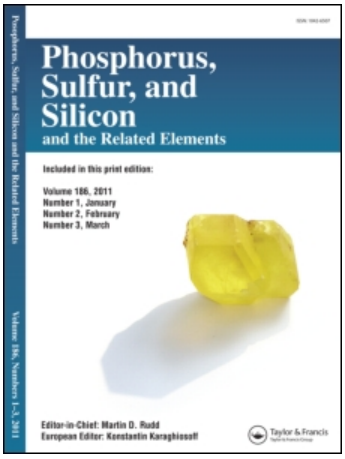

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SYNTHESIS OF LONG-CHAIN SATURATED AND UNSATURATED DIALKYL PHOSPHATES BY MEANS OF CYCLIC ENEDIOL PYROPHOSPHATES

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Symmetrical and unsymmetrical long-chain (C_{12}–C_{18}) saturated and unsaturated dialkyl phosphates are synthesized in 75–85% overall yields from the alcohols R^1OH and R^2OH by means of cyclic enediol phosphoryl (CEP) derivatives, di(1,2-dimethylethenylene) pyrophosphate, 1,2-dimethylethenylene phosphorochloridate, and N-(1,2-dimethylethenedioxyphosphoryl)imidazole.

INTRODUCTION

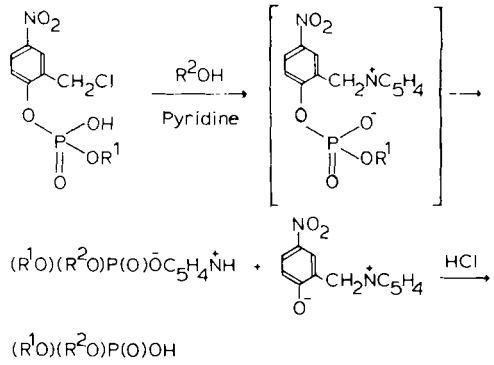
The need for pure samples of phosphodiesters derived from long-chain saturated and unsaturated alcohols, in the range C_{12}–C_{18} arose in connection with another investigation. Several symmetrical saturated C_{12}–C_{18} dialkyl phosphates have been synthesized from phenyl phosphorodichloridate as shown in Scheme 1.[2a] This procedure is satisfactory when the alkyl groups are saturated, but it is not applicable when double bonds are present, since removal of the phosphate-blocking group is performed by catalytic hydrogenation.

$$C_6H_5OP(O)Cl_2 \xrightarrow{2ROH/Pyridine} C_6H_5OP(O)(OR)_2 \xrightarrow{H_2\text{-}PtO_2/Acetic\ Acid} (RO)_2P(O)OH$$

SCHEME 1

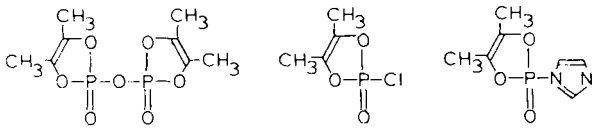
Some *unsymmetrical* saturated long-chain phosphodiesters have been prepared[3] from (2-chloromethyl-4-nitrophenyl)alkyl phosphates as outlined in Scheme 2; e.g., the reaction of 1-pentanol (R^2OH) with the 1-hexadecyl phosphate derivative afforded the corresponding diester in 92% yield, based on the second alcohol, R^2OH. This interesting procedure obviously requires additional steps beginning with the first alcohol, R^1OH.

This paper demonstrates that symmetrical and unsymmetrical saturated and unsaturated long-chain dialkyl phosphates are conveniently prepared in overall yields ranging from 75 to 85% by means of the cyclic enediol pyrophosphate,[4,5] **1**, the phosphorochloridate,[6,7]



SCHEME 2

2, or the N-phosphorylimidazole,[8] **3**. These reagents have been successfully applied to the synthesis of complex phospholipids[9,10] and oligonucleotides,[11] and represent significant additions to the growing list of non-enzymatic phosphorylating reagents.[12–56]



1 **2** **3**

RESULTS AND DISCUSSION

The general procedure for the synthesis of symmetrical diesters is shown in Scheme 3, where the abbreviation

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CEP-X refers to the cyclic enediol derivatives **1** and **2** (CEP = 1,2-dimethylethenylenedioxyphosphoryl or 2-oxo-4,5-dimethyl-1,3,2-dioxaphospholyl). The first stage of the synthesis is carried out at 20° in dichloromethane solution. Imidazole rapidly (<5 min, at ~0.2–0.3 M) converts CEP-X, **1** or **2**, into the actual phosphorylating reagent, CEP-IM, **3**, plus the innocuous imidazolium salts of the corresponding anions, X = $CEPO^{(-)}$ or $Cl^{(-)}$. The first mole of alcohol, ROH, performs a rapid (<30 min, at ~0.2–0.3 M) displacement at the cyclic phosphorus atom of CEP-IM, **3**, with complete ring-retention to give the cyclic enediol triester, CEP-OR:

$$\text{CEP-IM} + \text{ROH} \rightarrow \text{CEP-OR} + \text{IMH}$$

The imidazole thus generated effectively catalyzes the reaction of the second mole of alcohol with CEP-OR to give the acyclic triester, **4**. The reaction is complete within 4 hr. This technique obviates the isolation and purification of CEP-IM, **3**.

The acyclic triester **4** is not purified, and the 3-oxo-2-butyl or 1-methyl-acetonyl (Acn) group,[5,7] which is used to block the phosphate function, is removed by mild hydrolysis in the presence of a tertiary amine such as diisopropylethyl amine or triethyl amine, in aqueous pyridine solution. The free symmetrical acids, **5**, listed in Table I are isolated in pure state after one recrystallization.

$$\text{CEP-X (1 or 2)} \xrightarrow[\text{(b) 2 ROH}]{\text{(a) 2 Imidazole}} \underset{\textbf{4}}{(RO)_2P(O)OAcn} + [C_3H_5N_2]^{(+)}X^{(-)}$$

$$\xrightarrow[\text{(b) 5\% Aq-HCl}]{\text{(a) } R_3N,\ H_2O/\text{Pyridine}} (RO)_2P(O)OH + \underset{\textbf{5}}{AcnOH}$$

SCHEME 3, Acn = $-CH(CH_3)COCH_3$

The unsymmetrical acids, **7**, are prepared as outlined in Scheme 4. In this procedure, the phosphorylating reagent is the pyrophosphate itself, **1**. Triethyl amine is used as the proton-acceptor in the conversion of the first alcohol R^1OH into the cyclic enediol triester, CEP-OR.[1] Triethyl amine functions as catalyst in the reaction of the second alcohol R^2OH with CEP-OR^1 to give the acyclic triester, **6**.[8] The latter compound, **6**, is obtained in better yield using triethyl amine instead of imidazole, since the tertiary amine is more effective than the heterocycle in reducing the amount of symmetrical by-products resulting from the following side-reactions:

$$R^2OH + \text{CEP-}OR^1 \rightarrow R^1OH + \text{CEP-}OR^2$$
$$R^1OH + \text{CEP-}OR^1 \rightarrow (R^1O)_2P(O)OAcn$$
$$R^2OH + \text{CEP-}OR^2 \rightarrow (R^2O)_2P(O)OAcn$$

The transesterification step is a displacement at cyclic phosphorus with ring-retention; it occurs to an extent of about 5% *in the absence of catalysts* when R^1OH is secondary and R^2OH is primary, but less than 2% when either triethyl amine or imidazole are used as catalysts. The extent of transesterification increases in the uncatalyzed reaction when both alcohols are primary, and in this case triethyl amine is more effective than imidazole in reducing transesterification, and hence by-product formation. When transesterification is not a problem, e.g., in the synthesis of the symmetrical phosphodiesters, imidazole is preferred because it increases the rate of the reaction to a greater extent than triethyl amine.

$$\underset{\textbf{1}}{\text{CEP-OCEP}} \xrightarrow[\text{(b) } R^2OH/(C_2H_5)_3N]{\text{(a) } R^1OH/(C_2H_5)_3N,\ CH_2Cl_2} (R^1O)(R^2O)P(O)OAcn + \underset{\textbf{6}}{CEPO^{(-)}(C_2H_5)_3NH^{(+)}}$$

$$\xrightarrow[\text{(b) 5\% Aq-HCl}]{\text{(a) } R_3N,\ H_2O/\text{Pyridine}} (R^1O)(R^2O)P(O)OH + \underset{\textbf{7}}{AcnOH}$$

SCHEME 4, Acn = $-CH(CH_3)COCH_3$

The three CEP-X reagents, **1**–**3**, are prepared in high yields from biacetyl and trimethyl phosphite.[4–6] The reagents are, as expected, sensitive to moisture, but are stable over periods of months in an anhydrous environment; the pyrophosphate, **1**, and the phosphorylimidazole, **3**, are crystalline substances, while the phosphorochloridate **2** is a distillable liquid.

EXPERIMENTAL SECTION

All reactions with the CEP-X reagents were carried out in anhydrous solvents, with protection against moisture. Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

TABLE I

Properties of Long-Chain Saturated and Unsaturated Dialkyl Phosphates Prepared From CEP-X Reagents and Alcohols R^1OH, R^2OH[a]

Compd. No.	R^1 in R^1OH	R^2 in R^2OH	M.P.° (Solvent)	Reference
5	$CH_3(CH_2)_{10}CH_2$	$CH_3(CH_2)_{10}CH_2$	53-55 [$(C_2H_5)_2O$]	2a
5	$CH_3(CH_2)_{12}CH_2$	$CH_3(CH_2)_{12}CH_2$	68-69 (CH_2Cl_2)	2a
5	$CH_3(CH_2)_{14}CH_2$	$CH_3(CH_2)_{14}CH_2$	74-75 (CH_2Cl_2)	2a
5	$CH_3(CH_2)_{16}CH_2$	$CH_3(CH_2)_{16}CH_2$	77-78 (CH_3OH)	2a
7	$CH_3(CH_2)_{14}CH_2$	$CH_3(CH_2)_3CH_2$	40-42 (CH_3OH)	3a
5	Oleoyl	Oleoyl	19-21 (CH_3OH)	2b[b]
5	Linoleyl	Linoleyl	...[c]	New[d]
7	$CH_3(CH_2)_{12}CH_2$	Oleoyl	39-40.5 (CH_3OH)	New[e]

[a] 75-85% yields of recrystallized dialkyl hydrogen phosphates based on the first alcohol, R^1OH. ^1H nmr spectra ($CDCl_3$) agree with the structures.
[b] $C_{36}H_{71}O_4P$, Calcd., C, 72.2%; H, 11.9%; P, 5.2%. Found, C, 72.3%; H, 12.0%; P, 5.1%.
[c] Liquid at 20°. Crystallized from CH_3OH at −20°.
[d] $CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7CH_2$. $C_{36}H_{67}O_4P$, Calcd., C, 72.7%; H, 11.4%; P, 5.2%. Found, C, 72.8%; H, 11.4%; P, 5.0%.
[e] $C_{32}H_{65}O_4P$, Calcd., C, 70.5%; H, 12.0%; P, 5.7%. Found, C, 70.6%; H, 12.1%; P, 5.7%.

Symmetrical Phosphodiesters (Scheme 3).

A solution of imidazole (2 molequiv) in dichloromethane (~1 ml/mmole) was added to a stirred solution of the pyrophosphate (**1**; 1 molequiv) in dichloromethane (~3 ml/mmole) at 20°. After 5-10 min, a solution of the alcohol (ROH; 2 molequiv) in dichloromethane (~3 ml/mmole) was added to the stirred solution containing the CEP-IM, **3**. The solution was stirred for ~4 hr and was extracted, successively, with aq. Na_2CO_3 (2x), 3% aq-HCl (2x) and water (1x). The dried (Na_2SO_4) dichloromethane solution was evaporated (30°, 30 mm) to yield the crude phosphotriester **4**. The latter, **4**, was dissolved in pyridine (~5 ml/mmole) and water added to the point of turbidity (usually ½ to ⅔ the volume of pyridine used). Diisopropyl ethyl amine or triethyl amine (2 molequiv based on **4**) was added and the solution stirred at 85° for 24-48 hr to effect removal of the phosphate blocking group. The solution was cooled, diluted with $CHCl_3$ (~25 ml/mmole) and acidified with cold 10% aq-HCl. The layers were separated, the aqueous solution was extracted with $CHCl_3$, and the combined organic solution dried and evaporated to yield the crude phosphodiester, **5**, which was purified by recrystallization from the solvent indicated in Table I. In the case of the unsaturated esters the crystallization was carried out at −20°.

Unsymmetrical Phosphodiesters (Scheme 4).

A solution of the first alcohol R^1OH (1 molequiv) and triethyl amine (1 molequiv) in dichloromethane (~2 ml/mmole) was added to a solution of the pyrophosphate (**1**; 1 molequiv) in the same solvent (~1 ml/mmole) at 20°, and the mixture was stirred for about 45 min. The second alcohol R^2OH (1 molequiv), together with 1 molequiv of triethyl amine, was introduced as a dichloromethane solution (0.5-1.0 ml/mmole), and the mixture was stirred for about 18 hr at 20°. The crude phosphotriester **6** was isolated as described for the analogous compound **4**, and the phosphate blocking group was removed in aqueous-pyridine as described above. The crude phosphodiester **7** was purified by crystallization from the solvent indicated in Table I.

The purity of tetradecyl, oleoyl, 3-oxo-2-butyl phosphate was verified by mass spectrometry. The selected ion chromatogram showed the absence of ions at mass 561 (syn-bistetradecyl phosphate), and only a trace of ions at mass 669 (syn-bisoleoyl phosphate); the ion of mass 615 gave an intense absorption however, The complete mass spectrum of the 615 ion was obtained and agreed with the assigned structure.

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