2-Aryl-5-*tert*-butyl-1,3-dithianes and Their S-Oxidation Products: Structure–Activity Relationships of Potent Insecticides Acting at the GABA-Gated Chloride Channel†

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2-(4-Bromophenyl)-, 2-(4-ethynylphenyl)-, and 2-phenyl-5-*tert*-butyl-1,3-dithianes were prepared as their cis and trans isomers. Oxidation with *m*-chloroperoxybenzoic acid or permanganate yielded 12 S-oxidation products in each aryl series. The relative potencies of the dithianes and their oxidation products for both topical toxicity to houseflies and inhibition of [^{35}S]-*tert*-butylbicyclophosphorothionate binding to mouse brain membranes are generally ethynylphenyl > bromophenyl > phenyl. The 2-axial and 2-equatorial isomers, except for the monosulfoxides, are usually of similar potency at the receptor and to houseflies pretreated with piperonyl butoxide (PB) synergist. Monosulfoxides with the trans arrangement of the 2-aryl group and the S=O bond are more potent as receptor blockers, while the cis isomers are more toxic to PB-synergized houseflies. Maximum potency is always attained with the monosulfone; e.g., with *cis*- and *trans*-2-(4-ethynylphenyl)-5-*tert*-butyl-1,3-dithiane 1,1-dioxide the housefly LD_{50} is 0.6 μg/g alone or 0.01–0.02 μg/g with PB and the [^{35}S]TBPS receptor IC_{50} is 1 nM. Studies with [^{3}H]ethynylbicycloorthobenzoate and housefly brain membranes further indicate that the dithianes and their S-oxidation products act at the GABA-gated chloride channel.

INTRODUCTION

1,3-Dithianes with appropriate substitution at the 2- and 5-positions are potent insecticides acting at the γ-aminobutyric acid (GABA)-gated chloride channel (Elliott et al., 1992). These monocyclic 2,5-disubstituted dithianes have the same mode of action as the insecticidal bicyclic 1,4-disubstituted-2,6,7-trioxabicyclo[2.2.2]octanes with similar alkyl (e.g., *tert*-butyl) and aryl (e.g., 4-substituted-phenyl) substituents conferring high activity in both classes (Casida and Palmer, 1988; Casida et al., 1985, 1988; Elliott et al., 1992; Palmer and Casida, 1985, 1989).

The sulfur atoms of dithianes and related compounds are sensitive to a wide range of oxidants including peracids and permanganate (Henbest and Khan, 1968; Madesclaire, 1986). The biological activity of the dithiane oxidation products is of interest since they provide a large set of analogues varying only in the central portion of the molecule (see Figure 1 for nomenclature). Thus, for a particular 2,5-disubstituted-1,3-dithiane there are in theory six racemic and three meso S-oxidation products (Figure 2; Table I). This series may help define the relationship between structure and neuroreceptor affinity and toxicity.

The present study examines isomers of 2-(4-bromophenyl)- and 2-(4-ethynylphenyl)-5-*tert*-butyl-1,3-dithianes chosen for their high biological activity (Elliott et al., 1992) and of 2-phenyl-5-*tert*-butyl-1,3-dithiane selected on the basis of classical conformational studies (Eliel and Hutchins, 1969). The S-oxidation products of these dithianes were prepared and structurally assigned. All compounds were then tested for toxicity to houseflies, both alone and with piperonyl butoxide (PB) to minimize oxidative detoxification, and for potency in blocking the GABA-gated chloride channel, measured as inhibition of [^{35}S]-*tert*-butylbicyclophosphorothionate ([^{35}S]TBPS) binding in mouse brain membranes. Some of the derivatives were also assayed for toxicity to mice and for potency as inhibitors of [^{3}H]ethynylbicycloorthobenzoate ([^{3}H]-EBOB) binding in housefly brain membranes.

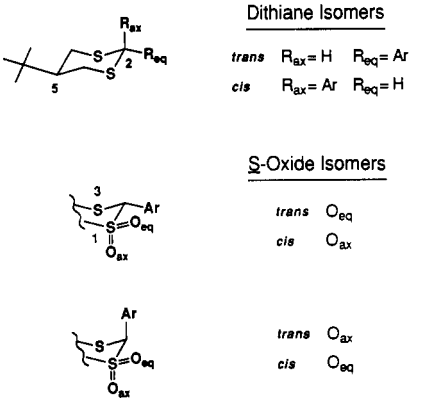

Figure 1. Stereochemistry of dithianes and their S-oxidation products. Orientations of dithiane ring substituents are designated axial (ax) or equatorial (eq). The 5-*tert*-butyl and sulfoxide groups are defined as cis or trans relative to the 2-aryl substituent.

MATERIALS AND METHODS

General. *m*-Chloroperoxybenzoic acid (MCPBA; 80–85%), benzaldehyde, and 4-bromobenzaldehyde were from Aldrich. The MCPBA used for oxidations was >98% pure after exhaustive washing of a dichloromethane solution with Tris buffer (pH 9). 4-Ethynylbenzaldehyde was prepared from 4-bromobenzaldehyde (Austin et al., 1981) and 2-*tert*-butylpropan-1,3-dithiol from diethyl *tert*-butylmalonate (from Alfa Products) (Eliel et al., 1975a). Tetrahydrofuran (THF) was dried by distillation over sodium and benzophenone.

Spectroscopy. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra (chloroform-*d* solutions at 21 °C unless otherwise specified) were recorded on a Bruker AM300 spectrometer at 300 and 75 MHz, respectively, and processed using an ASPECT

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3000 computer. Data are reported as δ relative to tetramethylsilane [number of protons, multiplicity, s = singlet, m = multiplet, J (Hz), and assignment]. The multiplicities of ^{13}C NMR resonances were assigned by the attached proton test (Patt and Shoolery, 1982). Absorbances of the methylene protons were assigned using C–H shift correlated two-dimensional (2D) NMR spectroscopy (Bax and Morris, 1981). Infrared (IR) spectra were recorded as KBr disks on a Perkin-Elmer 1620 series Fourier transform IR spectrophotometer with the bands reported as cm^{-1} and described as strong (s), medium (m), or weak (w). Mass spectra (MS) were obtained using a Hewlett-Packard 5985B GC/MS system with a direct insertion probe and an ion source temperature of 130 °C for chemical ionization (CI) or 200 °C for electron impact (EI) ionization.

Chromatography. Preparative thin-layer chromatography (TLC) involved silica gel GF plates (1- or 2-mm thickness; from Analtech) with visualization by ultraviolet light. Column chromatography utilized silica gel 60 (particle size 0.063–0.2 mm, 70–230 mesh ASTM; from Merck) and TLC monitoring of the fractions.

Receptor Assays. [^{35}S]TBPS was used to assay the potency of dithiane derivatives as inhibitors of the GABA-gated chloride channel in mouse brain (Obata et al., 1988; Squires et al., 1983). The receptor source was EDTA/water dialyzed brain P2 membranes in 200 mM NaCl–50 mM sodium phosphate (pH 7.4) assay buffer. Receptor assays involved the P2 protein (200 μg) in 1 mL of assay buffer containing [^{35}S]TBPS (2 nM) alone or with unlabeled TBPS (2 μM) to correct for nonspecific binding (12% relative to the total binding). The suspensions were incubated for 30 min at 37 °C to achieve equilibrium between [^{35}S]TBPS and its binding site and then subjected to rapid filtration on Whatman GF/C filters and rinsed three times with cold assay buffer (2 mL); the filter pads were analyzed by liquid scintillation counting. Inhibitor concentrations to reduce [^{35}S]TBPS binding by 50% (IC_{50}) were determined as previously described (Cole et al., 1984).

[^{3}H]EBOB was used for similar studies with housefly brain according to the procedure of Deng et al. (1991). Assay mixtures in a final volume of 1.0 mL involved the membrane protein (200 μg) and [^{3}H]EBOB (0.8 nM) in 300 mM NaCl–10 mM sodium phosphate (pH 7.5) with incubation for 70 min at 22 °C. Correction for nonspecific binding (25% relative to total binding) involved addition of unlabeled EBOB (5 μM).

Toxicity Studies. Housefly (*Musca domestica* L.) LD_{50} values (μg/g) were determined 24 h after topical application of a solution (0.5 μL) of the test compound to adult females. Test solutions were prepared by dissolving the compound in the minimum volume of THF and diluting to the required concentration with acetone. LD_{50} values were also determined following topical pretreatment (1 h) with PB at 250 μg/g.

Mouse LD_{50} values (mg/kg) were determined with albino males (Swiss-Webster, 18–22 g) 24 h after intraperitoneal treatment with the test compound as a solution in dimethyl sulfoxide (DMSO). Ten to 20 mice were normally involved in each LD_{50} determination.

RESULTS AND DISCUSSION

Synthesis. *General.* Twelve of the 18 possible oxidation products were obtained from each of the dithianes, 8 from the trans isomer (A) and 4 from the cis isomer (B). They involve four monosulfoxides (C–F), two monosulfones (G and H), three disulfoxides (I–K), two sulfoxide–sulfones (L and M), and one disulfone (N) (Figure 2; Table I). General methods applied and yields obtained are indicated in Table II. The five specific methods utilized to prepare the bromophenyl compounds are described along with their spectroscopic and analytical data in a section at the end of this paper (Synthesis Procedures). Melting point, MS, and IR data for the ethynylphenyl and phenyl compounds are reported in Table III. Although not detailed here, these compounds also gave ^{1}H and ^{13}C NMR spectra consistent with the assigned structures.

Dithianes. Condensations to prepare the dithianes were effected in acetonitrile with *p*-toluenesulfonic acid (*p*-TsOH) as catalyst (method 1), yielding an approximately equimolar mixture of trans and cis isomers (^{1}H NMR) which were readily separable by preparative TLC. Prolonged exposure to acid (*p*-TsOH or silica gel) results in epimerization of the higher R_f isomer (B) to the lower R_f isomer (A). The acid stability of the dithianes with respect to the aryl substituent decreases in the order bromophenyl ≫ phenyl > ethynylphenyl. Near quantitative formation of B can be achieved by treatment of A with lithium diisopropylamide (LDA) (Eliel et al., 1974).

Oxidation Products. Most of the S-oxidation products were prepared using MCPBA (method 2), varying the peracid:dithiane ratio from 1 to 4 depending on the desired derivative. MCPBA oxidation did not yield monosulfones G and H, but they were readily obtained from monosulfoxides C and F with permanganate (method 3) under

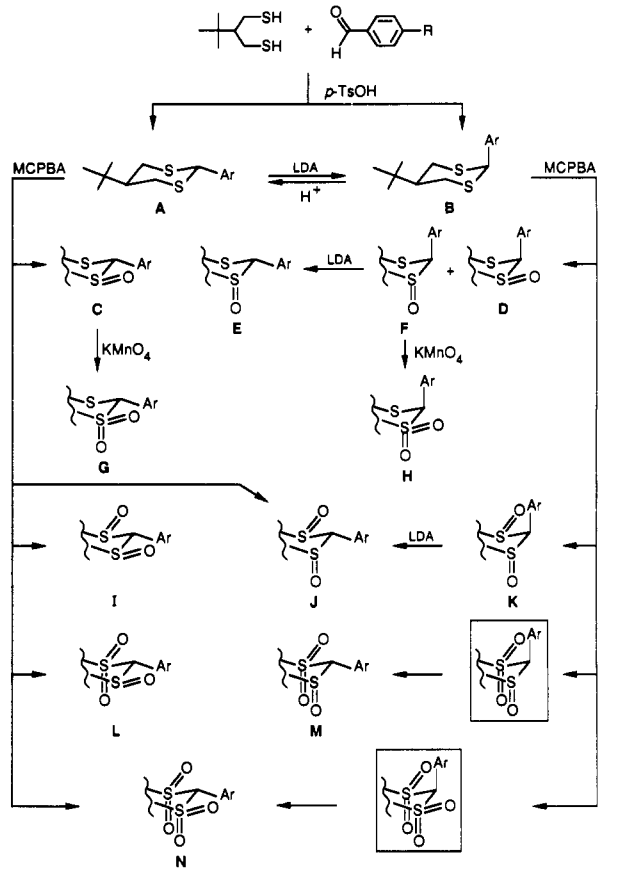

Figure 2. Preparation and stereochemistry of 2-aryl-5-*tert*-butyl-1,3-dithianes (R = bromo, ethynyl, or hydrogen) and their S-oxidation products. Compounds not isolated are shown in squares. See Table I for designations.

Table I. Designations for 2-Aryl-5-*tert*-butyl-1,3-dithianes and Their S-Oxidation Products by Compound Type (A–N, Figure 2) and Numbers (1–42)

oxidation at sulfur		compd type		4-bromophenyl		4-ethynylphenyl		phenyl	
		2_{eq}	2_{ax}	2_{eq}	2_{ax}	2_{eq}	2_{ax}	2_{eq}	2_{ax}
S	S	A	B	1	10	15	24	29	38
S	SO_{eq}[a]	C	D	2	11	16	25	30	39
S	SO_{ax}[a]	E	F	3	12	17	26	31	40
S	SO_2[a]	G	H	4	13	18	27	32	41
SO_{eq}	SO_{eq}[b]	I		5		19		33	
SO_{ax}	SO_{eq}[a,c]	J	K	6	14	20	28	34	42
SO_{eq}	SO_2[a]	L		7		21		35	
SO_{ax}	SO_2[a]	M		8		22		36	
SO_2	SO_2[b]	N		9		23		37	

[a] Racemate. [b] Meso compound. [c] The SO_{ax} SO_{ax} meso compounds are not isolated.

Table II. Preparation of 2-(4-Bromophenyl)-, 2-(4-Ethynylphenyl)-, and 2-Phenyl-5-*tert*-butyl-1,3-dithianes and Their S-Oxidation Products

compd type		synthesis procedure[a]		yield, %	
2_{eq}	2_{ax}	2_{eq}	2_{ax}	2_{eq}	2_{ax}
A	B	1[b-d]	1	100	see A
C	D	2[e]	2[f]	92–95	see F
E	F	4	2[g]	89–97	96–100
G	H	3[h]	3[h]	73–95	84–94
I		2[i]		95–99	
J	K	4	2[j]	98–100	92–96
L		2[k]		96–99	
M		5		89–94	
N		2		97–100	

[a] Isomers purified by preparative TLC or column chromatography on silica using dichloromethane–acetone (20:1) or solvent system specified below. [b] 57:43 mixture of A:B (bromophenyl series) separated using hexane–dichloromethane (10:1). [c] 60:40 mixture of A:B (ethynylphenyl series) separated using hexane–acetone (12:1). [d] 52:48 mixture of A:B (phenyl series) separated using hexane–acetone (8:1). [e] 63:31:6 mixture of C:I:J. [f] Required second chromatography using hexane–acetone (6:1). [g] 75:17:8 mixture of F:D:C. [h] Purified using hexane–dichloromethane–acetone (10:5:3). [i] 78:22 mixture of I:J. [j] 88:11:1 mixture of K:J:I. [k] 80:20 mixture of L:N.

sufficiently mild conditions that only minimal oxidation (<10%) occurred at the ethynyl moiety of **16** and **26**. Three other S-oxidation products of A not obtained by direct MCPBA oxidation were prepared by epimerization of the corresponding oxidation products of B using LDA (E and J) (method 4) or mild acid (*m*-chlorobenzoic acid) (M) (method 5); 2 equiv of LDA is required for epimerization of compounds containing an ethynyl substituent. The symmetrical disulfoxides of B were not observed; however, for the bromophenyl series, one trioxidized derivative of B and its tetraoxidized derivative (Table IV) appeared transiently and then rapidly epimerized to the corresponding oxidation products of A (Figure 2).

The oxidation products were separated by preparative TLC or column chromatography on silica gel except for the monosulfoxides (C vs F and D vs E). Within each of these sulfoxide pairs there is one major isomer with contamination by the minor isomer from epimerization of the starting material during oxidation; purification was achieved by careful crystallization. While the majority of the oxidation products are readily soluble in dichloromethane, the trioxidized compounds L and M are only sparingly soluble in a variety of solvents including DMSO and dichloromethane, and the tetraoxidized product N dissolves only in acetone of DMSO. Purification of these tri- and tetraoxidized compounds required preadsorption onto silica prior to column chromatography.

Stereochemical Assignments. *General.* The stereochemical assignments are discussed below for the bromophenyl series (Table IV), but the same relationships hold for the ethynylphenyl and phenyl series. The ^{13}C chemical shifts of C-5 and C-2 are readily assigned using 2D C–H correlation experiments since the protons at these centers have characteristic ^1H chemical shifts and multiplicities [δ 1.7–2.9 (m) and 4.0–6.0 (s), respectively]. The stereochemistry of C-2 is easily differentiated by ^{13}C NMR since, for all compounds studied, when the 2-aryl group is axial C-4 and C-6 are shielded by 2–5 ppm relative to the 2-equatorial isomer.

Dithianes. The 5-*tert*-butyl substituent adopts an equatorial orientation in both isomers evident by the chemical shift range observed for H-5, i.e., δ 1.76–1.87 vs 2.1 expected for an equatorial proton (Eliel et al., 1975b). C-4, C-6, and H-2 are deshielded in the lower relative to the higher R_f isomer; hence, the lower R_f isomer is assigned as trans (A) (Eliel et al., 1975b, 1976). Values for the vicinal couplings between the protons at C-4/C-6 and C-5 indicate a chair conformation for the lower R_f isomer (A: $J_{4ax,5}$ = 11.1–11.2 Hz; $J_{4eq,5}$ = 2.5–2.6 Hz) and a predominantly chair conformation for the higher R_f isomer (B: $J_{4ax,5}$ = 9.5–10.4 Hz; $J_{4eq,5}$ = 3.7–4.6 Hz) (Eliel and Hutchins, 1969).

Monosulfoxides. In agreement with the established conformational preference of the S=O bond in 1,3-dithiane sulfoxides (Carey et al., 1974; Cook and Tonge, 1973, 1974; Juaristi et al., 1984; Van Acker and Anteunis, 1974), monosulfoxide C formed from MCPBA oxidation of A has the S=O bond equatorial. The stereochemistry of each monosulfoxide from A is assigned on the basis of the NMR chemical shift of C-5 (Carey et al., 1978) and the IR stretching frequency of the sulfoxide bond (νSO) (Otting and Neugebauer, 1962) (Table IV). In comparison with the parent A, C-5 is deshielded by an equatorial S=O bond (δ C-5 *S*-oxide − δ C-5 parent dithiane = +5.22 for C) and shielded by an axial S=O bond [$\Delta(\delta C5)$ = −13.33 for E]. In the IR spectrum νSO is 20 cm^{-1} higher for an equatorial S=O bond (1051 cm^{-1} for C) than for an axial sulfoxide (1032 cm^{-1} for E).

Analogous stereochemical arguments apply to the monosulfoxides of B, but in contrast to the oxidation of A the major monooxidation product of B has the S=O bond axial (F). It is probable that MCPBA oxidation of B is under steric control, with the oxidizing agent approaching the sulfur atom anti to the 2-aryl group.

Dioxidized Products. Sulfones G and H and unsymmetrical 1,3-disulfoxides J and K are also differentiated by IR and ^{13}C NMR spectroscopy. The sulfones show two characteristic IR bands corresponding to asymmetric (ν_{as} SO) and symmetric (ν_s SO) S=O stretching vibrations (Otting and Neugebauer, 1962) (1305 and 1142 cm^{-1}, respectively, in G). The unsymmetrical 1,3-disulfoxides also show two S=O stretching bands but at lower wavenumber. For example, the IR spectrum of J has bands at 1051 and 1032 cm^{-1} characteristic of one equatorial and one axial S=O bond, respectively. The chemical shifts of C-4 and C-6 are also diagnostic. In the sulfone G the chemical shift of C-4 (31.91 ppm) is characteristic of an unoxidized sulfur, while C-6 resonates at much lower field (55.42 ppm). As expected, the anisotropy of the sulfone group was found to be similar to that of an equatorial sulfoxide (Barbarella et al., 1976; Carey et al., 1978; Duddeck, 1986). In *trans*-disulfoxides J and K the chemical shifts of C-4 and C-6 are in agreement with previously described criteria (Carey et al., 1978); i.e., the carbon α to the equatorial sulfoxide is deshielded relative to that α to the axial sulfoxide (e.g., in compound J, δ C-6 = 56.09 and δ C-4 = 49.83). C-5 is deshielded relative to the parent dithiane in all compounds where both sulfurs are oxidized (Table IV) and hence is not useful for determining their stereochemistry.

In the case of the disulfoxides J and K, additional evidence is available from determining C–H attachments by 2D NMR. In agreement with the literature (Khan et al., 1975), the protons α to the equatorial S=O bond (H-6_{eq}, H-6_{ax}) have a smaller geminal coupling (J_{gem}), a larger geminal chemical shift difference ($\delta H_{eq} - \delta H_{ax}$), and a lower field "quartet midpoint" ($[\delta H_{eq} + \delta H_{ax}]/2$) than those α to the axial S=O bond (H-4_{eq}, H-4_{ax}).

Trioxidized Products. Derivative L shows S=O stretching bands characteristic of a sulfone (1303 and 1135 cm^{-1}) and an equatorial sulfoxide (1050 cm^{-1}) and is therefore assigned as the 1,1-*trans*-3-trioxide. In addition, the carbon α to the sulfoxide is deshielded compared to that

Table III. Analytical Data for 2-(4-Ethynylphenyl)- and 2-Phenyl-5-*tert*-butyl-1,3-dithianes and Their S-Oxidation Products

compd type	mp, °C	MS, *m/z* (% base peak); IR, cm^{-1}
		Ethynylphenyl (Compounds **15–28**)
A	148–150	EI 276 (M^+; 100)
B	85–87	EI 276 (M^+; 66), 145 (100)
C	214–216	EI 292 (M^+; 44), 146 (100); ν(SO) 1040
D	116–117	EI 292 (M^+; 31), 57 (100); ν(SO) 1059
E	222–224	EI 292 (M^+; 100); ν(SO) 1034[a]
F	158–159	EI 292 (M^+; 42), 156 (100), 139 (100); ν(SO) 1038
G	236–237	EI 244 (M^+ – 64; 94), 145 (100); CI 309 (MH^+; 81), 179 (100); ν_{as}(SO) 1300; ν_s(SO) 1140[a]
H	190–191	EI 244 (M^+ – 64; 58), 145 (100); CI 309 (MH^+; 100); ν_{as}(SO) 1298; ν_s(SO) 1113
I	280[b]	EI 292 (M^+ – 16; 8), 129 (100); CI 309 (MH^+; 18), 163 (100); ν(SO) 1033
J	>300[b]	EI 178 (M^+ – 130; 5), 57 (100); ν(SO) 1046, 1032
K	>300[b]	EI 241 (M^+ – 67; 12), 122 (100); CI 309 (MH^+; 58), 163 (100); ν(SO) 1044, 1023
L	256[b]	EI 197 (M^+ – 127; 7), 163 (100); CI 325 (MH^+; 58), 113 (100); ν_{as}(SO) 1304; ν_s(SO) 1136; ν(SO) 1045
M	257[b]	EI 323 (M^+ – 1; 3), 57 (100); ν_{as}(SO) 1305; ν_s(SO) 1136; ν(SO) 1052
N	>300[b]	EI 340 (M^+; 16), 128 (100); ν_{as}(SO) 1320; ν_s(SO) 1141
		Phenyl (Compounds **29–42**)
A	125–126[c]	EI 252 (M^+; 100)
B	70–71[c]	EI 252 (M^+; 100)
C	179–180	EI 268 (M^+; 81), 121 (100); ν(SO) 1035
D	107–108	EI 268 (M^+; 96), 121 (100); ν(SO) 1048
E	182–183	EI 268 (M^+; 85), 57 (100); ν(SO) 1032[a]
F	144–145	EI 268 (M^+; 92), 121 (100); ν(SO) 1031[a]
G	188–189	EI 220 (M^+ – 64; 100); CI 285 (MH^+; 100); ν_{as}(SO) 1302; ν_s(SO) 1140[a]
H	153–154	EI 220 (M^+ – 64; 77), 121 (100); CI 285 (MH^+; 100); ν_{as}(SO) 1305; ν_s(SO) 1120
I	234–235	EI 284 (M^+; 22), 105 (100); ν(SO) 1036
J	258[b,d]	EI 178 (M^+ – 106; 16), 57 (100); ν(SO) 1044, 1025
K	196–197	EI 219 (M^+ – 65; 13), 139 (100), 121 (100); ν(SO) 1039, 1022
L	254–255	EI 285 (M^+ – 15; 4), 194 (100); CI 301 (MH^+; 28), 107 (100); ν_{as}(SO) 1309; ν_s(SO) 1141; ν(SO) 1037
M	220–222	EI 139 (M^+ – 161; 8), 57 (100); CI 301 (MH^+; 100); ν_{as}(SO) 1309; ν_s(SO) 1143; ν(SO) 1051
N	>300	EI 316 (M^+; 18), 104 (100); ν_{as}(SO) 1318; ν_s(SO) 1142.

[a] Other strong absorbances observed at 1050 (E, ethynylphenyl series), 1120 (G, phenyl and ethynylphenyl), and 1048 cm^{-1} (E and F, phenyl). Assignments were made by comparison to other oxidation products and to the literature (Otting and Neugebauer, 1962). [b] Decomposed. [c] Literature: A 126.5–127 °C; B 67–68 °C (Eliel and Hutchins, 1969). [d] Sublimation.

Table IV. ^{13}C and ^1H NMR and IR Data for 2-(4-Bromophenyl)-5-*tert*-butyl-1,3-dithiane and Its S-Oxidation Products (Compounds A–N and the 2-Axial Isomers of M and N)

	$\delta^{13}C$ ($CDCl_3$)				δ^1H ($CDCl_3$)				J_{gem}, Hz		
compd type	C-2	C-4	C-5	C-6	H-4_{eq}	H-4_{ax}	H-6_{eq}	H-6_{ax}	H-4	H-6	IR, cm^{-1} ν(SO)
A	50.46	33.53	46.18	33.53	2.98	2.83	2.98	2.83	14.1	14.1	
B	45.94	27.10	43.77	27.10	2.73	2.63	2.73	2.63	13.8	13.8	
C	68.60	32.71	51.40	56.71	2.79	2.70	3.63	2.60	13.9	12.5	1051
D	56.94	26.71	50.89	47.00	2.52	2.71	2.83	2.35	13.8	12.4	1057
E	63.86	31.80	32.85	49.29	*a*	*a*	*a*	*a*	*a*	*a*	1032
F	62.21	28.03	35.73	46.62	2.98	2.71	2.87	2.70	13.4	14.0	1044
G	66.63	31.91	50.82	55.42	2.94	2.82	3.42	2.91	14.2	14.2	1305, 1142[b]
H	63.57	28.32	45.57	51.98	3.13	2.74	3.17	3.29	13.2	13.9	1297, 1117
I	87.96	54.56	34.42	54.56	3.73	2.90	3.73	2.90	12.8	12.8	1044
J[c]	78.71	49.83	36.26	56.09	3.45	2.69	3.85	*a*	14.0	10.9	1051, 1032
K[c]	75.05	47.41	33.42	49.39	3.23	2.97	3.19	3.79	14.7	14.2	1041, 1025
L	85.33	55.62	38.23	53.92	3.86	2.82	3.42	3.07	12.8	14.3	1050, 1303, 1135
M[d]	72.95	49.70	37.49	56.09	3.53	2.60	3.58	3.06	14.1	14.0	1057, 1311, 1146
N[e,f]											1322, 1142

[a] Obscure multiplet not suitable for first-order analysis. Multiplets were resolved when spectra recorded in CD_3CN (see text). [b] Another strong absorbance was observed at 1120 cm^{-1} (see footnote to Table III). [c] For the unsymmetrical disulfoxides, J and K, C-6 is α to the equatorial S=O and C-4 is α to the axial S=O. [d] 2-Axial isomer observed transiently in the reaction mixture: δ ($CDCl_3$) C-2 79.07; C-4 47.66; C-5 37.63; C-6 54.61. [e] Not soluble in chloroform (see text for data in acetone). [f] 2-Axial isomer observed transiently in the reaction mixture: δ (acetone-d_6) C-2 81.27; C-4 and C-6 54.22; C-5 38.99.

α to the sulfone (δ C-4 = 55.62 and δ C-6 = 53.92), in keeping with the relative anisotropy of equatorial sulfoxides and sulfones (Barbarella et al., 1976; Carey et al., 1978; Duddeck, 1986). The situation is more complex for the 1,1-*cis*-3-trioxide isomer (M). While the IR spectrum of M shows the expected sulfone bands (1311 and 1146 cm^{-1}), the sulfoxide stretching frequency (1057 cm^{-1}) is 25 cm^{-1} higher than that expected for an axial orientation (1032 cm^{-1}; see compounds E and J, Table IV). This can be rationalized if the dithiane ring is partially flattened at C-2, allowing for a slight twist such that the S=O bond moves away from an axial orientation; however, the ^{13}C and ^1H NMR spectra do not indicate a distinct twist-boat conformation. Similar spectral properties are reported for 2,2-diphenyl-1,3-dithiane *cis*-1,3-dioxide, which was demonstrated by X-ray crystallography to adopt a chair conformation with both S=O bonds axial and some flattening of the ring at C-2 (Bryan et al., 1979). 2-(2,2-Dimethyl-3-piperidinopropyl)-1,3-dithiane 1,1,3,3-tetraoxide also adopts a chair conformation but with some twist about an axis between C-2 and C-5 (Li et al., 1983). In both of these cases, the deformation of the chair was rationalized on the basis of steric and dipolar interactions between the two axial S=O bonds.

Conformational Mobility. Examination of molecular models shows that by adopting a twist-boat conformation both the cis and trans isomers of the dithianes may approximate the space filling properties of the tri-

Table V. Biological Activity of 2-Aryl-5-*tert*-butyl-1,3-dithianes and Their S-Oxidation Products

compd type		housefly LD_{50}, μg/g with PB (and alone)[a]		housefly syn ratio (−PB/+PB)		mouse brain receptor IC_{50}, nM	
2_{eq}	2_{ax}	2_{eq}	2_{ax}	2_{eq}	2_{ax}	2_{eq}	2_{ax}
		Bromophenyl (Compounds 1–14)					
A	B	1.8 (4.0)	1.8 (4.0)	2	2	316	286
C	D	0.9 (5.5)	0.3 (1.6)	6	5	34	132
E	F	0.3 (6.5)	0.9 (3.8)	22	4	127	15
G	H	0.04 (1.0)	0.08 (0.6)	25	8	4	3
I		16 (>250, 30%)		>16		222	
J	K	0.9 (85)	0.4 (2.6)	94	7	386	412
L		2.6 (>50, 10%)		>19		18	
M		3.1 (21)		7		120	
N		0.04 (>100, 0%)		>2500		3	
		Ethynylphenyl (Compounds 15–28)					
A	B	0.1 (1.4)	0.6 (2.5)	14	4	4	8
C	D	0.2 (18)	0.03 (3.1)	90	103	1	12
E	F	0.01 (4.5)	0.04 (1.8)	450	45	4	1
G	H	0.01 (0.6)	0.02 (0.6)	60	30	1	1
I		3.6 (>63, 20%)		>18		79	
J	K	0.2 (>13, 10%)	0.06 (16)	>65	267	67	29
L		0.04 (>13, 10%)		>325		1	
M		3.6 (>13, 0%)		>4		44	
N		0.9 (>25, 10%)		>28		2	
		Phenyl (Compounds 29–42)					
A	B	13 (65)	36 (45)	5	1	283	1560
C	D	6.5 (>100, 0%)	15 (31)	>15	2	391	2438
E	F	3.0 (>100, 10%)	6 (41)	>33	7	2240	512
G	H	1.6 (>200, 10%)	2.5 (>200, 30%)	>125	>80	166	132
I		250 (>200, 10%)		>1		48000	
J	K	60 (>50, 0%)	50 (>100, 0%)	>1	>2	7380	18700
L		>125, 0% (>125, 0%)				542	
M		24 (>63, 10%)		>3		1690	
N		>125, 20% (>125, 0%)				573	

[a] LD_{50} or percent mortality at indicated maximum dose.

oxabicyclooctanes (Elliott et al., 1992). Various NMR spectroscopic (Bergesen et al., 1976a,b; Carey et al., 1978; Eliel 1970, 1972; Eliel and Hutchins, 1969; Pihlaja, 1974; Pihlaja and Björkqvist, 1977; Pihlaja and Nikander, 1977; Pihlaja et al., 1973) and molecular mechanics studies (Allinger and Kao, 1976) have shown that variously substituted dithianes, including *cis*-2-phenyl-5-*tert*-butyl-1,3-dithiane, can exist appreciably in a twist-boat conformation. The solution conformation of the dithianes and their S-oxidation products is therefore of toxicological interest. Preliminary ^1H NMR studies of a large number of the present compounds in organic solvents (chloroform, acetonitrile, or acetone) were conducted to observe whether large differences in biological activity among the dithianes and their S-oxidation products were reflected by variations in their conformational mobilities. Such a relationship was not observed; in all compounds studied the vicinal couplings of protons around the dithiane ring were constant over a temperature range from 21 to 50 °C, consistent with results reported previously (Elliott et al., 1992).

Biological Activity. *Toxicity to Houseflies (Table V).* The relation of structure to insecticidal activity was evaluated by three criteria: LD_{50} with PB to approximate intrinsic potency when oxidative detoxification is minimized; LD_{50} without synergist, in which case extensive metabolism is involved; and synergistic ratio reflecting the ease of oxidative detoxification. The PB-synergized toxicity of the 2-aryl-5-*tert*-butyl-1,3-dithianes and the S-oxidation products decreases in the order ethynylphenyl > bromophenyl ≫ phenyl. There is no consistent difference in toxicity between the 2-equatorial (A) and 2-axial (B) epimers of each of the parent dithianes. This relationship also applies to the monosulfones (G and H) and the unsymmetrical disulfoxides (J and K). The monosulfoxides where the S=O group is cis to the 2-aryl substituent (D and E) are generally more toxic than the isomers with the trans arrangement (C and F). For the disulfoxides, the asymmetrical isomer with one *cis*- and one *trans*-sulfoxide (J) is more toxic than the symmetrical isomer where both sulfoxides are trans (I). The monosulfones (G and H) are always the most toxic of the oxidation products in any series. The trioxidized products (L and M) are of relatively low potency except for isomer L in the ethynylphenyl series. The disulfone (N) either is equipotent to the monosulfone (G) (bromophenyl series) or is much less active (ethynylphenyl and phenyl series).

The unsynergized toxicity shows structure–activity relationships different from those with PB. The potency relative to the 2-substituent decreases in the order ethynylphenyl > bromophenyl > phenyl, and in general the 2-axial isomer is more potent than the 2-equatorial isomer. The most potent bromophenyl and ethynylphenyl derivatives are the monosulfones (G and H). The synergism factor for the bromophenyl monosulfone (*G*) with a free sulfur available for oxidation is 25, whereas for the bromophenyl disulfone (N) it is greater than 2500-fold; in the latter case PB apparently inhibits oxidative detoxification at a site other than sulfur. The high factors of synergism for all of the ethynylphenyl compounds suggest they are particularly sensitive to oxidative detoxification.

Toxicity to Mice. The intraperitoneal toxicity to mice of the bromophenyl dithianes and their derivatives where only one sulfur is oxidized is as follows (LD_{50}, mg/kg): A >40, B 15, C 4, D 6, E >40, F 4, G 6, and H 3. These findings establish that, in general, compounds with the aromatic substituent axial are more toxic than the corresponding equatorial isomers. In contrast to the fly, the *trans*-monosulfoxide is in each case (C and F) more toxic than the cis (D and E). The poisoning signs for each of the compounds were similar to or the same as those of

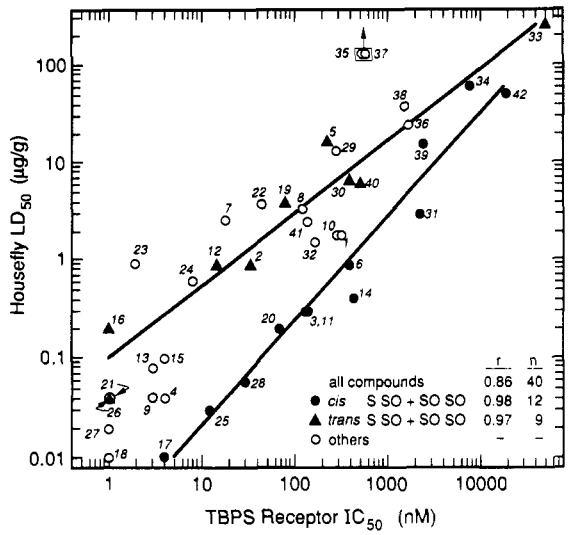

Figure 3. Relation of potency in inhibiting [^{35}S]TBPS binding to the mouse brain membrane receptor and toxicity to houseflies pretreated with PB of 2-aryl-5-*tert*-butyl-1,3-dithianes with bromophenyl (**1–14**), ethynylphenyl (**15–28**), and phenyl (**29–42**) substituents. Compound numbers refer to Table I. Linear regression plots were obtained using a least-squares fit to the equation $y = a_0 + a_1x$, where a_0 and a_1 are the regression coefficients (Jandel Scientific, 1990).

1-(4-bromophenyl)-4-*tert*-butyl-2,6,7-trioxabicyclo[2.2.2]-octane (Casida et al., 1985).

The bromophenyl dithianes and their S-oxidation products are generally more toxic to houseflies than to mice under the test conditions with a particularly high selectivity ratio for the monosulfone tested on houseflies with PB (LD_{50} ratio mouse/[housefly + PB] of 150 for G and 38 for H).

Potency at the Mouse Brain Receptor (Table V). Potency of the dithianes and their S-oxidation products at the mouse brain TBPS receptor decreases in the order ethynylphenyl ≫ bromophenyl > phenyl for both the 2-equatorial and 2-axial derivatives. Thus, the ethynyl group confers high receptor potency to the dithianes, as noted earlier with the trioxabicyclooctanes (Palmer and Casida, 1989). The most potent bromophenyl and ethynylphenyl compounds are generally the monosulfones (G and H) and the disulfones (N). In contrast to the synergized housefly toxicity, derivatives in which a sulfoxide and aryl group are trans to each other (C and F) are more potent than the cis isomers (D and E).

Potency at the Housefly Brain Receptor. The housefly receptor assayed with [^{3}H]EBOB is somewhat less sensitive than the mouse brain receptor assayed with [^{35}S]-TBPS to inhibition by the 2-equatorial bromophenyl and ethynylphenyl dithianes (A) (Deng et al., 1991) and their derivatives oxidized at only one sulfur atom (C, E, and G). Thus, the IC_{50} values with housefly brain for A, C, E and G, respectively, are as follows: bromophenyl series, 165, 38, 250, and 10 nM; ethynylphenyl series, 8, 10, 40, and 5 nM. The *trans*-monosulfoxide is more potent than the cis isomer, and the monosulfone is the most potent derivative with fly brain as also noted above with mouse brain. These findings support the proposal that the insecticidal activity of the dithianes and their S-oxidation products is due to their action at the GABA-gated chloride channel.

Correlation of Receptor Inhibition Data with Toxicity (Figure 3). The compounds that are most toxic to PB-synergized houseflies are also those most potent at the [^{35}S]TBPS binding site of the GABA-gated chloride channel. In a comparison of mouse brain receptor potency with PB-synergized housefly toxicity the correlation coefficient is 0.86 for all of the compounds, 0.98 for mono- and disulfoxides with a cis arrangement of a sulfoxide and the 2-aryl group, and 0.97 for mono- and disulfoxides where the sulfoxide(s) and the 2-aryl group are trans.

Some of the same trends are apparent in a comparison of the limited housefly receptor data (eight compounds) with housefly toxicity and the mouse receptor data with the few available mouse toxicity values (eight compounds), but the small data sets are not suitable for broader interpretations. It appears likely that metabolic sulfoxidation contributes to discrepancies in these correlations and more generally to the overall toxic action of the dithianes.

SYNTHESIS PROCEDURES

The procedures below specifically described for the bromophenyl series (**1–14**) are also directly applicable to the ethynylphenyl and phenyl compounds (**15–42**).

Method 1: Preparation of Dithianes 1 and 10. 2-*tert*-Butylpropane-1,3-dithiol (2.7 g, 16.5 mmol) was added to a solution of 4-bromobenzaldehyde (3.0 g, 16.2 mmol) in acetonitrile (50 mL) containing *p*-TsOH (20 mg). The solution was stirred at room temperature for 30 min, after which time the solvent was removed and the residue taken up in dichloromethane (50 mL). The dichloromethane solution was washed with saturated $NaHCO_3$ (2 × 10 mL) and dried (Na_2SO_4), and the solvent was removed to yield a white solid (5.4 g; 100%) which was determined to be a 57:43 mixture of **1**:**10** by ^{1}H NMR spectroscopy. The isomers were separated using multiple development preparative TLC in hexane–dichloromethane (10:1), and both were crystallized from dichloromethane–hexane as colorless needles.

1: mp 168–169 °C; ^{1}H NMR, see Table IV, also δ 7.47 (2 H, AA′BB′, aromatic), 7.36 (2 H, AA′BB′, aromatic), 5.09 (1 H, s, H-2), 1.76 (1 H, AA′BB′C, $J_{4ax,5}$ and $J_{6ax,5}$ = 11.2 Hz, $J_{4eq,5}$ and $J_{6eq,5}$ = 2.5 Hz, H-5), 0.97 [9 H, s, $(CH_3)_3$]; ^{13}C NMR, see Table IV, also δ 137.50, 131.85, 129.44, 122.33 (aromatic), 33.92 [$C(CH_3)_3$], 27.30 [$(CH_3)_3$]; IR 3058m, 2959s, 1480s, 1400m, 1362m, 1183m, 1066s, 1008s, 761s, 508s; EI-MS *m/z* (%) 332/330 (M^+; 82/74), 130 (100).

10: mp 103–104 °C; ^{1}H NMR, see Table IV, also δ 7.69 (2 H, AA′BB′, aromatic), 7.49 (2 H, AA′BB′, aromatic), 4.84 (1 H, s, H-2), 1.85 (1 H, AA′BB′C, $J_{4ax,5}$ and $J_{6ax,5}$ = 10.4 Hz, $J_{4eq,5}$ and $J_{6eq,5}$ = 3.7 Hz, H-5), 0.89 [9 H, s, $(CH_3)_3$]; ^{13}C NMR, see Table IV, also δ 138.98, 131.46, 130.44, 121.31 (aromatic), 34.14 [$C(CH_3)_3$], 27.10 [$(CH_3)_3$]; IR 3057w, 2960s, 1479s, 1390s, 1366s, 1229m, 1070m, 1006s, 822s, 486s; EI-MS *m/z* (%) 332/330 (M^+; 88/83), 203/201 (35/100), 201/199 (100/67).

Method 2: MCPBA Oxidation of Dithianes. Preparation of 2, 5, 7, 9, 11, 12, and 14. MCPBA (52 mg, 0.3 mmol) was added slowly with stirring to a cooled (0 °C) solution of **10** (100 mg, 0.3 mmol) in dichloromethane (20 mL). The solution was stirred at room temperature for 3 h and then diluted with dichloromethane (20 mL); the *m*-chlorobenzoic acid was removed by washing with Tris buffer (pH 9) (3 × 15 mL). The organic phase was dried (Na_2SO_4) and filtered, and the solvent was removed to yield a white solid (99 mg; 95%). The ^{1}H NMR spectrum of the crude product showed a 75:17 mixture of **12**:**11**, with 8% contamination by **2**. The major (lower R_f) isomer of the monooxidized product (**12**) was obtained by preparative TLC in dichloromethane–acetone (20:1). The minor (higher R_f) isomer (**11**) required further preparative TLC using hexane–acetone (6:1). The isomers were crystallized from dichloromethane–hexane as colorless prisms.

Disulfoxide **14** was obtained by oxidation of **10** with 2 equiv of MCPBA. Oxidation of **1** yielded **2**, **5**, **7**, and **9** with 1, 2, 3, and 4 equiv of MCPBA, respectively.

2: mp 203–204 °C; ^{1}H NMR, see Table IV, also δ 7.55 (2 H, AA′BB′, aromatic), 7.31 (2 H, AA′BB′, aromatic), 4.45 (1 H, s, H-2), 2.20 (1 H, AA′BB′C, $J_{6ax,5}$ = 12.5 Hz, $J_{4ax,5}$ = 10.8 Hz, $J_{4eq,5}$ = 3.4 Hz, $J_{6eq,5}$ = 2.1 Hz, H-5), 1.02 [9 H, s, $(CH_3)_3$]; ^{13}C NMR, see Table IV, also δ 132.22, 131.89, 130.17, 123.54 (aromatic), 34.18 [$C(CH_3)_3$], 27.20 [$(CH_3)_3$]; IR 3059w, 2958m, 1480m, 1402m,

1372m, 1051s, 1009m, 856m, 507m; EI-MS m/z (%) 348/346 (M^+; 58/58), 203/201 (29/100), 201/199 (100/88).

5: mp 199–200 °C; ^{1}H NMR, see Table IV, also δ 7.65 (2 H, AA'BB', aromatic), 7.44 (2 H, AA'BB', aromatic), 4.68 (1 H, s, H-2), 1.80 [1 H, AA'BB'C, $J_{4ax,5}$ and $J_{6ax,5}$ = 12.6 Hz, $J_{4eq,5}$ and $J_{6eq,5}$ = 1.6 Hz, H-5], 1.10 [9 H, s, $(CH_3)_3$]; ^{13}C NMR, see Table IV, also δ 132.90, 131.49, 126.94, 124.72 (aromatic), 34.11 [$C(CH_3)_3$], 27.22 [$(CH_3)_3$]; IR 3059w, 2915m, 1484m, 1405m, 1373m, 1044s, 1010m, 849m, 502m; EI-MS m/z (%) 364/362 (M^+; 8/4), 122 (100).

7: mp 249–250 °C; ^{1}H NMR, see Table IV, also δ 7.65 (2 H, AA'BB', aromatic), 7.50 (2 H, AA'BB', aromatic), 4.78 (1 H, s, H-2), 2.27 (1 H, m, $J_{4ax,5}$ = 12.8 Hz, $J_{6ax,5}$ = 12.7 Hz, $J_{6eq,5}$ = 2.2 Hz, $J_{4eq,5}$ = 2.0 Hz, H-5), 1.09 [9 H, s, $(CH_3)_3$]; ^{13}C NMR, see Table IV, also δ 132.77, 132.58, 125.67, 122.28 (aromatic), 33.77 [$C(CH_3)_3$], 27.18 [$(CH_3)_3$]; IR 3066w, 2953m, 1481m, 1404m, 1370m, 1303s, 1242m, 1135s, 1050s, 856s; EI-MS m/z (%) 219/217 (M^+ – 161; 12/8), 194 (100).

9: mp >300 °C; ^{1}H NMR (acetone-d_6) δ 7.70 (2 H, AA'BB', aromatic), 7.63 (2 H, AA'BB', aromatic), 6.08 (1 H, s, H-2), 3.63 (2 H, ABC, 14.4 Hz, 3.3 Hz, H-4_{eq} and H-6_{eq}), 3.56 (2 H, ABC, 14.4 Hz, 11.4 Hz, H-4_{ax} and H-6_{ax}), 2.46 (1 H, AA'BB'C, 11.4 Hz, 3.3 Hz, H-5), 1.10 [9 H, s, $(CH_3)_3$]; ^{13}C NMR (acetone-d_6) δ 134.96, 132.71 (aromatic), 81.14 (C-2), 54.66 (C-4 and C-6), 40.77 (C-5), 34.11 [$C(CH_3)_3$], 27.31 ($(CH_3)_3$); IR 3062w, 2965m, 1480m, 1343m, 1322s, 1279m, 1244m, 1154s, 1142s, 1119s, 1005m, 854s, 530s; EI-MS m/z (%) 396/394 (M^+; 12/13), 184/182 (92/100).

11: mp 136–138 °C; ^{1}H NMR, see Table IV, also δ 7.60 (2 H, AA'BB', aromatic), 7.56 (2 H, AA'BB', aromatic), 4.99 (1 H, s, H-2), 2.20 (1 H, AA'BB'C, $J_{6ax,5}$ = 12.4 Hz, $J_{4ax,5}$ = 11.5 Hz, $J_{4eq,5}$ = 3.4 Hz, $J_{6eq,5}$ = 1.90 Hz, H-5), 0.89 [9 H, s, $(CH_3)_3$]; ^{13}C NMR, see Table IV, also δ 131.52, 131.41, 129.32, 123.10 (aromatic), 34.24 [$C(CH_3)_3$], 26.93 [$(CH_3)_3$]; IR 3054w, 2965m, 1483s, 1368m, 1232m, 1057s, 1008m, 828s, 498m; EI-MS m/z (%) 348/346 (M^+; 43/42), 57 (100).

12: mp 134–135 °C; ^{1}H NMR, see Table IV, also δ 7.55 (2 H, AA'BB', aromatic), 7.43 (2 H, AA'BB', aromatic), 4.60 (1 H, s, H-2), 2.42 (1 H, AA'BB'C, $J_{6ax,5}$ = 10.7 Hz, $J_{4ax,5}$ = 10.3 Hz, $J_{4eq,5}$ = 4.5 Hz, $J_{6eq,5}$ = 2.5 Hz, H-5), 0.96 [9 H, s, $(CH_3)_3$]; ^{13}C NMR, see Table IV, also δ 132.15, 130.01, 122.84 (aromatic), 33.28 [$C(CH_3)_3$], 27.37 [$(CH_3)_3$]; IR 3058w, 2942m, 1477m, 1393m, 1044s, 1007m, 858m, 506s; EI-MS m/z (%) 348/346 (M^+; 83/75), 203/201 (31/100), 201/199 (100/75).

14: mp 189–190 °C; ^{1}H NMR (CD_3CN) δ 7.65 (2 H, AA'BB', aromatic), 7.49 (2 H, AA'BB', aromatic), 4.32 (1 H, s, H-2), 3.65 (1 H, ABC, 14.3 Hz, 12.1 Hz, H-6_{ax}), 3.31 (1 H, ABC, 14.7 Hz, 6.5 Hz, 1.6 Hz, H-4_{eq}), 3.12 (1 H, ABC, 14.3 Hz, 1.7 Hz, 1.6 Hz, H-6_{eq}), 2.85 (1 H, ABC, 14.7 Hz, 10.7 Hz, H-4_{ax}), 2.49 (1 H, m, H-5), 1.01 [9 H, s, $(CH_3)_3$]; ^{13}C NMR ($CDCl_3$), see Table IV, also δ 132.51, 131.25, 130.20, 124.48 (aromatic), 33.27 [$C(CH_3)_3$], 26.83 [$(CH_3)_3$]; IR 3065w, 2960m, 2904m, 1489m, 1396m, 1370m, 1232m, 1052s, 1041s, 1025s, 1013m, 830m, 508m; EI-MS m/z (%) 219/217 (M^+ – 145; 70/62), 178(100); CI-MS m/z (%) 365/363 (MH^+; 26/23), 163 (100).

Method 3: Permanganate Oxidation of Dithiane 1-Oxides. Preparation of 4 and 13 (Block et al., 1976; Henbest and Khan, 1968). $MgSO_4$ (240 mg, 2 mmol) in 1:1 acetone–water (14 mL) was added to a cooled (–5 °C) solution of **2** (250 mg, 0.72 mmol) in acetone (50 mL). The mixture was stirred vigorously, and then a solution of $KMnO_4$ (90 mg, 0.57 mmol) in water (150 mL) was added in portions. The temperature was raised to 50 °C, and the reaction mixture was stirred for 2 h and then filtered to remove precipitated MnO_2. Acetone was evaporated from the filtrate, and the remaining aqueous solution was saturated with NaCl and then extracted with dichloromethane (4 × 200 mL). The combined extracts were dried (Na_2SO_4), and the solvent was removed to yield a white solid (0.19 g; 73%). Sulfone **4** was obtained by fractionation of the crude product using preparative TLC in hexane–dichloromethane–acetone (10:5:3) and then crystallization from dichloromethane–hexane as colorless needles. The same procedure was used to convert **12** to **13**.

4: mp 233–234 °C; ^{1}H NMR, see Table IV, also δ 7.55 (2 H, AA'BB', aromatic), 7.41 (2 H, AA'BB', aromatic), 5.00 (1 H, s, H-2), 2.56 (1 H, AA'BB'C, $J_{4ax,5}$ and $J_{6ax,5}$ = 11.0 Hz, $J_{4eq,5}$ = 2.5 Hz, $J_{6eq,5}$ = 2.4 Hz, H-5), 1.00 [9 H, s, $(CH_3)_3$]; ^{13}C NMR, see Table IV, also δ 132.05, 131.69, 126.45, 124.57 (aromatic), 33.94 [$C(CH_3)_3$], 27.03 [$(CH_3)_3$]; IR 3066w, 2961s, 1487s, 1374m, 1305s, 1280m, 1240m, 1142s, 1120s, 1072m, 1012m, 859s, 760s, 534s; EI-MS m/z (%) 300/298 (M^+ – 64; 35/34), 219 (100); CI-MS m/z (%) 365/363 (MH^+, 45/42), 179 (100).

13: mp 180–181 °C; ^{1}H NMR, see Table IV, also δ 7.56 (2 H, AA'BB', aromatic), 7.45 (2 H, AA'BB', aromatic), 5.05 (1 H, s, H-2), 2.44 (1 H, AA'BB'C, $J_{6ax,5}$ = 12.2 Hz, $J_{4ax,5}$ = 11.4 Hz, $J_{4eq,5}$ = 5.3 Hz, $J_{6eq,5}$ = 2.3 Hz, H-5), 0.99 [9 H, s, $(CH_3)_3$]; ^{13}C NMR, see Table IV, also δ 131.93, 131.30, 128.03, 124.08 (aromatic), 33.95 [$C(CH_3)_3$], 28.86 [$(CH_3)_3$]; IR 3063w, 2958m, 1488m, 1370m, 1297s, 1226m, 1117s, 1074m, 534s; EI-MS m/z (%) 300/298 (M^+ – 64; 9/9), 57 (100); CI-MS m/z (%) 365/363 (MH^+; 58/53), 179 (100).

Method 4: Epimerization of Dithiane 1-Oxides and *trans*-1,3-Dioxides. Preparation of 3 and 6 (Carey et al., 1976). LDA (1.5 M in cyclohexane; 0.09 mL, 0.14 mmol) was added to a cooled (–5 °C) solution of **12** (44 mg, 0.13 mmol) in dry THF (50 mL) under nitrogen. The orange solution was stirred at low temperature for 30 min, and then deionized water (5 mL) and diethyl ether (50 mL) were added. After the mixture was stirred for 5 min, the organic phase was separated, dried (Na_2SO_4), and filtered, and the solvent was removed to yield an off-white solid (40 mg; 91%) consisting of **3** as the only dithiane product (^{1}H NMR). This was separated by preparative TLC using dichloromethane–acetone (20:1) and then purified by crystallization from dichloromethane–hexane as colorless needles. The same procedure was used to convert **14** to **6**. *Note*: The molar ratio of LDA to dithiane must be doubled for the ethynylphenyl series.

3: mp 220–221 °C; ^{1}H NMR (CD_3CN) δ 7.53 (2 H, AA'BB', aromatic), 7.30 (2 H, AA'BB', aromatic), 4.96 (1 H, s, H-2), 3.23 (1 H, ABC, 14.1 Hz, 2.2 Hz, 2.2 Hz, H-6_{eq}), 2.94 (1 H, ABC, 13.8 Hz, 11.4 Hz, H-4_{ax}), 2.77 (1 H, ABC, 13.8 Hz, 2.5 Hz, 2.2 Hz, H-4_{eq}), 2.61 (1 H, ABC, 14.1 Hz, 12.2 Hz, H-6_{ax}), 2.25 (1 H, AA'BB'C, 12.2 Hz, 11.4 Hz, 2.5 Hz, 2.2 Hz, H-5), 0.93 [9 H, s, $(CH_3)_3$]; ^{13}C NMR ($CDCl_3$), see Table IV, also δ 134.02, 132.03, 130.00, 123.39 (aromatic), 33.18 [$C(CH_3)_3$], 27.16 [$(CH_3)_3$]; IR 3048w, 2960s, 1484m, 1400m, 1368m, 1069m, 1047s, 1032s, 1007s, 854m, 501m; EI-MS m/z (%) 348/346 (M^+; 38/36), 57 (100).

6: mp 228 °C (sublimed); ^{1}H NMR (CD_3CN) δ 7.65 (2 H, AA'BB', aromatic), 7.52 (2 H, AA'BB', aromatic), 5.44 (1 H, s, H-2), 3.72 (1 H, ABC, 12.4 Hz, 2.1 Hz, 1.8 Hz, H-6_{eq}), 3.37 (1 H, ABC, 14.1 Hz, 2.2 Hz, 1.8 Hz, H-4_{eq}), 2.92 (1 H, ABC, 12.4 Hz, 12.3 Hz, H-6_{ax}), 2.87 (1 H, ABC, 14.1 Hz, 12.4 Hz, H-4_{ax}), 2.68 (1 H, m, 12.4 Hz, 12.3 Hz, 2.2 Hz, 2.1 Hz, H-5), 1.04 [9 H, s, $(CH_3)_3$]; ^{13}C NMR ($CDCl_3$), see Table IV, also δ 132.65, 131.45 (aromatic), 33.75 [$C(CH_3)_3$], 27.34 [$(CH_3)_3$]; IR 3021w, 2963m, 1476m, 1398m, 1380m, 1230m, 1051s, 1032s, 1005s, 851s, 507s; EI-MS m/z (%) 219/217 (M^+ – 145; 13/11), 57 (100); CI-MS m/z (%) 365/363 (MH^+; 100/94).

Method 5: Preparation of 1,1-*cis*-3-Trioxide (8). MCPBA (156 mg, 0.9 mmol) was added slowly, with stirring, to a cooled (0 °C) solution of **10** (100 mg, 0.3 mmol) in dichloromethane (20 mL). The solution was stirred at room temperature for 3 h and then diluted with dichloromethane (20 mL), and the *m*-chlorobenzoic acid was removed by washing with Tris buffer (pH 9) (3 × 15 mL). The organic phase was dried (Na_2SO_4) and filtered and the solvent removed to yield a white solid (108 mg; 94%) consisting of a mixture of **8** and its 2-aryl axial isomer (^{1}H NMR). The 2-axial isomer epimerized to leave only **8** with less than 2% contamination by **7**. The crude product was adsorbed onto silica and then purified by column chromatography using dichloromethane–acetone (20:1). Purified **8** crystallized from dichloromethane–hexane as colorless needles.

8: mp 209–211 °C; ^{1}H NMR, see Table IV, also δ 7.63 (2 H, AA'BB', aromatic), 7.57 (2 H, AA'BB', aromatic), 4.45 (1 H, s, H-2), 3.22 (1 H, m, $J_{6ax,5}$ = 12.5 Hz, $J_{4ax,5}$ = 12.0 Hz, $J_{4eq,5}$ and $J_{6eq,5}$ = 2.1 Hz, H-5), 1.08 [9 H, s, $(CH_3)_3$]; ^{13}C NMR, see Table IV, also δ 132.83, 132.41 (aromatic), 27.24 [$(CH_3)_3$]; IR 3096w, 2966m, 1482m, 1311s, 1146s, 1057s, 1041s, 1006s, 862s, 533s, 506s; EI-MS m/z (%) 219/217 (M^+ – 162; 9/8), 57 (100); CI-MS m/z (%) 381/379 (MH^+; 100/92).

ABBREVIATIONS USED

Ar, aryl; CI, chemical ionization; 2D, two dimensional; DMSO, dimethyl sulfoxide; [^{3}H]EBOB, 1-(4-ethynylphen-

yl)-4-[2,3-$^3H_2$]propyl-2,6,7-trioxabicyclo[2.2.2]octane, also known as [^{3}H]*ethynylbicycloorthobenzoate*; EI, electron impact; GABA, γ-aminobutyric acid; GC, gas chromatography; IC_{50}, inhibitor concentration to reduce [^{35}S]TBPS or [^{3}H]EBOB binding by 50%; IR, infrared; LDA, lithium diisopropylamide; MCPBA, *m*-chloroperoxybenzoic acid; MS, mass spectrometry; NMR, nuclear magnetic resonance; PB, piperonyl butoxide; [^{35}S]TBPS, [^{35}S]-*tert*-butylbicyclophosphorothionate; THF, tetrahydrofuran; TLC, thin-layer chromatography; *p*-TsOH, *p*-toluenesulfonic acid; ν_s (symmetrical) and ν_{as} (asymmetrical), IR S=O stretching frequencies of sulfones.

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