(31) Had this deshielding of the glycine NH been introduced as evidence for the partial structure -5-MeΔPhe-8-Gly- (or -11-MeΔPhe-2-Gly-) in deducing the limited set of structures which were compatible with the tentoxin ^{1}H NMR data, it would have eliminated five of the ten structures (two of the four sequences) with which the above presentation turned from the tentoxin spectrum to that of dimethyltentoxin. On analogous grounds, the observation that neither the alanyl *N*-methyl of tentoxin nor the glycyl, leucyl, nor alanyl *N*-methyls of dimethyltentoxin are unusually deshielded might have been used as an additional basis to exclude for those peptides partial structures which contain a 5- or 11-dehydrophenylalanyl unit followed by a 7- or 1-methyl, respectively.
(32) J. M. Manning and S. Moore, *J. Biol. Chem.*, **243**, 5591 (1968).
(33) This result regarding the configurations of the leucyl and *N*-methylalanyl units of tentoxin has also recently been reported in connection with an erroneous formulation of the amino acid sequence of tentoxin by M. Koncewicz, P. Mathiaparanam, T. F. Uchytil, L. Sparapano, J. Tam, D. H. Rich, and R. D. Durbin, *Biochem. Biophys. Res. Commun.*, **53**, 653 (1973).
(34) For an improved procedure, see S. H. Woodhead, G. E. Templeton, W. L. Meyer, and R. B. Lewis, *Phytopathology*, **65**, 495 (1975).
(35) The precision of conversion of specific to molecular rotations will suffer from uncertainty in the benzene content of this sample.
(36) The value reported earlier[1] is in error.
(37) Reduction was incomplete with lower catalyst:tentoxin ratios. It appears that **3a** is strongly adsorbed on the catalyst and acts as a catalyst poison.
(38) E. Stahl, Ed., "Thin-Layer Chromatography, A Laboratory Handbook", Springer-Verlag, Berlin, 1965: (a) p 399; (b) p 496.
(39) Cf. E. Fischer and L. v. Mechel, *Ber.*, **49**, 1355 (1916).
(40) J. R. Coggins and N. L. Benoiton, *Can. J. Chem.*, **49**, 1968 (1971).
(41) Whether racemization occurred during saponification or HBr treatment or both in this instance was not determined, cf. J. R. McDermott and N. L. Benoiton, *Can. J. Chem.*, **51**, 2555 (1973).
(42) R. R. Becker and M. A. Stahmann, *J. Biol. Chem.*, **204**, 737 (1953).
(43) The DL reference was used rather than the D isomer.[1b]
(44) P. Quitt, J. Hellerbach, and K. Vogler, *Helv. Chim. Acta*, **46**, 327 (1963).

Synthesis of Unsymmetrical Phosphodiesters by Means of Cyclic Enediol Pyrophosphates

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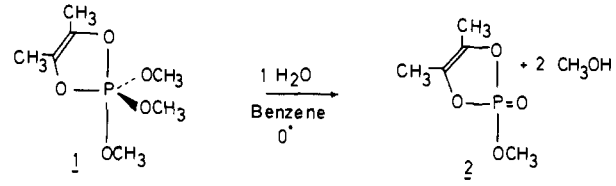
Abstract: Unsymmetrical phosphodiesters [(RO)(R'O)P(O)(OH)] are readily synthesized from the alcohols, ROH and R'OH, by means of the new reagent acetoin enediol cyclopyrophosphate. When one of the two alcohols is a diol with a primary and a secondary hydroxyl, the primary function is selectively phosphorylated in the presence of the unprotected secondary function. The method holds promise in the synthesis of oligonucleotides.

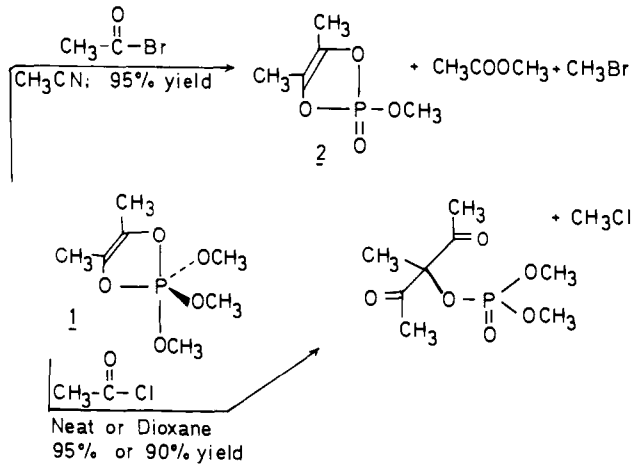
Methyl acetoin enediol cyclophosphate (2-methoxy-4,5-dimethyl-1,3,2-dioxaphosphole 2-oxide, **2**) was first obtained from the hydrolysis of the oxyphosphorane[2,3] **1**, (Scheme I).

Scheme I



A more practical synthesis of CEP-OCH_3[4] (**2**), based on the ability of the oxyphosphorane **1** to undergo C-acylation[5] or exocyclic O-acylation under different conditions, was announced recently[6] (Scheme II).[7]

Scheme II

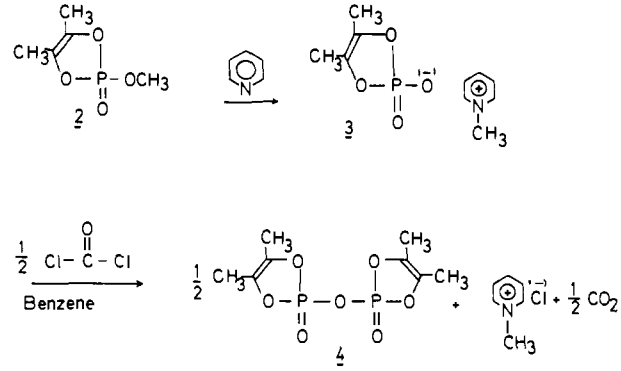


This paper describes the conversion of CEP-OCH_3 (**2**) into a cyclic pyrophosphate which can be used as reagent for the synthesis of unsymmetrical phosphodiesters [(RO)(R'O)P(O)(OH)].[8-19] The reagent needs no additional activation to carry out the double phosphorylation and does not generate, in most cases, symmetrical phosphodiesters as by-products. The primary alcohol of a diol can be phosphorylated selectively in the presence of an unprotected secondary alcohol. These properties suggest possible applications of the new reagent to the synthesis of oligonucleotides.[20-23]

Results

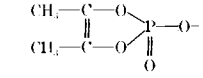
Preparation of (*N*-Methylpyridinium)$^+$ $^-$OCEP (3). This salt (**3**) (Scheme III) is obtained in high yield from the

Scheme III



reaction of the ester CEP-OCH_3 (**2**) with pyridine. The data summarized in Table I support the cyclic structure of the salt (**3**); note the similarity of its ^{31}P NMR shift and that of CEP-OCH_3 (**2**). The shifts of the acyclic analogs

Table I. Elemental Analyses and Spectral Data[a] of Cyclic Enediol Phosphoryl Derivatives, CEP-X, CEP-OR, CEP-OAr

Compd	Substituents X	Mp, and/or bp (mm), °C	Molecular formula CEP-X	Calcd, % C	Calcd, % H	Calcd, % P	Found, % C	Found, % H	Found, % P	δ^{31}P, ppm (J, Hz)	^{1}H NMR τ, ppm (J, Hz) CH_3C	^{1}H NMR τ, ppm (J, Hz) Signals in X	Main ir bands, cm^{-1}
3	$(C_5H_5NCH_3)^+ {}^-(O-)$	104–107	$C_{10}H_{14}O_4PN$	49.4	5.8	12.7[b]	49.0	5.7	12.5	−12.2	8.24	5.35	1390, 1230, 1140, 1115, 995, 820
4		84–86[c]	$C_8H_{12}O_7P_2$	34.1	4.3	22.0	34.0	4.4	22.3	+1.5	8.02		1333, 1183, 1130, 1031, 970, 877
6	HO–	108–110[d]	$C_4H_7O_4P$	32.0	4.7	20.6	31.9	4.7	20.5	−15.5	8.08[e]	−3.6	1186, 1134, 1040, 862
10	$(\gamma\text{-Col-H})^+ {}^-(O-)$									−11.2[e]	8.20	7.50; 7.34; 2.60	
	R		CEP-OR								CH_3C	Signals in R	
2	CH_3[f]	42–43[g] 64–65 (0.2)								−12.4 (11.5)	8.06	6.20 (11.5)	1316, 1295, 1198, 1134, 1060, 1000
11	$(CH_3)_2CHCH_2$	78–80 (0.25)	$C_8H_{15}O_4P$	46.6	7.3	15.0	46.8	7.4	14.8	−12.1	8.08	9.05 (7.8) 6.15 (mult)	1310, 1290, 1198, 1135, 1040, 1000
11	$C_6H_5CH_2$	[h]	$C_{11}H_{13}O_4P$	55.0	5.5	12.9	55.1	5.5	12.8	−11.2 (10.0)	8.16	2.70 4.96 (10.0)	1316, 1290, 1266, 1190, 1130, 1029
11	CH_2BrCH_2	106–107 (0.25)	$C_6H_{10}O_4PBr$	28.0	3.9	12.0	28.3	4.1	11.8	−11.1 (9.3)	8.10	5.65 (mult) 6.45 (mult)	1325, 1299, 1198, 1100, 1040, 1000, 918
11	CCl_3CH_2	[h]	$C_6H_8O_4PCl_3$	25.6	2.9	11.0[i]	25.9	3.0	10.7	−11.6 (10.0)	8.05	5.35 (10.0)	1136, 1081, 1031 1300, 1195, 1130.
16	c-C_5H_9	102–104 (0.2)	$C_9H_{15}O_4P$	49.5	6.9	14.2	49.3	7.0	14.0	−11.3 (4.8)	8.08	5.10 (mult) 8.17 (mult)	1312, 1290, 1258, 1198, 1134, 1026
11	$(CH_3)_2CH$	45–46[c] 75–76 (0.3)	$C_7H_{13}O_4P$	43.7	6.8	16.1	43.6	6.9	16.2	−11.2 (6.5)	8.10	5.28 (mult) 8.64 (6.1)	1312, 1290, 1258, 1193, 1130, 1031
11	$(CF_3)_2CH$	103–105[j]	$C_7H_7O_4PF_6$	28.0	2.3	10.3[k]	27.9	2.5	10.2	−12.4 (13.2)	8.04	4.70 13.2 6.3	1316, 1290, 1235, 1205, 1111, 1000
11	$(CCl_3)(CH_3)CH$	81–83[h]	$C_7H_{10}O_4PCl_3$	28.4	3.4	10.5[l]	28.3	3.5	10.4	−11.2	8.07	5.00 (mult) 8.30 (6.0)	1290, 1190, 1136 1064, 1026, 1000
11	$(CCl_3)_2CH$	158–161[c]	$C_7H_7O_4PCl_6$	21.1	1.8	7.8[m]	21.0	1.8	7.7	−11.9	8.01	4.35 (13.0)	1290, 1195, 1095, 1000, 985, 945
11	$(CH_3)_3C$	58–60	[n]							−7.6	8.08	8.42	1299, 1266, 1205 1136, 1042, 1220
5	$(CH_3)_3Si$	ca. 80 (0.5)	$C_7H_{15}O_4PSi$	37.8	6.8	13.9[o]	37.8	6.8	14.1	−3.4	8.13	9.70	1299, 1266, 1205, 1136, 1058, 1000
	Ar		CEP-OAr							^{31}P, ppm	CH_3C in CEP	Signals in Ar	
12	C_6H_5	[h]	$C_{10}H_{11}O_4P$	53.1	4.9	13.7	53.4	5.0	13.4	−6.2	8.20	2.80 (mult)	1488, 1389, 1319, 1312, 1220, 1183
12	p-$NO_2C_6H_4$	101–102[c]	$C_{10}H_{10}O_6NP$	44.3	3.7	11.4[p]	44.5	3.9	11.3	−5.4	8.10	1.86 2.70 (mult)	1540, 1345, 1230, 1180, 1002, 955, 862

[a] All NMR spectra at 25°. ^{1}H spectra in $CDCl_3$ unless otherwise specified; signals in parts per million from Me_4Si = 10 (τ); coupling constants, J, in Hz; all integrated intensities were as expected from the structures given. ^{31}P spectra in $CDCl_3$ or CH_2Cl_2; δ ^{31}P in ppm vs. H_3PO_4 = 0; negative and positive values correspond, respectively, to signals at lower and higher magnetic fields than the reference. Ir spectra in CH_2Cl_2 or as specified. [b] N (calcd, 12.7%, 12.5%. [c] From methylene chloride–hexane. [d] From methylene chloride–ether (2:5 v/v). [e] In 75% $CDCl_3$ + 25% DMSO-d_6. [f] References 5 and 6. [g] From benzene–hexane. [h] Purified by molecular distillation. [i] Cl (calcd, 37.8%), 37.5%). [j] Purified by vacuum sublimation. [k] F (calcd, 38.0%), 37.8%. [l] Cl (calcd, 36.0), 35.9%. [m] Cl (calcd, 53.3%), 53.3%. [n] Decomposes on standing to CEPOH (6). [o] Si (calcd, 12.6%), 12.4%. [p] N (calcd, 5.2%), 5.3%.

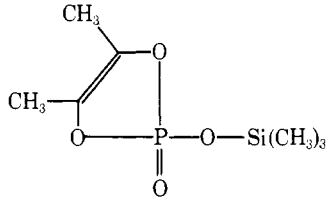
are near 0 ppm vs. H_3PO_4, and the five-membered ring causes a significant displacement of the shift to lower magnetic field.

Reaction of (*N*-Methylpyridinium)$^+$ $^-$OCEP (3) with Phosgene. Phosgene converts the CEPO salt (**3**) into the cyclic pyrophosphate CEP-OCEP (**4**) in excellent yield (Scheme III). The same product is obtained if phosgene is used in large excess. Apparently, the first step in this reaction[24] is the formation of the intermediate CEP-OCOCl. The second step, which in this case is relatively fast, is the displacement of CO_2 and chloride from the chlorocarbonate by the $CEPO^-$ anion to yield the pyrophosphate **4.** There is no evidence for the formation of a carbonate, CEP-OCOO-CEP intermediate.

The pyrophosphate **4** can also be made from the CEPO salt (**3**) and oxalyl chloride.

The spectral data in Table I, and the chemical reactions described below, support structure **4.** The ^{31}P NMR shift has the value expected from previous data on acyclic pyrophosphates[25a] displaced downfield by the five-membered ring effect.

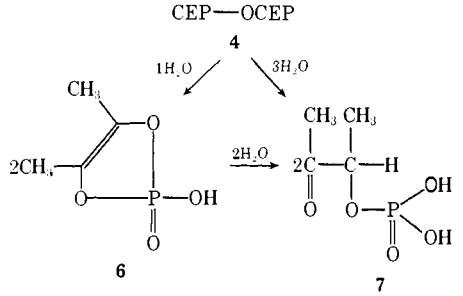
Reaction of (*N*-Methylpyridinium)$^+$ $^-$OCEP (3) with Trimethylchlorosilane. This reaction yields a new type of silyl phosphate, **5,** which is related to the silyl ester of a five-membered cyclic acylphosphate just reported.[25b]



5

Hydrolysis of the Cyclic Pyrophosphate CEP-OCEP (4). The pyrophosphate **4** reacts with 1 mol equiv of water at 0° in aprotic solvents to give the cyclic phosphodiester CEP-OH (**6**). There is very little ring opening in this displacement at phosphorus.[26]

The cyclic diester CEP-OH (**6**) is hydrolyzed further to acetoinyl phosphate (**7**). The properties of a salt, **7b,** of **7** are given in Table II. Three mole equivalents of water transforms the pyrophosphate **4** into acetoinyl phosphate (**7**).

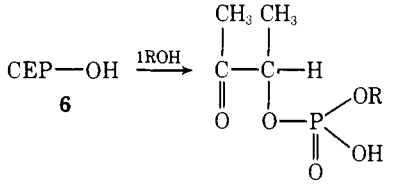


6 **7**

CEP-OH (**6**) can be reconverted into CEP-OCEP (**4**) by treatment of its pyridinium salt with phosgene: 2 $CEP\text{-}O^-$ $C_5H_5NH^+ + COCl_2 \rightarrow$ CEP-OCEP + $2C_5H_5NH^+ Cl^-$.

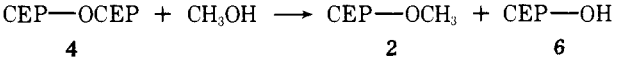
Reaction of the Cyclic Phosphodiester CEP-OH (6) with Alcohols. The reaction of CEP-OH (**6**) with methanol produces methylacetoinyl phosphate (**8**) in virtually quantitative yield (Table II). Benzylacetoinyl phosphate (**9**) is easily made by this procedure.

Reaction of the Cyclic Pyrophosphate 4 with Alcohols and Phenols. Incorporation of the CEP Group into Nucleophiles. The pyrophosphate **4** is transformed into the cyclic triester **2** and the cyclic diester **6** upon reaction with 1 mol equiv of



8, R = CH_3
9, R = $C_6H_5CH_2$

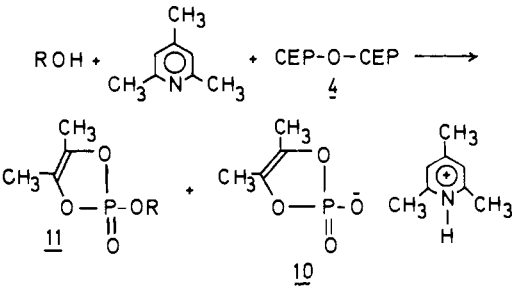
methanol in aprotic solvents at 0°. As in the hydrolysis, there is little or no ring opening in this reaction.



4 **2** **6**

The rate constant for the reaction of methanol with CEP-OCEP (**4**) must be significantly greater than the rate constants for the reactions of methanol with $CEP\text{-}OCH_3$ (**2**) and CEP-OH (**6**) since dimethylacetoinyl and methylacetoinyl phosphates are not formed in appreciable amounts. The same is true for the reactions of CEP-OCEP (**4**) with a number of primary, secondary, and tertiary alcohols, including highly substituted ones like 1,1,1-trichloro-2-propanol and hexafluoro-2-propanol. A convenient procedure for the "CEP-ylation"[4] of the alcohol involves the use of a base, e.g., γ-collidine (Scheme IV and Table I). The reaction is

Scheme IV



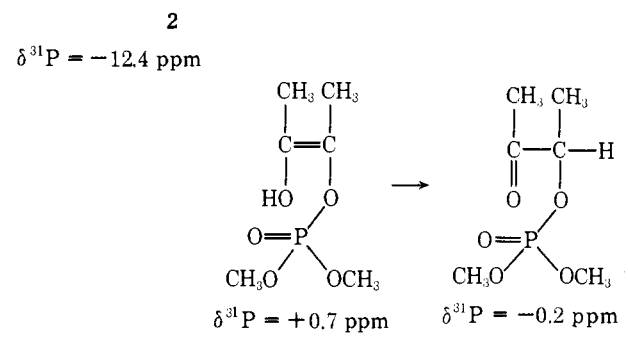
11 **10**

carried out in methylene chloride, the solvent is removed, and the CEP-OR (**11**) is extracted into diethyl ether, in which the CEPO salt **10** is virtually insoluble.

Phenols are also CEP-ylated by the pyrophosphate **4,** preferably with nicotinamide as the base. The reaction is performed in methylene chloride, or in methylene chloride–ether mixtures, where the CEPO salt is insoluble, and the CEP-OAr (**12**) is soluble.

The CEPO salts, e.g., **10,** formed as by-products of the CEP-ylation are reconverted into the pyrophosphate **4** by phosgene.

Reaction of the CEP-OR (11) with Alcohols. $CEP\text{-}OCH_3$ (**2**) is converted into dimethylacetoinyl phosphate by 1 mol equiv of methanol in aprotic solvents. The first observable intermediate is the enol form which, in some solvents like benzene, tautomerizes at a relatively slow rate. This can be shown by means of ^{31}P and ^1H NMR spectrometry (Table III, Experimental Section).[27]



2

$\delta^{31}P = -12.4$ ppm

$\delta^{31}P = +0.7$ ppm $\delta^{31}P = -0.2$ ppm

Table II. Elemental Analysis and Spectral Data[a] of Phosphate Esters

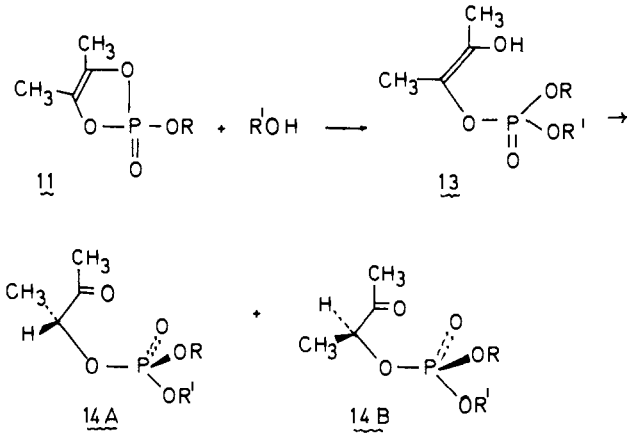
Compd	Substituents		Mp, °C	Molecular formula	Calcd, %			Found, %			δ^{31}P, ppm	^{1}H NMR		Main ir bands, cm^{-1}
					C	H	P	C	H	P		τ, ppm (J, Hz)	τ, ppm (J, Hz)	
	(RO)(R'O)P(O)OCH(CH$_3$)(COCH$_3$) R; R'											CH$_3$CO; CH$_3$CH[b]	Main signals in R; R'	
14	c-C$_5$H$_9$; C$_6$H$_5$CH$_2$		c	C$_{16}$H$_{23}$O$_5$P	58.9	7.1	9.5	59.0	7.3	9.3	+2.8	7.84; 8.60 (7.0)	4.94 (8.7)[d]	1745 (sh), 1730,
												7.90; 8.64 (7.0)	4.96 (8.7)	1274, 1010
14	c-C$_5$H$_9$; (CH$_3$)$_3$CHCH$_2$		c	C$_{13}$H$_{25}$O$_5$P	53.4	8.6	10.6	53.2	8.7	10.6	+3.0	7.75; 8.54 (6.8)	9.03 (6.5)[e]	1745 (sh), 1739,
												7.75; 8.54 (6.8)	9.03 (6.5)	1282, 1020
14	(CCl$_3$)(CH$_3$)CH; (CH$_3$)$_2$CHCH$_2$		c	C$_{11}$H$_{20}$O$_5$PCl$_3$	35.7	5.5		36.5	6.0		+4.0	7.75; 8.49 (6.6)	8.29 (6.0); 9.02 (6.4)[e]	1745 (sh), 1730,
												7.75; 8.49 (6.6)	8.29 (6.0); 9.03 (6.4)	1282, 1020
14	CH$_2$BrCH$_2$; (CH$_3$)$_2$CHCH$_2$		c	C$_{10}$H$_{20}$O$_5$PBr	36.3	6.1	9.4[f]	36.0	6.1	9.4	+2.4	7.77; 8.52 (6.8)	9.03 (6.6)[e]	1745 (sh), 1730,
												7.77; 8.52 (6.8)	9.03 (6.6)	1274, 1020
14	(CH$_3$)$_2$CH;[g] (CH$_3$)$_2$CHCH$_2$											7.77; 8.53 (6.6)	8.65 (6.2); 9.05 (6.5)[e]	
												7.77; 8.53 (6.6)	8.65 (6.2); 9.05 (6.5)	
14	(CH$_3$)$_2$CH;[h] CH$_3$											7.72; 8.53 (6.9)	8.63 (6.3); 6.18 (11.3)[e]	
												7.72; 8.53 (6.9)	8.63 (6.3); 6.20 (11.3)	
18	c-C$_5$H$_9$; (*trans*-2-hydroxycyclopentyl)methyl										+1.9	7.78; 8.56 (6.9)	5.30 (mult)	1740, 1430, 1255,
												7.78; 8.56 (6.9)	6.07 (mult)	1020
20	CH$_2$BrCH$_2$; (*trans*-2-hydroxycyclopentyl)methyl										+2.5	7.75; 8.50 (7.0)	5.85 (mult)	1740, 1275, 1240,
												7.75; 8.50 (7.0)	6.45 (mult)	1025
	(RO)(R'O)P(O)(OM) R; R'	M										Main signals in R	Main signals in R'	
15	c-C$_5$H$_9$; (CH$_3$)$_2$CHCH$_2$	H										5.20 (mult) 8.24 (mult)	6.27 (mult) 9.05 (6.8)	1210, 1050
15b	c-C$_5$H$_9$; (CH$_3$)$_2$CHCH$_2$	$(C_6H_{11})_2NH_2^+$	190–191[i]	C$_{21}$H$_{42}$O$_4$NP	62.5	10.5	7.7	62.7	10.6	7.7[j]	+0.1[k]	5.40 (mult) 8.30 (mult)	6.45 (mult)[l] 9.10 (6.8)	1450, 1225, 1155
15	CH$_2$BrCH$_2$; (CH$_3$)$_2$CHCH$_2$	H									+1.1	5.75 (mult) 6.52 (mult)	6.22 (mult) 9.05 (6.3)	1240, 1075, 1030
15b	CH$_2$BrCH$_2$; (CH$_3$)$_2$CHCH$_2$	$C_6H_{11}NH_3^+$	98–99[m]	C$_{10}$H$_{27}$O$_4$PBrN	40.0	7.6		39.0	7.4		0.0[k]	5.88 (mult) 6.45 (mult)	6.36 (mult)[k] 9.12 (6.3)	1235, 1075, 1025
15	c-C$_5$H$_9$; C$_6$H$_5$CH$_2$	H									+1.1	5.20 (mult) 8.25 (mult)	2.75 5.04 (8.0)	1225, 1020
15b	c-C$_5$H$_9$; C$_6$H$_5$CH$_2$	$C_6H_{11}NH_3^+$	160–164[m]	C$_{18}$H$_{30}$O$_4$PN·½H$_2$O	59.3	8.6		59.6	8.7		+0.6[k]	5.38 (mult) 8.29	2.72 5.16 (6.0)[k]	1225, 1080, 1060, 1010

19	c-C_5H_9; (*trans*-2-hydroxycyclopentyl)methyl	H						0.2	5.20 (mult) 8.25 (mult)	6.05 (mult) ca. 8.30 (mult)		1230, 1025
19b	c-C_5H_9; (*trans*-2-hydroxycyclopentyl)methyl	$C_6H_{11}NH_3^+$	166–169[m]	$C_{17}H_{34}O_5PN$	56.2	9.4	8.5	56.0	9.3	8.4[n]	0.0[k]	5.42 (mult) 8.25 (mult)	6.32 (mult) ca. 8.30 (mult[k])		1210, 1070, 1005
	(MO)(RO)P(O)OCH(CH_3)($COCH_3$)										CH$_3$CO; CH$_3$CH[b]	Signals in R			
8	R = CH_3	M									+1.3	7.72; 8.54 (7.0)	6.24 (11.5)		1724; 1220, 1031
9	R = $C_6H_5CH_2$	H[o]									+2.0	7.90; 8.50 (7.5)	4.96 (8.0)		1724, 1220, 1031
7b	H	$(C_6H_5NH_3)^+$	137–139[p]	$C_{10}H_{16}O_5PN$	46.0	6.2	11.9[q]	45.8	6.3	11.8	+0.8	7.83; 8.66 (6.5)	2.72	*r*	2590, 1725, 1150, 1045, 965, 745

[a] All NMR spectra at 25°. ^{1}H spectra in $CDCl_3$ unless otherwise specified; signals in parts per million from Me_4Si = 10 (τ); coupling constants, *J*, in Hz. ^{31}P spectra in $CDCl_3$ or CH_2Cl_2; δ ^{31}P in ppm vs. H_3PO_4 = 0. Ir spectra in CH_2Cl_2. [b] The methine carbinol ^{1}H gives a multiplet in the region τ 5.2–5.4 ppm due to J_{HCOP} and J_{HCCH} coupling. [c] Purified by molecular distillation. [d] The methine carbinol ^{1}H of the cyclopentyl group in the two diastereomers gives rise to a signal at ca. τ 5.14 ppm. The eight protons of the cyclopentyl group give a multiplet at ca. τ 8.24 ppm. [e] Alkyl multiplets (τ): cyclopentyl, 8.24, 5.14; isobutyl, 6.18, 8.0; isopropyl, 5.3; trichloroisopropyl, 6.12; 2-bromoethyl, 5.70, 6.47. [f] Br (calcd, 24.1%), 23.9%. [g] 10–15% of diisobutylacetoinyl phosphate was formed as by-product. [h] 10–15% of dimethylacetoinyl phosphate was formed as by-product. [i] From CH_2Cl_2–hexane or cyclohexane; 84% yield. [j] N (calcd, 3.5%), 3.4%. [k] In CD_2Cl_2. [l] In D_2O with DSS = 0 as standard. [m] From CH_2Cl_2–hexane. [n] N (calcd, 3.9%), 3.8%. [o] Reference 10. [p] From ethanol. [q] N (calcd, 5.4%), 5.3%. [r] In D_2O, using DSS as internal standard. Additional signals at τ 2.60 and 5.27 ppm.

The reactions of some alcohols, R′OH, with certain CEP-OR (**11**), produce exclusively the unsymmetrical dialkylacetoinyl phosphate **14** in 90–95% yield (Scheme V).[38] This

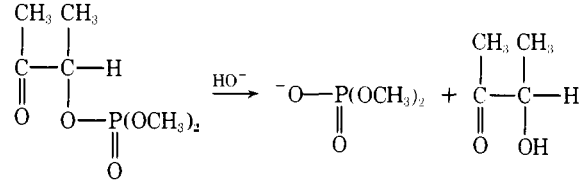
Scheme V



has been observed in the reactions of isobutyl alcohol and of benzyl alcohol with CEP-O-c-C_5H_9, of isobutyl alcohol with CEP-OCH(CH_3)(CCl_3), and of isobutyl alcohol with CEP-OCH$_2$CH$_2$Br (Table II). When both alkyl groups, R, R′ are nonchiral, two diastereomers, **14A**, **14B** are possible. In one case, the ^{1}H NMR spectrum clearly shows the presence of both isomers. This is not unexpected since the chiral center in the acetoinyl group is established in a tautomerization step, and the isomers are of comparable energies. The reaction of nonchiral alcohols with *rac*-CEP-OCH(CH_3)(CCl_3) can generate four diastereomers; however, ^{1}H NMR spectroscopy does not allow a determination of the number of diastereomers actually produced in the reaction. This question was not pursued further since the purpose of the work was to arrive at the phosphodiesters where no diastereoisomerism is encountered.

The reactions of methanol, and of isobutyl alcohol, with CEP-O-*i*-C_3H_7, give mixtures of phosphates, in which the unsymmetrical esters **14** are contaminated with about 10–15% of the respective symmetrical esters $(CH_3O)_2$-P(O)(OAcn) and $[(CH_3)_2CHCH_2O]_2$P(O)(OAcn). The symmetrical phosphates are formed as a result of a transesterification reaction, R′OH + CEP-OR → ROH + CEP-OR′, followed by R′OH + CEP-OR′ → $(R'O)_2$-P(O)(OAcn), and ROH + CEP-OR → $(RO)_2$-P(O)(OAcn).

Hydrolytic Cleavage of the Acetoinyl Blocking Group from Dialkylacetoinyl Phosphates. The phosphotriesters synthesized by means of the cyclic pyrophosphate CEP-OCEP (**4**) contain the acetoinyl group. It is known that the hydroxide ion catalyzed hydrolysis of dimethylacetoinyl phosphate is at least 2 × 10^6 times faster than that of trimethyl phosphate and yields dimethyl phosphate and acetoin in ca. 95% of the theory.[28] The undesirable loss of one alkyl group in this hydrolysis, which yields an alkylacetoinyl phosphate by-product, amounts to ca, 5%, when the alkyl group is methyl,[29b] and drops to even lower values for ethyl- and isopropyl groups.[29c]



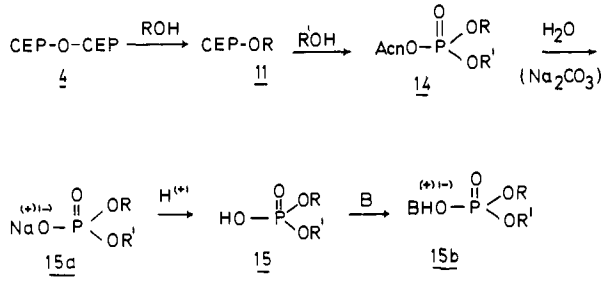
The acetoinyl group can be removed efficiently from several of the phosphotriesters listed in Table II. In one proce-

dure (A), the triester is kept several hr at 25° or at 60° in aqueous acetonitrile solution (2:1) containing 1 mol equiv of sodium carbonate. In another procedure (B), the triester is hydrolyzed at 70° in aqueous pyridine solution (1:1) containing 2 mol equiv of triethylamine. The corresponding salts of the diesters (RO)(R'O)P(O)(OM) are converted into the free acids, which are characterized as alkylammonium salts (Table II).

The hydrolysis by procedure A gives ca. 5% of the alkylacetoinyl phosphate by-product, while procedure B reduces the amount of the by-product to ca. 2%.[39] However, procedure B cannot be used when one of the alkyl groups in the ester is sensitive to tertiary amines, e.g., the 2-bromoethyl group.

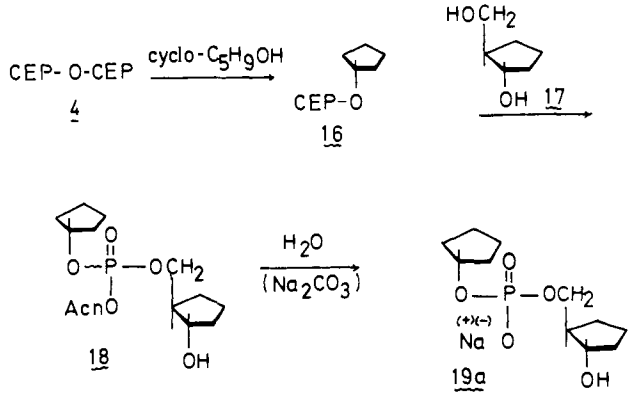
Scheme VI summarizes the phosphorylative coupling of two alcohols, ROH and R'OH, to the phosphodiester **15** by means of the cyclic pyrophosphate CEP-OCEP (**4**).

Scheme VI



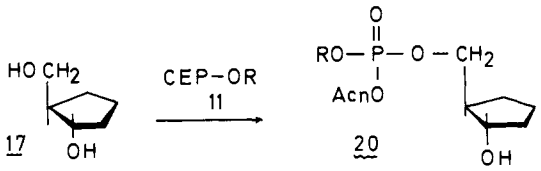
CEP-O-c-C_5H_9 (**16**) phosphorylates selectively the primary alcohol function of *trans*-2-hydroxymethylcyclopentanol[30] (**17**) in the presence of its unprotected secondary alcohol (Scheme VII). In reactions carried out with equimolar amounts of the two reagents (**16** and **17**) in 0.3 *M* methylene chloride at 20° for 6 hr, the proportion of primary OH to secondary OH phosphorylation is ca. 90:10, as established by the analytical procedures described in the Experimental Section. Hydrolysis of the triester by procedure A or B permits the isolation of the crystalline cyclohexylammonium salt **19b** (Table II) in 65% yield based on the diol **17**, or in 60% yield based on cyclopentanol (ROH). This experiment suggests possible uses of the pyrophosphate **4** in the synthesis of oligonucleotides without protection of the C3'-OH function of the nucleoside molecule.

Scheme VII



The reaction of isobutyl alcohol with CEP-OCH_2CH_2Br gives 2-bromoethylisobutylacetoinyl phosphate in 95% of the theory. The acetoinyl group can be removed from the alkyl(2-bromoethyl)acetoinyl phosphate by procedure A without any effect on the resulting phosphodiester. As shown in Scheme VIII, CEP-OCH_2CH_2Br phosphorylates selectively the primary OH of *trans*-2-hydroxymethylcyclopentanol in the presence of the unprotected secondary OH. The degree of selectivity, as well as the other features of the reaction, are analogous to those encountered in the phosphorylation with CEP-O-c-C_5H_9 (**16**). Compound **20** represents a model for the protection and simultaneous phosphorylation of a nucleoside at C5'-OH without protection at C3'-OH. Removal of the acetoinyl group from **20** is possible; work is now in progress to develop reagents to remove a 2-bromoethyl group from phosphodiesters to produce phosphomonoesters.

Scheme VIII

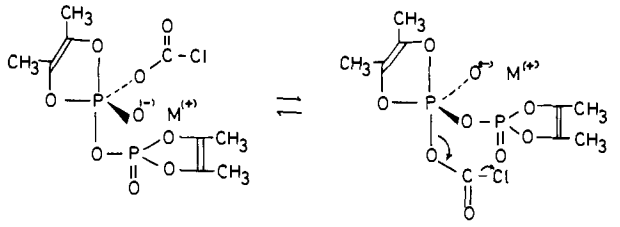


Discussion

The results of this investigation can be rationalized in terms of the oxyphosphorane concept.[31-34]

The formation of the pyrophosphate **4** via the hypothetical CEP-OCOCl intermediate is pictured in Scheme IX.

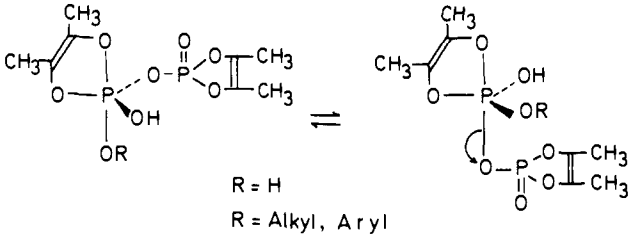
Scheme IX



The oxyphosphorane should be relatively stable because of the highly electronegative and fairly unencumbered ligands;[35] it undergoes regular PI and then loss of apical CO_2 and Cl^-, which is an adequate driving force for the formation of the "high-energy" pyrophosphate **4**. We speculate that the regular PI can occur by the single turnstile rotation mechanism[36,37] with the ring as the "ligand pair".

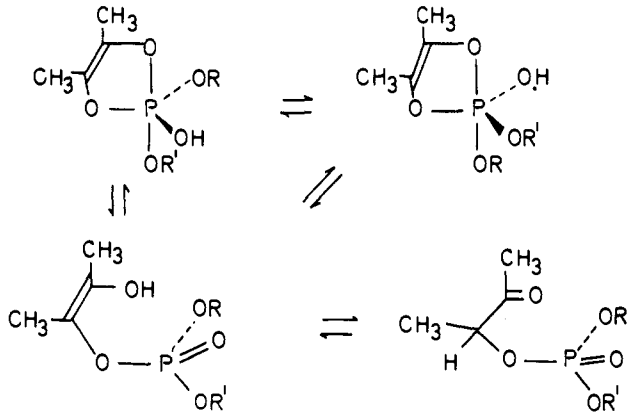
The retention of the ring in the CEP-ylation of alcohols, phenols, and water by the pyrophosphate **4** is pictured in Scheme X. The driving force is the apical departure of the $CEPO^-$ anion, which is a good leaving group; its departure results in a more stable product, i.e., CEP-OR (**11**) vs. CEP-OCEP (**4**).

Scheme X



The exclusive formation of unsymmetrical dialkylacetoinyl phosphates from the reaction of a CEP-OR with an alcohol (R'OH) is interpreted with the aid of Scheme XI. Apical entrance of R'OH produces an oxyphosphorane which collapses to the enol tautomer and ends as the keto tautomer before the regular or irregular PI has produced the second oxyphosphorane with apical OR. The loss of the RO group would probably result in the formation of symmetrical dialkylacetoinyl phosphates. It appears that, in these reactions, the tendency for ring opening vs. ring reten-

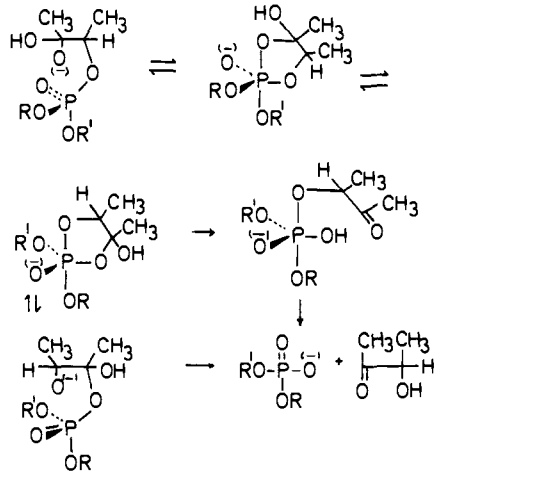
Scheme XI



tion is a very sensitive function of the overall bulk of the two alkyl groups involved, R and R′. The electronic structure of R plays also an important role in ring opening vs. ring retention in CEP-OR, and this phase of the problem will be discussed in a separate paper.

The new synthesis of unsymmetrical phosphodiesters depends on the preferential loss of the acetoinyl group from dialkylacetoinyl phosphates. In 1962, Ramirez, Hansen, and Desai[28] suggested an oxyphosphorane intermediate to explain this phenomenon. Brown,[29] Usher,[29] and their coworkers developed this hypothesis further and provided convincing data in its support. The kinetic expression which results from the oxyphosphorane intermediate hypothesis is extremely complicated[36b] and requires many assumptions and approximations in order to yield correlations between reaction rates, product ratios, and structure of the alkyl groups. Nevertheless, a useful working hypothesis is that the preferential loss of the acetoinyl group depends on the relatively rapid PI between the oxyphosphoranes shown in Scheme XII. The crucial rupture of the P-O bond of the

Scheme XII



new cyclic oxyphosphorane may occur before or after the rupture of the C-O bond, i.e., via a phosphate or via an acyclic phosphorane, but there is as yet no information on this point. The undesirable loss of an alkyl group in the hydrolysis involves apical departure of an alkoxy group from the oxyphosphorane intermediates.

Experimental Section

Elemental analyses in Tables I and II were done by Galbraith Laboratories, Knoxville, Tenn. Anhydrous solvents were employed.

Methyl Acetoin Enediol Cyclophosphate [CEP-OCH$_3$ (2)].[6] Freshly distilled biacetyl (86.0 g, 1.0 mol) was added (2 hr) to a stirred solution of freshly distilled trimethyl phosphite (126.0 g, 1.02 mol) in CH_2Cl_2 (120 ml) at 0°, under N_2. After 3 hr at 0°, the solvent was evaporated [30° (40 mm)], and the residue was distilled to yield **2,2,2-trimethoxy-4,5-dimethyl-2,2-dihydro-1,3,2-dioxaphosphole (1)** [186 g, 90% of the theory; bp 57–60° (0.5 mm)].

Freshly distilled acetyl bromide (20 ml) was added to a stirred solution of the oxyphosphorane (**1**; 230 g, 1.1 mol) in CH_3CN (700 ml). The reaction was exothermic; the remaining acetyl bromide (76 ml; total of 1.2 mol) was added at a rate which kept the solution at 60° (ca. 1 hr). The solution was stirred for 45 min, the solvent evaporated, and the residue distilled to yield **CEP-OCH$_3$ (2)**, which became crystalline on standing, yield 160 g or 90% of the theory.

Reaction of CEP-OCH$_3$ (2) with Pyridine. A solution of CEP-OCH$_3$ (**2**; 74.0 g, 0.45 mol) and pyridine (125 ml, 1.5 mol) in benzene (500 ml) was kept for 7 hr at reflux temperature, with stirring, under anhydrous conditions. The mixture was cooled to 20°, and the crystalline ***N*-methylpyridinium acetoin enediol cyclophosphate (3)** was decanted, with protection against moisture. The salt **3** was washed with benzene (2 × 300 ml), dried, and stored in a vacuum desiccator over P_2O_5, yield 105 g or 95% of the theory.

Reaction of Phosgene with (*N*-Methylpyridinium)$^+$ $^-$OCEP (3) in Benzene. Synthesis of CEP-OCEP (4). A solution of phosgene (22 ml, 0.33 mol) in benzene (40 ml) was dropped (45 min) into a stirred suspension of the salt **3** (96 g, 0.4 mol) in benzene (500 ml) at 0°. The mixture was stirred 1.0 hr at 0°, was brought to 20°, and was filtered to remove *N*-methylpyridinium chloride. The chloride was washed with benzene, the combined benzene solution was concentrated [30° (30 mm)] to ca. 125 ml, and the last traces of chloride were filtered. The filtrate was evaporated, and the residue was recrystallized from CH_2Cl_2–hexane to give the first crop (36.4 g; mp 84–86°) of **acetoin enediol cyclopyrophosphate** [CEP-OCEP (**4**)]. The filtrate was concentrated and cooled to −20° to give a second crop of CEP-OCEP (**4**; 12.9 g; mp 82–85°), total yield 49.3 g or 90% of the theory.

Reaction of (*N*-Methylpyridinium)$^+$ $^-$OCEP (3) with an Excess of Phosgene in Methylene Chloride. A CH_2Cl_2 solution containing 1 mol equiv of the salt **3** was dropped into a stirred CH_2Cl_2 solution containing 10 mol equiv of phosgene, at −80°. The mixture was stirred 3 hr at −80° and was allowed to reach 20°. The solvent and excess of phosgene were removed; the residue was triturated with benzene and filtered; the filtrate was evaporated; and the residue was recrystallized as above to give the CEP-OCEP (**4**) in 85% of the theory.

Reaction of Trimethylchlorosilane with (*N*-Methylpyridinium)$^+$ $^-$OCEP (3). Synthesis of Trimethylsilyl Acetoin Enediol Cyclophosphate (5). A solution of trimethylchlorosilane (2.3 g, 22 mmol) in benzene (20 ml) was added (15 min) to a stirred suspension of (*N*-methylpyridinium)$^+$ $^-$OCEP (**3**; 5.30 g, 22 mmol) in benzene (50 ml) at 0°. After 1 hr at 0°, *N*-methylpyridinium chloride was filtered off, the filtrate was evaporated, and the residual oil was purified by molecular distillation to yield **CEP-OSi(CH$_3$)$_3$ (5**; 3.1 g; 70% of the theory).

Reaction of the Pyrophosphate 4 with One Mole Equivalent of Water. (a) In Acetone. A solution of water (0.26 g, 14.7 mmol) in anhydrous acetone (20 ml) was dropped (30 min) into a stirred solution of CEP-OCEP (**4**; 4.14 g, 14.7 mmol) in anhydrous acetone (20 ml) at 0°. The mixture was stirred 15 min at 0°, was concentrated to ca. 10 ml, and was filtered. The residue was washed with ether (2 × 25 ml) to give the first crop of **CEP-OH (6**; 3.64 g; mp 107–109°). The ether and acetone filtrates were combined and cooled to 0°, yielding the second crop of CEP-OH (**6**; 0.3 g; mp 105–108°), total yield 87% of the theory.

(b) In Dioxane. Using a similar procedure, CEP-OH (**6**) was isolated in 80% of the theory. The acid **6** was sparingly soluble in dioxane at 25°; it underwent extensive decomposition upon heating in dioxane.

(c) In Benzene. The hydrolysis at 5° gave CEP-OH (**6**) in 70% of the theory.

Reaction of CEP-OH (6) with Water. Crystalline CEP-OH (**6**; 0.306 g, 2.04 mmol) was added to 10 ml of acetone (Fisher Scientific Co., Spectrograde acetone containing 0.5% of water, corresponding to 2.78 mmol of H_2O) at 20°. The solution was kept overnight at 20° and was evaporated to give **acetoinyl phosphate (7)** in nearly quantitative yield. The phosphomonoester **7** was charac-

Table III.

Time, min	CEP-OCH_3, %	Dimethylacetoinyl phosphate	
		Enol, %	Keto, %
3	50	50	0
12	19	60	21
32	15	41	44
90	0	0	100

terized as its anilinium salt **7b'** prepared in ethanol solution (cf. Table II).

Reaction of the Pyrophosphate 4 with an Excess of Water. Water (0.49 g; 27 mmol) in acetone (15 ml) was dropped (30 min) into a stirred solution of CEP-OCEP (**4**; 2.52 g, 9 mmol) in acetone (25 ml) at 0°. The solution was stirred 30 min at 0° and 30 min at 20°. The solvent was evaporated to give **acetoinyl phosphate** (**7**; 2.8 g) as an oil. A solution of the oil in ethanol (30 ml) was treated with aniline, and the crystalline **anilinium acetoinyl phosphate** (**7b**) was filtered.

Reaction of CEP-OH (6) with Alcohols. One mole equivalent of the alcohol ROH in CH_2Cl_2 solution was added dropwise (15 min) to 1 mol equiv of CEP-OH (**6**) in CH_2Cl_2 at 0°. The solution (molarity: 0.1–0.3 *M*) was stirred 1 hr at 0° and 30 min at 20°. The solvent was evaporated, and the residue was analyzed by ^1H NMR ($CDCl_3$) and ir (CH_2Cl_2) spectrometry. The **alkylacetoinyl phosphates** (**8** and **9**, Table II) were obtained virtually pure, and in nearly quantitative yields, upon removal of the solvent. If the solvents and reagents are not scrupulously dry, the alkylacetoinyl phosphate is contaminated by acetoinyl phosphate **7**; separation of the two phosphates is best carried out by fractional crystallization of the respective salts.

Reaction of CEP-OH (6) with Trimethylchlorosilane in the Presence of Base. A solution of trimethylchlorosilane (1.42 g, 13 mmol) and γ-collidine (1.57 g, 13 mmol) in benzene (15 ml) was dropped into a stirred solution of CEP-OH (**6**; 1.94 g, 13 mmol) in benzene (20 ml) at 0°. The mixture was kept 15 min at 0° and 30 min at 20°. The γ-collidinium chloride was filtered off, and the solvent was evaporated to give CEP-$OSi(CH_3)_3$ (**5**; 2.21 g; 80% of the theory).

Reaction of the Pyrophosphate 4 with Methanol. A solution of methanol (0.32 g, 10 mmol) in CH_2Cl_2 (10 ml) was dropped (15 min) into a stirred solution of CEP-OCEP (**4**; 2.82 g, 10 mmol) in CH_2Cl_2 (20 ml) at 0°. The solution was stirred 30 min at 0°, the solvent was evaporated, the residue was triturated with ether (10 ml), and the crystalline **acetoin enediol cyclophosphate** [**CEP-OH** (**6**)] was filtered off, yield 1.32 g or 90% of the theory. The ether-filtrate was evaporated, and the residue was recrystallized from benzene–hexane to give **CEP-OCH_3** (**2**) in 95% of the theory.

General Procedure for the CEP-ylation of Alcohols and Phenols. A CH_2Cl_2 solution, containing 1 mol equiv of the alcohol ROH or phenol ArOH and 1 mol equiv of γ-collidine, was added (15 min) to a stirred solution containing 1 mol equiv of the pyrophosphate CEP-OCEP (**4**) in CH_2Cl_2 at 0° (0.3–0.4 *M*). The reaction time depended on the reactivity of the nucleophile: (a) 30–60 min at 0° and 30 min at 20° for the more reactive alcohols; (b) 2 hr at 0° and 2–3 hr at 20° for the less reactive alcohols, e.g., hexafluoroisopropyl alcohol, and for the phenols. The CH_2Cl_2 solution was evaporated at 20° (30 mm), the residue was triturated with anhydrous ether, and the insoluble γ-collidinium-OCEP (**10**) was filtered off and saved for reconversion to CEP-OCEP (**4**). The ether-filtrate was evaporated, and the **CEP-OR** (**11**) and **CEP-OAr** (**12**) were purified as indicated in Table I. The compounds were obtained in 90% of the theory.

The CEP-ylation of alcohols was also carried out in the absence of γ-collidine. The results were similar to those in the presence of the base, but CEP-OH (**6**) is somewhat more soluble in ether than its γ-collidinium salt **10**, and some contamination of the CEP-OR (**11**) by **6** may result.

CEP-ylation of *p*-Nitrophenol in the Presence of Nicotinamide, Optimum Synthesis of *p*-Nitrophenyl Acetoin Enediol Cyclophosphate (12, Ar = *p*-$NO_2C_6H_4$). A solution of freshly crystallized *p*-nitrophenol (4.59 g, 33 mmol) in ether (30 ml) was dropped (30 min) into a solution of CEP-OCEP (**4**; 9.28 g, 33 mmol) in CH_2Cl_2 (150 ml) containing suspended nicotinamide (4.44 g, a slight excess over 33 mmol) at 20°. The mixture was stirred for 7 hr at 20° and was filtered. The insoluble salt was washed with CH_2Cl_2 (100 ml), and the combined washing and filtrate was concentrated in vacuum to ca. 20 ml. The mixture was diluted with ether (100 ml), and the total volume was again reduced to ca. 20 ml in vacuum; the resulting solid was filtered off and washed with ether (25 ml) to yield virtually pure **CEP-OC_6H_4-*p*-NO_2** (7.21 g, 85%; mp 100–102°).

Spectroscopic Study of the Reaction of Methanol with CEP-OCH_3 (2) in Benzene Solution.[27] A 0.5-ml aliquot of 1.11 *M* benzene solution of CEP-OCH_3 (**2**) was added to methanol (0.0188 g, 1.05 mol equiv) in an NMR sample tube cooled to 0°. The solution was shaken for 1 min at 0°. The ^1H NMR spectrum was immediately examined at ambient temperature. The results are shown in Table III. The pertinent ^1H NMR signals in the benzene solution are as follows (τ in ppm; *J* in Hz). **CEP-OCH_3:** 8.55; 6.60, J = 12.0. **Dimethylacetoinyl phosphate. Enol:** 8.21 and 8.31; 6.51, J = 11.5. **Keto:** 8.80, J = 7.3; 8.08; 6.49, J = 11.1 and 6.58, J = 11.1.

General Procedure for the Reaction of Alcohols, R'OH, with CEP-OR. Phosphorylative Coupling of Two Alcohols, ROH and R'OH. (a) Two Monofunctional Alcohols. The first alcohol (ROH) was CEP-ylated by CEP-OCEP (**4**) as described above. One mole equivalent of the second alcohol (R'OH), in CH_2Cl_2 solution, was added to a CH_2Cl_2 solution of the CEP-OR at 0° (0.2 *M*). The progress of the reaction was followed by the ^1H NMR spectra of aliquots, observing the disappearance of CEP-OR and the appearance of the dialkylacetoinyl phosphate. In the examples given in Table II, the solution was kept 8 hr at 20°, and the solvent was evaporated at 30° (30 mm). The **dialkylacetoinyl phosphate 14** was obtained in 95% of the theory according to ^1H NMR spectrometric analysis (in $CDCl_3$). An aliquot of the mixture of diastereomers (**14A** + **14B** . . .) was purified by molecular distillation to obtain the elemental analyses and the spectral data listed in Table I. The crude mixture of diastereomeric phosphotriesters was hydrolyzed as described below.

In the coupling of a secondary with a primary alcohol, the secondary alcohol (ROH) was CEP-ylated, and the primary alcohol added to the CEP-OR produced.

(b) A Monofunctional and a Difunctional Alcohol. The monofunctional alcohol (ROH) was CEP-ylated. The resulting CEP-OR (**11**) (1 mol equiv in CH_2Cl_2 solution) was added dropwise at 20° (30 min) *to* a 0.3 *M* CH_2Cl_2 solution of the polyfunctional alcohol (R'OH). After completion of the reaction, the solvent was evaporated, and the residue was analyzed by ^1H NMR spectrometry (in $CDCl_3$). The mixture of diastereomers was hydrolyzed as described, and the yield of the phosphodiester was determined from the crystalline ammonium salt. The solvent, the molarity of the solution, and the temperature and duration of the reaction were determined in preliminary experiments, in which the relative amounts of primary OH vs. secondary OH phosphorylation were established by ^1H NMR spectrometry of the crude reaction product, before and after reaction with $(CH_3)_3SiCl$. The trimethylsilyl ethers of the primary and secondary alcohol functions were formed quantitatively and were suitable for ^1H NMR spectrometric analysis. The analysis could also be performed by acetylating the mixture of phosphodiesters resulting from the alkaline hydrolysis using an excess of acetyl chloride.

General Procedure for the Hydrolysis of Unsymmetrical Dialkylacetoinyl Phosphates to Dialkyl Phosphates. Procedure A. The dialkylacetoinyl phosphate **14** was added to a water–acetonitrile solution (2:1 v/v) in which was dissolved 1 mol equiv of sodium carbonate (0.2–0.3 *M*). The mixture was stirred at 60° for 6 hr and extracted with CH_2Cl_2. The aqueous phase was acidified with dilute hydrochloric acid and extracted again with CH_2Cl_2. The extract was dried over Na_2SO_4 and evaporated leaving the dialkyl hydrogen phosphate **15** as a colorless oil. The phosphate was characterized as either the cyclohexyl or dicyclohexyl ammonium salt **15b** (Table II). The salts were isolated in the following yields based on the phosphotriesters: c-C_5H_9, $(CH_3)_2CHCH_2$, 82%; c-C_5H_9, $C_6H_5CH_2$, 81%; CH_2CH_2Br, $(CH_3)_2CHCH_2$, 70%.

Procedure B. The dialkylacetoinyl phosphate **14** (ca. 10 mmol) was dissolved in a mixture of pyridine (50 ml) and water (50 ml). Triethylamine (2 mol equiv) was added, and the solution was kept at 70° for 12 hr. The solution was evaporated in vacuum, the residue was dissolved in water, and the solution was extracted with CH_2Cl_2. The aqueous solution was acidified with dilute hydrochlo-

ric acid and extracted with CH_2Cl_2 to give the dialkyl hydrogen phosphate. The salt from $(c\text{-}C_5H_9O)(CH_3)_2CHCH_2OP(O)OH$ was isolated in 84% yield.

Synthesis of Cyclopentyl(*trans*-2-hydroxycyclopentyl)methyl Phosphate (19) as a Dinucleotide Model. CEP-O-c-C_5H_9 (**16**; 3.25 g, 15 mmol) in CH_2Cl_2 (30 ml) was added (30 min) to a solution of *trans*-2-hydroxymethylcyclopentanol (**17**; 1.74 g, 15 mmol) in CH_2Cl_2 (25 ml) at 20°. After 6 hr at 20°, the solvent was evaporated, yielding 4.95 g of cyclopentyl(*trans*-2-hydroxycyclopentyl)-methyl acetoinyl phosphate (**18**) as a colorless oil. It was contaminated with ca. 10–15% of the species with the secondary alcohol function phosphorylated. The crude dialkyl acetoinyl phosphate (**18**; 1.78 g, 5.3 mmol) was dissolved in a solution of sodium carbonate (0.58 g, 5.3 mmol) in 10 ml of water and 5 ml of acetonitrile and stirred 24 hr at 25°. The solution was diluted with water (15 ml) and extracted with CH_2Cl_2. It was acidified with dilute hydrochloric acid and extracted again with CH_2Cl_2 (4 × 20 ml). Evaporation of the CH_2Cl_2 left 1.2 g (90%) of crude cyclopentyl-(*trans*-2-hydroxycyclopentyl)methyl phosphate.[19] The crude ester[19] (0.60 g, 2.3 mmol) was dissolved in CH_2Cl_2 (1 ml) and ether (5 ml). Cyclohexylamine (0.5 ml, excess) was added and the solution left at 0° overnight. The cyclohexylammonium salt **19b** precipitated. There was isolated 0.5 g of the salt **19b**, mp 166–169°, which corresponded to 65% of the theory based on phosphotriester. The same salt (**19b**) was isolated in 71% of the theory based on phosphotriester, using procedure B [water-pyridine-$(C_2H_5)_3N$] for the hydrolysis.

References and Notes

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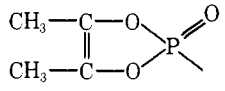
(4) The following abbreviations will be used in this paper:
CEP = cyclic enediol phosphoryl:



CEP-ylation = phosphorylation with ring retention by a CEP derivative
CEP-O-CEP = acetoin enediol cyclopyrophosphate
Acn = acetoinyl, $(CH_3CO)(CH_3)CH$–
PI = permutational isomerization of oxyphosphoranes.

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(37) The new oxyphosphorane can also be generated by the Berry pseudorotation mechanism [R. S. Berry, *J. Chem. Phys.*, **32**, 933 (1960)].

(38) **Note Added in Proof.** The reaction of alcohols and phenols with CEP-OR is significantly accelerated by certain bases, e.g., $(C_2H_5)_3N$, and to a lesser extent by acids, e.g., CF_3COOH. This and other mechanistic questions will be discussed in a separate paper.

(39) **Note Added in Proof.** Hydrolysis of the triesters at 70° in aqueous acetonitrile solution (2:1) containing 2 mol equiv of triethylamine yields also minimal amounts, ~2%, of the undesirable alkylacetoinyl phosphate by-products.