carbon dioxide, in a manner similar to that reported for diclofop acid (Martens, 1978).

At the end of the 84 day incubation period, the solvent extracted soils were analyzed by combustion to determine radioactivity remaining in an unextractable form. Between 34 and 57% of the aplied radioactivity remained on the soil (Table III). Thus the amounts of radioactivity that could be accounted for were 87, 66, and 67% of that applied to the clay loam, heavy clay, and sandy loam, respectively (Table III). The remaining radioactivity was presumably lost as [^{14}C]carbon dioxide, which was not assayed for in these experiments.

Alkaline extraction of the solvent extracted soils released between 8 and 19% of the applied radioactivity, and of this, about one-half was ether soluble and shown to consist mainly of [^{14}C]haloxyfop acid (Table III). No attempts were made to further isolate and characterize the radioactivity remaining in the aqueous fulvic acid extracts after ether extraction. Radioactivity associated with the humic and humin fractions ranged from 26 to 38% of that initially applied (Table III).

Treatment of the solvent extracted soils with 1 N sodium hydroxide for 24 h would result in the extraction of fulvic acid and humic acid soil components containing incorporated radioactivity derived from [^{14}C]fragments of the herbicide. The sodium hydroxide could also remove other [^{14}C]compounds that were either not, or only partially, removed from the soils by the ammoniated acetonitrile.

In summary, it has been demonstrated that on the three prairie soils, haloxyfop-methyl undergoes rapid hydrolysis to haloxyfop acid which itself is further transformed.

ACKNOWLEDGMENT

Thanks are due to The Dow Chemical Co., for the generous gift of chemicals. The assistance of A. Yarechewski who conducted the soil combustion analyses is greatfully recorded.

Registry No. 1 (R = $CH(CH_3)CO_2CH_3$), 69806-40-2; 1 (R = $CH(CH_3)CO_2H$), 69806-34-4; 1 (R = H), 69045-89-2; CO_2, 124-38-9.

LITERATURE CITED

Bartha, R.; Pramer, D. *Soil Sci.* **1965**, *100*, 68.
Fournier, J. C.; Coddaccioni, P.; Soulas, G.; Repiquet, C. *Chemosphere* **1981**, *10*, 977.
Martens, R. *Pestic. Sci.* **1978**, *9*, 27.
Ryder, J. C.; Saunders, E. S.; Vatne, R. D.; Wright, W. G. *Down Earth* **1983**, *39*, 1.
Smith, A. E. *Weed Res.* **1976**, *16*, 19.
Smith, A. E. *J. Agric. Food Chem.* **1977**, *25*, 893.
Smith, A. E. *J. Agric. Food Chem.* **1979**, *27*, 1145.
Smith, A. E. *J. Agric. Food Chem.* **1981**, *29*, 111.
Smith, A. E. *J. Agric. Food Chem.* **1985**, *33*, 483.
Smith, A. E.; Hayden, B. J. *Bull. Environ. Contam. Toxicol.* **1980**, *25*, 369.
Smith, A. E.; Milward, L. J. *J. Agric. Food Chem.* **1983**, *31*, 363.
Smith, A. E.; Muir, D. C. G. *Weed Res.* **1980**, *20*, 123.
Smith, A. E.; Muir, D. C. G. *J. Agric. Food Chem.* **1984**, *32*, 588.

Received for review February 25, 1985. Accepted May 30, 1985.

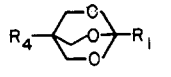
1,4-Disubstituted 2,6,7-Trioxabicyclo[2.2.2]octanes: A New Class of Insecticides

Christopher J. Palmer* and John E. Casida

A new class of insecticides, the 1,4-disubstituted 2,6,7-trioxabicyclo[2.2.2]octanes, was prepared either by acid-catalyzed condensation of a 2-substituted 2-(hydroxymethyl)-1,3-propanediol with a trimethyl orthocarboxylate or by Lewis acid catalyzed rearrangement of a 3-substituted 3-[(acyloxy)methyl]oxetane. Compounds of high toxicity to houseflies or American cockroaches have 4-substituents such as *n*-propyl, isopropyl, *n*-, *sec*- or *tert*-butyl, cyclopentyl, cyclohexyl, or phenyl and 1-substituents such as cyclohexyl, cycloheptyl, 4-cyanophenyl, 4-nitrophenyl, 4-halophenyl, or 3,4-dichlorophenyl. The toxicity to houseflies is generally increased by injection and by piperonyl butoxide indicating that the insecticidal activity is limited by the penetration rate and oxidative detoxification. The bicycloorthocarboxylates have a positive temperature coefficient in poisoning houseflies and act at the cockroach neuromuscular junction to inhibit GABAergic synaptic transmission possibly by closing off chloride channels.

INTRODUCTION

New types of insecticides are discovered by many approaches, one of which starts from known toxicants for other organisms and modifies their structure for potency on insects (Casida, 1976). Bicyclophosphorus esters such as *i*-Pr-$C(CH_2O)_3P{=}O$ might be considered as candidate prototypes but they have little or no insecticidal activity (Casida et al., 1976; Milbrath et al., 1979) except to houseflies on injection (Ozoe et al., 1983) and they are highly toxic to mammals (Bellet and Casida, 1973; Casida et al., 1976; Milbrath et al., 1979). The related bicycloorthocarboxylates are similar to the bicyclophosphorus esters in their mode of action (Casida et al., 1976; Milbrath et al., 1979; Squires et al., 1983) and offer considerable opportunity for structural modification in the 1- and 4-positions for optimizing insecticidal potency, penetration, and selective toxicity. This report considers the structural optimization of 1,4-disubstituted 2,6,7-trioxabicyclo-[2.2.2]octanes for insecticidal activity.



R_1, R_4 = alkyl or aryl

MATERIALS AND METHODS

Bioassays. Houseflies (*Musca domestica* L.) were adult females (~20 mg each) of the SCR strain used 3–5 days

Pesticide Chemistry and Toxicology Laboratory, Department of Entomological Sciences, University of California, Berkeley, California 94720.

0021-8561/85/1433-0976$01.50/0

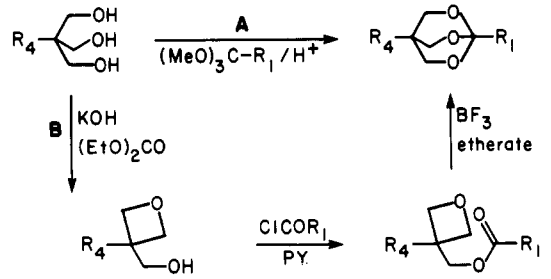


Figure 1. Two methods of synthesis of 1,4-disubstituted 2,6,7-trioxabicyclo[2.2.2]octanes.

after emergence and American cockroaches (*Periplaneta americana* L.) were adult males. The test compound was applied topically to the ventrum of the fly abdomen or cockroach thorax with acetone as the carrier solvent (or tetrahydrofuran for compounds insoluble in acetone) by using 0.5 μL per fly and 1.0 μL per cockroach. Alternatively the houseflies were injected with the test compound dissolved in methoxy triglycol administered at 0.2 μL per fly. In many cases the houseflies and cockroaches were pretreated topically with piperonyl butoxide (PB) at 250 μg/g 2 h before administering the toxicant. LD_{50} values were determined after 24 h at 25 °C (unless specifically stated otherwise) with repetition of the experiments until uniformity of results was achieved.

Abbreviations for Chemical Substituents. The abbreviations used are as follows: Me-methyl, Et-ethyl, Pr-propyl, Bu-butyl, Pen-pentyl, Hex-hexyl, Hept-heptyl, Ph-phenyl, *n*-normal, *i*-iso, *sec*-secondary, *t*-tertiary, and *c*-cyclo.

Spectroscopy. Proton nuclear magnetic resonance (NMR) spectra were obtained at 300 MHz with a Bruker WM-300 spectrometer for samples dissolved in deuteriochloroform. Mass spectrometry (MS) utilized a Hewlett Packard 5985 system with chemical ionization at 230 eV with methane (0.8 torr).

Syntheses. Two methods were used to prepare the bicycloorthocarboxylates (Figure 1). Each compound gave appropriate NMR and MS characteristics.

Acid-Catalyzed Condensation of a Triol with a Trimethyl Orthocarboxylate (Procedure A, Figure 1) (Boros et al., 1966; Bertrand et al., 1970). Intermediate triols were synthesized from the corresponding substituted acetaldehydes and formaldehyde by hydroxymethylation and subsequent crossed-Cannizzaro reaction (Dermer and Solomon, 1954; Ketslakh et al., 1963). Intermediate trimethyl orthocarboxylates were commercially available or were synthesized from either (a) the appropriate benzotrichloride or benzotribromide (from bromination of the corresponding toluene with *N*-bromosuccinimide) by halide displacement with methoxide (McElvain and Venerable, 1950) or (b) the appropriate nitrile via methanolysis of the imino ester hydrochloride (McElvain and Starn, 1955). For example, a mixture of 2-*tert*-butyl-2-(hydroxymethyl)-1,3-propanediol (0.4 g, 2.5 mmol), trimethyl orthocyclohexanecarboxylate (0.5 g, 2.5 mmol), and 4-toluenesulfonic acid (10 mg) was heated to 160 °C until methanol distilled over. The residue was vacuum dried (at 1 mmHg) and then passed down a short basic alumina column to give 1-cyclohexyl-4-*tert*-butyl-2,6,7-trioxabicyclo[2.2.2]octane (**60**) (0.6 g, 95%): mp 154–155 °C; $[M + 1]^+$ 255; δ 0.85 [9 H, s, $(CH_3)_3C$], 1.0–2.0 [11 H, m, $(CH_2)_5CH$], 4.0 [6 H, s, $(CH_2O)_3$]. 1-BrEt compound **66**, prepared by procedure A, was subjected to sequential dehydrobromination, bromination, and dehydrobromination to obtain vinyl derivative **63**, 1,2-Br_2Et compound **67**, and ultimately the ethynyl derivative **64**.

Table I. Effect of 4-Substituent on the Topical Toxicity to Houseflies of 1-(4-Chlorophenyl)-2,6,7-trioxabicyclo[2.2.2]-octanes and Three 1-Cyclohexyl Analogues

4-substituent	compd no.	LD_{50}, μg/g, with PB (and alone)
Et[a]	1	105 (>500)
n-Pr	2	2.5 (23)
i-Pr	3	8.3 (140)
n-Bu	4	3.5 (17)
sec-Bu	5	2.7 (58)
t-Bu	6	1.5 (10)
c-Pen	7	2.0 (21)
c-Hex[a]	8	0.53 (10)
Ph[a]	9	2.5 (41)
4-Me-Ph	10	>500 (>500)
NO_2	11	>500 (>500)

[a] Compound numbers and LD_{50} values [μg/g with PB (and alone)] in the 1-*c*-Hex series are: (**12**) 4-Et 350 (>500); (**13**)-*c*-Hex 0.63 (8.5); (**14**) 4-Ph 7.0 (375).

Rearrangement of an Acylated (Hydroxymethyl)-oxetane (Procedure B, Figure 1) (Corey and Raju, 1983). Acylation of 3-substituted 3-(hydroxymethyl)oxetanes (prepared from the appropriate triol via pyrolysis of the carbonate ester) (Pattison, 1957) gives the corresponding oxetane esters which can be rearranged in the presence of boron trifluoride etherate to form bicycloorthoesters. For example, 4-nitrobenzoyl chloride (2.28 g, 12.3 mmol) in dry dichloromethane (4 mL) was added to 3-isopropyl-3-(hydroxymethyl)oxetane (1.6 g, 12.3 mmol) in dry dichloromethane (15 mL) and dry pyridine (2 mL) at 0 °C under a nitrogen atmosphere. The solution was stirred overnight, then extracted with water, dried (sodium sulfate), filtered, and evaporated to leave the 4-nitrobenzoyl ester (3.4 g, 99%) as a residue which was not purified further: δ 1.0 [6 H, d, $(CH_3)_2C$], 2.3 [1 H, m, CCH], 4.55 [2 H, s, CH_2OCO], 4.6 [4 H, dd, CH_2OCH_2], 8.3 [4 H, q, aromatic]. This residue was dissolved in dry dichloromethane (15 mL) under a nitrogen atmosphere and cooled to −55 °C and boron trifluoride etherate (2 mL) was added. The mixture was allowed to warm to room temperature and was then quenched with triethylamine, evaporated to dryness, and partitioned between dichloromethane and water. The organic layer was separated, dried (potassium carbonate), and evaporated. The residue was purified by passage through a short basic alumina column to afford 1-(4-nitrophenyl)-4-isopropyl-2,6,7-trioxabicyclo[2.2.2]octane (**28**) as a pale yellow solid (1.7 g, 50%): mp 163–166 °C; $[M + 1]^+$ 280; δ 0.9 [6 H, d, $(CH_3)_2C$], 1.6 [1 H, m, CH-C], 4.1 [6 H, s, $(CH_2O)_3$], 7.75 [2 H, d, aromatic], 8.2 [2 H, d, aromatic]. Thioether **34** from procedure B was oxidized with 2 equiv of 3-chloroperoxybenzoic acid in dichloromethane to obtain sulfone **33**.

RESULTS

Structure Optimization for Topical Toxicity to Houseflies. Structure–activity relationships are discussed below on the basis of PB-synergized toxicity.

Effect of 4-Substituent (Table I). When the 1-substituent is 4-Cl-Ph, suitable 4-substituents are *n*-alkyl, branched alkyl, or cycloalkyl with 3–6 carbons (**2–8**) and Ph (**9**) whereas Et (**1**), 4-Me-Ph (**10**), and NO_2 (**11**) are not effective (Table I). These relationships also apply to a more limited series with 1-*c*-Hex substituents (**12–14**) where again the 4-*c*-Hex group is very effective. In further studies the 4-substituent was standardized as *n*-Pr, *i*-Pr, *t*-Bu, or *c*-Hex.

Effect of Substitution on 1-Phenyl Group (Table II). The activity of the orthobenzoates (**15–18, 44**) is increased by a 3-Cl or 4-halo substituent (**2, 3, 6, 8, 21,**

Table II. Effect of Substitution on 1-Phenyl Group on the Topical Toxicity to Houseflies of 4-Alkyl-2,6,7-trioxabicyclo[2.2.2]octanes and Two 4-Phenyl Analogues

1-phenyl substituent	compound no.				LD_{50}, μg/g, with PB (and alone)			
	4-*n*-Pr	4-*i*-Pr	4-*t*-Bu	4-*c*-Hex	4-*n*-Pr	4-*i*-Pr	4-*t*-Bu	4-*c*-Hex
H[a]	**15**	**16**	**17**	**18**	90 (>500)	90 (>500)	23 (>500)	13 (>500)
2-F			**19**				30 (>500)	
2-Cl			**20**				105 (>500)	
3-Cl			**21**				6.3 (375)	
3-PhO		**22**				>500 (>500)		
4-F[a]			**23**	**24**			5.5 (>500)	1.9 (>500)
4-Cl	**2**	**3**	**6**	**8**	2.5 (23)	8.3 (140)	1.5 (10)	0.53 (10)
4-Br			**25**	**26**			0.83 (3.5)	0.25 (6.5)
4-CF_3			**27**				53 (>500)	
4-NO_2		**28**	**29**			11 (>500)	5.0 (>500)	
4-CN			**30**	**31**			0.23 (4.8)	0.65 (115)
4-N_3			**32**				13 (160)	
4-$MeSO_2$	**33**				>500 (>500)			
4-MeS	**34**				>500 (>500)			
4-MeO		**35**				265 (>500)		
4-Me		**36**				250 (>500)		
4-*t*-Bu			**37**				>500 (>500)	
3,4-Cl_2			**38**	**39**			0.88 (4.3)	2.5 (30)
3-NO_2,4-Cl	**40**				>500 (>500)			
3,4-OCH_2O	**41**				>500 (>500)			
F_5		**42**	**43**			135 (>500)	18 (240)	

[a] Compound numbers and LD_{50} values [μg/g with PB (and alone)] in the 4-Ph series are (**44**) H 325 (>500) and (**45**) 4-F 250 (>500).

Table III. Effect of 1-Substituent on the Topical Toxicity to Houseflies of 4-Isopropyl- and 4-*tert*-Butyl-2,6,7-trioxabicyclo[2.2.2]octanes and Five 4-*n*-Propyl and Two 4-Cyclohexyl Analogues

1-substituent	compound no.		LD_{50}, μg/g, with PB (and alone)	
	4-*i*-Pr	4-*t*-Bu	4-*i*-Pr	4-*t*-Bu
H		**46**		>500 (>500)
Me		**47**		>500 (>500)
Et		**48**		>500 (>500)
n-Pr		**49**		425 (>500)
i-Pr		**50**		>500 (>500)
n-Bu[a]		**51**		55 (450)
sec-Bu	**52**		>500 (>500)	
n-Pen		**53**		33 (365)
neo-Pen	**54**		>500 (>500)	
n-Hex	**55**		160 (>500)	
c-Pr	**56**		>500 (>500)	
c-Bu	**57**		>500 (>500)	
c-Pen	**58**		500 (>500)	
c-Hex[a]	**59**	**60**	14 (>500)	3.5 (165)
c-Hept[a]	**61**	**62**	8.5 (300)	2.0 (44)
vinyl	**63**		>500 (>500)	
ethynyl	**64**	**65**	325 (>500)	90 (175)
1-BrEt	**66**		>500 (>500)	
1,2-Br_2Et	**67**		>500 (>500)	
benzyl		**68**		210 (>500)

[a] Compound numbers and LD_{50} values [μg/g with PB (and alone)] are as follows: in the 4-*n*-Pr series (**69**) 1-*n*-Bu 155 (>500), (**70**) 1-(1-bicyclo[2.2.1]heptyl) 125 (>500), (**71**) 1-(2-bicyclo[2.2.1]-heptyl) 10 (160), (**72**) 1-(cyclohex-3-enyl) 19 (110), and (**73**) 1-(5-bromo-2-furyl) 68 (500); in the 4-*c*-Hex series (**13**) 1-*c*-Hex 0.63 (8.5) and (**74**) 1-*c*-Hept 2.0 (13).

Table IV. Effect of Temperature on the Topical Toxicity to Houseflies of Three 1,4-Disubstituted 2,6,7-Trioxabicyclo-[2.2.2]octanes and Four Insecticides of Other Types

insecticide	compd no.	LD_{50}, μg/g, with PB (and alone) 11 °C	25 °C
Compounds with Positive Temperature Coefficient			
c-Hex-$C(CH_2O)_3$C-PhBr-4	**26**	1.3	0.25 (6.5)
t-Bu-$C(CH_2O)_3$C-Ph-CN-4	**30**	1.3	0.23 (4.8)
t-Bu-$C(CH_2O)_3$C-*c*-Hex	**60**	9.5	3.5 (165)
dieldrin		14	0.83 (0.65)
parathion		1.0	0.43 (1.3)
Compounds with Negative Temperature Coefficient			
DDT		4.8	12 (14)
allethrin (1*R*,*trans*,α*S*)		0.040	0.32 (14)

23–26, 45) but not by a 2-halo or 3-PhO substituent (**19**, **20**, **22**). Among other compounds with 4-substituents (**27–37**) the most effective groups in the 4-position are NO_2 (**28**, **29**), CN (**30**, **31**), and N_3 (**32**) with moderate activity for CF_3 (**27**) and notably low activity for $MeSO_2$ (**33**), MeS (**34**), MeO (**35**), Me (**36**), and *t*-Bu (**37**). The 3,4-Cl_2 derivative in the 4-*t*-Bu series (**38**) is more potent than the 3- or 4-Cl analogue (**6**, **21**) but in the 4-*c*-Hex series (**39**) it is less potent than the 4-Cl analogue (**8**). The 3-NO_2 substituent drastically lowers the activity of the 4-Cl compound (**40** vs. **2**). No or moderate activity is conferred by the 3,4-OCH_2O (**41**) or F_5 (**42**, **43**) substituents, respectively.

The preferred 4-substituent depends on the 1-substituent, i.e., 4-*c*-Hex is better than 4-*t*-Bu with 1-Ph or 1-(4-halo-Ph) (**8**, **18**, **24**, and **26** vs. **6**, **17**, **23**, and **25**, respectively) whereas 4-*t*-Bu is better than 4-*c*-Hex with 1-(4-CN-Ph) and 1-(3,4-Cl_2-Ph) (**30** and **38** vs. **31** and **39**, respectively).

Effect of 1-Substituents Other Than Phenyl Group (Table III). Compounds with hydrogen, *n*-alkyl, branched alkyl, and cycloalkyl substituents in the 1-position (**46–62**, **69**, **74**) are not effective with two exceptions: C_4–C_6 *n*-alkyl compounds (**51**, **53**, **55**, **69**) are moderately active; *c*-Hex and *c*-Hept analogues (**59–62**, **74**) are highly active. Vinyl, ethynyl, 1-BrEt, 1,2-Br_2Et and benzyl are not effective 1-substituents (**63–68**). Relative to other 1-substituents examined, 5-bromofuryl (**73**) and 1-bicyclo[2.2.1]heptyl (**70**) confer moderate activity while 2-bicyclo[2.2.1]heptyl (**71**) and cyclohex-3-enyl (**72**) give good potency.

Factors Affecting Toxicity to Houseflies. Synergism by Piperonyl Butoxide (Tables I–III). PB increases the topical toxicity of the bicycloorthocarboxylates by 2- to 263-fold with 22-fold or greater synergism when the 1-substituent is Ph (**17**, **18**), 3-Cl-Ph (**21**), 4-F-Ph (**23**, **24**), 4-NO_2-Ph (**28**, **29**), 4-CN-Ph (**31**), *c*-Hex (**59**, **60**), or *c*-Hept (**61**, **62**). Compounds synergized less than 5-fold are **4**, **25**, and **65**.

Temperature Coefficient (Table IV). Three bicycloorthocarboxylates (**26**, **30**, and **60**) are 3- to 6-fold

Table V. Comparison of Topical and Injected Toxicity to Houseflies of 1,4-Disubstituted 2,6,7-Trioxabicyclo[2.2.2]octanes

substituents		compd	LD_{50}, μg/g, with PB		
R_4	R_1	no.	topical	injection	ratio
n-Pr	4-Cl-Ph	**2**	2.5	1.4	1.8
Ph	4-Cl-Ph	**9**	2.5	2.3	1.1
c-Hex	*c*-Hex	**13**	0.63	0.65	1.0
Ph	*c*-Hex	**14**	7.0	3.5	2.0
t-Bu	Ph	**17**	23	3.1	7.4
t-Bu	4-F-Ph	**23**	5.5	1.4	3.9
t-Bu	4-Br-Ph	**25**	0.83	0.45	1.8
c-Hex	4-Br-Ph	**26**	0.25	0.20	1.3
i-Pr	4-NO_2-Ph	**28**	11	1.9	5.8
t-Bu	4-CN-Ph	**30**	0.23	0.063	3.7
t-Bu	3,4-Cl_2-Ph	**38**	0.88	0.32	2.8
c-Hex	3,4-Cl_2-Ph	**39**	2.5	1.7	1.5
t-Bu	H	**46**	>500	125	>4.0
t-Bu	*c*-Hex	**60**	3.5	0.40	8.8
t-Bu	ethynyl	**65**	90	14	6.4
t-Bu-C$(CH_2O)_3$P=S		TBPS	>500	1.6	>313

Table VI. Toxicity to American Cockroaches of Topically Applied 1,4-Disubstituted 2,6,7-Trioxabicyclo[2.2.2]octanes

substituents		compd	LD_{50}, μg/g, with PB[a]
R_4	R_1	no.	
n-Pr	4-Cl-Ph	**2**	2
n-Bu	4-Cl-Ph	**4**	3
t-Bu	4-Cl-Ph	**6**	1[b]
c-Pen	4-Cl-Ph	**7**	2
c-Hex	4-Cl-Ph	**8**	1[b]
Ph	4-Cl-Ph	**9**	7
c-Hex	*c*-Hex	**13**	>8
t-Bu	4-Br-Ph	**25**	1[b]
c-Hex	4-Br-Ph	**26**	1
t-Bu	3,4-Cl_2-Ph	**38**	>10
t-Bu	*c*-Hex	**60**	2[b]

[a] Estimated LD_{50} based on 6 cockroaches per concentration and a dose differential of 2-fold. [b] At least 20-fold synergism by PB.

more toxic at 25 °C than at 11 °C, falling between parathion and dieldrin in their positive temperature coefficients. In contrast, DDT and allethrin have negative temperature coefficients. The favorable activity of the bicycloorthocarboxylates is therefore more evident at high than at low temperature.

Topical vs. Injected Toxicity (Table V). The LD_{50} ratio for topical application vs. injection is very large for the bicyclophosphorothionate TBPS compared with any of the bicycloorthocarboxylates. Some of the orthocarboxylates are almost equitoxic applied topically or injected, i.e., **9**, **13**, and **26**. Substituents that help facilitate penetration, i.e., confer low topical/injected LD_{50} ratios, are *c*-Hex or Ph in the 4-position and 4-Cl-Ph, 4-Br-Ph, or 3,4-Cl_2-Ph in the 1-position.

Toxicity to American Cockroaches (Table VI). The bicycloorthocarboxylates tested on cockroaches are strongly synergized by PB to achieve a potency similar to that with PB-treated houseflies except for two compounds (**13** and **38**) which are >10-fold more toxic to houseflies than to cockroaches.

DISCUSSION

The 1,4-disubstituted 2,6,7-trioxabicyclo[2.2.2]octanes are a new class of insecticides derived by structural modification of the bicyclophosphorus esters. With optimal alkyl and aryl substituents they fall in the potency range for houseflies of many commercial insecticides. Preferred substituents in the 4-position include *n*- or *i*-Pr, *n*-, *sec*-, or *t*-Bu, *c*-Pen, *c*-Hex, or Ph and in the 1-position include *c*-Hex, *c*-Hept, 4-CN-Ph, 4-halo-Ph, or 3,4-Cl_2-Ph. Certain types of electron-withdrawing substituents greatly increase the potency of the orthobenzoates whereas electron-donating substituents generally reduce the activity. These structural features contribute importantly in fitting the target site, resisting detoxification, and facilitating penetration. The selectivity pattern for toxicity to mammals and insects is drastically changed within the compounds examined. TBPS is >9400-fold more toxic to ip-treated mice than topically treated houseflies whereas some of the bicycloorthocarboxylates are several-fold more toxic to houseflies than to mice, e.g., compounds with *c*-Hex in the 4-position and 4-Cl-Ph, *c*-Hex, or *c*-Hept in the 1-position.

Metabolic detoxification is primarily an oxidative process in houseflies and cockroaches based on the high degree of synergism by PB. Alkyl and aryl groups are possible sites of metabolic attack but the *O*-methylene substituents may also be involved based on analogy with the metabolism of bicyclophosphates (Milbrath et al., 1978).

The trioxabicyclo[2.2.2]octanes including the orthocarboxylates and phosphorus esters act in mammals at a chloride ionophore-associated binding site within the GABA receptor–ionophore complex (Bowery et al., 1976; Milbrath et al., 1979; Squires et al., 1983). Bicycloorthocarboxylate **25** exhibits picrotoxin-type action in a cockroach neuromuscular preparation (procedure of Adams and O'Shea, 1983) suggesting that in insects it also inhibits GABAergic synaptic transmission by closing off chloride channels (Adams, 1984). Other insecticides with a similar mode of action in mammals are picrotoxinin and several polychlorocycloalkanes (lindane, toxaphene components, and cyclodienes) (Lawrence and Casida, 1984; Casida and Lawrence, 1985). The 1,4-disubstituted 2,6,7-trioxabicyclo[2.2.2]octanes are therefore useful probes for studying the comparative neuropharmacology of the GABAergic system.

ACKNOWLEDGMENT

We thank our laboratory colleagues Hsi Liu for great skill in performing the bioassays and Luis Ruzo for the MS determinations.

Registry No. **1**, 85946-92-5; **2**, 97719-89-6; **3**, 97719-90-9; **4**, 97719-91-0; **5**, 97719-92-1; **6**, 97719-93-2; **7**, 97719-94-3; **8**, 97719-95-4; **9**, 97719-96-5; **10**, 97719-97-6; **11**, 97719-98-7; **12**, 97719-99-8; **13**, 97720-00-8; **14**, 97720-01-9; **15**, 70637-03-5; **16**, 70637-04-6; **17**, 70637-05-7; **18**, 97720-02-0; **19**, 97720-03-1; **20**, 97720-04-2; **21**, 97720-05-3; **22**, 97720-06-4; **23**, 97720-07-5; **24**, 97720-08-6; **25**, 97720-09-7; **26**, 97720-10-0; **27**, 97720-11-1; **28**, 97720-12-2; **29**, 97720-13-3; **30**, 97720-14-4; **31**, 97720-15-5; **32**, 97720-16-6; **33**, 97720-17-7; **34**, 97720-18-8; **35**, 97720-19-9; **36**, 97720-20-2; **37**, 97720-21-3; **38**, 97720-22-4; **39**, 97720-23-5; **40**, 97720-24-6; **41**, 97720-25-7; **42**, 97720-26-8; **43**, 97720-27-9; **44**, 85946-91-4; **45**, 97720-28-0; **46**, 70636-87-2; **47**, 70636-88-3; **48**, 70669-71-5; **49**, 70636-95-2; **50**, 70636-92-9; **51**, 70636-99-6; **52**, 97720-29-1; **53**, 97720-30-4; **54**, 97720-31-5; **55**, 97720-32-6; **56**, 97720-33-7; **57**, 97720-34-8; **58**, 97720-35-9; **59**, 97720-36-0; **60**, 97720-37-1; **61**, 97720-38-2; **62**, 97720-39-3; **63**, 97720-40-6; **64**, 97720-41-7; **65**, 97720-42-8; **66**, 97720-43-9; **67**, 97720-44-0; **68**, 97720-45-1; **69**, 70636-97-4; **70**, 97720-46-2; **71**, 97720-47-3; **72**, 97720-48-4; **73**, 97720-49-5; **74**, 97720-50-8; 2-*tert*-butyl-2-(hydroxymethyl)-1,3-propanediol, 67590-29-8; trimethyl orthocyclohexanecarboxylate, 51354-80-4; 4-nitrobenzoyl chloride, 122-04-3; 3-isopropyl-3-(hydroxymethyl)oxetane, 97720-51-9; 3-isopropyl-3-(hydroxymethyl)oxetane 4-nitrobenzoyl ester, 97720-52-0; 3-chloroperoxybenzoic acid, 937-14-4.

LITERATURE CITED

Adams, M. E., personal communication, 1984.

Adams, M. E.; O'Shea, M. *Science (Washington, D.C.)* **1983**, *221*, 286.

Bellet, E. M.; Casida, J. E. *Science (Washington, D.C.)* **1973**, *182*, 1135.

Bertrand, R. D.; Compton, R. D.; Verkade, J. G. *J. Am. Chem. Soc.* **1970**, *92*, 2702.
Boros, E. J.; Coskran, K. J.; King, R. W.; Verkade, J. G. *J. Am. Chem. Soc.* **1966**, *88*, 1140.
Bowery, N. G.; Collins, J. F.; Hill, R. G. *Nature (London)* **1976**, *261*, 601.
Casida, J. E. In "The Future for Insecticides: Needs and Prospects"; Metcalf, R. L., McKelvey, J. J., Jr., Eds.; Wiley-Interscience: New York, 1976; p 349.
Casida, J. E.; Eto, M.; Moscioni, A. D.; Engel, J. L.; Milbrath, D. S.; Verkade, J. G. *Toxicol. Appl. Pharmacol.* **1976**, *36*, 261.
Casida, J. E.; Lawrence, L. J. *Environ. Health Perspec.* **1985**, *61*, 123.
Corey, E. J.; Raju, N. *Tetrahedron Lett.* **1983**, *24*, 5571.
Dermer, O. C.; Solomon, P. W. *J. Am. Chem. Soc.* **1954**, *76*, 1697.
Ketslakh, M. M.; Rudkovskii, D. M.; Eppel, F. A. *Oksosintez* **1963**, 156; *Chem. Abstr.* **1963**, *60*, 9133h.
Lawrence, L. J.; Casida, J. E. *Life Sci.* **1984**, *35*, 171.
McElvain, S. M.; Starn, R. E. *J. Am. Chem. Soc.* **1955**, *77*, 4571.
McElvain, S. M.; Venerable, J. T. *J. Am. Chem. Soc.* **1950**, *72*, 1661.
Milbrath, D. S.; Eto, M.; Casida, J. E. *Toxicol. Appl. Pharmacol.* **1978**, *46*, 411.
Milbrath, D. S.; Engel, J. L.; Verkade, J. G.; Casida, J. E. *Toxicol. Appl. Pharmacol.* **1979**, *47*, 287.
Ozoe, Y.; Mochida, K.; Nakamura, T.; Shimizu, A.; Eto, M. *J. Pestic. Sci.* **1983**, *8*, 601.
Pattison, E. B. *J. Am. Chem. Soc.* **1957**, *79*, 3455.
Squires, R. F.; Casida, J. E.; Richardson, M.; Saederup, E. *Mol. Pharmacol.* **1983**, *23*, 326.

Received for review December 4, 1984. Accepted June 24, 1985.

Metabolism of the Synthetic Pyrethroid Fenpropathrin in Plants

Nobuyoshi Mikami,* Yoshiko Baba, Toshiyuki Katagi, and Junshi Miyamoto

The metabolic fate of fenpropathrin [(*RS*)-α-cyano-3-phenoxybenzyl 2,2,3,3-tetramethylcyclopropanecarboxylate] in cabbages was studied by using ^{14}C preparations labeled separately at the cyano group and the benzyl and cyclopropyl rings. By foliar treatment in a greenhouse, the insecticide disappeared with the the initial half-life of approximately 11–12 days. The insecticide underwent ester cleavage, hydroxylation at either or both of the *gem*-dimethyl groups with subsequent oxidation to the carboxylic acid, hydroxylation at the 2- or 4-position of the phenoxy group, and hydrolysis of the CN group to the $CONH_2$ and COOH groups. Most of the carboxylic acids and alcohols thus produced occurred as glycoside conjugates. 2,2,3,3-Tetramethylcyclopropanecarboxylic acid, the acidic half of the molecule, was converted mainly to glucose conjugate in abscised leaves of apple and vine, to malonylglucoside in cabbage, orange, and bean plants, and to gentiobioside in tomato. $H^{14}CN$ in abscised leaves of cabbage was rapidly incorporated into β-cyanoalanine, asparagine, aspartic acid, and γ-glutamyl-β-cyanoalanine, with ultimate formation of $^{14}CO_2$ and bound ^{14}C residues. Little ^{14}C was detected in the shoot portions of bean plants grown to maturity in soils treated with ^{14}C-fenpropathrin at a rate of 1 ppm.

INTRODUCTION

Fenpropathrin [(*RS*)-α-cyano-3-phenoxybenzyl 2,2,3,3-tetramethylcyclopropanecarboxylate] (I) is a synthetic pyrethroid, which has been developed as a commercial name of Danitol or Meothrin (Matsuo et al., 1976). It possesses a great potential for the control of various insects and mites that infest the fruit plants, vegetables, and other crops (Fujita, 1981). Although the metabolic studies in rats (Crawford and Hutson, 1977) and soils (Roberts and Standen, 1977; Mikami et al., 1985a), and photodegradation (Takahashi et al., 1985) were already performed from the view point of environmental safety, little is known about the persistence and metabolism in plants. However, as estimated from the results of plant metabolism of other pyrethroid insecticides such as permethrin (Ohkawa et al., 1977; Gaughan and Casida, 1979), deltamethrin (Ruzo and Casida, 1979), and fenvalerate (Ohkawa et al., 1980; Mikami et al., 1985b), the ester hydrolysis is anticipated to be one of the major metabolic routes of I in plants. The ester hydrolysis of I results in the formation of 2,2,3,3-tetramethylcyclopropanecarboxylic acid (VIII) from the acid moiety and α-cyano-3-phenoxybenzyl alcohol from the alcohol moiety. The latter compound is unstable and rapidly converted to 3-phenoxybenzaldehyde with a release of hydrogen cyanide. Although it has been clarified that 3-phenoxybenzaldehyde was rapidly metabolized to the corresponding acid and alcohol, with subsequent conjugation with various saccharides (More et al., 1978; Roberts and Wright, 1981; Mikami et al., 1984), metabolic fate of HCN or VIII in plants was not fully characterized.

In the present paper the metabolic fate of fenpropathrin in cabbage grown and treated in a greenhouse is reported, together with results of the subsequent work on the fate of hydrogen cyanide in abscised leaves of cabbage and of VIII in abscised leaves of apple, cabbage, kidney bean, orange, tomato, and vine. Uptake of the radiocarbon in soils treated with ^{14}C-labeled fenpropathrin by kidney bean plants was also examined.

MATERIALS AND METHODS

Chemicals. The following ^{14}C preparations were synthesized in Takarazuka Research Center of Sumitomo Chemical Co. Ltd. (Kanamaru et al., 1982): fenpropathrin labeled separately at the cyano group (^{14}CN), the C_1 position in the cyclopropyl ring (cyclopropyl-^{14}C), and the benzyl ring (benzyl-^{14}C) with the specific activity of 20.0, 25.6, and 15.7 mCi/mmol, respectively (radiolabeled positions are shown in Figure 6); 2,2,3,3-tetramethylcyclopropanecarboxylic acid (VIII) labeled at the C_1 position in the cyclopropyl ring (25.6 mCi/mmol). $K^{14}CN$ (60.2 mCi/mmol) was purchased from Radiochemical Center

Laboratory of Biochemistry and Toxicology, Takarazuka Research Center, Sumitomo Chemical Co., Ltd., 4-2-1 Takatsukasa, Takarazuka, Hyogo 665, Japan.

0021-8561/85/1433-0980$01.50/0