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[Z]-4-Alkylidene-1,3,2-benzodioxaphosphorinane 2-Oxides from Stereospecific Cyclization of 2-Alkylketophenyl Phosphonates and Phosphates

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O,O-Di(2-alkylketophenyl) phenylphosphonates and *O*-(2-alkylketophenyl) *O*-*O*-diphenyl phosphates undergo facile cyclization at 70°C in acetonitrile containing K_2CO_3 to 2-phenyl- and 2-phenoxy-4-alkylidene-1,3,2-benzodioxaphosphorinane 2-oxides, respectively. The *Z* isomer is exclusively formed with higher alkylidene derivatives. Metabolically formed 4-alkylidene- and 4-methyl-1,3,2-benzodioxaphosphorinane 2-oxides may contribute to the biological activity of some 2-ethylphenylphosphorus compounds.

INTRODUCTION

2-Substituted-4-alkylidene-1,3,2-benzodioxaphosphorinane 2-oxides (**1a**) (*1*) are both cyclic and enol phosphates, thereby combining some structural features and biological properties of 2-substituted-1,3,2-benzodioxaphosphorinane 2-oxides (**2a**) (*2–4*) and 2-chloro-1-(substituted-phenyl)-ethenyl dialkyl phosphates [e.g., the insecticide tetrachlorvinphos (**3**)] (*5, 6*). The toxicity and esterase inhibition are attributable to the reactivity of the P-O-aryl bond of **2a** (*2–4*) and presumably of the P-O-ethenyl bond of **3** (*5, 6*). Cyclic enol phosphates such as **1** are therefore of interest in respect to their synthesis, stereochemistry, reactivity, and biological properties.

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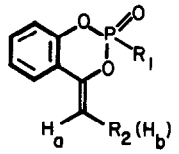
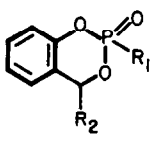
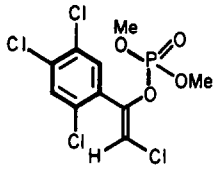


1a R_1 = alkoxy, PhO, Ph; R_2 = H, alkyl
1b R_1 = Ph; R_2 = H
1c R_1 = Ph; R_2 = Me
1d R_1 = Ph; R_2 = Et
1e R_1 = PhO; R_2 = H
1f R_1 = PhO; R_2 = Me
1g R_1 = PhO; R_2 = Et

2a R_1 = alkoxy, aryloxy, Ph; R_2 = H, Me
2b R_1 = Ph; R_2 = H
2c R_1 = PhO; R_2 = H
2d R_1 = Ph; R_2 = Me





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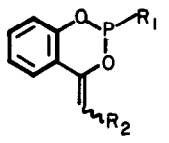
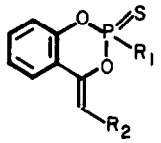


4 R_1 = alkoxy, PhO; R_2 = H, Et

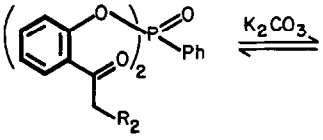


5 R_1 = alkoxy; R_2 = H, Me, Et

EXPERIMENTAL

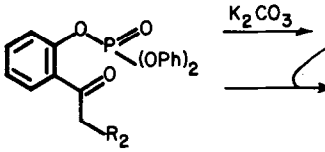
Alkylidene cyclic phosphorus esters (**1a**) have been prepared by two general procedures. Treatment of 2-alkylketophenols with PCl_3 and triethylamine followed by addition of an alcohol or phenol and triethylamine yields the cyclic phosphites (**4**, stereochemistry not assigned) (*7*), which can be oxidized to the analogous phosphates (**1a**) with peracid (*1*). Alternatively 2-alkylketophenyl thionophosphoryl chloridates undergo thermal cyclization to give **5** (*1*). We find that a particularly convenient method to prepare **1b–g** (Table 1) involves treatment of the appropriate 2-alkylketophenyl phosphonate (**6a–c**) or phosphate (**7a–c**) (0.01 mol) with K_2CO_3 (0.01 mol) in acetonitrile (50 ml) for 30 min at 70°C.

6a R_2 = H
6b R_2 = Me
6c R_2 = Et



+ **1b–d**

7a R_2 = H
7b R_2 = Me
7c R_2 = Et



HOPh + **1e–g**

+ $(PhO)_3P(O)$

Intermediates **6a–c** were obtained from reaction of phenylphosphonyl dichloride with 2 equiv sodium 2-alkylketophenylate in acetonitrile for 2 hr at 25°C whereas **7a–c** were prepared by addition of diphenyl chlorophosphate to 1 equiv 2-alkylketophenol suspension in 20% NaOH at 10°C and stirring for 2 hr at 10°C. Column chromatography (silicic acid, dichloromethane–acetone 9 : 1) gave **6a–c** and **7a–c** with appropriate ^1H and ^{31}P NMR and CI–MS. Phenol-free **7a–c** give optimal yields in further reactions.

In the conversion of **6a–c** to **1b–d** in 48 to 50% yields, the liberated alkylke-

TABLE 1

NMR AND CI-MS DATA FOR 4-ALKYLIDENE-1,3,2-BENZODIOXAPHOSPHORINANE 2-OXIDES

Compound[a]	^{1}H NMR, δ ppm[b]		^{1}H NMR, J (Hz)		^{13}C NMR, δ ppm[b]		^{31}P NMR, δ ppm[b]	CI–MS, *m/e* $(M + 1)^+$[c]
	H_a	H_b (or R_2)	H_a—P	H_a—H_b (or H_a—CH)	R_2CH= (or H_aCH=)	R_2		
1b	5.21 (dd)	4.99 (d, 1H)	4.7	2.9	96.1 (7.4)[d]		5.2	259
1c	5.67 (dq)	1.82 (dd, 3H)[e]	2.3	7.0	107.7 (7.4)	10.4	5.9	273
1d	5.62 (dt)	2.30 (m, 2H)	2.1	7.4	114.9 (7.1)	18.3	5.9	287
		1.00 (t, 3H)				13.7		
1e	5.27 (dd)	5.03 (d, 1H)	5.4	3.6	96.5 (8.2)		−22.9	275
1f	5.66 (dq)	1.76 (dd, 3H)[e]	3.8	7.1	108.2 (8.4)	10.2	−21.9	289
1g	5.64 (dt)	2.26 (m, 2H)	3.9	7.4	115.1 (8.7)	18.2	−22.1	303
		1.00 (t, 3H)				13.5		

[a] Mp 53–54°C for **1c** and 66–67°C for **1d**. Other compounds are oils.

[b] NMR: ^{1}H, 90 or 180 MHz; ^{13}C, 45.3 MHz (both $CDCl_3$/internal tetramethylsilane): ^{31}P, 72.9 MHz ($CDCl_3$, external 1% trimethyl phosphate in $CDCl_3$, signals upfield of trimethyl phosphate are given negative values).

[c] Chemical ionization–mass spectra (CI–MS) (methane) with $(M + 1)^+$ as the base peak and $(M + 29)^+$ second in relative intensity (12–36%).

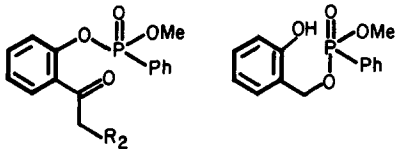
[d] $J_{C\text{-}P}$ (Hz).

[e] $^5J_{CH_3\text{-}P} \sim 0.8$ Hz.

tophenol can reattack the product in an essentially reversible process. Higher yields (60–70%) are obtained for **1e–g** in which case the by-product is triphenyl phosphate (^{31}P NMR δ −20.1 ppm) from reaction of phenol liberated on cyclization. Thus, cyclization of **7b** in the presence of 0.5 equiv phenol gave **1f** plus a large amount of triphenyl phosphate. Triphenyl phosphate is separable from **1e** and **1f** but not **1g** on HPLC (μPorasil, hexane–ethyl acetate 4:1); these compounds were not adequately separated in any TLC system examined. The cyclization reactions of **6a–c** and **7a–c** evident on treatment with base are also prominent under the conditions of CI–MS.

Compounds **2b–d** were prepared in 50 to 80% yields by holding the appropriate phosphorus dichloride with 2-hydroxymethylphenol or 2-(α-hydroxyethyl)phenol in pyridine for 2 hr at 0°C. The products gave appropriate ^{1}H and ^{31}P NMR and CI–MS following purification by crystallization from methanol (**2b** mp 149–150°C and **2c** mp 75–76°C) or column chromatography on silicic acid with dichloromethane (**2d**, oil).

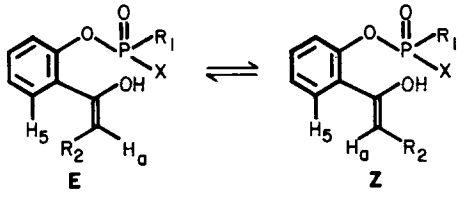
Phenylphosphonates **8** (R_2 = H, Me, and Et) (appropriate ^{1}H and ^{31}P NMR and CI–MS) and **9** (appropriate ^{1}H and ^{31}P NMR) were obtained by reaction of **1b–d** and **2b**, respectively, with methanol containing triethylamine for 1 hr at 25°C and TLC purification (silica gel, hexane–acetone 7:2).



8 **9**

RESULTS AND DISCUSSION

4-Alkylidene derivatives with R_2 = Me or Et might exist in *E* or *Z* forms, yet these derivatives were each a single isomer based on ^{1}H, ^{13}C, and ^{31}P NMR (**1c, d, f,** and **g**) and a single HPLC peak (**1f** and **g**). Proton H_a is coupled to phosphorus via the ^{4}J-^{31}P-^{1}H trans effect (*8*), establishing that **1c, d, f,** and **g** are formed exclusively with the *Z* configuration. A high degree of stereoselectivity is rarely encountered in the synthesis of acyclic enol phosphates (*5, 6, 9*), but in contrast, a stereospecific reaction is involved in the synthesis of **1a** (R_2 = Me or Et) under the basic or thermal conditions discussed above. Formation of an enolate species from **6b** and **c** and **7b** and **c** is a prerequisite for reaction, and the planar enolate must approach coplanarity with the aromatic ring for nucleophilic attack by oxygen at phosphorus. Two equilibrating *E* and *Z* enolates might be envisaged, but clearly only the *Z* enolate can lead to **1c, d, f,** and **g.** Inspection of molecular models reveals that in the *E*-enolate (and potential *E*-product) the vinylic alkyl group (R_2) is juxtapositioned to aromatic H-5, leading to maximum repulsive interaction between the two groups, while in the *Z*-enolate and *Z*-product the R_2-H-5 interaction is minimized. Thus, the observed selectivity can be rationalized on the basis of the *Z*-enolate being the lower energy intermediate.



Several findings are relevant to biological systems. 2-Phenyl-4-alkylidene-1,3,2-benzodioxaphosphorinane 2-oxides (**1b–d**) are phosphorylating agents which react with methanol by cleavage of the P-O-ethenyl linkage to give **8** (R_2 = H, Me, and Et), in contrast to **2b**, which undergoes cleavage at the P-O-aryl bond to give **9** (*2, 3*). Phosphorylation reactions with the enzyme chymotrypsin (Xtr) (inhibitor potency **2b** = **2c** > **2d** > **1b** > **1c** > **1d**) appear to parallel those noted with methanol in respect to the site of initial cleavage. Thus **2b** is cleaved at the P-O-phenyl linkage, since reaction of **2b** with Xtr yields free and bound 2-hydroxymethylphenol plus *O*-(2-hydroxybenzyl) phenylphosphonyl Xtr (*10, 11*). In contrast, **1b** does not yield protein-bound phenolics on inhibition of enzymatic activity, strongly suggesting that phosphorylation involves cleavage of the P-O-ethenyl bond.

Metabolic formation of cyclic phosphorus esters is evident from ^{31}P NMR and/or TLC analysis of acetone extracts of the intestine of rats treated orally with various compounds at 100 mg/kg; i.e., *O*-(2-ethylphenyl) *O,O*-diphenyl phosphate and **7a** yield trace levels of **1e**; *O,O*-di(2-ethylphenyl) phenylphosphonate tentatively gives **2d**; and *O*-(2-methylphenyl) *O,O*-diphenyl phosphate yields **2c**. The latter ^{31}P NMR finding on a sample 3 hr after oral dosing used a direct spectroscopic technique to confirm our earlier study (*2, 3*) on the related tri-2-methylphenyl phosphate. 2-Ethylphenyl phosphorus derivatives can therefore undergo a metabolic reaction sequence consisting of ethylphenyl → α-hydroxyethylphenyl → acetophenyl derivatives, ultimately forming trace levels of **1a** (R_2 = H) or **2a** (R_2 = Me) depending on the intermediate undergoing cyclization. An analogous oxidation sequence is known for tri-4-ethylphenyl phosphate (*12*). The toxicological consequences of these reactions are considered in our earlier reports (*2, 3*) and in an extensive review (*13*).

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