M-12.39a

Design of Some Delayed-Action Toxicants for Baits to Control Red Imported Fire Ants[1,2]

J. P. KOCHANSKY[3], W. E. ROBBINS[3], C. S. LOFGREN[4], AND D. F. WILLIAMS[4]

ABSTRACT

J. Econ. Entomol. 72: 655–658 (1979)

New candidate insecticides for *Solenopsis invicta* Buren were prepared which should require metabolism to the known toxicants fluoroacetic acid and trichlorfon before appreciable toxicity could be expressed. Cholesteryl fluoroacetate, sitosteryl fluoroacetate, N-dodecyl 2-fluoroacetamide, and, to a lesser extent, several fatty acid esters of trichlorfon gave delayed kill of imported fire ant workers. In certain cases, these compounds gave delayed kill over an increased range of concentrations, compared to the underivatized toxicants.

The red and black imported fire ants, *Solenopsis invicta* Buren and *S. richteri* Forel, have been present in the Southeastern U.S. since 1940 and 1919, respectively, and the area of infestation has been spreading. See Lofgren et al. (1975) for a review of history, physiology, and biochemistry of the imported fire ant. Large-scale attempts to contain or eradicate these insects, particularly *S. invicta*, have been carried out since 1957, originally with heptachlor and most recently and most efficiently using a granular bait containing mirex. Recently, environmental concerns have caused the discontinuation of mirex bait use, and therefore, a search for substitute chemicals has intensified. In addition to large numbers of conventional pesticides, alternative classes of compounds have been investigated, including juvenile hormone analogues (e.g., Banks et al. 1978, Wendel and Vinson 1978) and dyes (Anon. 1974, and David and Heitz 1978). Successful mound drenches (e.g., formulations of chlorpyrifos) are useful for local treatment of a few colonies, but large-area control requires baiting. Requirements for a successful bait toxicant are stringent, however (Stringer et al. 1964, Banks et al. 1977). The compound must be compatible with bait formulations and not repellent to ants, must be transferred from ant to ant in sufficient quantities to kill the recipient, and must be toxic over an extended range of concentrations. Implicit in the inter-ant transferral is a requirement for delayed toxicity.

We surmised that an effective way to delay the expression of toxic effects in a compound would be to design a molecule which would be inherently nontoxic but which would be metabolized to a toxic moiety within the insect. Furthermore, if we could design a molecule that would be metabolized selectively by castes or stages other than adult worker ants, particularly by the queen and brood, it might be possible to destroy the reproductive potential and viability of a colony without the necessity of killing all of its workers.

To this end, we synthesized 2 series of compounds. The 1st was one in which various nutrients (fatty acids and sterols) were linked to fluorinated groups which would eventually be metabolized to fluoroacetic acid. The 2nd series consisted of fatty acid and sterol derivatives of trichlorfon. The sterol derivatives in both series were of particular interest since the sterol requirements would be expected to be higher in queens (for egg production) and brood (for growth) than in the essentially homeostatic workers and these compounds might be selectively toxic to queen and brood.

Methods and Materials

Chemicals

Technical trichlorfon was a gift of the Chemagro Division of Mobay Chemical Corp., Kansas City, MO. Sodium fluoroacetate was purchased from Sigma Chemical Co. and 2-fluoroethanol from Aldrich.

The acetate and butyrate esters of trichlorfon were prepared by the method of Arthur and Casida (1958). Other esters were prepared by treatment of trichlorfon in ether with the appropriate acid chloride and pyridine. The esters were purified by chromatography.

Steryl fluoroacetates and alkyl fluoroacetamides and fluoroacetates were prepared by treatment of sodium fluoroacetate in ether with phosphoryl chloride at 0°C followed after 2 h by addition of the appropriate alcohol or amine and pyridine. 2-Fluoroethyl esters were prepared from 2-fluoroethanol and an acid chloride in the presence of pyridine. Fluorinated compounds were purified by chromatography and, usually, recrystallization to constant melting point. Sitosteryl fluoroacetate, prepared from commercial sitosterol, contained ca. 35% campesteryl fluoroacetate.

16-Fluoropalmitic acid was prepared by treatment of 16-hexadecanolide (Farchan) with HBr/acetic acid to give the 16-bromopalmitic acid, esterification with MeOH/toluenesulfonic acid, displacement of bromide with KF in the presence of 18-Crown-6, saponification, and purification by chromatography on Unisil® and recrystallization.

Spectral properties were in all cases consistent with the assigned structures.

Laboratory Tests

Bioassays were conducted on worker ants of *S. invicta* as described by Stringer et al. (1964) as modified by Banks et al. (1977). Compounds soluble in soybean oil were administered in oil, whereas oil-insoluble water-soluble materials were administered in 1:1 honey-water solution. Twenty worker ants were used/replicate. Larger numbers of replicates (>3) were carried in groups of 3 at different times.

[1] Hymenoptera: Formicidae.

[2] The use of trade names in this publication does not constitute a guarantee, warranty, or endorsement of the product by the USDA. Received for publication Apr. 19, 1979.

[3] Insect Physiology Laboratory, Agric. Res., SEA, USDA, Beltsville, MD 20705.

[4] Insects Affecting Man and Animals Research Laboratory, Agric. Res., SEA, USDA, Gainesville, FL 32604

Results and Discussion

Tables 1 and 2 give results of the tests, and as can be seen from the Tables, both sodium fluoroacetate and trichlorfon killed ants quite rapidly, but several of the derivatives did give quite delayed toxicity, albeit over a limited range of concentrations only. Particularly attractive were the 2 steryl fluoroacetates which gave essentially no kill after 24 h and complete or nearly complete kill only after 10–14 days. N-Dodecyl fluoroacetamide also showed delayed toxicity at 1%, as did 2-fluoroethanol at 0.1%. The latter at 1% concentration killed all ants within 24 h, however.

Saunders and Stacey (1948) reported the preparation of cholesteryl fluoroacetate in an attempt to determine if such a combination of a biologically important compound with fluoroacetic acid would give a substance of increased toxicity. They reported problems getting enough dissolved for injection but found that the compound appeared to be considerably less toxic to mice than methyl fluoroacetate. In our case, we were more interested in delay than in the exact level of toxicity, and in any case, our compounds did not seem to be appreciably less toxic on a molar basis than sodium fluoroacetate.

Bergmann and Levinson (1966) reported that cholesteryl fluoroacetate was nontoxic when injected into *Musca vicina* Macquart (=*domestica* L.) tissues devoid of lipases but caused rapid mortality when introduced into

Table 1.—Toxicity of fluoroacetyl derivatives and analogues when fed in soybean oil to worker ants of *S. invicta*.

Compound	mp(bp)°C	Concn (%)	(Replicates[a])	% kill after days						
				1	2	3	6	8	10	14
Sodium fluoroacetate (Compound 1080)		0.01[b]	(3)	3	8	15	22	22	23	25
		0.1[b]	(3)	88	100					
		1.0[b]	(3)	100						
2-Fluoroethanol		0.1[b]	(3)	10	25	32	45	53	85	95
		1.0[b]	(3)	100						
Cholesteryl fluoroacetate	142.5°–144.5°[c]	0.01	(9)	2	3	3	4	4	6	10
		0.1	(12)	0	0	0	2	2	3	6
		0.2	(3)	0	0	2	5	8	20	43
		0.4	(3)	0	2	2	5	25	38	80
		1.0	(12)	3	15	38	84	91	95	100
		2.0	(3)	27	70	77	87	92	95	97
		4.0	(3)	88	98	98	100			
Sitosteryl fluoracetate	167°–169°	0.01	(6)	2	2	5	9	11	13	22
		0.1	(9)	1	2	2	9	13	19	37
		0.2	(3)	2	2	2	3	8	12	20
		0.4	(3)	0	0	0	3	8	15	58
		1.0	(9)	7	21	42	66	79	87	96
		2.0	(3)	28	33	43	73	73	83	85
		4.0	(3)	23	37	58	78	87	90	93
Cholesteryl fluoroethyl carbonate	110°–111°	0.1	(3)	0	0	0	0	0	2	20
		1.0	(3)	0	0	0	0	3	22	62
N-Dodecyl 2-fluoroacetamide	65°–66°	0.01	(6)	1	1	2	3	4	5	8
		0.1	(6)	2	3	4	4	6	15	30
		1.0	(6)	8	13	26	65	78	83	96
Octadecyl fluoroacetate	42.5°–44°	0.01	(9)	0	1	1	6	10	11	15
		0.1	(9)	1	1	2	17	33	44	62
		1.0	(9)	98	99	99	99	99	99	99
Cholesteryl 16-fluoropalmitate (16-fluorohexadecanoate)	79°–80.5°	0.01	(12)	0	0	2	5	10	13	23
		0.1	(15)	0	0	2	2	3	5	11
		0.2	(3)	0	0	0	3	3	10	15
		1.0	(12)	0	2	6	16	22	29	51
		2.0	(6)	0	0	0	11	18	48	56
N-Octadecyl 2-fluoroacetamide	81.5°–82.5°	0.1	(3)	0	0	0	0	0	2	8
		1.0	(3)	0	0	2	2	3	3	7
2-Fluoroethyl stearate (octadecanoate)	50°–52.5°	0.1	(3)	0	0	0	0	0	2	5
		1.0	(3)	67	68	70	70	72	73	75
2-Fluoroethyl hemisuccinate	47°–50°	0.1	(3)	10	18	20	25	25	27	28
		1.0	(3)	70	73	75	75	75	77	80
		0.1[b]	(3)	0	0	2	10	12	22	33
		1.0[b]	(3)	100						
1-Dodecyl fluoroacetate	(127°–131°/2.4mm)[d]	0.1	(3)	0	0	0	2	2	2	3
		1.0	(3)	12	23	25	30	30	30	33
16-Fluoropalmitic acid (16-fluorohexadecanoic acid)	75°–76°[e]	0.1	(3)	0	0	2	2	2	2	5
		1.0	(3)	63	70	75	77	77	80	87
mirex		0.01	(15)	0	0	1	10	22	32	61
		0.1	(15)	0	1	15	84	91	96	98
		1.0	(15)	0	44	84	95	95	100	
check (soybean oil)		—	(30)	1	1	1	5	7	8	13

[a] Twenty workers/replicate.
[b] Administered in honey-water solution.
[c] Gryszkiewicz-Trochimowski et al. (1947) and Saunders and Stacy (1948) report mp 145–145.5° and 144–144.5°C, respectively.
[d] Payne (1949).
[e] The ethyl ester was reported by Pattison (1953).

Table 2.—Toxicity of trichlorfon derivatives when fed in soybean oil to worker ants of *S. invicta*.[a]

Ester	Concn (%)	(Replicates)[b]	% kill after days						
			1	2	3	6	8	10	14
(Trichlorfon)	0.01	(3)	7	12	15	23	23	23	25
	0.1	(3)	95	98	98	98	98	98	98
	1.0	(3)	100						
Acetate[c]	0.01	(3)	0	0	0	0	0	0	0
	0.1	(3)	0	0	0	2	2	3	3
	1.0	(6)	0	1	1	2	2	3	11
Butyrate[c] (butanoate)	0.01	(3)	0	0	0	0	0	0	7
	0.1	(3)	0	0	0	0	0	2	38
	1.0	(6)	0	1	2	2	3	4	6
Pivalate (2,2-dimethylpropanoate)	0.01	(3)	0	0	2	2	2	3	3
	0.1	(3)	0	0	0	2	5	5	7
	1.0	(6)	2	2	2	2	3	3	5
Caproate (hexanoate)	0.1	(6)	0	0	1	6	10	11	14
	0.2	(3)	3	5	5	10	20	22	40
	0.4	(3)	2	2	2	27	57	68	78
	1.0	(9)	12	28	44	57	61	66	67
	2.0	(6)	22	40	43	51	53	57	58
	4.0	(6)	7	12	13	14	15	17	22
Caprate (ca. 90% pure) (decanoate)	0.1	(6)	1	1	2	4	4	6	10
	0.2	(3)	0	0	0	0	3	8	35
	0.4	(3)	0	0	2	13	28	53	81
	1.0	(9)	5	30	53	79	82	83	86
	2.0	(6)	23	40	46	54	54	57	60
	4.0	(6)	26	39	39	45	46	49	49
Myristate (tetradecanoate)	0.01	(3)	0	0	0	2	3	3	8
	0.1	(6)	0	1	1	2	4	4	8
	0.2	(3)	3	5	7	10	15	27	50
	0.4	(3)	0	0	0	12	37	53	85
	1.0	(9)	5	22	42	67	68	72	75
	2.0	(6)	32	51	62	78	78	79	81
	4.0	(3)	15	25	37	40	40	40	40
Stearate (octadecanoate)	0.01	(6)	0	0	1	2	5	6	10
	0.1	(6)	2	3	9	24	26	29	35
	1.0	(6)	46	79	95	96	98	99	99
Cholesteryl carbonate	0.01	(3)	2	2	2	10	10	12	12
	0.1	(3)	0	0	3	7	8	10	10
	1.0	(3)	2	2	2	8	10	12	12

[a] Check and mirex data as in Table 1.
[b] Twenty worker ants/replicate.
[c] Arthur and Casida (1958).

the larval gut. Monroe et al. (1963) showed that cholesteryl fluoroacetate was also toxic to adult, *M. domestica* and reduced egg production and egg hatch when fed to the adults at 0.01% of the diet (higher levels killed the adults). This effect also was observed with sodium fluoroacetate.

We felt that this requirement for lipase cleavage would enable the steryl fluoroacetates to display delayed toxicity, particularly to worker ants whose sterol requirements would be expected to be minimal as compared to queen and brood. Such delayed toxicity was in fact observed in our tests. One % cholesteryl fluoroacetate caused 100% mortality to workers of *S. invicta* only after 14 days, causing 15% kill after 48 h (Table 1). Sodium fluoroacetate at 0.1% (ca. half the amount equivalent to 1% cholesteryl fluoroacetate on a fluoroacetic acid basis) killed 100% of the ants within 48 h. Sitosteryl fluoroacetate gave results similar to cholesteryl fluoroacetate, and only slightly less impressive ones were obtained with N-dodecyl fluoroacetamide. Other compounds in the series were either rapidly toxic or relatively nontoxic, killing <50% of the ants even at 1%. Tests at higher concentrations gave somewhat less attractive results, either because of repellency or too-rapid kill.

In the trichlorfon series (Table 2), the esters of longer chain acids (C_6–C_{14}) showed some delayed kill at 1% (essentially nontoxic at 0.1%) with the shorter chain esters essentially inactive. The cause of the lack of toxicity of the short-chain esters is not known, although repellency seems likely. Tests on other insect species (our unpublished data) indicate that all trichlorfon esters tested, with the exception of the apparently unmetabolizable pivalate and cholesteryl carbonate, were toxic to insects. (Note in Table 1 that cholesteryl fluoroethyl carbonate is much less toxic than cholesteryl fluoroacetate. Apparently cholesteryl carbonate esters are relatively resistant to biochemical hydrolysis, at least under these circumstances.) The stearate ester of trichlorfon was apparently hydrolyzed too fast, as there was 46% mortality after 24 h at 1%.

The tests reported here were all done on worker ants. This principle of "lethal synthesis" in the target insect pest also may be applicable in other cases where delayed activity is required.

REFERENCES CITED

Anonymous. 1974. Dyes show promise for control of fire ants. Chem. Eng. News. Sept. 23, 1974, p. 46.

Arthur, B. W., and J. E. Casida. 1958. Biological activity of several O,O-dialkyl alpha-acyloxyethyl phosphonates. J. Agric. Food Chem. 6: 360–5.

Banks, W. A., C. S. Lofgren, C. E. Stringer, and R. Levy. 1977. Laboratory and field evaluation of several organochlorine and organophosphorus compounds for control of imported fire ants. USDA-ARS-S-169: 13 pp.

Banks, W. A.,C. S. Lofgren, and J. K. Plumley. 1978. Red imported fire ants: effects of insect growth regulators on caste formation and colony growth and survival. J. Econ. Entomol. 71: 75–8.

Bergmann, E. D., and Z. H. Levinson. 1966. Utilization of steroid derivatives by larvae of *Musca vicina* (Macq.) and *Dermestes maculatus* (Deq.) J. Insect Physiol. 12: 77–81.

David, R. M., and J. R. Heitz. 1978. Toxicity of an imported fire ant bait based on Phloxin B(D & C Red 27). J. Agric. Food. Chem. 26: 99–101.

Gryszkiewicz-Trochimowski, E., A. Sporzyński, and J. Wnuk. 1947. Recherches sur les composés organiques fluorés dans la serie aliphatique. II. Sur les dérivés des acides mono-, di, et tri-fluoro-acétiques. Rec. Trav. Chim. Pays-Bas 66: 419–26.

Lofgren, C. S., W. A. Banks, and B. M. Glancey. 1975. Biology and control of imported fire ants. Annu. Rev. Entomol. 20: 1–30.

Monroe, R. E., W. E. Robbins, D. L. Chambers, and L. A. Tabor. 1963. Sterol antagonists and housefly reproduction. Ann. Entomol. Soc. Am. 56: 124.

Pattison, F. L. M. 1953. Toxic fluorine compounds. Nature (London) 172: 1139–41.

Payne, N. M. C. 1949. Insecticidal use of fluoroacetamide. U.S. Patent 2,469,340. (Chem. Abstr. 43: 6357i).

Saunders, B. C., and G. J. Stacey. 1948. Toxic fluorine compounds containing the C-F link. Part I. Methyl fluoroacetate and related compounds. J. Chem. Soc. 1773–9.

Stringer, C. E., Jr., C. S. Lofgren, and F. J. Bartlett. 1964. Imported fire ant toxic bait studies: evaluation of toxicants. J. Econ. Entomol. 57: 941–5.

Wendel, L. E., and S. B. Vinson. 1978. Distribution and metabolism of a juvenile hormone analogue within colonies of the red imported fire ant. Ibid. 71: 561–5.

Reprinted from the
JOURNAL OF ECONOMIC ENTOMOLOGY