flower oils with 1% or less of linoleic acid have the potential of achieving 100 hr AOM values.

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Derivatization of Keto Fatty Acids: VI. Synthesis, Oxidation and Mass Spectrometry of Dithiolanes

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ABSTRACT

The synthesis of alkyl chain-substituted dithiolanes, bisdithiolane and disulfolanes from oxo acids and their decomposition to original oxo acids are described. Reactions of ethanedithiol with 2 oxo esters, methyl 10-oxoundecanoate and methyl 12-oxooctadecanoate, give excellent yield of the corresponding dithiolanes, which are oxidized to the respective disulfolanes by m-chloroperbenzoic acid (m-CPBA). A similar reaction of ethanedithiol with methyl 9,10-dioxooctadecanoate affords bisdithiolane. Retroreactions of the dithiolanes and bisdithiolanes under acidic conditions and of disulfolanes under alkaline conditions yield the parent oxo acids. The structures of the individual reaction products have been established from analytical and spectral data and confirmed by a study of their mass spectra.

INTRODUCTION

Ketalization of ethanedithiol with various ketones using different reaction conditions (1,2) has been described both as a preparative method and masking methodology of oxo function. Compounds containing dithiolane grouping have become of interest in recent years due to their pharmacological (3) and industrial potential (4). Some dithiolanes have been identified as components of the anal gland secretion of the ferret (5) and also tested as radioprotectants (6). Interest for sulfones has been renewed recently for their antitubercular activity (7) and applications as primary plasticizers (8) and stabilizers (9). Thus, in recent years there has been increasing interest in the synthesis (10) and reactions (11,12) of dithiolanes. Peracid oxidation of dithiolanes to the corresponding disulfolanes (12,13) and its reactions (13-15) have been reported. For this reason, it was considered of interest to undertake the present work on the sulphur heterocyclic fatty derivatives.

Chain-substituted mono- and bisdithiolanes were prepared from oxo acids. Dithiolanes were oxidized to disulfolanes by m-CPBA. Retroreaction of these spiro compounds also was done, to regenerate the original oxo acids. Mass spectra (MS) of dithiolanes and one of the disulfolanes as a model compound were studied to obtain basic fragmentation patterns and to establish the nature and position of the heterocyclic ring in fatty acid chain.

EXPERIMENTAL PROCEDURES

Infrared (IR) spectra were obtained with a Perkin-Elmer 621 spectrophotomer (liquid film or in 1% solution in CCl_4). Nuclear magnetic resonance (NMR) spectra were recorded in $CDCl_3$ with a Varian A60 spectrometer. Chemical shifts were measured in ppm downfield from the internal standard, tetramethylsilane ($\partial = 0$). MS were measured with an AEI MS 902 mass spectrometer.

Thin layer chromatographic (TLC) plates (20 × 5 cm) were coated with a layer of silica gel G (0.25 mm thickness), and a mixture of petroleum ether-ether-acetic acid (80:20:1, v/v/v) was normally used as the developing solvent. Components on the TLC plates were visualized by charring the sprayed plates with a 20% aqueous solution of perchloric acid.

Methyl esters were prepared by refluxing the acids with absolute methanol containing catalytic amounts of H_2SO_4.

Materials and Methods

10-Oxoundecanoic acid (mp 58-59C), 12-oxooctadecanoic acid (mp 82-82.5C) and 9,10-dioxooctadecanoic acid (mp 86C) were prepared as discussed in our earlier publication (16).

Preparation of (Ia)

A solution of methyl 10-oxoundecanoate (I, 2.14 g, 10 mmol) in acetic acid (1 ml) and freshly distilled BF_3-etherate (10 ml) was treated with 1,2-ethanedithiol (2 ml) and allowed to stand at room temperature for 15 min. The TLC of the reaction mixture showed complete conversion to a product having higher R_f than the starting material. The reaction mixture was poured into water after addition of a few drops of methanol and extracted with ether. The ethereal layer was washed several times with water and sodium bicarbonate (5%) and then dried over anhydrous sodium sulfate. Removal of the solvent gave a product which on column chromatographic purification afforded a viscous liquid in 98% yield. (Found: C, 57.79; H, 8.98. Calcd. for $C_{14}H_{26}S_2O_2$: C, 57.89; H, 9.02%). IR(CCl_4): 1735 ($COOCH_3$), 1445 (CH_2-S deformation), 1250 (CH_2-S wag.) and 680 cm^{-1} (C-S stretch.). NMR: ∂ 1.75 (3H, C_{11}

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methyl protons alpha to thioketal ring), 1.85 (2H, C_9 methylene protons alpha to thioketal ring), 3.28 (4H, methylene protons of thioketal ring), 3.62 (3H, methylester), 2.3 (2H, C_2 methylene protons alpha to ester group) and 1.32 (chain methylene protons).

Preparation of (IIa)

A similar reaction of methyl 12-oxooctadecanoate (II, 3.12 g, 10 mmol) with ethanedithiol for 1 hr afforded an oil IIa in 90% yield. (Found: C, 64.92; H, 10.32. Calcd. for $C_{21}H_{40}S_2O_2$: C, 64.89; H, 10.37%). IR(CCl_4): 1735, 1440, 1250 and 680 cm^{-1}. NMR: ∂ 0.9 (3H, terminal methyl), 1.8, 3.3, 3.6, 2.3 and 1.3.

Preparation of (IIIa)

Methyl 9,10-dioxooctadecanoate (III, 3.26 g, 10 mmol) on similar treatment with ethanedithiol for 5 hr gave IIIa (88% yield) as a viscous oil. (Found: C, 57.72; H, 8.80. Calcd. for $C_{23}H_{42}S_2O_2$: C, 57.69; H, 8.84%). IR(neat): 1735, 1430, 1240 and 675 cm^{-1}. NMR: ∂ 0.85, 1.95, 3.35, 3.65, 2.25 and 1.3.

Preparation of (Ib)

A solution of dithiolane (Ia, 0.29 g, 1 mmol) in 10 ml dichloromethane (CH_2Cl_2) was stirred with m-CPBA (0.87 g, 5 mmol) at ice-bath temperature. The progress of reaction was monitored by TLC. Sodium sulfite was added to the reaction mixture after 12 hr and worked up with CH_2Cl_2, washed and dried. Evaporation of the solvent and column chromatographic purification gave a liquid Ib (90% yield). (Found: C, 47.45; H, 7.30. Calcd. for $C_{14}H_{26}S_2O_6$: C, 47.44; H, 7.39%). IR(neat): 1735, 1340 and 1135 (SO_2 stretch), 1534, 1255 and 695 cm^{-1}. NMR: ∂ 3.7 (4H, methylene protons of disulfolane ring), 1.8 (3H, C_{11} methyl protons alpha to disulfolane ring), 1.99 (2H, C_9 methylene protons alpha to disulfolane ring), 3.62 (3H, methylester), 2.25 (2H, C_2 methylene protons alpha to ester group) and 1.35 (chain methylene protons).

Preparation of (IIb)

A similar reaction of internal dithiolane (IIa, 0.39 g, 1 mmol) with m-CPBA afforded IIb (85%) as a viscous liquid. (Found: C, 55.68; H, 9.01. Calcd. for $C_{21}H_{40}S_2O_6$: C, 55.72; H, 8.91%). IR(neat): 1730, 1320 and 1130, 1420, 1250 and 665 cm^{-1}. NMR: ∂ 3.7, 2.25, 3.6, 0.88 and 1.3.

Retroreaction of (Ia, IIa, IIIa)

The dithiolanes reacted promptly with 10% methanolic sulfuric acid solution. Original oxo acids were recovered in 90% yield after heating the reaction mixture for 1/2 hr at reflux temperature. These oxo acids showed spectral properties identical to those of the corresponding starting materials.

Retroreaction of (Ib, IIb)

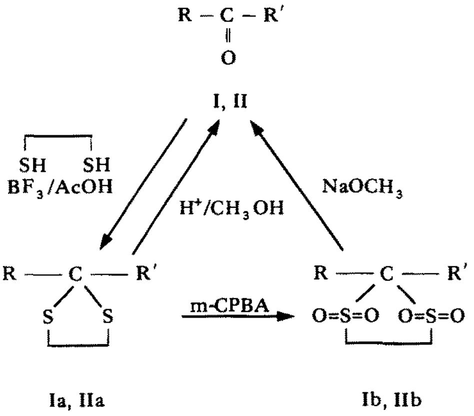
A methanolic solution of disulfolanes and equal weight of sodium methoxide were refluxed according to the procedure of Daum and Clarke (13) for 1 hr. Purification from column chromatography gave pure products (~75%) which had spectral and TLC characteristics identical to those observed for authentic samples.

RESULTS AND DISCUSSION

Four oxygenated acids possessing carbonyls at different positions (penultimate, internal mono- and vicinal dioxo, and 2-oxo) were selected as model compounds. The procedure of Fieser (2) for condensation of oxo compounds with ethanedithiol was followed in the present study. Optimum conditions were maintained for the oxidation and decomposition of dithiolanes. Disulfolanes were decomposed according to the procedure followed by Daum and Clarke (13).

Ketalization of ethanedithiol in presence of BF_3-etherate and acetic acid with oxo-esters I and II gave a quantitative yield of the corresponding dithiolanes. IR spectra of Ia and IIa were not of much significance in revealing the functionality except the quenching of the band observed for isolated oxo function. Dithiolanes have not been reported to show any characteristic band beyond CH_2-S wagging and deformation, which were pronounced in the spectra. The NMR spectrum of Ia exhibited a characteristic sharp singlet at ∂ 3.28, integrating for 4 protons. The signal experienced the identical environment for the 2 methylene groups, which could be possible only if cyclization had occurred to yield dithiolane. Other evidences in favor of the incorporation of ring at C_{10} were the downfield appearance of signal as a singlet at 1.75 attributable to terminal methyl and another one at 1.85 instead of 2.3 for C_9 methylene protons. Internal dithiolane (IIa) gave NMR characteristics similar to Ia but a signal at 0.9 for terminal methyl protons.

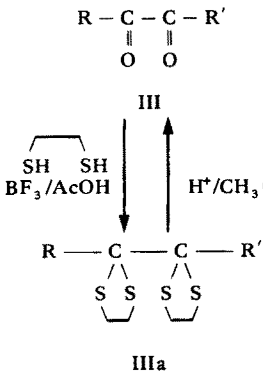
The interesting observation was in the reaction of methyl 9,10-dioxooctadecanoate (III) with ethanedithiol to afford bisdithiolane (IIIa). It showed IR characteristics similar to those of Ia and IIa. The NMR spectrum of IIIa was very



I,Ia,Ib: R = CH_3 ; R' = $(CH_2)_8COOCH_3$

II,IIa,IIb: R = $CH_3(CH_2)_5$; R' = $(CH_2)_{10}$-$COOCH_3$

SCHEME 1



III,IIIa: R = $CH_3(CH_2)_7$; R' = $(CH_2)_7$-$COOCH_3$.

SCHEME 2

similar to IIa except the signal at ∂ 3.35 integrated for 8 protons. This signal suggested the participation of both carbonyls in the formation of dithiolane rings.

Reaction of monodithiolanes (Ia, IIa) with m-CPBA gave almost a quantitative yield of oxidized products which were identified as disulfolanes (Ib,IIb). The IR spectra of both the products were similar and identified the sulfone groupings. The 2 strong bands at 1320-1340 and 1130-1135 cm^{-1} were observed as the characteristics of sulfone functions. The structure-revealing signal in NMR spectra of both Ib and IIb was at ∂ 3.7. The downfield appearance of this signal in comparison with those of Ia and IIa (3.28 and 3.3 respectively) clearly indicated the oxidation of the sulfide into the sulfone group. Other NMR characteristics of both Ib and IIb were similar, except the chemical shift observed for the terminal methyl group. While these protons of the methyl group in the spectrum of Ib appeared at ∂ 1.8 as a singlet, in IIb it was located at 0.88 as a triplet.

In the present study the retroreactions of dithiolanes and disulfolanes in acidic and alkaline media respectively have been observed.

MS Studies of Dithiolanes and Disulfolane

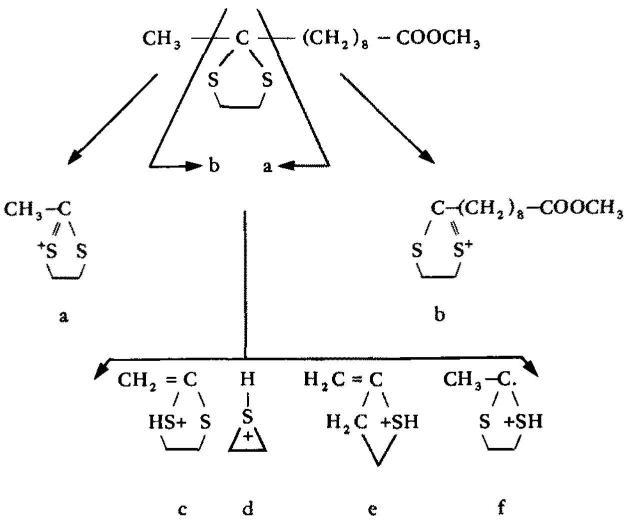
Primary study on thioether fragmentation was carried out by Levy and Stahl (17), who reported 3 main fragments: C-S cleavage, α-cleavage and olefin elimination to form mercaptan ions. Later, Sample and Djerassi (18) observed another significant fragment arising from further decomposition of the ion observed due to α-cleavage through 3-, 4-, 5- or 6-membered transition states. Similarly, very few reports are available on the study of mass fragmentation patterns of fatty acid sulfones (19). Molecular ions result by ionization at the oxygen atom. Cleavage of C-S, α, β and γ-bond with one or 2 hydrogen rearrangements and loss of OH, H_2O and (H_2O + OH) are characteristics of alkyl sulfones. However, mass spectrometric reports on such fatty acid-based spiro compounds are lacking. We now report the characteristic mass fragment ions of chain-substituted monodithiolanes Ia,IIa bisdithiolane IIIa and monodisulfolane derivatives.

Comments on Mass Spectra[1]

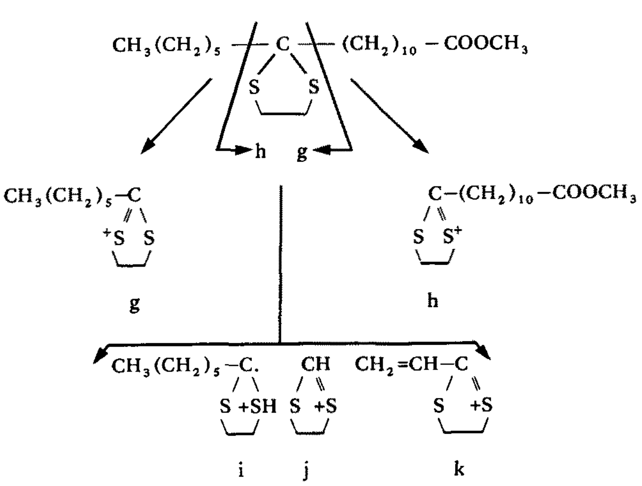
Methyl 10,10-ethylenedisulfideundecanoate (Ia): The peaks at 290(M$^+$,6) 259(M-OCH$_3$,2) and 231(M-COOCH$_3$,2) confirm the molecular weight of this compound. The 2 structure-revealing characteristic fragments rising from the α-cleavages to the ring are at 119(a, 100) and 275(b, 2). A diagnostic signal at 165(259-HSCH$_2$CH$_2$SH,2) indicates the nature of the substituent. Other significant mass ions are at 120(f, 10), 61(d, 10), 87(e, 7), 74(a-CHS, 9), 69(5), 59(24) and 55(20).

Methyl 12,12-ethylenedisulfideoctadecanoate (IIa): The molecular ion peak at 388 (3) and a diagnostic signal at 357 (1) resulting from the loss of methoxy radical directly from M$^+$ correspond with the molecular formula $C_{21}H_{40}S_2O_2$.

The characteristic α-cleavages to the ring give 2 prominent mass ions at 189(g, 100) and 303(h, 31). The other structure-revealing fragments at 190(i, 11) and 304(h+1, 5) arising from α-cleavages but with one hydrogen along with g and h establish the position and nature of the ring. Other dominant peaks observed are at 131(k, 11), 119(c, 6), 105(j, 14), 61(d, 51), 87(e, 15), 191(g+2, 9), 305(h+2, 3), 95([HS(CH$_2$)$_2$SH$_2$]$^+$, 15), 83(13), 69(38), 59(46), 55(91) and 74(31).



SCHEME 3



SCHEME 4

Methyl 9,9,10,10-bisethylenedisulfideoctadecanoate (IIIa): The MS of this bisthioketal shows a molecular ion peak at 478 (10), an associated peak at 447 (M-OCH$_3$, 11) and one of the most significant peaks at 386 (p, 13) emerging due to loss of SCH$_2$CH$_2$S from M$^+$. These valuable fragments prove the size and nature of the substituent.

The 2 interesting 'characteristic' fragments are encountered at 216(1, >100) and 260(M, <100) which arise from the cleavage of the C_9-C_{10} bond but with one hydrogen loss. This observation is considered unusual and attributed to the presence of 2 vicinal rings. The other mass fragments which dominate the spectrum are 131(k, 100), 119(c, 82), 145(o, 37), 218(n, 88), 105(j, 88), 219(218+1, 62), 106 (105+1, 6), 107(105+2, 18), 355(p-OCH$_3$, 19), 229 (m-OCH$_3$, 48), 232(m-CH$_2$CH$_2$, 2), 188(1-CH$_2$CH$_2$, 5), 189(1-C$_2$H$_3$, 9), 97(16), 83(13), 69(27), 59(60), 55(74) and 74(8).

Methyl 10,10-ethylenedisulfonylundecanoate (Ib): A small molecular ion peak at 354 (1) along with a dominating mass fragment appearing at 323(M-OCH$_3$, 17) are consistent with the molecular weight.

Characteristic fragments due to α-cleavage to ring, due to the loss of a larger group, appear at 183(q, 14) and 171(r, 7). A significant ion at 262(t, 13) originates from one C-S bond cleavage. Another diagnostic fragment arises

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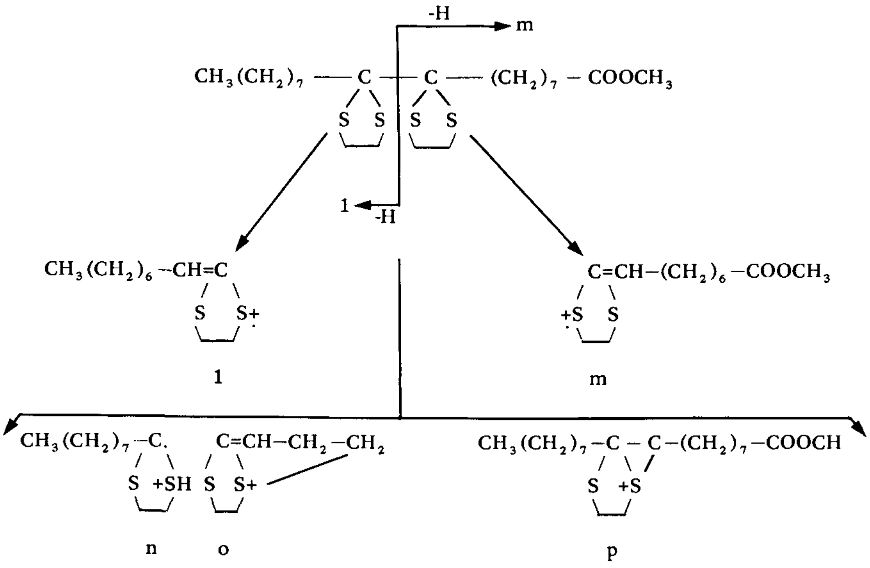
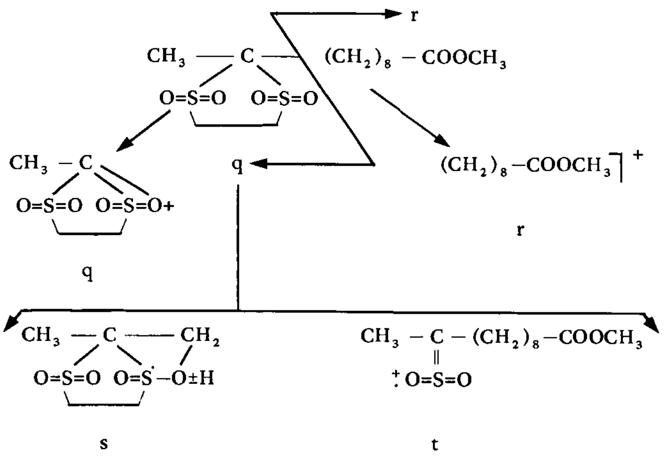
[1] MS values quoted are m/z. Figures in parentheses indicate the intensity of a peak relative to the base peak (100) and provide, where possible, some indication of its source.



SCHEME 5



SCHEME 6

from γ-cleavage to ring with one hydrogen transfer to oxygen and is observed at 198(s, 3). Other significant peaks observed are at 355(M+1, 2), 356(M+2, 0.5), 230(t-CH_3OH, 2), 202(230-CO, 4), 263(262+1, 3), 188(t-CH_3COOCH_3, 9), 184(q+1, 2), 166(q-OH, 25), 165(q-H_2O, 3), 148(q-H_2O+OH, 4), 147(q-$2H_2O$, 3), 149(q-2OH, 2), 139(7), 125(8), 111(10), 97(26), 83(40), 69(42), 73(8), 59(42), 55(96) and 74(98).

A few general comments may be made from the results of the present study of MS of dithiolanes. Molecular ion peaks, although of low intensity, were present. There are prominent α-cleavages to ring which unambiguously yield the structure of the compound and determine the position of the ring in the chain. The fragments (j, c and k) may be considered characteristic of alkyl chain-substituted dithiolane rings, and their relative intensities are found to depend upon the nature of substituents in the rings. The other 2 fragments (d and e) are of course characteristic of thioether moiety. The MS of disulfolane, like dithiolanes, also provided similar significant and characteristic information. As expected, the spectrum was dominated by hydrocarbon fragments.

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