Preparation of Fatty 3,5-Disubstituted Isoxazole Compounds from FA Esters

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ABSTRACT: Long-chain fatty compounds containing an isoxazole heterocyclic ring system substituted at the 3- and 5-ring positions were prepared in moderate to good yields (40–64%) in one pot by condensing FA esters such as methyl palmitate, stearate, oleate, or linoleate with the lithiated anion of *N*-(isopropylidene)isopropylamine followed by dehydrative cyclization. This approach allows readily available FA esters to be utilized and incorporated into the construction of the isoxazole ring system. These novel products were isolated then characterized by NMR, IR spectroscopy, GC-MS, and m.p. Mass spectra of the fatty isoxazole compounds, derived utilizing EI ionization, showed distinctive cleavage patterns that occurred uniformly along the fatty alkyl chain allowing the position of double bonds to be readily located. Two prominent ions at *m/z* 97 and 110 were common to all the fatty isoxazole compounds examined and were presumably from a McLafferty rearrangement and a cyclization–displacement reaction, respectively.

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KEY WORDS: 3,5-Disubstituted isoxazoles, FA esters, imines, lithiated imine anions, mass spectrometry, methyl linoleate, methyl oleate, methyl palmitate, methyl stearate, nuclear magnetic resonance.

Vegetable oils and their FA, renewable raw materials, are firmly established components in many industrial products, and their use continues to be of interest to many researchers (1). The development of new approaches to functionalize fatty ester compounds and to derive novel oleochemicals with unique chemical and physical properties is integral to extend the variety of compounds and uses obtainable from these oils. To meet these challenges, our laboratory has been pursuing various methods to functionalize vegetable oils and their FA to produce unique fatty compounds (2,3).

The diverse biological activities displayed by compounds containing the isoxazole heterocycle make them interesting in their own right, and have found use as anticancer (4), herbicide (5), insecticide (6), and fungicide (7) agents. Moreover, the isoxazole ring can serve as a versatile synthetic intermediate useful to construct other complex molecules because the ring can withstand a variety of chemical manipulations, after which the isoxazole ring's weak N–O bond (*ca.* 52 kcal/mol) can be readily opened under mild conditions to give β-enamino ketones (8–10) and β-dicarbonyl compounds (8,11). Interestingly, long-chain fatty compounds containing the β-diketone moiety are relatively common constituents of plant waxes (10,12,13).

Although several methods have been developed to prepare the isoxazole heterocycle, the two most widely used methods are based on the oximation of 1,3-dicarbonyl and the 1,3-dipolar cycloaddition reaction between nitrile oxides and alkynes (8). However, when unsymmetrical starting materials are utilized, poor regioselectivity is observed and complex isomeric mixtures are often obtained. In the early 1970s, Beam and coworkers (14) pioneered a different approach to prepare 3,5-disubstituted isoxazoles regioselectively by condensing lithiated oxime dianions with carboxylic acid derivatives followed by dehydrative cyclization under acidic conditions. This route has become an increasingly popular way to prepare 3,5-disubstituted isoxazole compounds due to the reaction's one-pot nature, regioselective control, and ability to utilize readily available carboxylic acid derivatives as starting materials. Recently, Bunnelle and coworkers (15) reported a variation on this method, suitable for scaleup, based on the condensation of lithiated imine anions and esters. This approach represents a straightforward method to prepare the isoxazole ring system and, to our knowledge, the FA esters found in vegetable oils have not been utilized in this approach.

The preparation of fatty isoxazole compounds not only would lead to a class of compounds that may possess interesting properties but also could be used to derive other uniquely functionalized fatty compounds, i.e., β-keto enamines and β-diketones, not readily available to the fats and oils industry. In this article we report the synthesis of several long-chain 3,5-disubstituted fatty isoxazole heterocycles by condensing FA esters with the lithiated anion of *N*-(isopropylidene)isopropylamine followed by dehydrative cyclization.

EXPERIMENTAL PROCEDURES

Materials. All chemicals were purchased from Aldrich Chemical Co. (Milwaukee, WI) and used without further purification unless otherwise noted. Ethyl acetate, methanol, THF, hexane, HCl, and H_2SO_4 were obtained from Fisher Scientific Co. (Fairlawn, NJ). THF was freshly distilled before use from sodium metal (chunks)/benzophenone. Lithium diisopropyl amide (LDA) was purchased from Aldrich Chemical

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Co. as a 2.0 M solution in heptane/THF/ethylbenzene and titrated against diphenyl acetic acid before use to establish its concentration (16). Hydroxylamine hydrochloride was purchased from Lancaster Chemical Co. (Lancaster, PA). *N*-(Isopropylidene)isopropylamine **1** (93% pure by ^{1}H NMR, remainder acetone) was prepared and purified as described in the literature before use (15). FA esters (99% pure) were purchased from Nu-Chek-Prep Inc. (Elysian, MN). Amine **1** was shown by ^{1}H and ^{13}C NMR and GC-MS to be similar to literature data in essential characteristics.

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

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

m.p. The m.p. 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 (Hewlett-Packard, Palo Alto, CA), 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). 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 held 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 [HP-5MS column (30 m × 0.25 mm i.d.)]; coupled with a Hewlett-Packard 5989B mass spectrometer using a mass range of 50–550 amu. 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. (Waukegan, IL). Conventional column chromatography was carried out using silica gel 22 (22–200 mesh purchased from the Aldrich Chemical Co. Chromatography fractions were collected in test tubes, and the fractions were subsequently analyzed by TLC or GC. The eluent used for analytical and preparative chromatography was either 6:94 ethyl acetate/hexane or 1:99 methanol/chloroform. Visualization was accomplished using iodine, UV light (254 nm), or $KMnO_4$ stain/charring. Analytical samples of solid products were obtained by recrystallization from a minimal amount of ethanol.

Representative procedure used to prepare fatty isoxazole compounds (15). To a magnetically stirred –11°C solution (cooled using a NaCl/ice bath) of lithium diisopropyl amide LDA [1.27 M; 32.0 mL, 40.6 mmol, molarity determined by titration using diphenyl acetic acid (16)] in THF (20.0 mL), *N*-(isopropylidene)isopropylamine **1** (2.36 g, 23.9 mmol) was added dropwise over 5 min while maintaining the temperature below –5°C. The solution was stirred for 30 min at –9°C. Methyl palmitate (5.0 g, 18.5 mmol) in THF (5 mL) was added dropwise over 30 min (reaction is exothermic) to the cooled solution while maintaining the temperature below –5°C (liquid esters were added neat). The reaction mixture was stirred for 2 h and then quenched (exothermic) by addition of water (1.5 mL), followed by concentrated HCl (1.5 mL) and water (1.5 mL). During the quench, the reaction solution temperature was allowed to rise to 15°C. The aqueous phase was removed, and the organic THF phase was concentrated *in vacuo* to obtain a crude yellow residue. The residue was dissolved in MeOH (15 mL), and $NH_2OH{\cdot}HCl$ (1.61 g, 22.9 mmol) was added to the stirred solution. The resulting solution had a pH of 5–6 and was allowed to react at room temperature for 3 h. Concentrated H_2SO_4 (3.0 g, 30.6 mmol) was then added, and the reaction mixture was heated at 60°C for 3 h. The cooled solution was diluted with H_2O (15 mL), extracted with ethyl acetate (3 × 30 mL), dried (Na_2SO_4), and concentrated *in vacuo* to give 6.96 g of a waxy solid. The crude material was purified by silica gel chromatography using silica gel 22 (180 g, 22–200 mesh; Aldrich Chemical Co.); column eluent $CHCl_3$/MeOH, 99:1. Compound **7a** was collected (2.19 g) as a white solid (40.4%), m.p.: 38–40°C.

^{1}H NMR 5-pentadecyl-3-methylisoxazole (**7a**): δ 5.78 (*s,* 1 H, isoxazole ring –*H*C=C–), 2.67 (*pseudo t*, 2 H, *J* = 7.6 Hz, –HC=C(–O)CH_2–CH_2–), 2.24 (*s*, 3 H, isoxazole ring –CH_3), 1.75–1.55 (*m*, 2 H, alkyl chain hydrogen), 1.40–1.20 (*m*, 24 H, alkyl chain hydrogen), 0.85 ppm (*t*, 3 H, *J* = 6.9 Hz, –CH_2CH_3). ^{13}C NMR: δ 173.6 (isoxazole ring), 159.7 (isoxazole ring), 101.4 (isoxazole ring), 32.0, 29.9, 29.7, 29.7, 29.5, 29.4, 29.3, 29.2, 27.6, 26.7, 22.8, 14.2 (–CH_2*C*H_3), 11.5 ppm (isoxazole ring –*C*H_3). IR (KBr) cm^{-1}: 2956, 2919, 2850, 1606, 1472, 1413, 823, 718. GC retention time 17.6 min. GC-MS (EI): *m/z* 293 (M^+, 16%), 110 ($C_6H_8NO^+$, 100%), 97 ($C_5H_7NO^+$, 74%).

^{1}H NMR of 5-heptadecyl-3-methylisoxazole (**7b**): δ 5.78 (*s*, 1 H, isoxazole ring –*H*C=C–), 2.67 (*pseudo t*, 2 H, *J* = 7.4 Hz, –(=C(–O)CH_2–), 2.24 (*s*, 3 H, isoxazole ring –CH_3), 1.75–1.60 (*m*, 2 H, alkyl chain hydrogen), 1.5–1.1 (*m*, 28 H, alkyl chain hydrogen), 0.87 ppm (*t*, 3 H, *J* = 6.9 Hz, –CH_2CH_3). ^{13}C NMR: δ 173.5 (isoxazole ring), 159.7 (isoxazole ring), 101.3 (isoxazole ring), 31.9, 29.7, 29.7, 29.7, 29.6, 29.6, 29.5, 29.4, 29.2, 29.1, 29.1, 27.5, 26.6, 22.7, 14.1 (–CH_2*C*H_3), 11.4 ppm (isoxazole ring –*C*H_3). IR (KBr) cm^{-1}: 2918, 2850, 1606, 1471, 1415, 822, 718. GC retention time 19.6 min. MS (EI): *m/z* 321 (M^+, 19%), 110 ($C_6H_8NO^+$, 100%), 97 ($C_5H_7NO^+$, 67%). MS (CI): *m/z* 322 (MH^+, 100%), 350 ($M^+ + C_2H_5$, 20%), 362 ($M^+ + C_3H_5$, 5%). m.p.: 47–48°C.

^{1}H NMR of 5-[(8*Z*)-heptadec-8-enyl)]-3-methylisoxazole (**7c**): δ 5.77 (*s*, 1 H, isoxazole ring –*H*C=C–), 5.37–5.30 (*m*, 2 H, alkyl chain –*H*C=*C*H–), 2.67 (*pseudo t*, 2 H, *J* = 7.6 Hz,

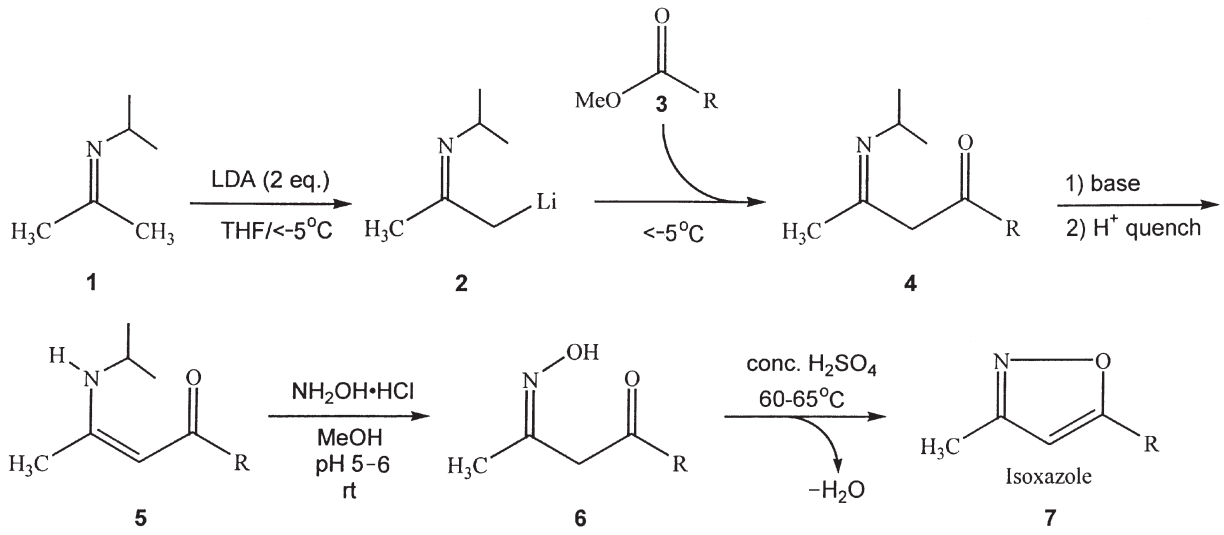
–HC=C(–O)CH_2–CH_2–), 2.24 (*s*, 3 H, isoxazole ring –CH_3), 2.10–1.90 (*m*, 4 H, –CH_2–CH=CH–CH_2–), 1.75–1.60 (*m*, 2 H, alkyl chain hydrogen), 1.5–1.1 (*m*, 20 H, alkyl chain hydrogen), 0.86 ppm (*t*, 3 H, *J* = 6.9 Hz, –CH_2CH_3). ^{13}C NMR: δ 173.4 (isoxazole ring), 159.6 (isoxazole ring), 130.0 (alkyl chain –*C*H=CH–), 129.7 (alkyl chain –*C*H=CH–), 101.3 (isoxazole ring), 31.9, 31.6, 29.8, 29.7, 29.5, 29.3, 29.1, 29.1, 29.0, 27.5, 27.2, 27.1, 26.6, 22.7, 14.1 (–CH_2CH_3), 11.4 ppm (isoxazole ring –CH_3). IR (NaCl) cm^{-1}: 3004, 2926, 2855, 1655, 1605, 1464, 1418, 1003, 894, 788, 723. GC retention time 19.4 min. MS (EI): *m/z* 319 (M^+, 9%), 110 ($C_6H_8NO^+$, 100%), 97 ($C_5H_7NO^+$, 50%). MS (CI): *m/z* 320 (MH^+, 100%), 348 ($M^+ + C_2H_5$, 19%), 360 ($M^+ + C_3H_5$, 5%).

^{1}H NMR of 5-[(8*Z*, 11*Z*)-heptadec-8,11-dienyl]-3-methylisoxazole (**7d**): δ 5.78 (*s*, 1 H, isoxazole ring –*H*C=C–), 5.50–5.20 (*m*, 4 H, alkyl chain –*H*C=C*H*–), 2.76 (*pseudo t*, 2 H, *J* = 6.45 Hz, –HC=CH–CH_2–CH=CH–), 2.67 (*t*, 2 H, *J* = 7.6 Hz, –HC=C(–O)CH_2–CH_2–), 2.24 (*s*, 3 H, isoxazole ring –CH_3), 2.10–1.95 (*m*, 4 H, alkyl chain allylic –CH_2–CH=CH–CH_2–), 1.75–1.55 (*m*, 2 H, alkyl chain hydrogen), 1.45–1.20 (*m*, 16 H, alkyl chain hydrogen), 0.87 ppm (*t*, 3 H, *J* = 6.9 Hz, –CH_2CH_3). ^{13}C NMR: δ 173.4 (isoxazole ring), 159.7 (isoxazole ring), 130.2 (alkyl chain –*C*H=CH–), 130.0 (alkyl chain –*C*H=CH–), 128.1 (alkyl chain –*C*H=CH–), 127.9 (alkyl chain –*C*H=CH–), 101.3 (isoxazole ring), 31.5, 29.6, 29.3, 29.1, 29.0, 29.0, 27.5, 27.2, 27.1, 26.6, 25.6, 22.6, 14.1 ppm (–CH_2CH_3), 11.4 (isoxazole ring –CH_3). IR (KBr) cm^{-1}: 3529, 3445, 2925, 2850, 1740, 1692. GC retention time: 19.3 min. GC-MS (EI): *m/z* 317 (M^+, 25%), 110 ($C_6H_8NO^+$, 100%), 97 ($C_5H_7NO^+$, 58%). MS (CI): *m/z* 318 (MH^+, 100%), 346 ($M^+ + C_2H_5$, 20%), 358 ($M^+ + C_3H_5$, 5%).

RESULTS AND DISCUSSION

Scheme 1 outlines the reaction sequence utilized to convert fatty esters **3** into their corresponding fatty isoxazoles, **7**. Treatment of imine **1** with an excess of LDA below –5°C in THF gave its corresponding lithiated imine anion, **2**. Although only imine **1** was utilized in our work, Bunnelle *et al.* (15) have shown that other imines (symmetrical and unsymmetrical) can be utilized. Subsequent reaction of lithiated anion **2** with fatty ester **3** gave condensation product **4**, whereby a second equivalent of LDA deprotonated **4** to yield the keto enamine **5**. The reaction was then quenched with water and concentrated HCl, the THF removed (*in vacuo*), and the oily residue redissolved in methanol. Enamine **5** was then converted into its corresponding β-keto oxime **6** by reacting **5** with hydroxylamine hydrochloride at pH 5–6. Treatment of **6** with concentrated H_2SO_4 and heating (55–65°C) in the same reaction flask gave the fatty isoxazoles, **7**. The dehydration cyclization reaction was typically complete in 2–3 h.

Table 1 shows the results and some pertinent physical data for the various fatty isoxazole compounds prepared from each of the FA esters. As can be seen, both saturated and unsaturated esters can be utilized successfully. Saturated isoxazole compounds, **7a** and **7b**, are solids, whereas the two unsaturated fatty isoxazoles, **7c** and **7d**, are oils.



Substituent R

a R = $-(CH_2)_{14}CH_3$ **c** R = $-(CH_2)_7$–CH=CH–$(CH_2)_7CH_3$

b R = $-(CH_2)_{16}CH_3$ **d** R = $-(CH_2)_7$–CH=CH–CH_2–CH=CH–$(CH_2)_4CH_3$

SCHEME 1

TABLE 1
Yields, m.p., and Selected ^{13}C NMR Data for Fatty Isoxazole Compounds, 7

	3,5-Disubstituted isoxazoles	Yield[a] (%)	m.p. (°C)	^{13}C NMR signals[b] (ppm)		
				Isoxazole	Ring	Carbons
7a	R = $-(CH_2)_{14}CH_3$	40.4	38–40	173.6	159.7	101.4
7b	R = $-(CH_2)_{16}CH_3$	51.2	47–48	173.5	159.7	101.3
7c	R = $-(CH_2)_7$–CH=CH–$(CH_2)_7CH_3$	63.0	Oil	173.4	159.6	101.3
7d	R = $-(CH_2)_7$–CH=CH–CH_2–CH=CH–$(CH_2)_4CH_3$	64.0	Oil	173.4	159.6	101.3

[a]Isolated yields.
[b]NMR spectra obtained in $CDCl_3$ as solvent.

The ^1H NMR spectra clearly showed the appropriate signals needed to identify the newly prepared compounds unambiguously. Because the ^1H NMR spectra of the fatty isoxazole compounds prepared have several characteristics related to the isoxazole functionality, the ^1H NMR spectrum of fatty isoxazole **7c**, derived from methyl oleate, serves to illustrate these general characteristics (Fig. 1). Two distinct sets of olefinic hydrogens are distinguishable. The lone vinyl hydrogen (labeled A, Fig. 1) on C4 of the isoxazole ring appears as a singlet at 5.77 ppm with an integral area equivalent to one hydrogen. The other olefinic hydrogen signals between 5.30 and 5.37 ppm (B, Fig. 1) not present in saturated isoxazoles,

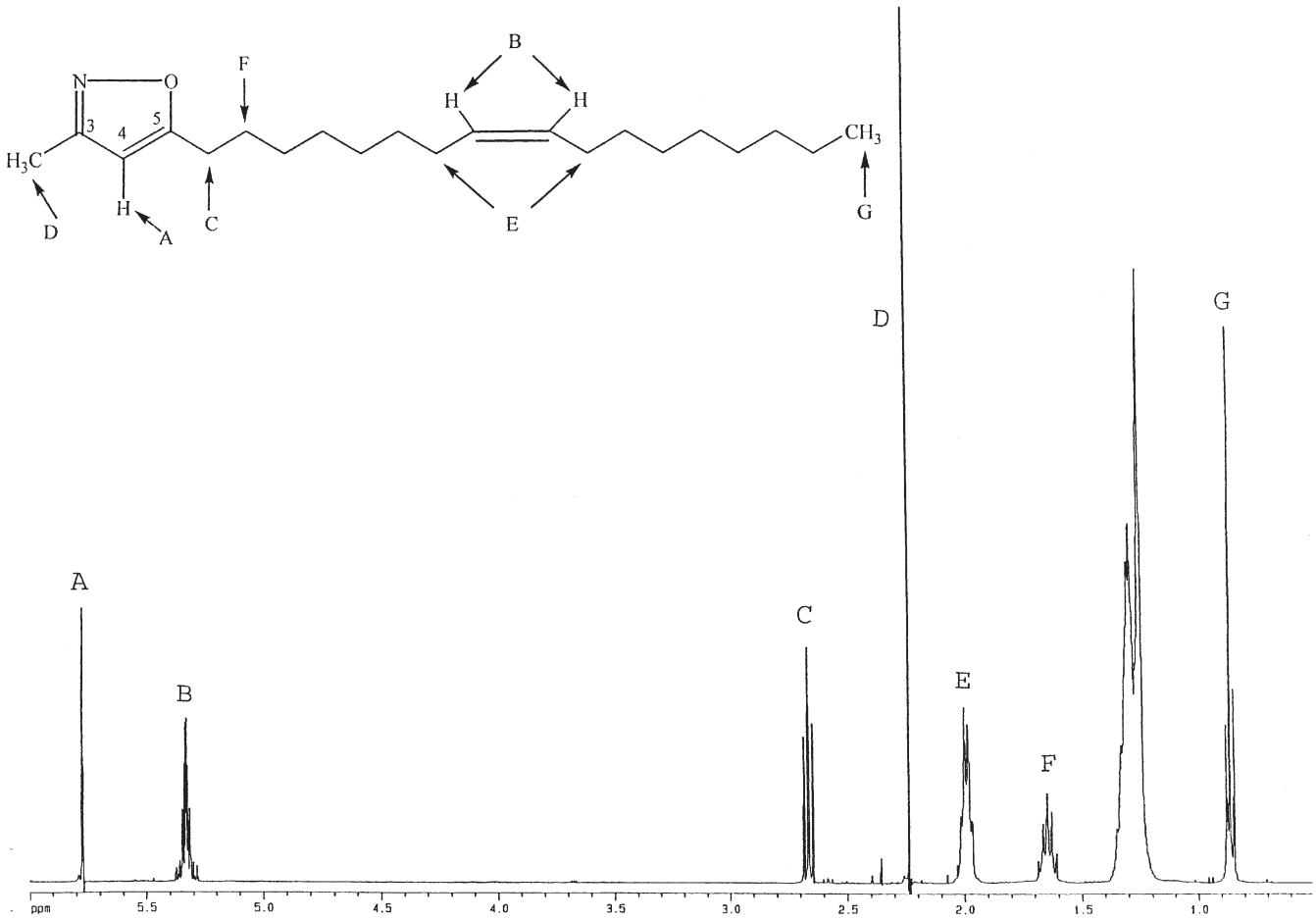


FIG. 1. Assignment of 400 MHz ^1H NMR spectrum of 5-[(8*Z*)-heptadec-8-enyl]-3 methylisoxazole **7c**.

7a and **7b**, correspond to the vinyl hydrogens located on the alkyl chain's C8 and C9 carbon atoms. The methylene hydrogens adjacent to the isoxazole ring (C, Fig. 1) are apparent at 2.67 ppm as a triplet with a coupling constant of 7.6 Hz. The singlet representing the methyl group located on C3 of the isoxazole ring (D, Fig. 1) is evident at 2.24 ppm. The allylic hydrogens positioned on the alkyl chain at C7 and C11 (E, Fig. 1) can be seen as a multiplet between 1.90 and 2.10 ppm. The remaining hydrogen signals are similar in character to those observed for typical long-chain fatty methyl esters, and their integration corresponds to the expected number of hydrogens.

For the unsaturated isoxazole compounds, **7c** and **7d**, it was of interest to establish that extensive *cis* to *trans* interconversion of the double bond did not occur during the reaction sequence. Accordingly, ^{13}C NMR was utilized to examine this possibility. Gunstone *et al.* (17) and others (18) have thoroughly studied the ^{13}C chemical shifts of *cis* and *trans* unsaturated FA and esters. They have shown that the chemical shifts of the allylic carbon atoms in methyl oleate (*cis* C9–10 alkene) and methyl elaidate (*trans* C9–10 alkene) are between 27.28–27.32 and 32.58–32.68 ppm, respectively. Presuming the isoxazole functionality does not significantly influence the chemical shifts of the distant alkyl chain alkene found in **7c**, we see in the spectrum of **7c** no signals in the chemical shift region corresponding to a *trans* double bond, signifying no detectable double-bond interconversion had taken place during the reaction (we estimate the lower limits of detection for *cis*- to *trans*-isomerization to be roughly 5–10%). Support suggesting that the isoxazole ring does not heavily influence the alkyl chain double bond comes from the ^{13}C chemical shifts of the two olefinic carbon atoms at 129.69 and 130.01 ppm in isoxazole **7c**. These chemical shifts are nearly identical to those reported by Gunstone *et al.* (17) for the olefinic carbon atoms of methyl oleates at 129.78 and 130.02 ppm (the corresponding chemical shifts of the olefinic carbon atoms in the *trans* isomer, methyl elaidate, are 130.23 and 130.54 ppm). A similar ^{13}C NMR analysis of the chemical shifts for isoxazole **7d**, containing a methylene-interrupted diene, also showed no evidence for *cis* to *trans* double-bond interconversion.

EI ionization MS was utilized to confirm the structures of the fatty isoxazole compounds, and Figure 2 shows a representative EI-derived mass spectrum for isoxazole **7c**. Two prominent fragmentation ions at *m/z* 97 and 110 are present. These ions are observed in all the isoxazole compounds examined, **7a–d**. The *m/z* 97 ion is explainable by a McLafferty rearrangement, while the base peak observed at *m/z* 110 is presumably due to a cyclization–displacement reaction that results in the observed C_6H_8NO *m/z* 110 fragment ion (19). The readily ionizable nitrogen atom contained in the isoxazole ring leads to a charge-site, allowing simple radical-induced cleavage to occur uniformly along the alkyl chain. An even-numbered series of *m/z* 110 + 14n is derived from cleavage at each C–C bond of the FA side chain. Because isoxazole **7c** contains a monounsaturated alkyl chain, a mass interval of 12 amu

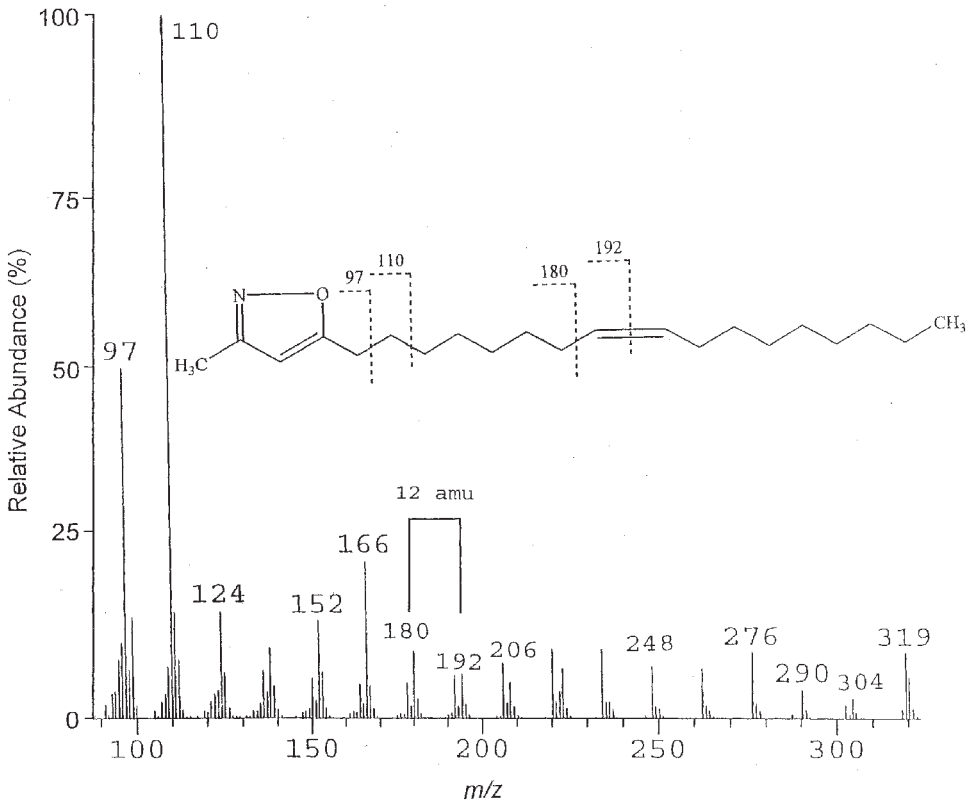


FIG. 2. The EI-derived mass spectrum of 5-[(8*Z*)-heptadec-8-enyl]-3-methylisoxazole **7c**.

(between *m/z* 180 and 192), instead of 14 amu, occurs between the allylic methylene group located nearer to the isoxazole ring and the C8 atom of the double bond. The "12 amu rule" commonly used to locate the position of double bonds in 4,4-dimethyloxazdine derivatives (19,20) appears to be applicable to the fatty isoxazole compounds. Finally, the molecular ion at *m/z* 319 is readily observed.

The mass spectrum of fatty isoxazole **7d** (not shown), which contains a methylene-interrupted diene unit in the alkyl chain, shows the same basic characteristics as previously described. The two double bonds were determined to be located between C8–9 and C11–12, respectively, by using the distinctive 12 amu gaps observed in the mass spectrum as just described for **7c**.

The reaction between the common FA esters and lithiated imine anions occurs readily to give good yields of their corresponding fatty isoxazole compounds. These long-chain compounds may be of use as intermediates to derive novel oleochemicals not currently available to the fats and oils industry. Further investigation into the ring-opening reactions of these compounds is currently underway.

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