Insecticidal 1,3-Dithianes and 1,3-Dithiane 1,1-Dioxides†

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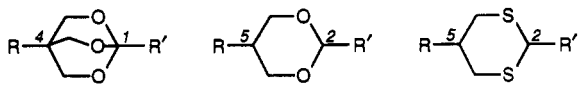
Replacement of the *tert*-butyl substituent of insecticidal *cis*- and *trans*-5-*tert*-butyl-2-(4-substituted-phenyl)-1,3-dithianes with cyclobutyl or 1-methylcyclopropyl groups affords compounds with equal or increased toxicity to houseflies. The 1,3-dithiane 1-oxides derived by *m*-chloroperoxybenzoic acid oxidation of the *trans*-dithianes are much less effective; unsynergized, their insecticidal activity is weak due to facile metabolic detoxification. The 1,3-dithiane 1-oxides similarly derived from the *cis*-dithianes generally exhibit a modest but significantly higher level of toxicity. Selective oxidation of the 1,3-dithiane 1-oxides with potassium permanganate afforded the corresponding 1,3-dithiane 1,1-dioxides, which alone and synergized with piperonyl butoxide are up to 11- and 37-fold more potent, respectively, than their parent dithianes. Housefly LD_{50}s for *trans*-2(e)-(4-ethynylphenyl)-5(e)-(1-methylcyclopropyl)-1,3-dithiane 1,1-dioxide are 0.36 and 0.0095 μg/g alone and with piperonyl butoxide, respectively. It is the most insecticidal analogue in the dithiane series and is equal in potency to (1*R*)-*cis*-permethrin and to the most potent trioxabicyclooctane insecticides.

INTRODUCTION

1,4-Disubstituted-2,6,7-trioxabicyclo[2.2.2]octanes (TBOs) (1) are a new 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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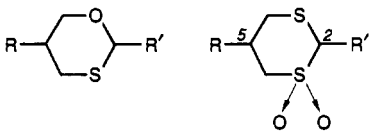
A recent paper suggested the possibility that the 2,6,7-trioxabicyclo[2.2.2]octane ring may function as a spacer unit maintaining the 1- and 4-substituents in a linear relationship and investigated related compounds with a single heterocyclic ring (Elliott et al., 1990, 1992). Examination of the 1,3-dioxane ring system (2) with one fewer CH_2O link led to analogues with only weak insecticidal activity; however, analogues containing the 1,3-dithiane ring (3) were quite potent. Suitable substituents for the 2-position in 1,3-dithianes are the same as those which confer high insecticidal activity in the 1-position of TBOs, i.e., 4-ethynylphenyl, 4-halophenyl, and 3,4-dihalophenyl groups. A *tert*-butyl group is also required at the 5-position in 1,3-dithianes for significant activity, and this site appears to correspond to the 4-position of the TBOs for which the *tert*-butyl group is also highly effective. While some dithianes exhibit a fairly high level of toxicity to houseflies, the activity of most dithianes is much less than that of the corresponding TBOs. The most potent dithianes reported are at least 10-fold less active to houseflies than the most potent TBOs. The insecticidal dithianes and the TBOs act at the same or closely coupled sites in the GABA-gated chloride channel (Deng et al., 1991).

Recent observations concerning structure–activity relationships in the TBOs (1) and 1,3-oxathianes (4) (Palmer et al., 1991a) prompted further investigations in the related 1,3-dithiane area.



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The present study describes attempts to improve the insecticidal activity of the 1,3-dithianes by effective replacement of the *tert*-butyl group at C-5 and by oxidation to the corresponding 1,3-dithiane 1,1-dioxides (5).

MATERIALS AND METHODS

Abbreviations. Substituents are designated Me, methyl; Pr, propyl; Bu, butyl; Ph, phenyl; *n*, normal; *s*, secondary; *t*, tertiary; *c*, cyclo; e, equatorial; and a, axial.

Nomenclature and Stereochemical Assignments (Figure 1). All of the 5-alkyl-2-(substituted-phenyl)-1,3-dithianes in this study adopt a chair conformation, and the 5-alkyl group is equatorially oriented. 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 ^1H NMR spectral data with nuclear Overhauser effect (NOE) ^1H NMR differential spectroscopy experiments to establish the orientation (axial or equatorial) of the substituent at C-2. [A similar conformational study on related 1,3-oxathianes using NOE ^1H NMR differential spectroscopy has been reported (De Lucchi et al., 1985).] Stereochemistry of the 1,3-dithiane 1-oxides (axial or equatorial monosulfoxide) is readily determined from their ^1H NMR spectra using the "*syn*-axial effect", a method used routinely for assigning configuration to appropriate pairs of stereoisomeric monosulfoxides (Foster et al., 1968; Carretero et al., 1984; Singer et al., 1987; Romanelli et al., 1988). ^{13}C NMR can provide further confirmation of sulfoxide orientation (Carey et al., 1978; Samuel et al., 1989).

Bioassays. LD_{50} values were determined for adult female houseflies (*Musca domestica* L., SCR strain, ~20 mg each) held for 24 h at 25 °C after application of the test compound in acetone

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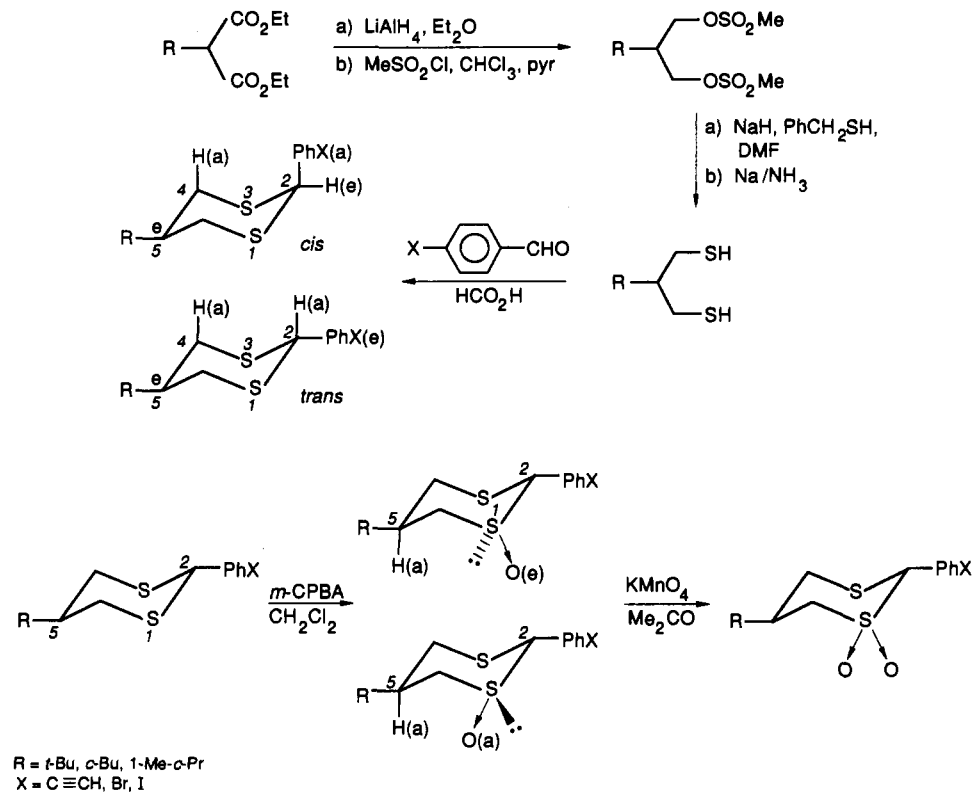


Figure 1. Synthesis of 2,5-disubstituted-1,3-dithianes and their 1-oxides and 1,1-dioxides.

solution to the ventrum of the abdomen (Palmer and Casida, 1985). Synergized toxicity was evaluated by using flies pretreated topically with 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

The various dithianes and their oxidation products used in this study were prepared via the general procedure shown in Figure 1. The appropriate diethyl 2-substituted malonate (Palmer et al., 1991b) was reduced to the corresponding 2-substituted propane-1,3-diol with lithium aluminum hydride (Eliel and Knoeber, 1968). The diol was converted to its dimethanesulfonate ester (Crossland and Servis, 1970), which upon treatment with benzylmercaptan and sodium hydride in dimethylformamide formed the dibenzyl thioether which was converted to the 2-substituted propane-1,3-dithiol with sodium in liquid ammonia (Corrie et al., 1977). Condensation of the dithiol with the appropriate benzaldehyde in formic acid (Elliott et al., 1990, 1992) formed the 2,5-disubstituted-1,3-dithianes as a mixture of trans 2-equatorial (e) and cis 2-axial (a) diastereomers (ratio ~7:1 e/a). Following chromatographic separation of the diastereomers, oxidation with *m*-chloroperoxybenzoic acid (Carey et al., 1976) gave a mixture of 1(e) and 1(a) monosulfoxides. [The *trans*-dithianes gave sulfoxide ratios ~24:1 e/a; the *cis*-dithianes gave sulfoxide ratios ~2:13 e/a. This is consistent with preferential (e)-sulfoxide formation from related 2(e)-phenyl-1,3-dithianes and preference for (a)-sulfoxide formation from 2(a)-phenyl-1,3-dithianes (Carey et al., 1976; Bryan et al., 1979).] The sulfoxide mixtures were separated chromatographically and selectively oxidized to the corresponding dithiane monosulfones with potassium permanganate (Block et al., 1976; Kabzinska and Kawecki, 1989; Khan et al., 1975). Examples of syntheses with compound characterization are given below for the 1-methylcyclopropyl series. The remaining compounds used in this study were prepared according to similar procedures and gave appropriate characterization.

***trans*- and *cis*-2-(4-ethynylphenyl)-5(e)-(1-methylcyclopropyl)-1,3-dithianes (26 and 30).** To a stirred solution of 4-ethynylbenzaldehyde (Austin et al., 1981) (320 mg, 2.4 mmol) dissolved in the minimum amount of formic acid at 0 °C was added 2-(1-methylcyclopropyl)propane-1,3-dithiol (400 mg, 2.4 mmol). After 1 h, the mixture was evaporated to dryness and the residue was purified on a silica column. Elution with hexane–dichloromethane (9:1 v/v) gave the cis (2-axial) isomer (**30**) (75 mg, 11%) as white needles: mp 116–117 °C; MS $[M + 1]^+$ 275; NMR δ 7.78 and 7.49 (each 2 H, AA'BB', J = 8 Hz, aromatic H), 4.80 (1 H, s, CHAr), 3.08 (1 H, s, C≡CH), 2.79 (2 H, dd, J = 11, 14 Hz, $CH_{ax}S \times 2$), 2.57 (2 H, dd, J = 3, 14 Hz, $CH_{eq}S \times 2$), 1.27 [1 H, tt, J = 3, 11 Hz, $CH(CH_2)_2$], 0.80 (3 H, s, CH_3), 0.36–0.24 (4 H, m, CH_2CH_2). This was followed by the trans (2-equatorial) isomer (**26**) (530 mg, 79%) as white needles: mp 149–152 °C; MS $[M + 1]^+$ 275; NMR δ 7.42 and 7.40 (each 2 H, AA'BB', J = 8.5 Hz, aromatic H), 5.10 (1 H, s, CHAr), 3.06 (2 H, dd, J = 11.5, 14 Hz, $CH_{ax}S \times 2$), 3.06 (1 H, s, C≡CH), 2.84 (2 H, dd, J = 2.5, 14 Hz, $CH_{eq}S \times 2$), 1.17 [1 H, tt, J = 2.5, 11.5 Hz, $CH(CH_2)_2$], 0.95 (3 H, s, CH_3), 0.40–0.31 (4 H, m, CH_2CH_2).

2(a)-(4-Ethynylphenyl)-5(e)-(1-methylcyclopropyl)-1,3-dithiane 1-Oxides (31 and 32). A solution of *cis*-2(a)-(4-ethynylphenyl)-5(e)-(1-methylcyclopropyl)-1,3-dithiane (320 mg, 1.16 mmol) and *m*-chloroperoxybenzoic acid (250 mg, 1.16 mmol) in dry dichloromethane (10 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 9:1 (v/v) gave the 1(e) sulfoxide (**31**) (40 mg, 12%) as yellow needles: mp 105–106 °C, MS $[M + 1]^+$ 291; NMR δ 7.70 and 7.55 (each 2 H, AA'BB', J = 8.5 Hz, aromatic H), 5.01 (1 H, s, CHAr), 3.12 (1 H, s, C≡CH), 2.91 (1 H, dd, J = 12, 14 Hz, $CH_{ax}S$), 2.78 (1 H, dq, J = 2, 12.5 Hz, $CH_{eq}SO$), 2.57 (1 H, t, J = 12.5 Hz, $CH_{ax}SO$), 2.40 (1 H, ddd, J = 1.5, 3.5, 14 Hz, $CH_{eq}S$), 1.64 [1 H, m, J = 2, 3.5, 12 Hz, $CH(CH_2)_2$], 0.83 (3 H, s, CH_3), 0.38–0.28 (4 H, m, CH_2CH_2). This was followed by the 1(a) sulfoxide (**32**) (260 mg, 77%) as yellow needles: mp 163–164 °C, MS $[M + 1]^+$ 291; NMR δ 7.53 (4 H, s, aromatic H), 4.66 (1 H, s, CHAr), 3.11 (1 H, s, C≡CH), 2.92 (1 H, dd, J = 10.5,

13.5 Hz, $CH_{ax}S$), 2.79–2.68 (2 H, m, $CH_{eq}SO$ and $CH_{eq}S$), 2.62 (1 H, dd, J = 10.5, 14 Hz, $CH_{ax}SO$), 1.86 [1 H, m, J = 3, 3.5, 10.5 Hz, $CH(CH_2)_2$], 0.88 (3 H, s, CH_3), 0.50–0.24 (4 H, m, CH_2CH_2).

2(e)-(4-Ethynylphenyl)-5(e)-(1-methylcyclopropyl)-1,3-dithiane 1-Oxides (27 and 28). Using the above procedure, oxidation of *trans*-2(e)-(4-ethynylphenyl)-5(e)-(1-methylcyclopropyl)-1,3-dithiane (630 mg, 2.3 mmol) with *m*-chloroperoxybenzoic acid (490 mg, 2.3 mmol) followed by purification on silica and elution with dichloromethane gave the 1(a) sulfoxide (**28**) (25 mg, 4%) as yellow needles: mp 207–208 °C; MS [M + 1]$^+$ 291; NMR δ 7.45 and 7.35 (each 2 H, AA′BB′, J = 8.5 Hz, aromatic H), 4.69 (1 H, s, CHAr), 3.20 (1 H, dt, J = 2, 14 Hz, $CH_{eq}SO$), 3.08 (1 H, s, C≡CH), 3.07 (1 H, dd, J = 12, 14 Hz, $CH_{ax}S$), 2.72–2.63 (2 H, m, $CH_{eq}S$ and $CH_{ax}SO$), 1.83 [1 H, tt, J = 2.5, 12 Hz, $CH(CH_2)_2$], 0.95 (3 H, s, CH_3), 0.50–0.29 (4 H, m, CH_2CH_2). This was followed by the 1(e) sulfoxide (**27**) (600 mg, 90%) as yellow needles: mp 211–212 °C, MS [M + 1]$^+$ 291; NMR δ 7.49 and 7.34 (each 2 H, AA′BB′, J = 8.5 Hz, aromatic H), 4.46 (1 H, s, CHAr), 3.54 (1 H, dt, J = 2, 12.5 Hz, $CH_{eq}SO$), 3.09 (1 H, s, C≡CH), 2.90 (1 H, dd, J = 11.5, 14 Hz, $CH_{ax}S$), 2.80 (1 H, t, J = 12.5 Hz, $CH_{ax}SO$), 2.65 (1 H, ddd, J = 2, 3, 14 Hz, $CH_{eq}S$), 1.61 [1 H, m, $CH(CH_2)_2$], 1.01 (3 H, s, CH_3), 0.46–0.38 (4 H, m, CH_2CH_2).

***cis*-2(a)-(4-Ethynylphenyl)-5(e)-(1-methylcyclopropyl)-1,3-dithiane 1,1-Dioxide (33).** To a stirred solution of 2(a)-(4-ethynylphenyl)-5(e)-(1-methylcyclopropyl)-1,3-dithiane 1-oxide (200 mg, 0.7 mmol) in dry acetone (50 mL) containing anhydrous magnesium sulfate (0.8 g) was added potassium permanganate (350 mg, 2.2 mmol). After 2 h, the solution turned colorless and the mixture was filtered through a short Florisil column; the filtrate was evaporated to leave a residue which was purified on a silica column. Elution with dichloromethane gave the monosulfone (**33**) (90 mg, 43%) as yellow crystals: mp 186–187 °C; MS [M + 1]$^+$ 307; NMR δ 7.58 and 7.51 (each 2 H, AA′BB′, J = 8.5 Hz, aromatic H), 4.94 (1 H, s, CHAr), 3.26 (1 H, dd, J = 12.5, 14 Hz, $CH_{ax}SO_2$), 3.13 (1 H, s, C≡CH), 3.08 (1 H, m, J = 14 Hz, $CH_{eq}SO_2$), 2.99 (1 H, dd, J = 11, 13.5 Hz, $CH_{ax}S$), 2.88 (1 H, m, J = 4.5, 13.5 Hz, $CH_{eq}S$), 1.94 [1 H, m, 4.5, 11, 12.5 Hz, $CH(CH_2)_2$], 0.94 (3 H, s, CH_3), 0.47–0.35 (4 H, m, CH_2CH_2).

***trans*-2(e)-(4-Ethynylphenyl)-5(e)-(1-methylcyclopropyl)-1,3-dithiane 1,1-Dioxide (29).** Using the above procedure, oxidation of 2(e)-(4-ethynylphenyl)-5(e)-(1-methylcyclopropyl)-1,3-dithiane 1-oxide (430 mg, 1.5 mmol) gave the monosulfone (**29**) (200 mg, 44%) as yellow crystals: mp 216–217 °C; MS [M + 1]$^+$ 307; NMR δ 7.50 and 7.45 (each 2 H, AA′BB′, J = 8.5 Hz, aromatic H), 5.00 (1 H, s, CHAr), 3.32 (1 H, dt, J = 2, 14 Hz, $CH_{eq}SO_2$), 3.14 (1 H, dd, J = 12.5, 14 Hz, $CH_{ax}SO_2$), 3.11 (1 H, s, C≡CH), 3.04 (1 H, dd, J = 11.5, 14 Hz, $CH_{ax}S$), 2.81 (1 H, dt, J = 2, 14 Hz, $CH_{eq}S$), 1.97 [1 H, m, J = 2, 11.5, 12.5 Hz, $CH(CH_2)_2$], 0.99 (3 H, s, CH_3), 0.52–0.32 (4 H, m, CH_2CH_2).

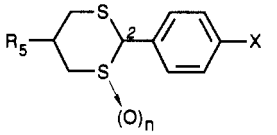
RESULTS (TABLE I)

1,3-Dithianes. In the dithianes the trans isomer (with the 2-substituent equatorial) is generally more toxic to houseflies than the corresponding cis isomer (2-substituent axial); i.e., *trans*-dithianes **6**, **14**, **18**, **26**, and **34** are more effective than their respective *cis*-dithianes **10**, **16**, **22**, **30**, and **36**. This is more pronounced in the 2-(4-ethynylphenyl) compounds. Like the 5-*t*-Bu-dithianes, the 5-*c*-Bu- and 5-(1-Me-*c*-Pr) analogues are potent insecticides. *trans*-(1-Me-*c*-Pr)-dithiane (**26**) is 2-fold more potent than the *trans*-*t*-Bu-dithiane (**18**) [the most potent previously reported dithiane (Elliott et al., 1990, 1992)], both alone and with PB. Generally the dithianes exhibit a fairly low factor of synergism, especially the 2-(4-halophenyl) compounds.

1,3-Dithiane 1-Oxides (Monosulfoxides). In the *trans*-dithiane series both the 1(e) and 1(a) monosulfoxides are much less toxic to houseflies unsynergized than their unoxidized parent dithianes; i.e., sulfoxides **7** and **8**, **19** and **20**, and **27** and **28** are less potent than dithianes **6**, **18**, and **26**, respectively. However, with PB these sulfoxides are typically 2–4-fold more potent than their parent dithianes. Both the 1(e) and 1(a) monosulfoxides of the *cis*-dithiane series are more toxic to houseflies alone and with PB than their parent dithianes, typically by 2–8-fold, i.e., sulfoxides **11** and **12**, **23** and **24**, and **31** and **32** are more toxic than their parent dithianes **10**, **22**, and **30**, respectively. Generally for each pair of monosulfoxides there is very little difference in potency between the 1-axial or 1-equatorial stereoisomer in both *cis*- and *trans*-dithiane series. With the exception of the two *cis*-(4-bromophenyl) analogues, the dithiane monosulfoxides exhibit a very high factor of synergism, particularly those of the *trans*-(4-ethynylphenyl) series.

1,3-Dithiane 1,1-Dioxides (Monosulfones). In the *trans*-dithiane series the monosulfones unsynergized are up to 3.5-fold more toxic to houseflies than their parent dithianes. However, synergized with PB there is a dramatic increase in activity; i.e., monosulfones **9**, **15**, **21**, **29**, and **35** are 7–22-fold more potent than their parent dithianes **6**, **14**, **18**, **26**, and **34**, respectively. Similarly, the monosulfones of the *cis*-dithiane series are also much more toxic to houseflies than their parent dithianes, alone by

Table I. Toxicity to Houseflies Alone and with Piperonyl Butoxide of 5(e)-Alkyl-2(e)- and 2(a)-(4-Substituted-phenyl)-1,3-dithianes and Their 1(e) and 1(a) Oxides and 1,1-Dioxides



no.	R_5	X	2[b]	n[c]	LD_{50},[a] μg/g alone	LD_{50},[a] μg/g PB	fac of syn
6[d]	*t*-Bu	Br	e	0	6.0	1.2	5.0
7			e	1_e	18	0.6	30
8			e	1_a	10	0.15	67
9			e	2	1.7	0.06	28
10[d]	*t*-Bu	Br	a	0	7.0	2.0	3.5
11			a	1_e	1.0	0.27	3.7
12			a	1_a	1.0	0.23	4.3
13			a	2	2.3	0.1	23
14[d]	*t*-Bu	I	e	0	2.3	1.5	1.5
15			e	2	5.0	0.068	74
16	*t*-Bu	I	a	0	3.0	2.1	1.4
17			a	2	0.55	0.1	5.5
18[d]	*t*-Bu	C≡CH	e	0	0.85	0.13	6.5
19			e	1_e	50	0.035	1429
20			e	1_a	11	0.050	220
21			e	2	0.80	0.0075	107
22	*t*-Bu	C≡CH	a	0	6.0	0.13	46
23			a	1_e	1.9	0.025	76
24			a	1_a	1.8	0.065	28
25			a	2	1.2	0.012	100
26	1-Me-*c*-Pr	C≡CH	e	0	0.45	0.065	6.9
27			e	1_e	6.5	0.050	130
28			e	1_a	7.0	0.032	219
29			e	2	0.36	0.0095	38
30	1-Me-*c*-Pr	C≡CH	a	0	3.4	0.16	21
31			a	1_e	1.9	0.070	27
32			a	1_a	1.8	0.065	28
33			a	2	1.3	0.013	100
34	*c*-Bu	C≡CH	e	0	1.1	0.15	7.3
35			e	2	1.6	0.011	145
36	*c*-Bu	C≡CH	a	0	9.5	1.1	8.6
37			a	2	0.90	0.030	30

[a] LD_{50} values for established insecticides and selected TBOs (alone and with PB) are 0.21 and 0.012 μg/g for (1*R*)-*cis*-permethrin, 1.3 and 0.43 μg/g for parathion, 3.5 and 0.83 μg/g for *t*-BuC$(CH_2O)_3$CPh-4-Br, 0.090 and 0.011 μg/g for *t*-BuC$(CH_2O)_3$CPh-4-C≡CH, 0.63 and 0.029 μg/g for 1-Me-*c*-PrC$(CH_2O)_3$CPh-4-C≡CH, and 0.56 and 0.015 μg/g for *c*-BuC$(CH_2O)_3$CPh-4-C≡CH, respectively (Palmer and Casida, 1989; Palmer et al., 1991b). [b] Stereochemistry of 2-substituent, equatorial (e) or axial (a) substituted phenyl group. [c] Entries denote parent dithiane (n = 0), equatorial sulfoxide (n = 1_e), axial sulfoxide (n = 1_a), and monosulfone (n = 2). [d] Compounds first reported by Elliott et al. (1990, 1992).

3–11-fold and with PB by 11–37-fold; i.e., sulfones **13**, **17**, **25**, **33**, and **37** are more toxic than their parent dithianes **10**, **16**, **22**, **30**, and **36**, respectively. Many of the dithiane monosulfones also exhibit a fairly high factor of synergism.

DISCUSSION

Initial studies concerning the insecticidal activity of the 2,5-disubstituted 1,3-dithianes concluded that a *tert*-butyl group in the 5-position is essential for high potency. The wide range of bridgehead (4-position) substituents conferring very high activity in the TBOs (i.e., *n*-alkyl, branched alkyl, cycloalkyl, and aryl) does not appear to extend to the 5-position of the dithianes. For example, compounds with *n*-butyl, *s*-butyl, cyclohexyl, or phenyl are only weakly active in the dithiane series (Elliott et al., 1990, 1992), and yet the corresponding TBOs are very potent insecticides and are of comparable activity to the 4-*t*-Bu-TBO (Palmer et al., 1991b). The more conformationally flexible nature of the dithiane ring in these analogues (compared to the rigid TBO cage structure) may be responsible for this, since the *tert*-butyl substituent, due to its steric bulk, tends to lock the dithiane conformation by its preference for an equatorial orientation (Eliel and Hutchins, 1969). In this study cyclobutyl and 1-methylcyclopropyl substituents were examined as possible replacements for *tert*-butyl at the 5-position. In the TBOs these two groups are very effective (Palmer et al., 1991b), and like *tert*-butyl they would also be expected to prefer the equatorial orientation in dithianes due to their steric size and shape. The results in Table I demonstrate that cyclobutyl and especially 1-methylcyclopropyl are very effective replacement groups for the 5-*tert*-butyl substituent, leading to a significant increase in activity in the dithiane series.

Initial investigations concerning the insecticidal activity of the closely related 1,3-oxathianes (**4**) and their S-oxidation products (Palmer et al., 1991a) indicated that the oxathiane sulfones were more potent than their unoxidized oxathiane parent compounds. This suggested that the 1,3-dithiane 1,1-dioxides (monosulfones) (**5**) may likewise lead to increased insecticidal potency in the dithiane series. Accordingly, examination of both the 1,3-dithiane 1,1-dioxides and their 1,3-dithiane 1-oxide (monosulfoxide) precursors led to compounds with very interesting levels of activity (Table I). The potency of the 1,3-dithiane 1-oxides (monosulfoxides) is generally rather disappointing, especially in the *trans*-dithiane series. These compounds are effective against houseflies only in the presence of PB, the very high factor of synergism indicating that their toxicity is severely limited by metabolic oxidative detoxification. While the insecticidal activity exhibited by the monosulfoxides of the *cis*-dithiane series is a significant improvement over that of their unoxidized *cis*-dithiane parent compounds, they are still much less active than the most potent TBOs. In contrast, the 1,3-dithiane 1,1-dioxides (monosulfones) of both the cis and trans series are much more potent than their unoxidized parent dithianes and in some cases exhibit greater insecticidal activity than their corresponding analogues in the TBO series. The most effective compounds in this study are 1,3-dithiane 1,1-dioxides (monosulfones) **21** and **29**; unsynergized, their activity approaches, and synergized with PB even slightly exceeds, that exhibited by the most potent TBOs and (1*R*)-*cis*-permethrin.

In conclusion, this study shows that (1) the 5-*tert*-butyl substituent of insecticidal 1,3-dithianes is not essential for activity and can be replaced with alternative groups to give analogues with equal or increased potency and (2) while in some cases the 1,3-dithiane ring is a suitable spacer unit replacement for the bicyclic ring of insecticidal 1,4-disubstituted-2,6,7-trioxabicyclo[2.2.2]octanes, the 1,3-dithiane 1,1-dioxide is a far more effective replacement.

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