Silyl Phosphites. 6.
Reactions of Tris(trimethylsilyl) Phosphite
## with α-Halocarbonyl Compounds

Sir:

In connection with the continuing studies on the synthesis of unesterified phosphonic acids,[1] our particular interest was focused on the facile conversion of bis(trimethylsilyl) esters of phosphonic acids to the corresponding free acids by simple addition of alcohols. The procedure might provide the convenient synthesis of their derivatives involving acid- or alkali-labile functional groups.

We now wish to report the reactions of 1 with α-halocarbonyl compounds (2a–n) which have not been described to date except for an analogous reaction of bis(trimethylsilyl) hypophosphite with chloroacetone reported by Pudovic and his co-workers.[2]

It is well recognized that trialkyl phosphites react with α-halocarbonyl compounds to give enol phosphates (Perkow reaction) and/or phosphonates (Arbuzov reaction) depending on the nature of the compounds and the reaction conditions employed.[3] A typical example appeared in the literature reported by Kirby.[3c] In contrast to the results, however, when 1 was allowed to react with chloroacetone (2a) in dry THF, an oily product (bp 102–103 °C (0.45 mmHg)) distilled was neither 3a nor 4a expected from Arbuzov or Perkow reaction, but bis(trimethylsilyl) 1-methyl-1-trimethylsilyloxy-2-chloroethylphosphonate (5a) obtained in an excellent yield of 92%

Scheme I
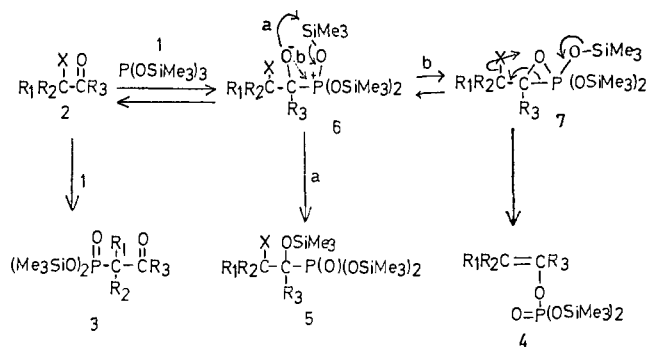
(Scheme 1). The structure of 5a was confirmed by its NMR and IR spectra.[4] The use of bromoacetone (2b) or mesyloxyacetone (2c), substituted with a stronger leaving group, also gave the corresponding carbonyl adduct (5b or 5c) in 92% yield each, while the reactions of trialkyl phosphites or triphenylphosphines with these reactive ketones were known to give

predominantly Arbuzov reaction products.[5] Next, 1 was allowed to react with a disubstituted α-choloro ketone (2d), with a trisubstituted cyclic α-chloro ketone (2e), and with two kinds of α-chloroaldehydes (2f and 2g). These α-halocarbonyl compounds usually gave the exclusive formation of Perkow reaction products when employed in the reactions with trialkyl phosphites.[3c] However, even in the case of the reactions of 1 with 2d–g, similar adducts (5d–g) were obtained in excellent yields. On the other hand, when 1 was employed to react with phenacyl chloride (2h), a Perkow reaction product (4h) was obtained in 74% yield under the same condition as mentioned in the above experiments. When phenacyl bromide (2i) was used in place of 2h, 4h and an Azbuzov reaction product (3h) were obtained as a mixture in 61 and 14% yields, respectively. Next, the reactions of 1 with ethyl chloroacetate (2k) and with ethyl bromoacetate (2l) were examined. It was found that 2k did not react sufficiently with 1 at room temperature, but, when 2k was allowed to react with 1 under reflux, the reaction proceeded to give an Arbuzov reaction product (3k) in 66% yield, while 2l reacted even at room temperature with 1 to afford only 3k in 84% yield.

Borowitz[6] has recently proposed a mechanism of the Perkow reaction involving initial attack of a trialkyl phosphite on the carbonyl carbon. It is suggested that *the isolation of several carbonyl adducts described here indicates the trapping of the initially formed intermediate* (6) *discussed by Borowitz* due to the rapid intermolecular rearrangement of a trimethylsilyl group of 6 to its oxygen anion via a five-membered transition state as described in Scheme I.

It is plausible that the ordinary Perkow and/or Arbuzov reactions in the case of 2h, 2i, 2m, and 2n proceed as a result of the predominant cleavage of P–C bond of the intermediate 7 in equilibrium with 6. The equilibria are affected by electron-withdrawing groups such as phenyl and ethoxycarbonyl groups (Perkow reaction) or relatively reactive halogen atoms (bromine) which make the direct displacement reaction possible, compared with those of alkyl-substituted α-halocarbonyl compounds 2a–h (Arbuzov reaction). The effect of a substituent adjacent to the carbonyl group was clearly elucidated from the fact that, when *p*-bromophenacyl chloride (2j), which has a stronger electron-withdrawing group, was used instead of 2i, the ratio of Perkow to Arbuzov reaction products increased from 4.4 to 10.0. The following results illustrate features of the reactions described here. When 5a was treated with
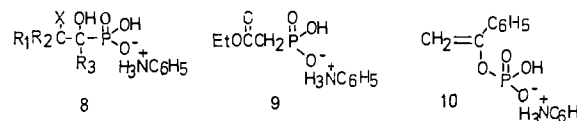

Table I. Reactions of 1 with α-Halocarbonyl Compounds[a]

					Yield, %			
2	R₁	R₂	R₃	X	3	4	5	Bp, C° (mmHg)
a	H	H	CH₃	Cl			97	102–103 (0.18)
b	H	H	CH₃	Br			89	104–107 (0.25)
c	H	H	CH₃	OSO₂Me			92	143–146 (0.12)
d	CH₃	H	CH₃	Cl			92	109–110 (0.13)
e	CH₃	(CH₂)₄		Cl			82	87–110 (0.23)
f	CH₃	H	H	Cl			92	102–103 (0.45)
g	CH₃	CH₃	H	Cl			92	104–105 (0.30)
h	H	H	C₆H₅	Cl		74		134–135 (0.25)
i	H	H	C₆H₅	Br	14	61		80–126 (0.30)
j	H	H	4-BrC₆H₅	Br	7	70		142–155 (0.19)
k	H	H	OEt	Cl	66			90–93 (0.10)
l	H	H	OEt	Br	84			92–97 (0.10)
m	H	H	COOEt	Cl		19	57	115–129 (0.31)
n	H	H	COOEt	Br		36	31	95–130 (0.35)

[a] All of the reactions were carried out in dry tetrahydrofuran for 3 h except in the case of the reaction of 1 with 2k (under reflux).

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ethanol (3 equiv) and aniline (2 equiv) in ether, a monoanilinium salt of 1-hydroxy-1-methyl-2-chloroethylphosphonic acid (**8a**) was obtained in 99% yield (**8a**, mp 156–157 °C). In a similar manner, **8b** and **8f** were obtained in 98 and 87% yields, respectively. Therefore, the reactions of **1** with alkyl-substituted α-halocarbonyl compounds provide the first method[7] for the synthesis of free 1-hydroxy-2-haloalkylphosphonic acids. However, from **2c, 2d**, and **2g**, the desired products were obtained only as crude materials because of the difficult separation from simultaneously formed by-products. From **3k**, a newly classified half ester, a monoanilinium salt of ethoxycarbonylmethylphosphonic acid (**9**) was obtained in 94% yield (**9**, mp 136–137 °C). Furthermore, it was of particular interest that *a quite unstable enolphosphate* (**10**) *was for the first time isolated as the crystalline form* from **4h** in 81% yield by treatment of **4h** with aniline-containing ethanol at room temperature for 2.5 h. Finally, it was shown that the carbonyl adducts could be converted to bis(trimethylsilyl) esters of 1,2-epoxyalkylphosphonic acids by treatment with sodium methoxide in methanol followed by retrimethylsilylation with trimethylsilyl chloride in dry THF. Thus, for instance, bis(trimethylsilyl) 1-methyl-1,2-epoxyethylphosphonate (**11**) bp (68–77 °C (0.10–0.12 mmHg)) was obtained from **5a** in 58% yield. **11** was readily converted to the corresponding free salt (**12**) (mp 126–127 °C).

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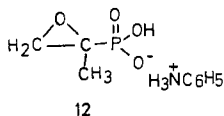
This facile conversion of 1-silyloxy-2-halo-alkylphosphonates to 1,2-epoxyalkylphosphonates reported here is noteworthy in the context of interest in the synthesis of such free epoxyalkylphosphonates[8] following discovery of a naturally occurring free epoxyalkylphosphonate, phosphonomycin,[9] which is a wide-spectrum antibiotic.

Extensions of this work are now in progress.

References and Notes

(1) (a) M. Sekine, I. Yamamoto, A. Hashizume, and T. Hata, *Chem. Lett.*, 485 (1977). For the reactions using **1**, see the following: (b) T. Hata and M. Sekine, *J. Am. Chem. Soc.*, **96**, 7363 (1974); (c) T. Hata and M. Sekine, *Tetrahedron Lett.*, 3943 (1974); (d) M. Sekine and T. Hata, *ibid.*, 1711 (1975); (e) T. Hata, M. Sekine, and N. Kagawa, *Chem. Lett.*, 635 (1975); (f) T. Hata, M. Sekine, and N. Ishikawa, *ibid.*, 645 (1975); (g) T. Hata, I. Yamamoto, and M. Sekine, *ibid.*, 601 (1976).
(2) A. N. Pudovic, G. V. Romanov, and R. Ya. Nazmutdinov, *Zh. Obshch. Khim.*, **44**, 221 (1974).
(3) (a) G. M. Kosolapoff, *Org. React.*, **6**, 273 (1951); (b) F. W. Lichtenthaler, *Chem. Rev.*, **61**, 607 (1961); (c) P. A. Chopard, V. M. Clark, R. F. Hudson, and A. J. Kirby, *Tetrahedron*, **21**, 1961 (1965).
(4) In our early work,[1e] the product from the reaction of **1** with **2a** was reported as the enolphosphate **4a** (the structure is now corrected as described in the text): NMR (CDCl₃) δ 0.22 (s, 9 H, CH₃SiOC), 0.33 (s, 18 H, CH₃SiOP), 1.37 (d, 3 H, J_{H-P} = 16 Hz, CH₃CP), 3.58 (d, J_{H-P} = 5 Hz, ClCH₂CP); IR (no absorption at 1600–1800 cm⁻¹).
(5) (a) H. Hoffmann and H. J. Diehr, *Angew. Chem., Int. Ed. Engl.*, **3**, 737 (1964); (b) I. J. Borowitz, P. E. Rusek, and R. Virkhaus, *J. Org. Chem.*, **34**, 1595 (1969); see also ref 3c.
(6) (a) I. J. Borowitz, S. Firstenberg, E. W. R. Casper, and R. K. Crouch, *J. Org. Chem.*, **36**, 3282 (1971). (b) I. J. Borowitz, S. Firstenber, G. B. Borowitz, and D. Schuessler, *J. Am. Chem Soc.*, **94**, 1623 (1972). A recent report on Perkow reaction appeared in the following: (c) E. M. Gaydov and J. P. Bianchini, *Can. J. Chem.*, **54**, 3626 (1976).
(7) In principle, there are two possible ways that **8** can be obtained: by hydrolysis from dialkyl esters of **8** obtained by the reactions of alkyl-substituted α-halocarbonyl compounds with trialkyl phosphites in the presence of alcohols³ or by the reactions of sodium dialkylphosphonates with **2** followed by neutralization. For example, see the following: V. S. Abramov and R. N. Savintseva, *Khim. Org. Soedin. Fosfora*, 129 (1967); *Chem. Abstr.*, **69**, 67465 (1968). However, there are great disadvantages in that the yields of dialkyl esters are relatively low and decomposition occurs during acid or alkaline hydrolysis.
(8) (a) C. E. Griffen and S. K. Kundu, *J. Org. Chem.*, **34**, 1532 (1969); (b) E. J. Glamkowski, G. Gal, R. Durick, A. J. Davidson, and M. Sletzinger, *ibid.*, **35**, 3510 (1970); (c) D. G. Smith and D. J. H. Smith, *Tetrahedron Lett.*, 1249 (1973); (d) H. M. R. Hoffmann and M. N. Iqbal, *ibid.*, 4487 (1975).
(9) (a) D. Hendlin, E. O. Stapley, M. Jackson, H. Wallick, A. K. Miller, F. J. Wolf, T. W. Muller, L. Chaiet, F. M. Kahan, E. L. Foltz, H. B. Woodruff, J. M. Mata, S. Hernandez, and S. Mochales, *Science*, **166**, 122 (1969); (b) B. G. Christensen, W. J. Leanza, T. R. Beattie, A. A. Patchett, B. H. Arison, R. E. Ormond, F. A. Kuehl, Jr. G. A. Schonberg, and O. Jardetzky, *ibid.*, **166**, 123 (1969).

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Tridachione, a Propionate-Derived Metabolite of the Opisthobranch Mollusc *Tridachiella diomedea*

Sir:

As part of a research program to study the relationship between the secondary metabolites of opisthobranch molluscs and dietary constituents,[1] we have investigated the secondary metabolites of *Tridachiella diomedea* (Bergh), commonly known as the Mexican Dancer.[2] *Tridachiella* was of particular interest because it is one of a group of sacoglossans which contain functional chloroplasts derived from siphonous marine algae.[3] In this communication we wish to report the structural elucidation of tridachione (**1**), the major secondary metabolite of *T. diomedea*.
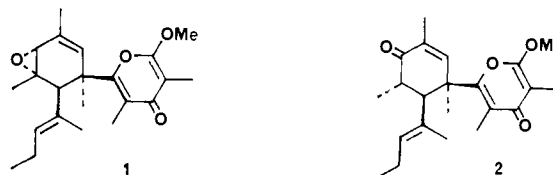
The ether-soluble fraction of acetone extracts of homogenized *T. diomedea* was chromatographed on silica gel to obtain tridachione (**1**) as a colorless oil (~1 mg per animal). Trichachione (**1**), $C_{22}H_{30}O_4$, gave the following spectral data: IR 1660, 1590 cm⁻; UV 257 nm (ε 6000); ¹H NMR (CDCl₃) δ 0.68 (t, 3 H, *J* = 7 Hz), 1.32 (s, 3 H), 1.36 (s, 3 H), 1.60 (s, 3 H), 1.80 (s, 3 H), 2.01 (s, 3 H), 2.07 (s, 3 H), 2.91 (s, 1 H), 3.11 (s, 1 H), 3.93 (s, 3 H), 5.18 (t, 1 H, *J* = 7 Hz), 6.00 (s, 1 H); ¹³C NMR (CDCl₃) 181.1 (s), 161.0 (s), 160.1 (s), 132.5 (s), 131.6 (d), 129.0 (d), 128.5 (s), 118.4 (s), 97.8 (s), 60.5 (s), 57.6 (q), 55.3 (s), 54.7 (d), 46.7 (d), 31.2 (t), 21.8 (q), 21.5 (q), 20.2 (q), 12.9 (q), 12.0 (q), 11.6 (q), 6.1 (q) ppm. The presence of eight methyl groups in a molecule containing only 22 carbon atoms indicated that **1** had a novel carbon skeleton.

The paucity of coupling between signals in the ¹H NMR spectrum prevented structural elucidation by interpretation of spectral data. Fortunately, treatment of **1** with boron trifluoride etherate in dry ether at 0 °C gave a crystalline isomeric diketone **2**: mp 194–197 °C; IR 1650, 1590 cm⁻¹; UV 251, 240 nm; ¹H NMR (CDCl₃) δ 0.98 (t, 3 H, *J* = 7 Hz), 1.00 (d, 3 H, *J* = 7 Hz), 1.25 (s, 3 H), 1.57 (s, 3 H), 1.84 (s, 3 H), 1.88 (s, 3 H), 2.06 (m, 2 H), 2.07 (s, 3 H), 2.43 (d, 1 H, *J* = 12 Hz), 2.65 (m, 1 H), 3.82 (s, 3 H), 5.36 (t, 1 H, *J* = 7 Hz), 6.50 (s, 1 H).

The structure of the rearranged product **2** was clarified with a single crystal x-ray diffraction experiment. The diketone **2** crystallized in the orthorhombic crystal class with cell constants, determined by a least-squares fitting of 15 moderate angle reflections, of *a* = 7.821 (2), *b* = 12.880 (3), and *c* = 20.359 (5) Å. Systematic extinctions and the known chirality required space group $P2_12_12_1$ and an observed density of ~1.16 g/cm³ indicated one molecule of $C_{22}H_{30}O_4$ per asymmetric unit. All unique diffraction maxima with $2\theta \leq 114°$ were collected on a computer-controlled four-circle diffractometer using graphite monochromated Cu Kα (1.54178 Å) x-rays. Of the 1637 maxima surveyed, 1342 (82%) were considered