Reaction of Dimethyl 1-Hydroxyalkylphosphonates with Some Chlorides[1)]

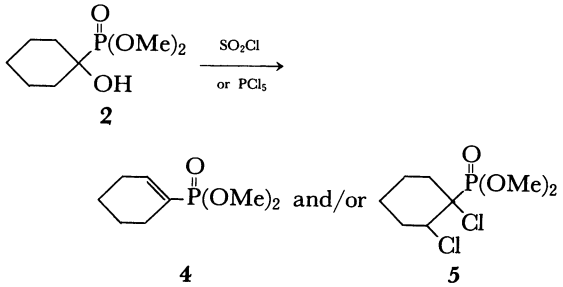
Mitsuji YAMASHITA,* Takashi MORIZANE, Keiji FUJITA, Kaname NAKATANI, and Saburo INOKAWA†
Department of Applied Chemistry, Faculty of Engineering, Shizuoka University, Hamamatsu 432
†Department of Chemistry, Faculty of Science, Okayama University, Okayama 700
(Received May 30, 1986)

Synopsis. The reactions of dimethyl 1-hydroxycycloalkylphosphonates having a five- to seven-membered ring with sulfuryl chloride and phosphorus pentachloride afforded olefinic and/or dichloro derivatives of phosphonates. The mechanism of the formation of new dichloro derivatives and the reactions of dimethyl 1-methylethylphosphonate with sulfuryl chloride and phosphorus pentachloride were also investigated.

A carbon-phosphorus bond formation is the key step for the preparation of a phosphorus sugar, a sugar analogue having a phosphorus atom in the hemiacetal ring.[2)] Addition of a P-H group of phosphorus compounds to carbonyl group is well-known to give α-hydroxy phosphorus compounds;[3,4)] the reactivity is dependent on the structures of carbonyl compounds, and α-hydroxy phosphorus compounds from aldehydes and ketones give α-halo- and α,β-unsaturated phosphorus compounds, respectively.[5)] Facile formation of α-carbocations from mesylate derivatives of diethyl 1-hydroxyalkylphosphonates are attributable to the potent electron-withdrawing power of the phosphoryl group.[6)] On the other hand, chloro derivatives of phosphonates such as dimethyl 1-hydroxy-2,2,2-trichloroethylphosphonate are biologically active substances (e.g., insecticides).[7)] This note deals with the reaction of cyclic α-hydroxy phosphonates with sulfuryl chloride and phosphorus pentachloride, known as chlorination or dichlorination reagents,[8-11)] as well as that of an acyclic homologue.

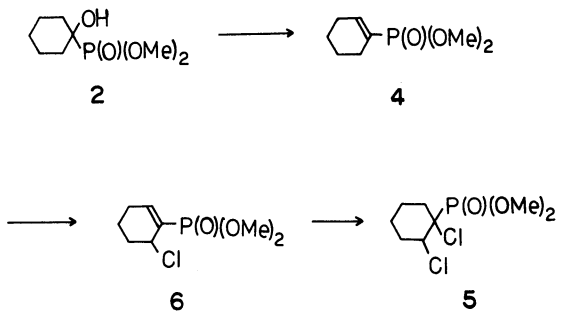
Results and Discussion

Cyclic α-hydroxy phosphonates (**1**—**3**) each having a five to seven-membered ring were prepared by the reaction of cyclic ketones with dimethyl phosphonate in the presence of triethylamine or sodium methoxide.[12)] The reaction of dimethyl 1-hydroxycyclohexylphosphonate (**2**) with sulfuryl chloride in benzene for 8 h at room temperature in the presence of an equivalent amount of pyridine gave dimethyl 1-cyclohexylphosphonate (**4**) in 6% yield and dimethyl 1,2-dichlorocyclohexylphosphonate (**5**) in 58% yield. In the presence of excess amount of pyridine at 50 °C **2** gave 1-cyclohexenylphosphonate **4** in 51% yield, when treated with sulfuryl chloride. Since elimination of chlorine from **5** does not proceed at 50 °C, **4** seems to be formed via **2**, as indicated by the reaction of α-hydroxy phosphonates with thionyl chloride.[5)] In contrast, the reaction of **2** with phosphorus pentachloride gave **4** in quantitative yield.



Reaction of dimethyl 1-hydroxycyclopentylphosphonate (**1**) with sulfuryl chloride or phosphorus pentachloride gave the corresponding 1,2-dichloro derivative (**8**) in 58% yield, or the olefin (**9**) in 49% yield. These results together with those for dimethyl 1-hydroxycycloheptyl- and 1-hydroxy-1-methylethylphosphonates (**3** and **12**) are summarized in Table 1. Dichlorination of cyclohexenones and ethylenic compounds and dehydration of sugar derivatives with sulfuryl chloride are known,[9,13,14)] however, the reaction of phosphonates presented here (Table 1) should be attributable to the activation by a phosphoryl group,[15)] whose powerful electron-withdrawing nature is typically shown by the σ_p (0.52) and σ^+ (0.505) values for the diethylphosphoryl group[6,16)] as well as the high reactivity of Horner-Emmons reaction.[17)]

The reaction of **4** with sulfuryl chloride in the presence of excess or equivalent amount of pyridine afforded monochloride **6** or dichloride **5** in 43 or 60% yield, respectively. Compound **6** was also prepared by treatment of **4** with NCS in 93% yield, while the bromo derivative (**7**) was prepared by the analogous reaction with NBS in quantitative yield. With sulfuryl chloride in the presence of equivalent amount of pyridine **6** afforded dichloride **5** in 79% yield. These findings suggest that the formation of dichloride **5** would proceed via intermediates **4** and **6** as shown in Scheme 1. The amount of pyridine suppressed the production of the dichloride, which may presumably be formed by addition of hydrogen chloride to the olefin.

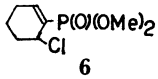
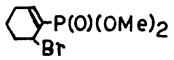
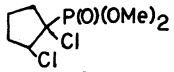
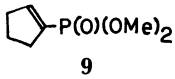
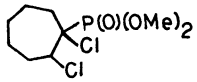
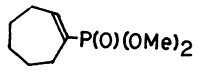
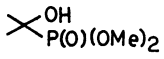
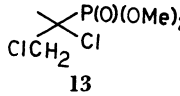
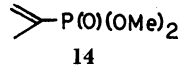


Scheme 1. Plausible mechanism for the reaction of compound **2** with sulfuryl chloride to form dichloro derivative **5**.

Experimental

Measurements. ^{1}H NMR spectra were measured on Hita-

Table 1. Reaction of α-Hydroxy Phosphonates with Some Halogenation Reagents

Substrate	Reaction condition			Product	
	Reagent	Time/h	Temperature/°C		Yield/%
2	SO_2Cl_2/Pyridine (excess)	18	50	**4**	51
	SO_2Cl_2/Pyridine (equivalent)	8	50	**4**	6
				5	58
	PCl_5	0.5	Room temp	**4**	100
4	SO_2Cl_2/Pyridine (excess)	8	50	 **6**	43
	N-Chlorosuccinimide (NCS)	5	60	**6**	93
	N-Bromosuccinimide (NBS)	5	60	 **7**	100
	SO_2Cl_2/Pyridine (equivalent)	8	50	**5**	60
6	SO_2Cl_2/Pyridine (equivalent)	8	50	**5**	79
1	SO_2Cl_2/Pyridine (equivalent)	20	50	 **8**	58
	PCl_5	1	Room temp	 **9**	49
3	SO_2Cl_2/Pyridine (equivalent)	20	50	 **10**	35
	PCl_5	1	Room temp	 **11**	37
 **12**	SO_2Cl_2/Pyridine (equivalent)	8	50	 **13**	27
	PCl_5	0.5	Room temp	 **14**	76

chi R-24 (60 MHz) or R-20 (60 MHz) spectrometer with tetramethylsilane as an internal standard. IR spectra were recorded with Japan Spectroscopic Co., Ltd. A-3 infrared spectrometer. MS spectra were measured by Hitachi RMU 7M GC-MS spectrometer.

Reaction of Dimethyl 1-Hydroxycyclohexylphosphonate (2) with Sulfuryl Chloride. To a solution of compound **2** (4.87 g, 23.4 mmol) in benzene (6 ml) and pyridine (1.85 g) was added sulfuryl chloride (1.89 ml), then the mixture was stirred for 8 h at 50 °C. The product was extracted with diethyl ether and the organic layer was washed with water and dried over anhydrous magnesium sulfate. Evaporation of the solvent in vacuo followed by chromatography on silica gel and recrystallization from carbon tetrachloride gave 1,2-dichlorocyclohexylphosphonate **5** (3.5 g, 58%), mp 76—77 °C, as well as dimethyl 1-cyclohexenylphosphonate (**4**, 0.27 g, 6%). Spectral data for **4**: ^{1}H NMR ($CDCl_3$) δ=1.4—2.5 (m, 8H, C_6H_8), 3.68 (d, 6H, J_{HP}=11.1 Hz, 2OMe), and 6.75 (dt, 1H, J_{HP}=22.2 Hz, J_{HH}=1.2 Hz, CH=CP); IR (neat) 1637 (C=C), 1238 (P=O), and 1180, 1028 cm^{-1} (P-O-C); MS *m/z*, 190 (M^+). Spectral data for **5**: ^{1}H NMR ($CDCl_3$) δ=1.2—2.3 (m, 8H, C_6H_8), 3.82, 3.88 (2d, 6H, J_{HP}=11.1 Hz, 2OMe), and 4.43 (ddd, 1H, J_{PCCH}=3.9 Hz, $J_{H_{ax}CC(Cl)H_{ax}}$=7.8 Hz, $J_{H_{eq}CC(Cl)H_{ax}}$=3.9 Hz, $CH_{ax}Cl$); IR (KBr) 1250 (P=O), 1186, 1015 (P-O-C), and 740, 691 cm^{-1} (C-Cl); MS *m/z*, 260 (M^+, rel intensity 100%), 262 ($M^+ + 2$, 65%), and 264 (H^+ 4, 9.7%).

Found: C, 36.37; H, 5.91%. Calcd for $C_8H_{15}Cl_2O_3P$: C, 36.80; H, 5.79%.

Reaction of compound **2** (4.00 g) with sulfuryl chloride (1.8 ml) in pyridine (7 ml) for 18 h at 50 °C afforded product **4** (1.86 g, 51%) after work-up and separation by TLC on silica gel.

Reaction of Compound 2 with Phosphorus Pentachloride. To a solution of compound **2** (3.01 g, 14.5 mmol) in benzene (8 ml) was added phosphorus pentachloride (3.50 g, 14.5 mmol) with stirring, and the mixture was then stand for 10 h at room temperature. The reaction mixture was poured into ice-water (50 ml) and extracted with chloroform (total 50 ml). The extract was washed with sodium hydrogencarbonate and water, and dried over anhydrous magnesium sulfate. Removal of the solvent in vacuo gave product **4** (2.75 g, quantitative).

Reaction of Dimethyl 1-Hydroxycyclopenthylphosphonate (1) or Dimethyl 1-Hydroxycycloheptylphosphonate (3) with Sulfuryl Chloride. Reaction of compound **1** or **3** with sulfuryl chloride in the presence of an equivalent amount of pyridine afforded the corresponding dichloride, dimethyl 1,2-dichlorocyclopentylphosphonate (**8**) or dimethyl 1,2-dichlorocycloheptylphosphonate (**10**) in 58 or 35% yield, respectively (Table 1). Spectral data for **8**: ^{1}H NMR ($CDCl_3$) δ=1.9—3.0 (m, 6H, C_5H_6), 3.98, 4.03 (2d, 6H, J_{HP}=10.2 Hz, 2OMe), and 4.4—4.7 (m, 1H, CHCl); MS *m/z*, 246 (M^+), 248

(M^+ +2), and 250 (M^+ +4). Spectral data for **10**: ^{1}H NMR ($CDCl_3$) δ=1.0—3.5 (m, 10H, C_7H_{10}), 3.37, 3.49 (2d, 6H, J_{HP}=10.1 Hz, 2OMe), and 4.4—4.8 (m, 1H, CHCl); MS *m/z*, 278 (M^+), 280 (M^+ +2), and 282 (M^+ +4).

Reaction of Compound 1 or 3 with Phosphorus Pentachloride. Reaction of compound **1** or **3** with phosphorus pentachloride gave the corresponding olefinic product, dimethyl 1-cyclopentenylphosphonate (**9**) or dimethyl 1-cycloheptenylphosphonate (**11**) in 49 or 37% yield, respectively. Spectral data for **9**: ^{1}H NMR ($CDCl_3$) δ=1.3—3.0 (m, 6H, C_5H_6), 3.82 (d, 6H, J_{HP}=15.8 Hz, 2OMe), and 6.75 (dt, 1H, J_{PCCH}=14.3 Hz, J_{HH}=2.0 Hz, CH=CP). Spectral data for **11**: ^{1}H NMR ($CDCl_3$) δ=1.3—2.2 (m, 10H, C_7H_{10}), 3.68 (d, 6H, J_{HP}=10.8 Hz, 2OMe), and 6.98 (dt, 1H, J_{PCCH}=24.3 Hz, J_{HH}=6.5 Hz).

Reaction of Compound 4 with Sulfuryl Chloride. Reaction of compound **4** (0.48 g, 2.5 mmol) with sulfuryl chloride (0.34 g, 2.5 mmol) in pyridine (0.19 ml, equivalent)-benzene (1 ml) or in pyridine (2 ml, excess) for 8 h at 50 °C afforded product **5** or **6** in 60 or 43% yield, respectively. Spectral data for **6**: ^{1}H NMR ($CDCl_3$) δ=1.2—2.4 (m, 6H, ring protons), 3.70 (d, 6H, J_{HP}=10.4 Hz, 2OMe), 4.0—4.6 (m, 1H, CHCl), and 6.67 (dt, 1H, J_{PCCH}=22.7 Hz, J_{HH}=1.7 Hz, CH=CP); IR (neat) 1230 (P=O), 1190, 1018 (P-O-C), and 735, 600 cm^{-1} (C-Cl); MS *m/z*, 224 (M^+, 100%) and 226 (M^+ +2, 29%).

Reaction of Compound 4 with *N*-Chlorosuccinimide (NCS) or *N*-Bromosuccinimide (NBS). Reaction of compound **4** (2.0 mmol) with NCS or NBS (2.0 mmol) was carried out in carbon tetrachloride (2 ml) for 5 h at 60 °C. Usual work-up of the reaction mixture afforded chloride **6** or bromide **7** in 93% or quantitative yield, respectively. Spectral data for **7**: ^{1}H NMR ($CDCl_3$) δ=1.3—2.7 (m, 6H, ring protons), 3.74 (d, 6H, J_{HP}=10.0 Hz, 2OMe), 4.3—5.1 (m, 1H, CHBr), and 6.83 (dt, 1H, J_{PCCH}=20.0 Hz, J_{HH}=1.3 Hz, CH=CP); IR (neat) 1240 (P=O), 1190, 1040 (P-O-C), and 580 cm^{-1} (C-Br); MS *m/z*, 268 (M^+, 100%) and 270 (M^+ +2, 91%).

Reaction of Compound 6 with Sulfuryl Chloride. Reaction of compound **6** (49 mg, 0.22 mmol) with sulfuryl chloride (30 mg, 0.22 mmol) in pyridine (25 μl, equivalent)-benzene (1 ml) for 8 h at 50 °C afforded product 5 (45 mg, 79%).

Reaction of Dimethyl 1-Hydroxy-1-methylethylphosphonate (12). Reaction of compound **12** (0.84 g, 5.0 mmol) with sulfuryl chloride or with phosphorus pentachloride afforded dimethyl 1,2-dichloro-1-methylethylphosphonate (**13**, 0.18 g, 27%) or dimethyl 1-methylvinylphosphonate (**14**, 0.57 g, 76%), respectively. Spectral data for compound **13**: ^{1}H NMR ($CDCl_3$) δ=1.73 (d, 3H, J_{HP}=15.0 Hz, PCMe), 3.69 (d, 2H, J_{HP}=15.0 Hz, $PCCH_2$), and 3.81 (d, 6H, J_{HP}=10.6 Hz, 2POMe); IR (neat) 1260 (P=O), 1040 (P-O-C), and 760, 602 cm^{-1} (C-Cl); MS *m/z*, 220 (M^+, 100%), 222 (M^+ +2, 54%) and 224 (M^+ 4, 19%). Spectral data for compound **14**; ^{1}H NMR ($CDCl_3$) δ=1.95 (ddd, 3H, J_{HP}=14.0 Hz, J_{HH}=1.7 Hz, J_{HH}=1.3 Hz, PCMe), 3.71 (d, 6H, J_{HP}=10.8 Hz, 2POMe), 5.80 (ddq, 1H, J_{HP}=47.0 Hz, J_{HH}=1.7 Hz, J_{HH}=1.3 Hz, $PC=CH_{(trans)}$), 5.97 (ddq, 1H, J_{HP}=22.7 Hz, J_{HH}=1.7 Hz, J_{HH}=1.3 Hz, $PC=CH_{(cis)}$); IR (neat) 1250 (P=O), 1040 cm^{-1} (P-O-C); MS *m/z*, 150 (M^+).

References

1) M. Yamashita, T. Morizane, K. Fujita, K. Nakatani, M. Yamada, H. Yamashita, T. Oshikawa, and S. Inokawa, 13th Annual Meeting of Chubu Kagaku Kankei Gakukyokai Shibu Rengo Shuki Taikai, Tsu, September 1982, Abstr., No. 2G04.

2) M. Yamashita, Y. Nakatsukasa, H. Yoshida, T. Ogata, and S. Inokawa, *Carbohydr. Res.*, **70**, 247 (1979).

3) A. J. Kirby and S. G. Warren, "The Organic Chemistry of Phosphorus," Elsevier, Amsterdam (1967), pp. 54, 57.

4) M. Yamashita, P. T. Long, M. Shibata, and S. Inokawa, *Carbohydr. Res.*, **84**, 35 (1980).

5) K. Gomyo, H. Yoshida, T. Ogata, H. Inokawa, and S. Inokawa, *Nippon Kagaku Kaishi*, **1974**, 1093.

6) X. Creary, C. C. Geiger, and K. Hilton, *J. Am. Chem. Soc.*, **105**, 2851 (1983).

7) J. Emsley and D. Hall, "The Chemistry of Phosphorus," Harper and Row, London (1976), Chap. 12.

8) A. Mooradian and J. B. Cloke, *J. Am. Chem. Soc.*, **68**, 785 (1946).

9) M. S. Kharasch and H. C. Brown, *J. Am. Chem. Soc.*, **61**, 2142 (1939); M. S. Kharasch and H. C. Brown, *ibid.*, **61**, 3432 (1939).

10) D. P. Wyman and P.R. Kaufman, *J. Org. Chem.*, **29**, 1956 (1964).

11) D. P. Wyman, J. Y. C. Wang, and W. R. Freeman, *J. Org. Chem.*, **28**, 3173 (1963).

12) V. S. Abramov, *Dokl. Akad. Nauk SSSR*, **95**, 991 (1954); *Chem. Abstr.*, **49**, 6084d (1955).

13) M. F. Grenier-Loustalot, P. Iratcabal, and F. Metras, *Synthesis*, **1976**, 33.

14) J. Cleophax, J. Leboul, D. Mercier, A. Gaudemer, S. D. Gero, *Bull. Soc. Chim. Fr.*, **1973**, 2992; *Chem. Abstr.*, **80**, 95328b (1974).

15) M. Yamashita, K. Tsunekawa, M. Sugiura, T. Oshikawa, and S. Inokawa, *Chem. Lett.*, **1983**, 1673.

16) E. N. Tsvetkov, D. I. Lobanov, L. A. Isosenkova, and M. I. Kabachnik, *J. Gen. Chem. USSR*, **39**, 2126 (1969).

17) J. C. Stowell, "Carbanions in Organic Synthesis," John Wiley, New York (1979), p. 182.