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Reactions of 2-Phospholene 1-Oxides with Bromine in Some Media: Facile Preparation of Bromohydrin Derivatives of 2-Phospholenes

Mitsuji Yamashita,* Akihito Iida, Hiroyuki Mizuno, Yasushi Miyamoto, Toru Morishita, Naoaki Sata, Kenji Kiguchi, Akihiro Yabui, and Tatsuo Oshikawa

Department of Applied Chemistry, Faculty of Engineering, Shizuoka University, Hamamatsu 432, Japan

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ABSTRACT

Reactions of 1-phenyl- and 1-methoxy-2-phospholene 1-oxides with bromine in aqueous organic solvents or in a protic medium, such as methanol, easily afforded the corresponding 2-bromo-3-hydroxy- or 2-bromo-3-methoxyphospholane 1-oxide derivatives. The reaction mechanism was postulated based on the stereochemistry of the products.

INTRODUCTION

Cycloaddition reactions of conjugated dienes with phosphorus halides were first reported by McCormack in 1953 [1]. Since Quin's studies on the structure of the adducts in 1968 [2,3], some reports concerning stereochemistry, ozonolysis, reaction with a carbene, photochemistry, and other reactions of the phospholenes have been published [4–7]. We previously reported the synthesis of tetrofuranose derivatives of phosphono sugars, which are sugar derivatives having a phosphorus atom instead of an oxygen atom in the hemiacetal ring, from 2-phospholene 1-oxides and showed that the 2-phospholene derivatives were potentially useful precursors for the synthesis of phosphono sugars [8]. The present article deals with the reaction of 2-phospholene 1-oxide derivatives with bromine in an organic solvent-water (either homogeneous or heterogeneous) system or in a protic solvent, such as methanol, to provide a convenient and novel route for the synthesis of bromohydrin derivatives of phospholanes from 2-phospholenes.

RESULTS AND DISCUSSION

1-Phenyl-2-phospholene 1-oxide (**1a**) was prepared by the reaction of phenylphosphonous dichloride with 1,3-butadiene [2]. Strangely, the well-known addition reaction of bromine to an olefin [9] did not smoothly take place in the case of the 2-phospholene **1a** to produce the dibromide [10]. From the reaction of the 2-phospholene **1a** and bromine in carbon tetrachloride or in chloroform for 1 day at 25°C, the phospholene was recovered unchanged from the reaction mixture. Only a very small amount of olefinic proton disappearance was observed by ^{1}H NMR spectral measurements of the reaction mixture. An addition reaction of hydrogen bromide to the 2-phospholene derivative in methanol also did not proceed during a reaction carried out for 1 day at 25°C. Actually, in a heterogeneous solvent system composed of chloroform and water, or in a homogeneous aqueous organic solvent system composed of acetone or THF and water, the 2-phospholene **1a** readily underwent reaction with

*To whom correspondence should be addressed.

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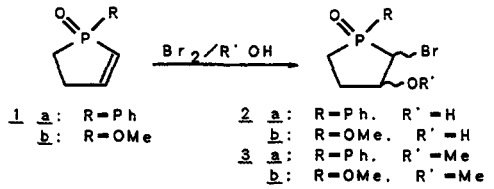
TABLE 1 Reaction of 2-Phospholene 1-Oxides with Bromine in Some Media

2-Phospholene 1-Oxide		*Reaction Conditions*[a]		*Product*		
No.	*R*	*Solvent*	*Time/Day*	*No.*	*R'*	*Yield/%*
1a	Ph	$CHCl_3$-H_2O	1	**2a**	OH	67
1a	Ph	Me_2CO-H_2O	1	**2a**	OH	75
1a	Ph	MeOH	1	**3a**	OMe	97
1b	OMe	$CHCl_3$-H_2O	1	**2b**	OH	98
1b	OMe	THF-H_2O	3	**2b**	OH	55
1b	OMe	MeOH	1	**3b**	OMe	97

[a]Reaction carried out at room temperature.

bromine to afford 2-bromo-3-hydroxy-1-phenylphospholane 1-oxide (**2a**) in good yield (see Table 1 and Scheme 1). When methanol was used as the solvent, **3a** was obtained.

The adduct **2a** showed two peaks (area ratio of the two peaks being 2:1) on silica gel HPLC chromatography. The ^{31}P NMR spectrum also showed two peaks at δ 63.0 and 65.8 in a ratio of 2:1. The results indicate that the adduct consists of diastereomers. The two diastereoisomeric adducts were separated by fractional crystallization from chloroform-carbon tetrachloride into a major component **2aT** (mp 180–183°C) and a minor one **2aE** (mp 136–139°C). From the ^1H NMR spectrum of **2aE**, the chemical shift for the P-C*H*-CH proton was δ = 4.1 and that for the P-CH-C*H* proton was δ = 4.7. These observations, together with the data for some bromohidrin derivatives prepared later, strongly suggested that the bromo substituent was attached to the α carbon atom (2-position) and the hydroxyl group to the β carbon (3-position) to the phosphorus atom of the original phospholene derivative [11]. The ^1H NMR chemical shifts for the P-CHBr-C*H*(OH) protons of **2aT** and **2aE** differed remarkably from each other, and the values were δ = 4.7 and 4.4, respectively. The IR spectra of **2aT** and **2aE** showed strong absorptions of the OH group at 3200 and 3250 cm^{-1} (KBr), respectively. The difference of the frequency suggested that the former isomer was subjected to intramolecular hydrogen bonding involving the OH group at the 3-position [12]. The



SCHEME 1 Reaction of 2-phospholene 1-oxides with bromine.

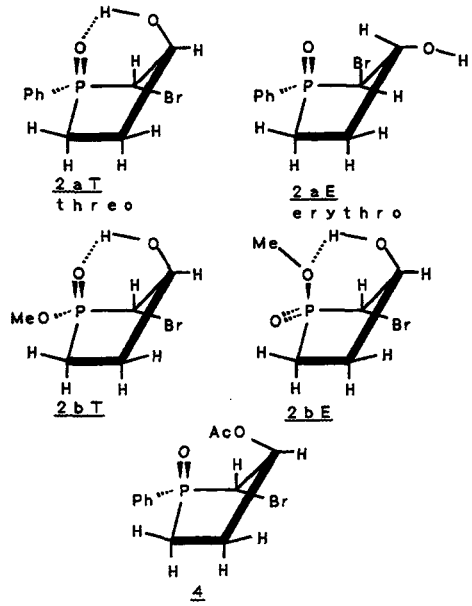


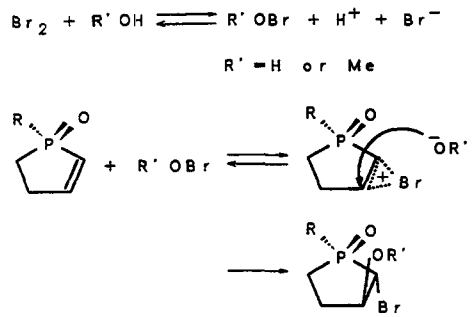
FIGURE 1 Structures of bromohydrins **2a,b** and **4**.

IR absorption of the OH group in solution was observed at 3220 and 3380 cm^{-1} ($CDCl_3$) for **2aT** and **2aE**, respectively.

Acetylation of **2aT** afforded 3-acetoxy-2-bromo-1-phenylphospholane 1-oxide (**4**) [13], whose coupling constants for the P-CHBr proton at δ = 4.15 of its ^1H NMR spectrum were $^2J_{PH}$ = 10.6 and $^3J_{HH}$ = 7.1 Hz. These values suggest that the oxygen of the phosphoryl group and the hydrogen at the 2-position are *cis* and the two hydrogens at the 2- and 3-positions are *trans* to each other (Figure 1) [14]. Thus, a *trans* addition of Br and OH had occurred. Therefore, it follows that the major isomer was *threo* **2aT** and the minor one *erythro* **2aE** [11,15].

1-Methoxy-2-phospholene 1-oxide (**1b**) reacted with bromine in an aqueous organic solvent system to afford adduct **2b** under the same reaction conditions as those for the formation of **1a**. The ^1H NMR spectrum of **2b** showed a pair of singlets for MeO protons in the ratio of 6:5. The lower stereoselectivity observed in the addition reaction of bromine to **1b** (isomer ratio = 6:5) than in that to **1a** (isomer ratio = 2:1) may be attributable to the relative degree of steric hindrance of the substituent on the phosphorus atom of the 2-phospholenes, i.e., Ph > OMe. The added stability caused by hydrogen bonding of the 3-OH and the oxygen atom of the phosphoryl group (P = O) may also affect the ratio (see **2aE**, **2aT**, **2bE**, and **2bT** in Figure 1) of diastereomers formed [16]. Stabilization by hydrogen bonding may be expected in **2aT**, **2bE**, and **2bT** but not in **2aE**; therefore, the relative amounts of diastereomers formed should be **2aT** > **2aE** and **2bT** ~ **2bE**.

Reaction of bromine with **1a** proceeded



SCHEME 2 A plausible mechanism for the reactions of 2-phospholene 1-oxides with bromine in protic media.

smoothly in methanol at room temperature to afford 2-bromo-3-methoxy-1-phenylphospholane 1-oxide (**3a**). The ^{1}H NMR spectrum obtained for **3a** showed a pair of doublets for the 3-OMe protons in a ratio of ca. 5:6. The observed nonstereoselectivity in the reaction of **1a** with bromine in methanol reflects the absence of added stability by hydrogen bonding in the 3-methoxyphospholane derivative formed.

The stereochemistry of addition of bromine to olefins is well established [9,17]. According to the reported mechanism, formation of a cyclic bromonium ion intermediate is achieved in the rate controlling step through mobile pre-equilibrium association of olefin and bromine, and then the intermediate is attacked by the nucleophilic bromide ion. Even if a similar mechanism is plausible for the present reaction, the bromonium intermediate formed may be destabilized by the presence of the powerful electron withdrawing phosphoryl group; therefore, the equilibrium formation of a π complex of olefin with bromine (i.e., the cyclic intermediate formation) should be depressed, and then dibromination might not be successful for 2-phospholene 1-oxides **1**.

On the other hand, bromine forms hypobromous acid or hypobromite ion in the presence of a protic solvent, such as water or methanol, in an equilibrium reaction [17,18]. The reactive species formed can react with the 2-phospholene affording a cyclic bromonium ion intermediate in a similar manner to the action of bromine on an olefin. The cyclic bromonium intermediate thus formed might then be attacked by a nucleophile (e.g., $^-$OH or $^-$OMe), as shown in Scheme 2. In the final step, the nucleophile attacks at the more positive carbon atom, i.e., the 2-position of the 2-phospholene, and from the less hindered direction in a stereospecific *trans* fashion; therefore, it may be rationalized that 2-bromo-3-hydroxy- or 2-bromo-3-methoxy-1-phenylphospholane 1-oxide is the sole product and that the major isomer is *threo* **2aT** and the minor one *erythro* **2aE**. The mechanism postulated in Scheme 2 well explains the present results; however, within the framework of the data obtained so far, the mechanism in which the cyclic bromonium intermediate is formed initially via association of a 2-phospholene derivative with bromine cannot be ruled out.

EXPERIMENTAL

Measurements

^{1}H NMR spectra were measured on either a Hitachi R-24B (60 MHz) or on a JEOL JNM-EX90 (90 MHz) spectrometer with tetramethylsilane (TMS, δ = 0 ppm) as an internal standard. ^{13}C and ^{31}P NMR spectra were recorded by a JEOL JNM-EX90 (22.4 MHz and 36.1 MHz, respectively) spectrometer with $CDCl_3$ (δ = 77.0) and Ph_3P (δ = −5.60), respectively, as the solvent and/or the internal standard. Mass spectra were measured on a Hitachi RMU 7M GC-MS spectrometer and IR spectra on a JASCO A-3 or a JASCO FT/IR-8000 infrared spectrophotometer. JASCO UNIFLOW-211 was used as an HPLC instrument with UNIDEC-100-II as the detector and Fine Pack Sil as the column. Melting and boiling points were uncorrected.

*Reaction of 1-Phenyl-2-phospholene 1-Oxide (**1a**) with Bromine in Chloroform-Water*

To a heterogeneous solution of 2-phospholene **1a** (1.00 g, 5.6 mmol; bp 133°C/0.15 mmHg [19], Ref. [2] bp 153–155°C/0.2 mmHg) in chloroform (10 mL) and water (10 mL) was added bromine (0.40 mL, 7.8 mmol), and the mixture was stirred for 24 hours at room temperature. After complete consumption of the starting material was confirmed by TLC, aqueous sodium sulfite (10 mL) was added. The separated organic layer was dried over anhydrous sodium sulfate and evaporated in vacuo to give the residue. The residual product was fractionally crystallized from chloroform-carbon tetrachloride to afford *threo*-2-bromo-3-hydroxy-1-phenylphospholane 1-oxide (**2aT**, 0.66 g, 43% yield, mp 180–183°C) and the *erythro* derivative **2aE** (0.37 g, 24%, mp 136–139°C). **2aT**: ^{1}H NMR ($CDCl_3$/TMS): δ = 2.0–2.8 (m, 4H, P-CH_2-CH_2), 4.1–4.8 (m, 2H, P-C*H*Br-C*H*(OH), 5.7–6.0 (m, 1H, OH), and 7.3–8.0 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$/$CDCl_3$): δ = 24.7 ($^1J_{CP}$ = 64.2 Hz, P-CH_2), 30.2 ($^2J_{CP}$ = 2.6 Hz, P-CH_2-CH_2), 47.2 ($^1J_{CP}$ = 62.8 Hz, CH-Br), 77.4 ($^2J_{CP}$ = 17.4 Hz, CH-OH), 128.3 ($^2J_{CP}$ = 12.0 Hz, *o*-CH), 129.7 ($^1J_{CP}$ = 99.6 Hz, *x*-CH), 131.6 ($^3J_{CP}$ = 9.4 Hz, *m*-CH), 132.7 ($^3J_{CP}$ = 3.4 Hz, *p*-CH); ^{31}P NMR ($CDCl_3$/Ph_3P): δ = 63.0; IR (KBr): ν = 3200 (OH), 1440 (P-Ph), 1180 (P=O), and 540 cm^{-1} (C-Br); IR ($CDCl_3$, 2 mg/80 μL): ν = 3220 (OH); MS (*m/z*): 274 (M^+) and 276 (M^+ + 2).

2aE: ^{1}H NMR ($CDCl_3$/TMS): δ = 1.6–2.8 (m, 4H, P-CH_2CH_2), 3.9–4.3 (m, 1H, P-CHBr), 4.7 (dm, 1H, J_{HCP} = 16Hz, P-CHBr-C*H*(OH), 5.8–6.1 (m, 1H, OH), and 7.3–8.3 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$/

$CDCl_3$): δ = 25.7 ($^1J_{CP}$ = 65.5 Hz, P-CH_2), 29.5 ($^2J_{CP}$ = 3.3 Hz, P-CH_2-CH_2), 48.8 ($^1J_{CP}$ = 61.5 Hz, CH-Br), 77.5 ($^2J_{CP}$ = 12.7 Hz, CH-OH), 128.6 ($^2J_{CP}$ = 12.7 Hz, *o*-CH), 130.6 ($^1J_{CP}$ = 96.2 Hz, *x*-CH), 130.7 ($^3J_{CP}$ = 10.0 Hz, *m*-CH), 132.3 ($^3J_{CP}$ = 3.3 Hz, *p*-CH); ^{31}P NMR ($CDCl_3$/Ph_3P): δ = 65.8; IR (KBr): ν = 3200 (OH), 1440 (P-Ph), 1180 (P=O), and 540 cm^{-1} (C-Br); IR ($CDCl_3$, 2 mg/80 μL): ν = 3380 (OH); MS (*m/z*): 274 (M^+) and 276 (M^+ + 2).

Reaction of 1-Methoxy-2-Phospholene 1-Oxide (**1b**) *with Bromine in Chloroform-Water*

To a heterogeneous solution of the 2-phospholene **1b** [20] (0.65 g, 5.6 mmol; bp 79°C/0.4 mmHg, Ref. [21] bp 143–146°C/0.08 mmHg, Ref. [22] bp 79°C/0.4 mmHg) in chloroform (10 mL) and water (10 mL) was added bromine (0.40 mL, 7.8 mmol), and the mixture was stirred for 24 hours at room temperature. After complete consumption of the starting material was confirmed by TLC, aqueous sodium sulfite (10 mL) was added. The separated organic layer was dried over anhydrous sodium sulfate and evaporated in vacuo to give 2-bromo-3-hydroxy-1-methoxy-phospholane 1-oxide (**2b**, 1.17 g, 98% yield); ^{1}H NMR ($CDCl_3$/TMS): δ = 1.5–3.4 (m, 4H, P-CH_2-CH_2), 4.0, 4.1 (2d, J_{HCOP} = 12 Hz, 3H, 2P-OMe), 4.0–5.0 (m, 2H, P-C*H*Br-C*H*OH), and 5.3 (bs, 1H, OH).

Reaction of 1-Phenyl-2-phospholene 1-Oxide (**1a**) *with Bromine in Methanol*

To a solution of the 2-phospholene **1a** (0.185 g, 1.04 mmol) in methanol (10 mL) was added bromine (0.10 mL, 1.94 mmol), and then the mixture was allowed to stand for 24 hours at room temperature. After complete consumption of the starting material was confirmed by TLC, chloroform (30 mL) and aqueous sodium sulfite (10 mL) were added. The separated organic layer was dried over anhydrous sodium sulfate and evaporated in vacuo to give the residue. The residue was chromatographed on silica gel to give 2-bromo-3-methoxy-1-phenylphospholane 1-oxide (**3a**, 0.291 g, 97% yield); oil; ^{1}H NMR ($CDCl_3$/TMS): δ = 1.8–2.9 (m, 4H, P-CH_2-CH_2), 3.20 (s, 1.35H, C-OMe), 3.29 (s, 1.65H, C-OMe; ratio of the two C-OMe areas = ca. 5:6), 3.7–4.8 (m, 2H, P-C*H*Br-C*H*OMe), and 7.2–7.8 (m, 5H, Ph); IR (KBr): ν = 1440 (P-Ph), 1200 (P=O), and 540 cm^{-1} (C-Br); MS (*m/z*): 288 (M^+) and 290 (M^+ + 2).

Reaction of 1-Methoxy-2-Phospholene 1-Oxide (**1b**) *with Bromine in Methanol*

To a solution of the phospholene **1b** (0.23 g, 1.74 mmol) in methanol (10 mL) was added bromine (0.10 mL, 1.94 mmol), and then the mixture was left to stand for 24 hours at room temperature. Workup as above gave 2-bromo-1,3-dimethoxy-phospholane 1-oxide (**3b**, 0.41 g, 97% yield; oil; ^{1}H NMR ($CDCl_3$/TMS): δ = 1.6–2.8 (m, 4H, P-CH_2-CH_2), 3.40 (s, 3H, C-OMe), 3.6, 4.2 (2d, 3H, J_{HCOP} = 12 Hz, P-OMe), and 3.7–4.7 (m, 2H, P-C*H*Br-C*H*OMe); IR (KBr): ν = 3500 (OH) and 1240 cm^{-1} (P=O).

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[13] ^{1}H NMR ($CDCl_3$/TMS) data for **4**: δ = 2.0–3.0 (m, 4H, P-CH_2-CH_2), 2.12 (s, 3H, OAc), 4.15 (dd, J_{HCCH} = 7.1 Hz, J_{HCP} = 10.6 Hz, CHBr), 5.25 (dq, 1H, J_{HCCH} = J_{HCCP} = 7.1 Hz, C*H*OAc), and 7.4–8.2 (m, 5H, Ph).

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[15] *Erythro* and *threo* forms are defined on the basis of relative configuration concerning the adjacent P=O and C–Br bonds: *erythro* refers to the *syn* and *threo* to the *anti* relationships.

[16] The reaction of 3-methyl-1-phenyl-2-phospholene 1-oxide with bromine in chloroform-water afforded only (1*S*, 2*R*, 3*S*)-2-bromo-3- hydroxy-3-methyl-1-phenylphospholane 1-oxide and the enantiomer, with ^2E (sugar numbering) conformation. The structure has 1-phenyl and also 3-hydroxyl groups. The former group exerts the steric hindrance and

the latter participates in the hydrogen bonding. If a product-like transition state is plausible for the present bromohydrination, the hydrogen bonding as well as the steric hindrance should control the ratio of diastereomers formed.

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[19] 1 mmHg = 133.322 Pa.

[20] NMR Data for **1b**: ^{1}H NMR ($CDCl_3$/TMS): δ = 1.7–2.1 (m, 2H, CH_2-CH=), 2.5–3.0 (m, 2H, P-CH_2), 3.73 (d, 3H, J_{HCOP} = 11.1 Hz, P-OMe), 6.21 (ddm, 1H, J_{HCCH} = 8.6 Hz, J_{HCCP} = 23.7 Hz, P-CH=C*H*), 7.05 (ddm, 1H, J_{HCCH} = 8.6 Hz, J_{HCP} = 49.0 Hz, P-CH=); ^{13}C NMR ($CDCl_3$/$CDCl_3$): δ = 18.3 (J_{CP} = 95.4 Hz, P-CH_2), 25.8 (J_{CCP} = 15.4 Hz, P-CH_2-CH_2), 50.4 (J_{COP} = 6.0 Hz, P-O-CH_3), 121.9 (J_{CP} = 120.9 Hz, P-CH=), and 151.4 (J_{CCP} = 31.6 Hz, P-CH=*C*H).

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