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Insecticidal 1,3-Oxathianes and Their Oxides

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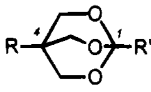
1,3-Oxathianes with suitable 2- and 5-substituents are highly potent insecticides. In some cases 1,3-oxathiane 3-oxides and 1,3-oxathiane 3,3-dioxides derived by *m*-chloroperoxybenzoic acid oxidation of the 1,3-oxathianes are even more effective. Housefly LD_{50}s for *trans*-5(e)-*tert*-butyl-2(e)-(4-ethynylphenyl)-1,3-oxathiane 3,3-dioxide are 0.3 and 0.03 μg/g alone and with piperonyl butoxide, respectively. It is the most insecticidal analogue in the oxathiane series and approaches the potency of (1*R*)-*cis*-permethrin.

Keywords: *Oxathianes; dioxanes; dithianes; trioxabicyclooctanes; insecticide*

INTRODUCTION

1,4-Disubstituted 2,6,7-trioxabicyclo[2.2.2]octanes (TBOs) (**1**) are a newly developed class of insecticide acting at the GABA-gated chloride channel (Palmer and Casida, 1985, 1987; Casida and Palmer, 1988; Casida *et al.*, 1985). With suitable substituents they can achieve a level of activity comparable to that of the most effective established insecticides acting at other target sites (Palmer and Casida, 1989).



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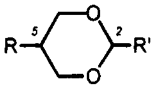

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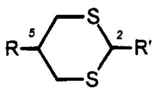
A recent report suggested the possibility that the 2,6,7-trioxabicyclo[2.2.2]octane ring may function as a spacer unit maintaining the 1- and 4-substituents in a linear relationship. Examination of the 1,3-dioxane ring system (**2**) with one fewer CH_2O link led to analogues with only very weak insecticidal activity; however, analogues containing the 1,3-dithiane ring (**3**) were quite potent (Elliott *et al.*, 1992). This report discusses the insecticidal activity of the related and as yet so far unexamined 1,3-oxathianes (**4**), and their 3-oxides and 3,3-dioxides.



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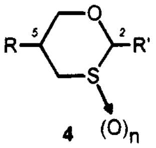

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MATERIALS AND METHODS

Abbreviations. Substituents are designated Me, methyl; Pr, propyl; Bu, butyl; Ph, phenyl; *tert*, tertiary; c, cyclo; e, equatorial; a, axial.

Nomenclature and Stereochemical Assignments (Figure 1). All the 5-alkyl-2-(substituted-phenyl)-1,3-oxathianes and -1,3-dioxanes in this study adopt a chair conformation and the 5-alkyl group is equatorially orientated (Eliel and Knoeber, 1968; Eliel and Hutchins, 1969). When the 2-(substituted-phenyl) group is axial it is the *cis* diastereomer and when it is equatorial it is the *trans* diastereomer. Stereochemical assignments for the individual *cis* and *trans* diastereomers were made on the basis of their ^{1}H-NMR spectral data with nuclear Overhauser effect difference spectroscopy (NOEDS). [For a conformational study on related 1,3-oxathianes using NOEDS see De Lucchi *et al.* (1985).] ^{1}H-NMR spectra can be used to routinely differentiate between axial and equatorial sulfoxides, the C-5 proton signal characteristically appearing at lower field for axial sulfoxides than for equatorial sulfoxides. This can be attributed to greater deshielding, and/or acetylenic type anisotropy of the $S{\rightarrow}O$ bond, known as the "*syn*-axial effect" (Foster *et al.*, 1968; Carretero *et al.*, 1984; Singer *et al.*, 1987; Romanelli *et al.*, 1988). All the compounds in this study with asymmetric centers have been synthesized as enantiomeric pairs.

Bioassays. LD_{50} values were determined for adult female houseflies (*Musca domestica* L., SCR strain, ~20 mg each) held 24 h at 25 °C after application of the test compound in acetone solution to the ventrum of the abdomen (Palmer and Casida, 1985). Synergized toxicity was evaluated by using flies pretreated topically with the mixed function oxidase inhibitor piperonyl butoxide (PB) at 250 μg/g 2 h before the toxicant was administered. Each experiment was repeated on at least three separate days with 10 or 20 flies per group and a dose differential of 2-fold. LD_{50} values for the houseflies were based on log dose−probit mortality plots and were reproducible within 1.5-fold.

Spectroscopy. Proton nuclear magnetic resonance (NMR) spectra were obtained at 300 MHz with a Bruker WM-300 spectrometer for samples dissolved in deuteriochloroform. Mass spectrometry (MS) utilized the Hewlett-Packard 5985 system with chemical ionization (CI) (230 eV with methane at 0.8 Torr).

Syntheses. *Intermediates: Alkyldiols and Alkylthiols.* 2-Substituted propane-1,3-diols were prepared by lithium aluminum hydride reduction (Eliel and Knoeber, 1968) of the appropriate 2-substituted diethyl malonate (Palmer *et al.*, 1991a).

2-(1-Methylcyclopropyl)propane-1,3-diol was obtained as a colorless oil: MS $[M + 1]^+$ 131; NMR δ 3.83 (4H, d, J = 7 Hz, $CH_2O \times 2$), 3.15 (2H, broad, OH × 2), 1.10 (1H, m, CH), 0.85 (3H, s, CH_3), 0.32 (2H, m, CHCH), 0.22 (2H, m, CHCH).

2-Cyclobutylpropane-1,3-diol was obtained as a white solid: mp 31−33 °C; MS $[M + 1]^+$ 131; NMR δ 3.80−3.50 (4H, m, $CH_2O \times 2$), 2.63 (2H, broad, OH × 2), 2.25−2.10 [1H, m, $CH(CH_2)_2$], 2.05−1.65 [7H, m, $(CH_2)_3$ and CH].

3,3-Dimethyl-2-hydroxymethylbutane-1-thiol was prepared as follows (Figure 1): (a) To a stirred solution of 3,3-dimethyl-2-(hydroxymethyl)butan-1-ol (14.1 g, 0.11 mol) in dry toluene (200 mL) under a nitrogen atmosphere was added NaH (3.3 g of 80% oil dispersion ≅ 0.11 mol) and the mixture was heated to gentle reflux for 30 min. Benzyl bromide (18.8 g, 0.11 mol) was added to the cooled solution and the mixture was heated to 110 °C for 12 h. The cooled solution was poured into ice−water and extracted with ether. The organic extracts were combined, dried ($MgSO_4$), and evaporated to leave the benzyl

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ether (23.7 g) as a colorless oil: MS [M + 1]$^+$ 223; NMR δ 7.35–7.25 (5H, m, aromatic), 4.52 (2H, s, CH_2Ar), 3.81 (2H, dd, CH_2-OH), 3.60 (2H, dd, J = 6 Hz, CH_2OCH_2Ar), 3.05 (1H, broad, OH), 1.72 [1H, m, $CH(CH_2)_2$], 0.90 [9H, s, $(CH_3)_3C$].

(b) To a stirred solution of 2-[(benzyloxy)methyl]-3,3-dimethylbutan-1-ol (23.7 g, 0.1 mol) in dry pyridine (80 mL) at 0 °C under a nitrogen atmosphere was added methanesulfonyl chloride (17 g, 0.15 mol). The mixture was stirred for 12 h at room temperature, poured into ice–water and extracted with ether. The ether extracts were combined, dried ($MgSO_4$), and evaporated to leave the methanesulfonate ester (30 g) as a yellow oil: MS [M + 1]$^+$ 301; NMR δ 7.35–7.25 (5H, m, aromatic H), 4.48 (2H, d, CH_2Ar), 4.39 (2H, dd, J = 4, 6 Hz, CH_2OSO_2], 3.62 (1H, dd, J = 4, 9.5 Hz, $CHHOCH_2Ar$), 3.54 (1H, dd, J = 6.5, 9.5 Hz, $CHHOCH_2Ar$), 2.90 (3H, s, CH_3SO_2), 1.70 [1H, m, $CH(CH_2)_2$], 0.97 [9H, s, $(CH_3)_3C$].

(c) To a stirred solution of benzyl mercaptan (15 g, 0.12 mol) in dry dimethylformamide (200 mL) at 0 °C under a nitrogen atmosphere was added sodium hydride (3.6 g of 80% oil dispersion ≅ 0.12 mol). After 30 min of stirring, 2-[(benzyloxy)-methyl]-3,3-dimethylbut-1-yl methanesulfonate (30 g, 0.1 mol) was added and the mixture was heated at 100 °C for 3 h. The cooled solution was poured into ice–water and extracted with ether. The extracts were combined, dried ($MgSO_4$), and evaporated to leave the crude benzyl thioether as a yellow oil: [M + 1]$^+$ 329; NMR δ 7.37–7.19 (10H, m, aromatic H), 4.46 (2H, s, OCH_2Ar), 3.67 (1H, dd, J = 4.5, 10 Hz, OC*H*CH), 3.56 (1H, dd, J = 4, 10 Hz, OC*H*CH), 2.61 (1H, dd, J = 3.5, 13 Hz, SC*H*CH), 2.49 (1H, dd, J = 9.5, 13 Hz, SC*H*CH), 1.50 [1H, m, $CH(CH_2)_2$], 0.90 [9H, s, $(CH_3)_3C$].

(d) To liquid ammonia (1 L) was added a solution of 2-[(benzylthio)methyl]-3,3-dimethylbut-1-yl benzyl ether (0.1 mol) in dry ether (50 mL). Sodium (19 g, 0.8 mol) was added and the mixture was stirred. After 3 h, ammonium chloride (44 g, 0.82 mol) was added and the ammonia was allowed to evaporate. The solid residue was washed with ether, and the combined washings were filtered and evaporated to leave 3,3-dimethyl-2-(hydroxymethyl)butane-1-thiol (11.1 g, 75%) as a pale yellow oil: MS [M + 1]$^+$ 149; NMR δ 3.94 (1H, dd, J = 3.5, 11.5 Hz, OC*H*CH), 3.75 (1H, dd, J = 5.5, 11.5 Hz, OC*H*CH), 2.86 (1H, ddd, J = 3.5, 13 Hz, SC*H*CH), 2.50 (1H, ddd, J = 9.5, 13 Hz, SC*H*CH), 2.10 (1H, broad, OH), 1.48 (1H, dd, J = 7.5, 9 Hz, CH_2SH), 1.39 [1H, m, J = 3.5, 5.5 Hz, $CH(CH_2)_2$], 0.93 [9H, s, $(CH_3)_3C$].

Preparation of Substituted 1,3-Dioxanes. A solution of the appropriate 2-substituted propane-1,3-diol (1 equiv), 4-ethynylbenzaldehyde (Austin *et al.*, 1981) (1 equiv), and *p*-toluenesulfonic acid (10 mg) in dry benzene (100 mL) was heated to reflux, and water was removed by means of a Dean–Stark apparatus. The solvent was evaporated and the residue was purified on a silica column; elution with hexane–dichloromethane (4:1 v/v) gave the *trans*-2,5-disubstituted-1,3-dioxane.

*5(e)-tert-Butyl-2(e)-(4-ethynylphenyl)-1,3-dioxane (**5**):* White needles; mp 113–114 °C; MS [M + 1]$^+$ 245; NMR δ 7.47 and 7.41 (each 2H, AA′BB′, J = 8.5 Hz, aromatic H), 5.35 (1H, s, CHAr), 4.28 (2H, dd, J = 4.5, 11.5 Hz, $CH_{eq}O$ × 2), 3.77 (2H, dd, J = 10, 11.5 Hz, $CH_{ax}O$ × 2), 3.05 (1H, s, $C{\equiv}CH$), 1.92 [1H, tt, J = 4.5, 11.5 Hz, $CH(CH_2)_2$], 0.93 [9H, s, $(CH_3)_3C$].

*5(e)-Cyclobutyl-2(e)-(4-ethynylphenyl)-1,3-dioxane (**6**):* White needles; mp 110–111 °C; MS [M + 1]$^+$ 245; NMR δ 7.47 and 7.41 (each 2H, AA′BB′, J = 8.5 Hz, aromatic H), 5.34 (1H, s, CHAr), 4.17 (2H, dd, J = 4.5, 11.5 Hz, $CH_{eq}O$ × 2), 3.44 (2H, dd, J =10, 11.5 Hz, $CH_{ax}O$ × 2), 3.05 (1H, s, $C{\equiv}CH$), 2.20–1.70 [8H, m, $(CH_2)_3CHCH$].

*2(e)-(4-Ethynylphenyl)-5(e)-(1-methylcyclopropyl)-1,3-dioxane (**7**):* Pale yellow needles; mp 87–88 °C; MS [M + 1]$^+$ 243; NMR δ 7.47 and 7.41 (each 2H, AA′BB′, J = 8.5 Hz, aromatic H), 5.39 (1H, s, CHAr), 4.20 (2H, dd, J = 4.5, 11.5 Hz, $CH_{eq}O$ × 2), 3.84 (2H, dd, J = 11.5 Hz, $CH_{ax}O$ × 2), 3.05 (1H, s, $C{\equiv}CH$), 1.48 [1H, tt, J = 4.5, 11.5 Hz, $CH(CH_2)_2$], 0.96 (3H, s, CH_3), 0.35–0.22 (4H, m, CH_2CH_2).

*Preparation of Substituted 1,3-Oxathianes (Figure 1). trans- and cis-5(e)-tert-Butyl-2-(4-ethynylphenyl)-1,3-oxathianes (**8** and **12**).* A solution of 3,3-dimethyl-2-(hydroxymethyl)butane-1-thiol (1.48 g, 10 mmol), 4-ethynylbenzaldehyde (1.3 g, 10 mmol), and *p*-toluenesulfonic acid (10 mg) in benzene (50 mL) was heated to reflux and water was removed by means of a Dean–Stark apparatus. The solvent was evaporated and the residue was purified on a silica column. Elution with hexane–dichloromethane (9:1 v/v) gave the cis (2-axial) isomer (**12**) (300 mg, 12%) as white needles: mp 102–103 °C; MS [M + 1]$^+$ 261; NMR δ 7.47 (4H, s, aromatic), 5.82 (1H, s, CHAr), 3.98 (1H, dd, J = 6.5, 12 Hz, $CH_{ax}O$), 3.87 (1H, dd, J = 4, 12 Hz, $CH_{eq}O$), 3.06 (1H, s, $C{\equiv}CH$), 2.95 (1H, dd, J = 4, 12 Hz, $CH_{eq}S$), 2.82 (1H, dd, J = 8, 13.5 Hz, $CH_{ax}S$), 1.62 [1H, m, $CH(CH_2)_2$], 0.98 [9H, s, $(CH_3)_3C$]. This was followed by the trans (2-equatorial) isomer (**8**) (1.6 g, 62%) as white needles: mp 117–119 °C; MS [M + 1]$^+$ 261; NMR δ 7.45 and 7.39 (each 2H, AA′BB′, J = 8.5 Hz, aromatic), 5.67 (1H, s, CHAr), 4.40 (1H, ddd, J = 2.5, 3.5, 11.5 Hz, $CH_{eq}O$), 3.55 (1H, dd, J = 11.5 Hz, $CH_{ax}O$), 3.05 (1H, s, $C{\equiv}CH$), 2.99 (1H, dd, J = 11.5, 13 Hz, $CH_{ax}S$), 2.86 (1H, dd, J = 3, 13 Hz, $CH_{eq}S$), 1.81 [1H, tt, J = 3.5, 11.5 Hz, $CH(CH_2)_2$], 0.93, [9H, s, $(CH_3)_3C$].

Oxathianes **15**–**17** were prepared in a similar fashion from 3,3-dimethyl-2-(hydroxymethyl)butane-1-thiol and 4-iodobenzaldehyde or 4-iodoacetophenone. Oxathianes **18** and **23** were prepared from the appropriate iodophenyl oxathiane using the published procedures (Palmer and Casida, 1989). Oxathiane **19** was prepared from oxathiane **15** using a similar procedure but with propyne gas in place of (trimethylsilyl)acetylene. Oxathiane **21** was prepared from oxathiane **8** using the published general procedure (Kende and Smith, 1988). All compounds gave appropriate characterization.

*Preparation of Substituted 1,3-Oxathiane 3-Oxides (Figure 1). 5(e)-tert-Butyl-2(e)-(4-ethynylphenyl)-1,3-oxathiane 3-Oxides (**9** and **10**).* A solution of 5(e)-*tert*-butyl-2(e)-(4-ethynylphenyl)-1,3-oxathiane (**8**) (520 mg, 2 mmol) and *m*-chloroperoxybenzoic acid (*m*-CPBA)(90%, 400 mg ≅ 2 mmol) in dry dichloromethane (35 mL) was stirred at room temperature overnight. The solution was washed with pH 8.0 sodium phosphate buffer, dried ($MgSO_4$), and evaporated to leave a residue which was purified on a silica column. Careful elution with hexane–acetone (7:1 v/v) gave the 3(e)-sulfoxide **9** (490 mg, 89%) as white needles: mp 155–157 °C; MS [M + 1]$^+$ 277; NMR δ 7.51 and 7.44 (each 2H, AA′BB′, J = 8.5 Hz, aromatic H), 4.82 (1H, s, CHAr), 4.32 (1H, ddd, J = 2, 4, 11.5 Hz, $CH_{eq}O$), 3.69 (1H, ddd, J = 2, 12 Hz, $CH_{eq}SO$], 3.58 [1H, dd, J = 12 Hz, $CH_{ax}O$], 3.09 (1H, s, $C{\equiv}CH$), 2.71 (1H, dd, J = 12 Hz, $CH_{ax}SO$), 1.99 [1H, m, J = 2, 4, 11.5 Hz, $CH(CH_2)_2$], 0.99 [9H, s, $(CH_3)_3$]. This was followed by the 3(a)-sulfoxide **10** (60 mg, 11%) as white needles: mp 186–187 °C; MS [M + 1]$^+$ 277; NMR δ 7.50 and 7.40 (each 2H, AA′BB′, J = 8.5 Hz, aromatic H), 5.15 (1H, s, CHAr), 4.47 (1H, ddd, J = 3, 11.5 Hz, $CH_{eq}O$], 3.69 (2H, dd, J = 11.5 Hz, $CH_{ax}O$), 3.37 (1H, ddd, J = 2.5, 13.5 Hz, $CH_{eq}SO$), 3.07 (1H, s, $C{\equiv}CH$), 2.67 (1H, dd, J = 13.5 Hz, $CH_{ax}SO$), 2.50 [1H, m, J = 2.5, 3, 11.5, 13.5 Hz, $CH(CH_2)_2$], 0.97 [9H, s, $(CH_3)_3C$].

*5(e)-tert-Butyl-2(a)-(4-ethynylphenyl)-1,3-oxathiane 3-Oxide (**13**).* Using the above procedure, 5(e)-*tert*-butyl-2(a)-(4-ethynylphenyl)-1,3-oxathiane (**12**) was reacted with *m*-CPBA (1 equiv) to give the 3(a)-sulfoxide **13** as yellow crystals: mp 107–108 °C; MS [M + 1]$^+$ 277; NMR δ 7.50 and 7.41 (each 2H, AA′BB′, J = 8.5 Hz, aromatic H), 4.91 (1H, s, CHAr), 4.21 (1H, dd, J = 5.5, 12 Hz, $CH_{eq}O$), 4.04 [1H, dd, J = 6, 12 Hz, $CH_{ax}O$), 3.14 (1H, dd, J = 8.5, 13.5 Hz, $CH_{ax}SO$), 3.09 (1H, s, $C{\equiv}CH$), 2.94 (1H, dd, J = 4, 13.5 Hz, $CH_{eq}SO$), 2.23 [1H, m, J = 4, 5.5, 6, 8.5 Hz, $CH(CH_2)_2$], 1.02 [9H, s, $(CH_3)_3C$]. (The 3(e)-sulfoxide could not be detected in this reaction.)

*5(e)-tert-Butyl-2(e)-(4-ethynylphenyl)-1,3-oxathiane 3,3-Dioxide (**11**).* Using the above procedure, 5(e)-*tert*-butyl-2(e)-(4-ethynylphenyl)-1,3-oxathiane (**8**) was reacted with *m*-CPBA (2 equiv) to give the 3-sulfone **11** as white needles: mp 204–206 °C; MS [M + 1]$^+$ 293; NMR δ 7.52 and 7.48 (each 2H, AA′BB′, J = 8.5 Hz, aromatic H), 5.29 (1H, s, CHAr), 4.45 (1H, ddd, J = 2.5, 3.5, 12 Hz, $CH_{eq}O$), 3.67 (1H, dd, J = 12 Hz, $CH_{ax}O$), 3.39 (1H, ddd, J = 2.5, 13.5 Hz, $CH_{eq}SO_2$), 3.11 (1H, s, $C{\equiv}CH$), 3.06 (1H, dd, J = 13.5 Hz, $CH_{ax}SO_2$), 2.48 [1H, m, J = 3.5, 13 Hz, $CH(CH_2)_2$], 0.97 [9H, s, $(CH_3)_3C$].

*5(e)-tert-Butyl-2(a)-(4-ethynylphenyl)-1,3-oxathiane 3,3-Dioxide (**14**).* Using the above procedure, 5(e)-*tert*-butyl-2(a)-(4-ethynylphenyl)-1,3-oxathiane (**12**) was reacted with *m*-CPBA

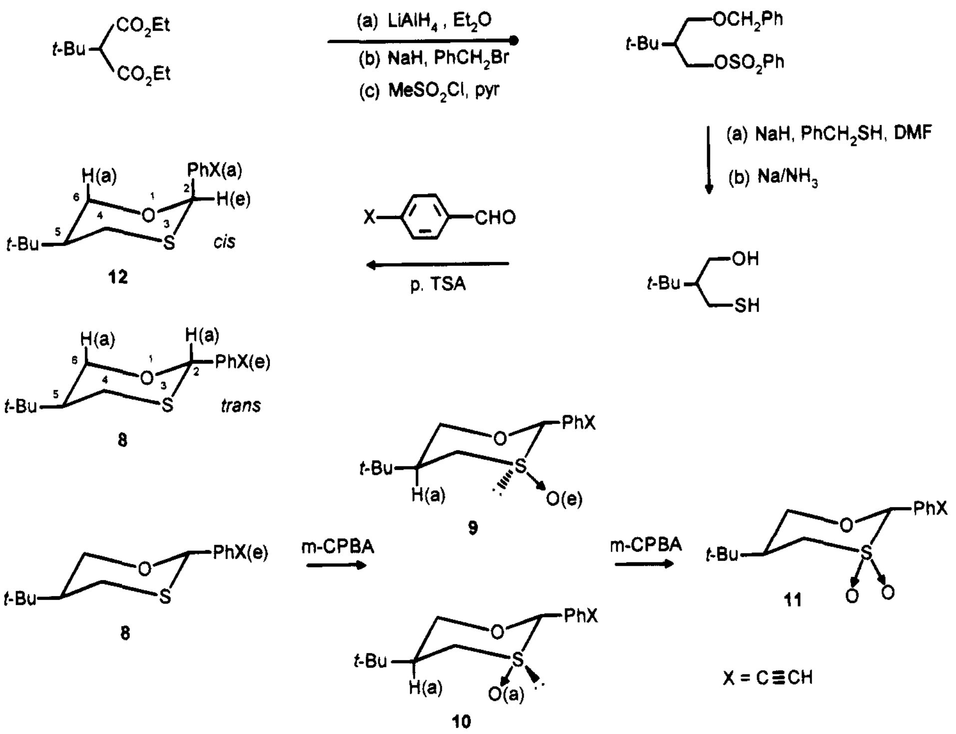


Figure 1. Synthesis of 2,5-disubstituted 1,3-oxathianes and their 3-oxides and 3,3-dioxides.

(2 equiv) to give the 3-sulfone **14** as white needles: mp 209–211 °C; MS $[M + 1]^+$ 293; NMR δ 7.53 and 7.42 (each 2H, AA′BB′, $J = 8.5$ Hz, aromatic H), 5.48 (1H, s, CHAr), 4.12 (1H, dd, $J = 7, 11$ Hz, $CH_{eq}O$), 3.97 (1H, dd, $J = 11$ Hz, $CH_{ax}O$), 3.25 (2H, m, $J = 13$ Hz, CH_2SO_2), 3.10 (1H, s, C≡CH), 2.51 [1H, m, $J = 7, 11, 13$ Hz, $CH(CH_2)_2$], 0.97 [9H, s, $(CH_3)_3C$].

Similarly oxathiane sulfones **20**, **22**, and **24** were prepared from their respective oxathianes **19**, **21**, and **23** and gave appropriate characterization.

RESULTS AND DISCUSSION

Reinvestigation of the 1,3-dioxane ring system revealed that with suitable substituents in the 5 position (*tert*-butyl, cyclobutyl, and 1-methylcyclopropyl), 2-(4-ethynylphenyl)-1,3-dioxanes can exhibit moderately high levels of insecticidal activity (Table 1). With LD_{50} to houseflies without synergist of 4–8 μg/g, and 0.75–1.15 μg/g with piperonyl butoxide, dioxanes **5**–**7** are 2 orders of magnitude more potent than those previously reported (Elliott *et al.*, 1992). While not as potent as the corresponding TBOs the activity of these 1,3-dioxanes approaches that of the corresponding 1,3-dithianes (Table 1). This unexpected level of activity was high enough to suggest that the 1,3-oxathianes (**4**) may also exhibit interesting levels of insecticidal activity.

Previous studies on the TBOs have shown that the most effective substituents at the bridgehead positions are 4-*tert*-butyl and 1-(4-ethynylphenyl) groups (Palmer and Casida, 1989; Palmer *et al.*, 1991a). These substituents are also highly effective in the 1,3-dithianes at the 5 and 2 positions, respectively (Elliott *et al.*, 1992). Accordingly, a series of 5-*tert*-butyl-2-(4-ethynylphenyl)-1,3-oxathianes and their sulfur oxidation products were prepared (Figure 1) and examined for insecticidal activity, particularly in comparison to the corresponding dithiane analogues (Table 2).

Unsynergized *trans*-oxathiane **8** is 1 order of magnitude more toxic to houseflies than its *cis* isomer **12**, although synergized with PB they are equipotent. Both these oxathianes are equally effective as their corresponding dithianes as insecticides, both alone and with PB. Oxathiane **8** is notable for exhibiting a low factor of synergism, indicating that it is not particularly sensitive to cytochrome P 450-mediated oxidative detoxification.

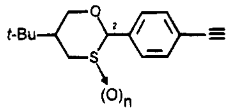
Table 1. Toxicity to Houseflies Alone and with Piperonyl Butoxide of 2(e)-(4-Ethynylphenyl)-1,3-dioxanes and Their Corresponding 1,3-Dithianes and 1-(4-Ethynylphenyl)-2,6,7-trioxabicyclo[2.2.2]octanes

	5-substituent	no.	LD_{50}, μg/g alone	LD_{50}, μg/g PB
1,3-dioxanes (**2**)	*t*-Bu	**5**	4.0	0.95
	c-Bu	**6**	6.5	0.75
	1-Me-c-Pr	**7**	8.0	1.15
1,3-dithianes[a] (**3**)	*t*-Bu		0.85	0.13
	c-Bu		1.1	0.15
	1-Me-c-Pr		0.45	0.065
2,6,7-trioxabicyclooctanes[b] (**1**)	*t*-Bu[c]		0.09	0.011
	c-Bu[c]		0.56	0.015
	1-Me-*c*-Pr[c]		0.63	0.029

[a] Data taken from Palmer and Casida (1992). [b] Data taken from Palmer *et al.* (1991a). [c] 4-Substituent.

Without synergist 3(e)-sulfoxide in the *trans* series (**9**) is much less toxic to houseflies than its parent (**8**), whereas the 3(a)-sulfoxide (**10**) is equipotent. However when synergized with PB, both sulfoxides are approximately 3 times more potent than their parent oxathiane. A similar structure–activity relationship is found between the corresponding dithianes and their monosulfoxides. Unsynergized the oxathiane sulfoxides are 20 times more potent than the corresponding dithiane monosulfoxides. However, when synergized with PB they are almost equipotent, indicating that these oxathiane sulfoxides may be less sensitive to metabolic detoxification because they lack a second sulfur oxidation site. In the *trans* series 3-sulfone **11** is 2- and 6-fold more potent than its parent oxathiane **8**, alone and with PB respectively. It is the most potent compound in the study and unsynergized is nearly 3 times more potent than the corresponding dithiane monosulfone. In the *cis* series, 3(a)-sulfoxide **13** is

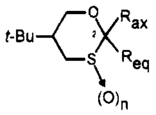
Table 2. Toxicity to Houseflies Alone and with Piperonyl Butoxide of 5(e)-*tert*-Butyl-2(e)-(4-ethynylphenyl)-1,3-oxathianes and Their 3(e)- and 3(a)-Oxides and 3,3-Dioxides



			LD$_{50}$, μg/g[a]		
no.	2[b]	n[c]	alone[d]	PB[d]	fac of syn
8	e	0	0.55 (0.85)	0.17 (0.13)	3.2
9	e	1_e	2.25 (50)	0.07 (0.035)	32
10	e	1_a	0.6 (11)	0.05 (0.05)	12
11	e	2	0.3 (0.8)	0.03 (0.0075)	10
12	a	0	6.0 (6.0)	0.23 (0.13)	26
13	a	1_a	10 (1.8)	0.33 (0.065)	30
14	a	2	0.95 (1.2)	0.023 (0.012)	41

[a] LD$_{50}$ values for established insecticides (alone and with PB) are as follows: 0.21 and 0.012 μg/g for (1*R*)-(*cis*)-permethrin; 1.3 and 0.43 μg/g for parathion (Palmer and Casida, 1989). [b] Stereochemistry of 2-substituent, equatorial (e) or axial (a) substituted phenyl group. [c] Entries denote the following: parent oxathiane (n = 0), equatorial sulfoxide ($n = 1_e$), axial sulfoxide ($n = 1_a$), sulfone (n = 2). [d] Values in parentheses are for the corresponding 1,3-dithianes (Palmer and Casida, 1992).

Table 3. Toxicity to Houseflies Alone and with Piperonyl Butoxide of 2(e)-Substituted and 2,2-Disubstituted 5(e)-*tert*-Butyl-1,3-oxathianes and Their 3,3-Dioxides



			LD$_{50}$, μg/g		
no.	2-substituent[a]	n[b]	alone	PB	fac of syn
15	4-IPh	0	10	10	1.0
16	4-IPh(ax), Me(eq)	0	10.5	4.0	2.6
17	4-IPh(eq), Me(ax)	0	78	50	1.6
18	4-HC≡CPh(eq), Me(ax)	0	23	1.6	14
19	4-MeC≡CPh	0	7.0	3.8	1.84
20	4-MeC≡CPh	2	75	0.024	3125
21	4-HC≡C−C≡CPh	0	2.5	1.25	2.0
22	4-HC≡C−C≡CPh	2	>500	>500	
23	4-[(Me$_3$Si)C≡C]Ph	0	11.5	>500	>0.023
24	4-[(Me$_3$Si)C≡C]Ph	2	1.1	0.095	11.6

[a] Substituted phenyl group is equatorial unless otherwise stated. [b] Entries denote the following: parent oxathiane (n = 0), sulfone (n = 2).

slightly less potent than its parent oxathiane **12**, both alone and with PB. 3-Sulfone (**14**) is 6- and 10-fold more potent than its parent oxathiane (**12**), alone and with PB respectively. A similar structure−activity relationship is found with the corresponding compounds in the *cis*-dithiane series. Generally, for the oxathianes and their oxides, activity is greater when the phenyl group is equatorial (*trans* series) rather than axial (*cis* series).

A number of other substituents were examined for their ability to confer insecticidal activity in the oxathiane series (Table 3). Groups chosen were those known to be effective in the 1,3-dithiane and 2,6,7-trioxabicyclooctane series. However in many cases these substituents were not as useful.

2-(4-Iodophenyl)oxathianes (**15**−**17**) exhibit only modest insecticidal activity alone and synergized with PB. Introduction of a methyl group at C-2 or to the terminal acetylene in the ethynylphenyl series reduces the toxicity to houseflies, oxathianes **18** and **19** being 1 order of magnitude less active than oxathiane **8**. Sulfone **20** unsynergized is only weakly active, but synergized with PB is equal in potency to oxathiane sulfones **11** and **14** and as such exhibits a remarkably high factor of synergism. This indicates that sulfone **20** is particularly sensitive to metabolic oxidative detoxification but at a site other than sulfur. 2-(Butadiynylphenyl)oxathiane **21** is moderately toxic to houseflies but somewhat surprisingly its sulfone **22** is completely inactive. As in the case of [(trimethylsilyl)ethynyl]phenyl-substituted trioxabicyclooctanes, oxathiane **23** exhibits proinsecticidal activity (Palmer *et al.*, 1990, 1991b). In contrast, silylated oxathiane sulfone **24** is not a proinsecticide and exhibits quite potent insecticidal activity with PB.

In conclusion, this study shows that with suitable 2- and 5-substituents, 1,3-oxathianes and their 3-oxides and 3,3-dioxides are potent insecticides. Generally their toxicity to houseflies is comparable to that of the corresponding 1,3-dithianes, and in some cases exceeds it. The most effective compound is oxathiane sulfone **11** which, alone and synergized with PB, approaches the level of activity of (1*R*)-*cis*-permethrin. The 1,3-oxathiane ring is yet another example of a suitable spacer unit replacement for the bicyclic ring of insecticidal 1,4-disubstituted 2,6,7-trioxabicyclo[2.2.2]octanes.

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