Avocadofurans and Their Tetrahydrofuran Analogues: Comparison of Growth Inhibitory and Insecticidal Activity

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The importance of the double bonds in the furan ring of avocadofurans with relation to their insecticidal activity was examined. The insecticidal activity of two naturally occurring avocadofurans, 2-(pentadecyl)furan and 2-(heptadecyl)furan, was compared to the toxicity of five tetrahydrofurans with alkyl chains at position 2 and varying side chains from 14 to 18 carbons. We found that eliminating the sites of unsaturation in the furan ring of avocadofurans significantly reduced the detrimental effects on the mortality and growth of the generalist insect herbivore *Spodoptera exigua*. In 7-day bioassays, *S. exigua* larvae were significantly more affected when fed a diet containing avocadofurans as compared to a larvae fed diet treated with the analogous tetrahydrofurans. Although larvae fed with the tetrahydrofurans showed reduced growth as compared to controls, larval mortality was not significantly increased. We conclude that the double bonds in the furan ring of avocadofurans play an important role in their insecticidal effects.

Keywords: *Avocadofurans; furan; tetrahydrofuran; toxicity; insect*

INTRODUCTION

Plants produce a wide variety of furan-containing compounds (Maga, 1979; Hannemann et al., 1989); however, the effects of these compounds on herbivores and their mode(s) of action are poorly understood. Various naturally occurring furans reportedly cause hepatic and pulmonary toxicity to several animal species (e.g., Mitchell et al., 1974; Boyd et al., 1975; Wilson et al., 1978). Nevertheless, Lam and Zheng (1992) indicated that the furan-containing natural product, 2-*n*-heptylfuran, induces increased activity of the glutathione *S*-transferase enzyme system, thereby reducing tumorigenesis in the lung and forestomach of mice.

The involvement of the furan moiety with respect to the activity of furan-containing compounds has been emphasized (Mitchell et al., 1974; Swenson et al., 1973). This was supported by Lam and co-workers (1987) who indicated that catalytic hydrogenation of the furan moiety in furan-containing products eliminated their activity in mice, specifying that the furan moiety is vital to their biological activity. The toxicity of these furan substances has mainly been attributed to the metabolic activation of the furan moiety to form a furan epoxide (Swenson et al., 1973). This reaction is catalyzed by microsomal P-450 oxygenase enzymes (Boyd et al., 1975; Nelson et al., 1992). The resulting epoxide, the activated form of the toxin, may potentially bind to tissue macromolecules such as proteins and nucleic acids (Boyd et al., 1975; Nelson et al., 1992).

With the exception of furanocoumarins, few studies have examined the effect of plant furans on insect herbivores. Furanocoumarins are photoactivated compounds that react with DNA, RNA, proteins, and lipids [see Diawara and Trumble (1997) for review]. Recently, Neal and Wu (1994) found that the furanocoumarin is oxidized by cytochrome P-450 at the double bond of the furan ring, indicating that the resulting unstable epoxide will inhibit the insect's cytochrome P-450. Other furan-containing compounds have been identified to possess anti-juvenile hormone activity (Bowers et al., 1995). They indicated that several furanyl compounds affect the corpora allata directly, causing precocious development in the milkweed bug, *Oncopeltus fasciatus* (Dallas).

Avocados, *Persea americana* Mill., and other *Persea* species contain a group of furan-containing compounds commonly referred to as avocadofurans (Kashman et al., 1969; Magalhaes Alves et al., 1970; Néeman et al., 1970; Murakoshi et al., 1976; Weyestahl et al., 1976; Fraga and Terrero, 1996). Few studies have investigated the toxicity of avocadofurans, and the mode(s) of action is not known. Néeman et al. (1970) first indicated the inhibitory effects of an avocadofuran from avocado seeds on bacterial growth. Murakoshi et al. (1976) tested (8Z, 11Z)-2-(8, 11-heptadecadienyl)furan on silkworm larvae, *Bombyx mori* L.; however, little effect was found at a concentration of 300 μg/g of diet. More recently, Rodriguez-Saona et al. (1998) identified a group of avocadofurans in specialized avocado oil cells. Low to moderate toxicity of these compounds was reported against the generalist herbivore *Spodoptera exigua* (Hübner). Of several avocadofurans and related analogues tested, Rodriguez-Saona et al. (1998, 1999) found 2-(pentadecyl)furan (**1**) and 2-(heptadecyl)furan (**2**) as the most biologically active to insects. Both of these avocadofurans had toxicological activity against young *S. exigua* larvae at concentrations of 600 μg/g of diet (equivalent to 2 μmol/g) or higher, while the LC_{50} values for older larvae were above 800 μg/g (>3 μmol/g)

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(Rodriguez-Saona and Trumble, 1999). Similar furan-containing lipids extracted from avocado seed oil were identified by Rosenblat et al. (1995a,b) as the active factor of lysyl oxidase inhibition in in vivo bioassays with rats. The furan lipids may prove to be a useful antifibrotic drug in the treatment of diseases involving excess collagen deposition (Rosenblat et al., 1995a,b).

In the present paper, we investigated the importance of the double bonds in the furan ring of avocadofurans in relation to their toxicity to *S. exigua* larvae. We hypothesized that the saturated tetrahydrofuran analogues would have little or no activity against herbivores. To test the hypothesis, a series of 2-alkyl tetrahydrofurans with saturated side chains ranging from 14 to 18 carbons were synthesized and examined for insecticidal effects. These compounds were selected because Rodriguez-Saona et al. (1999) showed that a series of 2-alkylfurans with the same side chain lengths (ranging from 14 to 18 carbons) at a concentration of 5 μmol/g significantly increased larval mortality (>40%) and reduced larval growth (>75%) of *S. exigua* as compared to controls. Thus, we compared the effects of the tetrahydrofurans of corresponding side chain length with those of two naturally occurring avocadofurans, 2-(pentadecyl)furan and 2-(heptadecyl)furan.

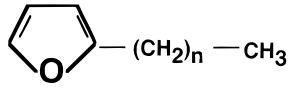
MATERIALS AND METHODS

The ^{1}H and ^{13}C NMR spectra were recorded at 270 and 67.9 MHz, respectively, using $CDCl_3$ as an internal standard. Chemical shifts (δ) are reported in ppm and coupling constants in hertz. IR spectra were obtained on a Mattson Galaxy Series 3000 FT-IR using KBr plates and CCl_4 as solvent. MS were obtained on a Shimadzu QP-5000 quadrapole GC/MS. All reagents were purchased from the Aldrich Chemical Co. and purified as needed.

Insects. *S. exigua* larvae are generalist herbivores that feed on over 35 host plants worldwide (Steiner, 1936). This species is known to feed on plants containing furan compounds (Diawara et al., 1992; Diawara et al., 1993) but has not been specifically reported to feed on avocados. Larvae were initially collected from Ventura Co. in 1998 and maintained on artificial diet (modified from Patana [1969]) at 28 ± 2 °C and 14:10 (L:D) photoperiod. A standardized cohort of neonates within 12 h of eclosion was used in all bioassays. Bioassays were maintained for 7 days inside environmental chambers. Conditions in environmental chambers were 28 ± 2 °C, 75% relative humidity, and 14:10 (L:D) photoperiod with fluorescent lighting.

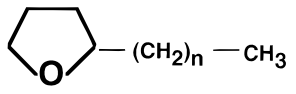
Alkylfurans. The two alkylfurans tested, 2-(pentadecyl)-furan (**1**) and 2-(heptadecyl)furan (**2**), were synthesized as described by Rodriguez-Saona et al. (1998).

Avocadofurans



1. *n* = 14
2. *n* = 16

Tetrahydrofurans



3. *n* = 13
4. *n* = 14
5. *n* = 15
6. *n* = 16
7. *n* = 17

Tetrahydrofurans. The syntheses of the tetrahydrofurans tested are as follows: The alkylfurans (**1**, **2**, and those described by Rodriguez-Saona et al. [1999]) were hydrogenated to the corresponding alkyltetrahydrofurans using palladium on carbon (Pd/C) (Henning and Urbach, 1985).

*2-(Tetradecyl)tetrahydrofuran (**3**).* A 5.0-mL flamed-dried flask was charged with 2-(tetradecyl)furan (Rodriguez-Saona et al., 1999) (200 mg, 0.757 mmol), and absolute ethanol (2 mL) was added and stirred at room temperature for 1 min. Pd/C (10% reagent, 0.3 g) was added and stirred for 2 min. Hydrogen gas (via a balloon) was added, and the reaction mixture was allowed to stir for 13 h at room temperature. The reaction was then filtered, and the catalyst washed with ether and then concentrated under vacuum. The crude residue was purified on a silica gel using 100% hexane followed by 95:5 hexane/EtOAc (R_f = 0.3) to yield the 2-(tetradecyl)tetrahydrofuran (193 mg, 96% yield) as a clear, colorless oil. The final product was assayed by GC/MS and found to be >99% free of furan starting material. ^{1}H NMR: δ 0.84 (3H, distorted triplet, $J \sim 6.7$ Hz), 1.1−1.6 (27, broad m), 1.7−2.0 (3H, m), 3.6−3.7 (2H, m), 3.7−3.8 (H1, m); ^{13}C NMR δ 14.15, 22.75, 25.76, 26.48, 29.49, 29.70, 29.74, 29.84, 31.44, 31.99, 35.82, 67.61, 79.50; IR: δ 2927 (s), 2857 (s), 1466 (m); MS 268 (<2, M), 99 (<2), 85 (<2), 71(base), 55 (17), 43 (27).

Using a procedure similar to the synthesis of **3**, the following tetrahydrofurans were synthesized:

*2-(Pentadecyl)furan (**4**).* ^{1}H NMR δ 0.84 (3H, distorted triplet, $J \sim 6.7$ Hz), 1.1−1.6 (29H, broad m), 1.7−2.0 (3H, m), 3.6−3.7 (2H, m), 3.7−3.8 (H1, m); ^{13}C NMR δ 14.16, 22.75, 25.72, 26.49, 29.44, 29.70, 29.74, 29.77, 29.84, 31.44, 31.99, 35.83, 67.62, 79.51; IR δ 2927 (s), 2855 (s), 1467 (m); MS 282 (<2, M), 99 (<2), 85 (<2), 71(base), 55 (20), 43 (35).

*2-(Hexadecyl)tetrahydrofuran (**5**).* ^{1}H NMR δ 0.84 (3H, distorted triplet, $J \sim 6.7$ Hz), 1.1−1.6 (31H, broad s), 1.7−2.0 (3H, m), 3.6−3.7 (2H, m), 3.7−3.8 (H1, m); ^{13}C NMR: δ 14.19, 22.76, 25.78, 26.48, 29.43, 29.69, 29.75, 29.76, 29.83, 31.44, 31.99, 35.82, 67.65, 79.56; IR δ 2926 (s), 2855 (s), 1466 (m); MS 296 (<2, M), 99(<2), 85(23), 71(base), 55(24), 43(27).

*2-(Heptadecyl)tetrahydrofuran (**6**).* ^{1}H NMR δ 0.84 (3H, distorted triplet, $J \sim 6.7$ Hz), 1.1−1.6 (33H, broad m), 1.7−2.0 (3H, m), 3.6−3.7 (2H, m), 3.7−3.8 (H1, m); ^{13}C NMR δ 14.18, 22.76, 25.79, 26.49, 29.44, 29.69, 29.74, 29.77, 29.83, 31.44, 32.00, 35.83, 67.65, 79.55; IR δ 2926 (s), 2854 (s), 1466 (m); MS 310 (<2, M), 99 (<2), 85 (<2), 71 (base), 55 (20), 43 (35).

*2-(Octadecyl)tetrahydrofuran (**7**).* ^{1}H NMR δ 0.84 (3H, distorted triplet, $J \sim 6.7$ Hz), 1.1−1.6 (35H, broad m), 1.7−2.0 (3H, m), 3.6−3.7 (2H, m), 3.7−3.8 (1h H1, m); ^{13}C NMR δ 14.19, 22.76, 25.78, 26.49, 29.43, 29.71, 29.74, 29.77, 29.83, 31.44, 32.00, 35.83, 67.66, 79.55; IR δ 2926 (s), 2854 (s), 1466 (m); MS 324 (<2, M), 99 (<2), 85 (<2), 71 (base), 55 (100), 43 (20).

Purity of the tetrahydrofurans was performed using a 30 × 0.25 DB-5 capillary column set initially at 200 °C for 5 min, then programmed at 10 °C/min to a final temperature of 250 °C. The GC retention times were 7.1 and 9.3 min for 2-(pentadecyl)furan and 2-(heptadecyl)furan, respectively; and 7.8, 9.2, 10.4, 11.6, and 13.0 min for 2-(tetradecyl)tetrahydrofuran, 2-(pentadecyl)tetrahydrofuran, 2-(hexadecyl)tetrahydrofuran, 2-(heptadecyl)tetrahydrofuran, and 2-(octadecyl)tetrahydrofuran, respectively. Although each run was manually started after injection, and consequently the reported retention times are approximate, there was no overlap between the furan and the tetrahydrofuran chromatograph peaks. In addition, we found no sp^2 aromatic hydrogen or carbon peaks observable in the corresponding tetrahydrofuran ^{1}H and ^{13}C NMR spectra (those being $\delta \sim 6.00$, 6.29, and 7.29 in the ^{1}H NMR [Rodriguez-Saona et al., 1998; Rodriguez-Saona et al., 1999] and 104, 110, 140, and 156 in the ^{13}C NMR [Rodriguez-Saona et al., 1999] for furan spectra).

Bioassays. Seven compounds, 2-(pentadecyl)furan (**1**), 2-(heptadecyl)furan (**2**), 2-(tetradecyl)tetrahydrofuran (**3**), 2-(pentadecyl)tetrahydrofuran (**4**), 2-(hexadecyl) tetrahydrofuran (**5**), 2-(heptadecyl)tetrahydrofuran (**6**), and 2-(octadecyl)tetrahydrofuran (**7**) (> 95% purity), were tested against *S. exigua* larvae. Treated diets were prepared at a concentration known to be insecticidal to *S. exigua* early instars for previously tested alkylfurans (5 μmol/g) (Rodriguez-Saona et al., 1999). Bioassays were conducted as described by Rodriguez-Saona et al. (1998). Each compound, in acetone solution, was transferred into a 50-mL polypropylene centrifuge tube (Fisher, Pittsburgh, PA). After the acetone evaporated, 2 mL of 0.1% Tween-

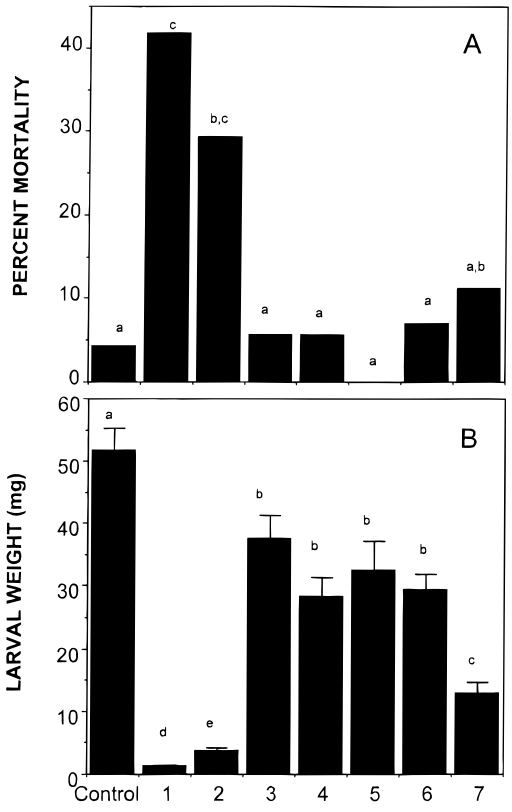


Figure 1. Percent mortality (A) and larval weights (B) of *Spodoptera exigua* fed either control diet or diets containing avocadofurans **1**−**2** or tetrahydrofurans **3**−**7** at a concentration of 5 μmol/g. Bars indicate standard errors. Treatments with the same letter are not significantly different at $\alpha = 0.05$ (Fisher's Protected LSD). Larval weights refer only to the survivors after 7 days.

80 solution (Fisher) was added, and the solution was homogenized with an ultrasonic homogenizer (Cole-Parmer, Chicago, IL). Artificial diet was added to produce a final weight of 20 g. Control diets were prepared by mixing 2 mL of Tween solution with artificial diet to obtain a final weight of 20 g. The mixtures were vortexed for 3 min before pouring into 16-well bioassay trays (C-D International Inc., Pitman, NJ). One neonate was added per well. Twenty-four neonates were used for each treatment (except for 2-[hexadecyl]tetrahydrofuran, where $n = 16$). Each treatment was replicated three times (total of 72 larvae/treatment), except for 2-(hexadecyl)tetrahydrofuran, in which the bioassay was replicated twice ($N = 32$). Trays were placed inside an incubator under the conditions described above. Larval mortality and weights were recorded after 7 days. Data were analyzed using ANOVA (Super Anova, 1989). Mortality data were transformed using the arcsine square-root transformation, while a log transformation was used for data on larval weights. Multiple comparisons were performed using Fisher's Protected LSD ($\alpha = 0.05$) (Super Anova, 1989). Control mortality for all bioassays was <10%.

RESULTS AND DISCUSSION

The absence of the double bonds in the furan ring of avocadofurans significantly reduced the activity of these compounds against the insect herbivore *S. exigua*. The effects of the avocadofurans on *S. exigua* larval mortality (Figure 1A) and growth (Figure 1B) significantly differed from those of the tetrahydrofurans. Both avocadofurans **1** and **2** had a significantly higher mortality ($F = 4.3$; df = 7, 15; $P = 0.009$) and stronger growth inhibitory ($F = 54.7$; df = 7, 453; $P < 0.001$) effects as compared to their comparable tetrahydrofurans **4** and **6**. 2-(Pentadecyl)furan (**1**) at 5 μmol/g inhibited larval growth by 98% as compared to controls, whereas the analogous 2-(pentadecyl)tetrahydrofuran (**4**) inhibited larval growth by only 45% at an equivalent concentration ($F = 162.9$; df = 1, 108; $P < 0.001$). Similarly, 2-(heptadecyl)furan (**2**) inhibited larval growth by 93% as compared to controls, whereas a lower growth inhibitory effect (59%) was obtained for 2-(heptadecyl)tetrahydrofuran (**6**) ($F = 86.3$; df = 1, 116; $P < 0.001$).

Although our results show greater inhibitory effects by the avocadofurans (**1**−**2**) on *S. exigua* larval growth as compared to all 2-alkyl tetrahydrofurans (**3**−**7**) tested, we also found that the tetrahydrofurans significantly reduced larval growth as compared to controls (Figure 1B). In addition, the side chain length influenced the toxicity of the tetrahydrofurans ($F = 8.7$; df = 4, 294; $P < 0.001$). Of all tetrahydrofurans tested, the one with the longest side chain, 2-(octadecyl)tetrahydrofuran (**7**), had the greatest inhibitory effect on *S. exigua* larval growth (Figure 1B). Growth inhibitory effects of some tetrahydrofurans are not surprising as other tetrahydrofurans, e.g., those from Annonaceous plants (Mikolajczak et al., 1989), are reported to have insecticidal and feeding deterrent activity.

In conclusion, we have shown that the unsaturation in the furan ring of avocadofurans plays an important role in the toxicity to insects. Our previous results indicated that changes in the length of the side chain may also affect the toxicity of these alkylfurans (Rodriguez-Saona et al., 1999). The alkylfuran with the shortest side chain length tested, 2-(tetradecyl)furan, had the lowest activity (Rodriguez-Saona et al., 1999). However, a reduced side chain length was not as critical as the presence of the double bonds in the furan ring with respect to the insecticidal effects of the alkylfurans.

Furthermore, because of the importance of the double bonds in the furan ring on the toxicity of avocadofurans, we speculate that one possible mechanism by which these furans from avocados could be toxic to insects is by a metabolic epoxidation of the double bond after ingestion, possibly involving cytochromes P-450, into an activated form. This phenomenon has been documented for other furan-containing natural products (Boyd et al., 1975; Nelson et al., 1992; Neal and Wu, 1994). However, this hypothesis requires further examination. In addition, the target organ(s) of the activated form, and the exact macromolecule(s) it binds to, remain to be identified.

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