1,3-Cycloaddition of Nitrile Oxide to Olefinic Fatty Acid Esters: Synthesis of Isoxazolines

M.A. Ahmed[1], J. Mustafa[a] and S.M. Osman*

Section of Oils and Fats, Department of Chemistry and [a]Applied Science Section, University Polytechnic, Aligarh Muslim University, Aligarh-202 002, India

Fatty acid isoxazolines were prepared as 1,3-cyclo adducts by the reaction of dipolar nitrile oxides and dipolarophilic olefinic fatty esters. The structures of the isoxazolines were established with the help of elemental analysis, infrared, nuclear magnetic resonance and mass spectrometry spectral data.

KEY WORDS: 1,3-Cycloaddition, hydroximoyl chloride, isoxazoline, methoxy carbonyl formonitrile oxide, methyl *cis*-9-octadecenoate, methyl 10-undecenoate.

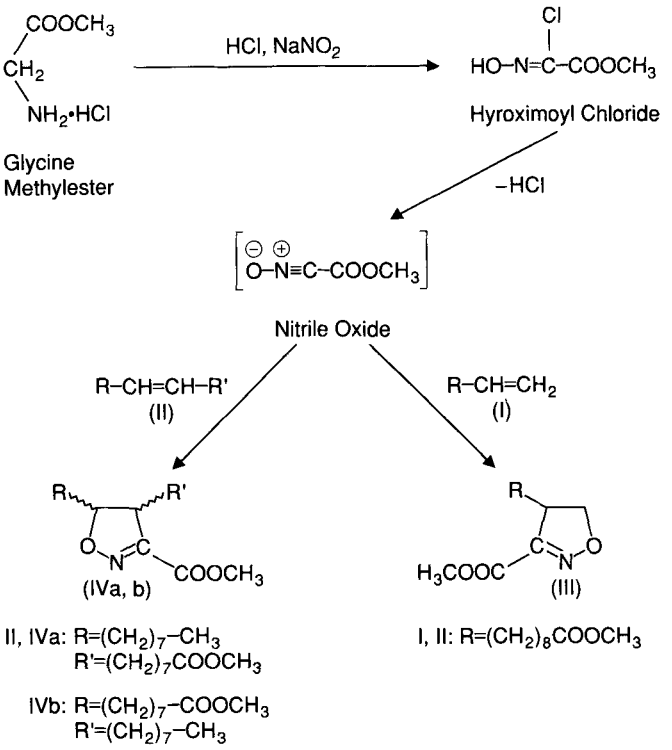
Isoxazole-containing compounds have attracted much attention due to their structural similarities with oxazolines, which have shown biological and nonbiological applications. Such heterocyclic compounds are extensively used as local anaesthetic (1,2), antibacterial (3,4), antihypertensive (5), neoglycogenetic (6), antigranulometry (6), antiinflammatory (7), protective coating (8) and vulcanizing agents (9). The 1,3-dipolar cycloaddition reaction with nitrile oxides (10–13) is a facile method for the preparation of isoxazolines (14,15). The present work is a continuation of our studies on introducing novel heterocyclic moieties into fatty acid chains (16–19). Here, we report the reaction of methyl 10-undecenoate (I) and methyl-*cis*-9-octadecenoate (II) with methoxy carbonyl formonitrile oxide.

MATERIALS AND METHODS

The infrared (IR) spectra were recorded with a Perkin-Elmer 621 spectrophotometer (Perkin-Elmer, Norwalk, CT). The nuclear magnetic resonance (NMR) spectra were run on a Varian-FX90 (90 MHz) spectrometer (Varian Associates, Palo Alto, CA), chemical shifts were measured in relation to tetramethylsilane (TMS). Mass spectrometry (MS) were recorded with an AEIMS-902 mass spectrometer. Thin-layer chromatography (TLC) plates were coated with silica gel G (0.25 mm). Olefinic fatty acids, 10-undecenoic and *cis*-9-octadecenoic acids were purchased from Fluka Chemika AG (Buchs, Switzerland) and S.D. Fine Chemicals (Bombay, India). Hydroximoylchloride was prepared by the nitrile decomposition of glycine methyl ester hydrochloride (20).

EXPERIMENTAL PROCEDURE

Reaction of olefinic fatty esters with methoxy carbonyl formonitrile oxide. Triethylamine (0.1 mole) in 100 mL of diethyl ether was added over 2 hr with vigorous stirring to a mixture of olefinic fatty esters (I, II: 0.1 mole) and hydroximoyl chloride (0.1 mole) in 100 mL of diethyl ether. Progress of the reaction was monitored by TLC. Water (100 mL) was added and the reaction mixtures were extracted with diethyl ether, dried (Na_2SO_4) and concentrated. Products were separated by column chromatography on silica gel G with petroleum ether/diethyl ether (70:30, v/v).



SCHEME 1

RESULTS AND DISCUSSION

Nitrile oxide reacted with methyl 10-undecenoate (I) and methyl *cis*-9-octadecenoate (II) gave methyl 10,11-isoxazoline-undecanoate (III) in excellent yield (90%) and methyl 9,10-isoxazoline-octadecanoate (IV) in moderate yield (40%), respectively. Unreacted II was recovered. Column chromatographic separation gave III as a white solid (m.p. 61–62°C) and IV as yellow oil.

Compound (III): Analysis (Found: C, 60.10; H, 8.28; N, 4.60% required for $C_{15}H_{25}O_5N$: C, 60.20; H, 8.36; N, 4.68%). IR (KBr): 1740, 1720 (2X-*COO*CH_3), 1585 cm^{-1} (>C=N-). NMR ($CDCl_3$): δ 4.5–4.7 m (1H, R-C*H*(O)-CH_2), 3.75 s (3H, -COO*C*H_3), 3.55 s (3H, -COO*C*H_3), 3.3 dd (1H, J=17 and 10Hz, -N=C(-)-C*H*R-), 2.6 dd (1H, J = 17 and 8Hz, -N=C(-)-C*H*R-), 2.18 t (2H, CH_2COOCH$_3$), 1.25 bars

*To whom correspondence should be addressed.

[1]Present address: Princess Shahkar College, Purani Hawaily, Hyderabad, India.

(14H, chain protons). Mass spectrum: *m/z* 299 (M^+, 61), 268 (M-OCH_3, 31), 267 (M-CH_3OH, 47), 240 (M-CH_3COO, 69), 239 (240-H, 27), 181 (M-2XCH_3COO, 37), 139 (240-ONC-$COOCH_3$, 38), 128 (87) and 69 (53%).

Compound (IV): Analysis (Found: C, 66.50; H, 9.80; N, 3.55%; required for $C_{22}H_{39}O_5N$: C, 66.32, H, 9.69; N, 3.52%). IR (Neat): 1745–1720 br (2X-*COO*CH_3), 1585 cm^{-1} (>C=N-). NMR ($CDCl_3$): δ 4.75 m (1H, R-CH-O), 4.43 m (1H, -N=C-CHR—-), 3.9 s (3H, -COO*CH*$_3$), 3.7 s (3H, -COO*CH*$_3$), 2.33 t (2H, *CH*$_2$-$COOCH_3$), 1.33 brs (26H, chain protons), 0.86 t (3H, -CH_3). Mass spectrum: *m/z* 397 (M^+, 44), 366 (M-OCH_3, 54), 365 (M-CH_3OH, 56), 338 (M-$COOCH_3$, 32), 337 (338-H, 20), 284 (47), 279 (M-2X$COOCH_3$, 36), 240 (69), 237 (338-ONC-$COOCH_3$, 54), 225 (71), 181 (36) and 166 (67%).

IR spectra of the fatty isoxazolines (III, IV) are similar and show structure-revealing bands in the carbonyl region at 1740 and 1720 cm^{-1} (two ester carbonyls) and a strong band near 1585 cm^{-1} (>C=N). The NMR spectrum of III had a multiplet at δ 4.5–4.7 for the C_{10} proton, two sharp singlets at 3.75 and 3.55 ppm were assigned to the methyl ester protons, and two C_{11} protons were observed as doublets of doublets at 3.3 and 2.6 ppm. The mass spectrum had the parent ion at *m/z* 299, which corresponded to molecular weight and confirmed the elemental composition. Significant ions were observed at 268 (M-OCH_3), 267 (M-CH_3OH), 240 (M-$COOCH_3$), 128 (M-$(CH_2)_8$-$COOCH_3$) and 69 (128-$COOCH_3$). The NMR spectrum for compound (IV) has shown two isoxazoline ring protons as multiplets at δ 4.75 (1H) and 4.43 (1H). Two ester group protons were observed as two singlets at 3.9 (3H) and 3.7 (3H). The mass spectrum gave molecular ion at *m/z* 397. The position of the isoxazoline ring was confirmed by two α-cleavage ions at *m/z* 284 and 240, along with other ions at 225 (284-$COOCH_3$), 166 (225-$COOCH_3$) and 181 (240-$COOCH_3$).

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