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Wu, Shao-Yong
Laboratory of Pesticide Chemistry, Faculty of Agriculture, Kyushu University

Hirashima, Akinori
Laboratory of Pesticide Chemistry, Faculty of Agriculture, Kyushu University

Takeya, Ryuko
Laboratory of Pesticide Chemistry, Faculty of Agriculture, Kyushu University

Eto, Morifusa
Laboratory of Pesticide Chemistry, Faculty of Agriculture, Kyushu University

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Synthesis and Insecticidal Activity of Bicyclic Phosphorothionates and Related Monocyclic Phosphorothionates

Shao-Yong Wu*, Akinori Hirashima, Ryuko Takeya and Morifusa Eto
Laboratory of Pesticide Chemistry, Faculty of Agriculture Kyushu University 46-02, Fukuoka 812, Japan.
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Some thiono-type bicyclic phosphorus esters (BPs) were synthesized and bioassayed for insecticidal activity against susceptible (SRS) houseflies. n-Propyl was most favorable as a substituent at position 4 for insecticidal activity. The introduction of substituents at position 3 did not improve the activity. Some functionized monocyclic phosphorothionates (MPs) were also synthesized as proBP candidates. Although some MPs were cyclized to the corresponding BPs by oxidation or by action of a base, they did not show insecticidal activity. Some other MPs with a chloro-functionized 5-substituent had an insecticidal activity but their cyclization to the corresponding BPs was not yet proved.

INTRODUCTION

The structural variation of 2, 6, 7-trioxa-1-phosphabicyclo[2.2.2]octane or so-called bicyclic phosphorus ester (BP) is very limited and its synthetic modification has been mainly carried out on the 4-substituent as RC(CH$_2$O)$_3$P=X (Ozoe and Eto, 1982). Oxo-type BPs with a branched hydrophobic alkyl group at position 4 are highly toxic to mammals (Bellet and Casida, 1973; Eto et al., 1976) and potent noncompetitive γ-aminobutyric acid (GABA) antagonists (Bowery et al., 1976; Korenaga et al., 1977). Although these compounds have only weak insecticidal activity when topically applied to insects, considerably high insecticidal activity has been observed by injecting or by topically applying them with piperonyl butoxide (PB) (Ozoe et al., 1983, 198613). Introduction of an alkyl group at position 3 appears to increase selective toxicity to insects (Ozoe et al., 1983).

Propesicide concept is often useful for the structure modification of biologically active compounds in order to reduce mammalian toxicity and to increase pesticidal activity (Fukuto, 1984). 5-Substituted 1, 3, 2-dioxaphosphorinanes of the type $\text{R}_1$-(HOCH$_2$)C(CH$_2$O)$_2$P(O)R$_2$ are potential proBPs by virtue of their cyclization ability and expected to be as candidates for propesicides (Toià and Casida, 1985, 1987).

Thiono-type BPs were not studied yet in detail as possible insecticides, though 4-t-butylbicyclophosphorothionate (TBPS) is known as a specific ligand for the GABA receptor-ionophore complex (Squires et al., 1983) and a relatively high insecticidal activity was found in its 4-n-propyl derivative (Ozoe et al., 1986a). This paper deals with the relationships between the structure and insecticidal activity of thiono-type BPs and monocyclic phosphorothionates (MPs) prepared as proBP candidates. Effect

*Present address: Institute of Applied Chemistry, Beijing Agricultural University, Beijing, China
of substitution at the position 3 of BPs on insecticidal activity by topical application was also investigated.

MATERIALS AND METHODS

Synthesis of triols
Triols were synthesized by the following exemplified reactions.

2-Cyclohexyl-2-hydroxymethyl-1,3-propanediol

1. Cyclohexylacetalddehyde

To pyridinium chlorochromate (32.3 g) suspended in 200 ml of dichloromethane, cyclohexylethanol (12.8 g) in 20 ml of dichloromethane was added. After stirred for 1.5 hr, 200 ml of dry ether was added and the supernatant was decanted from the black gum. The insoluble residue was washed with dry ether and the combined organic solution was passed through a short silica gel column, and then concentrated. Distillation gave the product in 65% yield, bp 74-75°C (18 mmHg). 1H-NMR: 0.7-2.0 (11H, m, CH2), 2.2 (2H, m, CH2CO), 10.4 (1H, CHO).

2. 2-Cyclohexyl-2-hydroxymethyl-1,3-propanediol

Cyclohexylacetalddehyde was transformed into 2-cyclohexyl-2-hydroxymethyl-1,3-propanediol by utilizing the Tollens condensation (Ozoe and Eto, 1982). Yield 16%, bp 156-159°C (0.06 mmHg), mp 85°C.

2-Propyl-2-hydroxymethyl-1,3-butanediol

1. Diethyl Acetylpropylmalonate

To sodium hydride (0.1 mol) in 75 ml of dry ether, diethyl propylmalonate (0.1 mol) in 75 ml of the same solvent was added dropwise and the mixture was refluxed for 3 hr. To the reaction mixture, 100 ml of a dry ether solution of acetyl chloride (0.1 mol) was added. After refluxed for 15 hr, the mixture was worked up in a usual way. Distillation gave the product in 74% yield, bp 77°C (0.1 mmHg). 1H-NMR: 0.94 (3H, t, J = 7 Hz, CH2), 1.30 (2H, m, MeCH2CO), 2.32 (3H, s, CH2CO), 4.23 (4H, q, J = 7 Hz, (MeCH2)2).

2. 2-Propyl-2-hydroxymethyl-1,3-butanediol

Diethyl acetylpropylmalonate (0.037 mol) in 60 ml of dry ether was added dropwise to a suspension of LiAlH4 (0.126 mol) in 350 ml of dry ether at 0°C. After stirring at room temperature for 3 days, an aqueous potassium hydroxide solution (19 g in 50 ml) was carefully added to the reaction mixture, followed by addition of a solution containing K2HPO4 (14 g) and KH2PO4 (11 g) in H2O (50 ml). After evaporation of ether, the aqueous solution was neutralized with acetic acid and concentrated. The residue was extracted with acetone and evaporation of the solvent gave crystals which were used for next synthesis without further purification.

Synthesis of BPs

BPs were synthesized in a similar manner as described by Ozoe and Eto (1982).

4-Ethyl-2,6,7-trioxa-1-phosphabicyclo[2.2.2]octane 1-Oxide (BP-1)

1H-NMR: 0.90 (3H, t, J = 7 Hz, CH2), 1.36 (2H, q, J = 7 Hz, MeCH2), 4.49 [6H, d, J = 6 Hz, (CH2O)], 3P-NMR: -7.4. MS: 178 (M+10), 150 (32), 68 (100).

4-Ethyl-2,6,7-trioxa-1-phosphabicyclo[2.2.2]octane 1-Sulfide (BP-2)

1H-NMR: 0.88 (3H, t, J = 7 Hz, CH2), 1.32 (2H, q, J = 7 Hz, MeCH2), 4.46 [6H, d,
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\[ J = 6 \text{ Hz, (CH}_2\text{O)}_3 \]. \( ^{31}\text{P-NMR: 52.2, MS: 194 (M}^+\text{, 100).} \]

4-Phenyl-2, 6, 7-trioxa-1-phosphabicyclo[2.2.2]octane 1-Sulfide (BP-3)

\[ 'H-NMR : 4.82 [6H, d, J = 6 Hz, (CH}_2\text{O)}_3], 7.0-7.5 (5H, m, Ph). \]

4-Cyclohexyl-2, 6, 7-trioxa-1-phosphabicyclo[2.2.2]octane 1-Sulfide (BP-4)

\[ 'H-NMR : 0.8-1.9 (11H, m), 4.49 [6H, d, J = 6 Hz, (CH}_2\text{O)}_3]. \]

4-Propyl-2, 6, 7-trioxa-1-phosphabicyclo[2.2.2]octane 1-Sulfide (BP-5)

\[ 'H-NMR : 0.92 [3H, t, J = 7 Hz, CH(CH}_2\text{CH})_2], 1.23 (4H, m, MeCHCH_2CH)_2, 4.46 [6H, d, J = 6 Hz, (CH}_2\text{O)}_3], \text{MS: 208 (M}^+\text{, 81), 83 (47), 79 (57), 55 (100).} \]

3-Methyl-4-propyl-2, 6, 7-trioxa-1-phosphabicyclo[2.2.2]octane 1-Sulfide (BP-6)

\[ 'H-NMR : 0.91 [3H, t, J = 6 Hz, CH(CH}_2\text{CH})_2], 1.16 (4H, m, MeCHCH_2CH)_2, 1.50 (3H, 2d, J = 6 Hz, OCCH), 4.45 [4H, d, J = 7 Hz, (CH}_2\text{O)}_3], \text{MS: 222 (M}^+\text{, 100).} \]

3-Isopropyl-4-propyl-2, 6, 7-trioxa-1-phosphabicyclo[2.2.2]octane 1-Sulfide (BP-7)

\[ 'H-NMR : 0.92 [3H, t, J = 6 Hz, CH(CH}_2\text{CH})_2], 1.14, 1.18 [6H, 2d, J = 7 Hz, C(CH}_3\text{)}_2], 1.25 (4H, m, MeCHCH_2CH), 2.13 (1H, m, Me_2CH), 4.40 [4H, d, J = 7 Hz, (CH}_2\text{O)}_3], 4.5 (1H, m, CHO). \text{MS: 250 (M}^+\text{, 100).} \]

3-Phenyl-4-propyl-2, 6, 7-trioxa-1-phosphabicyclo[2.2.2]octane 1-Sulfide (BP-8)

\[ 'H-NMR : 0.6-1.4 (7H, m, CH(CH}_2\text{CH})_2), 4.30, 4.56 [4H, 2d, J = 7 Hz, (CH}_2\text{O)}_3], 5.59 (1H, d, J = 7 Hz, CHO), 7.38 (5H, s, Ph). \text{MS: 284 (M}^+\text{, 59), 91 (100).} \]

3-Benzyl-4-propyl-2, 6, 7-trioxa-1-phosphabicyclo[2.2.2]octane 1-Sulfide (BP-9)

\[ 'H-NMR : 1.04 [3H, t, J = 7 Hz, CH(CH}_2\text{CH})_2], 1.2-1.8 (4H, m, MeCHCH_2CH), 2.3-2.9 (2H, m, PhCH_2), 4.0-4.8 [4H, m, (CH}_2\text{O)}_3], 4.80 (1H, m, CHO). \text{MS: 298 (M}^+\text{, 3), 243 (22), 92 (75), 58 (100).} \]

Synthesis of monocyclic phosphorothionates (MPs)

Monocyclic phosphorothionates (MPs) were synthesized by the reaction of a triol and a thiophosphoryl dichloride. In some cases, the methylo1 group at position 5 was protected with one of acetyl, mesyl or tosyl group by treating with the corresponding chloride. Others were converted to halides by using thionyl halide.

5-Chloromethyl-5-ethyl-2-methoxy-1, 3, 2-dioxaphosphorinane 2-Sulfide (MP-11)

1. 5-Ethyl-5-hydroxymethyl-2-methoxy-1, 3, 2-dioxaphosphorinane 2-Sulfide (MP-3)

To the mixture of methyl phosphorodichloridothionate (0.01 mol) and 2-ethyl-2-hydroxymethyl-1,3-propanediol (0.01 mol) in 5 ml of H_2O, NaOH (0.02 mol) was added at 0°C. After stirred at 0°C for 1 hr and at room temperature for 1 hr, the mixture was neutralized and extracted with ether. The product as a diastereomeric mixture was obtained after purification through column chromatography using a mixture of benzene and ether as a gradient elution system. Yield 33%. \( 'H-NMR : 0.92 [3H, t, J = 7 Hz, CH(CH}_2\text{CH})_2], 1.30, 1.64 (2H, 2q, J = 7 Hz, MeCH_2), 2.4, 2.7 (1H, OH), 3.54, 3.80 (2H, 2s, CH_2O), 3.99, 4.00 (3H, 2d, J = 14 Hz, POCH), 3.90-4.46 [4H, m, (CH}_2\text{O)}_3]. \text{MS: 226 (M}^+\text{, 10), 129 (100).} \]

2. 5-Chloromethyl-5-ethyl-2-methoxy-1, 3, 2-dioxaphosphorinane 2-Sulfide (MP-
To a solution of 5-ethyl-5-hydroxymethyl-2-methoxy-1, 3, 2-dioxaphosphorinane Z-sulfide (0.31 mmol) in hexamethyl phosphoramidate (4 ml), thionyl chloride (1.5 ml) was added slowly. After the mixture was stirred at room temperature for 12 hr, H₂O (5 ml) and ether (30 ml) were added. The ether layer was washed with successive 5% NaOH and saturated NaCl aq., and dried over anhydrous Na₂SO₄. The product was purified by column chromatography using a mixture of benzene and ether as a gradient elution system. Yield 46%. The cis- and trans-isomers were separated by a Lobar column using a mixture of hexane and ether as a gradient elution system. cis-isomer, 'H-NMR : 0.89 (3H, t, J = 7 Hz, CCH₂), 1.41 (2H, q, J = 7 Hz, MeCH₂), 1.9 (1H, OH), 3.94 (2H, s, CH₂O), 4.1-4.5 [4H, m, (CH₂O)₂], 6.34, 7.23 (4H, m, aromatic). MS : 375 (M⁺, 94), 236 (87), 179 (100). trans-isomer, 'H-NMR : 0.92 (3H, t, J = 7 Hz, CCH₂), 1.63 (2H, q, MeCH₂), 3.57 (2H, s, CH₂Cl), 3.86 (3H, d, J = 14 Hz, POCH₃), 4.26 [4H, d, J = 14 Hz, (CH₂O)₂]. MS : 244 (M⁺ + 30), 129 (100).

The following dioxaphosphorinanes were prepared in a similar manner.

5-Ethyl-5-hydroxymethyl-2-methoxy-1, 3, 2-dioxaphosphorinane Z-Sulfide (MP-1)
Cis-isomer, 'H-NMR : 0.92 (3H, t, J = 7 Hz, CCH₂), 1.41 (2H, q, J = 7 Hz, MeCH₂), 1.9 (1H, OH), 3.94 (2H, s, CH₂O), 4.1-4.5 [4H, m, (CH₂O)₂], 6.34, 7.23 (4H, m, aromatic). MS : 375 (M⁺, 15), 236 (87), 179 (100).

5-Acetoxymethyl-5-ethyl-2-methoxy-1, 3, 2-dioxaphosphorinane 2-Sulfide (MP-2)
' H-NMR : 0.90, 1.00 (3H,2t, J = 7 Hz, CCH₂), 1.3, 1.7 (1H, 2s, OH), 1.38, 1.78 (2H, 2q, J = 7 Hz, MeCH₂), 2.08, 2.12 (3H, 2s, OCOCH₂). 3.97, 4.36 (2H,2s, CH₂O), 4.1-4.5 [4H, m, (CH₂O)₂], 6.32, 7.24 (4H, m, aromatic). MS : 375 (M⁺, 15), 236 (87), 179 (100).

5-Acetoxymethyl-5-ethyl-2-methoxy-1, 3, 2-dioxaphosphorinane 2-Sulfide (MP-4)
' H-NMR : 0.88, 0.92 (3H, 2t, J = 7 Hz, CCH₂), 1.36, 1.62 (2H, 2q, J = 7 Hz, MeCH₂), 2.08 (3H, s, OCOCH₂), 3.80, 3.84 (3H, 2d, J = 14 Hz, POCH₃), 3.9-4.3 [6H, m, (CH₂O)₂, CH₂OCHO]. MS : 268 (M⁺, 94), 171 (70), 129 (100).

5-Ethyl-5-hydroxymethyl-2-methylthio-1, 3, 2-dioxaphosphorinane 2-Sulfide (MP-5)
Cis-isomer, 'H-NMR : 0.93 (3H, t, J = 7 Hz, CCH₂), 1.65 (2H, q, J = 7 Hz, MeCH₂), 1.83 (1H, OH), 2.42 (3H, d, J = 17 Hz, PSCH₃), 3.59 (2H, s, CH₂O), 4.0-4.4 [4H, m, (CH₂-O)₂]. Trans-isomer, 'H-NMR : 0.90 (3H, t, J = 7 Hz, CCH₂), 1.38 (2H, q, J = 7 Hz, MeCH₂), 1.92 (1H, OH), 2.41 (3H, d, J = 17 Hz, PSCH₃), 3.85 (2H, s, CH₂O), 4.0-4.4 [4H, m, (CH₂O)₂]. MS : 242 (M⁺, 100), 195 (90).

5-Acetoxymethyl-5-ethyl-2-methylthio-1, 3, 2-dioxaphosphorinane 2-Sulfide (MP-6)
Cis-isomer, 'H-NMR : 0.92 (3H, t, J = 7 Hz, CCH₂), 1.64 (2H, q, J = 7 Hz, MeCH₂), 2.10 (3H, s, OOCCH₂), 2.43 (3H, d, J = 17 Hz, PSCH₂), 4.0-4.4 [6H, m, (CH₂O)₂]. MS : 284 (M⁺, 64), 237 (27), 145 (100). Trans-isomer, 'H-NMR : 0.88 (3H, t, J = 7 Hz, CCH₂), 1.37 (2H, q, J = 7 Hz, MeCH₂), 2.09 (3H, s, OOCCH₂), 2.41 (3H, d, J = 17 Hz, PSCH₂), 4.0-4.4 [6H, m, (CH₂O)₂]. MS : 284 (M⁺, 100), 237 (60), 145 (61).

5-Ethyl-2-ethylthio-5-hydroxymethyl-1, 3, 2-dioxaphosphorinane 2-Sulfide (MP-7)
Cis-isomer, 'H-NMR : 0.93 (3H, t, J = 7 Hz, CCH₂), 1.39 (3H, t, J = 7 Hz, SCCH₃), 1.63 (2H, q, J = 7 Hz, MeCH₂C), 1.76 (1H, OH), 2.94, 3.12 (2H, 2q, J = 7 Hz, MeCH₂S),
3.58 (2H, s, CH₃O), 4.0-4.5 (4H, m, (CH₂O)₂).[³¹P-NMR : 95.98. Trans-isomer, 'H-NMR: 0.89 [3H, t, J = 7 Hz, CCCH₂], 1.38 (3H, t, J = 7 Hz, SCH₂), 1.2-1.5 (2H, q, J = 7 Hz, Me₂CH₂), 2.38 (1H, J = 5 Hz, OH), 2.92, 3.08 (2H, q, J = 7 Hz, Me₂CH₂), 3.81 (2H, d, J = 5 Hz, CH₂O), 3.9-4.4 [4H, m, (CH₂O)₂].[³¹P-NMR : 90.57.

5-Ethyl-2-methoxy-5-mesoxymethyl-1,3,2-dioxaphosphorinane 2-Sulfide (MP-8)

'¹H-NMR : 0.91, 0.95 (3H, 2t, J = 7 Hz, CCH₂), 1.40, 1.60 (2H, 2q, J = 7 Hz, Me₂CH₂), 3.41 (3H, s, O₂SCH₂), 3.80, 3.86 (3H, 2d, J = 14 Hz, POCH₃), 3.91, 4.23 (2H, 2s, Me₂SO₂CH₂), 4.0-4.5 [4H, m, (CH₂O)₂]. MS : 304 (M⁺, 48), 225 (100).

5-Ethyl-2-methoxy-5-tosylxymethyl-1,3,2-dioxaphosphorinane 2-Sulfide (MP-9)

'¹H-NMR : 0.81 (3H, t, J = 7 Hz, CCH₂), 1.34, 1.53 (2H, 2q, J = 7 Hz, Me₂CH₂), 2.44 (3H, s, PhCH₃), 3.74, 3.76 (3H, 2d, J = 14 Hz, POCH₃), 3.9-4.2 [6H, m, (CH₂O)₂], 7.2-7.8 (4H, m, aromatic). MS : 380 (M⁺, 26), 225 (100).

5-Bromomethyl-5-ethyl-2-methoxy-1,3,2-dioxaphosphorinane 2-Sulfide (MP-10)

'¹H-NMR : 0.92 (3H, t, J = 7 Hz, CCH₂), 1.2-1.8 (2H, q, J = 7 Hz, Me₂CH₂), 3.42, 3.70 (2H, 2s, CH₂Br), 3.81, 3.85 (3H, 2d, J = 14 Hz, POCH₃), 4.1-4.4 [4H, m, (CH₂O)₂]. MS : 290 (M⁺ + 2, 100), 288 (M⁺, 92).

2-Chloro-5-hydroxymethyl-5-ethyl-1,3,2-dioxaphosphorinane 2-Sulfide (MP-12)

G-isomer, '¹H-NMR : 0.97 (3H, t, J = 7 Hz, CCH₂), 1.78 (2H, q, J = 7 Hz, Me₂CH₂), 1.82 (1H, s, OH), 3.48 (2H, s, CH₂O), 3.9-4.7 [4H, m, (CH₂O)₂]. MS : 230 (M⁺ + 47, 133 (91), 98 (100).

2-Chloro-5-chloromethyl-5-ethyl-1,3,2-dioxaphosphorinane 2-Sulfide (MP-13)

cis-isomer, '¹H-NMR : 0.99 (3H, t, J = 7 Hz, CCH₂), 1.92 (2H, q, J = 7 Hz, Me₂CH₂), 3.37 (2H, s, CH₂Cl), 3.9-4.6 [4H, m, (CH₂O)₂]. MS : 248 (M⁺, 30), 116 (82), 81 (100) ; trans-isomer, '¹H-NMR : 0.92 (3H, t, J = 7 Hz, CCH₂), 1.43 (2H, q, J = 7 Hz, Me₂CH₂), 3.82 (2H, s, CH₂Cl), 4.0-4.6 [4H, m, (CH₂O)₂]. MS : 248 (M⁺, 42), 116 (94), 81 (100).

5-Chloromethyl-2-methoxy-5-propyl-1,3,2-dioxaphosphorinane 2-Sulfide (MP-14)

'¹H-NMR : cis-isomer, 0.88 (3H, t, J = 7 Hz, CCH₂), 1.28 (4H, m, Me₂CH₂CH₂), 3.77 (3H, d, J = 14 Hz, POCH₃), 3.80 (2H, 2s, CH₂Cl) 4.0-4.3 [4H, m, (CH₂O)₂] ; b amisomer, 0.96 (3H, t, J = 7 Hz, CCH₂), 1.1-1.7 (4H, m, Me₂CH₂CH₂), 3.59 (2H, s, CH₂Cl), 3.85 (3H, d, J = 14 Hz, POCH₃), 4.24 [4H, d, J = 14 Hz, (CH₂O)₂].

5-(1-Chloroethyl)-2-methoxy-5-propyl-1,3,2-dioxaphosphorinane 2-Sulfide (MP-15)

cis-isomer, '¹H-NMR : 0.92 (3H, t, J = 7 Hz, CCH₂), 1.1-1.5 (4H, m, Me₂CH₂CH₂), 1.61 (3H, d, J = 7Hz, CH₂Cl), 3.80 (3H, d, J = 14 Hz, POCH₃), 4.1-4.4 [4H, m, (CH₂O)₂], 4.62 (1H, q, J = 7 Hz, MeCHCl). MS : 272 (M⁺, 15), 195 (23), 129 (100) ; trans-isomer, '¹H-NMR : 0.98 (3H, t, J = 7 Hz, CCH₂), 1.1-1.9 (4H, m, Me₂CH₂CH₂), 1.52 (3H, d, J = 7 Hz, CH₂Cl), 3.83 (3H, d, J = 14 Hz, POCH₃), 4.20 (1H, q, J = 7 Hz, MeCHCl), 4.0-4.6 [4H, m, (CH₂O)₂].

5-(1-Chloropropyl)-2-methoxy-5-propyl-1,3,2-dioxaphosphorinane 2-Sulfide (MP-16)

'¹H-NMR : 0.94 [3H, t, J = 7 Hz, CH₃(Pr)], 1.14 (3H, t, J = 7 Hz, CH₂(CCH), 1.1-1.8 (6H, m, Me₂CH₂CH₂CH₂Me₂CH₂Cl), 3.78, 3.80 (3H, 2d, J = 14 Hz, POCH₃), 4.0-4.6 [4H, m, (CH₂O)₂], 4.28, 4.32 (1H, 2t, J = 7 Hz, CHCl). MS : 286 (M⁺, 2), 129 (75), 93 (100).

5-Isobutenyl-2-methoxy-5-propyl-1,3,2-dioxaphosphorinane 2-Sulfide (MP-17)

'¹H-NMR : 0.94 [3H, t, J = 7 Hz, CH₃(Pr)], 1.1-1.7 (4H, m, Me₂CH₂CH₂), 1.74 [6H, (CH₃), 3.76, 3.80 (3H, 2d, J = 14 Hz, POCH₃), 3.9-4.5 [4H, m, (CH₂O)₂], 4.66, 5.01 (1H,
2s, CH). MS: 264 (M+, 16), 136 (81), 107 (100).

5-α-Chlorobenzyl-2-methoxy-5-propyl-1, 3, 2-dioxaphosphorinane 2-Sulfide (MP-18)

$^1$H-NMR: 0.92 [3H, t, $J=7$ Hz, CH$_3$(Pr)], 1.1-1.9 (4H, m, MeCH$_2$CH$_2$), 3.79, 3.84 (3H, 2d, $J=14$ Hz, POCH$_3$), 4.0-4.8 [4H, m, (CH$_2$O)$_2$], 5.22, 5.64 (1H, 2s, PhCH), 7.32 (5H, s, Ph). MS: 334 (M+, 17), 209 (41), 171 (42), 129 (100).

2-Methoxy-5-(2-phenylvinyl)-5-propyl-1, 3, 2-dioxaphosphorinane 2-Sulfide (MP-19)

$^1$H-NMR: 0.94 [3H, t, $J=7$ Hz, CCH$_3$], 1.1-1.8 (4H, m, MeCH$_2$CH$_2$), 3.76, 3.79 (3H, 2d, $J=14$ Hz, POCH$_3$), 4.0-4.6 [4H, m, (CH$_2$O)$_2$], 5.7-6.7 (2H, m, CH=CH), 7.28 (5H, m, Ph). MS: 312 (M+, 100).

**Transformation of MP-1 and MP-5 into BP-I and BP-Z**

The reaction was carried out under the conditions shown in Table 1, monitored by $^{31}$P-NMR (Fig. 2). The reaction mixture in the appropriate solvent (1.5 ml) was put in an 8 mm NMR tube and the tube was inserted into a 10 mm NMR tube containing 0.5 ml CDCl$_3$ as a locking solvent to measure $^{31}$P-NMR. The reaction products were identified by comparing the chemical shift values with those of reference compounds (MP-1, 5 and BP-I, 2).

**Chromatographies, spectroscopies and other method**

Thin-layer silica gel plates (60F-254, 0.25 mm thick; Merck) were utilized for analytical thin-layer chromatography (TLC).

Column chromatography was performed on Merck silica gel 60 of particle size 0.063-0.2 mm.

$^1$H- and $^{31}$P-NMR were measured with a JEOL JNM-FX 100 spectrometer at 100 MHz and 40 MHz, respectively. Tetramethylsilane (TMS) was used as an internal standard for $^1$H-NMR and 85% phosphoric acid as an external standard for $^{31}$P-NMR measurements. Chemical shift values were expressed in δ (CDCl$_3$) ppm.

Mass spectra (MS) were obtained using two sets of mass spectrometer: an ESCO-05A equipped with an ESCO MD-DP05G data processing system and a JEOL JMS-D300 equipped with a JEOL JMA 3500 data processing system, ionizing voltage being at 70 eV and 30 eV, respectively. Ion peaks were expressed in m/z, followed by the percentage of intensity in parentheses.

All melting points were determined on an MRK (Mitamura Riken Kogyo) apparatus and are uncorrected.

**Methods of bioassay**

Three- to five-day old houseflies (*Musca domestica* Linne, WHO's standard susceptible strain, SRS) were used. Ten houseflies were topically treated with an acetone solution of a test sample. The mortality was counted 24 hr after treatment. Experiments were duplicated.
Bicyclic Phosphorothionates and Monocyclic Phosphorothionates

Fig. 1. Synthetic routes for bicyclic phosphorus esters (BPs) and related monocyclic phosphorothionates (MPs). X = 0, S, Y = OH, OAc, OMs, OTs, Br, Cl.

Table 1. Transformation of MP-1 into BP-1 (B) and BP-2 (A).

<table>
<thead>
<tr>
<th>Diastereomers</th>
<th>Reaction conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>cis</em></td>
<td>benzene, reflux, 2hr</td>
<td>0 1</td>
</tr>
<tr>
<td><em>cis</em></td>
<td>benzene, pyridine (2equiv.), r. t. 2hr</td>
<td>21 0</td>
</tr>
<tr>
<td><em>cis</em></td>
<td>acetone, pyridine (2equiv.), r. t. 2hr</td>
<td>14 0</td>
</tr>
<tr>
<td><em>cis</em></td>
<td>acetone, K₂CO₃ excess, r. t. 15min</td>
<td>10 0</td>
</tr>
<tr>
<td><em>cis</em></td>
<td>acetone, K₂CO₃ excess, reflux, 1hr</td>
<td>100 0</td>
</tr>
<tr>
<td><em>trans</em></td>
<td>acetone, K₂CO₃ excess, reflux, 1hr</td>
<td>0 0</td>
</tr>
<tr>
<td><em>cis</em></td>
<td>CHCl₃, MCPBA (equiv.), r. t. 10min</td>
<td>0 33</td>
</tr>
<tr>
<td><em>cis</em></td>
<td>CHCl₃, MCPBA (2equiv.), r. t. 30min</td>
<td>0 95</td>
</tr>
<tr>
<td><em>trans</em></td>
<td>CHCl₃, MCPBA (2equiv.), r. t. 30min</td>
<td>0 0</td>
</tr>
</tbody>
</table>

RESULTS AND DISCUSSIONS

Chemistry

Fig. 1 summarizes the synthetic schemes of BPs and MPs. The triols having different R and R' groups were synthesized from the corresponding aldehydes or
Table 2. Insecticidal activity of BP against susceptible housefly.

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>X</th>
<th>R</th>
<th>R'</th>
<th>LD₉₀ (µg/fly)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>alone</td>
</tr>
<tr>
<td>BP-1</td>
<td>O</td>
<td>Et</td>
<td>H</td>
<td>&gt; 50</td>
</tr>
<tr>
<td>BP-2</td>
<td>S</td>
<td>Et</td>
<td>H</td>
<td>14.42</td>
</tr>
<tr>
<td>BP-3</td>
<td>S</td>
<td>Ph</td>
<td>H</td>
<td>4.98</td>
</tr>
<tr>
<td>BP-4</td>
<td>S</td>
<td>c-Hex</td>
<td>H</td>
<td>1.76</td>
</tr>
<tr>
<td>BP-5</td>
<td>S</td>
<td>Pr</td>
<td>H</td>
<td>0.22</td>
</tr>
<tr>
<td>BP-6</td>
<td>S</td>
<td>Pr</td>
<td>Me</td>
<td>0.24</td>
</tr>
<tr>
<td>BP-7</td>
<td>S</td>
<td>Pr</td>
<td>Et</td>
<td>0.58</td>
</tr>
<tr>
<td>BP-8</td>
<td>S</td>
<td>Pr</td>
<td>i-Pr</td>
<td>0.75</td>
</tr>
<tr>
<td>BP-9</td>
<td>S</td>
<td>Pr</td>
<td>Ph</td>
<td>&gt; 100</td>
</tr>
<tr>
<td>BP-10</td>
<td>S</td>
<td>Pr</td>
<td>Bz</td>
<td>&gt; 100</td>
</tr>
</tbody>
</table>

*not tested.

Table 3. Insecticidal activity of MP against susceptible housefly.

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>R</th>
<th>R'</th>
<th>R₂</th>
<th>Y</th>
<th>LD₉₀ (µg/fly)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>cis</td>
</tr>
<tr>
<td>MP-1</td>
<td>Et</td>
<td>H</td>
<td>O- p-NO₂-Ph</td>
<td>OH</td>
<td>&gt; 50</td>
</tr>
<tr>
<td>MP-2</td>
<td>Et</td>
<td>H</td>
<td>O- p-NO₂-Ph</td>
<td>OAc</td>
<td>&gt; 50</td>
</tr>
<tr>
<td>MP-3</td>
<td>Et</td>
<td>H</td>
<td>OMe</td>
<td>OH</td>
<td>&gt; 100</td>
</tr>
<tr>
<td>MP-4</td>
<td>Et</td>
<td>H</td>
<td>OMe</td>
<td>OAc</td>
<td>&gt; 100</td>
</tr>
<tr>
<td>MP-5</td>
<td>Et</td>
<td>H</td>
<td>SMe</td>
<td>OH</td>
<td>&gt; 100</td>
</tr>
<tr>
<td>MP-6</td>
<td>Et</td>
<td>H</td>
<td>SMe</td>
<td>OAc</td>
<td>&gt; 100</td>
</tr>
<tr>
<td>MP-7</td>
<td>Et</td>
<td>H</td>
<td>SMe</td>
<td>OH</td>
<td>&gt; 100</td>
</tr>
<tr>
<td>MP-8</td>
<td>Et</td>
<td>H</td>
<td>OMe</td>
<td>OMe*</td>
<td>&gt; 100</td>
</tr>
<tr>
<td>MP-9</td>
<td>Et</td>
<td>H</td>
<td>OMe</td>
<td>OTs*</td>
<td>&gt; 100</td>
</tr>
<tr>
<td>MP-10</td>
<td>Et</td>
<td>H</td>
<td>OMe</td>
<td>Br</td>
<td>&gt; 50</td>
</tr>
<tr>
<td>MP-11</td>
<td>Et</td>
<td>H</td>
<td>OMe</td>
<td>Cl</td>
<td>&gt; 100</td>
</tr>
<tr>
<td>MP-12</td>
<td>Et</td>
<td>H</td>
<td>Cl</td>
<td>OH</td>
<td></td>
</tr>
<tr>
<td>MP-13</td>
<td>Et</td>
<td>H</td>
<td>Cl</td>
<td>Cl</td>
<td>&gt; 100</td>
</tr>
<tr>
<td>MP-14</td>
<td>Pr</td>
<td>H</td>
<td>OMe</td>
<td>Cl</td>
<td>15.19</td>
</tr>
<tr>
<td>MP-15</td>
<td>Pr</td>
<td>Me</td>
<td>OMe</td>
<td>Cl</td>
<td>10.29</td>
</tr>
<tr>
<td>MP-16</td>
<td>Pr</td>
<td>Et</td>
<td>OMe</td>
<td>Cl</td>
<td>56.57</td>
</tr>
<tr>
<td>MP-17</td>
<td>Pr</td>
<td>Me</td>
<td>OMe</td>
<td>Me</td>
<td>&gt; 100</td>
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<tr>
<td>MP-18</td>
<td>Pr</td>
<td>Ph</td>
<td>OMe</td>
<td>Cl</td>
<td>&gt; 100</td>
</tr>
<tr>
<td>MP-19</td>
<td>Pr</td>
<td>Ph</td>
<td>OMe</td>
<td>H</td>
<td>&gt; 100</td>
</tr>
</tbody>
</table>

*aMS; methanesulfonyl.
bTS; p-toluenesulfonyl.
diethyl malonates (Ozoe and Eto, 1982).

The structures of some MPs were designed as a monocyclic phosphorothionate having a nucleophilic group, which was either protected or non-protected by a biodegradable group, at position 5 and a leaving group at position 2. In addition, some MPs with a chloro-functionized 5-substituent were synthesized with expectations to form thiolate type BPs via intra-molecular S-alkylation (Hirashima and Eto, 1983). Table 1 illustrates that the cis-p-nitrophenyl ester MP-1 was transformed into BP-1 (B) or BP-2 (A), by MCPBA oxidation or with action of a base, respectively. With trans-MP-1 as a starting material, such transformations were not observed. However, both cis- and trans-dithioate MP-7 gave a mixture of BP-1 (B) and BP-2 (A) by MCPBA oxidation (Fig. 2). These transformations could also be expected to occur in vivo because similar oxidation and cyclization are known to occur in organism (Eto et al., 1967; Eto, 1974).

**Insecticidal activity**

Table 2 shows the insecticidal activity of the prepared BPs. Oxo-type BPs were not toxic to insects by topical application unless the insect was pretreated with PB (Ozoe et al., 1983). An alternation of P=O to P=S improved the insecticidal activity, supporting the finding of Ozoe et al. (1986b). n-Propyl group was most favorable as a substituent at position 4 for the insecticidal activity. In the case of oxo-type BPs, the introduction of methyl group at position 3 increased the insecticidal activity against houseflies by injection and decreased mammalian toxicity (Ozoe et al., 1983). In the case of thiono-type BPs, however, the introduction of an alkyl group at position 3 did not improve the topical insecticidal activity. The difference of insecticidal activity
between a 3-hydrogen derivative (BP-5) and 3-alkyl derivatives (BP-6, 7 and 8) might relate to the oxidative detoxication, because PB, a synergist which inhibits the oxidative metabolism (Eto, 1974), increased the insecticidal activity of BP-5, 6, 7 and 8 to a same level. Introduction of a phenyl group (BP-9) or a benzyl group (BP-10) at position 3 decreased the activity dramatically, compared with BP-5, 6, 7 and 8.

On the other hand, most of MPs (MP-1-9 and 16~19), examined as the diastereomeric mixtures, showed no insecticidal activity against houseflies at a dose of 50 or 100 µg/fly by topical application (Table 3), as opposed to the expectations to cyclize to the corresponding BP (Table 1 and Fig. 2). The difference of insecticidal activity between the cis- and trans-isomers of some MPs having a chloro-functionized 5-substituent (MP-11 and 13-15) was not large. Trans-MP-13, 14 and 15 showed a little higher insecticidal activity than the corresponding c&-isomers. Trans-MP-11 was much more active than cis-MP-11. However, their cyclization to thiolate type BPs was not proved yet. The insecticidal mode of action of the MPs having a chloro-functionized 5-substituent is not known.

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REFERENCES

Eto, M. 1974 Organophosphorus Pesticides : Organic and Biological Chemist?. CRC Press, Cleaveland
Squires, R. F., J. E. Casida, M. Richardson and E. Saederup 1983 [35S]I-butylbicyclophephoro-
