# Synthesis of Substituted Fatty Oxathiolanes and Thioethers from an Allylic Oxo Fatty Acid Ester

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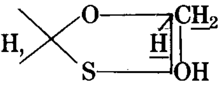
**Substituted oxathiolane and thioether derivatives have been synthesized from an allylic oxo fatty acid ester. The reaction of methyl 4-oxo-*trans*-2-octadecenoate with 3-mercaptopropan-1,2-diol (1-thioglycerol) affords methyl 4-(3′-hydroxymethyl-1′,4′-oxathiolane)-2(3)-(O-mercaptopropan-1″,2″-diol)-octadecanoate (II), methyl 4-oxo-2(3)-(O-mercaptopropan-1′,2′-diol)-octadecanoate (III), methyl 4-(3′-hydroxy-1′,5′-oxathiane)-2(3)-(S-mercaptopropan-1″,2″-diol)-octadecanoate (IV), methyl 4-oxo-2(3)-(S-mercaptopropan-1′,2′diol)-octadecanoate (V) and methyl 4-(3′-hydroxymethyl-1′,4′-oxathiolane)-2(3)-(S-mercaptopropan-1″,2″-diol)-octadecanoate (VI). Structures of the individual reaction products have been established on the basis of spectral data and microanalyses.**

Syntheses of compounds containing an oxathiolane moiety have attracted attention for their important biological applications (1-3). Sulfur-containing compounds of thioether nature have been synthesized and tested for various biological activities (4-7). Recently, we have reported the synthesis of a substituted fatty *bis*-oxathiolane (8) from the reaction of 9,12-dioxooctadecanoic acid with 1-thioglycerol in the presence of borontrifluoride-etherate ($BF_3$-etherate). Husain et al. have also reported the synthesis of substituted fatty oxathiolanes (9) and thioethers (10) from the reactions of oxo- and olefinic fatty acids with 1-thioglycerol, respectively. In view of the growing importance of these two functionalities and in continuation of our research programs related to the derivatization of saturated (8,9,11) as well as unsaturated (12) oxo fatty acids into fatty oxathiolanes and thioethers for their possible industrial utilization, it was considered desirable to carry out the synthesis of some new fatty acid derivatives containing both oxathiolane and thioether functionalities. This paper reports the reaction of methyl 4-oxo-*trans*-2-octadecenoate with 1-thioglycerol leading to the formation of both oxathiolane and thioether derivatives.

## EXPERIMENTAL PROCEDURES

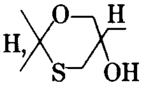
The spectroscopic and chromatographic methods used have been given in detail in an earlier communication (12). Mass spectra were recorded on a JEOL JMS D-300 mass spectrometer at 70 eV. The figures in parentheses denote the postulated source of the ions along with the intensity relative to the base peak. Methyl 4-oxo-*trans*-2-octadecenote (I) (m.p.68 C) was prepared and characterized by the method adopted earlier (13).

*Reaction of I with 1-thioglycerol (in excess).* I (2 g, 0.0064 mol) was stirred with 1-thioglycerol (10.1 g, 0.093 mol) in the presence of $BF_3$-etherate as catalyst at 25°C for 30 min. Progress of the reaction was monitored by thin-layer chromatography (TLC). The reaction mixture was diluted with water and extracted with ether. The ether extract was washed successively with 5% aqueous $NaHCO_3$ and water, and dried over anhydrous $Na_2SO_4$. Evaporation of the ether solvent in vacuo gave a viscous oil (1.9 g) which showed five distinct spots on TLC. The viscous oil was fractionated over a silica gel (40 g) column with mixtures of petroleum ether-ether as eluents into II (7%, 95:5, v/v), III (5%, 92:12, v/v), IV (13%, 80:20, v/v), V (20%, 70:30, v/v), and VI (54%, 55:45, v/v) as liquids. II: (Found: C, 59.14; H, 9.56. $C_{25}H_{48}O_6S_2$ requires: C, 59.01; H, 9.50%); IR (neat): 3400 (OH), 2585 w (S-H), 1735 ($\underline{CO}OCH_3$), 1440 ($CH_2$-S def.), 1240 ($CH_2$-S wag.) and 1030 $cm^{-1}$ (oxathiolane ring) (14); NMR ($CCl_4$): δ 4.5-3.75 br,m (7H,

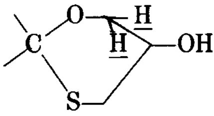


and $\begin{array}{l} -C\underline{H}-\qquad CH_2SH),\\ \ \ |\qquad\qquad\ \ |\\ -O-C\underline{H}_2-C\underline{H}-OH\end{array}$

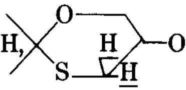
2.92 br, s (2H, $2xO\underline{H}$), 2.75-2.5 (proton α to sulfur in oxathiolane ring, $-C\underline{H}_2SH$), 2.3 (protons α to ester carbonyl), 1.7 m (protons α to oxathiolane ring), 1.6 m (1H, $S\underline{H}$), 1.3 br, s (chain-$C\underline{H}_2$-), 0.9 t (3H, terminal-$C\underline{H}_3$); MS(70 eV): m/z 508 ($M^{+\cdot}$, absent), 490(M-$H_2$0, parent ion,11), 499 (M-$COOCH_3$, 14.6), 435 (12.2), 417 (40.0), 339 (37.2), 325 (13.2), 315 (34.8), 311 (64.0), 193 (30.0), 179 (28.7) and 73(100). III: IR (neat): 3500 (OH), 1735 ($\underline{CO}OCH_3$), 1710 (CO), 2550 w (SH), 1430 ($CH_2$-S def.) and 1235 $cm^{-1}$ ($CH_2$-S wag.); NMR ($CCl_4$): δ 4.17 m (1H, $-\underset{\underset{\textstyle O}{\|}}{C}-\underset{\underset{\textstyle O-}{|}}{C\underline{H}}-$), 3·8m (3H, $\underset{\underset{\textstyle -O}{|}}{C\underline{H}_2}-\underset{\underset{\textstyle O-}{|}}{C\underline{H}}-$), 2.8 m (2H, $-C\underline{H}_2-SH$), 2.5 br, s (1H, $-O\underline{H}$, $D_2O$ exchangeable), 2.4 m (4H, $-C\underline{H}_2-\underset{\underset{\textstyle O}{\|}}{C}-\underset{\underset{\textstyle O-}{|}}{CH}-C\underline{H}_2COOCH_3$), 1.6 m (1H, $S\underline{H}$, 1.3 br, s (chain-$C\underline{H}_2$-) and 0.9 t (3H, terminal-$C\underline{H}_3$); MS (70 eV): m/z 418 ($M^{+\cdot}$, 14.6), 359 (M-$COOCH_3$, 29.9), 345 (16.5), 341 (15.2), 312 (345-SH, 34.8), 310 (22.0), 225 (61.0), 221 (43.3), 193 (34.8), 179 (52.5), 149 (38.4), 128 (39.0), 113 (55.5) and 73 (100). IV: (Found: C, 59.15; H, 9.54. $C_{25}H_{48}O_6S_2$ requires: C, 59.01; H, 9.50%); IR (neat): 3360 (OH), 2590 (SH), 1740 ($\underline{CO}OCH_3$), 1410 ($CH_2$-S def.), 1220 ($CH_2$-S wag.) and 1035 $cm^{-1}$(oxathiane ring vibration); NMR($CCl_4$): δ 4.8m (1H,



), 4.2-3.8 m (5H,



, $-\underset{\underset{\textstyle OH}{|}}{C\underline{H}}-\underset{\underset{\textstyle OH}{|}}{C\underline{H}_2}$), 2.6 br, s (3H, 3xOH, $D_2O$ exchangeable), 3.18-2.82 m (5H,



, $-C\underline{H}$-S-$C\underline{H}_2$-), 2.38 m (protons α to ester carbonyl), 1.68 (protons α to ring), 1.3 br, s (chain-$CH_2$-), and 0.88 t (3H, terminal-$C\underline{H}_3$); MS (70 eV): m/z 508 ($M^{+\cdot}$, 10.4), 449 (M-$COOCH_3$, 20.7), 447 [M-CH(OH).$CH_2OH$, 29.3], 435 (17.7), 400 (17.1), 315 (27.4), 311 (28.1), 310 (9.1), 283 (315 -$OCH_3$, 36.6), 255 [315-$(CHOH)_2$, 47.6], 251 [311-

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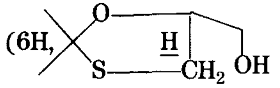
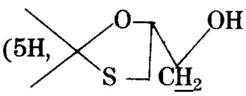
$(CHOH)_2$, 21.3], 203 (61.6), 193 (33.5), 179 (60.0), 128 (61.0), 113 (45.6) and 73 (100). V: (Found: C, 63.18; H, 10.16. $C_{22}H_{42}O_5S$ requires: C, 63.12; H, 10.11%); IR (neat): 3320 (OH), 1745 ($\underline{CO}OCH_3$), 1720 (CO), 1435 ($CH_2$-S def.) and 1250 cm$^{-1}$ ($CH_2$-S wag.); NMR ($CCl_4$): $\delta$ 4.2-3.8 m (3H,$-C\underline{H}(\underset{|}{}OH)-C\underline{H}_2(OH)$) $\left(3H,-\underset{\displaystyle OH}{\underset{|}{C\underline{H}}}-\underset{\displaystyle OH}{\underset{|}{C\underline{H}_2}}\right)$, 3.4 m $\left(-\underset{\displaystyle O}{\underset{\|}{C}}-C\underline{H}-S\right)$, 2.68 m (3H, $-C\underline{H}-S-C\underline{H}_2-$), 2.5 m (2H, 2xO$\underline{H}$,$D_2O$ exchangeable), 2.3 m (4H, protons $\alpha$ to carbonyl functions), 1.3 br, s (chain-$CH_2$-), 0.9 t (3H, terminal-$C\underline{H}_3$); MS (70 eV):m/z 418 ($M^{+}$, 17.0), 359 (M-$COOCH_3$, 25.6), 358 (M - CHOH.CHOH, 14.0), 345 (22.6), 342 (358 -$CH_2$, 15.2), 284 (345 - CHOH.$CH_2$OH, 34.2), 225 (59.2), 221 (12.8), 203 (221 -$H_2$0, 49.4), 193 (33.0), 179 (55.0), 128 (44.5), 113 (48.8) and 73 (100). VI: (Found: C, 59.17; H, 9.55. $C_{25}H_{48}O_6S_2$ requires: C, 59.01; H, 9.50%); IR (neat): 3240 (OH), 1745 ($\underline{CO}OCH_3$), 1410 ($CH_2$-S def.), 1250 ($CH_2$-S wag.) and 1040 cm$^{-1}$ (oxathiolane ring); NMR ($CCl_4$): $\delta$ 4.15-5.0 br, m (6H,



and $\underset{\displaystyle OH}{\underset{|}{-C\underline{H}}}-\underset{\displaystyle OH}{\underset{|}{C\underline{H}_2}}$), 3.17-2.65 br, m (5H,



and $-C\underline{H}-S-C\underline{H}_2-$), 2.6 m (3H, 3xO$\underline{H}$, $D_2O$ exchangeable), 2.3 m (protons $\alpha$ to ester group), 1.7 m (protons $\alpha$ to oxathiolane ring), 1.3 br, s (chain-$C\underline{H}_2$-) and 0.9 t (3H, terminal-$CH_3$); MS (70 eV): m/z 508 ($M^{+}$) (Fig. 1).

## RESULTS AND DISCUSSION

Methyl 4-oxo-*trans*-2-octadecenoate (I) when treated with 1-thioglycerol in presence of $BF_3$-etherate as catalyst afforded a viscous liquid which on fractionation over a silica gel column gave five products (II, III, IV, V and VI) (Scheme 1).

The product (II) obtained as liquid on microanalysis gave composition $C_{25}H_{48}O_6S_2$. It showed characteristic oxathiolane ring vibration at 1030 cm$^{-1}$. Disappearance of bands at 1640 and 970 cm$^{-1}$ and appearance of a weak band at 2585 cm$^{-1}$ (S-H) indicated the consumption of a double bond and formation of ether linkage. The NMR spectrum of II exhibited signals at $\delta$ 4.5-3.75 as a multiplet integrating for seven protons attached to oxygen. The two singlets at $\delta$ 3.69 and 3.63 for ester protons indicated the formation of an isomeric mixture of ethers on the $\alpha$-as well as the $\beta$- carbons. It gave a multiplet at $\delta$ 2.75-2.5 for methylene protons attached to sulfur. Mass spectral fragmentation data of II (Scheme 2) clearly confirmed its isomeric nature.

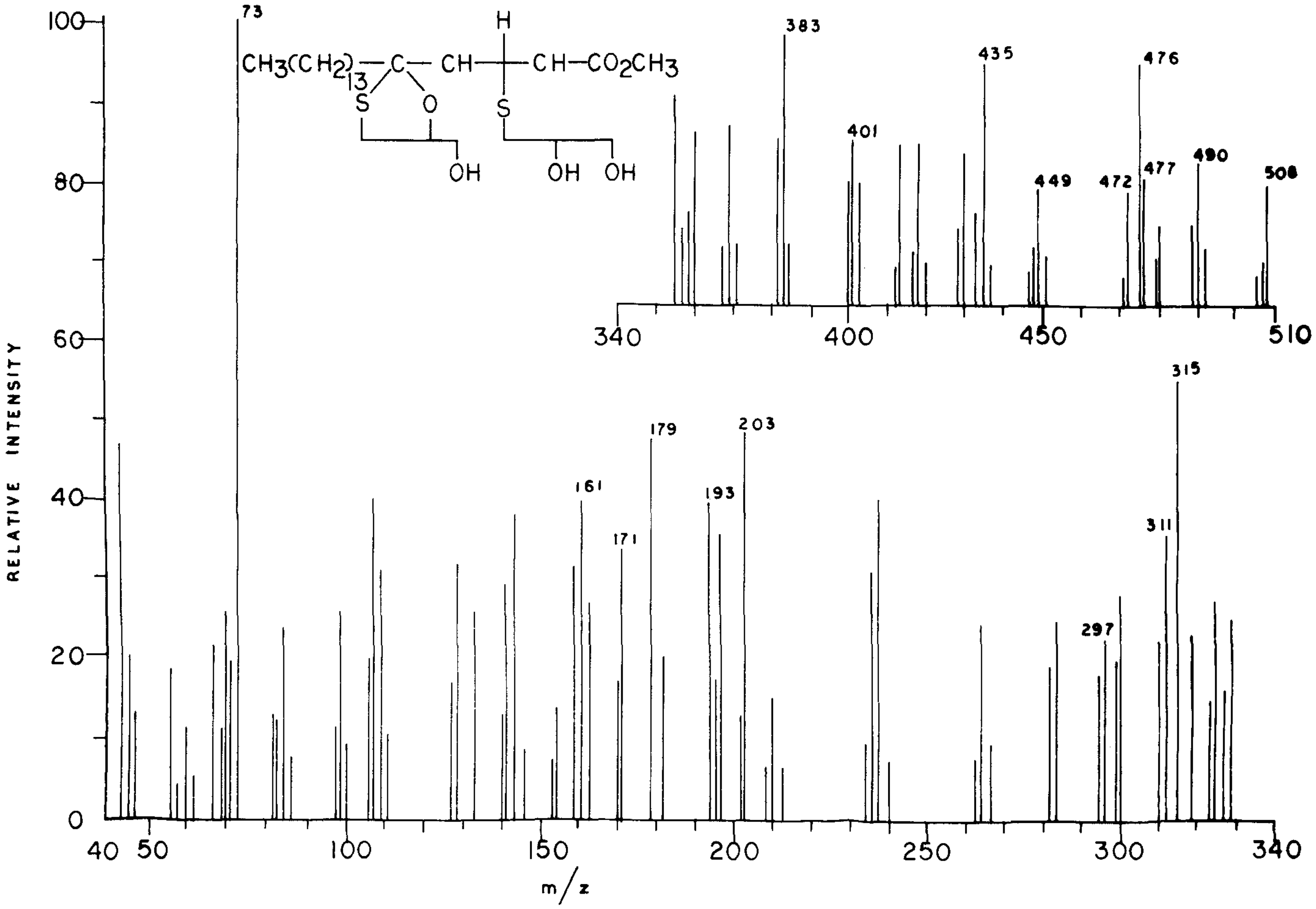
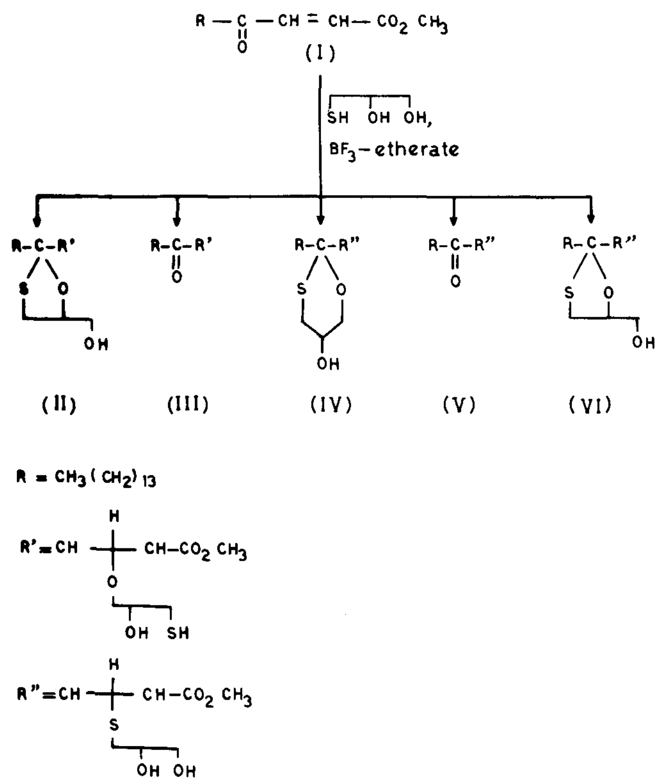


FIG. 1. MS of VI.



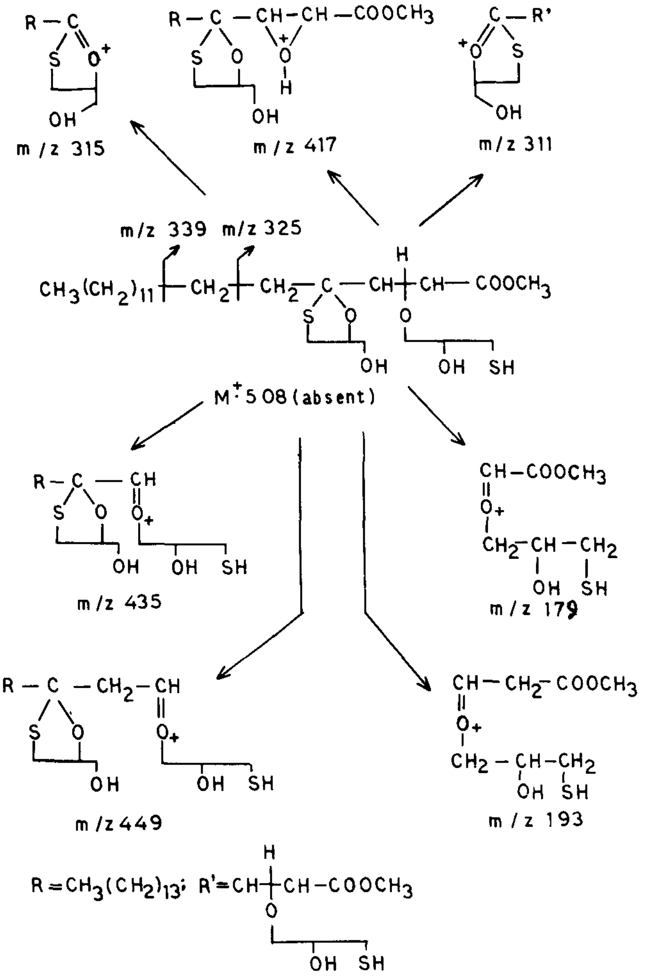
**SCHEME 1. Reaction Scheme.**

The α-cleavage ion peaks at m/z 315 and 311 and ion peaks at 449, 435, 193, 179 established the position of a ring at $C_4$ and an ether moiety at α- and β-carbons, respectively.

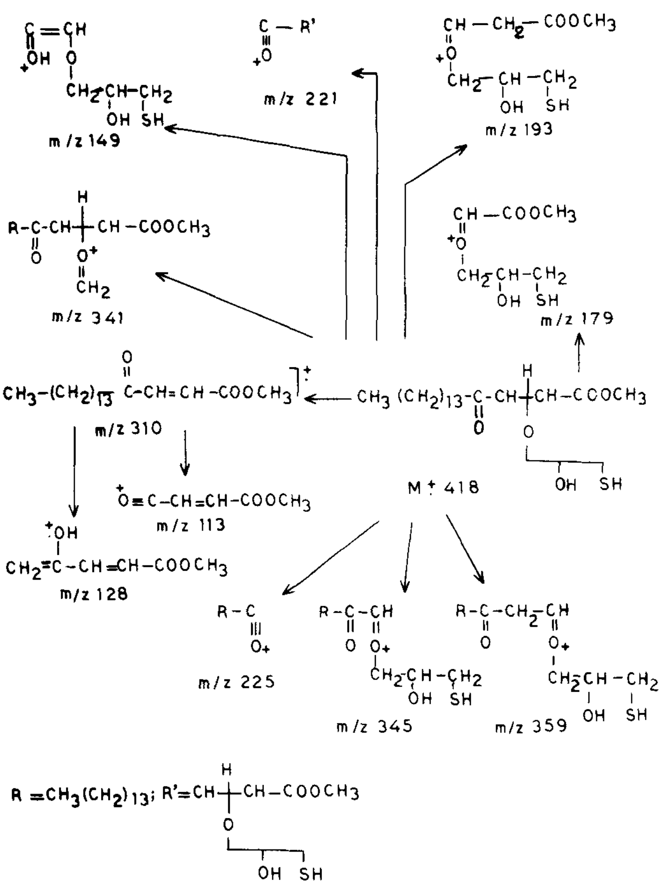
The product (III) obtained as a yellowish liquid gave an IR band at 1710 cm$^{-1}$ showing nonparticipation of 4-oxo function. It also gave bands at 1070 (ether linkage) along with bands at 3500 (OH), 2250 (SH), 1430 and 1235 cm$^{-1}$ ($CH_2$-S group). The NMR spectrum gave signals at δ 4.17 m (1H, $-\underset{\underset{O}{\|}}{C}-\underset{\underset{O}{|}}{\underline{CH}}-$), 3.8 m (3H, $-O-\underline{CH_2}-\underset{\underset{OH}{|}}{\underline{CH}}-$), 2.8 m (2H, $\underline{CH_2}$-SH) and 2.4 m (4H, methylene protons α to carbonyl groups) along with usual signals. Mass spectral fragmentation data (Scheme 3) clearly established the position of the side chain through oxygen at $C_2$ and $C_3$ by showing ion peaks at m/z 359, 179, 345 and 193. α-Cleavage ions at m/z 225 and 221 and a McLafferty ion at 128 confirmed the presence of an oxo group at $C_4$.

The product (IV) was analyzed for $C_{25}H_{48}O_6S_2$. It showed characteristic IR bands at 3360 (OH) and 1035 cm$^{-1}$ (oxathiane ring). Its NMR spectrum exhibited a downfield multiplet at δ 4.8 (one methine proton attached to a hydroxyl group in a six-membered ring). The disappearance of IR bands at 2590 (SH) and 1075 cm$^{-1}$ (ether linkage), and appearance of NMR signals at δ4 2-3.8 m ($-\underset{\underset{OH}{|}}{\underline{CH}}-\underset{\underset{OH}{|}}{\underline{CH_2}}$ and methylene protons α to oxygen in ring) and a multiplet at 3.18-2.82 integrating for 5 protons indicated the attack of 1-thioglycerol through sulfur; otherwise its integration would have been 4 protons. Its isomeric form, obtained by the attack of a primary hydroxyl group of reagent, may be formed but could not be isolated. The MS of compound (IV) showed important fragment ions at m/z 315 and 311 which indicated the position of an oxathiane ring at $C_4$. The location of side chain both at $C_2$ and $C_3$ was confirmed by the ion peaks at 449, 179, 435 and 193 (Scheme 4).

The product (V), obtained as a yellowish liquid, gave the elemental composition $C_{22}H_{48}O_5S$. It showed IR bands at 1435 and 1250 cm$^{-1}$ for thioether linkage along with a nonparticipating 4-oxo function at 1720 cm$^{-1}$. Its NMR spectrum was very similar to that of III. It showed disappearance of SH signal and appearance of signals at δ3.4 m (1H, $-\underset{\underset{O}{\|}}{C}-\underset{\underset{S}{|}}{\underline{CH}}-$), 2.68 m ($-\underline{CH}-S-\underline{CH_2}-$) along with δ4.2-3.8 m ($\underset{\underset{OH}{|}}{\underline{CH}}-\underset{\underset{OH}{|}}{\underline{CH_2}}$) which confirmed the attachment of sulfur both at $C_2$ and $C_3$. It was further confirmed by its mass spectral fragmentation pattern that is very similar to those of compound III as shown in Scheme 3. The ion peaks at m/z 359, 179, 345 and 193 located the side chain at $C_2$ and $C_3$, and ions at 225, 221 and 128 (McLafferty ion) showed the nonparticipation of the 4-oxo function.



**SCHEME 2. Mass fragmentation pattern of II.**

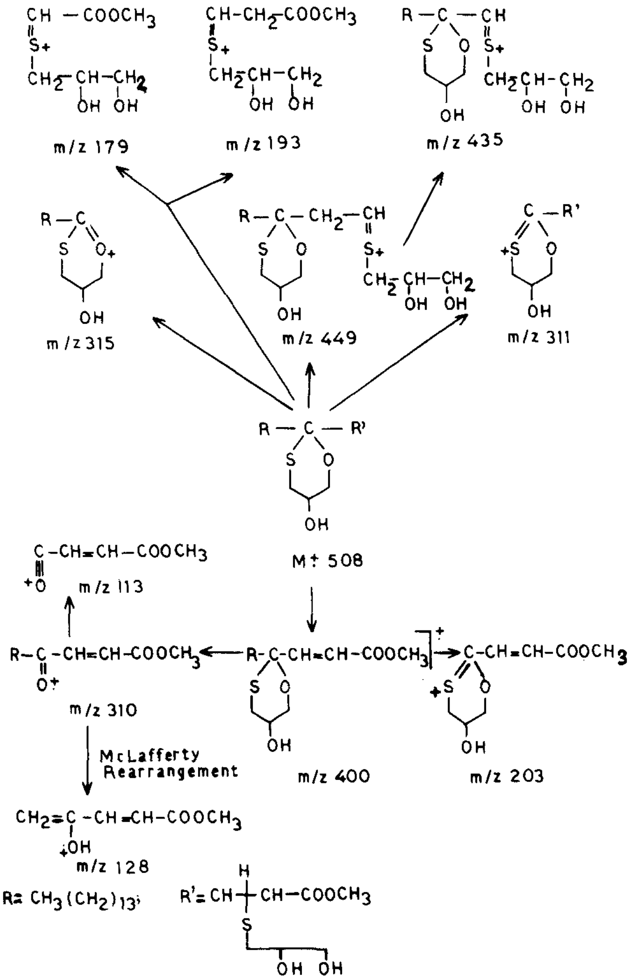


**SCHEME 3. Mass fragmentation of pattern III.**

The product (VI), obtained as a liquid, was found to have a composition of $C_{25}H_{48}O_6S_2$. It exhibited almost similar IR bands to those of V except the disappearance of bands at 2585 cm$^{-1}$ (SH grouping), which showed that the double bond was attached by a sulfur atom. NMR spectrum gave signals at $\delta$ 4.15-4.0 br, m (6H, two methine and four methylene protons attached to oxygen) and 3.3-2.65 br, m (5H, two methylene protons $\alpha$ to sulfur in ring and one methine and two methylene protons attached to sulfur in the chain) along with usual signals. Formation of the oxathiolane ring at $C_4$ and the side chain at $C_2$ and $C_3$ were confirmed by its mass spectral fragmentation patterns that are similar to those of I as shown in Scheme 2. The ion peaks at m/z 315, 311, 449, 179, 435 and 193 supported the assigned structure VI.

## ACKNOWLEDGMENT

The authors thank Prof. S.M. Osman for providing necessary facilities and CSIR, New Delhi, for financial assistance to one of us (MHA).



**SCHEME 4. Mass fragmentation of pattern IV.**

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[Received September 22, 1987; accepted December 26, 1988]
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