Preparation of Long-Chain β-Enaminones and β-Diketones from Long-Chain 3,5-Disubstituted Isoxazole Compounds

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ABSTRACT: A series of long-chain compounds containing the β-enaminone functionality were prepared in yields ranging from 71 to 88% from their corresponding long-chain 3,5-disubstituted isoxazole precursors utilizing a Raney nickel-catalyzed reductive ring-opening procedure. These newly prepared multifunctional compounds were subsequently hydrolyzed under mild acidic conditions (pH 4–5) to give their corresponding long-chain β-diketones in yields ranging from 79 to 98%. Both the β-enaminone and β-diketone functionalized compounds were characterized by NMR, IR spectroscopy, GC–MS, and m.p. The mass spectra for these two classes of compounds, derived by utilizing electron impact ionization, gave distinctive McLafferty rearrangement fragmentation ions that clearly established the newly introduced functionality to reside at the C-2 and C-4 positions of the lipid's alkyl chain. ^{1}H NMR spectra of the pure β-diketone compounds were complex owing to the keto enol tautomerism displayed by the β-diketone moiety. In solution the β-diketone compounds were shown to exist mainly in the enolic tautomeric form. Long-chain β-diketone compounds are known to be relatively common constituents of some plant waxes, and the overall procedure starting from soybean methyl esters provides a complementary approach to prepare these types of compounds.

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KEY WORDS: 3,5-Disubstituted long-chain isoxazoles, β-diketones, β-enaminones, hydrolysis, mass spectrometry, nuclear magnetic resonance, plant waxes, Raney nickel, reduction, ring-opening.

The development of new approaches to introduce functionality into soybean oil and its fatty derivatives so as to derive novel oleochemicals with unique chemical and physical properties is of interest to many researchers and is essential in broadening the type of compounds and uses obtainable from vegetable oils (1). To meet these challenges, we recently reported a one-pot reaction sequence that provided long-chain compounds possessing an isoxazole ring (five-membered ring system containing nitrogen and oxygen atoms) in moderate to good yields (2). This was accomplished by condensing the ester moiety of FA esters with a lithiated imine anion [*N*-(isopropylidene)isopropylamine] to give a keto enamine that subsequently reacted with hydroxylamine hydrochloride to provide the isoxazole ring after dehydration. This approach allowed readily available FA esters to be utilized and incorporated into the construction of the isoxazole ring system. The isoxazole ring, an interesting moiety in its own right because of its known biological activities (3,4), makes these newly reported long-chain isoxazole compounds potentially interesting from this standpoint. The isoxazole ring also serves as a versatile synthetic intermediate that can undergo a variety of chemical transformations useful to construct many types of interesting molecules (5). The isoxazole ring's weak N–O bond (approximately 52 kcal/mol) is readily opened under mild conditions to give β-enaminones (6–9). The β-enaminone functionality has found widespread use in synthesis (10) and also has been shown to display interesting pharmacological properties (11,12).

Simple acidic hydrolysis of β-enaminones under mild reaction conditions gives their corresponding β-diketone compounds (7,13). Although the β-diketone moiety is well known, only more recently has their identity been reported as constituents of plant waxes. Long-chain β-diketones have been reported as wax components in several cereal species (14) including wheat, barley, oats, and rye, and they are the major wax component in species such as *Eucalyptus* (14), *Festuca* (14), *Agropyron* (14), and *Vanilla* bean (15).

As can be envisioned, long-chain isoxazole compounds represent attractive starting materials from which to obtain other interesting functionalized compounds. In this article, we report the conversion of several long-chain isoxazole compounds into their corresponding long-chain β-enaminones. This transformation is conveniently carried out in good yields (71–88%) using a Raney nickel-mediated reductive ring-opening methodology. The newly prepared long-chain β-enaminones were subsequently hydrolyzed in acidic (pH 4–5) media to convert them into their corresponding long-chain β-diketone compounds in yields ranging from 79 to 98%. The straightforward transformations of the long-chain isoxazole compounds reported herein demonstrate the utility of the isoxazole ring in fat and oil chemistry and its potential as a starting material to prepare other types of interesting functionalized long-chain compounds.

EXPERIMENTAL PROCEDURES

Materials. All long-chain isoxazole compounds were prepared and purified before use as previously reported (2). Chemicals purchased from Aldrich Chemical Co. (Milwaukee, WI) were used without further purification unless otherwise noted. HPLC-grade ethyl acetate, ethyl ether, ethanol,

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methanol, methylene chloride, chloroform, and hexane were obtained from Fisher Scientific Co. (Fairlawn, NJ). Concentrated HCl was obtained from Fisher Scientific. The Raney 2800 nickel catalyst (Aldrich Chemical Co.) was carefully washed with water 20–30 times by stirring and decanting the water. The washed catalyst was stored at −20°C under methanol and used as needed.

NMR. ^{1}H NMR and ^{13}C NMR spectra were recorded using a Bruker ARX 400 spectrometer with a 5-mm dual proton/carbon probe (400.13 MHz ^{1}H/100.61 MHz ^{13}C) using $\mathrm{CDCl_3}$ as solvent.

FTIR. FTIR spectra were obtained using a PerkinElmer Spectrum RX FT-IR spectrophotometer. Samples were analyzed either as a film on NaCl plates (liquids) or in a KBr matrix (solids).

Melting points. Melting points were determined on a Fisher-Johns m.p. apparatus and are uncorrected.

GC. GC was performed using a Hewlett-Packard 5890 Series II gas chromatograph, equipped with an FID and an autosampler/injector. Analyses were conducted on an HP-5MS capillary column, 30 m × 0.25 mm i.d. (Hewlett-Packard, Palo Alto, CA). Column flow was 1.0 mL/min helium at a head pressure of 15 psi (776 torr); split ratio of 75:1; oven temperature 100°C for 2 min, then programmed to 210°C at 20°C/min, then to 250°C at 10°C/min and hold 20 min at 250°C; injector and detector temperatures were set at 280°C.

GC–MS. GC–MS analyses were conducted using a Hewlett-Packard 5890 Series II Plus GC [column: HP-5MS column (30 m × 0.25 mm i.d.; Hewlett-Packard Co.] coupled with a Hewlett-Packard 5989B mass spectrometer using a mass range of 50–550 amu. Electron-impact (EI) ionization was performed at 70 eV, and positive chemical ionization (CI) used methane as reagent gas. GC conditions: helium head pressure 3 psi (155 Torr); injector temperature set at 250°C; transfer line temperature set at 280°C; the oven temperature program was identical to that described in the GC section.

TLC, column chromatography, and recrystallization. Analytical TLC was carried out using silica gel 60F254 (250 mm) purchased from Alltech Associates Inc. (Deerfield, IL). Conventional column chromatography was carried out using silica gel 22 (22–200 mesh) purchased from the Aldrich Chemical Co. Chromatographic fractions were collected in test tubes, and the fractions subsequently analyzed by TLC or GC. The eluent used for both analytical and preparative chromatography was 5:95 methanol/chloroform. Visualization was accomplished using iodine vapor and/or UV light (254 nm). Analytical samples of solid products were obtained by recrystallization from a minimal amount of ethanol.

*Representative procedure used for the Raney nickel reduction of long-chain isoxazoles, **1**, to β-enaminones, **2** (7).* To a solution of 5-heptadecyl-3-methylisoxazole **1b** (324 mg, 1.01 mmol) in ethanol (17 mL) was added a spatula tip of Raney 2800 nickel (*ca.* 10–20 mg). The reaction vessel was sealed, and the reaction atmosphere was replaced with hydrogen gas by repeated evacuation and flushing with hydrogen (10 times); a balloon filled with $\mathrm{H_2}$ was used to maintain the reaction flask's $\mathrm{H_2}$ atmosphere. The mixture was placed in a water bath at 30°C and stirred vigorously using a magnetic stir bar. Reaction progress was monitored by removing an aliquot and analyzing it by TLC. After 21.5 h the reaction was deemed complete by TLC, the catalyst was removed by vacuum-filtering the reaction mixture through a medium glass frit, the frit was washed with additional ethanol (20 mL), and the combined ethanol washings were concentrated *in vacuo* to obtain the crude β-enaminone **2b** as an off-white solid. Recrystallization from warm *n*-hexane gave 232 mg (71.1%), m.p.: 75.7–77.0°C.

^{1}H NMR of 2-aminoheneicos-2-en-4-one (**2b**): δ 5.01 (*s*, 1H, $-(\mathrm{NH_2})\mathrm{C{=}C}\mathit{H}\mathrm{{-}C({=}O){-}}$), 4.95–4.80 (*br s*, 2H, $-\mathrm{N}\mathit{H}_2$), 2.24 (*t*, 2H, J = 7.7 Hz, $-\mathrm{C({=}O)C}\mathit{H}_2-$), 1.90 (*s*, 3H, $\mathrm{C}\mathit{H}_3\mathrm{{-}C({-}NH_2){=}}$), 1.60–1.50 (*m*, 2H,$-\mathrm{(O{=})C{-}CH_2{-}C}\mathit{H}_2-$), 1.35–1.15 (*m,* 28H, alkyl chain hydrogen), 0.86 ppm (*t*, 3H, J = 6.9 Hz, $-\mathrm{CH_2C}\mathit{H}_3$). 13C NMR: δ 200.2 ($\mathit{C}$=O), 160.7 ($-(\mathrm{NH_2})\mathit{C}\mathrm{{=}CH}-$), 95.5 ($-(\mathrm{NH_2})\mathrm{C{=}}\mathit{C}\mathrm{H}-$), 42.6 ($-\mathrm{(O{=})C{-}}\mathit{C}\mathrm{H_2}-$), 32.0, 29.8, 29.7, 29.6, 29.6, 29.4, 26.0, 22.8, 22.5 ($\mathrm{{=}C(NH_2){-}}\mathit{C}\mathrm{H_3}$), 14.2 ppm ($-\mathrm{CH_2}\mathit{C}\mathrm{H_3}$). IR (KBr) $\mathrm{cm^{-1}}$: 3338, 3196, 2955, 2920, 2851, 1620, 1604, 1525, 1467, 1147, 892, 724. GC retention time 23.0 min. MS (EI): *m/z* 323 (M^+, 3%), 112 ($\mathrm{C_6H_{10}NO^+}$, 9%), 99 ($\mathrm{C_5H_9NO^+}$, 100%), 84 ($\mathrm{C_4H_6NO^+}$, 70%). MS (CI): *m/z* 324 ($\mathrm{MH^+}$, 100%), 352 ($\mathrm{M^+ + C_2H_5}$, 19%), 364 ($\mathrm{M^+ + C_3H_5}$, 4%).

^{1}H NMR of 2-aminononadec-2-en-4-one (**2a**): δ 5.01 (*s*, 1H, $-(\mathrm{NH_2})\mathrm{C{=}C}\mathit{H}\mathrm{{-}C({=}O){-}}$), 4.95–4.80 (*br s*, 2H, $-\mathrm{N}\mathit{H}_2$), 2.24 (*t*, 2H, J = 7.7 Hz, $-\mathrm{C({=}O)C}\mathit{H}_2-$), 1.90 (*s*, 3H, $\mathrm{C}\mathit{H}_3\mathrm{{-}C({-}NH_2){=}}$), 1.65–1.50 (*m*, 2H, $-\mathrm{(O{=})C{-}CH_2{-}C}\mathit{H}_2-$), 1.35–1.15 (*m*, 24H, alkyl chain hydrogen), 0.86 ppm (*t*, 3H, J = 6.9 Hz,$-\mathrm{CH_2C}\mathit{H}_3$). ^{13}C NMR: δ 200.1 ($\mathit{C}$=O), 160.7 ($-(\mathrm{NH_2})\mathit{C}\mathrm{{=}CH}-$), 95.5 ($-(\mathrm{NH_2})\mathrm{C{=}}\mathit{C}\mathrm{H}-$), 42.6 ($-\mathrm{(O{=})C{-}}\mathit{C}\mathrm{H_2}-$), 32.0, 29.8, 29.7, 29.6, 29.6, 29.4, 26.0, 22.8, 22.5 ($\mathrm{{=}C(NH_2){-}}\mathit{C}\mathrm{H_3}$), 14.2 ppm $-\mathrm{CH_2}\mathit{C}\mathrm{H_3}$). IR (KBr) $\mathrm{cm^{-1}}$: 3336, 3191, 2955, 2920, 2851, 1621, 1603, 1525, 1466, 1414, 1147, 892, 724. MS (EI): *m/z* 295 ($\mathrm{M^+}$, 7 %), 112 ($\mathrm{C_6H_{10}NO^+}$, 11%), 99 ($\mathrm{C_5H_9NO^+}$, 100%), 84 ($\mathrm{C_4H_6NO^+}$, 87%). MS (CI): *m/z* 296 ($\mathrm{MH^+}$, 100%), 324 ($\mathrm{M^+ + C_2H_5}$, 20%), 336 ($\mathrm{M^+ + C_3H_5}$, 4%). m.p.: 69.5–70.0°C.

^{1}H NMR of 2-aminoheneicos-2,12-dien-4-one (**2c**): δ 5.32 (*m*, 2H, alkyl chain $-\mathit{H}\mathrm{C{=}C}\mathit{H}-$), 5.01 (*s*, 1H, $-(\mathrm{NH_2})\mathrm{C{=}C}\mathit{H}\mathrm{{-}C({=}O){-}}$), 5.00–4.80 (*br s*, 2H, $-\mathrm{N}\mathit{H}_2$), 2.24 (*t*, 2H, J = 7.7 Hz, $-\mathrm{C({=}O)C}\mathit{H}_2-$), 2.05–1.95 (*m*, 4H, $-\mathrm{C}\mathit{H}_2\mathrm{{-}CH{=}CH{-}C}\mathit{H}_2-$), 1.89 (*s*, 3H, $\mathrm{C}\mathit{H}_3\mathrm{{-}C({-}NH_2){=}}$), 1.65–1.50 (*m*, 2H, $-\mathrm{(O{=})C{-}CH_2{-}C}\mathit{H}_2-$), 1.40–1.15 (*m*, 18H, alkyl chain hydrogen), 0.86 ppm (*t*, 3H, J = 6.9 Hz, $-\mathrm{CH_2C}\mathit{H}_3$). ^{13}C NMR: δ 200.1 ($\mathit{C}$=O), 160.7 ($-(\mathrm{NH_2})\mathit{C}\mathrm{{=}CH}-$), 129.9 (alkyl chain olefinic carbon atom), 129.9 (alkyl chain olefinic carbon atom), 95.4 ($-(\mathrm{NH_2})\mathrm{C{=}}\mathit{C}\mathrm{H}-$), 42.5 ($-\mathrm{(O{=})C{-}}\mathit{C}\mathrm{H_2}-$), 32.0, 29.8, 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 27.3, 26.0, 22.8, 22.4 ($\mathrm{{=}C(NH_2){-}}\mathit{C}\mathrm{H_3}$), 14.2 ppm ($-\mathrm{CH_2}\mathit{C}\mathrm{H_3}$). IR (NaCl) $\mathrm{cm^{-1}}$: 3348, 3176, 3004, 2925, 2854, 1620, 1530, 1464, 1284, 757. MS (EI): *m/z* 321 ($\mathrm{M^+}$, 7%), 112 ($\mathrm{C_6H_{10}NO^+}$, 18%), 99 ($\mathrm{C_5H_9NO^+}$, 100%), 84 ($\mathrm{C_4H_6NO^+}$, 96%). MS (CI): *m/z* 322 ($\mathrm{MH^+}$, 100%), 350 ($\mathrm{M^+ + C_2H_5}$, 23%), 362 ($\mathrm{M^+ + C_3H_5}$, 5%).

^{1}H NMR of 2-aminoheneicos-2,12,15-trien-4-one (**2d**): δ 5.45–5.25 (*m*, 4H, alkyl chain $-\mathit{H}\mathrm{C{=}C}\mathit{H}-$), 5.01

(*s*, 1H, –(NH$_2$)C=C*H*-C(=O)–), 5.00–4.80 (*br s*, 2H, –N*H*$_2$), 2.75 (*t*, 2H, *J* = 6.6 Hz, –HC=CH–C*H*$_2$–CH=CH–), 2.24 (*t*, 2H, *J* = 7.6 Hz, –C(=O)C*H*$_2$–), 2.10–1.95 (*m*, 4H, –C*H*$_2$–CH=CH–CH$_2$–CH=CH–C*H*$_2$), 1.90 (*s*, 3H, C*H*$_3$–C–(–NH$_2$)=), 1.65–1.50 (*m*, 2H, –(O=)C–CH$_2$–C*H*$_2$–), 1.40–1.20 (*m*, 14H, alkyl chain hydrogen), 0.87 ppm (*t*, 3H, *J* = 6.9 Hz, –CH$_2$C*H*$_3$). ^{13}C NMR: δ 200.1 (*C*=O), 160.7 (–(NH$_2$)*C*=CH–), 130.3 (alkyl chain olefinic carbon atom), 130.2 (alkyl chain olefinic carbon atom), 128.0 (alkyl chain olefinic carbon atom), 95.4 (–(NH$_2$)C=*C*H–), 42.5 (–(O=)C–*C*H$_2$–), 31.6, 29.7, 29.6, 29.5, 29.4, 29.3, 27.3, 27.3, 26.0, 25.7, 22.7, 22.5 (=C(NH$_2$)–*C*H$_3$), 14.1 ppm (–CH$_2$*C*H$_3$). IR (NaCl) cm^{-1}: 3350, 3176, 3009, 2927, 2855, 1621, 1531, 1456, 1415, 1284, 758. MS (EI): *m/z* 319 (M$^+$, 11%), 112 ($C_6H_{10}NO^+$, 17%), 99 ($C_5H_9NO^+$, 72%), 84 ($C_4H_6NO^+$, 100%). MS (CI): *m/z* 320 (MH$^+$, 100%), 348 (M$^+$ + C_2H_5, 21%), 360 (M$^+$ + C_3H_5, 5%).

Representative procedure used for the conversion of β-enaminones, ***2****, into long-chain β-diketones,* ***3*** *(7).* To a stirred solution of 2-aminononadec-2-en-4-one **2a** (212.2 mg, 0.719 mmol) in ethanol (8.0 mL), concentrated HCl was added dropwise (approximately 20 drops) to adjust the pH between 4 and 5. The solution was then stirred magnetically at 30°C and the progress of the reaction was monitored by TLC. After 24 h the reaction was judged complete by TLC, and the reaction mixture was neutralized with a saturated K_2CO_3 solution, extracted with ethyl ether (3 × 25 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to obtain **3a** as a white solid. Recrystallization from methanol gave 208.6 mg (97.9%), m.p.: 46–48°C.

^{1}H NMR nonadecane-2,4-dione (**3a**): Enolic tautomer, δ 15.5 (*s*, C-2 or C-4 enolic hydroxyl H), 5.48 (*s,* C-3 vinyl H), 2.25 (*t*, C-5 H, *J* = 7.7 Hz, –HC=C(–OH)–C*H*$_2$–), 2.04 (*s*, C-1 H), 1.65–1.50 (*m*, alkyl chain –C*H*$_2$–), 1.40–1.15 (*m*, alkyl chain H), 0.87 ppm (*t*, *J* = 6.9 Hz, C-19 H, –CH$_2$C*H*$_3$). Ketonic tautomer, δ 3.56 (*s*, C-3 H, –(O=)C–C*H*$_2$–C(=O)–), 2.48 (*t*, *J* = 7.4 Hz, C-5 H, –(O=)CC*H*$_2$CH$_2$–), 2.23 ppm (*s*, C-1 H, C*H*$_3$-C(=O)–). ^{13}C NMR: Mixture of enol and keto tautomers, δ 204.2 (C-2 or C-4, keto), 202.3 (C-2 or C-4, keto), 194.4 (C-2 or C-4, enol), 191.6 (C-2 or C-4, enol), 99.8 (C-3 –*C*H–, enol), 58.0 (C-3 –*C*H$_2$–, keto), 43.9 (C-6 –*C*H$_2$–), 38.3, 32.0, 29.8, 29.7, 29.7, 29.5, 29.4, 29.3, 29.1, 25.8, 25.1, 23.5, 22.8, 14.2 ppm (C-19 –CH$_2$*C*H$_3$). IR (KBr) cm^{-1}: 3425, 2956, 2917, 2850, 1648 (br), 1602, 1469, 1413, 788, 720. GC–MS (EI): *m/z* 296 (M$^+$, 1%), 278 (M$^+$ – H_2O, 2%), 113 ($C_6H_9O_2$, 14%), 100 ($C_5H_8O_2^+$, 100%), 85 ($C_4H_5O_2^+$, 45%), 57 ($C_3H_5O^+$ and/or C_4H_9, 11%), 43 ($C_2H_3O^+$, 49%).

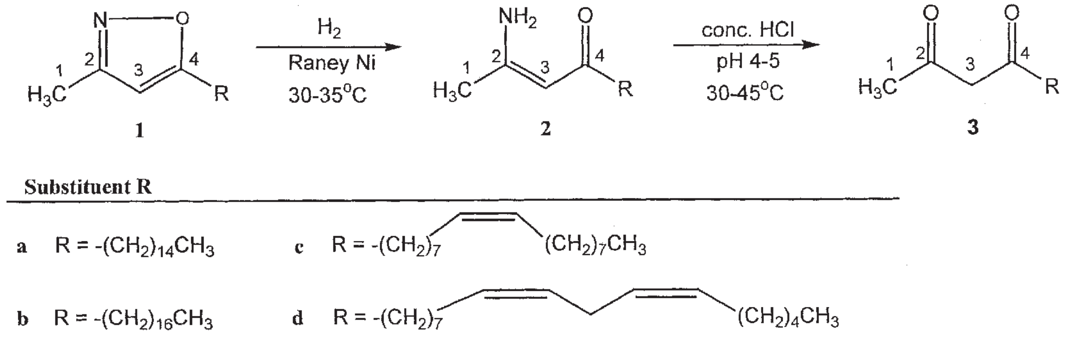
^{1}H NMR heneicosane-2,4-dione (**3b**): Enolic tautomer, δ 15.5 (*s*, C-2 or C-4 enolic hydroxyl H), 5.48 (*s,* C-3 vinyl H), 2.25 (*t*, C-5 H, *J* = 7.7 Hz, –HC=C(–OH)–C*H*$_2$–), 2.04 (*s*, C-1 H), 1.65–1.50 (*m*, C-6 –C*H*$_2$–), 1.3–1.15 (*m*, alkyl chain H), 0.87 ppm (*t*, *J* = 6.9 Hz, C-21 H, –CH$_2$C*H*$_3$). Ketonic tautomer, δ 3.56 (*s*, C-3 H, –(O=)C–C*H*$_2$–C(=O)–), 2.48 (*t*, *J* = 7.4 Hz, C-5 H, –(O=)CC*H*$_2$CH$_2$–), 2.23 ppm (*s*, C-1 H, C*H*$_3$–C(=O)–). ^{13}C NMR: Mixture of enol and keto tautomers, δ 204.4 (C-2 or C-4, keto), 202.2 (C-2 or C-4, keto), 194.4 (C-2 or C-4, enol), 191.6 (C-2 or C-4, enol), 99.8 (C-3 –*C*H–, enol), 58.0 (C-3 –*C*H$_2$–, keto), 43.9 (C-6 –*C*H$_2$–), 38.3, 32.0, 30.1, 29.7, 29.7, 29.6, 29.5, 29.4, 29.3, 29.1, 25.8, 25.1, 23.5, 22.8, 14.2 ppm (C-21 –CH$_2$*C*H$_3$). IR (KBr) cm^{-1}: 3425, 2955, 2917, 2850, 1700, 1648, (br), 1599, 1470, 1413, 1379, 905, 788, 775, 720. GC–MS (EI): *m/z* 324 (M$^+$, 1%), 306 (M$^+$ – H_2O, 2%), 113 ($C_6H_9O_2$, 13%), 100 ($C_5H_8O_2^+$, 100%), 85 ($C_4H_5O_2^+$, 44%), 57 ($C_3H_5O^+$ and/or C_4H_9, 12%), 43 ($C_2H_3O^+$, 44%).

^{1}H NMR heneicos-12-ene-2,4-dione (**3c**): Enolic tautomer, δ 15.5 (*s*, C-2 or C-4 enolic hydroxyl H), 5.47 (*s*, C-3 vinyl H), 5.40–5.25 (*m*, C-12 C-13 vinyl H), 2.25 (*t*, C-5 H, *J* = 7.6 Hz, –HC=C(–OH)–C*H*$_2$–), 2.03 (*s*, C-1 H), 2.10–1.90 (*m*, C-11 C-14 allylic H), 1.65–1.50 (*m*, C-6 –C*H*$_2$–), 1.40–1.15 (*m*, alkyl chain H), 0.86 ppm (*t*, *J* = 6.9 Hz, C-21 H, –CH$_2$C*H*$_3$). Ketonic tautomer, δ 3.55 (*s*, C-3 H, –(O=)C–C*H*$_2$–C(=O)–), 2.48 (*t*, *J* = 7.4 Hz, C-5 H, –(O=)CC*H*$_2$CH$_2$–), 2.22 ppm (*s*, C-1 H, C*H*$_3$–C(=O–). ^{13}C NMR: Mixture of enol and keto tautomers, δ 204.3 (C-2 or C-4, keto), 202.2 (C-2 or C-4, keto), 194.3 (C-2 or C-4, enol), 191.5 (C-2 or C-4, enol), 130.1 (C-12 or C-13), 129.8 (C-12 or C-13), 99.8 (C-3 –*C*H–, enol), 58.0 (C-3 –*C*H$_2$–, keto), 43.9 (C-6 –*C*H$_2$–), 38.3, 32.0, 29.8, 29.7, 29.6, 29.4, 29.3, 29.3, 29.2, 29.1, 27.3, 27.2, 25.8, 25.1, 23.4, 22.8, 14.2 ppm (C-21 –CH$_2$*C*H$_3$). IR (NaCl) cm^{-1}: 3420, 3004, 2926, 2855, 1730, 1712, 1614 (br), 1464, 1363, 1239, 953, 775, 725. GC–MS (EI): *m/z* 322 (M$^+$, 2%), 304 (M$^+$– H_2O, 4%), 113 ($C_6H_9O_2$, 33%), 100 ($C_5H_8O_2^+$, 93%), 85 ($C_4H_5O_2^+$, 100%), 57 ($C_3H_5O^+$ and/or C_4H_9 15%), 43 ($C_2H_3O^+$, 86%).

^{1}H NMR heneicos-12,15-diene-2,4-dione (**3d**): Enolic tautomer, δ 15.5 (*s*, C-2 or C-4 enolic hydroxyl H), 5.47 (*s*, C-3 vinyl H), 5.45–5.25 (*m*, C-12 C-13 C-15 C-16 vinyl H), 2.75 (*t*, C-14, *J* = 6.5 Hz, –CH=CHC*H*$_2$CH=CH–), 2.24 (*t*, C-5 H, *J* = 7.6 Hz, –HC=C(–OH)–C*H*$_2$–), 2.03 (*s*, C-1 H), 2.10–1.95 (*m*, C-11 C-17 allylic H), 1.65–1.50 (*m*, C-6 –C*H*$_2$–), 1.40–1.20 (*m*, alkyl chain H), 0.87 ppm (*t*, *J* = 6.9 Hz, C-21 H, –CH$_2$C*H*$_3$). Ketonic tautomer, δ 3.55 (*s*, C-3 H, –(O=)C–C*H*$_2$–C(=O)–), 2.48 (*t*, *J* = 7.4 Hz, C-5 H, –(O=)CC*H*$_2$CH$_2$–), 2.22 ppm (*s*, C-1 H, C*H*$_3$–C(=O)–). ^{13}C NMR: Mixture of enol and keto tautomers, δ 204.3 (C-2 or C-4, keto), 202.2 (C-2 or C-4, keto), 194.3 (C-2 or C-4 enol), 191.5 (C-2 or C-4 enol), 130.3 (alkyl chain olefinic carbon atom), 130.1 (alkyl chain olefinic carbon atom), 128.1 (alkyl chain olefinic carbon atom), 128.0 (alkyl chain olefinic carbon atom), 99.8 (C-3 enol), 58.0 (C-3 keto), 43.9 (C-6 –*C*H$_2$–), 38.3, 31.6, 29.7, 29.4, 29.3, 29.3, 29.2, 27.3, 27.3, 25.8, 25.7, 25.1, 23.4, 22.6, 14.1 (C-21 –*C*H$_3$) ppm. IR (NaCl) cm^{-1}: 3424, 3010, 2928, 2855, 1732, 1705, 1613, 1464, 1363, 1241, 954, 775, 759, 724. GC–MS (EI): *m/z* 320 (M$^+$, 2%), 302 (M$^+$ – H_2O, 10%), 113 ($C_6H_9O_2$, 21%), 100 ($C_5H_8O_2^+$, 35%), 85 ($C_4H_5O_2^+$, 100%), 57 ($C_3H_5O^+$ and/or C_4H_9, 10%), 43 ($C_2H_3O^+$, 90%).

RESULTS AND DISCUSSION

Scheme 1 outlines the general reaction sequence utilized to convert long-chain isoxazole compounds, **1**, into their corresponding β-enaminones, **2**, and subsequently β-diketones, **3**. Various methods based on Raney nickel (6,7), samarium



SCHEME 1

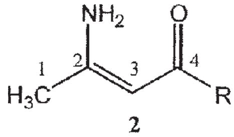
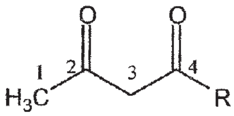
diiodide (8), and molybdenum hexacarbonyl (9) have been used to convert the isoxazole ring into β-enaminones *via* cleavage of the isoxazole's weak N–O bond. Initially, we tried using the procedure based on $Mo(CO)_6$ (9) to open the isoxazole ring of these compounds, but our initial attempts proved unsuccessful. Therefore, this approach was abandoned in favor of the procedures based upon Raney nickel (6,7).

Accordingly, stirring an ethanol solution containing isoxazole **1** with a catalytic amount of Raney nickel under a hydrogen atmosphere cleanly converted the isoxazole ring into its corresponding long-chain β-enaminone, **2**, under mild reaction conditions. Table 1 (entries **2a**–**d**) summarizes the reaction conditions used to obtain the long-chain β-enaminones. As can be seen, the reactions were typically completed within 21–30 h at 30–35°C and gave good yields of the purified products. The two β-enaminones containing long saturated alkyl chains (entries **2a** and **2b**) were obtained as solids, whereas the mono- and diunsaturated β-enaminones (**2c** and **2d**) were isolated as oils.

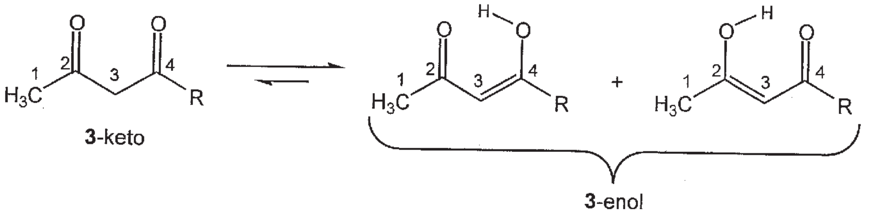
In conjunction with literature data reported for compounds containing the β-enaminone structure (10–12), the ^{1}H and ^{13}C NMR data (reported in the Experimental Procedures section) of the newly prepared β-enaminone compounds, **2**, clearly possessed the appropriate signals needed to identify these compounds unambiguously. By ^{1}H NMR, the lone C-3 vinyl hydrogen for all the β-enaminone compounds appeared as a singlet at 5.01 ppm, with an integral area equivalent to one hydrogen. In the case of the two unsaturated β-enaminones **2c** and **2d**, additional vinyl hydrogen signals corresponding to the unsaturated sites contained on the alkyl chain were also observed as a multiplet at 5.32 ppm and 5.25–5.45 ppm, respectively. A singlet observed at 1.90 ppm in these spectra corresponds to the C-1 methyl group. The ^{13}C NMR results also supported the β-enaminone structure by the observation of signals in the region of 200 (C-4 carbonyl carbon atom), 160 (C-2 vinyl carbon atom), and 95 ppm (C-3 vinyl carbon atom).

The EI ionization mass spectra of β-enaminone compounds **2a–d** showed low-intensity molecular ions at *m/z* 295, 323, 321, and 319, respectively. Additionally, three ions at *m/z* 84, 99, and 112 were readily observed in all spectra of these compounds. The *m/z* 84 ion, corresponding to a C_4H_6NO fragment, results from cleavage between C-4 and C-5 α to the C-4 carbonyl atom. This type of α-cleavage is commonly observed in the mass spectra of carbonyl-contain-

TABLE 1
Reaction Conditions, Yields, and m.p. of Long-Chain β-Enaminones (1) and β-Diketones (2)

Product^a		Reaction time (h)	Reaction temp. (°C)	Yield (%)^b	m.p. (°C)
 2	**2a**	23	30	72.3	69.5–70
	2b	21.5	30	71.1	75.5–77
	2c	25.5	30	87.7	Oil
	2d	30	35	83.3	Oil
 3	**3a**	28	45	97.9	46–48^c
	3b	23	40	90.0	54–55^c
	3c	20	30	79.0	Oil
	3d	24	30	82.0	Oil

^{a}See Scheme 1 for designation of R substituents.
^{b}Isolated yields.
^{c}**3a**, literature m.p.: 50.5°C (17); **3b**, literature m.p.: 58.0°C (17).



SCHEME 2

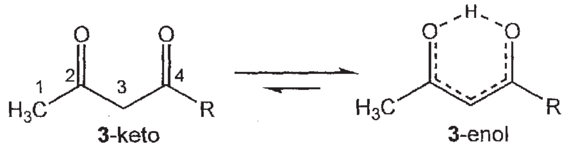
ing compounds. The *m/z* 99 C_5H_9NO ion is likely derived from McLafferty rearrangement, whereas the *m/z* 112 ion is presumably due to a cyclization-displacement reaction that results in the observed $C_6H_{10}NO$ fragment ion. This cyclization-displacement rearrangement reaction has been proposed to occur in other types of fatty derivatives (16). Interestingly, in contrast to the mass spectra of the starting long-chain isoxazole compounds, **1c** and **1d** (2), the mass spectra of β-enaminone compounds **2c** and **2d** did not provide distinctive fragmentation ions that allowed the location of the double bonds in the alkyl chain to be easily established.

The isolated long-chain β-enaminones **2** were subsequently dissolved in ethanol and hydrolyzed at pH 4–5 to give their corresponding β-diketones, **3**. Table 1 (entries **3a–d**) summarizes the reaction conditions and yields obtained for the long-chain β-diketones prepared. The reaction times needed to complete the hydrolysis typically ranged between 20 and 28 h at temperatures between 30 and 45°C. Reaction progress was readily monitored by TLC, and good yields of the purified products were obtained. As in the case of the β-enaminones, the two β-diketones containing long saturated alkyl chains (entries **3a** and **3b**) were isolated as solids, whereas the unsaturated β-diketones (**2c** and **2d**) were oils. Although the synthesis of compounds **3a**, **3b**, and **3c** have been reported in the literature, only limited physical data concerning these compounds have been reported (17).

From the ^1H and ^{13}C NMR spectra obtained for the isolated β-diketone compounds **3**, it was apparent that there were contributions from the various keto-enol tautomeric forms available to the β-diketone structure (Scheme 2). Signals in the ^1H NMR spectra (reported in the Experimental Procedures section) corresponding to both the enol and keto tautomeric forms were readily apparent, and the observed chemical shifts corresponding to both tautomeric forms were in agreement with reported literature data for similar short- and long-chain β-diketone compounds (14,15,18,19).

As can be seen in Table 2, the C-3 hydrogens for the keto tautomer of the β-diketone compounds had an approximate chemical shift of 3.55 ppm, whereas the C-3 hydrogen in the enol tautomers resided at approximately 5.47 ppm. Table 2 also summarizes the relative percentages of the keto and enol tautomers present, determined by taking the ratio of the integral areas corresponding to the keto and enol resonance signals in the ^1H NMR and statistically correcting for the number of C-3 hydrogens present in each tautomeric form. Additional evidence for the enolic form was provided by the distinctive chemical shift of the enolic hydroxyl hydrogen that appeared at 15.5 ppm in the β-diketones. As can be seen, in solution 81–85% of the β-diketone molecules exist in the enolic tautomeric form. The results of our study compare favorably with keto-enol equilibrium studies reported in the literature. For example, Bassetti and coworkers (20) reported that 2,4-pentanedione exists predominantly in the enol form (83.5%) in a $CDCl_3$ solution. They also showed the equilibrium to be solvent-dependent, and in DMSO the enolic form of 2,4-pentanedione was present in 55.7%. Similarly, Koshimura and coworkers (19) reported 2,4-pentanedione and 3,5-heptanedione to be 81.2 and 80.0% enolized, respec-

TABLE 2
^1H NMR Chemical Shifts (400 MHz) Observed for the C-3 Hydrogens Corresponding to the Keto and Enol Tautomeric Forms of β-Diketone 3 and Their Relative Percentages in $CDCl_3$

		C-3 Hydrogen chemical shifts (ppm)		Relative %[a]		Equilibrium constant
		$-CH_2-$ keto tautomer	$-CH=$ enol tautomer	Enol	Keto	log *K* = [enol]/[keto]
a	$R = -(CH_2)_{14}CH_3$	3.56	5.48	81.2	18.8	0.635
b	$R = -(CH_2)_{16}CH_3$	3.56	5.47	85.5	14.5	0.771
c	$R = -(CH_2)_7$  $(CH_2)_7CH_3$	3.55	5.47	85.2	14.8	0.760
d	$R = -(CH_2)_7$  $(CH_2)_4CH_3$	3.55	5.47	84.9	15.1	0.750

[a] Relative percentage determined by ^1H NMR. Measurements taken at 23 ± 2°C.

tively, although it was not clear what solvent was used in this study. They also reported equilibrium constants for 2,4-pentanedione and 3,5-heptanedione of 0.636 and 0.602, respectively. These equilibrium constants are similar to those reported in Table 2 for our compounds (0.635–0.760). Finally, Tulloch (18) reported pentacosane-8,10-dione to be 80% enolized in solution.

In the ^{13}C NMR spectra of the β-diketone compounds, distinctive chemical shifts corresponding to both the keto and enol tautomeric forms were apparent. For example, the C-2 and C-4 carbon atoms in the keto tautomeric form had chemical shifts of roughly 204 and 202 ppm, whereas the C-2 and C-4 carbon atoms in the enol form were at approximately 194 and 191 ppm, respectively. Again, this was consistent with literature data for similar β-diketone compounds (14,15, 18,19). Additionally, the C-3 carbon atom for both the keto and enol tautomeric forms were visible at approximately 58 and 99 ppm, respectively, for all the β-diketones. Beyond these assignments, accurate assignment of the remaining signals to one or the other tautomeric form was difficult due to the number of aliphatic alkyl chain carbon atoms and the similarity of their chemical shifts.

The EI ionization mass spectra of the β-diketone compounds **3a–d** all exhibited low-intensity molecular ions at *m/z* 296, 324, 322, and 320, respectively. Loss of water, presumably from the enol form, gave the corresponding $(M - 18)^+$ fragment ion (21). McLafferty rearrangement accounted for the large fragment ion at *m/z* 100 exhibited in all the mass spectra for β-diketones and clearly established the β-diketone position. Fragmentation ions at *m/z* 43 ($C_2H_3O^+$), and 85 ($C_4H_5O_2^+$) likely result from cleavage α to the carbonyl carbon atoms, whereas the ion at *m/z* 57 results from α-cleavage ($C_3H_5O^+$) and/or a C_4H_9 fragment.

The reductive ring opening of long-chain isoxazole compounds using Raney nickel represents a simple method to obtain long-chain β-enaminone compounds. Subsequent hydrolysis of the β-enaminone compounds gave their corresponding long-chain β-diketones, an interesting class of compounds commonly found in plant waxes. This overall methodology complements other available approaches used to prepare long-chain β-diketone compounds.

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REFERENCES

1. Biermann, U., W. Friedt, S. Lang, W. Lühs, G. Machmüller, J.O. Metzger, M. Rüsch gen. Klaas, H.J. Schäfer, and M.P. Schneider, New Syntheses with Oils and Fats as Renewable Raw Materials for the Chemical Industry, *Angew. Chem. Int. Ed. 39*:2206–2224 (2000).
2. Kenar, J.A., and A.R. Wetzel, Preparation of Fatty 3,5-Disubstituted Isoxazole Compounds from FA Esters, *J. Am. Oil Chem. Soc. 80*:711–716 (2003).
3. Pallet, K.E., S.M. Cramp, J.P. Little, P. Veerasekaran, A.J. Crudace, and A.E. Slater, Isoxaflutole: The Background to Its Discovery and the Basis of Its Herbicidal Properties, *Pest Manage. Sci. 57*:133–142 (2001).
4. Raffa, D., G. Daidone, B. Maggio, D. Schillaci, F. Plescia, and L. Torta, Synthesis and Antifungal Activity of New *N*-Isoxazolyl-2-iodobenzamides, *Farmaco 54*:90–94 (1999).
5. Grünanger, P., and P. Vita Finzi, Isoxazoles, in *The Chemistry of Heterocyclic Compounds*, edited by E.C. Taylor, Wiley Interscience, New York, 1991, Vol. 49, part I, pp. 1–416.
6. Casnati, G., A. Quilico, A. Ricca, and P. Vita Finzi, Some Synthetic Applications of the Reaction of Reductive Opening of the Isoxazole Ring, *Tetrahedron Lett.*:233–238 (1966).
7. Kashima, C., S. Tobe, N. Sugiyama, and M. Yamamoto, The Alkylation of 3,5-Dimethylisoxazole, *Bull. Chem. Soc. Jap. 46*:310–313 (1973).
8. Natale, N.R., Selective Reduction of Isoxazoles with Samarium Diiodide, *Tetrahedron Lett. 23*:5009–5012 (1982).
9. Nitta, M., and T. Kobayshi, Reductive Ring Opening of Isoxazoles with $Mo(CO)_6$ and Water, *J. Chem. Soc. Chem. Commun.*:877–888 (1982).
10. Greenhill, J.V., Enaminones, *Chem. Soc. Rev. 6*:277–294 (1977).
11. Fuentes, J.A., A. Maestro, A.M. Testera, and J.M. Báñez, Synthesis of Optically Active β′-Hydroxy-β-enaminoketones *via* Enzymatic Resolution of Carbinols Derived from 3,5-Disubstituted Isoxazoles, *Tetrahedron Asym. 11*:2565–2577 (2000).
12. Edafiogho, I.O., J.A. Moore, M.S. Alexander, and K.R. Scott, Nuclear Magnetic Resonance Studies of Anticonvulsant Enaminones, *J. Pharm. Sci. 83*:1155–1170 (1994).
13. Bianchi, G., and M. De Amici, Synthesis of Hentriacontane-14,16-dione, a β-Diketone found in Plant Waxes, *J. Chem. Soc. Chem. Commun.*:962–963 (1978).
14. Tulloch, A.P., Chemistry of Waxes of Higher Plants, in *Chemistry and Biochemistry of Natural Waxes*, edited by P.E. Kolattukkudy, Elsevier, Amsterdam, 1976, pp. 235–287.
15. Ramaroson-Raonizafinimanana, B., E.M. Gaydou, and I. Bombarda, Long-Chain Aliphatic β-Diketones from Epicuticular Wax of *Vanilla* Bean Species. Synthesis of Nervonoylacetone, *J. Agric. Food Chem. 48*:4739–4743 (2000).
16. Spitzer, V., Structure Analysis of Fatty Acids by Gas Chromatography–Low Resolution Electron Impact Mass Spectrometry of Their 4,4-Dimethyloxazoline Derivatives—A Review, *Prog. Lipid Res. 35*:387–408 (1997).
17. Douglas, D.E., and L.E. Francis, The Preparation, Gas–Liquid Chromatography, and Some Physical and Chemical Properties of Certain Higher Aliphatic 2,4-Diketones—A New Class of Lipids, *Lipids 12*:635–640 (1977).
18. Tulloch, A.P., Carbon-13 NMR Spectra of β-Diketones from Wax of the Gramineae, *Phytochemistry 24*:131–137 (1985).
19. Koshimura, H., J. Saito, and T. Okubo, Effect of Substituents on the Keto-Enol Equilibrium of Alkyl-Substituted β-Diketones, *Bull. Chem. Soc. Jpn. 46*:632–634 (1973).
20. Bassetti, M., G. Cerichelli, and B. Floris, Substituent Effects in Keto-Enol Tautomerism. Part 3. Influence of Substitution on the Equilibrium Composition of β-Dicarbonyl Compounds, *Tetrahedron 44*:2997–3004 (1988).
21. Jackson, L.L., β-Diketone, Alcohol and Hydrocarbons of Barley Surface Lipids, *Phytochemistry 10*:487–490 (1971).

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