A Novel Synthesis of Phosphate Esters

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Summary A new phosphate synthesis (suitable for highly hindered phosphates) is described, based on the reaction of an alkoxy-radical (generated by nitrite photolysis) with a trialkyl, or other appropriate, phosphite.

MUCH effort has been spent on the development of methods for the conversion of alcohols into phosphate esters.[1] In general, current methods achieve the required P–O bond formation through nucleophilic attack at phosphorus.[1] In connection with another problem we have had occasion to seek a phosphate ester synthesis which *did not* involve nucleophilic substitution at phosphorus and which would be applicable to highly hindered alcohols. We report the realization of such a synthesis.

The valence expansion of a suitable trivalent phosphorus species affords a phosphate synthesis (equation 1) and the problem is to define the nature of X. In principle such a valence expansion can be initiated by the co-ordination of P^{III} species with an alkoxy-radical. However, earlier studies of such reactions have been limited to easily deoxygenated alkoxy-radicals as in equation 2. We now report that the photolysis of organic nitrites provides a convenient general source of alkoxy-radicals for phosphate synthesis. Thus, 3β-hydroxycholestane nitrite (1a) on irradiation† in the presence of tri-isopropyl phosphite

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† All photolyses in benzene; appropriate controls were run to ensure that the observed reactions were initiated by nitrite *photolysis*.

affords 3β-hydroxy-5α-cholestane di-isopropyl phosphate (2a). The yield of (2a) is limited by difficulties attendant to crystallization but it is virtually the only steroidal reaction product (t.l.c.). Capture of the cholestanyloxy-radical by a phosphite tri-ester (equation 3) is quite efficient as one equiv. of tri-isopropyl phosphite largely supresses, while more than three equiv. almost completely supresses, the formation of (1b) and (1c) derived from the competing reduction and oxidation of the intermediate cholestanyloxy-radical. The Table indicates a number of phosphates prepared by our method.

$$\text{(Eq. 1)}\quad R^1OX + P(OR^2)_3 \rightarrow R^1OP(X)(OR^2)_3 \rightarrow R^1OP(:O)(OR^2)_2$$

$$\text{(Eq. 2)}\quad R^1O\cdot + P(OR^2)_3 \rightarrow R^1O\dot{P}(OR^2)_3 \rightarrow R^1\cdot + O:P(OR^2)_3$$

$$\begin{tikzcd} & R^1O\overset{+}{P}(OR^2)_3 \arrow[r] & ROP(:O)(OR^2)_2 + {}^+R^2 \\ \text{(Eq. 3)}\quad R^1O\cdot + P(OR^2)_3 \arrow[r] & R^1O\dot{P}(OR^2)_3 \arrow[u, "b"] \arrow[r, "a"] \arrow[d, "c"] & R^1OP(:O)(OR^2)_2 + R^2\cdot \\ & R^2O\cdot + R^1OP(OR^2)_2 \arrow[r] & R^1OP(:O)(OR^2)_2 \end{tikzcd}$$

TABLE

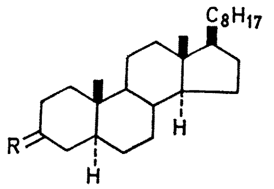
Phosphate	% Yield[a]	M.p.	[α]D (CHCl3)
2a	50(64)	84—87°	+ 21°
2b	62[b](75)	164—166°	+ 16°
2c	40(63)	65—68°	+ 16°
3	41(60)	118—122°	+ 6°
4	20(80)	75—85°	+ 15°
5	42(75)	160—161°	+ 18°

[a] The first yield refers to isolated, crystallised and analytically pure product. The yield in parentheses refers to homogeneous phosphate estimated by n.m.r. or other technique.

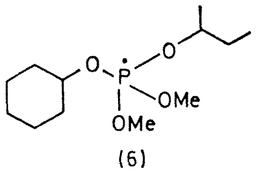
[b] As the monodemethylated derivative.

Observations pertinent to the mechanism of the photochemical phosphorylation reactions are as follows: The nitrite (1a) on irradiation in the presence of trineopentyl phosphite afforded the stereoidal dineopentyl phosphate (3), and, in the presence of tris-(βββ-trifluoroethyl) phosphite the corresponding steroidal phosphate ester (4). Irradiation of (1a) in the presence of tris-benzhydryl phosphite again afforded the expected steroidal ester (5) together with a small amount of benzophenone oxime. The formation of this later product, presumably from the benzhydryl radical and nitric oxide, is greatly impeded by the highly competitive reduction of nitric oxide by the phosphite,[3] as indicated by the presence of an appreciable amount of tris-benzhydryl phosphate in the reaction mixture. The synthesis of compounds (3) and (4) is not compatible with S_N1 or S_N2 processes on neopentyl or neopentyl-like systems. These data together with others presented in the sequel[4] suggest that the course of the photochemical phosphorylation (in the absence of addenda which react with the phosphoranyl radical intermediate[4]) is best expressed by equation 3 (path a). An alternative pathway involving loss of an electron from the phosphoranyl radical intermediate [equation 3 (path b)] followed by dealkylation of the phosphonium intermediate[4] is not compatible with the observations (*vide supra*) while ejection of an alkoxy-radical from the phosphoranyl intermediate [equation 3 (path c)] followed by fortuitous oxidation is ruled out by our failure to observe steroidal ***phosphite*** under conditions appropriate to its survival.[4]

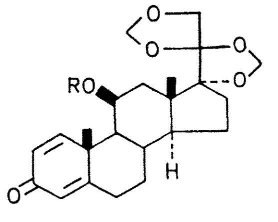
We have briefly investigated those factors determining which of the four alkyl groups is lost from the phosphoranyl intermediate (if the newly introduced ligand were as susceptible to ejection as the other three the phosphorylation would be limited to a maximum yield of 75%). Such effects, to the extend that they have been detected, seem to stem from ponderal factors, *i.e.* massive ligands seem to be retained preferentially. Thus the reactions set out in the



	α	R	β
(1) a;	H		ON:O
b;	H		OH
c;		O	
(2) a;	H		OP(:O)(OPr^i)$_2$
b;	H		OP(:O)(OMe)$_2$
c;	H		OP(:O)(OEt)$_2$
(3)	H		OP(:O)(OCH$_2$Bu^t)$_2$
(4)	H		OP(:O)(OCH$_2$CF$_3$)$_2$
(5)	H		OP(:O)(OCH$_2$Ph)$_2$



(6)



(7) R = N:O

(8) R = P(:O)(OPr^i)$_2$

Table did not lead to detectable amounts of the products (cholestane and cholestene) expected to arise from the cholestanyl radical had it been ejected from the intermediate. Finally, the phosphoranyl radical (6) has been prepared by the reaction of cyclohexyl nitrite with s-butyl dimethyl phosphite as well as by reaction of s-butyl nitrite with cyclohexyl dimethyl phosphite. The yields of methyl 2-butyl cyclohexyl phosphate were 42% and 43% respectively showing that the decomposition of the phosphoranyl intermediate is not dependent on the mode of formation of this intermediate. The stereochemistry of phosphoranyl radicals and the stereoelectronic effects governing the transformation of these radicals are virtually unknown.[5]

The advantages of the photochemical phosphorylation stem from the ease, very mild reaction conditions, and the selectivity of the method (mononitrites may often be formed from polyhydric alcohols[6]). The easy formation of nitrites from highly hindered alcohols coupled with the formation of the P–O bond without involvement of polar, highly solvated intermediates make this method applicable to the formation of highly hindered phosphates. An example is provided by the conversion of the nitrite (7) into the phosphate (8) m.p. 209—213°, $[\alpha]_D + 6°$ ($CHCl_3$).

All new compounds were characterised by microanalysis and showed the appropriate spectral data.

Under different solvent conditions we have been able to observe the more conventional cationic mechanism. The data will be presented in our full paper.

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[1] See, *e.g.*, D. M. Brown, *Adv. Org. Chem.*, 1963, **3**, 75.

[2] C. Walling and R. Rabinowitz, *J. Amer. Chem. Soc.*, 1959, **81**, 1243. C. Walling and M. S. Pearson, *ibid.*, 1964, **86**, 2262.

[3] L. P. Kuhn, J. O. Doali, and C. Wellman, *J. Amer. Chem. Soc.*, 1960, **82**, 4792.

[4] Unpublished work from these laboratories.

[5] See, *e.g.*, W. G. Bentrude and R. A. Wielesek, *J. Amer. Chem. Soc.*, 1969, **91**, 2406.

[6] R. H. Hesse, *Free Radical Chem.*, 1969, **3**, 130.