Pestic. Sci. 1995, **44**, 69–74

Insecticidal Isomers of 4-tert-Butyl-1-(4-ethynylcyclohexyl)-2,6,7-trioxabicyclo[2.2.2]octane and 5-tert-Butyl-2-(4-ethynylcyclohexyl)-1,3-dithiane*

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(Received 15 August 1994; revised version received 14 November 1994; accepted 3 January 1995)

Abstract: 4-tert-Butyl-2,6,7-trioxabicyclo[2.2.2]octanes and 5-tert-butyl-1,3-dithianes with the 4-ethynylcyclohexyl substituent in the 1- and 2-positions, respectively, are potent insecticides modeled on their 4-ethynylphenyl and hex-5-ynyl analogs. The compounds were prepared from dimethyl 1,4-cyclohexanedicarboxylate, 4-(2,2-dibromovinyl)cyclohexanecarboxylic acid, methyl 4-(1-chlorovinyl)cyclohexanecarboxylate, and 4-ethynylcyclohexylmethanol by well-established chemistry. The *cis* and *trans* isomers of the 1-cyclohexyltrioxabicyclooctane and all four geometric isomers of the 2-cyclohexyl-1,3-dithiane were separated by chromatography of the final products or suitable intermediates. High levels of insecticidal activity were found against houseflies, German cockroaches and aphids for trioxabicyclooctanes and dithianes with the *trans* ethynylcyclohexyl configuration.

Key words: dithiane insecticides, ethynylcyclohexyl derivatives, trioxabicyclooctane insecticides

1 INTRODUCTION

2,6,7-Trioxabicyclo[2.2.2]octanes with a range of selected substituents in the 1- and 4-positions[1,2] and 1,3-dithianes with appropriate moieties in the 2- and 5-positions[3] have insecticidal activities comparable with those of some of the most effective commercial compounds. Preferred groups for toxicity to houseflies are *tert*-butyl (4-position of a 2,6,7-trioxabicyclo[2.2.2]octane; 5-position of a 1,3-dithiane) and 4-ethynylphenyl (1-position of a 2,6,7-trioxabicyclo[2.2.2]octane; 2-position of a 1,3-dithiane) as in compounds **1** and **2** (Fig. 1). Trioxabicyclooctanes with the 1-(hex-5-ynyl) substituent, such as in **3**,[4] replacing the 4-ethynylphenyl substituent, such as in **1**,[2] are also highly insecticidal. The four methylenes may resemble the spatial characteristics of a phenyl ring and allow the ethynyl group to occupy the same volume of receptor

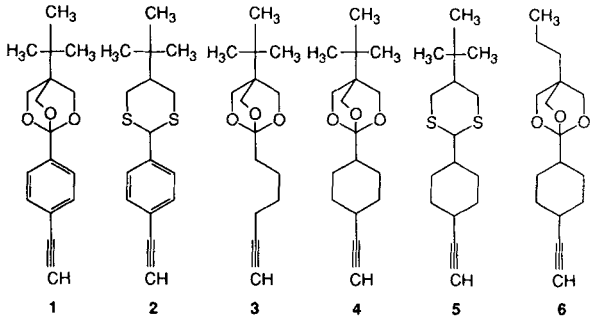

Fig. 1. Structures of compounds discussed.

* Presented in part at the 8th International Congress of Pesticide Chemistry (IUPAC). Washington, DC, USA, 4–9 July 1994.

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Pestic. Sci. 0031-613X/95/$09.00

space as when attached at the 4-position of an aryl moiety.[4]

The acetylenic cyclohexyl analogs **4**,[5] **5**[6] and **6**[5] (the *n*-propyl analog of **4**) combine some of the structural features of the ethynylphenyl (**1** and **2**) and hexynyl (**3**) compounds and introduce the additional aspect of two and four geometrical isomers for the trioxabicyclooctanes and dithianes, respectively. It was therefore of interest to prepare the cyclohexyl compounds (**4** and **5**) as individual isomers and compare their insecticidal activities with the earlier series.

2 SYNTHESIS

2.1 Approach

Dimethyl 1,4-cyclohexanedicarboxylate from Aldrich Chemical Co. (Milwaukee, WI) was used as a convenient starting material. Trioxabicyclooctanes **4** and **6** were prepared first as mixtures of *cis* and *trans* isomers by the route outlined in Fig. 2 without isomer separation and with the *n*-propyl intermediate for **6**. Key steps were the partial hydrolysis of starting material to give a mono-acid which allowed selective introduction of the required dibromovinyl moiety in **8**. Elaboration to the trioxabicyclooctanes was carried out as described previously,[1] followed by treatment with base as the final step to give the desired target compounds. This approach was not amenable to 'scale-up' chemistry to give larger quantities of compounds, as aldehyde **7** was obtained in low yield.

The route in Fig. 3, although not detailed here, was developed to obtain improved yields of suitable 1,4-disubstituted cyclohexane derivatives. The key step was

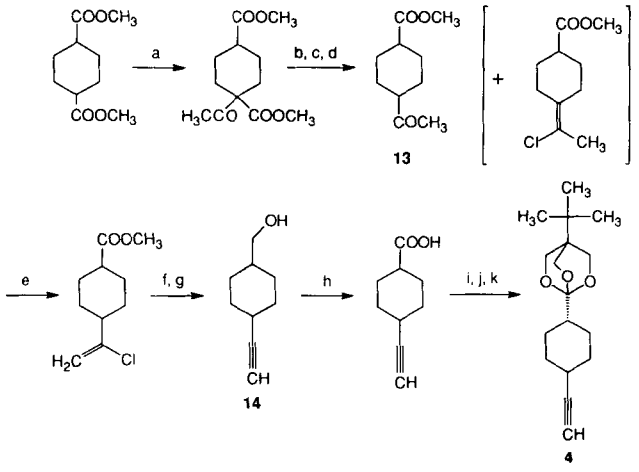
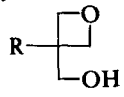


Fig. 3. Alternative route to 2,6,7-trioxabicyclo[2.2.2] octanes—(a) LDA, CH_3COCl, THF; (b) HCl, CH_3OH; (c) $SOCl_2$, benzene; (d) CH_3OH, $(C_2H_5)_3N$; (e) PCl_5, pyridine, benzene; (f) $LiAlH_4$, ether; (g) $(CH_3)_2CHCH_2Li$, THF; (h) pyridinium dichromate, DMF; (i) $SOCl_2$, benzene; (j)  , pyridine, ether; (k) BF_3, $(C_2H_5)_2O$, CH_2Cl_2, $-70°C$.

a... ...f the starting material followed by decarboxylation to give ultimately **13**, which permitted sequential formation of acetylenic and hydroxymethyl groups yielding intermediate acetylenic alcohol **14**. This compound was the critical intermediate to prepare the desired bicyclooctanes (for example **4**) (Fig. 3) and dithianes such as **5**. Full syntheses and product characterization data are given in appropriate patents for trioxabicyclooctanes **4**[5] and **6**[5] and dithiane **5**.[6]

The trioxabicyclooctanes and dithianes as mixtures of *cis* and *trans*-isomers were found to have high insecticidal activities. The preparation route for the tri-

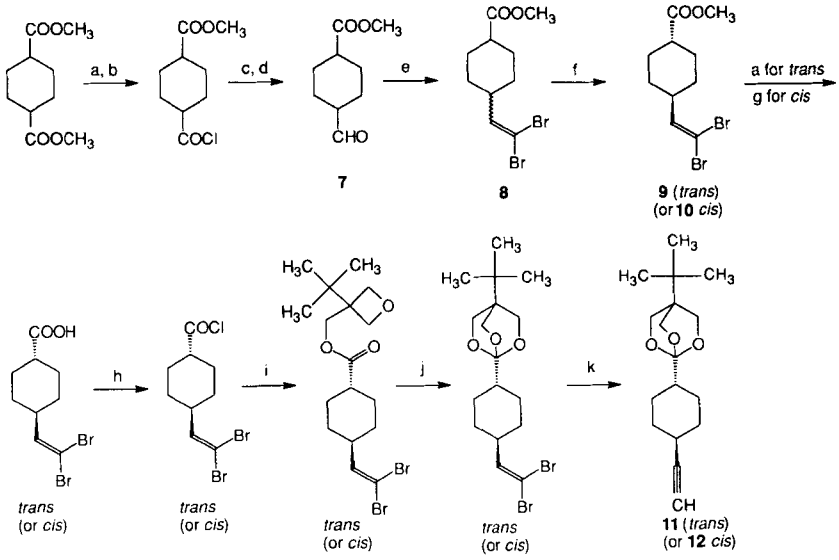
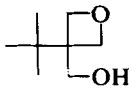


Fig. 2. Route to 2,6,7-trioxabicyclo[2.2.2]octanes—(a) KOH, CH_3OH; (b) $SOCl_2$, benzene; (c) $Zn(BH_4)_2$, THF, $(CH_3)_2N(CH_2)_2N(CH_3)_2$; (d) $(COCl)_2$, DMSO, $(C_2H_5)_3N$; (e) CBr_4, $P(C_6H_5)_3$, CH_2Cl_2; (f) chromatography; (g) HBr, CH_3COOH; (h) $(COCl)_2$, DMF, CH_2Cl_2; (i)  , pyridine, CH_2Cl_2; (j) BF_3, $(C_2H_5)_2O$, CH_2Cl_2, $-70°C$; (k) C_4H_9Li, THF.

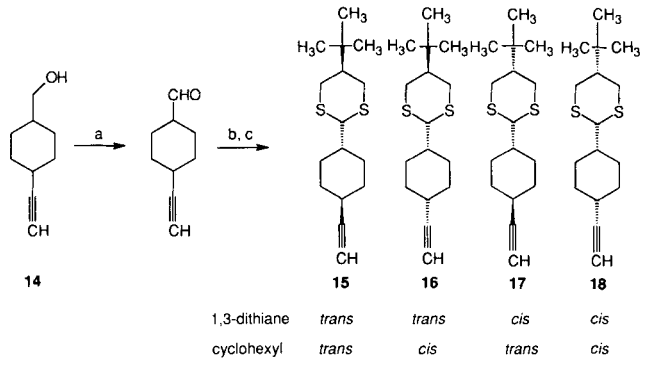


Fig. 4. Route to 1,3-dithianes—(a) $(COCl)_2$, DMSO, $(C_2H_5)_3N$; (b) $(CH_3)_3CCH(CH_2SH)_2$, pTSA, benzene, (c) chromatography, crystallization

oxabicyclooctanes was therefore modified to include separation of cyclohexane isomers **9** and **10**, which allowed the preparation of pure bicyclooctanes **11** and **12** (Fig. 2) as detailed in Section 2.2. The individual dithiane isomers **15**, **16**, **17** and **18** were each isolated by chromatography and crystallization (Fig. 4) as detailed in Section 2.3. The [^{1}H] NMR spectra of trioxabicyclooctanes **11** and **12** and of dithianes **15–18** were assigned using standard one-and two-dimensional methods; the important diagnostic features are summarized in Table 1.

2.2 *trans* and *cis* Isomers of 4-*tert*-Butyl-1-(4-ethynylcyclohexyl)-2,6,7-trioxabicyclo[2.2.2]octane (11,12) (Fig. 2)

Methyl 4-(2,2-dibromovinyl)cyclohexanecarboxylate (**8**), prepared from dimethyl 1,4-cyclohexanedicarboxylate via 4-methoxycarbonylcyclohexylcarbonyl chloride and methyl 4-formylcylohexanecarboxylate (**7**) as decribed,[5] was chromatographed on silica gel with hexane + diethyl ether (9 + 1 by volume) to obtain pure *trans* isomer (**9**) and *cis* isomer (**10**) in a 2 : 3 ratio.

2.2.1 trans-*Ethynylcyclohexyl-trioxabicylooctane* (11)

(i) Methyl *trans*-4-(2,2-dibromovinyl)cyclohexanecarboxylate (**9**) (4·2 g, 13 mmol) was hydrolysed with potassium hydroxide (1·09 g) in methanol (50 ml) by stirring at 25°C overnight. After evaporating the solvent, water (50 ml) was added, followed by dilute hydrochloric acid (50 ml, 2 M) and the product obtained by extraction with diethyl ether as a colorless solid (3·6 g).

(ii) Oxalyl chloride ($(COCl)_2$; 360 μl) and dimethylformamide (DMF; 25 μl) were added to a solution of *trans*-4-(2,2-dibromovinyl)cyclohexanecarboxylic acid (1·3 g, 4·2 mmol) in dichloromethane (25 ml) at 25°C. The reaction mixture was stirred for 2 h. Evaporation of the solvent gave the acid chloride which, without further purification, was added to a stirred solution of 3-*tert*-butyl-3-hydroxymethyloxetane (0·6 g, 4·1 mmol) and pyridine (0·65 mml, 8·0 mmol) in diethyl ether (25 ml) at 25°C.[2] After stirring for 2 h the reaction mixture was washed with water (2 × 25 ml), dilute hydrochloric acid (2 × 25 ml, 2 M), a saturated solution of sodium hydrogen carbonate (2 × 25 ml) and brine (25 ml). The solution was dried over anhydrous magnesium sulphate and the solvent evaporated under reduced pressure. Purification (silica pre-eluted with hexane + diethyl ether + triethylamine (85 + 14 + 1 by volume)) gave 3-*tert*-butyloxetan-3-ylmethyl *trans*-4-(2,2-dibromovinyl)cyclohexylcarboxylate (1·4 g) as a colorless solid.

(iii) This ester (1·4 g, 3 mmol) was stirred in dry dichloromethane (20 ml) at −70°C under nitrogen. Boron trifluoride etherate (92 μl, 0·75 mmol) was added and the reaction mixture allowed to warm to room temperature overnight. Triethylamine (2 ml) was added and the mixture washed with brine. After drying (magnesium sulphate) the crude product was obtained by evaporation. Pure *trans*-1-[4-(2,2-dibromovinyl)cyclohexyl]-4-*tert*-butyl-2,6,7-trioxabicyclo[2.2.2]octane was obtained as a colorless solid (m.p. 155°C, 0·86 g) by

TABLE 1
Partial [^{1}H] NMR Assignments for Cyclohexyl Moieties of Geometrical Isomers

Compound No.	*Cyclohexyl isomer*	*NMR (deuterochloroform), ppm*			
		H-1	*H-2*	*H-3*	*H-4*
	4-*tert*-butyl-1-(4-ethynylcyclohexyl)-2,6,7-trioxabicyclo[2.2.2]octanes				
11	*trans*	1·54	1·05, 2·15	1·15, 1·85	2·15
12	*cis*	1·65	1·6	1·45, 1·85	2·75
	5-*tert*-butyl-2-(4-ethynylcyclohexyl)-1,3-dithianes				
15[a]	*trans*	1·65	1·40, 1·95	1·30, 2·05	2·20
16[a]	*cis*	1·65	1·45, 1·86	1·6	2·75
17[b]	*trans*	1·70	1·00, 2·08	1·40, 2·10	2·20
18[b]	*cis*	1·65	1.5–1.8		2·70

[a] *trans*-1,3-Dithiane moiety: **15** H-2 3·98, H-5 1·65; **16** H-2 4·03, H-5 1·65.
[b] *cis*-1,3-Dithiane moiety: **17** H-2 3·25, H-5 1·80; **18** H-2 3·34, H-5 1·80.

chromatography on basic alumina, eluting with dichloromethane saturated with ammonia + hexane (30 + 70 by volume).

(iv) This 2,6,7-trioxabicyclo[2.2.2]octane (0·86 g, 2·0 mmol) was stirred in dry tetrahydrofuran (THF; 20 ml) at − 70°C under nitrogen. To this solution was added *n*-butyl lithium (1·6 M, 3·56 ml, 5·6 mmol) and the mixture allowed to warm to room temperature over 2 h. Diethyl ether (25 ml) was then added and the solution washed with brine. Drying (magnesium sulphate) followed by evaporation gave the crude bicyclooctane product. *trans*-Trioxabicyclooctane **11** (m.p. 185°C, 0·45 g) was obtained as a colorless solid by chromatograhy on alumina and elution with dichloromethane saturated with ammonia + hexane (30 + 70 by volume).

2.2.2 cis-*Ethynylcyclohexyl-trioxabicyclooctane* (**12**)

(i) Methyl *cis*-4-(2,2-dibromovinyl)cyclohexanecarbocylate (**10**) (4·0 g, 12 mmol) was hydrolysed by heating under reflux with acetic acid (40 ml) and hydrobromic acid (48%, 20 ml) for 4 h. Solvent was removed under reduced pressure to give the crude product. Diethyl ether (25 ml) and saturated sodium hydrogen carbonate solution (25 ml) were added to this residue. The aqueous layer was acidified with dilute hydrochloric acid (2 M) and, after extraction with diethyl ether, washing with brine, drying (magnesium sulphate) and evaporation, gave *cis*-4-(2,2-dibromovinyl)cyclohexanecarboxylic acid as a colorless solid (3·5 g).

(ii) The above acid (1·3 g, 4·2 mmol) was converted to 3-*tert*-butyloxetan-3-yl *cis*-4-(2,2-dibromovinyl)cyclohexanecarboxylate (1·3 g), a colorless solid, by the method described in Section 2.2.1 (ii) above.

(iii) The ester (1·3 g, 3·1 mmol) was transformed into *cis*-1-[4-(2,2-dibromovinyl)cyclohexyl]-4-*tert*-butyl-2,6,7-trioxabicyclo[2.2.2]octane (m.p. 121°C, 0·93 g) by the method described in Section 2.2.1 (iii) above.

(iv) The above bicyclooctane (0·93 g, 2·2 mol) was converted into *cis*-4-*tert*-butyl-1-(4-ethynylcyclohexyl)-2,6,7-trioxabicyclo[2.2.2]octane (**12**) (m.p. 139°C, 0·53 g) as described in Section 2.2.1 (iv) above.

2.3 Four isomers of 5-*tert*-butyl-2-(4-ethynylcyclohexyl)-1,3-dithiane (15, 16, 17, 18) (Fig. 4)

4-Ethynylcyclohexylmethanol (**14**)[6] was oxidized under Swern conditions with $(COCl)_2$ and dimethyl sulfoxide (DMSO) to give 4-ethynylcyclohexanecarboxaldehyde (95% *trans*: 5% *cis*) in 95% yield.

2.3.1 trans-*Ethynylcyclohexyl-dithianes* (*15, 17*)

A mixture of the above aldehyde (19 g, 0·14 mol), 2-*tert*-butylpropane-1,3-dithiol (22·9 g, 0·14 mol) and *p*-toluenesulfonic acid (pTSA; 1·0 g) in benzene (250 ml) was refluxed in a Dean and Stark apparatus for 6 h. GLC analysis indicated complete reaction (3% OV17, 230°C). Diethyl ether (500 ml) was added to the cooled reaction mixture and the solution was washed with water (100 ml) and brine (100 ml) before drying (magnesium sulphate). A mixture of four isomeric dithianes was obtained by evaporation under vacuum to give a colorless solid. Crystallization from hexane gave a mixture of *trans* isomers of 5-*tert*-butyl-2-(4-ethynylcyclohexyl)-*cis*- and *trans*-1,3-dithianes **15** and **17** (32 g). Chromatography of the solid mixture of **15** and **17** on silica gel and elution with hexane, followed by hexane + diethyl ether (9 + 1 by volume), gave 5-*tert*-butyl-2-(*trans*-4-ethynylcyclohexyl)-*trans*-1,3-dithiane (**15**) as a colorless solid (m.p. 134°C) and 5-*tert*-butyl-2-(*trans*-4-ethynylcyclohexyl)-*cis*-1,3-dithiane (**17**) as a colorless solid (m.p. 100–102°C).

2.3.2 cis-*Ethynylcyclohexyl-dithianes* (*16, 18*)

Evaporation of the mother liquor from crystallization of **15** and **17** above gave 13·7 g of an oily mixture which contained all four isomers, chromatography of which on silica gel, and elution with diethyl ether + hexane (10 + 90 by volume) gave further quantities of **15** and **17** and fractions enriched in the *cis*-cyclohexyl isomers **16** and **18**. These latter fractions were purified by preparative HPLC on silica gel [elution with dichloromethane + hexane (20 + 80 by volume)] to give 5-*tert*-butyl-2-(*cis*-4-ethynylcyclohexyl)-*cis*-1,3-dithiane, **18**, as a colorless solid (m.p. 68–9°C) with 0.1% recovery. Further chromatography on reverse phase HPLC (C-18)/elution with acetonitrile + water (4 + 1 by volume) gave 5-*tert*-butyl-2-(*cis*-4-ethynylcyclohexyl)-*trans*-1,3-dithiane, **16**, as a colorless solid (m.p. 102–104°C) with 0·9% recovery

3 ACTIVITY AGAINST INSECTS AND MICE

3.1 Activity against houseflies

Initial activity was assessed with adult male *Musca domestica* L. (25–30 mg each) (WRL strain) by spraying the compound as an emulsion in acetone + water + 'Symperonic' surfactant (5 + 94·5 + 0·5 by volume) over a mesh-covered cylinder containing 20 flies. Mortality was determined after 24 h. Alternatively, individual flies were dosed on the dorsal thoracic surface with 0·3 μl of a butanone solution of the test compound and held at 25°C for 48 h, when mortality was assessed. The toxicity was determined by co-treatment of the test compound with the synergist piperonyl butoxide (PB) at 3 μg per insect. An average of 20 flies were treated at each dose level and LD_{50} values were determined by the probit method.

3.2 Activity against cockroaches

Adult male *Blatella germanica* L. (~300 mg each) were anesthetized with carbon dioxide and dosed with 0·5 μl of a butanone solution of the test compound applied between the legs. They were held in batches of 10, with a supply of food and water, until mortality was determined after six days.

3.3 Activity against aphids

The activity of the compounds was assessed by spraying a formulation as above onto a leaf disc of Chinese cabbage infested with 10 *Myzus persicae* Suly. as newly-hatched first-instar larvae. Mortality was assessed after 48 h.

3.4 Toxicity to mice

The test compound was administered orally as a solution in DMSO, with mortality recorded at 24 h.

4 RESULTS

The insecticidal activity of several of the new compounds equalled or surpassed that of permethrin (Table 2). In the trioxabicyclooctanes, clearly the phenyl moiety in **1** and hexynyl in **3** can be replaced with cyclohexyl in **4** and **6** with respect to insecticidal activity, and the *trans*-cyclohexyl compound (**11**) was better against houseflies and cockroaches than the *cis*-cyclohexyl compound (**12**). In the dithianes, the trans-cyclohexyl moiety (**15** and **17**) was preferable to *cis*-cyclohexyl (**16** and **18**) for achieving highly active compounds, whereas *trans*-dithianes (e.g. **15**) and *cis*-dithianes (e.g. **17**) showed approximately the same levels of activity. Unfortunately the compounds are also more toxic to rodents (Table 2) than is acceptable for a new series of insecticides.

5 DISCUSSION

An ethynyl substituent introduced onto either an aryl ring[2] or an alkyl chain at the optimum position[4] leads to very greatly enhanced insecticidal activity. The same relationship also applies to the cyclohexyl ring, since unsubstituted 4-tert-butyl-1-cyclohexyl-2,6,7-trioxabicyclo[2.2.2]octane has a much lower level of activity against houseflies.[1] The 4-ethynylcyclohexyl substituent may resemble the spatial characteristics of the hex-5-ynyl and 4-ethynylphenyl groups by allowing the acetylene to occupy the same volume of receptor space. The hex-5-ynyl group can much more readily resemble a benzene ring than can the cyclohexyl group. Apart from the differences in overall volume (sp^3 *vs.* sp^2 carbons and two hydrogens rather than one hydrogen), the cyclohexyl acetylene group is about 1·5 Angstroms above the central plane of the dithiane/bicyclooctane, whereas, in the phenyl series, it is co-planar. The near equivalent potency of the *trans*- and *cis*-dithianes has

TABLE 2
Toxicity to Insects and Mice

	Musca domestica		Blatella germanica	Myzus persicae	
Compound	*Spray application* LC_{50} (*mg litre*$^{-1}$)	*Topical application (+PB)* LD_{50} (*μg per insect*)	*Topical application* LD_{50} (*μg per insect*)	*Spray application* LC_{50} (*mg litre*$^{-1}$)	*Mouse Oral* LD_{50} (*mg kg*$^{-1}$)
New Trioxabicyclooctanes					
4	<200	0·0095	0·11	—	
6	>1000[a]	0·0056	0·03–0·1	1000[a]	
11	<40	<0·0024	0·1	80	2–20
12	<40	0·0056	0·23	70	2–20
New Dithianes[b]					
15	<200	0·0046	0·057	10	2–20
16	270	—	0·5	>5000	> 200
17	<200	0·0045	0·08	6	20–200
18	—	0·25	>0·3	300	> 200
Standard Compounds					
1	—	0·00054	0·13	—	~2
3	—	0·018	0·20	—	
Permethrin[c]	—	0·05	0·3	25	

[a] Unstable in acetone/water formulation.
[b] Mouse oral LD_{50} of **2** < 2 mg kg^{-1}.
[c] (1*RS*)-Permethrin (75% *trans*, 25% *cis*).

been noted previously[7] and does not appear to be attributable to the *cis* compounds readily adopting a twist-boat conformation in solution.[3] The observed activity may be due to isomerization of the *cis* compound to the *trans* compound or conversion to the twist-boat form at the receptor prior to binding.

Generally, the introduction of *trans*-cyclohexyl between the acetylenic function and the heterocycle is a favorable one in terms of biological activity. The synthesis of the cyclohexyl compounds is, however, much more lengthy than that used to prepare the highly active phenyl analogues. The hex-5-ynyl series is less active, suggesting that limiting the conformation, as in the cyclohexyl compounds, provides better fit at the binding site.

ACKNOWLEDGEMENTS

We thank Matthew Moss for bioassays and Malcolm Black, Steven Irving, Michael Elliott and Ian Smith for helpful discussions. The project described was supported in part by Grant No. PO1 ES00049 from the United States National Institute of Environmental Health Sciences, NIH.

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