Syntheses and Biological Activities of 3-Fluoropropionic Acid Derivatives and Related Compounds

Kuwano, Eiichi
Laboratory of Pesticide Chemistry, Faculty of Agriculture, Kyushu University

Yamashita, Toru
Laboratory of Pesticide Chemistry, Faculty of Agriculture, Kyushu University

Ota, Hiromi
Laboratory of Pesticide Chemistry, Faculty of Agriculture, Kyushu University

Eto, Morifusa
Laboratory of Pesticide Chemistry, Faculty of Agriculture, Kyushu University

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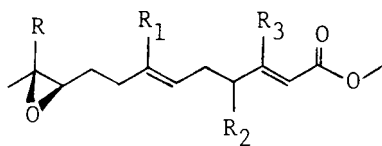**Eiichi Kuwano, Toru Yamashita, Hiromi Ota
and Morifusa Eto**

Laboratory of Pesticide Chemistry, Faculty of Agriculture,
Kyushu University 46-02, Fukuoka 812

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3-Fluoropropionates, 3-fluoropropyl ethers, fluorinated homomevalonolactone and related compounds were synthesized, and bioassayed on the silkworm, *Bombyx mori*, and the housefly, *Musca domestica.* A number of 3-fluoropropionates showed moderate acute toxicity against both *B. mori* and *M. domestica,* and 3-fluoropropyl ethers at high doses showed insecticidal activity against *B. mori*. *No* acute toxicity was found for fluorinated homomevalonolactone, but weak inhibition of pupation, None of the compounds produced clear anti-juvenile hormone activity on *B. mori*.

INTRODUCTION

Juvenile hormones (JH) and ecdysones are the principal hormones regulating molting, metamorphosis, diapause and reproduction in insects (Wigglesworth, 1985). There have been so far discovered five naturally occurring JHs, that is, JH 0, JH I, JH II, JH III and iso-JH 0 (Scheme 1). These hormones are ethyl-branched (homo-) sesquiterpenoids except for JH III. In the biosynthesis of common sesquiterpenoids such as JH III, mevalonic acid is a precursor, while homomevalonic acid, which is formed from propionyl-CoA and two acetyl-CoA units, has been known to be a precursor of homosesquiterpenoids. Propionate has been established as the source of the ethyl side branches in JH 0, I, II and iso-JH 0 (Schooley et al., 1985). The biosynthesis of these homosesquiterpenoids offers several potentially attractive targets for insect-specific control agents, because the biosynthetic pathway involving

JH 0: R = R, = R$_3$ = C$_2$H$_5$, R$_2$ = H
JH I: R = R, = C$_2$H$_5$, R$_2$ = H, R$_3$ = CH,
JH II : R = C$_2$H$_5$, R, = R$_3$ = CH,. R$_2$ = H
JH III : R = R, = R$_3$ = CH,, R$_2$ = H
iso-JH 0: R = R$_1$ = C$_2$H$_5$, R$_2$ = R$_3$ = CH,

Scheme 1. Chemical structures of the juvenile hormones

homomevalonate is unique to insects.

It is well known that the use of fluorine as an isosteric replacement for a hydrogen atom in an organic molecule can produce compounds which masquerade effectively as ligands or substrates in biological systems (Prestwich, 1986). For example, the anti-JH activity of fluoromevalonolactone (tetrahydro-4-fluoromethyl-4-hydroxy-2*H*-pyran-2-one, FMev) has been due to inhibition of JH biosynthesis at the level of enzymatic phosphorylation of mevalonate and homomevalonate (Quistad et al., 1981). So we synthesized a number of 3-fluoropropionic acid derivatives, fluorinated homomevalonolactone and related compounds, and assayed for acute and delayed effects on the housefly, *Musca domestica* and the silkworm, *Bombyx mori*.

<div align="center">EXPERIMENTAL</div>

Syntheses

Melting points were uncorrected. NMR spectra were measured with a JEOL FX -100 spectrometer with tetramethylsilane as an internal standard.

3-Fluoropropanol (1)

A mixture of 3-chloropropanol (76 g, 0.8 mol) and potassium fluoride (70 g, 1.7 mol) in ethyleneglycol (100 ml) was heated at 150-180°C with stirring and subsequently the distillate at 100-180°C was collected in the course of 6 hr. Redistillation at 120°C gave 44 g (70%) of 3-fluoropropanol. NMR (CDCl$_3$)δ: 1.06-2.25 (2H, m), 2.33 (1H, s), 3.75 (2H, t, J=6 Hz), 4.20-4.90 (2H, dt, Ja=48 Hz, Jb=6 Hz).

3-Fluoropropionic acid (2)

To a solution of potassium bichromate (143 g, 0.49 mol) in water (500 ml), Concentrated sulfuric acid (155 ml) was added with stirring. After cooling a solution of 3-fluoropropanol (47 g, 0.6 mol) in water (200 ml) was added dropwise to the mixture over a period of 4 hr. The reaction mixture which turned from deep red to dark green was stirred overnight at room temperature. The product was extracted with ethyl acetate (250 mlX5) and the combined organic layer was dried over Na$_2$SO$_4$, concentrated under reduced pressure. The residue was distilled to give 32 g (58%) of 3-fluoropropionic acid as a colorless oil, bp 120°C (0.4 mm). NMR (CDCl$_3$)δ: 2.30-3.40 (2H, dt, Ja=25 Hz, Jb=6 Hz), 4.3-5.06 (2H, dt, Ja=48 Hz, Jb=6 Hz), 11.10 (1H, s).

General *method for the preparation of esters of 3-fluoropropionic acid.* (compounds 3 -15, Table 1)

(Method A)

To a mixture of 3-fluoropropionic acid and an alcohol (large excess) was added a few drops of conc. sulfuric acid and the mixture was allowed to stand for 3-5 days. To the reaction mixture, ether was added and the ether layer was washed with 5% NaHCO$_3$, dried over Na$_2$SO$_4$. After removal of the solvent, the residue was purified by distillation or column chromatography on silica gel by elution with solvent mixtures (hexane-ethyl acetate) of increasing polarity.

(Method B)

A mixture of 3-fluoropropionic acid and an alcohol (excess) in benzene containing a catalytic amount of *p*-toluenesulfonic acid was refluxed for 3 hr removing water by using a water separator. After cooling, the solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel, distilla-

Table 1. Structures, yields and physical properties of 3–fluoropropionates.

No	FCH_2CH_2COOR R	Method	Yield (%)	Bp or Mp*	^{1}H NMR (CDCl$_3$) δ ppm
3	C$_2$H$_5$	A	17	96	1.28 (3H, t, J = 6 Hz), 2.72 (2H, dt, Ja = 26 Hz, Jb = 6 Hz), 4.16 (2H, q, J = 6 Hz), 4.70 (2H, dt, Ja = 48 Hz, Jb = 6 Hz)
4	CH$_2$CH$_2$F	A	17	67 (31 mm)	1.6-2.3 (2H, m), 2.70 (2H, dt, Ja = 26 Hz, Jb = 6 Hz), 4.14 (2H, t, 6 Hz), 4.50 (2H, dt, Ja = 48 Hz, Jb = 6 Hz), 4.66 (2H, dt, Ja = 48 Hz, Jb = 6 Hz)
5	n-C$_3$H$_7$	B	78	147	0.94 (3H, t, J = 6 Hz), 1.42-2.0 (2H, m), 2.72 (2H, dt, Ja = 24 Hz, Jb = 6 Hz), 4.08 (2H, t, J = 6 Hz), 4.70 (2H, dt, Ja = 46 Hz, Jb = 6 Hz)
6	n-C$_5$H$_{11}$	B	93	–	0.94 (3H, t, J = 6 Hz), 1.1-2.0 (6H, m), 2.92 (2H, dt, Ja = 26 Hz, Jb = 6 Hz), 4.48 (2H, t, J = 6 Hz), 5.10 (2H, dt, Ja = 48 Hz, Jb = 6 Hz)
7	n-C$_8$H$_{17}$	C	17	–	0.92 (3H, deformed t), 1.1-2.2 (12H, m), 2.82 (2H, dt, Ja = 24 Hz, Jb = 6 Hz), 4.50 (2H, t, J = 6 Hz), 4.90 (2H, dt, Ja = 48 Hz, Jb = 6 Hz)
8	n-C$_{10}$H$_{21}$	C	22	–	0.92 (3H, deformed t), 1.1-2.2 (16H, m), 2.82 (2H, dt, Ja = 24 Hz, Jb = 6 Hz), 4.50 (2H, t, J = 6 Hz), 4.90 (2H, dt, Ja = 48 Hz, Jb = 6 Hz)
9	n-C$_{12}$H$_{25}$	B	86	–	0.92 (3H, deformed t), 1.1-2.0 (20H, m), 2.84 (2H, dt, Ja = 24 Hz, Jb = 6 Hz), 4.34 (2H, t, J = 6 Hz), 4.96 (2H, dt, Ja = 48 Hz, Jb = 6 Hz)
10	Oleyl	A	74	–	0.90 (3H, deformed t), 1.0-1.6 (26H, m), 1.8-2.14 (1H, m), 2.72 (2H, dt, Ja = 24 Hz, Jb = 6 Hz), 4.14 (2H, t, J = 6 Hz), 4.72 (2H, dt, Ja = 48 Hz, Jb = 6 Hz), 5.1-5.5 (2H, m)
11	Geranyl	C	7	–	1.70 (3H, s), 1.80 (6H, s), 2.0-2.5 (4H, m), 2.86 (2H, dt, Ja = 24 Hz, Jb = 6 Hz), 4.90 (2H, d, J = 8 Hz), 4.98 (2H, dt, Ja = 48 Hz, Jb = 6 Hz), 5.2-5.8 (2H, m)
12	Benzyl	A	11	–	2.74 (2H, dt, Ja = 24 Hz, Jb = 6 Hz), 4.68 (2H, dt, Ja = 46 Hz, Jb = 6 Hz), 5.12 (2H, s), 7.2-7.5 (5H, m)
13	Piperonyl	C	39	–	2.86 (2H, dt, Ja = 24 Hz, Jb = 6 Hz), 4.90 (2H, dt, Ja = 48 Hz, Jb = 6 Hz), 5.26 (2H, s), 6.18 (2H, s), 6.6-7.3 (3H, m)
14	m-Phenoxy benzyl	B	55	–	2.84 (2H, dt, Ja = 26 Hz, Jb = 6 Hz), 4.92 (2H, dt, Ja = 48 Hz, Jb = 6 Hz), 5.40 (2H, s), 7.1-8.0 (9H, m)
15	Cholesteryl	B	84	94'	0.68 (3H, s), 0.7-2.2 (41H, m), 2.68 (2H, dt, Ja = 24 Hz, Jb = 6 Hz), 4.70 (2H, dt, Ja = 48 Hz, Jb = 6 Hz), 5.2-5.4 (1H, m)

tion, or recrystallization.
(Method C)

A catalytic amount of 4-dimethylaminopyridine was added to the mixture of 3-fluoropropionic acid, an alcohol (large excess) and N, N'-dicyclohexylcarbodiimide (1.1 eq.) in methylene chloride at 0°C, and the mixture was stirred for 15 min at same temperature. After stirring overnight at room temperature, the precipitates were filtered off. The filtrate was dried over Na_2SO_4, concentrated, and the residue was purified by column chromatography on silica gel.

General *procedure for the preparation of 3-fluoropropyl ethers.*

A solution of 3-fluoropropanol (1, 1eq.) in dry tetrahydrofuran was added to the emulsion of sodium hydride (1 eq.) in tetrahydrofuran, and the mixture was stirred for 15 min. To the resulting solution, catalytic amount of tetra-n-butylammonium iodide was added followed by addition of geranyl chloride or benzyl chloride (1 eq.) solution in tetrahydrofuran, and the mixture was stirred at room temperature overnight. After removing the solvent, the residue was extracted with ether and the ether layer was concentrated. The crude product was purified with column chromatography on silica gel.

Benzyl 3-fluoropropyl ether (16). Yield 59%. NMR (CDCl,) δ: 1.70-2.25 (2H, m), 3. 58 (2H, t, J=6 Hz), 4.16-4.86 (2H, tt, Ja=48 Hz, Jb=6 Hz), 4.48 (2H, s), 7.29 (5H, m).

Geranyl 3-fluoropropyl ether (17). Yield 38%. NMR (CDCl,) δ: 1.59 (3H, s), 1.67 (6H, s), 1.70-2.30 (7H, m), 3.52 (2H, t. J=6 Hz), 3.95 (2H, d, J=6 Hz), 4.15-4.85 (2H, tt, Ja=48 Hz, Jb=6 Hz), 5.05 (1H, broad s), 5.30 (1H, t, J=6 Hz).

(E)-6,7-epoxy-3,7-dimethyl-1-(3-fluoropropyloxy)-2-octene (**18**) *and 2, 3, 6, 7-diepoxy-3, 7-dimethyl-1-(3-fluoropropyloxy)-octane* (19)

A solution of m-chloroperbenzoic acid (1.2 eq.) in methylene chloride was added to a solution of a 3-fluoropropyl geranyl ether (1'7, 1 eq.) in methylene chloride at 0°C with stirring and the mixture was stirred overnight at 5°C. To the resulting mixture, 10% Na_2SO_3 was added, and the methylene chloride solution was separated and washed with 5% $NaHCO_3$, dried over Na_2SO_4. After removing the solvent, the residue was purified with column chromatography on silica gel eluted with hexane-ether (5 : 1) and (3 : 1).

Monoepoxy compound **18** was obtained from the hexane-ether (5 : 1) eluate by concentrating of the eluate under reduced pressure, yield 42%. NMR (CDCl,) δ: 1.27 (3H, s), 1.30 (3H, s), 1.45-2.33 (12H, m), 2.70 (1H, t, J=6 Hz), 3.52 (2H, t, J=6 Hz), 3.97 (2H, d, 6 Hz), 4.13-4,82 (2H, tt, Ja=48 Hz, Jb=6 Hz), 5.35 (1H, t, J=6 Hz).

Diepoxy compound **19** was eluted after 18 with hexane-ether (3 : 1). Yield 25%. NMR (CDCl,) δ: 1.28 (3H, s), 1.30 (3H, s), 1.32 (3H, s), 1.5-2.24 (6H, m), 2.70 (1H, deformed t), 2.96 (1H, t, J=6 Hz), 3.3-3.8 (4H, m), 4.54 (2H, dt, Ja=48 Hz, Jb=6 Hz).

4-(2-Chloroethyl)-4-hydroxy-1,6-heptadiene (20).

A solution of ethyl 3-chloropropionate (20.0 g, 147 mmol) in ether (100 ml) was added dropwise to a solution of allylmagnesium bromide (440 mmol) in ether over a period of 3 hr. After stirring overnight, the mixture was quenched with 1 N HCl solution and the product was extracted with ether. The ether layer was dried over Na_2 SO, and concentrated under reduced pressure. The residue was distilled affording 8. 2 g (32%) or 19, bp 112°C (22 mm). NMR (CDCl,) δ: 1.75 (1H, s), 1.96 (2H, m), 2.24 (4H, d, J=8 Hz), 3.64 (2H, m), 5.92-6.04 (6H, m).

4-(2-Fluoroethyl)-4-hydroxy-1,6-heptadiene (21)

A mixture of hydroxydiene 20 (7.1 g, 40.7 mmol), potassium fluoride (10.0 g, 172.4 mmol) and ethyleneglycol (15 ml) was heated at 160°C for 3 hr. After cooling the product was extracted with ether (50 ml *x* 7) and the combined ether solution was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was distilled affording 3.8 g (58%) of fluorinated hydroxydiene 21, bp 94°C (33 mm). NMR (CDCl,) δ: 1.80 (1H, broad s), 1.68–2.08 (2H, tt, Ja = 25 Hz, Jb = 6 Hz), 2.26 (4H, d), 4.32–4.92 (2H, tt, Ja = 48 Hz, Jb = 6 Hz), 4.92-6.04 (6H, m).

3-(2-Fluoroethyl)-1, 3, 5-trihydroxypentane (22)

A solution of compound 21 (3.2 g, 20.3 mmol) in methanol (150 ml) was cooled to -78°C in a methanol-dry ice bath and ozone was passed through until the solution turned pale blue (about 3 hr). After additional 15 min, a solution of sodium borohydride (19 g, 500 mmole) in 50% ethanol (100 ml) cooled in an ice bath was added dropwise to the ozonide solution at − 55°C. The mixture was allowed to stand at room temperature for 30 min and heated at 50°C for 1 hr. After cooling, the solution was acidified with 1N HCl solution, and neutralized with 5% $NaHCO_3$ solution. After removal of the solvent under reduced pressure, the product was extracted with ethylacetate (100 ml × 4). The combined organic layer was dried over Na_2SO_4 and concentrated to give 2.43 g of residue. Purification with silica gel column chromatography afforded 1.3 g (40%) of trio1 22. NMR (CDCl,) δ: 1.60-2.20 (7H, m), 3.00 (2H, broad s), 3.85 (4H, t, J = 6 Hz), 4.20–4.90 (2H, tt, Ja = 48 Hz, Jb = 6 Hz).

Fluorohomomevalonolactone (23)

A mixture of trio1 22 (650 mg, 3.9 mmol) and freshly prepared silver carbonate on cerite (30.5 g, 53.5 mmol active compound) in dry benzene (150 ml) was refluxed for 20 hr. The mixture was filtered and the filtrate was concentrated to give 510 mg of oil. Distillation under reduced pressure (0.24 mm) using microdistillation oven (Buchi, GKR -50) at 230–280°C gave 360 mg (50%) of compound 23. NMR (CDCl,) δ: 1.70-2.20 (4H, m), 2.30-2.85 (2H, m), 3.42 (1H, s), 4.18-5.00 (4H, m).

Bioassays

1. *Housefly* (*Musca domestica,* WHO's standard susceptible strain)

The larvae were reared on a mixture of commercial housefly feed and rat feed (Oriental Yeast Co., Ltd.) at a 6: 1 ratio and the adults with sugar, skin milk and water. In the larval test, 25 larvae (2-day after hatch) were placed in a beaker to which was added the larval medium and the test compounds at 1000 or 5000 ppm concentration. The compounds were mixed as aqueous solutions with diet and 3-fluoropropionic acid and propionic acid were used after neutralization with $NaHCO_3$. The percentages pupating and subsequently emerging as adults were recorded.

Three to five-day old female adults were treated topically by using acetone solutions. Mortalities were recorded after 24 hr.

2. *Silkworm* (*Bombyx mori*, Gunpo *X* Shugyoku)

Larvae were reared on artificial diets, Silkmate 1S and 2M (Nippon Nosan Kogyo Co., Ltd.) for the 1st instar and from the 2nd to 5th instar larvae, respectively, under a 12 hr light and 12 hr dark photoperiod at 26 ± 2°C.

For the topical assay, newly molted 3rd instar larvae were topically treated on the dorsal surface with acetone dilutions of test compounds (single application). After

treatment of newly molted 3rd instar larvae, the larvae were treated with the test solution at 24-hour intervals during the 3rd instar stage (daily application).

For the feeding assay, test compounds were mixed with artificial diet as acetone solutions or powders. The diet was provided successively to 2nd instar larvae within 24 hr after ecdysis through 2nd instar stage.

RESULTS AND DISCUSSION

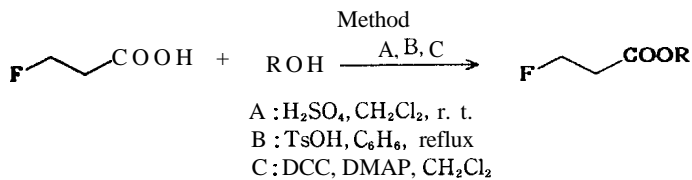### Syntheses

3-Fluoropropanol (1) was prepared by the reaction of 3-chloropropanol with potassium fluoride in ethyleneglycol according to a method described by Pattison *et al.* (1956). The NMR spectrum for 1 exhibited characteristic proton-fluorine coupling constants ($J_{H-F} = 48$ Hz, $J_{CH-F} = 26$ Hz). The oxidation of 1 with potassium bichromate and sulfuric acid gave 3-fluoropropionic acid (2) in 58% yield (Scheme 2).
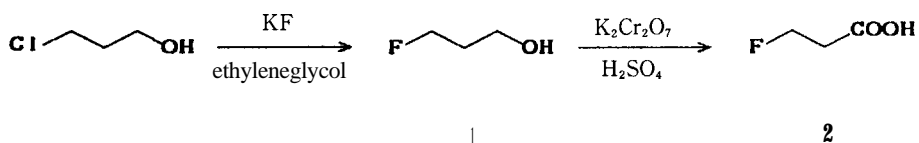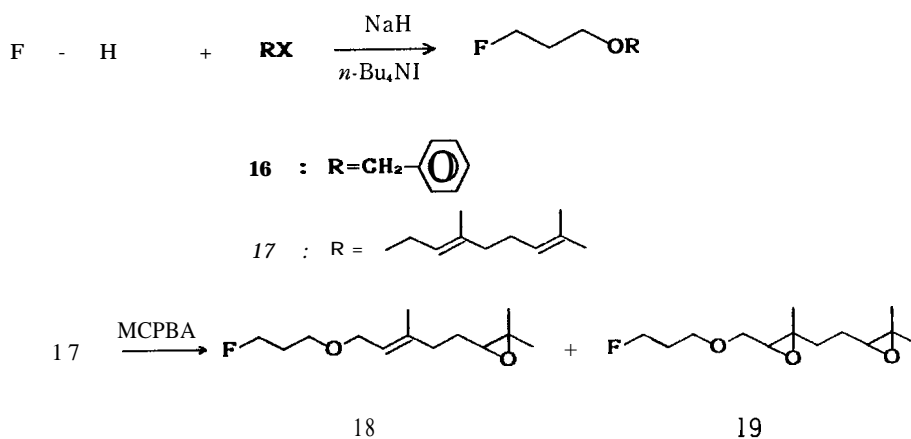

Scheme 2. Synthesis of 3-fluoropropionic acid

The esters of 3-fluoropropionic acid were prepared by three different procedures, Methods A, B and C, as shown in Scheme 3. Methods A and B were standard acid-catalyzed esterifications, whereas in Method C dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) were used. Table 1 shows yields and some physicochemical properties of the esters. The NMR spectra for the esters were in agreement with the assigned structures and showed the characteristic proton-fluorine coupling constants.
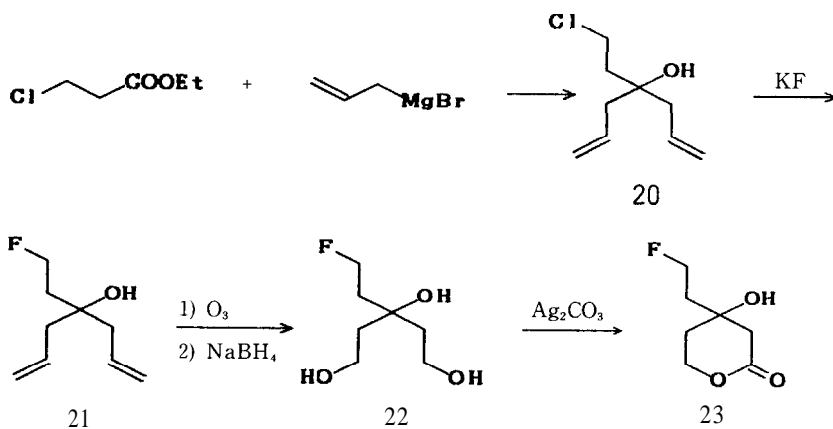

A : H_2SO_4, CH_2Cl_2, r. t.
B : TsOH, C_6H_6, reflux
C : DCC, DMAP, CH_2Cl_2

Scheme 3. Synthesis of 3-fluoropropionates

3-Fluoropropyl ethers were synthesized by the reaction of 3-fluoropropanol (1) with alkyl halides in the presence of sodium hydride and tetra-n-butyl ammonium iodide. The epoxidation of 3-fluoropropyl geranyl ether **17** with m-chloroperbenzoic acid afforded monoepoxy ether **18** (42%) and diepoxy ether **19 (25%)** which were seperated by column chromatography on silica gel (Scheme 4).

The preparation of fluorinated homomevalonolactone 23 was carried out as shown in Scheme 5. The synthesis of hydroxy diene 20 was accomplished by the Grignard reaction between ethyl 3-chloropropionate and allyl magnesium bromide. Compound

F - H + **RX** $\xrightarrow[\text{$n$-Bu}_4\text{NI}]{\text{NaH}}$ F⌒⌒OR

16 : R=CH₂-⟨O⟩

17 : R = ⌒⌒⌒⌒

17 $\xrightarrow{\text{MCPBA}}$ [structure 18] + [structure 19]

18   19

Scheme 4. Synthesis of 3-fluoropropyl ethers

Cl⌒⌒COOEt + ⌒⌒MgBr → [structure 20] $\xrightarrow{\text{KF}}$

20

[structure 21] $\xrightarrow[\text{2) NaBH}_4]{\text{1) O}_3}$ [structure 22] $\xrightarrow{\text{Ag}_2\text{CO}_3}$ [structure 23]

21   22   23

Scheme 5. Synthesis of fluorinated homomevalonolactone

20 was heated with potassium fluoride in ethyleneglycol to give fluorinated compound 21 in 58% yield. Ozonolysis of 21 followed by reduction with sodium borohydride afforded fluorinated triol 22. Oxidation of 22 with silver carbonate on cerite in refluxing benzene (Fetizon *et al., 1969)* afforded fluorinated homomevalonolactone 23 in 50% yield. The NMR spectrum for lactone 23 was consistant with the assigned structure.

Biological activities

Table 2 shows the effects of 3-halopropanol, 3-fluoropropionic acid and related compounds on development of *M. domestica* larvae. Only 3-fluoropropanol and 3-fluoropropionic acid inhibited both pupation and adult emergence in *M. domestica* at a high concentration of 5000 ppm.

Table 2.   Effects of 3-halopropanols, 3-fluoropropionic acid and analogs on development of *M. domestica* larvae.

Compounds	Dose (ppm)	Pupation (%)	Adult emergence (%)
CH₃CH₂CH₂OH	1000	100	58
	5000	98	70
BrCH₂CH₂CH₂OH	1000	96	56
	5000	92	62
ClCH₂CH₂CH₂OH	1000	98	76
	5000	94	54
FCH₂CH₂CH₂OH	1000	96	80
	5000	38	7
CH₃CH₂COOH	1000	96	60
	5000	80	66
FCH₂CH₂COOH	1000	92	80
	5000	32	16
Control		92	88

Table 3. Insecticidal activities of 3-fluoropropionates.

Compounds No	Dose (μg/insect)	Mortality (%)			
		Silkworm (3rd instar)		Housefly (adults)	
		100	10	100	10
3		0		20	0
4		0		85	15
5		0		90	10
6		0		100	0
7		100	0	90	0
8		70	0	80	0
9		100	0	100	5
10		0		50	5
11		100	0	100	0
12		70	10	100	5
13		90	0	15	0
14		0		47	15

Single topical appication

The data for the insecticidal activity of 3-fluoropropionates on *B. mori* and *M. domestica* are given in Table 3. None of the compounds showed anti JH activity when applied to 3rd instar larvae of *B. mori*. For *B. mori* the octyl **7**, dodecyl **9** and geranyl **11** esters showed 100% mortality at a high dose of 100 μg and the toxicity in this series decreased rapidly with decreasing size of the alcohol moiety (compounds 3, 5 and 6). The 3-fluoropropionates showing insecticidal activity on *B. mori* were also active to

Table 4. Effects of fluorinated compounds on 3rd instar larvae of *B. mori* (daily topical application).

Compounds No.	Dose (μg/larva)	Mortality (%)	Abnormal pupation (%)
16	100	100	
17	100	100	
	10	0	40
18	100	100	–
19	100	100	
21	100	0	0
22	100	0	0
23	100	0	60

Table 5. Effects of 3–fluoropropionates and related compounds treated in feeding assay on growth of 2nd instar larvae of *B. mori*.

Compounds	Mortality (%)	
No.	Conc. (ppm) 1000	100
1	11	0
4	100	10
10	0	0
12	100	30
15	0	
22	0	
23	0	

the housefly. The fact that decyl propionate and dodecyl propionate had no insecticidal activity on the housefly at $100\,\mu$g suggested that the fluorine substituent was significantly affecting the toxicity in this series of compounds. The lower alkyl ester 4, 5 and 6 which were quite inactive on the silkworm showed moderate activity on the housefly. The oleyl ester 10 showed comparatively low activity. The benzyl ester 12 had some activity on both insects, but m-phenoxybenzyl ester 14 showed lower activity.

In Table 4 there are presented bioassay data for 3-fluoropropyl ethers, fluorinated homomevalonolactone and related compounds, which were applied to the larvae of *B. mori* at 24-hour intervals during the 3rd instar stage. All of these compounds also failed to elicit anti JH effects. The ethers 16, 17, 18 and 19 showed 100% mortality at 100 /*g/larva. The diene 21 and the diol 22 were quite inactive. It was hoped that fluorinated homomevalonolactone 23, in anlogy with FMev, might inhibit phosphorylation of homomevalonic acid in the JH biosynthetic pathway, because homomevalonic acid is a precursor of JH 0, JH I, JH II or iso-JH 0; however no anti JH activity was found for compound 23. Lactone 23 showed no toxicity in larval *B. mori* even at 100 μg/larva, but delayed toxicity such as inhibition of pupation. The lack of anti JH activity for lactone 23 was particularly noteworthy.

The effects of several fluorinated compounds were investigated in a feeding

bioassays (Table 5). When the diets containing each compound were given during 2nd instar stage, 3-fluoropropyl-3-fluoropropionate 4 and the benzyl ester 12 showed 100% mortality at 1000 ppm, but low activity at 100 ppm. The lactone 23 and other compounds were quite non-toxic at 1000 ppm. None of the compounds showed any anti JH activity.

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