hydroperoxides produced in randomized oil must somehow be more subject to scission. This might lead to an increased rate of the initiation reaction. There is considerable evidence that the hydroperoxides in oxidized fats associate (13). Possibly the glyceride structure of fats alters the associations that occur or the stress placed on the associated molecules so that the rate of decomposition of the hydroperoxides and their tendency to scission is altered.

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Derivatization of Keto Fatty Acids: I. Synthesis and Mass Spectrometry of Thiazolidinones[1]

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ABSTRACT

The synthesis of alkyl chain-substituted thiazolidinones from oxo acids is described. Reactions of mercaptoacetic acid with three oxo-esters, methyl 10-oxoundecanoate, methyl 12-oxooctadecanoate and methyl 9,10-dioxooctadecanoate gives excellent yields of the corresponding thazolidinones. Mass spectral fragmentation patterns of these long-chain thiazolidinone derivatives are discussed.

INTRODUCTION

Fatty acid derivatives that are chain-substituted by nitrogen or sulfur are, with few exceptions, rather obscure laboratory curiosities and are not found naturally except in the antibiotic actithiazic acid (1-3). Compared to the acyclic sulfur/nitrogen-containing fatty acid derivatives, scant literature is available for heterocycles such as thiazolidinones (4-6) and oxathiolane (7). Thiazolidinone derivatives are known to possess fungicidal, insecticidal, pesticidal and bactericidal properties. A number of pharmacological activities such as anesthetic, narcotic, sedative, anticonvulsant, anti-inflammatory and antithroidal effects have been found to be associated with these compounds (4-8). This paper reports the synthesis of chain-substituted sulfur/nitrogen heterocyclics from oxo-esters. Thiazolidinone derivatives have been identified spectroscopically. Only a few literature reports deal with the mass spectra (MS) of these compounds. MS of chain-substituted thiazolidinones have not been reported previously. Thus, MS of chain-substituted thiazolidinone derivatives was studied to obtain the basic fragmentation and to establish the position of the heterocyclic ring in the fatty acid chain.

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EXPERIMENTAL PROCEDURES

Infrared (IR) spectra were obtained with a Perkin-Elmer 621 spectrophotometer, using a 1% solution in carbon tetrachloride. Nuclear magnetic resonance (NMR) spectra were recorded in $CDCl_3$ with a Varian A60 spectrometer. Chemical shifts were measured in ppm downfield from internal tetramethylsilane ($\delta = 0$). MS were measured with an AEI MS 902 mass spectrometer.

Analytical thin layer chromatography (TLC) was done on glass plates (20 × 5 cm) with a layer of Silica Gel G (0.25 mm thickness). Mixtures of diethyl ether and petroleum were used as developing solvents. Components on TLC plates were made visible by spraying with an aqueous solution (20%) of perchloric acid and heating at 120 C.

Methyl esters were preapred by refluxing the acids with absolute methanol containing catalytic amounts of sulfuric acid.

Preparation of Oxo-Fatty Acids

10-Oxoundecanoic acid (I). Solvomercuration-demercuration of 10-undecenoic acid yielded 10-hydroxyundecanoic acid (9), mp 49 C. (All melting points are uncorrected.) The pure 10-hydroxyundecanoic acid, upon Jones' oxidation (10), afforded 10-oxoundecanoic acid, mp 58-59 C. IR (CCl_4) 1710, 1720 cm^{-1}. NMR ($CDCl_3$), δ 2.36 (4 protons), 1.9 (3 protons, singlet).

12-Oxooctadecanoic acid (II). Pure 12-hydroxy-*cis*-9-octadecenoic acid was isolated from castor (*Ricinus communis*) seed oil by Gunstone's partitioning procedure (11). This hydroxyolefinic acid, upon hydrogenation with palladium on charcoal in ethyl acetate, yielded 12-hydroxyoctadecanoic acid, mp 79 C. Jones' oxidation of saturated 12-hydroxy acid gave 12-oxooctadecanoic acid, mp 82-82.5 C IR (CCl_4) 1710, 1720 cm^{-1}.

9,10-Dioxooctadecanoic acid (III). Permanganate hydroxylation of oleic acid afforded 9,10-dihydroxyoctadecanoic acid. Jones' oxidation of dihydroxy acid gave 9,10-dioxooctadecanoic acid, mp 86 C.

Preparation of (Ia)

To a solution of 1.5 g of methyl 10-oxoundecanoate in 50 mL of dry benzene in a 100-mL round-bottomed flask was added 6.45 g of mercaptoacetic acid and 11.0 g of ammonium carbonate. A vigorous reaction occurred. The contents were refluxed and the progress of reaction was monitored by TLC. At the end of reaction, the solvent was removed under reduced pressure. The residue was extracted with ether, washed and dried. After evaporation of solvent, 1.0 g of a solid was obtained which, upon crystallization in light petroleum benzene (4:1, v/v), melted at 59 C. (Found: C, 58.88; H, 8.79; N, 5.29. Calcd. for $C_{14}H_{25}O_3NS$: C, 58.53; H, 8.71; N, 5.1%.) IR (CCl_4), 3390, 3170, 1730, 1680, 1410 cm^{-1}. NMR ($CDCl_3$), δ 8.98, 1.35, 1.63, 2.19, 3.57 and 3.63.

Preparation of (IIa)

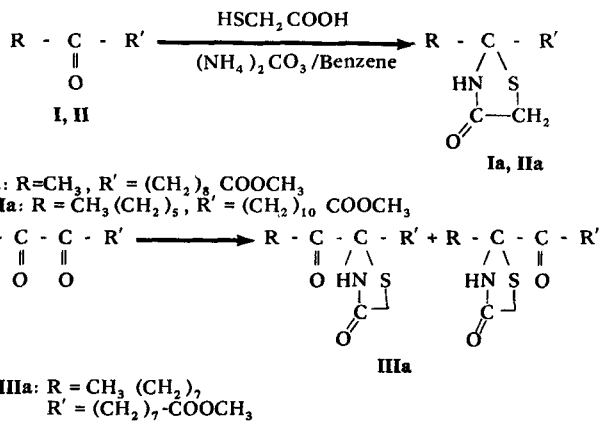
Reaction of mercaptoacetic acid with 12-oxooctadecanoic acid (1.0 g) as described earlier yielded a viscous oily product (1.1 g). (Found: C, 64.8; H, 10.0; N, 3.4. Calcd. for $C_{21}H_{39}O_3NS$: C, 65.13; H, 10.13 and N, 3.63%.) IR (neat), 3175, 3065, 1740, 1680 and 1435 cm^{-1}. NMR ($CDCl_3$) δ 0.88, 1.38, 2.15, 2.50, 3.5 and 3.68.

Preparation of (IIIa)

A similar reaction of methyl 9,10-dioxooctadecanoic (1.0 g) with mercaptoacetic acid yielded an oily product (1.3 g). (Found: C, 63.5; H, 9.5; N, 3.5. Calcd. for $C_{21}H_{37}O_4NS$; C, 63.16; H, 9.27; N, 3.50%.) IR (neat), 3180, 3070, 1745, 1715, 1690, 1420 cm^{-1}. NMR ($CDCl_3$) δ 0.88, 1.38, 2.46-2.18, 3.48, 3.68 and 8.56.

RESULTS AND DISCUSSION

Four different long-chain fatty acid esters possessing chain carbonyls at different positions (penultimate, internal mono- and vicinal diketo, and 2-keto) were selected as model compounds.



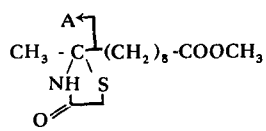
Reaction of mercaptoacetic acid in the presence of ammonium carbonate with oxo-esters I and II gave almost a quantitative yield of the corresponding thiazolidinones (Ia, IIa). Thiazolidinone (Ia) was obtained as a solid crystalline product (mp 59 C) whereas others (IIa, IIIa) were liquid. IR spectra showed characteristic bands at 3390 and 3170 cm^{-1} for the free and associated NH grouping, 1730 and 1680 cm^{-1} for ester and lactam carbonyls, and at 1410 cm^{-1} for thiazolidinone ring stretching. The NMR spectra of (Ia) showed a characteristic sharp singlet at δ 1.63 for terminal methyl protons and other singlet at δ 3.5 for ring methylene protons. A broad singlet at δ 8.98 can be attributed to N-H protons. Methoxyl chain methylene and α-methylene protons appears at δ 3.63, 1.35 and 2.19 respectively. Thiazolidinone IIa gave similar IR and NMR characteristics as Ia except for the appearance of terminal CH_3 protons at δ 0.88 as a distorted triplet.

Reaction of α-dioxo derivative (III) with mercaptoacetic acid gave a single TLC homogenous product IIIa which showed IR characterisitics similar to those of Ia and IIa except for the appearance of the free carbonyl band at 1710 cm^{-1}. Similarly, NMR spectra showed the presence of four methylene protons alpha to the carbonyl group. These data indicated that out of two carbonyls, only one chain carbonyl participated in the formation of the thiazolidinone ring. With mid-chain carbonyls, it is expected that the product (IIIa) will be an isomeric mixture.

MS Studies of Thiazolidinones

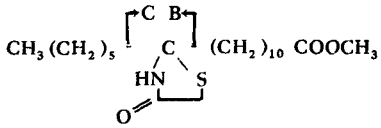
Sporadic reports have appeared dealing with the MS of thiozolidinone derivatives. Behara and Nayak (12) have recently reported the MS of 1-thio-4-azaspiro(4,4)nonan-3-one. We now report the MS and characteristic fragment ions of chain-substituted thiazolidinone derivatives Ia, IIa and IIIa. These fragment ions were also supported by accurate mass measurement studies.

MS of Ia (Fig. 1)



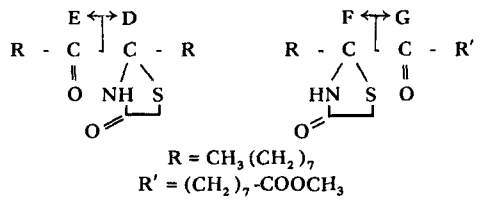
m/z 287 (M^+, $C_{14}H_{25}O_3NS$, 10), m/z 272 (M-CH_3, 2.0); m/z 256 (M-CH_3O, 14.0), m/z 116 (A, base peak); m/z 115 (A-H, 10.0), m/z 254 (M-SH, 3.0); m/z 212 (M-$COCH_2SH$, 5.0), m/z 214 (M-COCHS, 11.0); m/z 74 (CH_2SCO, 4.0), m/z 46 (CH_2S, 6.0); m/z 43 (CONH, 14.0), and m/z 42 (CON, 31.0).

MS of IIa (Fig. 2)



m/z 385 (M^+, $C_{21}H_{39}O_3NS$, 7.0), m/z 352 (M-SH, 10.0); m/z 311 (M-$COCH_2S$, 4.0), m/z 310 (M-$COCH_2SH$, 17.0); m/z 300 (C, 65.0), m/z 268 (C-CH_3OH, 60.0); m/z 186 (B, base peak), m/z 187 (B+H, 38.0); m/z 74 (17.0), m/z 46 (5.0); m/z 43 (9.0), and m/z 42 (11.0).

MS of IIIa (Fig. 3)



m/z 399 (M^+, $C_{21}H_{37}O_4NS$, 0.5), m/z 366 (M-SH, 0.7); m/z 326 (M-COCHS, 1.0), m/z 324 (M-$COCH_2SH$, 3.0); m/z 259 (D+H, 12.0), m/z 258 (D, 60.0); m/z 226 (D-32, 33.0), m/z 215 (F+H, 25.0); m/z 214 (F, base peak), m/z 185 (G, 22.0); m/z 141 (E, 26.0), m/z 74 (16.0); m/z 46 (5.0), m/z 43 (80.0), and m/z 42 (19.0).

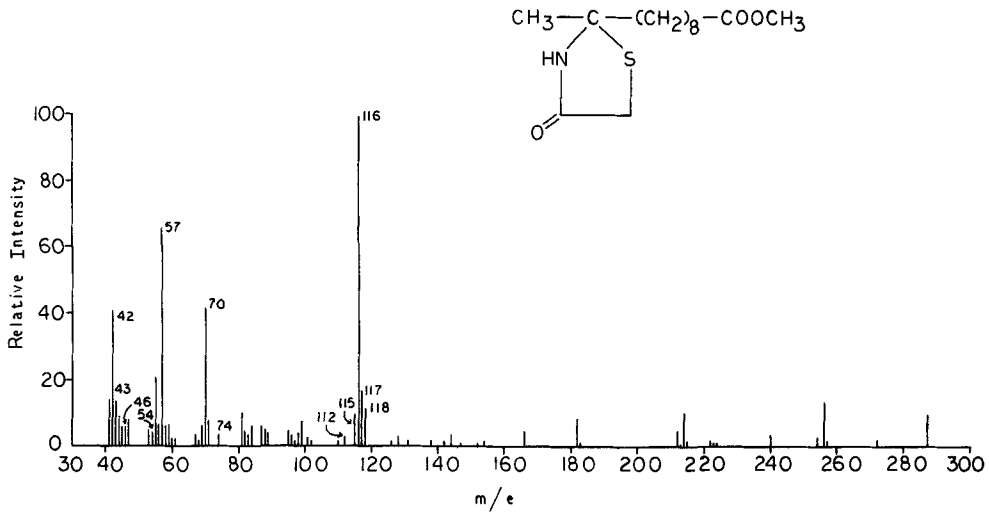


FIG. 1. Mass spectrum of derivative Ia.

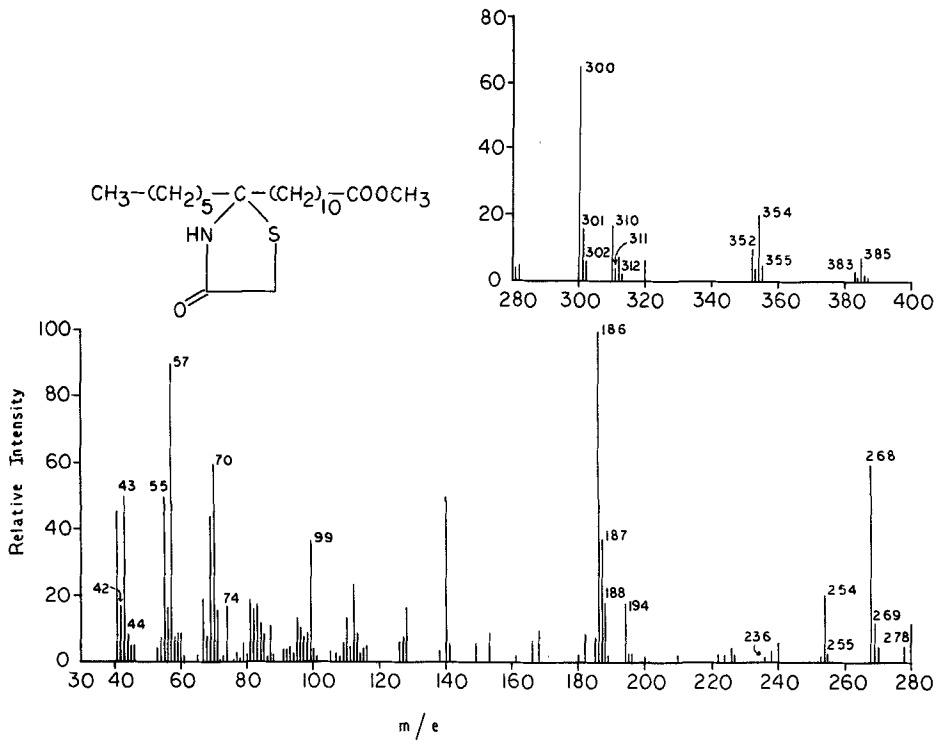


FIG. 2. Mass spectrum of derivative IIa.

Although MS of thiazolidinone compounds has not been extensively studied, a few general comments could be made from the results of the present investigation. In contrast to the C_2 and C_5 spirothiazolidinones (10) in which the parent peaks usually are the base peak, fatty acid chain-substituted thiazolidinones showed very low intensity M^+ peaks. However, cleavage on ester side of the heterocyclic nucleus gives ions which appear as the base peak. Other common peaks are M-SH and M-$COCH_2S$ of low intensities. As reported (10) earlier, the appearance of m/z 74 seems to be characteristic of fragmentation of thiazolidinones from the cleavages of 1,2 and 3,4 bonds, as with thiazoles. Two significant peaks, m/z 42 and 43, of comparatively moderate intensity are also observed in the spectra of all the three thiazolidinones. These two peaks can also be considered characteristic of thiazolidinones ring fragmentation which is triggered by the ring oxo function. Additional data of similar fragmentation would be required to establish this characteristic feature.

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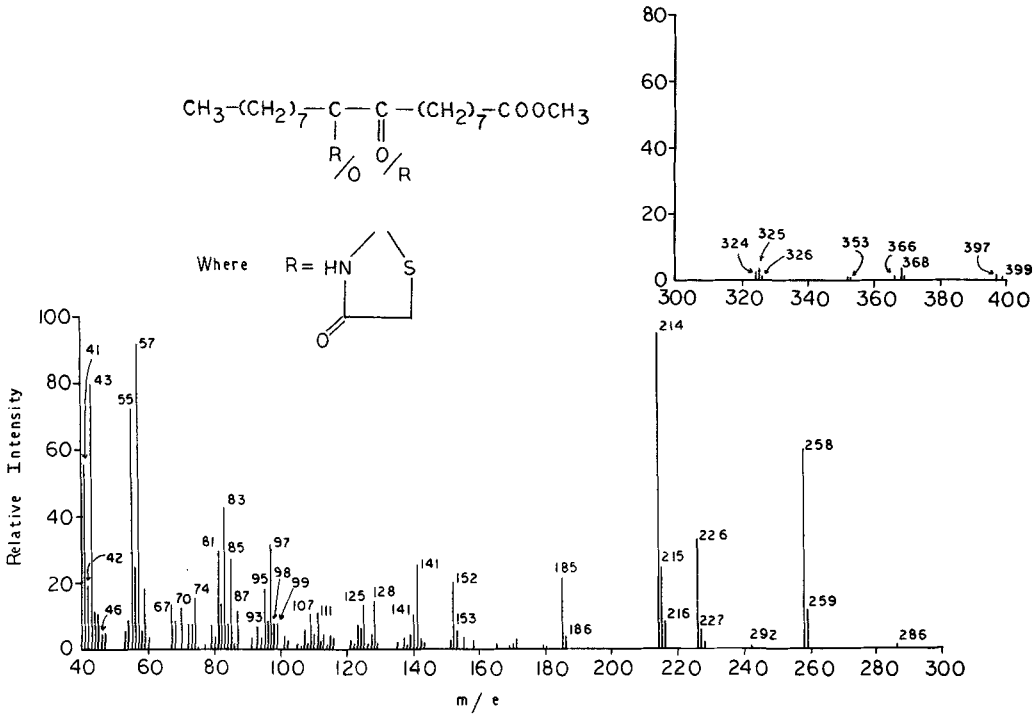

FIG. 3. Mass spectrum of derivative IIIa.

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