Synthesis and Insecticidal Activity of Bicyclic Phosphorothionates and Related Monocyclic Phosphorothionates

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

<https://doi.org/10.5109/23939>

出版情報：九州大学大学院農学研究院紀要. 33 (3/4), pp.275-285, 1989-03. Kyushu University
バージョン：
権利関係：

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.

(Received November 11, 1988)

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 $\text{RC}(\text{CH}_2\text{O})_3\text{P}=\text{X}$ (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, 1986, 1987). Introduction of an alkyl group at position 3 appears to increase selective toxicity to insects (Ozoe *et al.*, 1983).

Propesticide 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 $\text{R}_1\text{-(HOCH}_2\text{)C(CH}_2\text{O)}_2\text{P(O)R}_2$ are potential proBPs by virtue of their cyclization ability and expected to be as candidates for propesticides (Toia and Casida, 1985, 1987).

Thiono-type BPs were not studied yet in detail as possible insecticides, though 4-*t*-butylbicyclopophosphorothionate (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. Cyclohexylacetaldehyde

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). $^1\text{H-NMR}$: 0.7-2.0 (11H, m, C_6H_{11}), 2.2 (2H, m, CH_2CO), 10.4 (1H, CHO).

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

Cyclohexylacetaldehyde 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). $^1\text{H-NMR}$: 0.94 [3H, t, $J = 7$ Hz, $\text{CH}_3(\text{Pr})$], 1.30 (2H, m, MeCH_2C), 1.29 [6H, t, $J = 7$ Hz, $(\text{COOCCH}_3)_2$], 2.04 (2H, m, EtCH_2), 2.32 (3H, s, CH_3CO), 4.23 [4H, q, $J = 7$ Hz, $(\text{MeCH}_2\text{O})_2$].

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 LiAlH_4 (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 K_2HPO_4 (14 g) and KH_2PO_4 (11 g) in H_2O (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)

$^1\text{H-NMR}$: 0.90 (3H, t, $J = 7$ Hz, CH_3C), 1.36 (2H, q, $J = 7$ Hz, MeCH_2), 4.49 [6H, d, $J = 6$ Hz, $(\text{CH}_2\text{O})_3$]. $^{31}\text{P-NMR}$: -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)

$^1\text{H-NMR}$: 0.88 (3H, t, $J = 7$ Hz, CH_3), 1.32 (2H, q, $J = 7$ Hz, MeCH_2), 4.46 [6H, d,

$J = 6$ Hz, $(\text{CH}_2\text{O})_3$. ^{31}P -NMR : 52.2. MS : 194 (M^+ , 100).

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

^1H -NMR : 4.82 [6H, d, $J = 6$ Hz, $(\text{CH}_2\text{O})_3$], 7.0-7.5 (5H, m, Ph).

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

^1H -NMR : 0.8-1.9 (11H, C_6H_{11}), 4.49 [6H, d, $J = 6$ Hz, $(\text{CH}_2\text{O})_3$].

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

^1H -NMR : 0.92 (3H, t, $J = 7$ Hz, CH_3), 1.23 (4H, m, MeCH_2CH_2), 4.46 [6H, d, $J = 6$ Hz, $(\text{CH}_2\text{O})_3$]. MS : 208 (M^+ , 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)

^1H -NMR : 0.91 [3H, t, $J = 6$ Hz, $\text{CH}_3(\text{Pr})$], 1.16 (4H, m, MeCH_2CH_2), 1.50 (3H, 2d, $J = 6$ Hz, OCCCH_3), 4.45 [4H, d, $J = 7$ Hz, $(\text{CH}_2\text{O})_2$], 4.72 (1H, m, MeCH). MS : 222 (M^+ , 100).

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

^1H -NMR : 0.91 [3H, t, $J = 6$ Hz, $\text{CH}_3(\text{Pr})$], 1.16 [3H, t, $J = 7$ Hz, $\text{CH}_3(\text{Et})$], 1.2 (4H, m, MeCH_2CH_2), 1.78 (2H, m, MeCH_2CO), 4.4 (1H, m, EtCH), 4.45 [4H, d, $J = 7$ Hz, $(\text{CH}_2\text{-O})_2$], MS : 236 (M^+ , 100).

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

^1H -NMR : 0.92 [3H, t, $J = 7$ Hz, $\text{CH}_3(\text{Pr})$], 1.14, 1.18 [6H, 2d, $J = 7$ Hz, $\text{C}(\text{CH}_3)_2$], 1.25 (4H, m, MeCH_2CH_2), 2.13 (1H, m, Me_2CH), 4.40 [4H, d, $J = 7$ Hz, $(\text{CH}_2\text{O})_2$], 4.5 (1H, m, CHO). MS : 250 (M^+ , 100).

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

^1H -NMR : 0.6-1.4 (7H, m, $\text{CH}_3\text{CH}_2\text{CH}_2$), 4.30, 4.58 [4H, 2d, $J = 7$ Hz, $(\text{CH}_2\text{O})_2$], 5.59 (1H, d, $J = 7$ Hz, CHO), 7.38 (5H, s, Ph). MS : 284 (M^+ , 59), 91 (100).

3-Benzyl-4-propyl-2, 6, 7-trioxa-1-phosphabicyclo[2.2.2] octane 1-sulfide (BP-10)

^1H -NMR : 1.04 (3H, t, $J = 7$ Hz, CH_3), 1.2-1.8 (4H, m, MeCH_2CH_2), 2.3-2.9 (2H, m, PhCH_2), 4.0-4.8 [4H, m, $(\text{CH}_2\text{O})_2$], 4.80 (1H, m, CHO). MS : 298 (M^+ , 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 methylol 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 phosphorodichloridithionate (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%. ^1H -NMR : 0.92 (3H, t, $J = 7$ Hz, CCH₃), 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), 3.90-4.46 [4H, m, $(\text{CH}_2\text{O})_2$]. MS : 226 (M^+ , 10), 129 (100).

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

11)

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, ¹H-NMR : 0.89 (3H, t, *J* = 7 Hz, CCH₃), 1.40 (2H, q, *J* = 7 Hz, MeCH₂), 3.81 (3H, d, *J* = 14 Hz, POCH₃), 3.82 (2H, s, CH₂Cl), 4.1-4.3 [4H, m, (CH₂O)₂]. MS : 244 (M⁺, 52), 129 (100); *trans*-isomer, ¹H-NMR : 0.92 (3H, t, *J* = 7 Hz, CCH₃), 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-p-nitrophenoxy-1, 3, 2-dioxaphosphorinane Z-Sulfide (MP-1)

Cis-isomer, ¹H-NMR : 0.92 (3H, t, *J* = 7 Hz, CCH₃), 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). ³¹P-NMR : 53.5. MS : 333 (M⁺, 10), 236 (96), 179 (100). *Trans*-isomer, ¹H-NMR : 0.99 (3H, t, *J* = 7 Hz, CCH₃), 1.77 (2H, q, *J* = 7 Hz, MeCH₂), 3.56 (2H, s, CH₂O), 4.1-4.7 [4H, m, (CH₂O)₂], 6.39, 7.24 (4H, m, aromatic). ³¹P-NMR : 54.7.

5-Acetoxymethyl-5-ethyl-2-p-nitrophenoxy-1, 3, 2-dioxaphosphorinane 2-Sulfide (MP-2)

¹H-NMR : 0.90, 1.00 (3H, 2t, *J* = 7 Hz, CCH₃), 1.3, 1.7 (1H, 2s, OH), 1.38, 1.78 (2H, 2q, *J* = 7 Hz, MeCH₂), 2.08, 2.12 (3H, 2s, OCOCH₃), 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)

¹H-NMR : 0.88, 0.92 (3H, 2t, *J* = 7 Hz, CCH₃), 1.36, 1.62 (2H, 2q, *J* = 7 Hz, MeCH₂), 2.08 (3H, s, OCOCH₃), 3.80, 3.84 (3H, 2d, *J* = 14 Hz, POCH₃), 3.9-4.3 [6H, m, (CH₂O)₂, CH₂OCO]. MS : 268 (M⁺, 94), 171 (70), 129 (100).

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

Cis-isomer, ¹H-NMR : 0.93 (3H, t, *J* = 7 Hz, CCH₃), 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, ¹H-NMR : 0.90 (3H, t, *J* = 7 Hz, CCH₃), 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, ¹H-NMR : 0.92 (3H, t, *J* = 7 Hz, CCH₃), 1.64 (2H, q, *J* = 7 Hz, MeCH₂), 2.10 (3H, s, OOCCH₃), 2.43 (3H, d, *J* = 17 Hz, PSCH₃), 4.0-4.4 [6H, m, (CH₂O)₃]. MS : 284 (M⁺, 64), 237 (27), 145 (100). *Trans*-isomer, ¹H-NMR : 0.88 (3H, t, *J* = 7 Hz, CCH₃), 1.37 (2H, q, *J* = 7 Hz, MeCH₂), 2.09 (3H, s, OOCCH₃), 2.41 (3H, d, *J* = 17 Hz, PSCH₃), 4.0-4.4 [6H, m, (CH₂O)₃]. MS : 284 (M⁺, 100), 237 (60), 145 (61).

5-Ethyl-2-ethylthio-5-hydroxymethyl-1, 3, 2-dioxaphosphorinane 2-Sulfide (MP-7)

Cis-isomer, ¹H-NMR : 0.93 (3H, t, *J* = 7 Hz, CCH₃), 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, CH₂O), 4.0-4.5 (4H, m, (CH₂O)₂). ³¹P-NMR : 95.98. *Trans*-isomer, ¹H-NMR : 0.89 [3H, t, *J* = 7 Hz, CCCH₃), 1.38 (3H, t, *J* = 7 Hz, SCCH₃), 1.2-1.5 (2H, q, *J* = 7 Hz, MeCH₂C), 2.38 (1H, *J* = 5 Hz, OH), 2.92, 3.08 (2H, 2q, *J* = 7 Hz, MeCH₂S), 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-mesyloxymethyl-1, 3, 2-dioxaphosphorinane 2-Sulfide (MP-8)

¹H-NMR : 0.91, 0.95 (3H, 2t, *J* = 7 Hz, CCH₃), 1.40, 1.60 (2H, 2q, *J* = 7 Hz, MeCH₂), 3.41 (3H, s, O₃SCH₃), 3.80, 3.86 (3H, 2d, *J* = 14 Hz, POCH₃), 3.91, 4.23 (2H, 2s, MeSO₃-CH₂), 4.0-4.5 [4H, m, (CH₂O)₂]. MS : 304 (M⁺, 48), 225 (100).

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

¹H-NMR: 0.81 (3H, t, *J* = 7 Hz, CCH₃), 1.34, 1.53 (2H, 2q, *J* = 7 Hz, MeCH₂), 2.44 (3H, s, PhCH₃), 3.74, 3.76 (3H, 2d, *J* = 14 Hz, POCH₃), 3.9-4.2 [6H, m, (CH₂O)₃], 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, CCH₃), 1.2-1.8 (2H, q, *J* = 7 Hz, MeCH₂), 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, CCH₃), 1.78 (2H, q, *J* = 7 Hz, MeCH₂), 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, CCH₃), 1.92 (2H, q, *J* = 7 Hz, MeCH₂), 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, CCH₃), 1.43 (2H, q, *J* = 7 Hz, MeCH₂), 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, CCH₃), 1.28 (4H, m, MeCH₂CH₂), 3.77 (3H, d, *J* = 14 Hz, POCH₃), 3.80 (2H, s, CH₂Cl) 4.0-4.3 [4H, m, (CH₂O)₂]; *trans*-isomer, 0.96 (3H, t, *J* = 7 Hz, CCH₃), 1.1-1.7 (4H, m, MeCH₂CH₂), 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, CCH₃), 1.1-1.5 (4H, m, MeCH₂CH₂), 1.61 (3H, d, *J* = 7 Hz, CH₃CCl), 3.80 (3H, d, *J* = 14 Hz, POCH₃), 4.1-4.4 [4H, m, (CH₂-O)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, CCCH₃), 1.1-1.9 (4H, m, MeCH₂CH₂), 1.52 (3H, d, *J* = 7 Hz, CH₃CCl), 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, CH₃CCCl), 1.1-1.8 (6H, m, MeCH₂CH₂, MeCH₂CCl), 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-Isobuteryl-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, MeCH₂CH₂), 1.74 [6H, C(CH₃)₂], 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)

$^1\text{H-NMR}$: 0.92 [3H, t, $J=7$ Hz, $\text{CH}_3(\text{Pr})$], 1.1-1.9 (4H, m, MeCH_2CH_2), 3.79, 3.84 (3H, 2d, $J=14$ Hz, POCH_3), 4.0-4.8 [4H, m, $(\text{CH}_2\text{O})_2$], 5.22, 5.64 (1H, 2s, PhCH), 7.32 (5H, s, Ph). MS : 334 (M^+ , 7), 209 (41), 171 (42), 129 (100).

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

$^1\text{H-NMR}$: 0.94 (3H, t, $J=7$ Hz, CCH_3), 1.1-1.8 (4H, m, MeCH_2CH_2), 3.76, 3.79 (3H, 2d, $J=14$ Hz, POCH_3), 4.0-4.6 [4H, m, $(\text{CH}_2\text{O})_2$], 5.7-6.7 (2H, m, $\text{CH}=\text{CH}$), 7.28 (5H, m, Ph). MS : 312 (M^+ , 100).

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

The reaction was carried out under the conditions shown in Table 1, monitored by $^{31}\text{P-NMR}$ (Fig. 2). The reaction mixture in the appropriate solvent (1.5 ml) was put in an 8 mm ϕ NMR tube and the tube was inserted into a 10 mm ϕ NMR tube containing 0.5 ml CDCl_3 as a locking solvent to measure $^{31}\text{P-NMR}$. The reaction products were identified by comparing the chemical shift values with those of reference compounds (MP-1, 5 and BP-1, 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.

$^1\text{H-}$ and $^{31}\text{P-NMR}$ 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 $^1\text{H-NMR}$ and 85% phosphoric acid as an external standard for $^{31}\text{P-NMR}$ measurements. Chemical shift values were expressed in $\delta(\text{CDCl}_3)$ 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.

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

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

Diastereomers	Reaction conditions	Yield (%)	
		A	B
<i>cis</i>	benzene, reflux, 2hr	0	0
<i>cis</i>	benzene, pyridine (2equiv.), r. t. 2hr	21	0
<i>cis</i>	acetone, pyridine (2equiv.), r. t. 2hr	14	0
<i>cis</i>	acetone, K ₂ CO ₃ excess, r. t. 15min	10	0
<i>cis</i>	acetone, K ₂ CO ₃ excess, reflux, 1hr	100	0
<i>trans</i>	acetone, K ₂ CO ₃ excess, reflux, 1hr	0	0
<i>cis</i>	CHCl ₃ , MCPBA (equiv.), r. t. 10min	0	33
<i>cis</i>	CHCl ₃ , MCPBA (2equiv.), r. t. 30min	0	95
<i>trans</i>	CHCl ₃ , MCPBA (2equiv.), r. t. 30min	0	0

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.

Compd. No.	X	R	R'	LD ₅₀ (μg/fly)	
				alone	+PB (5 μg)
BP- 1	O	Et	H	> 50	NT*
BP- 2	S	Et	H	14.42	NT
BP- 3	S	Ph	H	4.98	NT
BP- 4	S	c-Hex	H	1.76	NT
BP- 5	S	Pr	H	0.22	0.12
BP- 6	S	Pr	Me	0.24	0.13
BP- 7	S	Pr	Et	0.58	0.16
BP- 8	S	Pr	i-Pr	0.75	0.11
BP- 9	S	Pr	Ph	> 100	NT
BP-10	S	Pr	Bz	> 100	NT

*not tested.

Table 3. Insecticidal activity of MP against susceptible housefly.

Compd. No.	R	R'	R ₁	Y	LD ₅₀ (μg/fly)	
					cis	trans
MP- 1	Et	H	O- <i>p</i> -NO ₂ -Ph	OH	> 50	
MP- 2	Et	H	O- <i>p</i> -NO ₂ -Ph	OAc	> 50	
MP- 3	Et	H	OMe	OH	> 100	
MP- 4	Et	H	OMe	OAc	> 100	
MP- 5	Et	H	SMe	OH	> 100	
MP- 6	Et	H	SMe	OAc	> 100	
MP- 7	Et	H	SEt	OH	> 100	
MP- 8	Et	H	OMe	OMs ^a	> 100	
MP- 9	Et	H	OMe	OTs ^b	> 100	
MP-10	Et	H	OMe	Br	> 50	
MP-11	Et	H	OMe	Cl	> 100	27.15
MP-12	Et	H	Cl	OH		—
MP-13	Et	H	Cl	Cl	> 100	3.96
MP-14	Pr	H	OMe	Cl	15.19	10.32
MP-15	Pr	Me	OMe	Cl	10.29	7.73
MP-16	Pr	Et	OMe	Cl		56.57
MP-17 ^c	Pr	Me	OMe	Me	> 100	
MP-18	Pr	Ph	OMe	Cl	> 100	
MP-19 ^c	Pr	Ph	OMe	H	> 100	

^a Ms ; methanesulfonyl.

^b Ts ; *p*-toluenesulfonyl.

Fig. 2. The transformation of *cis*- and *trans*-MP-7 into BP-1 (B) and BP-2 (A) with MCPBA monitored by ^{31}P -NMR.

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 $\text{P}=\text{O}$ to $\text{P}=\text{S}$ 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 $\mu\text{g}/\text{fly}$ 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 *cis*-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.

ACKNOWLEDGEMENT

This work was supported in part by the research grant from the Ministry of Education, Science, and Culture of Japan.

REFERENCES

- Bellet, E. M. and J. E. Casida 1973 Bicyclic phosphorus esters. *Science*, 182 : 1135-1136
- Bowery, N. G., J. F. Collins and R. G. Hill 1976 Bicyclic phosphorus esters that are potent convulsants and GABA antagonists. *Nature*, 261: 601-603
- Eto, M. 1974 *Organophosphorus Pesticides : Organic and Biological Chemist?*. CRC Press, Cleveland
- Eto, M., Y. Oshima and J. E. Casida 1967 Plasma albumin as a catalyst in cyclization of diaryl *o*-(α -hydroxy)tolyl phosphates. *Biochem. Pharmacol.*, 16 : 295-308
- Eto, M., Y. Ozoe, T. Fujita and J. E. Casida 1976 Significance of branched bridge-head substituent in toxicity of bicyclic phosphorus esters. *Agric. Biol. Chem.*, 40: 2113-2115
- Fukuto, T. R. 1984 Propesticides. In "Pesticide Synthesis through Rational Approaches", ed. by P. S. Magee, G. K. Kohn and J. J. Menn, ACS Symposium Series 255, American Chemical Society, Washington, D. C., pp. 87-101
- Hirashima, A. and M. Eto 1983 Stereochemistry and reactions of aziridinylphosphinothionates derived from amino acids. *Agric. Biol. Chem.*, 47: 829-838
- Korenaga, S., Y. Ito, Y. Ozoe and M. Eto 1977 The effects of bicyclic phosphate esters on the invertebrate and vertebrate neuro-muscular junctions. *Comp. Biochem. Physiol.*, 57C: 95-100
- Ozoe, Y. and M. Eto 1982 Synthesis and some spectral characteristics of bicyclic phosphate GABA antagonists. *Agric. Biol. Chem.*, 46 : 411-418
- Ozoe, Y., M. Eto, K. Mochida and T. Nakamura 1986a Characterization of high affinity binding of [^3H]propyl bicyclic phosphate to house fly head extracts. *Pestic. Biochem. Physiol.*, 26 : 263-274
- Ozoe, Y., H. Karino, K. Mochida, T. Nakamura and M. Fujii 1986b Penetration and metabolism of bicyclic phosphorus esters which affect their insecticidal activity against the housefly. *J. Pesticide sci.*, 11: 433-439
- Ozoe, Y., K. Mochida, T. Nakamura, A. Shimizu and M. Eto 1983 Toxicity of bicyclic phosphate GABA antagonists to the housefly, *Musca domestica* L. *J. Pesticide Sci.*, 8: 601-605
- Squires, R. F., J. E. Casida, M. Richardson and E. Saederup 1983 [^{35}S]*t*-butylbicyclophosphoro-

thionate binds with high affinity to brain-specific sites coupled to γ -aminobutyric acid-A and ion recognition sites. *Mol. Pharmacol.*, **23**: 326-336

Toia, R. F. and J. E. Casida 1985 Probicyclopophosphates: Monocyclopophosphates as potential prodrugs for bicyclopophosphate GABA antagonists. *Toxicol. Appl. Pharmacol.*, **81**: 50-57

Toia, R. F. and J. E. Casida 1987 Probicyclopophosphates as novel GABA antagonists. In "Biophosphates and Their Analogues-Synthesis, Structure, Metabolism and Activity," ed. by K. S. Bruzik and W. J. Stec., Elsevier Science Publishers B. V., Amsterdam, The Netherlands, pp. 465-468