Insecticidal 1-(Alkynylalkyl)-3-cyano-2,6,7-trioxabicyclo[2.2.2]octanes†

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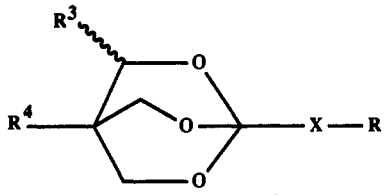
The high insecticidal activity and potency at the insect GABA-gated chloride channel of 4-alkyl-3-cyano-2,6,7-trioxabicyclo[2.2.2]octanes with the 1-(4-ethynylphenyl) substituent is also achieved with the corresponding 1-(hex-5-ynyl) analogs. Conceptually the four-methylene linkage resembles the spatial characteristics of a phenyl ring and allows the ethynyl group to occupy the same area of receptor space as when attached at the 4-position of an aryl moiety. This is the first example of chloride channel blockers with the ability to replace a phenyl group by a conformationally flexible alkyl linkage and retain a significant portion of the activity.

INTRODUCTION

2,6,7-Trioxabicyclo[2.2.2]octanes with suitable substituents (1) are the most potent and versatile probes for the γ-aminobutyric acid (GABA)-gated chloride channel



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(Milbrath *et al.*, 1979; Casida *et al.*, 1985, 1988; Obata *et al.*, 1988). The most potent compounds for houseflies (*Musca domestica*) are the 4-bromo- and 4-cyanophenyl analogs (Palmer and Casida, 1985) and particularly the 4-ethynylphenyl compounds (Palmer and Casida, 1989; Palmer *et al.*, 1991) (Table I). Replacement of substituted phenyl by *n*-alkyl groups at the 1-position gives only moderate activity (Palmer and Casida, 1985) (Table I). The potency order for insecticidal activity generally corresponds to that for inhibiting the binding of [^{35}S]-*tert*-butylbicyclophosphorothionate ([^{35}S]TBPS) to mammalian brain membranes, *i.e.*, block of the GABA-gated chloride channel (Table I), suggesting that the structural features conferring insecticidal potency are those for optimal receptor interaction. The most potent mammalian $GABA_A$-receptor antagonist reported to date contains not only the 4-ethynylphenyl moiety but also the 3-cyano substituent (**3** in Figure 1) (Palmer *et al.*, 1988).

This structure–activity study examines the effects of (a) the 3-cyano group compared with the non-cyano analog, (b) replacing the rigid phenyl template (X in **1**) by a series of conformationally flexible alkyl linkages of varying lengths, and (c) stepwise saturation of the terminal ethynyl group (R in **1**). These modifications allow the optimal spatial relationship between the ethynyl group and the bicyclooctane nucleus to be probed. The success in achieving these goals for ethynyl-containing compounds **2–9** (Figure 1) and their alkenyl and alkyl analogs (**10** and **11**) is evaluated as insecticidal activity against houseflies and German cockroaches (*Blattella germanica*) and target-site potency in an insect preparation.

Table I. Effect of 1-(4-Substituted-Phenyl) and 1-Alkyl Substituents on Topical Toxicity to Houseflies of 4-*tert*-Butyl-2,6,7-trioxabicyclo[2.2.2]octanes and Potency at the [^{35}S]-*tert*-Butylbicyclophosphorothionate Receptor of Mammalian Brain (Structure 1, R^4 = *t*-Bu, R^3 = H)

structure 1 X	structure 1 R	housefly LD_{50}, μg/g with PB (and alone)	TBPS receptor IC_{50}, nM
Effect of 1-(4-Substituted-Phenyl) Substituent			
C_6H_4	4-Br	0.83 (3.5)[a]	10[b]
C_6H_4	4-CN	0.23 (4.8)[a]	5[b]
C_6H_4	4-C≡CH	0.011 (0.090)[c]	1[c]
Effect of 1-Alkyl Substituent			
CH_2	CH_3	>500 (>500)[a]	100000[b]
$(CH_2)_2$	CH_3	425 (>500)[a]	1150[b]
$(CH_2)_3$	CH_3	55 (450)[a]	118[b]
$(CH_2)_4$	CH_3	33 (365)[a]	27[b]

[a] Palmer and Casida (1985). [b] Casida *et al.* (1985). [c] Palmer and Casida (1989) and Palmer *et al.* (1991).

MATERIALS AND METHODS

Spectroscopy. Proton nuclear magnetic resonance (NMR) spectra were recorded at 250 MHz with a Bruker AM-250 spectrometer for samples dissolved in deuteriochloroform. Mass spectra (MS) after chemical ionization (methane at 0.5 Torr) were recorded on a Finnigan 4500 mass spectrometer connected to the output of a gas-phase chromatography column (DB17, 15-m capillary).

Syntheses. Preparation of the 2,6,7-trioxabicyclo[2.2.2]octanes is summarized in Figure 2. Acylation of 3-*tert*-butyl-3-(hydroxymethyl)oxetane (**12**) (Casida *et al.*, 1985) with the requisite acid chloride gives the corresponding oxetane ester (**13**) which, under Lewis-acid catalysis, can be rearranged to form the 1,4-substituted bicyclooctane (**14**). The 4-ethynylphenyl-substituted compound (**2**) was prepared from the 4-iodophenyl derivative by Heck-type coupling with trimethylsilylacetylene and subsequent desilylation (Palmer and Casida, 1989). 4-*tert*-Butyl-1-(hex-5-ynyl)-2,6,7-trioxabicyclo[2.2.2]octane (**4**), prepared from hept-6-ynoic acid, was obtained as a white crystalline solid: mp 75 °C; MS $[M + 1]^+$ 253; NMR δ 4.00 (6H, s, CH_2O), 2.20 (2H, m, $CH_2C{\equiv}CH$), 1.95 (1H, t, $C{\equiv}CH$), 1.66 (2H, m, CCH_2), 1.55 (4H, m, CH_2CH_2), 0.85 [9H, s, $(CH_3)_3$]. The 3-cyano-substituted bicyclooctanes are accessible from the corresponding 3-alkyl-3-formyloxetanes (**15**), resulting from Swern oxidation of the alcohol (**12**). Addition of aqueous sodium cyanide to a mixture of the aldehyde and appropriate acid chloride in diethyl ether gave the oxetane ester (**16**) *via* acylation of the intermediate oxetane cyanohydrin. Boron trifluoride etherate mediated cyclization

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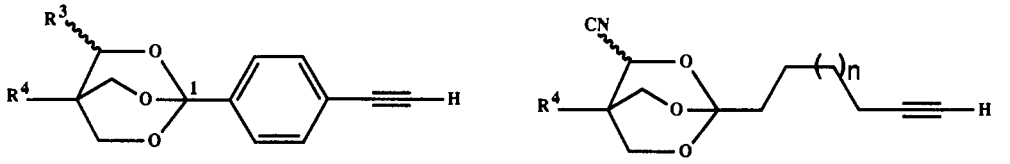

2 (R^3 =H ; R^4 = t-Bu)
3 (R^3 = CN ; R^4 = t-Bu)

4 - 9 n= 0, 1, 2
R^4 = t-Bu , n-Pr , Et

Figure 1. Trioxabicyclooctanes in the 1-phenyl and 1-alkyl series used to determine the optimal spatial relationship between the ethynyl group and the bicyclooctane nucleus.

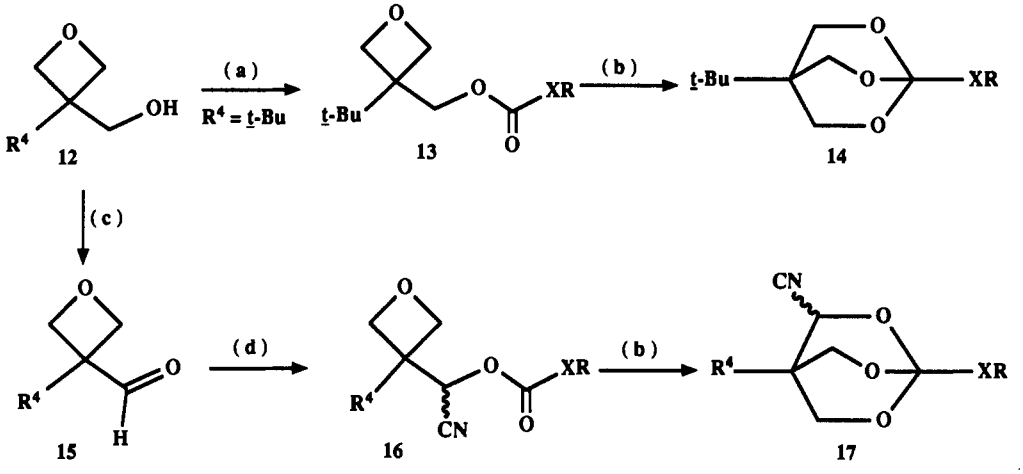

Figure 2. Synthesis routes for 1-substituted-2,6,7-trioxabicyclo[2.2.2]octanes and their 3-cyano analogs. Reagents: (a) RXC(O)Cl, pyridine, ether; (b) BF_3·OEt_2, CH_2Cl_2; (c) DMSO, oxalyl chloride then Et_3N, CH_2Cl_2; (d) NaCN, RXC(O)Cl, ether, water.

Table II. Characterization Data for 3-Cyano-1,4-dialkyl-2,6,7-trioxabicyclo[2.2.2]octanes

	structure 1 (R^3 = CN)			mp,	CI-MS,	
no.	R^4	X	R	°C	$[M+1]^+$	NMR ($CDCl_3$), ppm
5	*t*-Bu	$(CH_2)_4$	C≡CH	59	278	4.83 (1H, d, C*H*CN), 4.35 (1H, dd, C*H*O), 4.03 (2H, m, CH_2O), 3.86 (1H, dd, C*H*O), 2.18 (2H, m, $CH_2C{\equiv}CH$), 1.93 (1H, t, C≡C*H*), 1.72 (2H, m, CCH_2), 1.55 (4H, m, CH_2CH_2), 1.00 (9H, s, *t*-Bu)
6	*n*-Pr	$(CH_2)_3$	C≡CH	oil	250	4.77 (1H, d, C*H*CN), 4.18 (1H, dd, C*H*O), 3.95 (3H, m, CH_2O), 2.25 (2H, m, $CH_2C{\equiv}CH$), 1.95 (1H, t, C≡C*H*), 1.85 (2H, m, CCH_2), 1.65 (2H, m, CH_2), 1.30 (4H, m, CH_2), 0.95 (3H, t, CH_3)
7	*n*-Pr	$(CH_2)_4$	C≡CH	oil	264	4.77 (1H, d, C*H*CN), 4.20 (1H, dd, C*H*O), 3.95 (3H, m, CH_2O), 2.20 (2H, m, $CH_2C{\equiv}CH$), 1.95 (1H, t, C≡C*H*), 1.73 (2H, m, CCH_2), 1.55 (4H, m, CH_2), 1.30 (4H, m, CH_2), 0.95 (3H, t, CH_3)
8	*n*-Pr	$(CH_2)_5$	C≡CH	oil	278	4.75 (1H, d, C*H*CN), 4.16 (1H, dd, C*H*O), 3.95 (3H, m, CH_2O), 2.18 (2H, m, $CH_2{=}CH$), 1.93 (1H, t, C≡C*H*), 1.70 (2H, m, CCH_2), 1.15–1.60 (10H, m, CH_2), 0.95 (3H, t, CH_3)
9	Et	$(CH_2)_4$	C≡CH	oil	250	4.77 (1H, d, C*H*CN), 4.18 (1H, dd, C*H*O), 3.95 (3H, m, CH_2O), 2.18 (2H, m, $CH_2C{\equiv}CH$), 1.95 (1H, t, C≡C*H*), 1.72 (2H, m, CCH_2), 1.55 (4H, m, CH_2CH_2), 1.45 (2H, q, CH_3CH_2), 0.92 (3H, t, CH_3)
10	*n*-Pr	$(CH_2)_4$	CH=CH_2	oil	266	5.80 (1H, m, C*H*=CH_2), 4.90–5.05 (2H, m, CH=CH_2), 4.75 (1H, d, C*H*CN), 4.20 (1H, dd, C*H*O), 3.95 (3H, m, CH_2O), 2.05 (2H, m, $CH_2CH{=}CH_2$), 1.70 (2H, m, CCH_2), 1.15–1.55 (8H, m, CH_2), 0.95 (3H, t, CH_3)
11	*n*-Pr	$(CH_2)_4$	CH_2CH_3	oil	268	4.76 (1H, d, C*H*CN), 4.20 (1H, dd, C*H*O), 3.95 (3H, m, CH_2O), 1.70 (2H, m, CCH_2), 1.15–1.50 (12H, m, CH_2), 0.95 (3H, t, CH_3), 0.86 (3H, t, CH_3)

then gave the required 3-cyano-2,6,7-trioxabicyclo[2.2.2]octane structure (17) (Palmer *et al.*, 1988). For compounds containing primary alkyl substituents (ethyl, *n*-propyl) at the 4-position, this rearrangement was accomplished by addition of boron trifluoride etherate (1 equiv) to a dichloromethane solution of the substrate at −70 °C and subsequent warming to room temperature; *tert*-butyl analogs required heating at reflux temperature. The aliphatic acids required were either available commercially or prepared according to literature methods (Eglinton and Whiting, 1953; Newman and Wotiz, 1949). Characterization data for new 3-cyano-2,6,7-trioxabicyclooctanes prepared for this study are given in Table II.

Toxicity to Houseflies. Adult female *M. domestica* (WRL strain) were anaesthetized with carbon dioxide and held at 0 °C prior to testing. 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. Synergized toxicity was determined by cotreatment of the test compound with piperonyl butoxide (PB) at 3 μg/insect. An average of 20 flies were treated at each dose level, and LD_{50} values were determined by the probit method. Adult male *B. germanica* were anaesthetized with carbon dioxide and dosed with 0.5 μL of a butanone solution of the test compound applied between the legs. They were then held in batches of 10, with a supply of food and water, until mortality was assessed after 6 days.

LD_{50} values for houseflies are reported as micrograms per gram for literature values or as micrograms per insect for the present determinations. Where a direct comparison can be made (*e.g.*, compound 2) the synergized LD_{50} value is about 2-fold different (with higher potency for the literature value) when expressed on the same basis. This is not surprising considering that the published values are for the SCR strain, 1–2-h pretreatment with the synergist before the insecticide, and holding for 24 h, compared

Table III. Effect of 3-Cyano and 1-(4-Alkynylalkyl) Substituents on Topical Toxicity of 2,6,7-Trioxabicyclo[2.2.2]octanes to Houseflies and German Cockroaches

	structure 1				LD_{50}, μg/insect		
					M. domestica		
no.	R^4	R^3	X	R	alone	PB[a] (syn fac)[b]	*B. germanica*
			Effect of 3-Cyano Substituent				
2	*t*-Bu	H	C_6H_4	4-C≡CH	0.012	0.00054 (22)	0.13
3	*t*-Bu	CN	C_6H_4	4-C≡CH	0.026	0.0024 (11)	1.1
4	*t*-Bu	H	$(CH_2)_4$	C≡CH	0.14	0.018 (8)	0.20
5	*t*-Bu	CN	$(CH_2)_4$	C≡CH	0.067	0.009 (7)	0.21
			Effect of 1-(Alkynylalkyl) Substituent				
6	*n*-Pr	CN	$(CH_2)_3$	C≡CH	0.45	0.20 (2)	2.4
7	*n*-Pr	CN	$(CH_2)_4$	C≡CH	0.066	0.0077 (9)	0.11
8	*n*-Pr	CN	$(CH_2)_5$	C≡CH	0.40	0.16 (3)	1.5
9	Et	CN	$(CH_2)_4$	C≡CH	0.12	0.033 (4)	0.25
10	*n*-Pr	CN	$(CH_2)_4$	CH=CH_2	0.85	0.19 (5)	2.5
11	*n*-Pr	CN	$(CH_2)_4$	CH_2CH_3	12	7 (2)	>10
permethrin[c]					0.047	0.0042 (11)	0.18

[a] Piperonyl butoxide, 3 μg/insect. [b] Synergism factor. [c] 75 *trans*/25 *cis*.

with the current study using the WRL strain, cotreatment of the synergist and insecticide, and holding for 48 h.

Insect Target Site Assay. Crude synaptosomal (P2) fractions, prepared from the central nervous system of the American cockroach (*Periplaneta americana*), were loaded with [^{3}H]choline in superfusion buffer consisting of 215 mM NaCl, 3.1 mM KCl, 2.04 mM $CaCl_2$, 3.29 mM Na_2HPO_4, 0.19 mM NaH_2PO_4, 6.6 mM $MgCl_2$, and 16.5 mM glucose. Ivermectin was added at ~10 nM to stimulate the release of radioactivity, presumably ^{3}H-labeled acetylcholine. This neurotransmitter efflux is inhibited by picrotoxinin and endosulfan, selective chloride-channel blockers, thus implicating the chloride channel in the release process. Putative GABA antagonists can therefore be ranked by their ability to inhibit ivermectin-stimulated release of radiolabeled neurotransmitter from *P. americana* synaptosomes and expressed as an IC_{50}, the concentration required to inhibit the release by 50%. This target site assay is described in detail by Nicholson *et al.* (1987, 1988).

RESULTS

Effect of 3-Cyano Substituent on Insecticidal Activity (Table III). The insecticidal properties of **2** have been reported previously (Palmer and Casida, 1989); although the corresponding 3-cyano-substituted analog (**3**) is known to be a potent mammalian chloride-channel antagonist (Palmer *et al.*, 1988), this is the first report of its insecticidal activity. Clearly, incorporation of a 3-cyano substituent on the bicyclooctane ring is an acceptable modification with regard to housefly activity since, although **3** is less active than **2**, both compounds are very potent insecticides, superior in activity to the standard permethrin. Furthermore, examination of the activities of the corresponding 1-(hex-5-ynyl)-substituted compounds, **4** and **5**, shows that this is a general phenomenon. In fact, in this series the 3-cyano-substituted analog **5** is more active than the unsubstituted compound **4**. For these reasons and for consistency, the investigation of the structure–activity relationships within the 1-(alkynylalkyl)-substituted bicyclooctane series of compounds has been conducted on the 3-cyano analogs.

Effect of 1-(Alkynylalkyl) Substituents on Insecticidal Activity (Table III). The optimal 1-substituent for toxicity to houseflies is clearly hex-5-ynyl (compounds **4**, **5**, and **7**), incorporating a four-methylene spacer between the bicyclooctane nucleus and the ethynyl group. Shorter or longer linkages, as in pent-4-ynyl (**6**) and hept-6-ynyl (**8**), respectively, are of reduced activity. At the 4-position of the bicyclooctane ring, *tert*-butyl (**5**) and *n*-propyl (**7**) are equivalent substituents in contrast to the 1-aryl series, in which *tert*-butyl is preferred. The 4-ethyl substituent is somewhat less effective than 4-*n*-propyl and 4-*tert*-butyl (**9** vs **7** and **5**). The importance of the ethynyl group is confirmed by comparison with the olefinic and fully saturated analogs. The acetylene-containing compound (**7**) has a synergized activity which is 25 times that of the corresponding olefin (**10**) and over 900 times that of the saturated variant (**11**). These results against *M. domestica* are duplicated against *B. germanica*. However, whereas against houseflies the optimum 4-*n*-propyl-1-(hex-5-ynyl) compound (**7**) is less active than permethrin, against cockroaches it is significantly more active. Furthermore, it is also as active or more so than the model 1-(4-ethynylphenyl) compounds (**2** and **3**).

Table IV. Inhibition of Ivermectin-Induced Release of Neurotransmitter from *P. americana* Synaptosomes

compd	IC_{50}, nM	compd	IC_{50}, nM
3	4	**7**	11
5	8	**11**	724

[a] Data from Nicholson *et al.* (1988) are 2 nM for **3**, ca. 10 nM for endosulfan, and ca. 300 nM for picrotoxinin.

Effect of 1-(Alkynylalkyl) Substituents on Insect Target Site Potency (Table IV). The highly effective $GABA_A$ receptor antagonist **3** is particularly potent in this assay (IC_{50} = 4 nM). The 1-(hex-5-ynyl)-substituted bicyclooctanes (**5**, 4-*t*-Bu, and **7**, 4-*n*-Pr) are similarly potent (IC_{50} = 8 and 11 nM, respectively), indicating a high level of target site compatibility. In contrast, the fully saturated 1-*n*-hexyl analog (**11**) is a poor inhibitor, which is in accord with its performance as an insecticide.

DISCUSSION

The 3-cyano substituent either increases or decreases insecticidal activity depending on the 1-substituent. Although the influence of this modification may be due to a favorable interaction with the receptor, the cyano substituent also has the effect of increasing the hydrolytic stability of the trioxabicyclooctane nucleus. Thus, the electron-withdrawing cyano group reduces the electron density on the adjacent oxygen atom, thereby minimizing acid attack at this position and stabilizing the bicyclic structure to hydrolysis.

The 1-alkynylalkyl substituent is optimal with a four-methylene linkage, which obviously most closely resembles the spatial characteristics of a phenyl ring and allows the ethynyl group to occupy the same area of receptor space as when attached at the 4-position of an aryl moiety. However, with the far greater degree of rotational freedom

associated with a flexible alkyl chain, it is surprising that the levels of insecticidal activity achieved with the 1-(hex-5-ynyl)-substituted compounds (**5** and **7**) compare so favorably with the 1-(4-ethynylphenyl) analog (**3**).

The role of the acetylene moiety in this group of compounds and its interaction at the target site is unclear. However, its introduction onto an aryl ring or into an alkyl chain, at the optimum position, clearly leads to the most potent compounds in terms of both insecticidal efficacy and target site activity. The high insecticidal activity of these new 1-(hex-5-ynyl)-substituted trioxabicyclooctanes indicates that a broader range of effective 1-substituents, other than substituted phenyl, is possible. Furthermore, the ability to replace a phenyl group by a conformationally flexible alkyl linkage and retain a significant proportion of the activity is unusual.

ABBREVIATIONS USED

GABA, γ-aminobutyric acid; IC_{50}, concentration to inhibit the receptor or neurotransmitter release by 50%; MS, mass spectrometry; NMR, nuclear magnetic resonance spectroscopy; PB, piperonyl butoxide; [^{35}S]TBPS, [^{35}S]-*tert*-butylbicyclophosphorothionate; Et, ethyl; *n*-Pr, *n*-propyl; *t*-Bu, *tert*-butyl.

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