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Antimicrobial activity of long-chain (*E*)-3-alken-2-ones

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ABSTRACT

(*E*)-3-Tridecen-2-one, a compound identified from the interdigital glands of black-tailed deer (*Odocoileus hemionus columbianus*), has been shown to inhibit the growth of bacteria and fungi. Homologues of (*E*)-3-tridecen-2-one were prepared and screened for antimicrobial activity. For the fungus, *Trichophyton mentagrophytes*, the minimum inhibitory concentration (MIC) of *(E)-3-Tetradecen-2-one* was 12.5 μg/mL, and for the bacteria, *Propionibacterium acnes*, the MIC of *(E)-3-heptadecen-2-one* was 3.13 μg/mL.

Compounds with antimicrobial activity have been documented from the skin and skin glands of a number of mammalian species. Nonanal, octanal and heptanal were found in the hair of Mexican free-tailed bats (*Tadarida brasiliensis mexicana*) at concentrations known to inhibit the growth of pathogenic skin fungi.[1] Hair from the reticulated giraffe (*Giraffa camelopardalis reticulata*) also has nonanal, octanal and heptanal at high concentrations and *p*-cresol, indole, tetradecanoic acid and hexadecanoic acid, compounds which inhibit the growth of pathogenic skin fungi and bacteria.[2] Several antimicrobial long-chain alcohols were found in the interdigital glands of the American pronghorn (*Antilocapra americana*).[3] (*E*)-3-Tridecen-2-one (**3**), the major compound from interdigital glands of the black-tailed deer (*Odocoileus hemionus columbianus*) has significant antimicrobial activity.[4] Because of the activity of this compound, we prepared, C_{11} to C_{17} (*E*)-3-alken-2-ones (**1–7**, Fig. 1) and assayed them for antibacterial and antifungal activity.

Long-chain 3-alken-2-ones have been previously identified as natural products from several sources. 3-Undecan-2-one was in the essential oil of the California live oak, *Querqus agrifolia*.[5] 3-Dodecan-2-one has been found in the preorbital gland of the gray duiker, *Sylvicapra grimmia*, an African antelope.[6] The seventeen carbon (*E*)-3-heptadecen-2-one was identified as a minor component from the brown alga *Caulocystis cephalornithos*.[7]

Long-chain 3-alken-2-ones have been prepared by several synthetic methods. A few of these follow. 3-Undecen-2-one was prepared in a general synthesis of α,β-unsaturated ketones using nitroalkenes and sulfones as starting materials.[8] 3-Dodecen-2-one and 3-pentadecen-2-one were prepared by reaction of nonanal and decanal respectively, with 1-bromo-2-propanone and tributylstibine.[9] We prepared our 3-alken-2-ones by condensation of an appropriate aldehyde with acetone using piperidine and acetic acid as a catalyst.[10,11] The 3-alken-2-ones prepared by this method were shown to be the (*E*)-isomer by the ^{1}H NMR coupling constant of 15.9 Hz for the olefinic protons.[12]

The minimum inhibitory concentration (MIC) of these 3-alken-2-ones was determined using a two-fold serial broth dilution. Each test compound was dissolved in DMF and 30 μL of this sample was dissolved in 3 mL of the applicable medium. A 30 μL sample of a culture of the microorganism was added to the various medium solutions.[13] After two days the cultures of *Bacillus subtilis* ATCC 9372, *Saccharomyces cerevisiae* ATCC 7754, *Candida utilis* ATCC 9226, *Brevibacterium ammoniagenes* ATCC 6872, *Enterobacter aerogenes* ATCC 13048, *Staphylococcus aureus* ATCC 12598, *Streptococcus mutans* ATCC 25175, *Propionibacterium acnes* ATCC 11827,

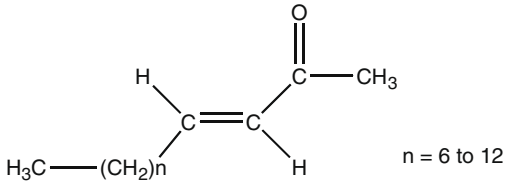

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Figure 1. The long-chain (*E*)-3-alken-2-ones assayed for antimicrobial activity.

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Table 1
Minimum inhibitory concentration (MIC) of (*E*)-3-Alken-2-ones (μg/mL)

Organism	Compound tested						
	C_{11} (**1**)	C_{12} (**2**)	C_{13} (**3**)	C_{14} (**4**)	C_{15} (**5**)	C_{16} (**6**)	C_{17} (**7**)
B. subtilis	100	100	100	>800	>800	>800	>800
B. ammoniagenes	200	100	100	>800	>800	>800	>800
S. aureus	200	100	50	>800	>800	>800	>800
S. mutans	100	50	25	25	200	400	800
P. acnes	50	25	12.5	12.5	6.25	3.13	3.13
P. vulgaris	50	50	800	>800	>800	>800	>800
C. utilis	50	400	>800	>800	>800	>800	>800
P. ovale	100	100	100	100	400	>800	>800
P. chrysogenum	100	100	800	800	>800	>800	>800
T. mentagrophytes	100	100	25	12.5	800	>800	>800

Pseudomonas aeruginosa ATCC 10145, *Eschericia coli* ATCC 9637 and *Proteus vulgaris* ATCC 133315 were examined for turbidity (OD at 660 nm). The fungi, *Pityrosporum ovale* ATCC 14521 was examined visually for growth at 3 days. *Penicillium chrysogenum* ATCC 10106 and *Trichophyton mentagrophytes* ATCC 18748, were examined visually for growth at 5 days. The MIC was determined as the lowest concentration for each compound that no growth was observed. The highest concentration used in these tests was 800 μg/mL.

The antimicrobial assays of the 3-alken-2-ones are listed in Table 1 for organisms they were active against. No activity was observed with the Gram-negative bacteria *P. aeruginosa*, *E. coli* and *E. aerogenes* or the yeast *S. cerevisiae*. Since the naturally occurring compound from black-tailed deer, (*E*)-3-tridecen-2-one (**3**), is secreted from the interdigital glands where it can be spread on the animal's skin, we included a number of pathogenic skin flora in the assay panel (*S. aureus*, *P. acnes*, *P. aeruginosa*, *P. ovale*, and *T. mentagrophytes*). For *P. acnes* the MIC decreased as the chain length increased: the C_{11} homologue (**1**) had a MIC of 50 μg/mL that went to 3.13 μg/mL for the C_{17} compound (**7**). The activity for *T. mentagrophytes* went from 100 to 12.5 μg/mL between the C_{11} to C_{14} compounds (**1**–**4**), but became inactive for longer chain homologues. For other microorganisms in the assay panel, antimicrobial activity of the C_{11} homologue (**1**) generally decreased as the carbon chain increased in length.

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11. *Synthesis of (E)-3-alken-2-ones:* To 5.0 g of piperidine, 5.0 g of glacial acetic acid and 250 mL of acetone at reflux in a 500 mL round-bottomed flask was added 0.10 mol of one of the following aldehydes (octanal, nonanal, decanal, undecanal, dodecanal, tridecanal, or tetradecanal) in 50 mL of acetone dropwise over 0.5 h. After addition, the solution was refluxed for an additional 5 h. The acetone was removed in vacuo and the residue was placed in 50 mL of diethyl ether. The ether solution was washed 2 × 50 mL with water, 2 × 50 mL of 1 M HCl and finally 2 × 50 mL saturated $NaHCO_3$. The ether solution was dried with anhydrous $CaCl_2$ and the ether was removed in vacuo. A sample of each compound was purified by preparative gas chromatography before antimicrobial analysis.
12. *(E)-3-Undecen-2-one* **1**; yield 64%. Liquid, 300 MHz ^{1}H NMR ($CDCl_3$) δ = 6.78 (dt, 1H, *J* = 15.9 Hz, 6.9 Hz), 6.03 (dt, 1H, *J* = 15.9 Hz, *J* = 1.48 Hz), 2.21 (s, 3H), 2.19 (quart, 2H), 1.44 (m, 2H), 1.26 (m, 8H) and 0.85 (t, 3H); 75 MHz; ^{13}C NMR ($CDCl_3$) δ = 198.74, 148.68, 131.29, 32.50, 31.75, 29.17, 29.08, 28.12, 26.82, 22.65, and 14.09; and EI-MS *m*/*z* = 97(7), 83(5), 81(6), 71(15), 69(18), 68(6), 55(50), 43(100), 41(40) and 39(19).
(E)-3-Dodecen-2-one **2**; yield 60%. Liquid, 300 MHz ^{1}H NMR ($CDCl_3$) δ = 6.73 (dt, 1H, *J* = 15.9 Hz, 6.9 Hz), 5.99 (dt, 1H, *J* = 15.9 Hz, *J* = 1.48 Hz), 2.18 (s, 3H), 2.15 (quart, 2H), 1.38 (m, 2H), 1.21 (m, 10H) and 0.81 (t, 3H); 75 MHz; ^{13}C NMR ($CDCl_3$) δ = 198.80, 148.72, 131.31, 32.53, 31.87, 29.39, 29.23, 28.13, 26.84, 22.69, and 14.13; and EI-MS *m*/*z* = 97(15), 83(11), 82(9), 81(8), 71(25), 69(18), 55(50), 43(100), 41(37) and 36(18).
(E)-3-Tridecen-2-one **3**; yield 66%. Liquid, 300 MHz ^{1}H NMR ($CDCl_3$) δ = 6.81 (dt, 1H, *J* = 15.9 Hz, 6.9 Hz), 6.06 (dt, 1H, *J* = 15.9 Hz, *J* = 1.48 Hz), 2.24 (s, 3H), 2.22 (quart, 2H), 1.46 (m, 2H), 1.26 (m, 12H) and 0.88 (t, 3H); 75 MHz; ^{13}C NMR ($CDCl_3$) δ = 198.80, 148.69, 131.24, 32.47, 31.85, 29.46, 29.37, 29.27, 29.17, 28.07, 26.79, 22.65, and 14.09; EI-MS *m*/*z* = 196 (M^+, 2), 181(8), 97(31), 96(14), 83(22), 81(20), 71(34), 69(31), 55(65), 43(100), 41(44); and FT-IR (neat) 2925, 2854, 1700, 1677, 1628, 1467, 1360, 1253, 1189 and 980 cm^{-1}.
(E)-3-Tetradecen-2-one **4**; yield 69%. Liquid, 300 MHz ^{1}H NMR ($CDCl_3$) δ = 6.79 (dt, 1H, *J* = 15.9 Hz, 6.9 Hz), 6.05 (dt, 1H, *J* = 15.9 Hz, *J* = 1.48 Hz), 2.23 (s, 3H), 2.21 (quart, 2H), 1.45 (m, 2H), 1.26 (m, 14H) and 0.87 (t, 3H); 75 MHz; ^{13}C NMR ($CDCl_3$) δ = 198.79, 148.71, 131.31, 32.53, 31.94, 29.62, 29.57, 29.43, 29.36, 29.23, 28.13, 26.84, 22.72, and 14.15; and EI-MS *m*/*z* = 97(21), 84(9), 83(8) 81(12), 71(30), 69(18), 55(50), 43(100), 41(50) and 39(18).
(E)-3-Pentadecen-2-one **5**; yield 72%. Liquid, 300 MHz ^{1}H-NMR ($CDCl_3$) δ = 6.80 (dt, 1H, *J* = 15.9 Hz, 6.9 Hz), 6.05 (dt, 1H, *J* = 15.9 Hz, *J* = 1.48 Hz), 2.23 (s, 3H), 2.21 (quart, 2H), 1.46 (m, 2H), 1.26 (m, 16H) and 0.88 (t, 3H); 75 MHz; ^{13}C NMR ($CDCl_3$) δ = 198.79, 148.71, 131.31, 32.53, 31.96, 29.66, 29.57, 29.44, 29.38, 29.33, 29.24, 28.14, 26.85, 22.73, and 14.16; and EI-MS *m*/*z* = 97(18), 84(10), 81(11), 71(28), 69(16), 68(10), 67(10), 55(46), 43(100), and 41(40).
(E)-3-Hexadecen-2-one **6**; yield 71%. Liquid, 300 MHz ^{1}H NMR ($CDCl_3$) δ = 6.80 (dt, 1H, *J* = 15.9 Hz, 6.9 Hz), 6.06 (dt, 1H, *J* = 15.9 Hz, *J* = 1.48 Hz), 2.24 (s, 3H), 2.22 (quart, 2H), 1.47 (m, 2H), 1.26 (m, 18H) and 0.88 (t, 3H); 75 MHz; ^{13}C NMR ($CDCl_3$) δ = 198.83, 148.74, 131.31, 32.54, 31.97, 29.71, 29.68, 29.58, 29.54, 29.44, 29.41, 29.25, 28.15, 26.85, 22.74, and 14.17; and EI-MS *m*/*z* = 97(18), 84 (8), 83(8), 82(8), 81(9), 71(30), 69(15), 55(42), 43(100), and 41(50).
(E)-3-Heptadecen-2-one **7**; yield 74%. Liquid, 300 MHz ^{1}H-NMR ($CDCl_3$) δ = 6.80 (dt, 1H, *J* = 15.9 Hz, 6.9 Hz), 6.07 (dt, 1H, *J* = 15.9 Hz, *J* = 1.48 Hz), 2.24 (s, 3H), 2.22 (quart, 2H), 1.47 (m, 2H), 1.26 (m, 20H) and 0.88 (t, 3H);
75 MHz ^{13}C NMR ($CDCl_3$) δ = 198.83, 148.77, 131.34, 32.56, 32.00, 29.79, 29.73, 29.73, 29.69, 26.59, 29.49, 29.43, 29.27, 28.17, 26.87, 22.76, and 14.18;
75 MHz ^{13}C NMR ($CDCl_3$) δ = 198.83, 148.74, 131.32, 32.54, 31.97, 29.70, 29.58, 29.44, 29.41, 29.34, 29.25, 28.15, 26.87, 22.74, and 14.18; and EI-MS *m*/*z* = 252 (M^+, 3), 97(19), 84(8), 83(10), 81(11), 71(28), 69(14), 55(39), 43(100), and 41(50).
13. The bacterial culture media except for *S. mutans* was 0.8% nutrient broth (BBL), 0.5% yeast extract (Difco) and 0.1% glucose (NYG broth). *S. mutans* was cultured in 3.7% brain heart infusion broth (Difco). All fungi, except *P. ovale* and *T. mentagrophytes* were cultured in a 2.5% malt extract broth (BBL). *P. ovale* was cultured in 1% bactopeptone (Difco), 0.5% yeast extract, 1% glucose and 0.1% corn oil. For *T. mentagrophytes* the culture media was 1% bactopeptone and 4% glucose. Freeze dried samples were prepared for testing as follows. *B. subtilis*, *S. cerevisiae*, *C. utilis*, and *P. ovale*, were shake-cultured for two days at 30 °C. *P. chrysogenum* and *T. mentagrophytes* were shake-cultured for 5 days at 30 °C. *B. ammoniagenes* and *E. aerogenes* were stationarily cultured at 30 °C. *S. aureus*, *S. mutans*, *P. acnes*, *P. aeruginosa*, *E. coli* and *P. vulgaris* were stationarily cultured at 37 °C.