Oxidation of α-Lipoic Acid

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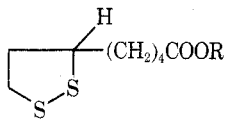
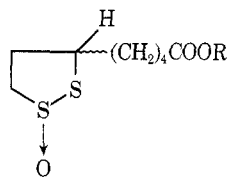
α-Lipoic acid has been oxidized (as its methyl ester, **3**) by a variety of oxidants, including singlet oxygen. An nmr chemical shift reagent, Eu(fod)$_3$-d_{27}, has been used to show that the products include four thiolsulfinates in all cases, and, in the case of singlet oxygen oxidation, two thiolsulfonates. The singlet oxygen oxidations are interpreted in terms of a mechanism involving initial formation of zwitterions by reaction of singlet oxygen at each of the two sulfur atoms in **3** followed by intramolecular or intermolecular reaction to give thiolsulfonate or thiolsulfinate, respectively.

α-Lipoic acid (1,2-dithiolane-3-valeric acid, thioctic acid, protogen-A),[1] **1**, has been of interest to biological chemists for some time but particularly since its isolation[2] and identification.[3] It has been identified as a growth factor for many bacteria and protozoa.[4-12] α-Lipoic acid is also known to be a coenzyme in oxidative decarboxylation reactions. Calvin and coworkers have suggested that **1** is involved in the primary quantum conversion act of photosynthesis.[1b,13]

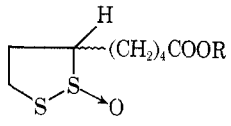
Interest in the oxidation products of α-lipoic acid began with the isolation from beef liver of a monooxidation product along with the parent compound.[14,15] This product was called β-lipoic acid (protogen-B) (**2a** or **2b**) and it was not



1, R = H
3, R = CH_3



2a, R = H
4a, R = CH_3



2b, R = H
4b, R = CH_3

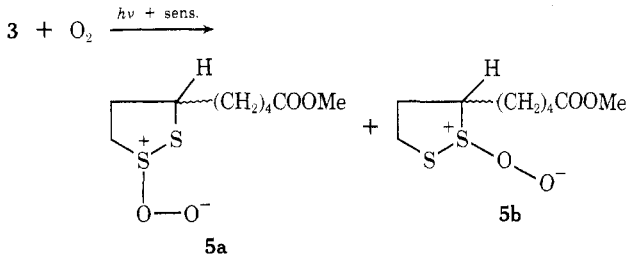
known whether it was a naturally occurring substance or whether it was produced by oxidation of α-lipoic acid during the work-up. Likewise it was not possible to determine which sulfur atom had been oxidized. Structure **2a** has generally been favored for β-lipoic acid since the specific rotation of the thiosulfinate prepared from (+)-α-lipoic acid is almost identical with that of the parent compound.[1e] Saito and Fukui[16] have oxidized *dl*-α-lipoic acid with hydrogen peroxide and isolated two monosulfoxides. They suggested that one of these is β-lipoic acid (assigned structure **2a**) and that the other is either a compound in which the other sulfur atom has been oxidized, **2b**, or a "conformational isomer" of β-lipoic acid by which they presumably meant the cis or trans isomer of **2a**.

The acid has also been oxidized to β-lipoic acid by *tert*-butyl hydroperoxide[17] and by hydrogen peroxide and potassium permanganate.[18] In most cases identification of the product was made by comparison of the infrared spectrum with that of protogen-B (β-lipoic acid) isolated from natural sources. In no case was it possible to distinguish between structure types **2a** and **2b** although Reed, *et al.*,[18] recognized that both possibilities existed.

We have been interested in the possible role of singlet oxygen in the photodynamic effect.[19,20] In particular, we have been studying the reactions of singlet oxygen with disulfides as models for biological substrates containing the cysteine residue or other disulfide linkage.[21-25] As part of this study we have oxidized *dl*-α-lipoic acid under singlet oxygen conditions as well as with other oxidants.

Results and Discussion

Preliminary results from the photosensitized oxidation of **1** indicated that work-up of the reaction mixture was made difficult by the presence of the polar acid group. Consequently, all further oxidation studies used the methyl ester, **3**. Photosensitized oxidation of **3** in chloroform, followed by preparative tlc work-up, led to the isolation of four tlc bands with R_f values of 0.27, 0.39, 0.68, and 0.77. On the basis of infrared and mass spectral analyses the bands with R_f values of 0.27 and 0.39 were determined to be thiolsulfinates, and the band with R_f of 0.68 was determined to be thiolsulfonate. The fourth band which is present only in trace amount was not identified. Total yield of thiolsulfinates was 64% and total yield of thiolsulfonates was 25.7%. A photosensitized oxidation of **3** in methanol solvent gave similar tlc results. However, in this case total yield of thiolsulfinates was 75.4% and total yield of thiolsulfonates was 15.4%. The photosensitized oxidation is almost completely quenched in the presence of 1,4-diazabicyclo[2.2.2]octane (Dabco), a known[24] singlet oxygen quencher. Likewise, the reaction does not proceed in the absence of photosensitizer. Also pertinent to these results is the recent observation by Stevens and coworkers[25] that **1** can act as an inhibitor of rubrene autoperoxidation. The photosensitized oxidation thus is presumably a singlet oxygen oxidation and probably involves a zwitterionic intermediate (**5a** and **5b**) similar to that invoked in the singlet oxygen oxidation of dialkyl disulfides[22,23] and dialkyl sulfides.[26,27] These zwitterionic intermediates then can react further with **3** to give thiolsulfinates **4a**, **4a'**, **4b**, and **4b'** or react intramolecularly to give thiolsulfonates **6a** and **6b**.



5a **5b**

Operation of this mechanism requires 0.5 mol of O_2/mol of **3** which compares reasonably favorably with the observed values of 0.477 and 0.622 in chloroform and methanol, respectively. Additional support for the mechanism is available from a consideration of the thiolsulfinate–thiolsulfonate distribution as a function of solvent. In a very elegant and convincing study[27] of the effect of solvent, temperature, and concentration on product distribution in the

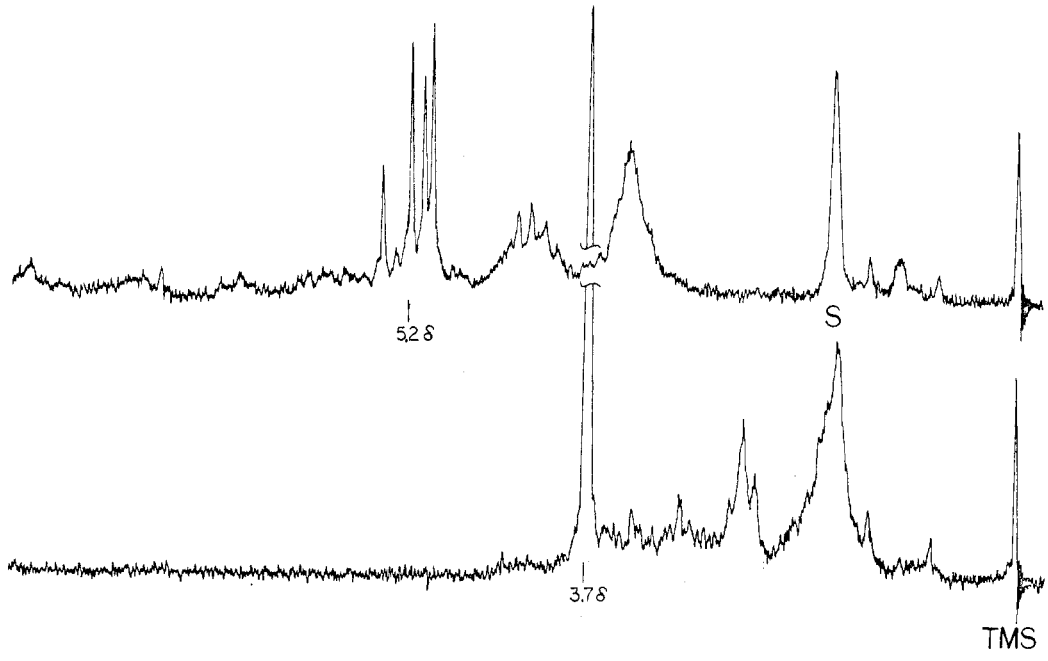
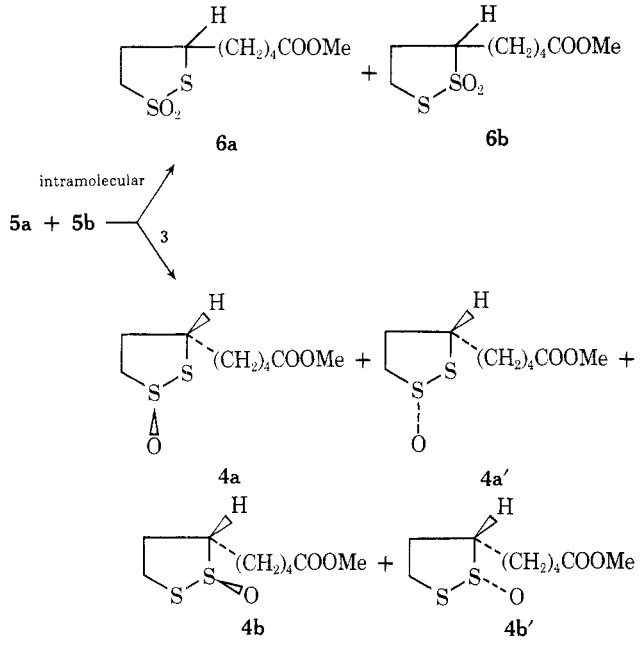


Figure 1. Effect of Eu(fod)$_3$-d_{27} on the nmr spectrum of the thiolsulfinate oxidation products of methyl α-lipoate. The bottom spectrum is the unshifted spectrum. The top spectrum was obtained with a ratio of shift reagent to substrate of 0.61. The peak marked S is due to the shift reagent.



singlet oxygen oxidation of sulfides, Foote and Peters have concluded that the sulfide-derived zwitterionic intermediate comparable to **5a** and **5b** is more likely to undergo the bimolecular reaction to give sulfoxide in protic solvents and high temperatures. On the other hand, the intramolecular reaction to give sulfone would be favored by aprotic solvent and low temperatures. These correlations were observed in the Foote and Peters work[27] and these workers have suggested that protic solvents favor intermolecular reaction by decreasing the negative charge density on the oxygen of the zwitterion by hydrogen bonding thus favoring nucleophilic attack by another molecule of sulfide. In aprotic solvents such stabilization is not present and the intramolecular reaction to sulfone (or decomposition to sulfide and ground state oxygen) is favored. Application of similar reasoning to the cases of **5a** and **5b** suggests that more thiolsulfonate should be formed in chloroform solvent than in methanol. The product distribution observed was 71.3% thiolsulfinate and 28.7% thiolsulfonate in chloroform solvent as compared to 83% thiolsulfinate and 17% thiolsulfonate in methanol. The product distribution results are thus consistent with a prediction based on the intermediacy of a zwitterionic species. It should be pointed out that our photosensitized oxidations were carried out at *ca.* 3–5° in both solvents. Presumably if a much lower temperature had been used for the chloroform case a higher percentage of thiolsulfinate would have been observed as predicted by the Foote and Peters scheme.

The singlet oxygen mechanism proposed for the oxidation of **3** suggests that four thiolsulfinate and two thiolsulfonate products are possible. During a major part of this investigation the available experimental results were very difficult to reconcile with this prediction. As indicated above, tlc analysis of the products in both reactions gave only two bands assignable to thiolsulfinate on the basis of ir and mass spectral analysis and only one band assignable to thiolsulfonate on the same grounds. Repeated analyses under a variety of tlc conditions did not change these results. Column and dry column chromatography did not disclose any evidence for the presence of additional products. Attempts to analyze the thiolsulfinate mixture by glpc led to disproportionation. This experience coupled with the approach we used to finally disclose the full range of products suggests that previous workers in this area may have treated difficultly separable mixtures as homogeneous substances.

We previously reported[28] the use of the nmr chemical shift reagent, tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-d_6-4,6-octanedione-d_3)europium(III), Eu(fod)$_3$-d_{27}, in studying heterosteric groups in acyclic thiolsulfinates. Use of the same reagent in the present study proved to be very rewarding. By obtaining the Eu(fod)$_3$-d_{27} shifted nmr spectra of the combined thiolsulfinate fractions we were able to conclude that all four thiolsulfinates, **4a, 4a′, 4b,** and **4b′,** were included in the products. Separate spectra run on the tlc band with R_f 0.27 indicated that it contained three thiolsulfinates while the band at R_f 0.39 contained a single thiolsulfinate. An example of the results obtained on the combined fractions is shown in Figure 1. The unshifted spectrum is complex with the sharp methyl singlet as a

Table I
Summary of Results of Oxidation of Methyl α-Lipoate

Oxidant	Solvent	Percentage Distribution of Thiolsulfinates A	B	C	D	% Total Yield of Thiolsulfinates	Percentage Distribution of Thiolsulfonates[a] E	F	% Total Yield Thiolsulfonates
O_2, *hν*, S	$CHCl_3$	9	48	28	16	64	59	41	25.7
O_2, *hν*, S	MeOH	14	29	25	32	75.4	14	86	15.4
$(NH_4)_2S_2O_8$	90% EtOH	15	30	25	30	21			Trace
t-BuOOH	MeOH	10	35	20	34	69			Trace
$CH_3C(O)OOH$	Et_2O	4	37	26	33	42	10	90	Not determined
$CH_3C(O)OOH$	MeOH	11	29	26	34	52			Trace
$(PhO)_3PO_3$[b]	CH_2Cl_2	12	33	23	32	26			Trace
$(PhO)_3PO_3$[c]	CH_2Cl_2	8	33	24	35	21			Trace
$CH_3C(O)OOH$[d]	MeOH	10	28	27	35	~26			Trace

[a] Where no data are given there was insufficient material for an accurate analysis. [b] "Fast" warm up as described in text. [c] "Slow" warm up as described in text. [d] With deliberate light exposure (about 50% loss of products).

prominent feature at δ 3.7. In the shifted spectrum this sharp singlet becomes four sharp singlets at 4.98, 5.07, 5.17, and 5.42, corresponding to the four thiolsulfinates. Various ratios of shift reagent to substrate were used in order to obtain these near-optimum results for the methyl region. By near optimum we refer to conditions which clearly show the four methyl absorptions while at the same time moving underlying absorptions from this region as much as possible. This is important since the distribution of the thiolsulfinates given in Table I was determined from the methyl absorption peak heights in the shifted spectrum. The thiolsulfinates are arbitrarily assigned the designations A–D with A having the furthest downfield methyl absorption and D having the furthest upfield absorption in the shifted spectrum. By examining various cuts of the tlc band at R_f 0.27 it was possible to show a nonhomogeneous distribution of the three thiolsulfinates within this band. It was never possible, however, to further resolve this band into separate bands. Examination of the thiolsulfonate tlc band at R_f 0.68 in a similar fashion indicated that the single methyl absorption in the unshifted spectrum at δ 3.7 is split into two sharp singlets at δ 7.37 and 7.66 in the shifted spectrum corresponding to the presence of the two expected thiolsulfonates, **6a** and **6b**. Again the thiolsulfonates are given the arbitrary designations of E and F with E being the compound with the methyl group furthest downfield in the shifted spectrum. After obtaining these results attempts were made to examine the thiolsulfonate mixture with glpc. In this case disproportionation is not a problem and glpc evidence for the presence of two thiolsulfonates can be obtained.

The thiolsulfinate and thiolsulfonate products all have two possible sites for coordination with the shift reagent. Some information on the major site of coordination in all cases was obtained by examining the shifted spectrum of unoxidized **3**. In this case, the shifted spectrum was obtained with a ratio of shift reagent to substrate of 0.279 and the methyl absorption was observed to move downfield from δ 3.7 to 7.0 in the shifted spectrum. When the thiolsulfonate mixture was examined at the same ratio of shift reagent it was observed that the methyl groups are shifted to approximately the same extent as in the unoxidized ester, **3**. For the shift reagent, tris(dipivalomethanoto)-europium(III), $Eu(dpm)_3$, it is known[29] that the coordination at an ester group leads to a greater shift than coordination at the less basic sulfonyl group. Thus for the thiolsulfonates we are observing shifts which are almost identical with those observed for the ester **3**, presumably because coordination is occurring primarily at the ester group. This conclusion is further strengthened by an examination of the shifts in the thiolsulfinates (Figure 1). In this case a larger ratio of shift reagent to substrate (0.61) leads to a smaller shift than for either the unoxidized ester or the thiolsulfonates. In this case the more basic sulfinyl group is presumably coordinating to a much larger extent with the shift reagent. In all cases, coordination to the ester group must be making the greatest contribution to the observed shift because of its greater proximity to the methyl group.

Use of the nmr shift reagent has been successful in permitting us to show the presence of expected products which could not be revealed in the thiolsulfinate case by any other analytical technique used. It is possible that application of the same technique would be fruitful in similar cases such as in the oxidation of *cis*- and *trans*-3,6-dimethyl-o-dithiane[30] where products cannot be easily separated and where complex nmr spectra are obtained.

Chemical Oxidation Studies

We next turned our attention to a number of chemical oxidations of **3** using some reagents which had been used previously for the oxidation of **1** and where, theoretically at least, the range of products also include **4a, 4a', 4b, 4b', 6a,** and **6b** or their acid analogs. In all cases we used the nmr shift reagent technique to examine thiolsulfinate fractions obtained by tlc. In most cases these oxidations did not give enough thiolsulfonate product under the reaction conditions to permit application of the shift reagent technique. The results of this study as well as the data from the photosensitized oxidations are given in Table I. In all cases the oxidations gave all four predicted thiolsulfinates. The distribution of the thiolsulfinate products is somewhat, but not markedly, different. A determination of the further significance if any, of this distribution and distribution variation, awaits detailed structural assignments in the products.

Saito and Fukui[16] oxidized α-lipoic acid with excess *tert*-butyl hydroperoxide and reported obtaining a single thiolsulfinate. Although their product was homogeneous to paper chromatography, the results obtained here suggest that it may have been a mixture of the two possible thiolsulfinates. Likewise the oxidation of α-lipoic acid by hydrogen peroxide which was reported by these same workers[16] to give only two thiolsulfinates based on paper chromatography analysis may actually have given all four possible thiolsulfinates. Similar comments may apply to other reported oxidations using *tert*-butyl hydroperoxide[17] and potassium permanganate.[18]

Attempted Structure Assignments

Assignment of the structures **4a, 4a', 4b, 4b', 6a,** and **6b** to the products A–F has proven to be an extremely difficult problem. Kato and Numata[31] have been quite successful in making structural assignments in the isomeric 4-hydroxy-1,2-dithiolane 1-oxides based on an analysis of the $Eu(dpm)_3$, shifted nmr spectra. In our case the presence of four isomers has made a similar approach using our $Eu(fod)_3$-d_{27} shifted spectra a more difficult and to-date insolvable problem. Unlike Kato and Numata we do not have available an analytical technique which permits isolation of all of the individual thiolsulfinates. The use of deuterium exchange followed by nmr analysis has also proven unsuccessful. In the case of the thiolsulfonates some exchange occurred, but since we were always dealing with a mixture of the two possible products analysis of the resulting nmr spectrum does not provide conclusive results. In the case of the thiolsulfinates attempted exchange led only to complete or near-complete decomposition. We are now attempting to make individual assignments of the structures **4a, 4a', 4b, 4b', 6a,** and **6b** to compounds A–F through the use of ^{13}C nmr spectroscopy. When such assignments are available it may be possible to further interpret the data in Table I. The significance of the results reported here is that each of the oxidants used gives a full range of the possible thiolsulfinate products as well as some thiolsulfonate product which results suggest that some previously reported oxidation studies of α-lipoic acid may have to be reevaluated.

Experimental Section

The nmr spectra were measured on a Varian T-60 high-resolution nmr spectrometer. Chemical shift values are δ values relative to internal TMS. The spectra were measured in $CDCl_3$ solution unless otherwise noted. Infrared spectra were measured on a Perkin-Elmer 137 infrared spectrophotometer. The photolysis apparatus was similar to one described in the literature[32] and used a General Electric DWY 650-W lamp without filter. The mass spectral analyses were carried out on a AEI MS-12 mass spectrometer and were run at 70 eV. The glpc analyses were performed on a Varian-Aerograph Model 705 gas chromatograph, using a 0.25 in. × 6 ft column of 10% Carbowax on 60–80 mesh Chromosorb, operated at 140° with a He flow rate of 40 ml/min.

Materials. Reagent grade benzene (Fisher), chloroform (Mallinckrodt), diethyl ether (Fisher), ethanol (U. S. Industrial Chemicals Co.), ethyl acetate (Fisher), methanol (Fisher), and Methylene Blue (Fisher) were used without further purification. Methylene chloride was stirred with concentrated sulfuric acid, washed successively with H_2O, 5–10% $NaHCO_3$, and H_2O, and dried twice with $CaCl_2$. It was then distilled from CaH_2 after refluxing for *ca.* 30 min.

Other materials used were $Eu(fod)_3$-d_{27} (Merck), *dl*-α-lipoic acid (Fluka AG, Germany, mp 60–61°), methanol-d_4 (Bio-Rad, 99.5 atom % D), and chloroform-*d* (Merck, 99.8 atom % D). Diazomethane was prepared from a Diazald kit (Aldrich). Tlc analyses were carried out on Merck precoated silica gel, F-254, 5 × 10 cm plates with 0.25-mm thickness. Preparative tlc plates were made from Merck silica gel, PF-254, on 20 × 20 cm glass plates with a thickness of *ca.* 1 mm. All plates were activated by heating in an oven at 125° for a minimum of 3 hr. Products were visualized by ultraviolet radiation.

Preparation of Methyl α-Lipoate. To a solution of 3.32 g (16.1 mmol) of α-lipoic acid in 50 ml of $CHCl_3$ was added a solution of 0.676 g (16.1 mmol) of diazomethane in 40 ml of diethyl ether.[33] The addition generated some heat and gas (N_2) evolution. The resulting solution was then stored for 24 hr with light excluded and then used as a stock solution of the ester. Aliquot analysis indicated that the reaction had proceeded in an essentially quantitative fashion. The pure ester is a pale yellow oil. It has nmr absorptions at 3.65 (s, 3 H, CH_3) superimposed on triplet at 3.6 (t, 1 H), 3.2 (rough t, 2 H), 2.3 (m, 4 H), and 1.6 (broad s, 6 H). The mass spectrum of α-lipoic acid has a peak at *m/e* 206 (M^+) and the ester has a peak at *m/e* 220 (M^+). The infrared spectrum of the neat ester has a strong doublet at 1715 cm^{-1}.

Photosensitized Oxidation of Methyl α-Lipoate in Chloroform. A solution of 1.01 g (4.59 mmol) of methyl α-lipoate and 0.0522 g of Methylene Blue in 200 ml of $CHCl_3$ was photooxidized for *ca.* 10 min at which time oxygen absorption had essentially ceased. A total of 49 ml (2.19 mmol) of O_2 had been absorbed. The temperature of the reaction solution was maintained at 3–5°. Solvent was removed *in vacuo* to give 1.17 g of residue. A portion (40.2 mg) of this residue was analyzed by preparative tlc using ethyl acetate–benzene (1:1) for development. Four bands were obtained with weights, R_f, and spectral data as follows:

Band No.	R_f	Wt (mg)	% of Total	*m/e*	ir
1	0.27	13.4	36	236	1070 cm^{-1} (thiolsulfinate)
2	0.39	10.4	28	236	1080 cm^{-1} (thiolsulfinate)
3	0.68	10.2	26	252	1310 cm^{-1} 1130 cm^{-1} (thiolsulfonate)
4	0.77	2.8	6	279	Unidentified

The nmr spectrum of band 1 had absorptions at 3.65 (s, 3 H, CH_3), 3.2 (t), 2.4 (m), 1.6 (broad s), 1.3 (s), and 0.9 (m). The nmr spectrum of band 2 had absorptions at 3.65 (s, 3 H, CH_3), 3.6–2.6 (m), 2.4 (t) and 1.6 (broad s). The nmr spectrum of band 3 had absorptions at 4.3 (broad m), 3.65 (s, 3 H, CH_3), 3.6–3.1 (m), 2.9 (d), 2.8 (d), 2.4 (t), and 1.6 (broad s). These materials were analyzed further with the aid of an nmr shift reagent as described below. Total yield of thiolsulfinates was 64% and of thiolsulfonates was 25.7%. Analysis of the thiolsulfonate band by glpc showed the presence of two peaks.

Photosensitized Oxidation of Methyl α-Lipoate in Methanol. A solution of 0.52 g (2.36 mmol) of methyl α-lipoate and 0.0567 g of Methylene Blue in 300 ml of methanol was photooxidized for *ca.* 5 min at which time oxygen absorption had essentially ceased. A total of 33 ml (1.47 mmol) of O_2 had been absorbed. Removal of solvent gave 0.62 g of residue. A portion (91.5 mg) of this material was analyzed by preparative tlc as previously described. Four bands were obtained with weights, R_f, and spectral data as follows:

Band No.	R_f	Wt (mg)	% of Total	*m/e*	ir
1	0.27	53.6	60	236	1070 cm^{-1} (thiolsulfinate)
2	0.39	8.5	9.5	236	1080 cm^{-1} (thiolsulfinate)
3	0.68	13.5	14	252	1310 cm^{-1} 1130 cm^{-1} (thiolsulfonate)
4	0.77	4.0	4	279	Unidentified

Total yield of thiolsulfinates was 75.4% and of thiolsulfonates was 15.4%.

Use of an Nmr Chemical Shift Reagent. The thiolsulfinates obtained by photosensitized oxidation of methyl α-lipoate in methanol were examined further using the chemical shift reagent, tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-d_6-4,6-octanedione-d_3)europium(III), $Eu(fod)_3$-d_{27}. When the material with R_f of 0.39 was treated with $Eu(fod)$-d_{27} all of the nmr absorptions were shifted to lower field. At ratios of shift reagent to substrate up to *ca.* 1.0 the methyl absorption remained a single sharp singlet. However, when the material with R_f of 0.27 was similarly treated the methyl absorption was shifted downfield and split into three sharp singlets at a ratio of shift reagent to substrate of 0.67. These observations are taken to indicate that these two tlc bands correspond to 1 and 3 thiolsulfinates, respectively. These thiolsulfinates are the cis and trans isomers arising from oxidation of each of the sulfur atoms of methyl α-lipoate and are designated thiolsulfinates A, B, C, and D with A being at lowest and D at highest field in the shifted spectrum. While it was never possible to completely separate by tlc the three thiolsulfinates found in the band with an R_f of 0.27, it was possible, by taking separate cuts of this broad band and using the nmr shift reagent, to show that the three thiolsulfinates are not distributed homogeneously in this band.

The thiolsulfonate tlc band (R_f 0.68) obtained from the photosensitized oxidation of methyl α-lipoate in chloroform was similarly treated with Eu(fod)$_3$-d_{27}. The nmr spectrum of the resulting solution now contains two sharp singlets for the methyl absorption thus indicating the presence of two thiolsulfonates. These are the thiolsulfonates corresponding to oxidation at each of the two sulfur atoms and are designated thiolsulfonates E and F with E being at lowest field in the shifted spectrum. The ratio of shift reagent to substrate at which the splitting of the methyl group was clearly visible was *ca.* 0.27.

By using methyl absorptions peak heights in the shifted spectra it was possible to determine the distribution of thiolsulfinates A–D, and thiolsulfonates E and F in the products of the photosensitized oxidations in the two solvents, methanol and chloroform. The results of this analysis are given in Table I.

Oxidation of Methyl α-Lipoate with Ammonium Persulfate. To a solution of 0.102 g (0.463 mmol) of methyl α-lipoate in 2.5 ml of diethyl ether and 5 ml of 90% ethanol was added 470 μl (0.47 mmol) of 1 *M* aqueous ammonium persulfate. The reaction solution was allowed to stand at room temperature for 16 hr and then analyzed by preparative tlc using ethyl acetate–benzene (1:1) for development as before. Bands corresponding to thiolsulfinate were removed and weighed (22.6 mg, 21%). A small band corresponding to thiolsulfonate was also present. The distribution of thiolsulfinates was determined using the shift reagent, Eu(fod)$_3$-d_{27} and methyl peak heights as before. This distribution of thiolsulfinates A–D is given in Table I.

Oxidation of Methyl α-Lipoate with *tert*-Butyl Hydroperoxide. A solution of 0.102 g (0.463 mmol) of methyl α-lipoate in 2.5 ml of diethyl ether was added to 8 ml of methanol. To this solution was added a solution of 0.0416 g (0.463 mmol) of *tert*-butyl hydroperoxide in 2 ml of methanol. The resulting solution was allowed to stand overnight at room temperature. The volume of solution was reduced to *ca.* 2 ml and then analyzed by preparative tlc as before. Total thiolsulfinate product was 75.7 mg (69%). The distribution of thiolsulfinates A–D was determined as before and is reported in Table I.

Oxidation of Methyl α-Lipoate with Peracetic Acid. To a solution of 0.102 g (0.463 mmol) of methyl α-lipoate in 2.5 ml of diethyl ether cooled to 0° was added slowly 74 μl (0.46 mmol) of 40% aqueous peracetic acid. The solution was allowed to warm to room temperature and stand for 17 hr. It was then analyzed by preparative tlc as before. Total thiolsulfinate product was 45.6 mg (42%). The distribution of thiolsulfinates A–D was determined as before and is reported in Table I. This reaction was repeated except using 10 ml of methanol in addition to 2.5 ml of diethyl ether as solvent for the methyl α-lipoate. The yield of thiolsulfinates in this case was 57.3 mg (52%). Distribution of thiolsulfinates A–D in this case are also shown in Table I.

Oxidation of Methyl α-Lipoate with Triphenyl Phosphite Ozonide. To 50 ml of methylene chloride at −78° saturated with ozone was added a solution of 0.310 g (1 mmol) of triphenyl phosphite in 10 ml of methylene chloride over a period of *ca.* 30 min. Ozone was always present in excess as indicated by the blue color of the solution. After addition of the triphenyl phosphite the reaction mixture was flushed with nitrogen to remove excess ozone. A solution of 0.22 g (1 mmol) of methyl α-lipoate in 5.4 ml of diethyl ether was added to the phosphite ozonide solution over a period of 2 min and in the dark. A portion (32 ml) of the resulting solution was withdrawn with a syringe and allowed to warm to room temperature, and the solvent was evaporated. The residue was analyzed by tlc and the thiolsulfinate distribution determined as before. Total yield of thiolsulfinates was 60.6 mg (26%). The distribution of thiolsulfinates is given in Table I under fast warm up. The remainder of the reaction solution was allowed to stand at −78° for an additional 48 hr. It was then warmed up and analyzed in the same fashion. Yield of thiolsulfinates in this portion was 50.3 mg (21%). Thus the total yield of thiolsulfinates from the phosphite ozonide oxidation was 47%. The distribution of thiolsulfinates obtained in the latter procedure is reported in Table I under slow warmup.

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Registry No.—, **1,** 62-46-4; **3,** 46236-19-5; **4a,** 53142-12-4; **4a′,** 53142-13-5; **4b,** 53142-14-6; **4b′,** 53142-15-7; **5a,** 53142-16-8; **5b,** 53142-17-9; **6a,** 53178-58-8; **6b,** 53142-18-0; O_2, 7782-44-7; ammonium persulfate, 7727-54-0; *tert*-butyl hydroperoxide, 75-91-2; peracetic acid, 79-21-0; triphenyl phosphite ozonide, 12568-76-2.

References and Notes

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