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Synthesis and Biological Activity of Furanyl Anti-Juvenile Hormonal Compounds

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Abstract: Twenty-one synthetic compounds, containing one or more furan rings, were demonstrated to possess anti-juvenile hormone (AJH) activity as evidenced by their induction of premature metamorphosis in the milkweed bug, *Oncopeltus fasciatus* (Dallas) by contact, topical application or fumigation. The ED_{50} of the four most active analogs required to induce precocious metamorphosis from 3rd-instar nymphs by residue contact in a Petri dish compared favorably with that of precocene II (6,7-dimethoxy-2,2-dimethyl 2*H*-chromene) a naturally occurring phytochemical AJH. Precocious metamorphosis was fully reversible by co-treatment with juvenile hormone (JH III) or JH analogs, demonstrating that the observed AJH activity resulted from an induced deficiency of juvenile hormone.

Key words: *Oncopelrus fasciatus*, juvenile hormone, furan, precocene II, synthesis, biological activity.

1 INTRODUCTION

The discovery of the precocenes and their anti-juvenile hormonal (AJH) action in insects[1] in the bedding plant *Ageratum houstonianum* Mill. suggested a novel, biorational approach to insect control. Thus, the precocenes chemically induced the cessation of juvenile hormone (JH) production in insects, causing immature stages to undergo a precocious metamorphosis into diminutive non-viable adults, while normal adults were sterilized. These biological actions, affecting insect-specific developmental and reproductive processes could, if extended to important pest species, constitute an additional biorational method for insect control, complementing the already successful commercialization of juvenile hormone analogs and mimetics. More importantly, AJHs target both immature and adult stages, whereas the JH products achieve their control effectiveness principally through disruption of only the ultimate developmental stages of insects. Although active against many insect species, the precocenes were insufficiently effective against important pest species to warrant commercial development. Other phytochemicals, subsequently discovered to possess AJH activity, demonstrated similar limitations.[2] Synthetic approaches revealed compounds with AJH activity, but none with a sufficiently broad spectrum of action against pest species to motivate further developments.[3–9] Seeking new chemistry targeted to interfere with JH biosynthesis, secretion or transport we discovered that certain compounds containing the furan ring possessed AJH activity

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and we report here their synthesis, structure and biological activity relationships.

2 MATERIALS AND METHODS

2.1 Biological evaluations

A series of compounds (Figs 1 and 2) were synthesized and tested on the milkweed bug, *Oncopeltus fasciatus* (Dallas) (Heteroptera: Lygaeidae) for AJH activity as revealed by the induction of precocious metamorphosis.

Milkweed bugs were cultured at 30°C and 16:8 h light:dark cycle on sunflower seeds and water. Routine bioassays were performed by the contact method of Bowers.[1] Test compounds, dissolved in acetone, were applied to the bottom of a 9-cm Petri dish at doses of 0·1, 0·2, 0·3 and 0·5 mg. Following evaporation of the acetone, a residue of the test compound remained on the bottom surface (area = 61 cm^2) of the Petri dish, giving a dose rate of 1·64, 3·28, 4·92 and 8·20 $\mu g\ cm^{-2}$, respectively. Twenty newly molted (<1 h old) 3rd-instar milkweed bug nymphs were placed in the treated Petri dish and covered with the Petri dish cover. The sides of the Petri dish bottom were coated with 'Fluon' AD-1 (Northern Products Inc., Woonsocket, RI) to prevent the insects from climbing on the sides and lid. The insects were deprived of food for 24 h after exposure in the treated dish and then given sunflower seeds and water (provided on pieces of cotton wick). Insects were confined to the Petri dish throughout development to the adult stage; they were examined daily to note mortality, molting and metamorphosis. Compounds showing a high level of AJH activity at 1·64 $\mu g\ cm^{-2}$ were evaluated at lower doses (0·16, 0·20, 0·41 and 0·82 $\mu g\ cm^{-2}$), and with replications.

Three compounds (**5**, **6** and **17**) which showed relatively high activity were also tested by fumigation. In fumigation

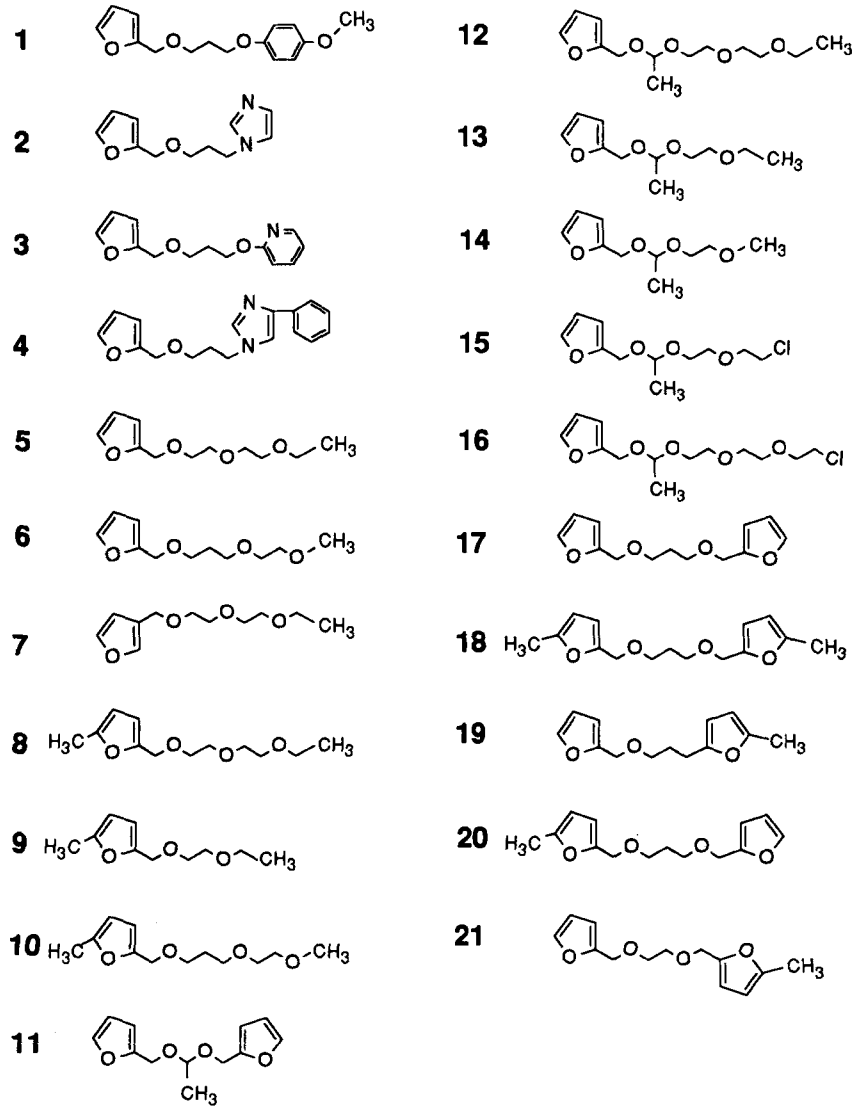

Fig. 1. Compounds inducing anti-juvenile hormonal activity in the milkweed bug, *Oncopeltus fasciatus*.

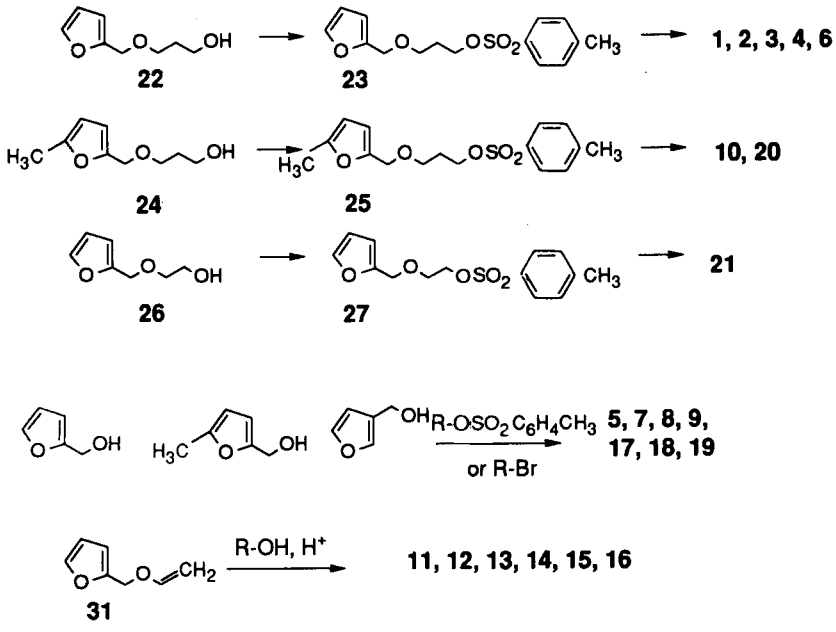

Fig. 2. Synthetic schemes for preparation of furanyl compounds possessing anti-juvenile hormonal activity.

tests, different doses (see Table 3) of the compounds were applied to the inside of the Petri dish cover. Twenty newly molted 3rd-instar or 10 newly molted 4th-instar (<1 h old) milkweed bugs were confined to the Petri dish bottom by Fluon treatment of the sides. Thus, the insects were exposed exclusively to the vapors of the test compound. These insects were maintained and examined as described above. AJHs **5** and **17** were also tested by contact for only 24 h and by topical application. Twenty 3rd-instars each were treated topically with 1 μl of acetone containing the desired dose (see Table 4) of the compound; they were fed soon after treatment and confined to 9-cm Petri dishes throughout development to the adult stage. Appropriate untreated or solvent-only treated controls were maintained for all of the above treatments.

Doses required for induction of precocious metamorphosis in 50% of the treated insects (ED_{50}) were calculated by regression analysis of log(x) dose and probits of percentages of surviving insects which molted to precocious adults and/or larval-adult intermediates. LD_{50}s were calculated in the same way for AJHs which induced high mortality at the doses tested. Mean ($\pm$SE) percentage mortality, precocious adults at first and second molt and normal adults after treatment of 3rd instars, by contact and fumigation with different doses of AJHs **5**, **6** and **17** were determined.

2.2 Rescue experiment

In order to determine whether the treated insects could be rescued from the effects of the AJHs, we treated 3rd instars simultaneously with selected AJHs and juvenile hormone III (JH III) or the JH-mimic, fenoxycarb (Ro 13-5223, Maag Agrochemicals).[10] In these experiments 10 μg of fenoxycarb or 50–200 μg of JH III was applied to the Petri dish bottom and the AJH **5** (100 μg), **6** (100 μg) or **17** (200 μg) was applied on the inside of the Petri dish cover (fumigation) (only AJHs **5** and **17** were used with JH III). Twenty 3rd-instar milkweed bugs were confined in each treated Petri dish throughout adult development or until death. They were fed 24 h after treatment and examined daily to monitor development and molting. Controls were treated with AJH alone by fumigation.

2.3 Synthetic procedures

Compounds with AJH activity are shown in Fig. 1 and their synthetic schemes are given in Fig. 2. Open column chromatography over Florisil (60–100 mesh) was used for purification of compounds. During synthesis, all intermediates and isolated products were evaluated for purity by silica thin-layer chromatography in solvent systems of ethyl acetate + hexane and by capillary gas chromatography on a Hewlett-Packard 5890 instrument fitted with a 15-m DB-1701 (phenyl, cyanopropyl methyl silicone, 0·32-mm i.d. × 0·25 μm film thickness) capillary column programmed from 60°C to 200°C at 5°C min^{-1}, utilizing flame ionization detection. In addition, prior to biological evaluation, all final products were purified to at least 99% purity, by the above criteria, and all structural formulas characterized by analysis on gas-chromatography coupled mass spectrometry with a Hewlett-Packard 5890 mass selective detector coupled with a 5890 gas chromatograph using a 12-m HP-1 (methyl silicone, 0·2 mm diameter, 0·33 μm film thickness) capillary column, with hydrogen carrier gas.

Fragmentation was by electron ionization at 70 eV. Structures were also confirmed by NMR spectra (250 MHz) obtained with a Bruker WM-250 spectrometer equipped with an Aspect 2000 computer, using deuterochloroform as solvent and tetramethysilane as internal standard.

2.3.1 3-(2-Furanylmethoxy)-1-propanol (**22**)
To an ice-cold solution of furfuryl alcohol (17·6 g) in dry benzene (100 ml) was added a total 1·16 g of small pieces of sodium metal. After the sodium metal dissolved completely, a solution of 3-bromo-1-propanol (5·0 g; 0·036 mol) in benzene (50 ml) was added dropwise at room temperature, followed by stirring for 3 h at 70°C. After cooling to room temperature, the mixture was poured into ice-water and extracted three times with diethyl ether. The organic layer was washed with brine and dried over magnesium sulfate. Following removal of excess furfuryl alcohol by reduced pressure distillation, the residue was purified by column chromomatography. Finally, 2·4 g (42·7%) of product was obtained. [^{1}H]NMR δ: 1·86 (m, 2, $OCH_2\underline{CH_2}$), 3·65 (t, 2, J = 5·9 Hz, $O\underline{CH_2}CH_2$), 3·75 (t, 2, J = 5·8 Hz, $CH_2\underline{CH_2}OH$), 4·46 (s, 2, $O\underline{CH_2}$-furan α), 6·33 (m, 2), 7·41 (m, 1).

2.3.2 3-(5-Methyl-2-furanylmethoxy)-1-propanol (**24**)
A solution of 5-methylfurfuryl alcohol (5·28 g) in *N,N*-dimethylformamide (DMF: 30 ml) was added dropwise to a suspension of sodium hydride (1·2 g) in DMF (40 ml) followed by stirring for 15 min at room temperature. Prior to use, the sodium hydride (80% dispersion in mineral oil) was washed with petroleum ether to remove the mineral oil. A solution of 3-bromopropanol (5·0 g) in DMF (30 ml) was added to the mixture and then stirred overnight at 70°C. After cooling, the mixture as poured into ice-water and extracted with ether. The extract was washed with brine and dried over magnesium sulfate. Removal of the solvent afforded 6·3 g of crude product. After purification by column chromatography, 2·48 g (40·5%) of product was obtained. [^{1}H]NMR δ: 1·84 (m, 2, $OCH_2\underline{CH_2}$), 2·29 (s, 3, $\underline{CH_3}$-furan α), 3·64 (t, 2, J = 5·9 Hz, $O\underline{CH_2}CH_2$), 3·75 (t, 2, J = 5·6 Hz, $CH_2\underline{CH_2}$-OH), 4·39 (s, 2, $O\underline{CH_2}$-furan α), 5·91 (m, 1), 6·19 (d, 1, J = 3·5 Hz).

2.3.3 2-(2-Furanylmethoxy)ethanol (**26**)
2-(2-Furanylmethoxy)ethyl tetrahydropyranyl (THP) ether was prepared by same method as **22**, using 2-bromoethyl THP ether instead of 3-bromopropanol. After reaction, the crude product was dissolved in methanol and stirred with catalytic amount of *p*-tolenesulfonic acid overnight. After neutralization with sodium hydrogen carbonate and removal of methanol under reduced pressure, the product was purified by chromatography over Florisil. (Yield; 16·5%). [^{1}H]NMR δ: 3·56 (m, 2, $OCH_2\underline{CH_2}OH$), 3·69 (m, 2, $OCH_2\underline{CH_2}OH$), 4·48 (s, 2, $O\underline{CH_2}$-furan α), 6·33 (m, 2), 7·40 (m, 1).

2.3.4 3-(2-Furanylmethoxy)-1-propyl p-*toluenesulfonate* (**23**)
To an ice-cold solution of **22** (3·4 g) in dry pyridine (40 ml) was added of *p*-toluenesulfonyl chloride (4·2 g) in one portion followed by stirring for 16 h at room temperature. The mixture was poured into ice-water and extracted with diethyl ether. The ethereal layer was washed with hydrochloric acid (1 M) and brine, and dried over magnesium sulfate. Removal of the solvent afforded 2·6 g (40·5%) of product, which was used for the next reaction directly. [^{1}H]NMR δ: 1·88 (m, 2, $OCH_2\underline{CH_2}$), 2·44 (s, 3), 3·48 (t, 2, J = 5·6 Hz, $O\underline{CH_2}CH_2$), 4·12 (t, 2, J = 6·2 Hz, $CH_2\underline{CH_2}$-OTs), 4·34 (s, 2, $O\underline{CH_2}$-furan α), 6·27 (m, 1), 6·32 (m, 1), 7·34 (d, 2, J = 8·2 Hz), 7·38 (m,1), 7·77 (d, 2, J = 8·2 Hz).

All *p*-toluenesulfonates were prepared by the same method as **23** from the corresponding alcohols except 1,3-propanediol *bis*(*p*-toluenesulfonate), which was obtained from commercial sources.

2.3.5 3-(5-Methyl-2-furanylmethoxy)-1-propyl p-*toluenesulfonate* (**25**)
(Yield; 43·8%). [^{1}H]NMR δ: 2·03 (m, 2, $OCH_2\underline{CH_2}$O-Ts), 2·28 (d, s, J = 0·6, $\underline{CH_3}$-furan α), 2·45 (s, 3), 3·45–3·70 (m, 4), 4·28 (s, 2, $O\underline{CH_2}$-furan α), 5·91 (m, 1), 6·15 (d, 1, J = 3·0), 7·35 (m, 2), 7·79 (m, 2).

2.3.6 2-(2-Furanylmethoxy)ethyl p-*toluenesulfate* (**27**)
(Yield: 49·0%). [^{1}H]NMR δ: 2·44 (s, 3), 3·6–3·7 (m, 2, $OCH_2\underline{CH_2}$O-Ts), 4·1–4·2 (m, 2, $CH_2\underline{CH_2}$-Ts), 4·42 (s, 2, $O\underline{CH_2}$-furan α), 6·28–6·35 (m, 2), 7·32 (d, 2, J = 8·4 Hz), 7·38 (dd, 1, J = 1·8 and 0·8 Hz), 7·79 (d, 2, 8·4 Hz).

2.3.7 2-(2-Ethoxyethoxy)ethyl p-*toluenesulfonate* (**28**)
(Yield; 54·4%). [^{1}H]NMR δ: 1·18 (t, 3, J = 7·0 Hz, $\underline{CH_3}CH_2O$), 2·44 (s, 3), 3·4–3·6 (m, 6), 3·69 (t, 2, J = 4·8 Hz, $O\underline{CH_2}CH_2$O-Ts), 4·17 (t, 2, J = 4·8 Hz, $OCH_2\underline{CH_2}$O-Ts), 7·34 (d, 2, J = 8·2 Hz), 7·79 (d, 2, J = 8·2 Hz).

2.3.8 2-Ethoxyethyl p-*toluenesulfonate* (**29**)
(Yield; 52·0%). [^{1}H]NMR δ: 1·13 (t, 3, J = 7·0 Hz, $\underline{CH_3}CH_2$O-Ts), 2·45 (s, 3), 3·45 (q, 2, J = 7·0 Hz, $CH_3\underline{CH_2}$O-Ts), 3·61 (m, 2), 4·16 m, 2), 7·35 (d, 2, J = 8·3 Hz), 7·80 (d, 2, J = 8·3 Hz).

Compounds **1–4** and **6** were prepared from **23** by the Williamson synthesis, while **20** and **21** were prepared from **25** and **27** respectively.

2.3.9 Furfuryl 3-(4-methoxyphenoxy)propyl ether (**1**)
(Yield; 12·5%). [^{1}H]NMR δ: 2·03 (m, 2, $OCH_2\underline{CH_2}$), 3·64 (t, 2, J = 6·2 Hz, $O\underline{CH_2}CH_2$), 3·75 (s, 3, $\underline{CH_3}O$), 3·99 (t, 2, J = 6·2 Hz, phenoxy-$C\underline{H_2}CH_2$), 4·45 (s, 2, $O\underline{CH_2}$-furan α), 6·30–6·33 (m, 2), 6·82 (s, 4), 7·38 (m, 1).

2.3.10 1-[3-(2-Furanylmethoxy)propyl]imidazole (**2**)
(Yield; 27·7%). [^{1}H]NMR δ: 1·99 (m, 2, $OCH_2\underline{CH_2}$), 3·38 (t, 2, J = 5·8 Hz, $O\underline{CH_2}CH_2$), 4·05 (t, 2, J = 6·7 Hz,

1-imidazole-$C\underline{H}_2$), 4·42 (s, 2, $OC\underline{H}_2$-furan α), 6·32 (m, 1), 6·36 (m, 1), 6·86 (m, 1), 7·03 (m, 1), 7·42–7·43 (m, 2).

2.3.11 2-[3-(2-Furanylmethoxy)propyoxy]pyridine (**3**)
(Yield; 13·3%). [^{1}H]NMR δ: 2·06 (m, 2, $OCH_2C\underline{H}_2$), 3·64 (t, 2, J = 6·4 Hz, $OC\underline{H}_2CH_2$), 4·37 (t, 2, J = 6·4 Hz, pyridine-$OC\underline{H}_2$), 4·46 (s, 2, $OC\underline{H}_2$-furan α), 6·29–6·32 (m, 2), 6·71 (m, 1), 6·86 (m, 1), 7·38 (dd, J = 1·7 and 0·8 Hz), 7·54 (m, 1), 8·14 (dd, 1, J = 5·0 and 1·9 Hz, 3-proton of pyridine).

2.3.12 1-[3-(2-Furanylmethoxy)propyl]-4-phenylimidazole (**4**)
(Yield; 24·5%). [^{1}H]NMR δ: 2·02 (m, 2, $OCH_2C\underline{H}_2$), 3·41 (t, 2, J = 5·8 Hz, $OC\underline{H}_2CH_2$), 4·06 (t, 2, J = 6·7 Hz, 1-imidazole-$C\underline{H}_2$), 4·43 (s, 2, $OC\underline{H}_2$-furan α), 6·30–6·36 (m, 2), 7·1–7·5 (m, 6), 7·75 (dd, 2, J = 8·1 and 1·4 Hz, *o*-protons of phenyl).

2.3.13 Furfuryl 3-(2-methoxyethyoxy)propyl ether (**6**)
(Yield; 35·7%). [^{1}H]NMR δ: 1·88 (m, 2, $OCH_2C\underline{H}_2$), 3·38 (s, 3, $C\underline{H}_3O$), 3·52–3·59 (m, 8), 4·43 (s, 2, $OC\underline{H}_2$-furan α), 6·30–6·35 (m, 2), 7·40 (m, 1).

2.3.14 3-(2-Methoxyethoxy)propyl 5-methylfurfuryl ether (**10**)
(Yield; 37·9%). [^{1}H]NMR δ: 1·89 (m, 2, $OCH_2C\underline{H}_2$), 2·28 (3, d, J = 0·9 Hz, $C\underline{H}_3$-furan α), 3·38 (s, 3, $C\underline{H}_3O$), 3·5–3·6 (m, 8), 4·37 (s, 2, furan α-$C\underline{H}_2O$), 5·91 (dd, 1, J = 3·0 and 0·9 Hz), 6·18 (d, 1, J = 3·0 Hz).

2.3.15 Furfuryl 3-(5-methyl-2-furylmethoxy)propyl ether (**20**)
(Yield; 21·9%). [^{1}H]NMR δ: 1·87 (m, 2, $OCH_2C\underline{H}_2$), 2·28 (3, d, J = 0·8 Hz, $C\underline{H}_3$-furan α), 3·55 (t, 4, J = 6·4 Hz, $OC\underline{H}_2CH_2$), 4·35 (s, 2, furan α-$C\underline{H}_2O$), 4·42 (s, 2, furan α-$C\underline{H}_2O$), 5·90 (dd, 1, J = 3·0 and 0·8 Hz), 6·17 (d, 1, J = 3·0 Hz), 6·29 (d, 1, J = 3·2 Hz), 6·33 (dd, 1, J = 3·2 and 1·8 Hz), 7·39 (d, 1, J = 1·8 Hz).

2.3.16 Furfuryl 2-(5-methyl-2-furylmethoxy)ethyl ether (**21**)
(Yield; 11·7%). [^{1}H]NMR δ: 2·28 (s, 3, $C\underline{H}_3$-furan α), 3·63 (s, 4, $OCH_2C\underline{H}_2O$), 4·43 (s, 2, furan α-$C\underline{H}_2O$), 4·50 (s, 2, furan α-$C\underline{H}_2O$), 5·90 (dd, 1, J = 3·0 and 1·0 Hz), 6·19 (d, 1, J = 3·0 Hz), 6·32 (m, 2), 7·39 (m, 1).

Compounds **27** and **18** were prepared in one step with 1,3-propandiol bis (*p*-toluenesulfonate) and two equivalents of furfuryl alcohol or 5-methylfurfuryl alcohol. The Williamson synthesis afforded good yields with sodium metal as base.

2.3.17 Furfuryl 3-(2-furanylmethoxy)propyl ether (**17**)
(Yield; 44·3%). [^{1}H]NMR δ: 1·86 (m, 2, $OCH_2C\underline{H}_2$), 3.54 (t, 4, J = 6·5 Hz, $OC\underline{H}_2CH_2$), 4·41 (s, 4, $OC\underline{H}_2$-furan α), 6·28–6·34 (m, 4), 7·39 (dd, 2, J = 1·8 and 0·7 Hz).

2.3.18 5-methylfurfuryl 3-(5-methyl-2-furanylmethoxy)-propyl ether (**18**)
(Yield; 47·3%). [^{1}H]NMR δ: 1·88 (m, 2, $OCH_2C\underline{H}_2$), 2·28 (d, 6, J = 0·8 Hz, $C\underline{H}_3$-furan α), 3·55 (t, 4, J = 6·5 Hz, $OC\underline{H}_2CH_2$), 4·36 (s, 4, $OC\underline{H}_2$-furan α), 5·91 (m, 2), 6·17 (d, 2, J = 3·0 Hz).

Compound **5** was prepared from **28** and furfuryl alcohol by the use of sodium metal as base, and compounds **7–9** were prepared in the same way, using 3-furanylmethanol or 5-methylfurfuryl alcohol and using sodium hydride instead of sodium metal. Compound **30**, produced by methylation of 2-methylfuran, was used for synthesis of **19** with furfuryl alcohol.

2.3.19 2-(2-Ethoxyethoxy)ethyl furfuryl ether (**5**)
(Yield; 67·3%). [^{1}H]NMR δ: 1·20 (t, 3, J = 7·0 Hz, $C\underline{H}_3CH_2O$), 3·54 (q, 2, J = 7·0 Hz, $CH_3C\underline{H}_2O$), 3·55–3·70 (m, 8), 4·50 (s, 2, furan α-$C\underline{H}_2O$), 6·32 (m, 2), 7·39 (m, 1).

2.3.20 2-(2-Ethoxyethoxy)ethyl 3-furylmethyl ether (**7**)
(Yield; 16·0%). [^{1}H]NMR δ: 1·21 (t, 3, J = 7·0 Hz, $C\underline{H}_3CH_2O$), 3·52 (q, 2, J = 7·0 Hz, $CH_3C\underline{H}_2O$), 3·6–3·7 (m, 8), 4·44 (s, 2, furan α-$C\underline{H}_2O$), 6·42 (m, 1), 7·38 (m, 1), 7·41 (m, 1).

2.3.21 2-(2-Ethoxyethoxy)ethyl 5-methylfurfuryl ether (**8**)
(Yield; 10·5%). [^{1}H]NMR δ: 1·21 (t, 3, J = 7·0 Hz, $C\underline{H}_3CH_2O$), 2·28 (d, 3, J = 0·8 Hz, $C\underline{H}_3$-furan α), 3·52 (q, 2, J = 7·0 Hz, $CH_3C\underline{H}_2$-O), 3·57–3·68 (m, 8), 4·44 (s, 2, furan α-$C\underline{H}_2O$), 5·90 (m, 1), 6·19 (d, 1, J = 2·9 Hz).

2.3.22 2-Ethoxyethyl 5-methylfurfuryl ether (**9**)
(Yield; 26·3%). [^{1}H]NMR δ: 1·21 (t, 3, J = 7·0 Hz, $C\underline{H}_3CH_2O$), 2·28 (s, 3, $C\underline{H}_3$-furan α), 3·52 (q, 2, J = 7·0 Hz, $CH_3C\underline{H}_2O$), 3·61 (m, 4), 4·45 (s, 2, furan α-CH_2O), 5·91 (m, 1), 6·20 (d, 1, J = 3·1 Hz).

2.3.23 1-Bromo-3-(5-methyl-2-furyl)propane (**30**)
A solution of 2-methylfuran (2·5 g; 0·03 mol) in dry tetrahydrofuran (THF; 30 ml) was cooled in a dry-ice/acetone bath at −25°C. Under nitrogen atmosphere, *n*-butyllithium in cyclohexane (2·0 M, 15 ml ≡ 1·92 g as butyllithium) was added to the solution. The mixture was kept at −25°C for 4 h under nitrogen atmosphere with stirring. A solution of 1,3-dibromopropane (12·1 g) in THF (15 ml) was added dropwise to the above mixture for 10 min, followed by stirring 1 h at −20°C. The mixture was allowed to stand overnight at room temperature, then poured into ice-water, extracted with ether, washed with brine, and dried over magnesium sulfate. After removal of residual starting materials by reduced pressure distillation, the residue was purified by chromatography over Florisil. Finally, 3·34 g (51·0%) of product was obtained. [^{1}H]NMR δ: 2·15 (m, 2, $OCH_2C\underline{H}_2$), 2·24 (s, 3, $C\underline{H}_3$-furan α), 2·73 (t, 2, J = 7·2 Hz,

furan α-CH_2CH_2), 3·41 (t, 2, J = 6·6 Hz, CH_2CH_2-Br), 5·84–5·89 (m, 2).

2.3.24 Furfuryl 3-(5-methyl-2-furfyl)propyl ether (**19**)
(Yield; 6·9%). [^{1}H]NMR δ: 1·90)m, 2, OCH_2CH_2), 2·24 (s, 3, CH_3-furan α), 2·64 (t, 2, J = 7·4 Hz, furan α-CH_2CH_2), 3·50 (t, 2, J = 6·5 Hz, CH_2CH_2O), 4·44 (s, 2, furan α-CH_2O), 5·82 (s, 2, α-disubstituted furan β-protons), 6·29–6·34 (m, 2), 7·40 (dd, 1, J = 1·7 and 0·9 Hz).

2.3.25 Furfuryl vinyl ether (**31**)
A mixture of furfuryl alcohol (15·0 g), mercuric acetate (1·0 g), and ethyl vinyl ether (210 ml) was refluxed for 17 h. After cooling, anhydrous potassium carbonate (1·5 g) was added followed by stirring for 30 min. Following removal of excess ethyl vinyl ether by distillation, the mixture was filtered and the solid portion was washed with pentane. The pentane layer and the filtrate were combined, concentrated by evaporation, and purified by column chromatography over Florisil. A fraction which eluted with diethyl ether + hexane (5 + 95 by volume) afforded 6·0 g (31·6%) of product. [^{1}H]NMR δ: 4·09 [dd, 1, J = 7·0 and 2·3 Hz, CH_2(*trans*) = CHO-], 4·32 [dd, 1, J = 14·3 and 2·3 Hz, CH_2(*cis*) = CHO-], 4·69 (s, 2, furan α-CH_2O), 6·36 (m, 2), 6·52 (dd, 1, J = 14·3 and 7·0 Hz, CH_2 = CHO-), 7·42 (m, 1).

2.3.26 Acetaldehyde difurfuryl acetal (**11**)
A mixture of **31** (0·5 g), furfuryl alcohol (1·0 g), catalytic amount of *p*-toluenesulfonic acid, and dry THF (10 ml) was stirred overnight at room temperature. The mixture was diluted with diethyl ether, washed with a saturated aqueous solution of sodium hydrogen carbonate and brine, and dried over magnesium sulfate. Following removal of the solvent, purification by chromatography over Florisil afforded 133 mg (15%) of pure product which eluted with diethyl + hexane (10 + 90 by volume). [^{1}H]NMR δ: 1·39 (d, 3, J = 5·4 Hz, CH_3-CHOO), 4·53 (m, 2), 4·67 (m, 2), 4·93 (q, 1, J = 5·4 Hz, CH_3-CHOO), 6·33 (m, 4), 7·42 (m, 2).

The following acetals were prepared in the same manner as **11** from **31** and the corresponding alcohols.

2.3.27 Acetaldehyde 2-(2-ethoxyethoxy)ethyl furfuryl acetal (**12**)
(Yield; 26·9%). [^{1}H]NMR δ: 1·21 (t, 3, J = 7·0 Hz, CH_3CH_2O-), 1·35 (d, 3, J = 5·3 Hz, CH_3-CHOO), 3·53 (q, 2, J = 7·0 Hz, CH_3CH_2O-), 3·58–3·78 (m, 8), 4·48–4·60 (m, 2, furan-CH_2O), 4·88 (q, 1, J = 5·3 Hz, CH_3-CHOO), 6·33 (m, 2), 7·45 (m, 1).

2.3.28 Acetaldehyde 2-ethoxyethyl furfuryl acetal (**13**)
(Yield: 19·8%). [^{1}H]NMR δ: 1·23 (t, 3, J = 7·0 Hz, CH_3CH_2O-), 1·36 (d, 3, J = 5·3 Hz, CH_3-CHOO), 3·45–3·80 (m, 6), 4·48–4·62 (m, 2, furan α-CH_2O), 4·89 (q, 1, J = 5·3 Hz, CH_3-CHOO), 6·33 (m, 2), 7·40 (m, 1).

2.3.29 Acetaldehyde furfuryl 2-methoxyethyl acetal (**14**)
(Yield: 25·8%). [^{1}H]NMR δ: 1·37 (d, 3, J = 5·4 Hz, CH_3-CHOO), 3·41 (s, 3, CH_3O), 3·55–3·79 (m, 4), 4·52–4·55 (m, 2, furan α-CH_2O), 4·89 (q, 1, J = 5·3 Hz, CH_3-CHOO), 6·33 (m, 2), 7·40 (dd, 1, J = 1·7 and 1·0 Hz).

2.3.30 Acetaldehyde 2-(2-chloroethoxy)ethyl furfuryl acetal (**15**)
(Yield: 15·8%). [^{1}H]NMR δ: 1·36 (d, 3, J = 5·4 Hz, CH_3-CHOO), 3·6–3·8 (m, 8), 4·55 (m, 2, furan α-CH_2O), 4·88 (q, 1, J = 5·4 Hz, CH_3-CHOO), 6·33 (m, 2), 7·40 (m).

2.3.31 Acetaldehyde 2-[2-(2-chloroethoxy)ethoxy]ethyl furfuryl acetal (**16**)
(Yield: 21·0%). [^{1}H]NMR δ: 1·35 (d, 3, J = 5·4 Hz, CH_3-CHOO), 3·6–3·6 (m, 12), 4·55 (m, 2, furan α-CH_2O), 4·88 (q, 1, J = 5·4 Hz, CH_3-CHOO), 6·33 (m, 2), 7·40 (dd, 1, J = 1·7 and 1·0 Hz).

3 RESULTS AND DISCUSSION

The furanyl AJHs induced varying degrees of precocious metamorphosis from treated immatures, depending on the stage of treatment, dosage and level of activity of the test compounds. Thus, treated 3rd-instar nymphs molted directly into precocious adults or to morphologically normal 4th instars, which subsequently molted to precocious adults or to normal 5th instars. Insects reaching the 5th stage invariably developed into normal adults. Rarely, treatment of 3rd- or 4th-stage nymphs prompted development into nymphal-adult intermediates composed of a blend of immature and adult characters at the next molt. These were invariably incapable of further metamorphosis. Twenty-one experimental compounds (Fig. 1) induced precocious metamorphosis in milkweed bugs when treated by contact in the 3rd instar. The most active compounds promoted precocious metamorphosis to premature adults directly from the treated stage.

Table 1 lists the ED_{50} dosages of AJHs required for the induction of precocious metamorphosis and the LD_{50} values for some of the more active compounds. Five compounds **5**, **6**, **8**, **13** and **17** yielded at ED_{50} of <1 μg cm^{-2}. The effects of treatment by contact of all 21 AJHs at the dose of 1·64 μg cm^{-2} are presented in Table 2. Treatment with compounds **5**, **6** and **17** induced the appearance of the highest percentage of precocious adults at the first molt, whereas precocious adults were generally produced following the second molt after treatment with compounds **8**, **10**, **13** and **21**. The results of treatment by contact and fumigation with several doses of compounds **5**, **6** and **17** are given in Table 3. Although all three compounds induced precocious metamorphosis of 3rd-instar milkweed bugs by contact and by fumigation, the greater effect of compound **17** by contact compared to fumigation may be due to its higher molecular weight

TABLE 1

ED_{50} for the Induction of Precocious Metamorphosis,[a] and LD_{50} of AJHs in 3rd-Instar Milkweed Bugs, Treated by the Contact Method

AJH	ED_{50} ($\mu g\ cm^{-2}$)	LD_{50} ($\mu g\ cm^{-2}$)
1	5·14	[c]
2	5·31	[c]
3	1·56	3·05
4	[b]	[c]
5	0·31	4·13
6	0·37	4·47
7	2·58	2·76
8	0·83	3·55
9	3·41	[c]
10	2·09	4·27
11	1·60	4·75
12	1·05	[c]
13	0·68	5·03
14	1·70	6·93
15	1·85	3·1
16	4·91	[c]
17	0·71	3·97
18	5·20	[c]
19	4·36	7·03
20	1·73	4·10
21	1·29	[c]
Precocene II[d]	0·55	—

[a] Precocious metamorphosis occurred at first and/or second molt after treatment.
[b] Only 30% precocious adults were produced at the highest dose (8·2 $\mu g\ cm^{-2}$) tested.
[c] LD_{50} higher than the highest dosage (8·2 $\mu g\ cm^{-2}$) tested.
[d] No significant mortality at doses tested (Unnithan & Bowers, unpublished).

TABLE 2

Effects of Treatment, by Contact, of 1·64 $\mu g\ cm^{-2}$ of AJH on Development of 3rd-Instar Milkweed Bugs

AJH	*Mortality* (%)	*Precocious adults* (%)		*Normal adults* (%)
		At 1st molt	*Total*[a]	
1	5	0	0	95
2	5	0	0	95
3	7	33	65	28
4	0	0	0	100
5	7	83	93	0
6	0	95	100	0
7	5	25	25	70
8	5	2	60	35
9	0	0	0	100
10	0	0	75	25
11	0	15	40	60
12	0	15	50	50
13	0	15	90	10
14	0	30	30	70
15	0	15	40	60
16	0	0	0	100
17	3	84	94	3
18	0	0	0	100
19	5	0	0	95
20	0	5	10	90
21	5	10	80	15
Control	0	0	0	100

[a] Sum of precocious adults produced at first and second molts.

and consequent lower volatility. Contact of 3rd-instar nymphs with **5** and **17** for 24 h (0·82 $\mu g\ cm^{-2}$) induced precocious metamorphosis in 50% and 75%, respectively. AJHs **5**, **6** and **17** also induced precocious metamorphosis from 4th-instar nymphs by fumigation, with ED_{50} values of 0·62, 0·76 and 2·11 $\mu g\ cm^{-2}$, respectively. All (100%) molted directly to precocious adults following exposure to the vapors from 1·64 $\mu g\ cm^{-2}$ of compounds **5** and **6** and 4·92 $\mu g\ cm^{-2}$ of compound **17**. Precocious metamorphosis could also be induced by topical application of **5** and **17** to 3rd-stage nymphs (ED_{50}, 0·52 and 1·85 μg, respectively) (Table 4) and similarly with 4th-stage nymphs (data not presented).

The ability of the furanyl AJHs to induce premature metamorphosis varied considerably with minor modifications of their chemical structure, indicating some fairly specific requirements for activity. In general, the presence of a furan ring coupled to a variety of chemical functionalities *via* an ether or acetal linkage was required for AJH activity. Since the furan ring appears to be the metabolically reactive grouping, cuticular penetration, transport within the insect, *via* the hemolymph, and ultimately access to allatal tissues must depend largely on the solubility characteristics conferred by the side chain substituents. Polyether linkages have been widely employed in natural and synthetic insecticide synergists as a vehicle for penetration and transport of the methylenedioxy moiety (e.g. sesamin, sesamolin, piperonyl butoxide, sesamex, etc.). Although other chemical groups, including aromatic and heteroaromatic rings, yielded active compounds the polyether combinations possessed the highest activity. The overall length of the molecules seemed to be important, since the most active analogs (**5**, **6**, **17**) possessed similar linear size relationships. Nevertheless, clear rules for optimum size cannot be drawn from the few examples contained in this study. Although the chemistry of the furanyl AJHs differs completely from that of the precocenes[1,11] and other reported anti-juvenile hormone agents[6–9] their relative activity (induction of precocious metamorphosis) against *O. fasciatus* has been compared with that of precocene II. The ED_{50} of the latter for induction of precocious metamorphosis in 3rd-instar milkweed bugs is 0·55 $\mu g\ cm^{-2}$ (Unnithan, G. C. and Bowers, W. S., unpublished). The activity of the furanyl AJHs ranged from 10 to 180% of that of precocene II. Compounds **5** and **6** were

TABLE 3
Biological Activity of Furanyl AJHs **5**, **6** and **17** on 3rd-Instar Milkweed Bugs Treated (A) by Contact or (B) by Fumigation

	AJH	*Dose* ($\mu g\ cm^{-2}$)	*Mortality* (%) (±*SE*)	*Precocious adults* (%) (±*SE*)[a]			*Normal adults* (%) (±*SE*)
				At 1st molt	*At 2nd molt*	*Total*[b]	
Control		—	4·0 (±2·91)	0·0	0·0	0·0	96·0 (±2·0)
A	**5**	0·16	0·0	0·0	5·0 (±5·0)	5·0 (±5·0)	95·0 (±5·0)
	5	0·41	1·7 (±1·7)	6·7 (±6·7)	75·0 (±2·9)	81·7 (±7·3)	16·7 (±8·8)
	5	0·82	3·3 (±3·3)	56·7 (±22·1)	38·3 (±17·4)	95·0 (±5·0)	1·7 (±1·7)
	5	1·64	6·7 (±3·6)	82·5 (±12·9)	10·0 (±10·0)	93·3 (±3·6)	0·0
	6	0·20	0·0	3·3 (±1·7)	8·3 (±8·3)	11·7 (±9·3)	88·3 (±9·3)
	6	0·41	3·3 (±1·7)	13·3 (±1·7)	40·0 (±11·6)	53·3 (±10·1)	43·3 (±10·1)
	6	0·82	3·3 (±3·3)	58·3 (±16·4)	35·0 (±13·2)	93·3 (±3·3)	3·3 (±3·3)
	6	1·64	0·0	95·0 (±2·9)	5·0 (±2·9)	100	0·0
	17	0·41	1·7 (±1·7)	1·7 (±1·7)	5·0 (±2·9)	6·7 (±4·4)	91·7 (±4·4)
	17	0·82	5·0 (±2·9)	16·7 (±3·3)	25·0 (±7·6)	41·7 (±4·4)	53·3 (±4·4)
	17	1·64	3·3 (±3·3)	83·3 (±8·3)	10·0 (±7·6)	93·3 (±6·7)	3·3 (±3·3)
	17	3·28	10·0 (±10·0)	87·5 (±7·5)	2·5 (±2·5)	90·0 (±10·0)	0·0
B	**5**	0·16	1·7 (±1·7)	0·0	18·3 (±9·3)	18·3 (±9·3)	81·7 (±9·3)
	5	0·41	1·7 (±1·7)	6·7 (±1·7)	86·7 (±8·3)	93·3 (±6·7)	5·0 (±5·0)
	5	0·82	1·7 (±1·7)	1·7 (±1·7)	91·7 (±6·7)	93·3 (±6·7)	5·0 (±5·0)
	5	1·64	1·7 (±1·7)	93·3 (±1·7)	5·0 (±0·0)	98·3 (±1·7)	0·0
	6	0·20	0·0	1·7 (±1·7)	5·0 (±2·9)	6·7 (±4·4)	93·3 (±4·4)
	6	0·41	3·3 (±1·7)	1·7 (±1·7)	40·0 (±15·3)	41·7 (±14·2)	55·0 (±15·3)
	6	0·82	3·0 (±2·0)	58·0 (±15·4)	39·0 (±16·2)	97·0 (±2·0)	0·0
	6	1·64	5·0 (±2·9)	83·3 (±4·4)	11·7 (±4·4)	95·0 (±2·9)	0·0
	17	0·82	5·0 (±5·0	0·0	10·0 (±7·6)	10·0 (±7·6)	85·0 (±7·6)
	17	1·64	0·0	0·0	78·3 (±12·0)	78·3 (±12·0)	21·7 (±12·0)
	17	3·28	3·3 (±3·3)	40·0 (±23·6)	56·7 (±23·2)	96·7 (±3·3)	0·0

[a] Includes nymphal-adult intermediates, if any.
[b] Compare contact treatment with precocene II at 0·16, 0·41, 0·82, 1·64 $\mu g\ cm^{-2}$ which gave 0, 15, 84 and 100% precocious adults respectively, without mortality at any dosage.

TABLE 4
Effects of Topical Application of AJH Compounds **5** and **17** on the Development of 3rd-Instar Milkweed Bugs

Anti-JH	*Dose* (μg)	*Mortality* (%)	*Precocious adults* (%)		*Normal adults* (%)
			At 1st molt	*Total*[a]	
5	0·1	0	0	0	100
5	0·5	5	0	45	50
5	1·0	5	30	90	5
5	5·0	15	70	85	0
17	0·1	0	0	0	100
17	0·5	0	0	5	95
17	1·0	0	10	20	80
17	5·0	0	70	90	10
Control		0	0	0	100

[a] Sum of precocious adults produced at first and second molts.

respectively 1·8 and 1·5 times more active than precocene II. Several of the furanyl AJHs demonstrated activity quite superior to the precocenes, since precocious metamorphosis in milkweed bugs occurred at the first molt after treatment, whereas with precocene II, except at high doses, a normal-appearing intercalary stage often occurred before premature metamorphosis supervened.[1,11]

Higher doses (8·20 $\mu g\ cm^{-2}$) of 13 compounds (**3**, **5–8**, **10**, **11**, **13–15**, **17**, **19** and **20**) resulted in 85–100% mortality within the first 24–72 h. All compounds except **1**, **2**, **8**, **10**, **16**, and **18**, induced significant and dose-dependent delays in molting. The mean (±SE) duration of 3rd instars treated with AJHs **5**, **6** and **17** at doses of 1·64, 3·28 and 4·92 $\mu g\ cm^{-2}$, respectively were: 7·2 (±0·1), 11·2 (±0·4) and 14·7 (±0·8); 6·5 (±0·1), 8·3 (±0·4) and 13·7 (±0·8); and 8·6 (±0·2), 12·0 (±0·3) and 15·1 (±1·0) days. Thus, the increased duration of the treated stage was relative to the increase in dosage in all cases. In controls, the length of the 3rd instars was 5·8 (±0·4) days. Rarely, treated insects died after a prolonged period without molting. Delayed molting and retarded growth

TABLE 5
Development of 3rd-Instar Milkweed Bugs following Simultaneous Treatment with AJH Compounds **5**, **6** and **17** by Fumigation, and Fenoxycarb (0·16 $\mu g\ cm^{-2}$) by Contact

AJH	Dose ($\mu g\ cm^{-2}$)	No. treated	No. molted to: 4th instar	5th instar	6th instar[a]	Normal adults
5	1·64[b]	20	20	20	20	0
6	1·64[b]	20	20	20	20	0
17	3·28[b]	20	19	19	19	0
Control (untreated)		20	20	20	0	20

[a] Supernumerary nymphs.
[b] All 3rd-instar nymphs treated only with an equal dose of the respective AJH compound developed into precocious adults at the first or second molt.

were usually accompanied by reduced or no feeding, particularly during the first few days after treatment. It is unknown at this time whether the delayed molting, reduced feeding and retarded growth are due to the AJHs' effect on the corpus allatum, prothoracic glands, or other target tissues. Precocene II also affects feeding in *O. fasciatus*[12] and *Rhodnius prolixus* (Stahl)[13] and inhibits molting in *O. fasciatus*.[1,11,14] *R. prolixus*[15,16] and *Locusta migratoria* (R & F).[17] In *O. fasciatus*,[11,14] *L. migratoria*[17] and *R. prolixus*[18] delayed molting was reported to be due to direct effects of precocene on the prothoracic/ventral glands.

All insects treated simultaneously with AJHs **5**, **6** or **17** and the commercial juvenoid fenoxycarb molted into normal 4th- and 5th-star nymphs and subsequently to perfect supernumerary 6th-stage nymphs (Table 5) all of which died during the next attempted molt. Controls (treated with AJH only) molted into precocious adults at the next molt. However, when 3rd-instar nymphs were treated with AJHs **5** and **17** (at dosages which induced 100% precocious adults at the first molt) and simultaneously with varying dosages of their natural hormone[19] (i.e. JH III at 0·82, 1·64 and 4·92 $\mu g\ cm^{-2}$), they molted first to normal 4th instars and subsequently to nymphal-adult intermediates or normal 5th instars (data not presented). These results show that both the natural JH and the highly persistent juvenoid could replace endogenous JH and permit normal nymphal development. However, following metabolism of the more labile JH III, further development of the doubly treated insects demonstrated a continuing inhibition of any endogenous juvenile hormone production. The duration of the treated stage was significantly shorter in insects receiving simultaneous applications of the AJHs **5**, **6** or **17** and fenoxycarb compared to those treated with the AJHs alone. Therefore, it is questionable whether the increase in stadium duration, observed following treatment with the furanyl AJHs alone, resulted from a direct action on the prothoracic glands as reported for the precocenes.[14,17,18]

Precocious adults produced as a result of treatment with the furanyl AJHs were identical with those obtained following treatment of milkweed bug nymphs with precocene II.[1,11] Precocious adults from the first molt (i.e., from 3rd instar) were diminutive with unexpanded wings. However, they possessed the adult pigmentation pattern and distinct ocelli (an adult character), but their tarsi possessed only two segments, as in the nymphs. Precocious adults produced at the second molt (from 4th instar) were larger, with fully expanded, but short, wings, adult pigmentation pattern, ocelli and three-segmented tarsi as occurs in normal adults. They also possessed well differentiated gonads, but were unable to reproduce. Precocious males, appearing after a second molt, were often found attempting to mate, albeit unsuccessfully. Dissection of 30 precocious adults, 2–3 weeks old, obtained at the second molt after treatment with AJHs **5** and **17**, showed no vitellogenic (developing) or resorbing oocytes, except in one insect which possessed one mature egg and several developing oocytes. Treatment of precocious adults with fenoxycarb induced oocyte development (Unnithan, G. C. and Bowers, W. S., unpublished). Normal-appearing adults, which developed after treatment of nymphs with moderate dosages of the furanyl AJHs, were not sterilized. In contrast, normal adults obtained after treatment with precocene II to sensitive nymphal stages (4th-instar or earlier stadia) of the milkweed bugs were sterile.[1,11,20] However, certain of the furanyl compounds (**1**, **3**, **5**, **6** and **17**) delayed or inhibited egg maturation in normal adults (Unnithan, G. C. and Bowers, W. S., unpublished).

Although the mode of action of the new AJHs is not established, the results of the rescue experiments with JH III and fenoxycarb unambiguously demonstrate that precocious metamorphosis is caused by an induced deficiency of JH, similar to that induced by treatment with the precocenes.[1,11] Since treatment of nymphs with JH III (their natural hormone[19]) relieved the AJH effects only temporarily, it may be inferred that, following metabolism of the exogenous JH III, the insects remained

unable to produce endogenous JH, indicating that the action of the furanyl AJHs must induce a permanent condition of allatal incompetence. When insects received combined treatments of AJHs and fenoxycarb (which is known to be very persistent[10]), its JH activity simply replaced that of the natural hormone, overshadowing the absence of any natural JH from the insect's own corpus allatum.

Whereas the precocenes are clearly allatal cytotoxins[14,21–27] we have not established if the furanyl AJHs affect the corpus allatum (CA) directly, or if they do, whether the effect is reversible. We did find, however, that the CA of precocious adults is small, difficult to distinguish and does not appear to increase in size as occurs in normal adults.[27] Our results suggest that the furanyl compounds may limit the development of the CA or cause it to atrophy thereby terminating JH production/release. Studies in progress should clarify whether this new class of AJHs induces degeneration of the CA similar to that of precocene II and whether their insect growth-regulant action can be extended to other more commercially important pest species.

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