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Preparation and Biological Activity of Potential Inhibitors of Insect Juvenile Hormone Biosynthesis

Gary B. Quistad,* Luana E. Staiger, and David C. Cerf

Fluoromevalonolactone (tetrahydro-4-(fluoromethyl)-4-hydroxy-2*H*-pyran-2-one, FMev) is an inhibitor of juvenile hormone production in lepidopterous insect species. Numerous structural analogues of FMev were synthesized and bioassayed on the tobacco hornworm (*Manduca sexta*) in order to assess anti-juvenile hormone activity. Such activity was greatest with FMev while the difluoro analogue (tetrahydro-4-(difluoromethyl)-4-hydroxy-2*H*-pyran-2-one) was about 9-fold less active. Three other analogues show reduced anti-juvenile hormone activity, which may result from metabolic conversion to FMev. A number of structurally unrelated hypocholesterolemic agents were also assayed as potential inhibitors of juvenile hormone biosynthesis, but only negative results were obtained.

Although the theoretical basis for insect control by anti-juvenile hormones (AJH agents) has been widely discussed [e.g., Slama (1978)], relatively few compounds with AJH activity have been reported. Several derivatives of abietic acid and hydrofluorene are alleged by Murakoshi et al. (1975, 1977) to cause precocious metamorphosis (an AJH effect) in *Bombyx mori*, but this activity was not always definitive since treatment of some larval stages resulted in prolonged larval development (an agonistic or juvenile hormone effect). This property of antagonistic and agonistic effects from the same antihormone compound is also evidenced when larval *Manduca sexta* are treated with ETB [ethyl 4-[2-[(*tert*-butylcarbonyl)oxy]]-butoxybenzoate (Staal, 1977)] where the elicited morphological response is dose dependent, a fact that suggests severe limitations for usage of such compounds for practical insect control. The most unequivocal AJH effects have been described for the precocenes (Bowers et al., 1976; Slama, 1978), which are clearly AJH agents for certain Hemiptera and Orthoptera. The biological effects of precocenes are attributed to selective destruction of the source of biosynthesis of juvenile hormones, the corpora allata (Schooneveld, 1979), by formation of a highly reactive epoxide within the gland (Soderlund et al., 1980; Brooks et al., 1979). Matolcsy et al. (1980) have also reported AJH activity against the cotton bug, *Dysdercus*, for a precocene analogue that lacks the chromene ring.

The similarities between the biosynthesis of juvenile hormones in insects (Schooley et al., 1973) and cholesterol in mammals suggest the possibility of finding mutual inhibitors of several enzymatic steps. Indeed, this hypothesis was tested previously by Matolcsy et al. (1974, 1975), who unsuccessfully assayed analogues of mevalonolactone and 3-hydroxy-3-methylglutaric acid (HMG) as insect anti-juvenile hormones. Our hope when we initiated this work was that prudent selection of known hypocholesterolemic agents for insect bioassay might reveal compounds with AJH activity. As we have reported previously (Quistad et al., 1981), tetrahydro-4-(fluoromethyl)-4-hydroxy-2*H*-pyran-2-one (fluoromevalonolactone, FMev) is an AJH in Lepidoptera, in addition to being a known hypocholesterolemic agent (Tschesche et al., 1963). FMev was synthesized first by Tschesche and Machleidt (1960), who shortly thereafter patented it (Tschesche et al., 1963) as useful for treating disorders caused by excessive cholesterol biosynthesis (e.g., atherosclerosis). FMev is known to inhibit the biosynthesis of cholesterol from both acetate and mevalonate in rat liver (Singer et al., 1959; Brauser and Hermann, 1965), and it is also alleged to block transformation of cystolic HMG–CoA to cholesterol in rat hepatocytes (Barth, 1978). In this paper we report the structure–activity relationships for a number of FMev analogues

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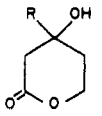
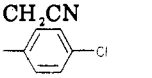
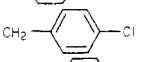
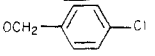
Table I. Lactone Analogues of Fluoromevalonolactone (FMev, 4)



no.	R	no.	R	no.	R
1	CH_3	7	CF_2CF_3	13	CH_2CN
2	CH_2CH_3	8	CHClF	14	
3	$(CH_2)_{16}CH_3$	9	CH_2Cl		
4	CH_2F	10	CH_2Br	15	
5	CHF_2	11	CH_2CH_2Br		
6	CF_3	12	CH_2OEt	16	

with respect to insect AJH effects, as well as probes for AJH activity with other hypocholesterolemic agents. This report is a detailed amplification of our preliminary work (Quistad et al., 1981).

EXPERIMENTAL SECTION

The synthesis and structural verification of all compounds in this report are given in the supplementary material section (see paragraph at end of paper regarding supplementary material).

Bioassay. *M. sexta* larvae were kept at 27 °C with a 16-h photoperiod throughout the breeding cycles and the bioassay procedures. They were reared in mass culture on a modified Yamamoto (1969) artificial diet.

For the feeding assay, compounds to be tested were mixed as acetone solutions with this diet while it was still warm. After solidification, 0.5-in. cubes of treated food were placed in individual 1-oz plastic cups along with a single first-instar larva (0–24 h posthatch). Larvae (20 per dosage) were reared in these containers until the fifth instar.

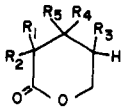
For the topical assay, third-instar larvae (0–24 h postmolt, ca. 40 mg) were individually placed on fresh artificial food medium in 1-oz plastic cups and topically treated (1 μL) with acetone dilutions of test compounds. Larvae (20 per dose) were reared in these containers until they reached fifth instars.

Developmental abnormalities were evaluated after each larval molt in both assays. A correction was made for any mortality in the acetone control groups by using Abbott's formula (Abbott, 1925). The scores of at least two replicate dose series for each test compound (bioassayed on different days) were accumulated.

RESULTS AND DISCUSSION

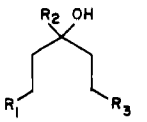
Our initial bioassays for anti-juvenile hormone (AJH) effects utilized larval *M. sexta* (tobacco hornworm). FMev and its analogues were investigated in separate bioassays involving topical application and incorporation of compounds into the artificial diet. The morphogenetic effects were qualitatively similar in the two types of bioassay for FMev (and active analogues) although the assays varied in their sensitivity to detect AJH activity (e.g., several analogues were inactive by topical application). A positive AJH response was registered when larvae displayed signs of precocious metamorphosis. Such a prothetelic effect was evidenced by (1) prepupal burrowing behavior that normally occurs at least one instar later and (2) formation of premature pupae or larval–pupal intermediates. The development of black pigmentation in larvae after subsequent molts, while a result of JH deficiency (Staal, 1977; Safranek and Riddiford, 1975), was not used as a scoring criterion since this effect was sometimes reversible in later instars.

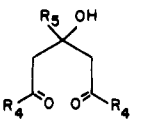
Table II. Additional Lactone Analogues of FMev



no.	R_1	R_2	R_3	R_4	R_5	
17	F	H	H	OH	CH_3	66:34 isomer ratio
18	F	H	H	OH	CH_3	22:78 isomer ratio
19	F	H	H	OH	CH_2CH_3	
20	F	F	H	OH	CH_3	
21	H	H	F	OH	CH_3	isomer I
22	H	H	F	OH	CH_3	isomer II
23	F	H	CH_3	OH	CH_3	
24	F	F	CH_3	OH	CH_3	
25	H	H	H	$OCOCH_3$	CH_2F	
26	H	H	H	$OCOCH_3$	CH_3	
27	H	H	H	OCH_2SCH_3	CH_2F	
28	H	H	H	OCH_2SCH_3	CH_3	
29	H	H	H	H	CH_3	
30	H	H	H	CH_2CH_3	CH_3	
31	H	H	H	SH	CH_3	
32	H	H	H	$SCOCH_3$	CH_3	

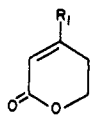
Table III. Triol and Diacid Analogues of FMev

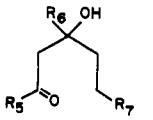


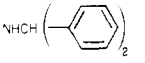


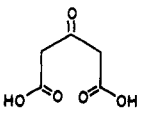
no.	R_1	R_2	R_3	no.	R_4	R_5
33	OH	CH_2F	$OCOCH_3$	38	OH	CH_3
34	$OCOCH_3$	CH_2F	$OCOCH_3$	39	OH	CF_3
35	OH	CF_3	OH	40	OH	CH_2F
36	OH	CF_2CF_3	OH	41	OH	CH_2Cl
37	OH	CH_2F	OH	42	OH	CH_2CH_3
				43	OCH_3	CH_2F
				44	OCH_3	CH_2Cl
				45	OCH_3	CF_2CF_3
				46	OCH_3	CF_3

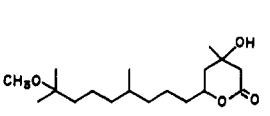
Table IV. Miscellaneous Analogues of FMev and Related Compounds

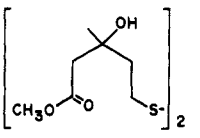




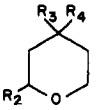
no.	R_1	no.	R_5	R_6	R_7
47	CH_3	52	OCH_2CH_3	CH_3	$SCOCH_3$
48	CH_2F	53		CH_2F	OH

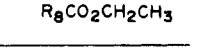






no.	no.		no.
49	54	isomer I	56
	55	isomer II	





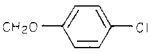
no.	R_2	R_3	R_4	no.	R_8
50	$OCOCH_3$	CH_2F	OCH_2SCH_3	57	CH_2F
51	OH		OH	58	CH_2CH_2F

Table V. Analogues of Fluoromevalonolactone (FMev) with Anti-Juvenile Hormone Activity on *M. sexta* Larvae

		% of larvae responding																	
		topical, μg/larva									diet, ppm								
	effect:	AJH			toxicity			total			AJH			toxicity			total		
no.	compound dose:	10	100	250	10	100	250	10	100	250	10	100	250	10	100	250	10	100	250
4	FMev, CH_2F	8	88		8	8		16	96		11			29	100	100	40	100	100
5	CHF_2		10	13		0	8		10	21	0	12		3	50		3	62	
6	CF_3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
9	CH_2Cl	0	0	0[a]	0	0	0[a]	0	0	0	0	0	0	0	0	0	0	0	0
25	acetylated FMev	0	52	75	0	0	5	0	52	80	0	0	0	0	0	0	0	0	0
37	CH_2F triol	0	0	0[b]	0	0	0[b]	0	0	0	0	18	30	0	25	70	0	43	100
53	benzhydrylamide of FMev	0	0	0	0	0	0	0	0	0	0	15	90	0	0	10	0	15	100

[a] No AJH or acute toxicity at 500 μg/larva. [b] 15% AJH activity and 5% acute toxicity at 500 μg/larva.

Structure–Activity Relationships. The analogues of FMev (and related compounds) considered in this report are listed in Tables I–IV. Although a number of compounds caused acute toxicity in a variety of insect species (particularly at high doses), the analogues causing AJH effects in *M. sexta* are given in Table V. Thus, compounds not listed in Table V can be presumed to be devoid of AJH activity against *M. sexta*.

A number of mevalonolactone-type compounds were prepared with varied substituents in the 3 position (Table I). Other than FMev, only the difluoro analogue (**5**) showed any AJH activity; it was about 9-fold less active than FMev upon topical application to *M. sexta* third-instar larvae at 100 μg/larva (Table V). The trifluoromethyl analogue (**6**), the chloromethyl compound (**9**), mevalonolactone, homomevalonolactone, and all other lactone analogues in Tables I and II failed to elicit AJH effects. Interestingly, the analogue of FMev corresponding to fluorinated homomevalonate (i.e., R = 2-fluoroethyl, Table I, structure not shown) is also devoid of AJH activity.

Although FMev was selected for insect bioassay on the basis of its known hypocholesterolemic activity (Tschesche et al., 1963; Singer et al., 1959), the lack of insect AJH activity for several analogues in Table II is particularly noteworthy since the same compounds are known either to be hypocholesterolemic in vivo or biosynthetic inhibitors in vitro or to have related biological activity. For example, Kirschner et al. (1961) found an 86% inhibition of squalene biosynthesis of 2-fluoromevalonate (**17** and **18**) in vitro using baker's yeast. In fact, these authors showed that only one of the four possible stereoisomers of 2-fluoromevalonate was responsible for the observed competitive inhibition. In their system 2-fluoromevalonate was converted to its pyrophosphate, but decarboxylation to the corresponding fluorinated isopentenyl pyrophosphate was contraindicated. FMev was also tested by Kirschner et al. (1961) using the enzymes from baker's yeast and found to behave qualitatively similar to 2-fluoromevalonate. 4-Fluoromevalonolactone (**21** and **22**) has also been shown to inhibit cholesterol biosynthesis from acetate and mevalonate with a potency similar to that of FMev by using a rat liver homogenate in vitro (Bergmann and Cohen, 1960, 1961). However, we found no insect AJH activity with 4-fluoromevalonolactone. Stewart and Woolley (1959) tested several mevalonate analogues as antimetabolites to suppress sterol biosynthesis in bacteria, yeast, and mice. 4-Methylmevalonolactone was the most active mevalonate antimetabolite for *Lactobacillus* and *Saccharomyces* but did not inhibit sterol formation in mice in vivo. We found no AJH activity on 4-methyl substitution (**23** and **24**), and Matolcsy et al. (1975) failed to find AJH activity for 4-methylmevalonolactone with *Pyrrhocoris*. The thiomevalonolactone (**31**) is an alleged antagonist of mevalonate (Ogawa et al., 1965) and its acetyl derivative (**32**) is a growth inhibitor for the fungus *Trichophyton* (Ogawa et al., 1964), but neither compound exhibited AJH effects in our assays.

We tested several triol analogues and their acetylated derivatives (Table III), but none showed any AJH activity with the exception of the triol precursor of FMev (i.e., **37**). Triol **37** was inactive by topical application to larval *M. sexta*, a result that is not surprising considering that its high polarity would likely contribute to difficulties in penetration through membranes. However, when **37** was bioassayed as a dietary constituent (Table V), AJH activity was observed, a finding that suggests metabolism of **37** to the biologically active FMev. Similarly, the AJH activity of the benzhydrylamide (**53**), acetylated (**25**), and silylated (not shown; prepared by Dr. R. Carney, Zoecon Corp.) derivatives may not be a reflection of inherent AJH properties but rather a result of metabolic activation to FMev.

Since 3-hydroxy-3-methylglutaric acid is reported to be hypocholesterolemic in mammals (Yousufzai and Siddiqi, 1976), we assayed a number of diacid analogues as both free acids and as dimethyl esters (Table III). No insect AJH activity was found for either HMG itself or its *S*-butyl half-ester, which is one of the more potent hypocholesterolemic agents described by Longino (1975). The free diacid analogue of FMev (**40**) elicited moderate acute toxicity in larval *M. sexta*, but since the juvenoid hydroprene was relatively unsuccessful at rescuing the insects from this toxicity, we conclude that the biological activity of diacid **40** is not AJH related. All other acids and their dimethyl esters (Table III) were inactive.

In addition to analogues of FMev we have tested a number of mammalian hypocholesterolemic agents with diverse chemical structures. Of course, the mode of hypocholesterolemic action in mammals may be quite unrelated to our intentions of identifying a biosynthesis inhibitor. Although clofibrate is the most widely used hypolipidemic agent in the United States and Europe (Reddy et al., 1980), we found no AJH activity for either clofibrate or its analogue, procetofen (prepared by Dr. R. J. Anderson, Zoecon Corp.), in larval *M. sexta*. Similarly, Hammock et al. (1978) could not detect AJH activity for clofibrate and a number of analogues on *Oncopeltus fasciatus* and *Tenebrio molitor*. Insect AJH activity on *M. sexta* was also absent for the following hypocholesterolemic agents: α-(2-pyridinyl)-α-phenyl-2-chloroacetophenone (Hewitt et al., 1978); 1,3-bis(4-chlorophenoxy)-2-propanone (Piantadosi et al., 1976) and its 2-propanol analogue [cf. Grill et al. (1978)]. We also found no activity for AMO-1618 [a gibberellin biosynthetic inhibitor (Wada, 1978)] or for kojic and abietic acids, which are reported to have

AJH activity on *B. mori* [cf. Murakoshi and Ichimoto (1972) and Murakoshi et al. (1977)].

Mode of Action of FMev. The morphological changes associated with premature pupation are manifest in internal organs as well as epidermal structures. In contrast to precocene, topical treatment of *M. sexta* larvae with FMev produces no visible alterations in the morphology of the corpora allata in subsequent pupae (i.e., pycnosis and vacuolization were absent; Judy, 1979).

The AJH activity of FMev seems to be limited to Lepidoptera. Even in this order there is a wide variation in responsiveness, with *M. sexta* being the most sensitive of the insect species tested (Quistad et al., 1981). As with many other pesticides, the economically important pests, *Spodoptera* and *Heliothis*, appear to be less sensitive to FMev. Even with *M. sexta* the dose necessary to elicit AJH effects is relatively high. A clear interpretation of AJH activity was compromised for some analogues by nondescript mortality, particularly at high doses (Table V). For *M. sexta*, only 5–10% of the third-instar larvae topically treated with FMev died of acute toxicity at 10–100 μg/larvae, but for other less effective analogues, larvae often died before showing AJH effects. Dietary bioassay of FMev resulted in greater acute toxicitiy, indicating less relative sensitivity to the AJH mode of action with dietary larval treatment.

A number of observations are consistent with our designation of FMev as an inhibitor of juvenile hormone biosynthesis (Quistad et al., 1981). FMev inhibits the biosynthesis of JH in vitro (Kramer and Staal, 1980), and when applied topically to *M. sexta* larvae at the physiologically effective dose, it reduces the titer of JH in vivo (Bergot and Edwards, 1979). As expected, a mutant black strain of *M. sexta* with an already reduced JH titer (Safranek and Riddiford, 1975) is more sensitive to FMev than the normal strain.

On an enzymatic basis FMev seems to inhibit JH biosynthesis at the level of enzymatic phosphorylation of mevalonate and homomevalonate (Baker, 1979; Quistad et al., 1981). Since a 5-fold excess of either mevalonate or homomevalonate prevents the AJH activity of FMev when the compounds are applied concurrently in vivo, FMev may simply act as a competitive enzymatic inhibitor. The high dose of FMev necessary to elicit AJH activity may also be a reflection of its role as a competitive inhibitor for the conversion of mevalonate (or homomevalonate) to JH. Indeed, if FMev is a representative reversible inhibitor of JH biosynthesis, one may question the utility of such inhibitors as practical insect control agents. FMev also has herbicidal and fungicidal activity at high doses (King and Henrick, 1981).

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Supplementary Material Available: Synthesis and structural verification of all compounds (20 pages). Ordering information is given on any current masthead page.

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