The Preparation of Mixed Dialkyl Phosphates

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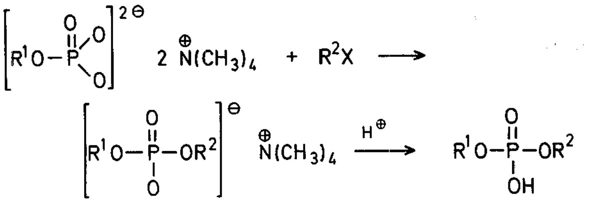
Reported methods for the synthesis of mixed dialkyl phosphates usually involve replacement of one alkyl group of a dialkyl phosphate by another[1], or selective monodealkylation of a trialkyl phosphate[2,3,4]. Direct conversion of a monoalkyl phosphate to a diester has been accomplished in nucleotide synthesis by Khorana[5], but this method employing dicyclohexylcarbodiimide was not satisfactory when applied to simple aliphatic compounds; low yields of the desired products were obtained which required chromatography for purification.

Recently there has been reported an esterification by alkyl halides of carboxylic acids in the form of their quaternary aminium salts[6]. In phosphorus chemistry it was already known that trialkyl phosphates can be produced by a similar reaction[7,8]. Since $[\mathrm{ROP(O)O_2}]^{2\ominus}$ should be a much better nucleophile than $[\mathrm{(RO)_2P(O)O}]^{\ominus}$[9], it seemed possible that alkylation of a monoalkyl phosphate could be stopped at the dialkyl phosphate stage. This proved, indeed, to be the case and the reaction has been developed into a convenient general synthesis of dialkyl phosphates.



The monoalkyl phosphates used in this work were obtained by phosphorylation of alcohols with pyrophosphoric acid[10]. By dissolving in methanolic tetramethylaminium hydroxide they were converted to quaternary aminium salts which were isolated by solvent removal in vacuum at 40°; it was not found necessary to remove the last traces of solvent. Subsequent reaction with an alkyl halide was carried out in acetonitrile, the time depending on the reactivity of the halide. (One attempt to use dimethylformamide resulted in extensive decomposition to alcohol.) For the best yields, it was necessary to make the bis[tetramethylaminium] salt, probably because of the greater nucleophilicity of the dianion.

Excess alkyl halide carries the reaction on to the trialkyl phosphate stage. But with equimolar quantities of phosphate and halide the yields were consistently about 80% dialkyl phosphate and no more than 5% trialkyl phosphate.

Table 1. Reaction of Monoalkyl Phosphates ($R^1OP(O)(OH)_2$, x equiv) with Tetramethylaminium Hydroxide (y equiv) and an Alkyl Halide (R^2X, z equiv).

R^1	R^2X	Ratio x:y:z	Reaction time[a]	Yield (%)[b]	of Products	
				di-	mono-	tri-
C_8H_{17}	$C_{14}H_{29}Cl$	1:2:1	24 h	81	3	7
$C_{10}H_{21}$	$C_{16}H_{33}Cl$		20 h	78	6	7
$C_{12}H_{25}$	$C_6H_5CH_2Cl$		3 h	87	4	3
$C_{10}H_{21}$	s-C_4H_9Cl		24 h	20	69	
$C_{10}H_{21}$	s-C_4H_9Cl		50 h	23	55	4
$C_{10}H_{21}$	n-C_4H_9Cl		7 h	79	14	2
$C_{10}H_{21}$	n-C_4H_9Cl		15 h	78	7	5
$C_{12}H_{25}$	$C_7H_{15}Cl$		19 h	81	6	2
C_8H_{17}	$C_{18}H_{37}Br$		2 h	71	4	—
$C_{10}H_{21}$	C_3H_7Br		0.25 h	71	11	7
$C_{10}H_{21}$	C_3H_7Br		1 h	77	9	9
$C_{10}H_{21}$	C_3H_7Br		2 h	76	6	9
$C_{10}H_{21}$	C_3H_7Br	1:2:1.5	1 h	67	3	19
$C_{10}H_{21}$	C_3H_7Br	1:1.5:1	1 h	30	45	11
$C_{10}H_{21}$	C_3H_7Br	1:1:1	1 h	19	59	7
$C_{10}H_{21}$	C_3H_7Br	1:3:1	2 h[c]	9	74	—
$C_{12}H_{25}$	C_3H_7Br	1:2:1	2.5 h	80	12	4
$C_{12}H_{25}$	s-$C_8H_{17}Br$		6.5 h	20	69	4
$C_{12}H_{25}$	$(C_4H_9)(C_2H_5)CHCH_2Br$		1.5 h	53	41	7
$C_{10}H_{21}$	$C_6H_{13}Br$		16 h[c]	81	10	6
$C_{12}H_{25}$	$C_6H_{13}Br$		2.5 h	79	8	3
$C_{10}H_{21}$	CH_3J		0.25 h[c]	76	10	8
$C_{10}H_{21}$	CH_3J	1:2:2.5	1 h	—	—	95
$C_{10}H_{21}$	C_2H_5J	1:2:1	16 h[c]	83	5	12
$C_{12}H_{25}$	$C_8H_{17}J$		0.5 h	74	16	5

[a] In refluxing acetonitrile unless otherwise noted.

[b] Based on titration of the ether soluble isolate.

[c] Room temperature reaction.

Table 2. New Dialkyl Phosphates

R^1	R^2	M.p.	I.R. spectra[a], cm^{-1}	Elemental Analysis					
n-C_6H_{13}	n-$C_{12}H_{25}$	34–36°	1229, 1034[b]	$C_{18}H_{39}O_4P$ (350.5)	calc. found	C 61.68 62.04	H 11.22 11.15	P 8.84 8.87	
$C_6H_5CH_2$	n-$C_{12}H_{25}$	48–50°	1219, 1033	$C_{19}H_{33}O_4P$ (356.4)	calc. found	C 64.02 63.98	H 9.33 9.55	P 8.69 8.44	
n-C_7H_{15}	n-$C_{12}H_{25}$	38–39°	1234, 1036	$C_{19}H_{41}O_4P$ (364.5)	calc. found	C 62.60 62.28	H 11.34 11.46	P 8.50 8.54	
n-C_8H_{17}	n-$C_{12}H_{25}$	41–42°	1230, 1036	$C_{20}H_{43}O_4P$ (378.5)	calc. found	C 63.46 63.16	H 11.45 11.38	P 8.18 8.21	
n-C_8H_{17}	n-$C_{14}H_{29}$	45–46.5°	1230, 1034	$C_{22}H_{47}O_4P$ (406.6)	calc. found	C 64.99 64.84	H 11.65 11.68	P 7.62 7.76	
n-C_8H_{17}	n-$C_{18}H_{37}$	58–59.5°	1215, 1042	$C_{26}H_{55}O_4P$ (462.7)	calc. found	C 67.48 67.54	H 11.98 12.10	P 6.70 6.74	
n-$C_{10}H_{21}$	n-$C_{16}H_{33}$	57–58°	1215, 1040	$C_{26}H_{55}O_4P$ (462.7)	calc. found	C 67.48 67.13	H 11.98 11.92	P 6.70 6.73	
n-$C_{10}H_{21}$	$-(CH_2)_4-$	81.5–83.5°	1215, 1036	$C_{24}H_{52}O_8P_2$ (530.6)	calc. found	C 54.32 54.10	H 9.88 9.91	P 11.68 11.75	
n-$C_{10}H_{21}$	$H_3CO-CO-C_{10}H_{20}$	52–53.5°	1212, 1042	$C_{22}H_{45}O_6P$ (436.6)	calc. found	C 60.52 60.38	H 10.39 10.35	P 7.10 7.20	
n-$C_{10}H_{21}$	$H_2N-CO-C_{10}H_{20}$	92.5–93.5°	1222, 1040	$C_{21}H_{44}NO_5P$ (421.6)	calc. found	C 59.85 59.65	H 10.52 10.65	P 7.35 7.40	
n-$C_{12}H_{25}$	$Cl-CH_2CH_2CH_2$	40–41.5°	1226, 1034	$C_{15}H_{32}ClO_4P$ (342.8)	calc. found	C 52.54 52.37	H 9.41 9.57	P 9.04 9.18	Cl 10.34[c] 10.42

[a] Nujol mull.

[b] Center of a 50 cm^{-1} wide multiplet

[c] Br found <0.06%

When the dialkyl hydrogen phosphate was a solid it could be readily purified by recrystallization; otherwise it was converted to the sodium salt by neutralization in alcohol, which procedure simultaneously removed the unreacted monoalkyl phosphate as the insoluble disodium salt.

Purity was demonstrated by T.L.C. on silica gel in the system chloroform/methanol/water (60:35:9) which gave clean separations of mono-, di- and trialkyl esters (visualized with bromophenol blue).

While activity of the halides is in the usual order J > Br > Cl, it is quite feasible to utilize the cheaper alkyl chlorides by refluxing the reaction mixture overnight to give yields the equal of those obtained in an hour or two from bromides.

It is also possible to exploit this difference in halide reactivity as was shown in the preferential reaction of 1-bromo-3-chloropropane to form dodecyl 3-chloropropyl phosphate. Secondary halides gave low yields as did a highly branched primary bromide. The reaction was satisfactorily carried out with halides containing either an ester or an amide group.

Table 1 contains a summary of the experimental results, demonstrating that this synthesis can be the method of choice for mixed dialkyl phosphates. Table 2 describes the new compounds isolated.

Preparation of Dialkyl Phosphates; General Procedure:
Alkyl dihydrogen phosphate (21 mmol) is dissolved in 15 ml of 20% methanolic tetramethylaminium hydroxide (determined by titration to contain 42 mmol of base), and the solvent is removed by vacuum evaporation at 40° for 30 minutes. The tacky solid is taken up in acetonitrile (50 ml) and an alkyl halide (21 mmol) is added. The reaction mixture is stirred and refluxed for 1–2 hours in the case of bromides or 24 hours for chlorides. After removal of the solvent in vacuo, the residue is dissolved in water (100 ml), acidified with concentrated hydrochloric acid (5 ml), and extracted with ether (3 × 60 ml). The ether solution is washed with water (3 × 25 ml) and then dried (Na_2SO_4). After removal of the ether, the residue is weighed and analyzed by titration with standard alkali, which distinguishes monoalkyl phosphate and dialkyl phosphate, the neutral remainder being taken as trialkyl phosphate. To isolate the pure dialkyl phosphate, the mixture is dissolved in 2-propanol and neutralized with the calculated amount of 50% sodium hydroxide. After centrifugation, the supernatant contains sodium dialkyl phosphate, which can be isolated as such by evaporation, or reconverted to the acid by the above procedure.

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[1] T. Hata, Y. Mushika, T. Mukaiyama, *Tetrahedron Lett.* **1970**, 3505.

[2] L. Zervas, I. Dilaris, *J. Amer. Chem. Soc.* **77**, 5354 (1955).

[3] J. Cheymol, P. Chabrier, M. Selim, P. Leduc, *C. R. Acad. Sci., Paris* **247**, 1014 (1958).

[4] R. J. W. Cremlyn, G. W. Kenner, J. Mather, A. Todd, *J. Chem. Soc.* **1958**, 528.

[5] P. T. Gilham, H. G. Khorana, *J. Amer. Chem. Soc.* **80**, 6212 (1958), and references cited therein.

[6] J. H. Wagenknecht, M. M. Baizer, J. L. Chruma, *Syn. Comm.* **2**, 215 (1972).

[7] J. Cheymol, P. Chabrier, M. Selim, P. Leduc, *C. R. Acad. Sci., Paris* **249**, 2573 (1959).

[8] A. Zwierzak, M. Kluba, *Tetrahedron* **27**, 3163 (1971).

[9] M. Smith, J. G. Moffatt, H. G. Khorana, *J. Amer. Chem Soc.* **80**, 6204 (1958).

[10] A. K. Nelson, A. D. F. Toy, *Inorg. Chem.* **2**, 775 (1963).