CHCH_2$	*p*-$NO_2C_6H_4O^-(C_2H_5)_3NH^+$	2 s
c-C_5H_9	None	20 min
c-C_5H_9	$(C_2H_5)_3N$	1 min
c-C_5H_9	*p*-$NO_2C_6H_4O^-(C_2H_5)_3NH^+$	2 s
$[(CH_3)_2CH]_2CH$	None	22 h
$[(CH_3)_2CH]_2CH$	$(C_2H_5)_3N$	4 h
$[(CH_3)_2CH]_2CH$	*p*-$NO_2C_6H_4O^-(C_2H_5)_3NH^+$	45 min
$(CH_3)_3C$	None	30 h
$(CH_3)_3C$	$(C_2H_5)_3N$	3 h
$(CH_3)_3C$	*p*-$NO_2C_6H_4O^-(C_2H_5)_3NH^+$	45 min
	$X=P(O)OC_6H_4F$-*p*	
$(CH_3)_2CHCH_2$	None	20 min
$(CH_3)_2CHCH_2$	Et_3N	1 min
$(CH_3)_2CHCH_2$	*p*-$FC_6H_4O^-(C_2H_5)_3NH^+$	30 s
c-C_5H_9	None	2.5 h
c-C_5H_9	Et_3N	20 min
c-C_5H_9	*p*-$FC_6H_4O^-(C_2H_5)_3NH^+$	[c]

[a] Equimolar amounts of reagents and catalyst; $t_{1/2}$ from ^1H NMR spectra. [b] The reaction is autocatalytic in the presence of $(C_2H_5)_3N$; $t_{1/2}$ is the time at which [X=P(O)OAr] = [X=P(O)OR]. [c] Products of ring opening are observed.

Table III shows that in reaction $R^1OH + X=P(O)OAr$, the order of reactivity is Ar = C_6F_5 > *p*-$NO_2C_6H_4$, in the absence of catalyst. This sequence corresponds to the acidities of C_6F_5OH > *p*-$NO_2C_6H_4OH$, pK_a = 5.5 and 7.2, respectively;[9,10] hence, the effect may result from the greater leaving group ability, or the higher reagent electrophilicity, or both, in $X=P(O)OC_6F_5$ vs. $X=P(O)OC_6H_4NO_2$-*p*. In contrast, if the corresponding salt, $ArO^-(C_2H_5)_3NH^+$, is initially introduced into the reaction, the relative reactivities become $X=P(O)OC_6H_4NO_2$-*p* > $X=P(O)OC_6F_5$, which is consistent with the higher nucleophilicity of *p*-$NO_2C_6H_4O^-$ vs. $C_6F_5O^-$ in their role as catalysts. It is noteworthy that the catalytic effect of $C_6F_5O^-$ in the reactions of $X=P(OC)OC_6F_5$ (but not of *p*-$NO_2C_6H_4O^-$, in the reactions of $X=P(O)OC_6H_4NO_2$-*p*) vanishes in the case of the two bulkiest alcohols, R^1OH, included in Table III, which suggests that additional steric considerations are involved.

Table IV discloses the effective phenoxide ion catalysis of the reaction $R^2OH + X=P(O)OR^1$, and shows that *p*-$NO_2C_6H_4O^-$ is more efficient than $C_6F_5O^-$ for all combinations of alkyl groups. $C_6F_5O^-$ does not accelerate the reaction when R^1 = $[(CH_3)_2CH]_2CH$ and R^2 = c-C_5H_9, or when R^1 = $(CH_3)_3C$ and R^2 = $(CH_3)_2CHCH_2$. The free phenol has no significant effect on the reaction rate. The pure $X=P(O)OR^1$ used for the study summarized in Table IV was prepared from

Table IV. Phenoxide Ion Catalysis of the Reaction of Alcohols with Alkyl(1,2-dimethylethenylene) Phosphates in 0.2 M $CDCl_3$ at 25 °C:[a] $R^2OH + X{=}P(O)OR^1 \rightarrow (R^1O)(R^2O)P(O)OCH(CH_3)COCH_3$

R^2	Catalyst	$t_{1/2}$
	$X{=}P(O)OCH_2CH(CH_3)_2$	
$(CH_3)_2CHCH_2$	None	4 h
$(CH_3)_2CHCH_2$	p-$NO_2C_6H_4O^-(C_2H_5)_3NH^+$	2 min
$(CH_3)_2CHCH_2$	$C_6F_5O^-(C_2H_5)_3NH^+$	25 min
	$X{=}P(O)OCH_2CH_2Br$	
$(CH_3)_2CHCH_2$	None[b]	25 min
$(CH_3)_2CHCH_2$	p-$NO_2C_6H_4O^-(C_2H_5)_3NH^+$	0.5 min
$(CH_3)_2CHCH_2$	$C_6F_5O^-(C_2H_5)_3NH^+$	3 min
	$X{=}P(O)OCH(CH_3)(CCl)_3$	
$(CH_3)_2CHCH_2$	None	10 min
$(CH_3)_2CHCH_2$	p-$NO_2C_6H_4O^-(C_2H_5)_3NH^+$	0.5 min
$(CH_3)_2CHCH_2$	$C_6F_5O^-(C_2H_5)_3NH^+$	4 min
	$X{=}P(O)O$-c-C_5H_9	
$(CH_3)_2CHCH_2$	None[c]	7.5 h
$(CH_3)_2CHCH_2$	p-$NO_2C_6H_4O^-(C_2H_5)_3NH^+$	3 min
$(CH_3)_2CHCH_2$	p-$NO_2C_6H_4OH$	9.5 h
$(CH_3)_2CHCH_2$	$C_6F_5O^-(C_2H_5)_3NH^+$	1 h
$(CH_3)_2CHCH_2$	C_6F_5OH	10 h
$C_6H_5CH_2$	None	2.5 h
$C_6H_5CH_2$	p-$NO_2C_6H_4O^-(C_2H_5)_3NH^+$	2 min
$C_6H_5CH_2$	$C_6F_5O^-(C_2H_5)_3NH^+$	30 min
c-C_5H_9	None	28 h
c-C_5H_9	p-$NO_2C_6H_4O^-(C_2H_5)_3NH^+$	15 min
c-C_5H_9	$C_6F_5O^-(C_2H_5)_3NH^+$	6 h
$(CH_3CH_2)(CH_3)CH$	None	34 h
$(CH_3CH_2)(CH_3)CH$	p-$NO_2C_6H_4O^-(C_2H_5)_3NH^+$	35 min
$(CH_3CH_2)(CH_3)CH$	$C_6F_5O^-(C_2H_5)_3NH^+$	12 h
	$X{=}P(O)OCH[CH(CH_3)_2]_2$	
$(CH_3)_2CHCH_2$	None	22 h
$(CH_3)_2CHCH_2$	p-$NO_2C_6H_4O^-(C_2H_5)_3NH^+$	25 min
$(CH_3)_2CHCH_2$	$C_6F_5O^-(C_2H_5)_3NH^+$	9.5 h
c-C_5H_9	None	70 h
c-C_5H_9	p-$NO_2C_6H_4O^-(C_2H_5)_3NH^+$	2.5 h
c-C_5H_9	$C_6F_5O^-(C_2H_5)_3NH^+$	78 h
	$X{=}P(O)C(CH_3)_3$	
$(CH_3)_2CHCH_2$	None	45 h
$(CH_3)_2CHCH_2$	p-$NO_2C_6H_4O^-(C_2H_5)_3NH^+$	1.5 h
$(CH_3)_2CHCH_2$	$C_6F_5O^-(C_2H_5)_3NH^+$	46 h

[a] Equimolar amounts of reagents and catalyst; $t_{1/2}$ from ^1H NMR spectra. [b] Small amounts (3–4%) of symmetrical triester detected in all cases. [c] Addition of 1 molar equiv of $X{=}P(O)O^-(C_2H_5)_3NH^+$ to the mixture of 2-butanol and $X{=}P(O)O$-c-C_5H_9 had no significant effect.

Table V. Half-Times of the Reaction of Phenols with Alkyl(1,2-dimethylethenylene) Phosphates in 0.2 M $CDCl_3$ at 25 °C:[a] $ArOH + X{=}P(O)OR^1 \rightarrow (R^1O)(ArO)P(O)$-$OCH(CH_3)COCH_3$

Catalyst[b]	$t_{1/2}$
$C_6H_5OH + X{=}P(O)OCH_2CH(CH_3)_2$[c]	
None	No reaction[d]
$[(CH_3)_2N]_2C{=}NH$	1.5 min
$(i$-$C_3H_7)_2(C_2H_5)N$	4
$(C_2H_5)_3N$	2 h
Imidazole	3 h
γ-Collidine	No reaction
$C_6H_5OH + X{=}P(O)O$-c-C_5H_9	
None	No reaction
$[(CH_3)_2N]_2C{=}NH$	2 min
$(i$-$C_3H_7)_2(C_2H_5)N$	45 min
Quinuclidine	2 h
$(C_2H_5)_3N$	3 h
Imidazole	4 h
γ-Collidine	No reaction
C_5H_5N	No reaction
$C_6H_5OH + X{=}P(O)OCH[CH(CH_3)_2]_2$	
None	No reaction
$(i$-$C_3H_7)_2(C_2H_5)N$	70 h
$(C_2H_5)_3N$	70 h
Imidazole	30 h
p-$NO_2C_6H_4OH + X{=}P(O)O$-c-C_5H_9	
None	No reaction
$(i$-$C_3H_7)_2(C_2H_5)N$	~7 days
$(C_2H_5)_3N$	~8 days
Imidazole	~10 days

[a] Equimolar amounts of reagents; $t_{1/2}$ from ^1H NMR spectra. [b] pK_B of amines: tetramethylguanidine, 0.4; diisopropylethylamine, 2.0; quinuclidine, 2.9; triethylamine, 3.0; imidazole, 6.9; γ-collidine, 6.7; pyridine, 8.7 (ref 11). [c] Small amounts of symmetrical phosphotriesters observed in this particular system. [d] Within 3 days, in all cases.

the reaction of the alcohol R^1OH with the pyrophosphate[4,6] 3. The reaction $R^1OH + X{=}P(O)OAr$ is not a practical method to make pure $X{=}P(O)OR^1$.

The data in Tables III and IV suggest an interplay of electronic and steric factors associated with the aryl and alkyl groups in the *phenoxide catalyzed* reactions $R^1OH + X{=}P(O)OAr$ and $R^2OH + X{=}P(O)OR^1$. Similar phenomena have been observed[6] in the *tertiary amine catalyzed* reaction $R^2OH + X{=}P(O)OR^1$ in $CDCl_3$ solution. Triethylamine is an effective catalyst when R^2OH is a primary alcohol and R^1 is a primary or secondary alkyl group; however, the rate enhancement decreases as the steric requirements of R^1 increase, e.g., when $R^1 = [(CH_3)_2CH]_2CH$, and the catalysis vanishes when $R^1 = (CH_3)_3C$. Triethylamine does not increase the rate of the reaction of secondary alcohols (R^2OH) with esters $X{=}P(O)OR^1$, even if R^1 is primary. On the other hand, the less hindered quinuclidine is an effective catalyst when R^2OH is a primary or a secondary alcohol, and R^1 is primary, secondary, or tertiary.

Table V shows that phenols are quite unreactive toward $X{=}P(O)OR^1$ in the absence of amines. Amines accelerate the reaction, and their effectiveness correlates mainly with their basicity,[11] except in the case of imidazole, which is more efficient than it would be expected from its basicity. γ-Collidine, which is slightly more basic than imidazole, but more hindered around the nitrogen, is inactive. It appears that amines can exert their catalytic action in two ways: by converting the phenol into the more nucleophilic phenoxide ion, and by activating the $X{-}P(O)OR^1$ reagent. As expected, p-nitrophenoxide is less reactive than the more nucleophilic unsubstituted phenoxide toward a given $X{=}P(O)OR^1$, in the presence of the same amine. Two new arylalkyl (1-methyl

Table VI. Half-Times of the reaction of Phenols with Aryl(1,2-dimethylethenylene) Phosphates in 0.2 M $CDCl_3$ at 25 °C:[a] ArOH + X=P(O)OAr → $(ArO)_2P(O)OCH(CH_3)$-$COCH_3$

Catalyst	$t_{1/2}$
C_6H_5OH + X=P(O)OC_6H_5	
None	No reaction[b]
$[(CH_3)_2CH]_2C{=}NH$	2 min
$(i\text{-}C_3H_7)_2(C_2H_5)N$	35 min
$(C_2H_5)_3N$	45 min
Imidazole	1.5 h
γ-Collidine	36 h
C_5H_5N	No reaction
$p\text{-}NO_2C_6H_4OH$ + X=P(O)$OC_6H_4NO_2$-p	
None	No reaction
$(i\text{-}C_3H_7)_2(C_2H_5)N$	45 h
Imidazole	80 h
C_5H_5N	No reaction

[a] Equimolar amounts of reagents. The structures of the diaryl(1-methylacetonyl) phosphates are based on ^1H and ^{31}P NMR spectra; the compounds were not isolated in pure state. [b] Within 3 days in all cases.

acetonyl) phosphates, **18** and **19**, made by this reaction are described in Table I.

Table VI shows some analogy with Table V, since both refer to reactions of phenols; however, the higher reactivity of X=P(O)OAr vs. X=P(O)OR^1 is reflected in the catalysis by γ-collidine shown in Table VI. The weakest base, pyridine, is ineffective in the reaction of the phenols with X=P(O)OAr. From an analysis of the data in Tables III–VI it can be seen that there is no difficulty in making unsymmetrical dialkyl(1-methylacetonyl) phosphates free from aryl-containing triesters, and from symmetrical by-products resulting from the first step (eq 1, above). To verify these points consider the $t_{1/2}$ values for reactions such as c-C_5H_9OH and $p\text{-}NO_2C_6H_4OH$ with X=P(O)$OC_6H_4NO_2$-p vs. X=P(O)OR^2, including R^2 = c-C_5H_9, in the presence of $ArO^-R_3NH^+$ or R_3N, as appropriate.

Symmetrical dialkyl(1-methylacetonyl) phosphates can, in principle, be produced during the second step of the synthesis, as shown in eq 4, which is a displacement at phosphorus with ring retention:

$$R^2OH + X{=}P(O)OR^1 \rightarrow X{=}P(O)OR^2 + R^1OH \quad (4)$$

This transesterification would be followed by the reaction of eq 1, and by that of eq 5:

$$R^2OH + X{=}P(O)OR^2 \rightarrow (R^2O)_2P(O)OCH(CH_3)COCH_3 \quad (5)$$

It has been found that the relative amounts of unsymmetrical vs. symmetrical triesters vary according to the sequence in which the two alcohols are submitted to the phosphorylative coupling, *in the absence of catalyst*. This is shown by a study of reactions R^2OH + X=P(O)OR^1 and R^1OH + X=P(O)-OR^2. Symmetrical triester formation is minimized if the smaller alcohol is added to the cyclic triester containing the bulkier alkyl group, or if a more electronegative alcohol is added to the triester with the less electronegative alkyl group; cf. Table II.

The formation of the symmetrical triester by-product in a particular uncatalyzed reaction is significantly reduced by the presence of the *p*-nitrophenoxide ion, and the synthetic procedure is practicable even if the uncatalyzed reaction R^2OH + X=P(O)OR^1 yields ca. 6–8% of symmetrical triester, since this value becomes <2% in the presence of phenoxide ion. This effect is best studied in the system $(CH_3)_2CHCH_2OH$ + X=P(O)OCH_3, where the proportion of unsymmetrical vs. symmetrical triesters varies from 54:46% to 75:25%, in the absence and in the presence of $p\text{-}NO_2C_6H_4O^-(C_2H_5)_3{}^+NH$, respectively.

Discussion

To our knowledge, the phenoxide ion catalysis of the phosphorylation of alcohols in aprotic solvents, or in aqueous solution, has not been previously described. We have reported imidazole,[6] tertiary amine,[6] and carboxylate ion[12] catalysis of the reaction R^2OH + X=P(O)OR^1 in aprotic solvents. Westheimer and co-workers[13] observed imidazole catalysis of the solvolysis of tetrabenzyl pyrophosphate in 1-propanol. Van Boom, Reese, et al.[14] noted 5-chloro-1-methylimidazole catalysis of the reaction of alcohols with diphenylphosphorochloridate in acetonitrile. The role played by imidazole, tertiary amines, carboxylate ions, and other nucleophiles in the reactions of phosphotriesters, phosphodiesters, and related compounds, *in aqueous solutions*, has been extensively investigated, in particular by Jencks,[15] Kirby,[16] Benkovic,[17] Westheimer,[18] Haake,[19] and Simons.[20] It has been generally accepted[15-20,21-23] that in those types of compounds, the catalysis is exerted by conversion of the P(4)[24] into a more reactive P(4)′ intermediate via a P(5)[24] intermediate, e.g.[35]

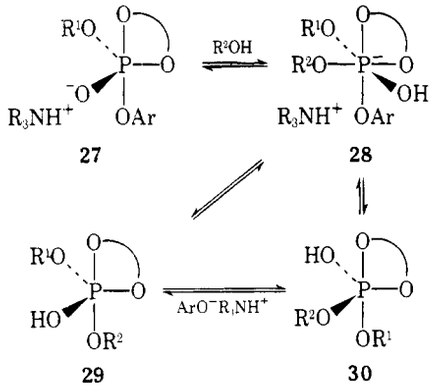
$$Nu + \rangle P(O)X \longrightarrow \rangle P(O)(X)(Nu) \longrightarrow \rangle P(O)Nu + X$$

$$ROH + \rangle P(O)Nu \longrightarrow \rangle P(O)OR + Nu + H^+$$

(with the appropriate charge distribution depending on the type of nucleophile and leaving group).

The phosphorylations in aprotic solvents described in this and in the previous papers[4,6,12] are difficult to explain except under the assumption that the nucleophilic catalyst converts the phosphate into a P(5) intermediate, and that the reagent being phosphorylated then transforms the P(5) into a P(6)[24] intermediate. The products are obtained from the subsequent transformations: P(6) → P(5)′ → P(4)″. The underlying assumptions, as well as the literature references in support of these hypotheses, have been given.[4,6] These hypotheses can be applied to the observations reported in the present paper. The significant findings are (1) the phenoxide ion catalysis of the reaction R^2OH + X=P(O)OR^1 without incorporation of the phenoxide into the product or into any detectable P(4) intermediate; (2) the amine catalysis of the reaction ArOH + X=P(O)OR^1 with incorporation of the phenoxide into the product; (3) the variation of the proportion of unsymmetrical vs. symmetrical dialkyl(1-methylacetonyl) phosphate with the order in which the two alcohols are phosphorylated, in the absence of catalyst; (4) the decrease in the amount of symmetrical triester, in any given order of phosphorylation, in the presence of phenoxide ion.

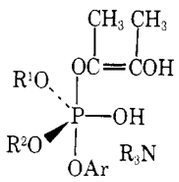
In the oxyphosphorane-intermediate hypothesis, the first step of the phenoxide-catalyzed reaction of alcohol R^2OH with X=P(O)OR^1 involves the formation of the P(5) **27**. The second step is the conversion of **27** into the P(6) **28**. The latter, **28**, can collapse[25] to one or to both isomeric P(5)′, **29** or **30**, which are also interconvertible by an intramolecular permutational isomerization, possibly by the TR mechanism[26] with the ring as ligand pair.[27] Isomer **29** is generated, directly, by apical addition of R^2OH to X=P(O)OR^1, in the uncatalyzed reaction. If isomer **29** is formed exclusively, and if it collapses by ring opening before it equilibrates with **30**, the unsymmetrical acyclic triester is exclusively formed in the uncatalyzed reaction. If equilibration **29** ⇌ **30** takes place, and there is apical departure of R^1O ligand from **30**, the new X=P(O)OR^2 is produced and eventually there is formation of symmetrical



27 28 29 30

acyclic triesters by eq 1 and 5. The variation in the relative amounts of unsymmetrical vs. symmetrical triesters with the order in which the two alcohols are allowed to react implies that ring opening is competitive with the equilibration of isomers **29** and **30** by permutational isomerization.

A possible explanation for the decrease in the amount of symmetrical triesters in the phenoxide-catalyzed couplings is that ring opening may occur at the P(6) intermediate stage, **28**; the resulting acyclic P(5)′ **31** yields the unsymmetrical triester by loss of ArO^-. This interpretation has been ad-



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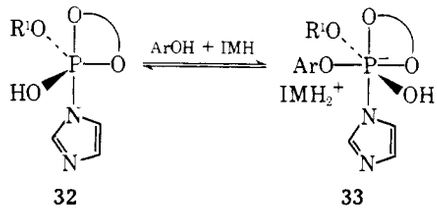
vanced to account for a similar effect in the imidazole- and triethylamine-catalyzed reactions.[6] It is also speculated that the catalysis results from a higher nucleophilicity of the phenoxide anion vs. neutral alcohol, R^2OH. The P(4) ⇌ P(5) step is assumed to be relatively rapid in this particular case.[28] The various ways in which the P(5) and P(6) intermediates can collapse and the possibility of a permutational isomerization of P(5) provide for product control in this and in the other related reactions of Tables III–VI.

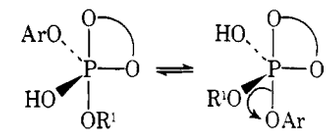
The P(5) intermediate **27** accounts for part of the effect of the amine, R_3N, on the reaction $ArOH + X{=}P(O)OR^1$ (Table V); i.e., dissociation, $ArOH + R_3N \rightleftharpoons ArO^-R_3NH^+$, followed by addition of ArO^- to P(4) to give **27**. In the absence of alcohol, **27** eventually collapses to the observed arylalkyl(1-methylacetonyl) phosphate by ring opening. The second effect of the amine is probably related to the amine catalysis[6] of the reaction $R^2OH + X{=}P(O)OR^1$. Imidazole can add to P(4) to give the P(5) **32**, and the latter is converted into the P(6) **33**



32 33

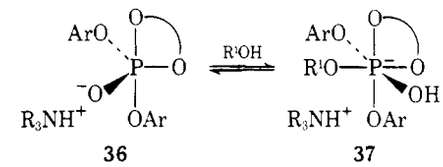
by the phenol in the presence of imidazole. The loss of imidazole from **33** generates a P(5) analogous to **27** which eventually collapses to the arylalkyl triester.

The reaction $R^1OH + X{=}P(O)OAr$, which results in ring retention, and the reaction $ArOH + X{=}P(O)OAr$, which results in ring opening, can be rationalized as follows. The uncatalyzed reactions of the alcohols (Table III) are relatively rapid and can be viewed as involving the formation of the P(5) **34**, *followed by a relatively rapid permutational isomerization* to **35**, which places the apicophilic[26] ArO^- at the apical position, from which it can depart to give the observed product $X{=}P(O)OR^1$.



34 35

The phenoxide ion catalysis of $R^1OH + X{=}P(O)OAr$ would involve the P(5) intermediate **36**, which adds R^1OH to give the P(6) intermediate **37**. The latter collapses to a P(5) interme-

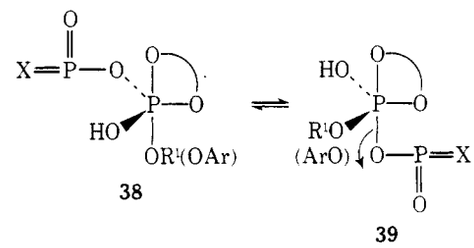


36 37

diate analogous to **35**. The P(5) intermediate **36** also accounts for the product of the reaction $ArOH + X{=}P(O)OAr + R_3N$ (Table VI), which results from ring opening of **36**.

The loss of catalysis by $C_6F_5O^-$ in some of the reactions $R^1OH + X{=}P(O)OC_6F_5$, when R^1OH is relatively bulky (entries 8, 9, 11, 12 in Table III), could result from an inability of the alcohol to add to P(5), **36**, and form P(6), **37**. Since the catalysis is retained in the comparable reactions involving the *p*-nitrophenyl analogues (entries 20, 21, 23, 24 in Table III), this rationale implies a lower degree of steric hindrance in the transformation **36** + R^1OH → **37** in the latter case.[29]

The mechanism of the reaction of alcohols and phenols with the pyrophosphate **3** has already been discussed.[4,6] These reactions proceed with ring retention and can be explained by the P(5) intermediates **38** and **39**. The amine catalysis of



38 39

the phenol reaction may simply result from the generation of the more nucleophilic phenoxide ion.

The experimental results, and the hypotheses offered to explain them, may be related to some of the mechanisms operating in enzymes which are involved in biological phosphoryl group transfers.[30-32] It is apparent that phenoxide ion is capable of exerting a strong phosphate activation *in aprotic solvents of low polarity*. Tyrosine residues have been implicated in the catalytic activity of enzymes such as fructose 1,6-diphosphatase[33] and ATP-creatine phosphotransferase,[34] in the latter case, in conjunction with lysine and histidine residues. The possible involvement of hexacoordinate as well as pentacoordinate phosphorus species in the hydrophobic active sites of these enzymes is an attractive hypothesis.

Experimental Section

The physical properties of new compounds are given in Table I. Analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Compounds with the X=P(O)- group are very sensitive to moisture. Solvents were purified, and were stored over molecular sieves. A dry N_2 atmosphere is advisable in all reactions.

2-*p*-Nitrophenoxy-4,5-dimethyl-1,3,2-dioxaphosphole 2-Oxide (6). Yields of **6** higher than those reported[4] were obtained by the following procedure. A solution of *p*-nitrophenol (8.76 g, 63 mmol) in anhydrous ether (60 ml) was added dropwise in 20 min to a stirred solution of the pyrophosphate (**3**, 17.75 g, 63 mmol) in dichloro-

methane (200 ml), containing nicotinamide (8 g, slight excess over 63 mmol) in suspension, at 25 °C. After 4.5 h at 25 °C, the nicotinamide salt of 2-hydroxy-4,5-dimethyl-1,3,2-dioxaphosphole 2-oxide was filtered off and washed with dichloromethane (100 ml). The combined washing and filtrate were concentrated to ca. 40 ml and diluted with ether (150 ml) to induce the crystallization of the product. The mixture was concentrated to ca. 30 ml, and X=P(O)$OC_6H_4NO_2$-*p* (**6**) was filtered off, washed with a small volume of ether, and dried under vacuum. Yield of first crop: 15.5 g (90%); the chilled filtrate gave 0.2 g (2%) of additional **6**. Both materials had mp 102–104 °C, as reported.[4]

2-Pentafluorophenoxy- and 2-*p*-Fluorophenoxy-4,5-dimethyl-1,3,2-dioxaphosphole 2-Oxides (7 and 5). A dichloromethane solution (50 ml) containing pentafluorophenol (6.95 g, 37.8 mmol) and γ-collidine (4.57 g, 37.8 mmol) was added over a 30-min period to a dichloromethane solution (100 ml) of the pyrophosphate (**3**, 10.66 g, 37.8 mmol), at 0 °C. The mixture was stirred at 0 °C for 30 min, and at 20 °C for 2 h. The solution was evaporated, and the residue was extracted with anhydrous ether (4 × 75 ml). The extract was filtered and evaporated, leaving a residue which was purified by molecular distillation (Table I) to give X=P(O)OC_6F_5 (**7**) in 90% of the theory.

The same procedure yielded X=P(O)OC_6H_4F-*p* (**5**) in 82% of the theory.

Procedure 1. One-Flask Synthesis of Dialkyl(1-methylacetonyl) Phosphates by X=P(O)$OC_6H_4NO_2$-*p* (6). A dichloromethane solution containing R^1OH (1 molar equiv) and triethylamine (1 molar equiv) is added dropwise (5 min) to a stirred dichloromethane solution of **6** (1 molar equiv, 0.6–0.8 M) at 25 °C. After 15–60 min, 1 molar equiv of R^2OH is added dropwise (5 min) in the same solvent. The solution (0.4–0.6 M) is stirred at 25 °C for periods which depend on the structures of R^1 and R^2 (1–12 h; see Table IV), and is then diluted with dichloromethane (0.1–0.2 M) and repeatedly extracted with dilute, aqueous alkali (Na_2CO_3 or NaOH) to remove *p*-nitrophenol. The dichloromethane solution is dried over Na_2SO_4 and evaporated under vacuum to give the dialkyl(1-methylacetonyl) phosphate, which was then hydrolyzed to the dialkyl phosphate, before or after purification by short-path distillation. The crude acyclic triester may have a slight yellow color owing to traces of *p*-nitrophenol, but the contamination is insignificant (<0.5% by ^1H NMR), and it does not affect the quality of the final dialkyl phosphate.

Procedure 2. One-Flask Synthesis of Dialkyl(1-methylacetonyl) Phosphates by X=P(O)OC_6F_5 (7). Analogous to procedure 1. Alternatively, the pentafluorophenol by-product can be removed by short-path vacuum distillation, after evaporation of the original dichloromethane solution, instead of by alkaline extraction, if the dialkyl(1-methylacetonyl) phosphate has alkali-sensitive substituents.

Hydrolysis of Dialkyl(1-methylacetonyl) Phosphates. Procedure A. With Triethylamine. The crude or distilled acyclic triester is dissolved in a 2:1 v/v mixture of water and acetonitrile (0.1 M solution) containing 2 molar equiv of triethylamine or of diisopropylethylamine. The mixture is stirred for 10 h at 70 °C; triesters with the bulkiest substituents, e.g., compounds **12** and **14**, Table II, require longer times, 70–100 h at 70 °C. The acetonitrile is evaporated at 40 °C (30 mm) and the aqueous residue is diluted with water to a volume that is convenient for ether extraction to remove neutral contaminants. The aqueous phase, after ether extraction, is acidified with 5% hydrochloric acid, and is extracted with dichloromethane. The organic extract is dried (Na_2SO_4), and is evaporated to yield the crude dialkyl phosphate, $(R^1O)(R^2O)P(O)OH$, analyzed by ^1H NMR spectrometry (Table I); less than 2% of by-product monoalkyl(1-methylacetonyl) phosphate is found in the examples given in Table II. The dialkyl phosphates are converted into crystalline salts as indicated in Table I. The salts are isolated in about 75% of the theoretical yield based on the first alcohol, R^1OH.

Procedure B. With Sodium Carbonate. If the alkyl groups in the dialkyl(1-methylacetonyl) phosphate are sensitive to the tertiary amine, the hydrolysis is carried out as in procedure A, except that the amine is replaced by 2 molar equiv of Na_2CO_3. This procedure is indicated for the synthesis of 2-bromoethylalkyl phosphates, e.g., **22a**; in this example, a relatively large (ca. 7%) amount of alkyl(1-methylacetonyl) phosphate by-product is formed in the hydrolysis.

Synthesis of Cyclopentylisobutyl Phosphate by X=P(O)-$OC_6H_4NO_2$-*p* (6) in the Absence of Triethylamine. Cyclopentanol was added to **6** as in procedure 1, *but without triethylamine*. In this case, 4.5 h was required for the preparation of the intermediate X=P(O)O-c-C_5H_9, as monitored by ^1H NMR spectrometry. An equimolar mixture of 2-butanol and triethylamine was introduced at this point, and the cyclopentylisobutyl(1-methylacetonyl) phosphate (**8**) was obtained in ca. 45 min (90% yield); total reaction time 6 h vs. 1.5 h by procedure 1. The corresponding salt of the dialkyl phosphate was isolated in 75% yield based on cyclopentanol.

Isolation of 2-Alkoxy-4,5-dimethyl-1,3,2-dioxaphosphole 2-Oxides. A. From Pyrophosphate 3. The pure X=P(O)OR^1 for the experiments in Tables IV and V was made as described.[4,6]

B. From X=P(O)OC_6F_5 (7). Cyclopentanol (0.74 g, 8.6 mmol) in dichloromethane solution (10 ml) was added in 15 min to X=P(O)OC_6F_5 (**7**, 2.71 g, 8.6 mmol) in the same solvent (30 ml) at 0 °C. The solution was kept at 0 °C for 30 min, and at 25 °C overnight. The solution was evaporated at 0.15 mm, first at 45 °C, then at 90 °C (15 min) to remove pentafluorophenol, leaving X=P(O)O-c-C_5H_9 (1.85 g, 92% of the theory) as the residue. The ^1H NMR of the latter (in $CDCl_3$) was identical with that of the distilled product,[4] bp 102–104 °C (0.2 mm).

Registry No.—**3**, 55894-94-5; **4**, 55895-03-9; **5**, 61010-62-6; **6**, 55895-04-0; **7**, 57204-50-9; **10**, 57204-53-2; **11**, 61010-63-7; **12**, 61010-64-8; **13**, 61010-65-9; **14**, 61010-66-0; **15**, 57204-55-4; **16**, 57204-54-3; **18** isomer A, 61010-67-1; **18** isomer B, 61010-68-2; **19** isomer A, 61010-69-3; **19** isomer B, 61010-70-6; **20a**, 61010-72-8; **21a**, 61010-74-0; **22a**, 61010-76-2; **23a**, 61010-77-3; **24a**, 61010-79-5; **25a**, 61010-81-9; **26a**, 61010-83-1; R^1OH (R^1 = c-C_5H_9), 96-41-3; R^1OH (R^1 = $(CH_3CH_2)_2CH$), 584-02-1; R^1OH (R^1 = c-C_6H_{11}), 108-93-0; R^1OH (R^1 = $[(CH_3)_2CH]_2CH$), 600-36-2; R^1OH (R^1 = $(CH_3)_3CCH_2$), 75-84-3; R^1OH ((±)-3-*p*-menthanyl), 15356-70-4; R^1OH (R^1 = $(CH_3)_3C$), 75-65-0; R^2OH (R^2 = $(CH_3)_2CHCH_2$), 78-83-1; R^2OH (R^2 = $C_6H_5CH_2$), 100-51-6; R^2OH (R^2 = CH_2=$C(CH_3)CH_2CH_2$), 763-32-6; R^2OH (R^2 = CH_3CH_2), 64-17-5; R^2OH (R^2 = $BrCH_2CH_2$), 540-51-2; R^2OH (R^2 = $(CH_3CH_2)(CH_3)CH$), 78-92-2; R^2OH (R^2 = C_6H_5), 108-95-2; X=P(O)$OCH_2CH(CH_3)_2$, 16764-09-3; X=P(O)-OCH_2CH_2Br, 55894-97-8; X=P(O)$OCH(CH_3)(CCl_3)$, 55894-01-7; X=P(O)O-c-C_5H_9, 55894-98-9; X=P(O)$OCH[CH(CH_3)_2]_2$, 60807-32-1; X=P(O)$OC(CH_3)_3$, 55895-02-8; *p*-nitrophenol, 100-02-7; pentafluorophenol, 771-61-9.

References and Notes

(1) Research supported by Grant GM-20672 from the National Institute of General Medical Sciences. Acknowledgment is also made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support.
(2) Preliminary communication: F. Ramirez and J. F. Marecek, *J. Org. Chem.*, **40**, 2849 (1975).
(3) X is the 1,2-dimethylethenylenedioxy group. Pyrophosphate **3** is $[X=P(O)]_2O$ or oxybis(1,2-dimethylethenylenedioxyphosphoryl).
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(35) **Note Added in Proof.** This mechanism—P(4) → P(5) → P(4)′ → P(5)′ → P(4)″—is inconsistent with the following data: $t_{1/2} \sim 15$ h for the reaction R^2OH + (ArO)(R^1O)P(O)OCH(CH_3)$COCH_3$ + R_3N → (R^2O)(R^1O)P(O)OCH(CH_3)$COCH_3$ + $ArO^-R_3NH^+$, at 25 °C in 0.2 M $CDCl_3$, while $t_{1/2}$ = 3 min for R^2OH + X=P(O)OR^1 → (R^2O)(R^1O)P(O)OCH(CH_3)$COCH_3$, under comparable conditions (Table IV), when R^2 = $(CH_3)_2CHCH_2$, R^1 = c-C_5H_9, Ar = p-$NO_2C_6H_4$, R = C_2H_5. It is clear that the acyclic P(4)′ intermediate, that should have been formed from the cyclic triester according to this mechanism, reacts at a much slower rate (~15 h) than the cyclic triester itself (~3 min). Hence the latter reaction must proceed by a different mechanism, possibly that postulated here: P(4) → P(5) ≡ **27** → P(6) ≡ **28** → P(5)′ ≡ **31** → P(4)″. Moreover, the reaction ROH + (ArO)P(O)(OC_6H_5)$_2$ → (RO)P(O)(OC_6H_5)$_2$ + ArOH is *effectively catalyzed* by $ArOR_3NH^+$, as well as by $ArO^-R_4N^+$, in either $CDCl_3$ or CD_3CN (0.2 M, 25 °C), although it is evident that in this case the intermediate P(4)′ postulated by the mechanism P(4) → P(5) → P(4)′ → P(5)′ → P(4)″ is identical with the starting triester, P(4), and therefore the catalysis must be exerted via a different mechanism (F. Ramirez and J. Marecek, *Tetrahedron Lett.*, submitted for publication).

Synthesis, Structure Analysis, and Stereochemistry of Some Reactions of *cis*- and *trans*-2,2,5-Trimethyl-3-phenyl-1,3-oxaphospholane

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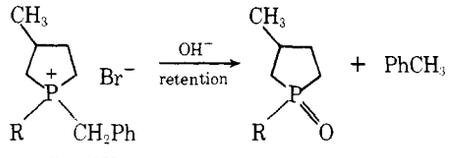
The syntheses of *cis*- and *trans*-2,2,5-trimethyl-3-phenyl-1,3-oxaphospholane are reported and a detailed analysis of the NMR spectra given from which stereochemical assignments were made and conformational structure suggested. Hydroxide cleavage of *cis*- and *trans*-3-benzyl-2,2,5-trimethyl-3-phenyl-1,3-oxaphospholanium bromide occurred stereospecifically with retention of configuration at phosphorus to yield the corresponding diastereomers of 2,2,5-trimethyl-3-phenyl-1,3-oxaphospholane 3-oxide.

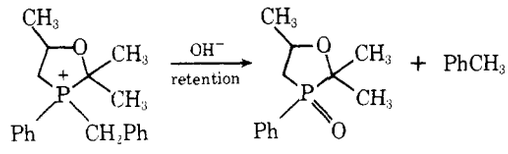
Stereochemistry of nucleophilic displacement at a phosphonium phosphorus atom confined to a five-membered ring (phospholanium salts) has been the subject of a number of investigations which are briefly summarized in a recent paper.[1] One of the most significant findings in this system is the hydroxide-induced displacement of benzyl from both the cis and trans isomers of **1** and **2** with complete retention of configuration at phosphorus.[2a-d]



1, R = CH_3
2, R = Ph

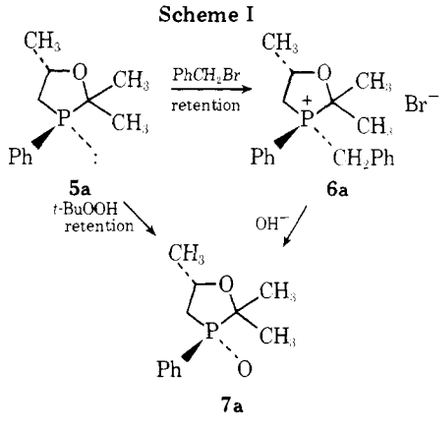
3

The possible influence of any "element effect" of a second heteroatom on the stereochemistry of this reaction has prompted us to synthesize the cis and trans isomers of 3-benzyl-2,2,5-trimethyl-3-phenyl-1,3-oxaphospholanium bromide (**4**). The 1,3-oxaphospholane system is a newly synthesized one,[3a] and its chemistry has been essentially limited to a few NMR studies.[4-6] Also no pure geometric isomers have been isolated until this report. With this appropriately substituted 1,3-oxaphospholane system in hand, chosen especially for its relatively simple NMR spectra, we have now discovered that the presence of oxygen in the ring provokes no stereochemical change. Indeed, **4** behaves precisely as **1** and **2** toward base cleavage, which again occurs with complete retention of configuration. The stereochemistry for eq 1 was demonstrated by completion of the stereochemical cycle shown in Scheme I for which the stereochemistry of reduction[2,7] and oxidation[8]



4 (1)

Scheme I



is known. Stereospecific oxidation of **5a** produces the same isomer as cleavage of **6a**. Although racemic mixtures of both cis and trans isomers were used, the cycle is illustrated with one enantiomer of the trans phosphine **5a**.

Since the completion of this work, Cooper and others[9] have