Insecticidal 1,3-Dithianes†

Michael Elliott,‡,§ David A. Pulman,‖ John P. Larkin,‖ and John E. Casida*,‡

Pesticide Chemistry and Toxicology Laboratory, Department of Entomological Sciences, University of California, Berkeley, California 94720, and Wellcome Research Laboratories, Berkhamsted, Hertfordshire HP4 2DY, U.K.

1,3-Dithianes with selected 2- and 5-substituents, e.g., 5-*tert*-butyl-2-(substituted-aryl)-1,3-dithianes, are a new group of insecticides; the most active with a 4-bromo, 4-chloro, 3,4-dichloro, or 4-ethynyl substituent(s) on the aryl ring and a *tert*-butyl group in the 5-position have housefly topical LD_{50}s ranging from 0.1 to 4 μg/g without or with piperonyl butoxide (PB). Insertion of a methyl group at C-2, C-4, or C-5 has relatively little influence on activity. The 2-aryl axial and 2-aryl equatorial isomers have similar potency in some series but differ in others. Housefly LD_{50}s for a spirodithiane, 3-*tert*-butyl-9-methyl-9-(trichloromethyl)-1,5-dithiaspiro[5.5]undeca-7,10-diene, are 0.5 and 0.2 μg/g alone and with PB, respectively. The dithiane ring in effective 2,5-disubstituted- or 2,2,5-trisubstituted-1,3-dithianes may replace the bicyclic cage of the insecticidal 1,4-disubstituted-2,6,7-trioxabicyclo[2.2.2]octanes; both classes of heterocyclic compounds act at the same or closely coupled sites in the GABA-gated chloride channel.

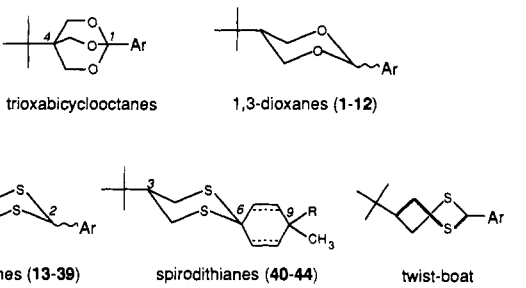
INTRODUCTION

2,6,7-Trioxabicyclo[2.2.2]octanes (TBOs) with a range of selected substituents in the 1- and 4-positions have insecticidal activities comparable with those of some of the most effective established insecticides (Palmer and Casida, 1985, 1989). Preferred substituents for toxicity to houseflies or cockroaches in the absence or in the presence of piperonyl butoxide (PB) are *tert*-butyl in the 4-position and 4-halophenyl or 4-ethynylphenyl in the 1-position. Here the function of the central TBO ring was investigated by examining the influence on potency of alternative links between the 1- and 4-groups established as effective in the TBO series.

Substituted 1,3-dioxanes were first synthesized as simpler and more readily accessible relatives of the TBOs, with two rather than three oxymethylene (–O–CH_2–) central links. Appropriate dioxanes were found to be weakly but definitely active to houseflies, with or without PB. Comparably simple, related 1,3-dithianes were then discovered to have much greater potency to houseflies under similar conditions. Structure–activity relationships of 5-alkyl-2-(substituted-phenyl)-1,3-dioxanes and -1,3-dithianes and several spirodithianes were therefore examined in detail.

MATERIALS AND METHODS

Intermediates: Aldehydes and Ketones. Compounds not available commerically and synthesized according to literature procedures were 4-ethynylbenzaldehyde (Austin et al., 1981), 4-ethynylacetophenone (Takahashi et al., 1980), 4-methyl-4-(trichloromethyl)-2,5-cyclohexadienone (mp 103 °C from hexane) (Newman and Pinkus, 1954), and 4-methyl-4-(trichloromethyl)-cyclohexanone (from hydrogenation of the corresponding cyclohexadienone with 10% palladium on charcoal in methanol) (de Beule et al., 1974). 4-Dichloromethyl-4-methyl-2,5-cyclohexadienone was prepared according to the method of Auwers and Keil (1902). The yellow oil from steam distillation of the product was collected in ether, dried ($MgSO_4$), and distilled. The upper fraction, bp 115–118 °C at 2 Torr, which crystallized on cooling, was recrystallized (hexane/benzene) to give a solid, mp 51–52 °C. 4,4-Dimethyl-2,5-cyclohexadienone was prepared by oxidation of 4,4-dimethylcyclohexenone (3.91 g) with 2,3-dichloro-5,6-dicyanobenzoquinone (14 g) in refluxing carbon tetrachloride (120 mL) with vigorous stirring for 24 h in the dark. The reaction mixture was cooled, filtered, and diluted with ether. The organic solution was washed with 10% KOH solution and brine, dried ($MgSO_4$), and distilled to give the desired dienone (2.22 g, 58%, bp 60–62 °C/2.25 Torr, n^{25}_D 1.4987).



Intermediates: Alkyldiols and Alkyldithiols. Propane-1,3-diol, 2-ethyl-2-methylpropane-1,3-diol, 2,2-diethylpropane-1,3-diol, 2-methyl-2-*n*-propylpropane-1,3-diol, 2-ethylhexane-1,3-diol, and 2-bromo-2-nitropropane-1,3-diol were commercially available. Other propane-1,3-diols were prepared by reduction (Eliel and Knoeber, 1968) of commercially available substituted diethyl malonates, i.e., *n*-butyl, *sec*-butyl, *tert*-butyl, 1,1-dimethylpropyl, cyclohexyl, and phenyl. Diethyl *tert*-butylmethylmalonate (Bush and Beauchamp, 1953), 3-*tert*-butylpenta-2,4-dione, and ethyl *tert*-butyl acetoacetate (Boldt and Militzer, 1966) were prepared according to literature methods and reduced as described above and then converted to the dithiol derivatives via tosylate (Eliel and Hutchins, 1969) or mesylate (Eliel et al., 1975) intermediates.

Preparation of 2-Aryl-1,3-dioxanes (1–12) and 2-Aryl-1,3-dithianes (13–39). Dioxanes and dithianes were prepared according to established procedures in a Dean and Stark apparatus. Some were synthesized in the presence of the *N*,*N*-dimethylformamide/dimethyl sulfate adduct. This latter method was used for condensation of aldehydes and ketones with 1,3-

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‡ University of California.

§ Present address: Lawes Trust Senior Fellow, Rothamsted Experimental Station, Harpenden, Hertfordshire, AL5 2JQ, U.K.

‖ Wellcome Research Laboratories.

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diols (Kantlehner and Gutbrod, 1979) but was also found to be suitable for small-scale preparation of 1,3-dithianes. Reactions usually required 48 h at room temperature with addition of dichloromethane as necessary to maintain a homogeneous reaction medium. Alternatively, the dithiol (about 1.0 mL) and carbonyl compound (10% molar excess) were mixed with formic acid (5 mL, 95–97%) in a reaction flask which was then stoppered firmly and agitated (where appropriate by sonication) for 2–18 h. If solid separated, water was added and the product was collected by filtration, dried, and recrystallized from hexane or ethanol. For nonsolid products, the formic acid layer was separated from the oil, diluted with ice/water, and extracted with dichloromethane. The organic layers were combined, washed (saturated $NaHCO_3$ and then saturated NaCl solutions), and dried ($MgSO_4$). After evaporation, the residue was distilled at 0.2–0.5 Torr to give 1.0–1.3 g of product.

5-*tert*-Butyl-2-[4-(prop-1-ynyl)phenyl]-1,3-dithiane (**32**) was prepared from 5-*tert*-butyl-2-(4-iodophenyl)-1,3-dithiane (**16**) as follows: 1-Propyne (gas) was passed for 1 h into a stirred solution of the iodophenyl compound (0.19 g) in diethylamine (20 mL, dried on NaOH) with bis(triphenylphosphine)palladium(II) chloride (ca. 10 mg) and cuprous iodide (ca. 2 mg); the reaction mixture was sealed and stirred (3 h). After evaporation of solvent, the residue was extracted into dichloromethane (20 mL), washed with water and dried ($MgSO_4$), and then purified by TLC (tapered silica plates) with hexane/dichloromethane (1:1). The product (0.12 g, 80%) was recrystallized from hexane/benzene.

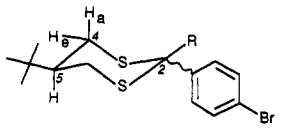
Procedures for chromatographic separation of the axial (*a*) and equatorial (*e*) isomers and trans → cis isomerization of 2-unsubstituted-dithianes with lithium diisopropylamide are reported (Eliel et al., 1974; Wacher et al., 1990).

9,9-Disubstituted-1,5-dithiaspiro[5.5]undecanes (40–42) and -undeca-7,10-dienes (43–45). The 9,9-dimethylundecane (**40**) was prepared by reduction of 4,4-dimethylcyclohexenone followed by condensation of the resulting ketone with the appropriate dithiol as for **41** below. To prepare the 9-dichloromethyl-9-methylundecane (**41**), 4-dichloromethyl-4-methylcyclohexa-2,5-dienone (0.25 g) was hydrogenated in methanol (15 mL) over 10% palladium on charcoal (TLC control). The catalyst was removed by filtration using filtercel which was washed with dichloromethane. The solvents were evaporated, and formic acid (2 mL, 96%) and 2-*tert*-butylpropane-1,3-dithiol (0.21 mL) were added to the residue. The required product, which separated almost immediately, was isolated by dilution of the reaction mixture with water, filtration, and recrystallization from ethanol (0.25 g, fine needles). The 9-methyl-9-(trichloromethyl)undecane derivative (**42**) was obtained by treating 4-methyl-4-(trichloromethyl)cyclohexanone (0.09 g) in formic acid (1 mL) with 2-*tert*-butylpropane-1,3-dithiol (0.06 mL). After 5 min, the reaction mixture was processed as above, and the product (0.09 g) was recrystallized from ethanol.

The 9-dichloromethyl-9-methylundeca-7,10-diene derivative (**43**) was prepared by adding 2-*tert*-butylpropane-1,3-dithiol (1 mL) to 4-(dichloromethyl)-4-methyl-2,5-cyclohexadienone (1.16 g) in formic acid (96%, 5 mL). After agitation by sonication for 3 h, the mixture was poured into water and the product was extracted into dichloromethane, washed with saturated $NaHCO_3$ solution, and dried ($MgSO_4$). The viscous residue remaining after removal of solvent was recrystallized from hexane to give **43**. The 9-methyl-9-(trichloromethyl)undeca-7,10-diene derivative (**44**) was obtained similarly. 2-*tert*-Butylpropane-1,3-dithiol (1 mL) was added to 4-methyl-4-(trichloromethyl)-2,5-cyclohexadienone (1.34 g) in formic acid (96%, 5 mL). After 15 h, the reaction mixture was diluted with water, and the solid product was collected by filtration, washed, dried in vacuo (2.36 g), and recrystallized from ethanol to give **44** (1.47 g). An analogous procedure gave 9-methyl-9-(trichloromethyl)-1,5-dithiaspiro[5.5]undeca-7,10-diene (**45**), i.e., the analogue of (**44**) lacking the *tert*-butyl substituent, from propane-1,3-dithiol.

Spectroscopy and Structural Assignments. Structures of the compounds synthesized were confirmed by chemical ionization MS (methane at 0.8 Torr, 230 eV, Hewlett-Packard 5985 system) and ^1H NMR (deuteriochloroform solutions, 250 or 300 mHz, Bruker AM-250 or WM-300 spectrometer). The ^1H NMR spectra of the 1,3-dioxanes and 1,3-dithianes were as expected; those of the 1,3-dithianes are given in the supplementary material. Chemical shifts of the ring and 2-methyl protons of representative dithianes are shown in Table I.

Table I. Chemical Shifts (δ) of Ring and 2-Methyl Protons[a]



no.	isomer	R	2-*a*	2-*e*	4H-*a*	4H-*e*	5H-*a*
14	trans	H	5.1		2.9	3.0	1.7
15	cis	H		4.8	2.6	2.7	1.8
20	trans	Me	2.2		3.0	2.8	1.8
19	cis	Me		1.7	2.4	2.7	1.8

[a] Nomenclature: In 2-aryl-5-*tert*-butyl-1,3-dithianes the ring adopts a chair conformation and the 5-*tert*-butyl group is equatorially oriented. For simplicity in this paper, when the 2-aryl group is equatorial, it is referred to as the trans isomer and when axial as the cis isomer. Axial and equatorial with reference to isomers implies the orientation of the aromatic ring.

Table II. Toxicity to Houseflies of Substituted 1,3-Dioxanes

	substituent[a]				% kill, 500 μg/g	
no.	2	other	5	mp, °C	-PB	+PB
1	4-Cl-Ph		*t*-Bu, H	109–111	70	100
2	4-Br-Ph		*t*-Bu, H	128–130	70	100
3	4-CN-Ph		*t*-Bu, H	108	50	50
4	4-Br-Ph		H, H	59	0	0
5	4-Cl-Ph		Me, Et	oil	10	30
6	4-Cl-Ph		Me, *n*-Pr	oil	40	80
7	4-Cl-Ph		Et, Et	45	0	0
8	4-Cl-Ph	4-*n*-Pr	Et, H	oil	10	0
9	4-Cl-Ph		Br, NO_2	oil	0	0
10	4-Br-Ph	4-Me	*t*-Bu, H	51–61	0	
11	4-Br-Ph	4-Me, 6-Me	*t*-Bu, H	oil	0	
12	4-Br-Ph		*t*-Bu, Me	110–114	0	

[a] Mixed isomers not separated.

Bioassays. Adult female houseflies (*Musca domestica* L., SCR strain, 3–5 days after emergence, ~20 mg each) were treated topically on the ventrum of the abdomen with the test compound in 0.5 μL of acetone. Alternatively, the houseflies were pretreated similarly with PB at 250 μg/g 1 h before the toxicant was applied. LD_{50} values, determined after 24 h at 25 °C, were based on log dose-probit mortality plots and were reproducible within 1.5-fold.

RESULTS

Substituted 1,3-Dioxanes (Table II). Initially the effect of replacing the bicyclic ring system of the TBOs with the monocyclic 1,3-dioxane spacer group was examined. The 4-chloro-, 4-bromo-, and 4-cyanophenyl-1,3-dioxanes (mixed cis and trans isomers) were prepared because related TBOs were active. The effect of structure on potency was assessed at the discriminating level of 500 μg/g, due to low activity.

Dioxanes **1–3** showed significant insecticidal activity both alone and with PB; the chloro (**1**) and bromo (**2**) analogues were more potent than the cyano (**3**) compound. 4-Methyl (**10**), 4,6-dimethyl (**11**), or 5-methyl (**12**) substituents lowered the potency of compound **2**. Of the 5,5-dialkyl analogues **5–7**, the most active was the 5-methyl-5-*n*-propyl derivative **6**. Compounds with smaller substituents [two hydrogens (**4**) or hydrogen and ethyl (**8**)] at the 5-position were inactive, as was the 5-bromo-5-nitro compound **9**.

Substituted 5-*tert*-Butyl-2-halophenyl-1,3-dithianes (Table III). Next, the effect of substituting the dioxane by an equivalent dithiane ring was studied, maintaining constant the *tert*-butyl group, the 5-substituent in the

Table III. Toxicity to Houseflies of Substituted 5-*tert*-Butyl-2-(halophenyl)-1,3-dithianes

	substituents			LD_{50},[a] μg/g	
no.	2	other	mp, °C	-PB	+PB
13	(*e*)-4-Cl-Ph		162	2.5	1.5
14	(*e*)-4-Br-Ph		150–155	4.0	1.8
15	(*a*)-4-Br-Ph[b]		92	4.0	1.8
16	(*e*)-4-I-Ph		185–186	15	10
17	(*e*)-3,4-Cl_2Ph		100–123	4.0	2.5
18	(*e*)-4-Cl-Ph	(*a*)-2-Me	115–117	2.5	3.5
19	(*a*)-4-Br-Ph	(*e*)-2-Me	141	8.0	1.2
20	(*e*)-4-Br-Ph	(*a*)-2-Me	106	3.0	2.0
21	(*e*)-4-Br-Ph	(*a*)-2-Et	135–136	2.5	2.5
22	(*e*)-3,4-Cl_2-Ph	(*a*)-2-Me	153	0.7	0.22[c]
23	(*a*)-3,4-Cl_2-Ph	(*e*)-2-Me	130	5.5	3.4[c]
24	(*e*)-4-Cl-Ph	(*a*)-2-(4-Cl-Ph)	158	>500 (0)[d]	>500 (0)[d]
25	(*e*)-4-Br-Ph	4-Me	95	5.8	1.0
26	(*e*)-4-Br-Ph	5-Me	155	2.8	0.7
27	(*a*)-4-Br-Ph	5-Me	oil	1.7	1.4

[a] LD_{50} values (μg/g) for commercial insecticides alone and with PB, respectively, are 14 and 0.32 for (1R,αS)-*trans*-allethrin; 0.21 and 0.012 for (1R)-*cis*-permethrin; 1.3 and 0.43 for parathion; 23 and 1.4 for propoxur (Palmer et al., 1989). [b] The analogue lacking the 5-*tert*-butyl substituent (mp 91–92 °C) is inactive (no mortality at 500 μg/g alone or with PB). [c] Potency increased by ~3-fold at 48 h. [d] Percent mortality at 500 μg/g.

Table IV. Toxicity to Houseflies of Substituted 2-(Alkylphenyl)-, 2-(Cyanophenyl)-, and 2-(Alkynylphenyl)-5-*tert*-butyl-1,3-dithianes

	substituents			LD_{50}, μg/g	
no.	2	other	mp, °C	-PB	+PB
28	(*e*)-4-*t*-Bu-Ph		157	>500 (0)[a]	>500 (10)[a]
29	4-CN-Ph[b]		146	20	1.0
30	4-CN-Ph[b]	2-Me[b]	103–112	0.6	0.4
31	(*e*)-4-HC≡C—Ph		149	1.4	0.1
32	(*e*)-4-MeC≡C—Ph		160–161	3.5	0.25
33	(*e*)-4-HC≡C—Ph	(*a*)-2-Me	96	2	0.1
34	(*a*)-4-HC≡C—Ph	(*e*)-2-Me	105	14	2.4

[a] Percent mortality at 500 μg/g. [b] Isomer mix.

most active dioxanes. Replacing oxygen with sulfur dramatically increased potency to houseflies so that the insecticidal activity fell in the range of commerical insecticides. This justified more extensive structure–activity investigations including the influence of stereochemistry.

trans-2-(Chloro- or bromophenyl)-1,3-dithianes **13**, **14**, and **17** were almost equally effective and more active than iodophenyl analogue **16**. The activities of 4-halophenyldithianes **13** and **14** were essentially unaltered with a methyl (**18** and **20**) or ethyl (**21**) group at the 2-axial position. The *trans*-dithiane (**22**) from 3,4-dichloroacetophenone was particularly active. A larger 2-substituent, axial-4-chlorophenyl, gave an inactive compound (**24**). The potency of the *trans*-bromophenyl compound (**14**) was not greatly influenced by a methyl group in the 4- or 5-position (dithiane **25** or **26**, respectively).

The *cis*- and *trans*-2-(halophenyl)-1,3-dithianes had similar activity in most cases (**14** vs **15**, **19** vs **20**, and **26** vs **27**), the exception being the 3,4-dichlorophenyl series where trans isomer **22** was much more potent than cis isomer **23**.

Substituted 2-(Alkylphenyl)-, 2-(Cyanophenyl)-, and 2-(Alkynylphenyl)-5-*tert*-butyl-1,3-dithianes (Table IV). The influence of alkyl-, cyano-, and alkynylphenyl groups in place of halophenyl was examined. Potency depended on the substituent in the 4-position of the phenyl group: *tert*-butyl compound **28** was inactive, the 4-cyano (**29**) and 4-propynyl (**32**) derivatives were intermediate in potency, and the 4-ethynylphenyl compound (**31**) was very active.

The 2-methyl group in cyanophenyl compound **30** made it more potent than **29**, but a 2-methyl substituent in ethynylphenyl compound **33** did not render it more active than the unmethylated dithiane **31**. With a 2-methyl group, *trans*-(4-ethynylphenyl) compound **33** was much more active than cis isomer **34** as in the 2-(3,4-dichlorophenyl) series (**22** vs **23**).

Table V. Toxicity to Houseflies of 5-Substituted 2-(4-Bromophenyl)-1,3-dithianes

	substituents			LD_{50}, μg/g	
no.	5	other	mp, °C	-PB	+PB
14	*t*-Bu	(*a*)-2-H	150–155	4.0	1.8
35	*n*-Bu	2-H	65–80	~100	
36	*s*-Bu	2-Me	oil	400	250
37	$EtMe_2C$	(*a*)-2-Me	126	>500	15
38	cyclohexyl	2-Me	oil	>500 (0)[a]	>500 (0)[a]
39	Ph	(*a*)-2-Me	144	400	200

[a] Percent mortality at 500 μg/g.

Table VI. Toxicity to Houseflies of Spirodithianes Derived from 4-Methylcyclohexanones and 4-Methylcyclohexadienones

			LD_{50}, μg/g	
no.	R	mp, °C	-PB	+PB
		Cyclohexanone Derivatives		
40	CH_3	117	>500 (0)[a]	~500 (50)
41	$CHCl_2$	163	>500 (0)	>500 (5)
42	CCl_3	162	11	0.3
		Cyclohexadienone Derivatives		
43	$CHCl_2$	120	20	1
44	CCl_3[b]	183	0.5	0.15

[a] Percent mortality at 500 μg/g. [b] The corresponding cyclohexadienone (mp 103 °C) and spirodithiane lacking the 5-*tert*-butyl substituent (**45**) (mp 149 °C) are inactive (no mortality at 500 μg/g along or with PB).

5-Substituted-2-(4-bromophenyl)-1,3-dithianes (Table V). The similar high potency of the 5-*tert*-butyl-2-(*e*)-(4-bromophenyl) compounds with axial 2-hydrogen (**14**) or 2-methyl substituents (**20**) (Table III) prompted examination of the influence of other 5-substituents in this series. Although much less potent, the most active of the five compounds examined were the *n*-butyl (**35**) and 1,1-dimethylpropyl (**37**) dithianes. Other 5-substituents including *s*-butyl, cyclohexyl, and phenyl (compounds **36**, **38**, and **39**, respectively) conferred much lower activity.

Spirodithianes Derived from 4-Methylcyclohexanones and 4-Methylcyclohexadienones (Table VI). That insecticidal activity is not limited to 2-aryl compounds was demonstrated in spirodithianes derived from 4-methyl-4-(trichloromethyl)cyclohexanone (**42**) and -cyclohexadienone (**44**), particularly the latter compound. Analogous 4-(dichloromethyl)-4-methyl compounds (**41** and **43**) and 4,4-dimethyl compound **40** were much less active or inactive. The intermediate 4-methyl-4-(trichloromethyl)-2,5-cyclohexadienone and the corresponding spiro compound (**45**) lacking the *tert*-butyl were inactive, emphasizing the importance of the *tert*-butyldithiane moiety.

DISCUSSION

This study examined the hypothesis that the TBO system might be replaced with a monocyclic alternative. In the TBO system the 4- and 1-substituents, e.g., *tert*-butyl and 4-bromophenyl, have a linear orientation and

the molecules may be regarded as cylindrical in shape. This relationship should be held or be readily attained in the monocyclic alternative. The *tert*-butyl and 4-halophenyl substituents were used initially as they confer considerable potency in the TBO series and also because the *tert*-butyl group acts as a conformational lock to maintain 6-membered rings in the chair form. Conformations of both dioxanes and dithianes have been examined in detail (Eliel and Hutchins, 1969; Eliel and Knoeber, 1968).

The dioxanes, although only weakly active compared with the corresponding TBOs, were of sufficient potency to encourage further studies, particularly structure–activity relationships at the 5-position. The findings for the dioxanes generally parallel those for the TBOs (Palmer and Casida, 1985), the *tert*-butyl substituent being optimal.

Replacement of the dioxane ring with a dithiane system gave compounds that are as potent as the TBOs, permitting significant intercomparisons of their structure–activity relationships. The potency order for 4-aryl substituents, i.e., ethynyl > chloro, bromo, or cyano > *tert*-butyl, is closely paralleled in the *tert*-butyl series of C2-hydrogen dithianes and in the TBOs. Such dithianes retain high activity with additional 2-methyl, 2-ethyl, 4-methyl, and 5-methyl substituents. In the TBO series 4-substituents including *n*-butyl, *sec*-butyl, cyclohexyl, and phenyl have activities approaching that of the *tert*-butyl compound (Palmer and Casida, 1985; Palmer et al., 1991). However, in the dithiane series tested with PB the only effective substituent other than *tert*-butyl is one of similar steric bulk (i.e., 1,1-dimethylpropyl). The dithianes are obtained as mixtures of geometrical isomers. The relative potencies of isomeric 2-aryldithianes depend on the nature of the other substituent at the 2-position. Thus, potency differences are greater with a 2-methyl than with a 2-hydrogen. Activity is generally greater when the aryl group is equatorial rather than axial.

The insecticidal activity of the 2-aryl (*a*) compounds is surprising from a simple comparison of the overall shapes of these molecules with their cylindrical TBO progenitors. Both dithiane isomers exist at room temperature in solution with the dithiane ring in a chair conformation, as indicated by ^1H–^1H vicinal coupling constants ($J_{H_{5a}-H_{4/6a}}$ = 11 Hz and $J_{H_{5a}-H_{4/6e}}$ = 3.5 Hz). As expected, there is also a strong ^1H–^1H NOE interaction between the 4/6 axial protons and the 2 and 6 aryl protons in the cis isomers. The activity of the cis isomers may be associated with the ability of their dithiane rings to assume a twist-boat conformation which more readily relates to the linear and cylindrical *trans*-dithianes and TBOs. However, when a dimethyl-d_6 sulfoxide solution of **19** was heated to 400 K in the probehead of the NMR spectrometer, the ^1H–^1H coupling constants did not change, indicating conformational inflexibility. Although there appears to be no tendency for the ring to adopt a twist-boat conformation in solution, this is still possible at the receptor site.

In the spirodithianes no axial–equatorial isomerism is possible, and the conformation of the molecules differs considerably from that of the 2-aryl compounds. The contribution of the 4-trichloromethyl substituent is particularly noteworthy in both the cyclohexanone and cyclohexadienone series, the 4-dichloromethyl, 4-methyl, and 4,4-dimethyl compounds being much less potent.

This is the first report of insecticidal 5-alkyl-2-substituted-1,3-dithianes. Although the natural product nereistoxin (Hagiwara et al., 1965) and related synthetic compounds (e.g., cartap and thiocyclam) are dithio derivatives or precursors thereof, they differ considerably in structure from the present series in having a basic dimethylamino group and no systematically varied equivalent of the 2-substituent. They also differ in that the optimal dithianes are at least an order of activity more potent than nereistoxin to houseflies (Jacobsen and Pedersen, 1983) and act on the GABAergic system rather than on the cholinergic system. The insecticidal dithianes and TBOs act at the same or closely coupled sites in the GABA-gated chloride channel (Deng et al., 1990). Pursuit of the relation between structure and insecticidal activity in the dithianes may therefore contribute to providing a new class of insect control agents.

ABBREVIATIONS USED

PB, piperonyl butoxide; TBO, 2,6,7-trioxabicyclo[2.2.2]-octane; TLC, thin-layer chromatography; Me, methyl; Et, ethyl; Pr, propyl; Bu, butyl; Ph, phenyl or substituted phenyl; *a*, axial; *e*, equatorial.

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Supplementary Material Available: ^1H NMR spectral assignments of 1,3-dithianes **13–44** (4 pages). Ordering information is given on any current masthead page.

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