Lithium/Ammonia Reductions of 2-Thiophenecarboxylic Acids

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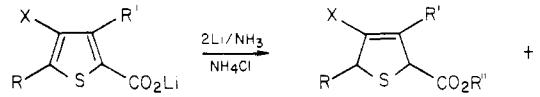
Lithium/ammonia reductions of 2-thiophenecarboxylic acids (**1**) in the absence of a proton source afforded mixtures of products. In the presence of methanol acyclic mercapto carboxylic acids (**4**) were the major products. Ring closure of **4** to the corresponding thiolactones (**12**) showed the double bonds in **4** to be of cis geometry. Attempts were made to prepare *Z* olefinic compounds derived from these mercapto carboxylic acids. Lithium 2-thiophenecarboxylate salts (**2**) afforded good yields of the corresponding 2,5-dihydro-2-thiophenecarboxylic acids (**3**). The presence of substituents on the ring and the ratio of metal to acid were significant factors in determining the nature of the products. A mechanism is proposed to explain the products observed.

In previous publications[1a,b] we have reported our preliminary findings on the lithium/ammonia reductions of 2-thiophenecarboxylic acids (**1**). Although many investigations of the metal/ammonia reductions of heteroaromatic systems have been reported,[2a] only a few have dealt with thiophene derivatives.[2b-d] Related investigations in our laboratory on both dissolving metal reductions of furoic acids and the synthesis of furanomycin[3a,b] led us to study related reactions of 2-thiophenecarboxylic acids.

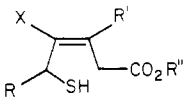
Results and Discussion

As previously reported,[1b] the lithium/ammonia reductions of the lithium carboxylate salts of 2-thiophenecarboxylic acids afforded 2,5-dihydro-2-thiophenecarboxylic acids uncontaminated by other products. This procedure gave good yields (50–75%) of dihydro compounds when a methyl substituent was present in the thiophene ring. The reduction of lithium 2-thiophenecarboxylate (**2a**) was still accompanied by ring opening, but (*Z*)-5-mercapto-3-pentenoic acid (**4a**) was the only byproduct detected. The reduction of dilithium 3,4-dimethyl-2,5-thiophenedicarboxylate (**2d**) likewise afforded a mixture of the corresponding dihydrothiophene (**3d**) and the corresponding acyclic mercaptan **4d** (eq 1).



2a, R = X = R′ = H
2d, R = CO_2Li, X = R′ = CH_3

3a,4a, R = X = R′ = H
3d,4d, R = CO_2R'', X = R′ = CH_3

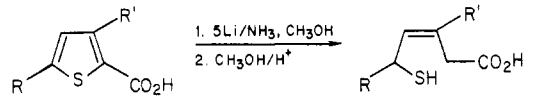


4

R′′ = H or CH_3 (1)

Preparative TLC of the esterified diacid mixture provided the pure cis isomer of the dimethyl ester of **3d**. Identification of the cis geometry of **3d** was made by comparison of its ^1H NMR spectrum with the known spectra of the 2,5-dihydro-2,5-furandicarboxylate dimethyl esters.[4]

Compounds **1a–c**, when reduced with 5 equiv of lithium and methanol is used as the proton source, afforded the open-chain (*Z*)-5-mercapto-3-alkenoic acids (**4a–c**).[5] This reaction is very efficient, affording isolated yields greater than 90% (eq 2). The infrared spectra of all three com-

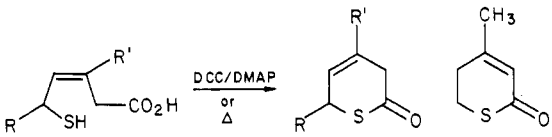


(2)

1 **4**

a, R = R′ = H; b, R = CH_3, R′ = H; c, R = H, R′ = CH_3

pounds (**4a–c**) supported a *Z* olefinic bond (olefinic stretching band[6] at 1645–1650 cm^{-1} and absence of a strong band at 970–980 cm^{-1}). This geometry was confirmed by the conversion of **4a–c** to the corresponding δ-thiolactones **12a–c** (eq 3) by two different procedures.



(3)

4 **12** **13**

a, R = R′ = H; b, R = CH_3, R′ = H; c, R = H, R′ = CH_3

First, the mercapto carboxylic acids were heated, neat, at 150–160 °C to effect dehydration.[7] The equilibrium of this reaction, however, did not favor the thiolactone,[8] and the yields were low (30–35%). A more efficient method involved the reaction between the mercapto carboxylic acid (**4**) and dicyclohexylcarbodiimide (DCC), catalyzed by 4-(dimethylamino)pyridine (DMAP).[9]

Both **4a** and **4b** afforded, upon heating at 150–160 °C, the corresponding β,γ-unsaturated thiolactones, **12a** and **12b**. The infrared spectra of these compounds exhibited

(1) (a) Blenderman, W. G.; Joullié, M. M.; Preti, G. *Tetrahedron Lett.* **1979**, 4985. (b) Blenderman, W. G.; Joullié, M. M. *Synth. Commun.* **1981**, *11*, 881.

(2) (a) Birch, A. J.; Slobbe, J. *Heterocycles* **1976**, *5*, Special Issue, 905. (b) Birch, S. F.; McAllan, D. T. *J. Chem. Soc.* **1951**, 2556. (c) Krug, R. C.; Tocker, S. *J. Org. Chem.* **1955**, *20*, 1. (d) Gol'dfarb, Ya. L.; Zakharov, E. P. *J. Org. Chem. USSR (Engl. Transl.)* **1970**, *6*, 1765.

(3) (a) Divanfard, H. R.; Joullié, M. M. *Org. Prep. Proceed. Int.* **1978**, *10*, 94. (b) Semple, J. E.; Wang, P. C.; Lysenko, Z.; Joullié, M. M. *J. Am. Chem. Soc.* **1980**, *102*, 7505.

(4) Gensler, W. J.; Chan, S.; Ball, D. B. *J. Org. Chem.* **1981**, *46*, 3407.

(5) (a) This reaction was reported simultaneously by: Gol'dfarb, Ya. L.; Semenovskii, A. V.; Zakharov, E. P.; Davydova, G. V.; Stoyanovich, F. M. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1979**, 448. (b) After submission of this manuscript, we obtained a copy of Gol'dfarb et al. (Gol'dfarb, Ya. L.; Zakharov, E. P.; Shashkov, A. S.; Stoyanovich, F. M. *J. Org. Chem. USSR (Engl. Transl.)* **1980**, *16*, 1310). Their results on the preparation of mercapto acids **4** and **15** are in generally good agreement with ours.

(6) Silverstein, R. M.; Bassler, G. C. "Spectrometric Identification of Organic Compounds", 2nd Ed. Wiley: New York, 1967; p 108.

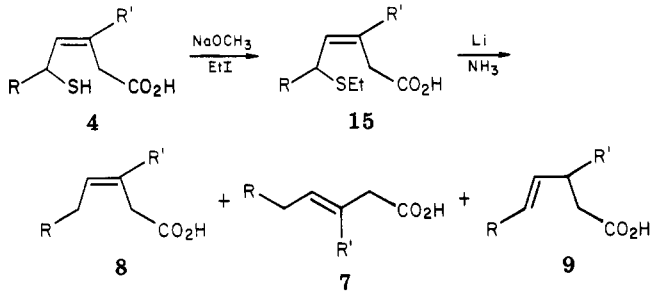
(7) Schjanberg, E. *Chem. Ber.* **1941**, *74*, 1751.

(8) Grunwell, J. R.; Foerst, D. L. *Synth. Commun.* **1976**, *6*, 453.

(9) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522.

0022-3263/83/1948-3206$01.50/0

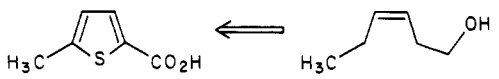
Scheme I



a, R = R′ = H; b, R = CH_3, R′ = H; c, R = H, R′ = CH_3

carbonyl stretching bands at 1670 cm^{-1}. Cyclization of (*Z*)-5-mercapto-3-methyl-3-pentenoate (**4c**) via heating at 150–160 °C afforded two isomeric thiolactones, 3,6-dihydro-4-methyl-2*H*-thiopyran-2-one (**12c**) and the conjugated 5,6-dihydro-4-methyl-2*H*-thiopyran-2-one (**13**). The ratio of **12c**/**13** was about 3:2. The infrared carbonyl stretching band of **12c** appeared at 1665 cm^{-1}, while that of **13** was observed at 1645 cm^{-1}.

The regiospecificity and stereoselectivity of the ring opening of thiophene suggested that the reductive cleavage could be utilized for the synthesis of *Z* olefinic compounds. A seemingly easy target for this reductive cleavage process was leaf alcohol, (*Z*)-3-hexen-1-ol (**14b**). The relationship between 5-methyl-2-thiophenecarboxylic acid (**1b**) and leaf alcohol is readily apparent in eq 4. Because 2-



1b **14b**

thiophenecarboxylic acid (**1a**) was available in larger quantities than **1b**, conversion of **1a** to (*Z*)-3-penten-1-ol was examined first. Desulfurization of (*Z*)-5-mercapto-3-pentenoic acid (**4a**) with W-2 Raney nickel[10] did not afford the desired (*Z*)-3-pentenoic acid (**8a**) but a mixture of isomers. Reduction of this carboxylic acid mixture using lithium aluminum hydride afforded the corresponding mixture of isomeric alcohols. Analysis of GC/MS and NMR showed the presence of (*Z*)- and (*E*)-3-penten-1-ol as well as a third isomer.

Desulfurization by reductive cleavage with lithium in ammonia was examined next. Cleavage of allylic carbon–sulfur bonds with lithium in ammonia or lithium in ethylamine has been reported by several investigators.[2c,11] Mercaptans were not cleaved efficiently, but sulfides gave good yields of the corresponding olefinic hydrocarbons.

Thus, (*Z*)-5-mercapto-3-pentenoic acid (**4a**, R″ = H) was converted to (*Z*)-5-(ethylthio)-3-pentenoic acid (**15a**) via reaction with sodium methoxide and ethyl iodide. Reduction of **15a** with 3 equiv of lithium in ammonia afforded a mixture of pentenoic acids (Scheme I). ^1H NMR and IR spectroscopy showed (*Z*)-3-pentenoic acid (**8a**) to be the major product. 4-Pentenoic acid was also present. The mixture was reduced with lithium aluminum hydride to give the corresponding alcohols. Gas chromatographic analysis indicated that (*Z*)-3-penten-1-ol (**14a**) constituted about 85% of this mixture.

Treatment of (*Z*)-5-mercapto-3-hexenoic acid (**4b**, R″ = H) under the conditions described for **4a** led to similar results. Mercapto acid **4b** was readily converted to (*Z*)-5-(ethylthio)-3-hexenoic acid (**15b**). Reductive cleavage of this compound with lithium in ammonia afforded a mixture of (*E*)-4-hexenoic acid (**9b**) and the two 3-hexenoic acids **7b** and **8b**. NMR spectroscopy indicated a ratio of about 3:1 for the 4-hexenoic acid (**9b**) as compared to the combined 3-hexenoic acids (**7b** and **8b**). The identities of the acids were confirmed via lithium aluminum hydride reduction to the corresponding alcohols.

Analysis of the mixture of alcohols by gas chromatography/mass spectrometry aided identification of the isomers. Honkanen reported that these isomeric hexen-1-ols eluted from Carbowax-type columns in the following order: (*E*)-3-hexen-1-ol, (*Z*)-3-hexen-1-ol, and (*E*)-4-hexen-1-ol.[12] The first component of the mixture we obtained was not present in quantity to give a reliable mass spectrum. However, the mass spectra of the second and third components agreed very well with the published spectra for (*Z*)-3-hexen-1-ol and (*E*)-4-hexen-1-ol, respectively. In particular, the ratio of ions *m*/*z* 67:*m*/*z* 69 in the published spectrum of (*Z*)-3-hexen-1-ol (3:1) is quite different from the ratio of those same ions in the spectrum of (*E*)-3-hexen-1-ol (1.3:1). The mass spectrum of the second component of the alcohol mixture showed a *m*/*z* 67:*m*/*z* 69 ratio of 5.5:1 which resembles more the ratio reported for the *Z* isomer. Co-injection with pure **14b** confirmed the identity of our product.

Alkylation of (*Z*)-5-mercapto-3-methyl-3-pentenoic acid (**4c**) proceeded smoothly to afford (*Z*)-5-(ethylthio)-3-methyl-3-pentenoic acid (**15c**). Reaction of **15c** with lithium in ammonia afforded the desulfurized compound (*Z*)-3-methyl-3-pentenoic acid[13] (**8c**) in 75% yield. The corresponding methyl ester (**8c**, R″ = CH_3) was prepared by the reaction of **8c** with methanol and sulfuric acid. Gas chromatographic analysis of this ester revealed the presence of about 5% of the *E* isomer. After we completed this study, similar results were reported by Russian investigators who desulfurized substituted α-(dehydro)thienyl methanols with lithium in ethylamine to their respective *E*-homoallylic alcohols stereoselectively in yields of 30–75%.[14]

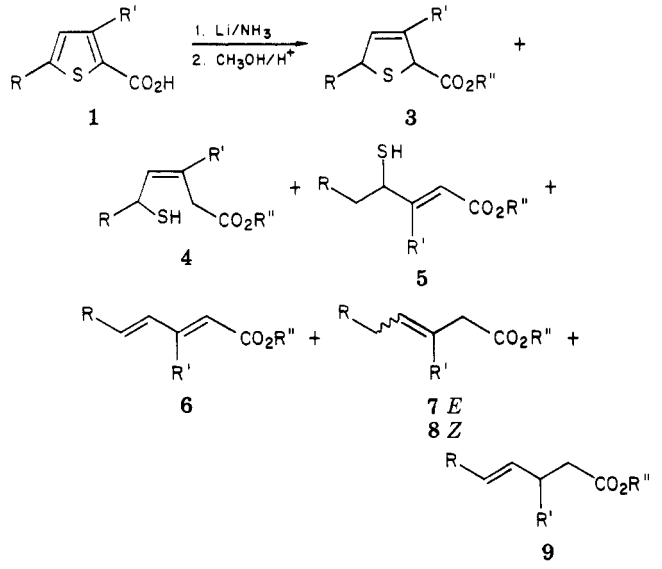
In a preliminary communication,[1a] we had reported the complex nature of the lithium/ammonia reduction of 2-thiophenecarboxylic acids without a proton source. Several additional examples have provided us with a better understanding of the processes ocurring during these reductions. The results of our experiments are summarized in Table I, which gives retention times and percentage compositions for the methyl esters derived from the carboxylic acid mixtures obtained directly from the reductions. Scheme II shows the products obtained from reduction of the acids (**1**).

All carboxylic acid mixtures were esterified with excess dry methanol and sulfuric acid. The mixtures of methyl esters were analyzed by GC/MS to identify the components and to determine their relative amounts. Esterification of the carboxylic acid mixtures with diazomethane also alkylated the mercapto groups to afford methyl sulfides which did not always separate clearly from the other components.

Reduction of a 2-thiophenecarboxylic acids (**1a–c**) with 3 equiv of lithium afforded a mixture in which the 2,5-dihydro-2-thiophenecarboxylic acids (**3a–c**) were the major product (see Table I). However, the number of byproducts formed and the separation problems made this procedure

(10) Horning, E. C. "Organic Syntheses", Wiley: New York, 1955; Collect. Vol. III, 181.
(11) Biellmann, J. F.; Ducep, J. B. *Tetrahedron* **1971**, *27*, 5861.
(12) Honkanen, E.; Moisio, T.; Ohno, M.; Hatanaka, A. *Acta Chem. Scand.* **1963**, *17*, 2051.
(13) Cornforth, R. H. *J. Chem. Soc.* **1959**, 4052.
(14) Lozanova, A. V.; Moiseenkov, A. M.; Semenovskii, A. V. *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)* **1981**, *30*, 619.

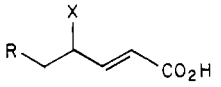
Scheme II[a]



[a] a, R = R′ = H; b, R = CH_3; R′ = H; c, R = H; R′ = CH_3 R″ = CH_3

impractical for the preparation of pure **3**. Reduction of carboxylate salts (**2a–c**) described earlier was a more efficient method to obtain **3**.

An interesting finding was the formation of mercapto acid **5** upon reduction of **1a**. Compounds **5a** and **5b** were prepared via a modification of a procedure reported by Tschesche.[15] The (*E*)-4-(acetylthio)-2-alkenoic acids (**11a,b**) were obtained from the corresponding bromo compounds **10a,b**. Solvolysis of **11** with methanol and



10a, R = H; X = Br
10b, R = CH_3; X = Br
11a, R = H, X = SAc
11b, R = CH_3, X = SAc

sodium methoxide afforded the mercapto carboxylic acids **5**. GC/MS experiments showed that **5a** was present in the mixture of products obtained from the reduction of **1a**. However, **5b** was absent in the mixture obtained from **1b**. Compound **5c** was not synthesized, but there was no evidence of its formation in the mixture obtained from the reduction of **1c**.

The use of 10 equiv of lithium in these dissolving metal reductions produced significant changes in the observed product distribution. As shown in Table I, a greater variety and a greater proportion of desulfurized products were obtained in this case than in the examples using 3 equiv of lithium. This observation is especially true in the case of substituted thiophenecarboxylic acids **1b,c** for which **3b,c** make up 10% or less of the product mixture.

Some of the methyl pentenoates (**7a** and **8a**) co-eluted under the GC conditions employed, a phenomenon also noted by other authors.[16] The isomeric methyl 3-hexenoates (**7b** and **8b**) coeluted just as did the methyl 3-pentenoates. This observation was supported by results obtained from the previously discussed desulfurization of **4b**. Estimation of the *E*:*Z* ratio was based on the desulfurization results obtained from ^1H NMR and GC data.

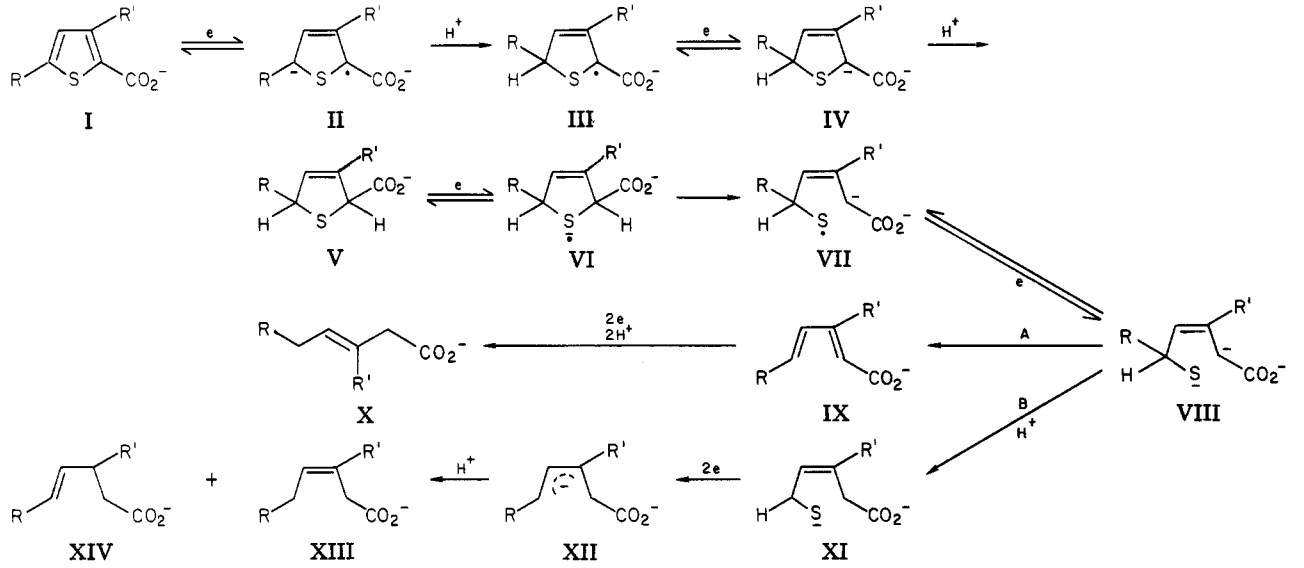
Table I. Retention Times and Percentage Composition of Reaction Products[a]

acid	lithium equiv	R, R′	 **3**	 **4**	 **5**	**6**	**7**	 **8**	 **9**
	3	H, H	31 (1.07), 78%	29 (1.00), 9.4%	27 (0.93) 7.3%		9 (0.31), 5.2%		
	10	H, H	32.2 (1.10), 37%	29.3 (1.00), 18%		12 (0.41), 5%	8.4 (0.29), 35%[b]	8.4 (0.29), 35%[b]	6.2 (0.21), 5%
	3	CH_3, H	28.3 (1.06), 28.8 (1.09), 71%	26.7 (1.00), 18%		18.1 (0.68), 2%	10.9 (0.41), 8.5%		10.2 (0.38), <1%
	10	CH_3, H	28.2 (1.07), 28.7 (1.09), 10%	26.4 (1.00), 8.6%		18.1 (0.69), 0.4%	11 (0.42), 65%	11 (0.42), 3%	10.3 (0.39), 11%
	3	H, CH_3	32.3 (1.06), 50%	30.3 (1.00), 46%			11.8 (0.39), 2.0%		
	10	H, CH_3	33.4 (1.06), 3.0%	31.5 (1.00), 32%			12.8 (0.41), 13%	11.4 (0.36), 48%	8.5 (0.27), 2.0%

[a] Given as retention time in min. (normalized retention time relative to the 5-mercaptoacids (**4**)) % of mixture. [b] **7a** and **8a** combined.

(15) Tschesche, R.; Barkemeyer, H.; Heuschkel, G. *Chem. Ber.* **1955**, *88*, 1258.
(16) Gajewski, J. J.; Weber, R. J.; Braun, R.; Manion, M. L.; Hymen, B. *J. Am. Chem. Soc.* **1977**, *99*, 816.

Scheme III



The large diversity of products obtained in the lithium/ammonia reduction of 2-thiophenecarboxylic acids suggests a complex set of reactions. Several reaction pathways, either sequential or simultaneous, must be available to account for the various products formed in these reductions. The changes made in reaction conditions, such as varying the metal to substrate ratio or changing the proton source, produced striking changes in the nature of the products. Analysis of these changes has led to the postulation of a mechanism which is consistent with our observations (Scheme III).

The initial addition of one electron to a 2-thiophenecarboxylate anion (I) affords a radical anion (II) which may be easily protonated to afford III. In the presence of excess metal, III should be rapidly reduced to the anionic species IV. This behavior parallels that of benzoic acids, whose reduction has been well investigated.[17] However, the allylic nature of the carbon–sulfur bonds in IV makes them vulnerable to further fission under Birch conditions.[11] Protonation of IV to give V, the 2,5-dihydro-2-thiophenecarboxylate species, allows further reduction to occur. Addition of another electron to V affords radical anion VI, undoubtedly involving the d orbitals of sulfur. Species VI may cleave to give acyclic radical anion VII or add a second electron to form directy trianion VIII. Similar trianions have been suggested by other authors.[2a,18a,b] Some investigators believe that carbon–sulfur fissons are a two-electron process not involving a free radical.[19]

In the absence of an added proton source the protonation of IV to give V only occurs to a small extent. This assumption is supported by the large amount of 2,5-dihydro-2-thiophenecarboxylic acids formed in the reductions of 1 with 3 equiv of lithium and final quenching with ammonium chloride. However, the cleavage of the carbon–sulfur bond adjacent to the carboxylate group leads to the formation of the other, acyclic products. The presence of the 2-carboxylate function should favor cleavage at this position over the 5-position, as this group should stabilize carbanions VII and VIII via both inductive and resonance effects.

Further reaction of VIII can occur by two pathways (A or B). Pathway A involves loss of sulfide and generation of a conjugated diene system (IX). Conjugated alkadienoic acids have indeed been detected in the product mixtures. Further reduction of diene (IX) to E olefins (X) is a known reaction previously investigated by Birch.[20] The isolated olefin (X) is resistant to additional reduction.[21]

An alternate path to the loss of sulfide involves protonation of VIII to XI to afford the mercapto acids **4a–c** (path B). Additionally, the sulfur may be reductively cleaved from XI to form resonance-stabilized anion XII. Although the carbon–sulfur bonds of saturated mercaptans do not cleave easily under reducing conditions, allylic mercaptans are more readily reducible.[2c] Reductions with 10 equiv of metal produced significant quantities of (*E*)-4-alkenoic and (*Z*)-3-alkenoic acids, thereby supporting the formation of species such as XIII and XIV.

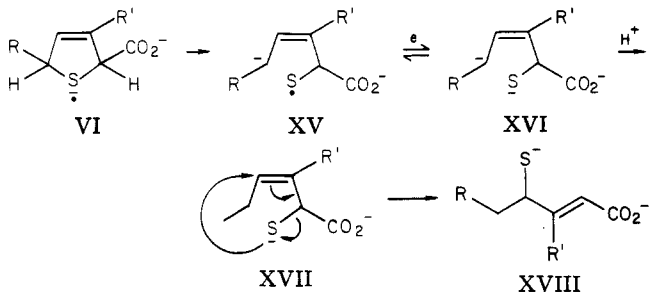
In contrast to the reductions carried out without a proton source, reductions performed in the presence of methanol with 5 equiv of lithium afforded single products, the mercapto acids **4a–c**. The added proton source makes possible the complete protonation of IV, and the additional metal can then easily cause further reduction to give XI. With an adequate proton source available, no sulfur is lost from the molecule via diene formation as in path A.

The reductive desulfurization of the S-alkylated mercapto acids follows pathway B. Delocalized anion XII can lead to isomeric olefinic carboxylic acids. When R′ = CH_3, position isomerization is suppressed and 95% *Z* geometry is obtained in the resulting 3-alkenoic acid. Some related factors suggested that reduction of carboxylate salts would eliminate ring cleavage. First, excess lithium (3 equiv where stoichiometry required 2) was employed in the reduction of the thiophenecarboxylic acids. This is common practice in the Birch reduction of carboxylic acids,[17] and in fact, a reaction of **1a** with only 2.5 equiv of lithium led to the recovery of a significant portion of starting material. Second, the carboxylic acid proton acts at least partially as an internal proton source, quenching anion IV and facilitating further reduction by the excess metal.

Elimination of the carboxylic acid proton, via formation of the lithium carboxylate salt, allows the reduction to be carried out with 2 equiv of metal, as excess of metal is no longer required to counter possible hydrogen formation.

(17) House, H. O. "Modern Synthetic Reactions"; W. A. Benjamin: Menlo Park, CA, 1972; pp 145–227.
(18) (a) Rabideau, P. W.; Burkholder, E. G.; Yates, M. J. *Synth. Commun.* **1980**, *10*, 627. (b) Radhakrishna Murthy, A.; Shyma Sundar, N.; Subbarao, G. S. R. *Tetrahedron* **1982**, *38*, 2831.
(19) Grovenstein, E., Jr.; Chandra, S.; Collum, C. E.; Davis, W. E. Jr., *J. Am. Chem. Soc.* **1966**, *88*, 1275.
(20) Birch, A. J.; Slobbe, J. *Aust. J. Chem.* **1976**, *29*, 2737.
(21) Birch, A. J.; Rao, G. S. *Adv. Org. Chem.* **1972**, *8*, 1.

Scheme IV



Ring opening during the reduction of lithium 2-thiophenecarboxylate (**2a**) was not completely eliminated, and ~12% of mercapto acid **4a** was formed. The presence of a methyl group on either the 3- or 5-position of the thiophene ring had a dramatic effect on the reduction. Ring opening did not occur at all, and only the corresponding 2,5-dihydro-3(5)-methyl-2-thiophenecarboxylic acids were isolated. The greater electron-releasing effect of a methyl group as compared to that of a hydrogen apparently suppresses further electron addition that would lead to acyclic products.

The formation of (*E*)-4-mercapto-2-pentenoic acid (**5a**) from **1a** was noteworthy, and may be explained by the mechanism shown in Scheme IV.

Cleavage of the carbon–sulfur bond in the less favored direction can account for the formation of **5a**. Further reduction to VI and opening of the carbon–sulfur bond on the side opposite to the carboxylate group would result in trianion XVI, via radical anion XV. Protonation of XVI leads to XVII, the anionic precursor of a 2-mercapto-3-alkenoic acid. However, a sigmatropic rearrangement of the nucleophilic sulfur anion converts XVII to XVIII. This rearrangement places the double bond in conjugation with the carbonyl and changes its geometry from *Z* to *E*, both processes being stabilizing forces.

We believe the mechanism shown in Scheme IV explains the formation of **5a** more adequately than the previously postulated sulfurane intermediate.[1a] Although such intermediates exist, they usually have been observed in compounds where the sulfur is attached to groups such as phenyl that can delocalize the negative charge and would be less probable when sulfur is attached to hydrogen.

In addition, the absence of any products derived from XVIII, when R or R′ = CH_3, is consistent with carbanion stability. When R and R′ = H, the allylic anion XVI is primary and secondary. When R = CH_3, both carbanion centers are secondary, and when R′ = CH_3, the two carbons involved are primary and tertiary. Thus, both alkylated thiophenecarboxylates would have less favorable anions than the unsubstituted derivatives. These substituent effects may be sufficient to suppress carbon–sulfur bond fission on the side opposite the carboxylate group. Attempts to prepare 2-mercapto-3-alkenoic acids via the apparently unknown 2-bromo-3-alkenoic acids were not successful.

Experimental Section

General Information. IR spectra were obtained on a Perkin-Elmer 137 spectrophotometer. Solid samples were examined as KBr disks; liquid samples were recorded as neat films between sodium chloride plates. NMR spectra were recorded in the designated solvents on a Varian A-60 (60 MHz), EM-360 (60 MHz), Bruker WP-250 (250 MHz), or Bruker WH-360 (360 MHz) spectrometer. ^{13}C NMR spectra were recorded in the designated solvents on a JEOL-JNM-PS-100 (25 MHz) or a Bruker WP-250 (62.9 MHz) spectrometer. Chemical shifts are reported as parts per million (δ) relative to internal Me_4Si. Gas chromatography/mass spectrometry experiments were performed on a Perkin Elmer 990 gas chromatograph equipped with 10 ft × 2 mm column packed with 10% Carbowax 20 M on Chromosorb W. The GC was connected to a Hitachi-Perkin Elmer RMU-6L mass spectrometer by use of a Watson–Biemann interface.[22] The temperature program was 4 min at an initial temperature of 70 °C and a heating cycle of 4 °C/min to 220 °C. The carrier gas (He) flow rate was 40 mL/min. The ionizing voltage of the spectrometer was 70eV, with an ion source temperature of 200–210 °C. Retention times are in min. Low-resolution mass spectra were recorded with a Hitachi-Perkin Elmer RMH-2 mass spectrometer. High-resolution mass spectra were recorded with the RMH-2 or a Vacuum Generator's V.G. 7070H spectrometer. Both the RMH-2 and the V.G 7070H were equipped with a Kratos DS-50-S data system. Melting points were determined on a Thomas-Hoover Unimelt capillary melting point apparatus (<200 °C) or a Mel-temp capillary melting point apparatus (>200 °C) and are uncorrected. Elemental analyses were performed by Robertson Laboratory, Florham Park, NJ. Solvents and chemicals were used as received with the following exceptions. Ether and tetrahydrofuran were dried by distillation from sodium and benzophenone. Methanol was dried by refluxing over magnesium methoxide and then was distilled from the same reagent. Carbon tetrachloride was dried by distillation from phosphorus pentoxide. 2-Thiophenecarboxaldehydes (Aldrich) were distilled under reduced pressure prior to use. Chromatography was carried out by using Merck (70–230 mesh) silica gel. Preparative TLC was performed on precoated 20 × 20 cm silica gel plates (1000 μ) supplied by Analtech.

Reduction of Lithium 2-Thiophenecarboxylate (2a). Lithium 2-thiophenecarboxylate was prepared from **1a** (10.0 g, 78.1 mmol) as described previously.[1b] Reduction of 3.50 g (26.1 mmol) of **2a** was effected with lithium (0.361 g, 0.0521 g at) in 126 mL of ammonia. After 40 min ammonium chloride (3.0 g, 56 mmol) was added. Isolation of the products afforded 3.0 g of a mixture containing **3a** (75%), **4a** (12.5%), and **1a** (12.5%), as determined by NMR spectroscopy. Three recrystallizations from petroleum ether gave pure **3a**: mp 70–72 °C [lit.[23] mp 71–72 °C]; ^1H NMR ($CDCl_3$) δ 3.82 (2 H, m), 4.77 (1 H, m), 5.91 (2 H, m), and 10.02 (1 H, s); ^{13}C NMR δ 39.5 (C5), 55.5 (C2), 126.9 (C3), 132.3 (C4), and 177.8 (C=O); IR (KBr) 1690, 1630 cm^{-1}.

4,5-Dihydro-2-thiophenecarboxylic Acid (16a). In a solution of potassium hydroxide (1.0 g, 18 mmol) in 10 mL of water was dissolved 1.0 g (7.7 mmol) of **3a**. This solution was refluxed for 7 h, and then acidified at 0 °C with 9 N sulfuric acid. The aqueous solution was extracted with 3 × 10 mL ether. Drying the combined ether layers over magnesium sulfate followed by removal of the solvent in vacuo afforded crude **16a** mixed with **3a**. Recrystallization from chloroform gave 0.10 g (0.77 mmol) of **16a**: mp 137.5–138.5 °C; 360-MHz ^1H NMR (CD_3COCD_3) δ 2.95, (2 H, td, J_1 = 8.5 Hz, J_2 = 3.0 Hz), 3.31 (2 H, t, J = 8.5 Hz), 6.59 (1 H, t, J = 3.0 Hz), and 10.22 (1 H, s); ^{13}C NMR (CD_3COCD_3) δ 32.8 (C5 or C4), 37.1 (C4 or C5), 134.9 (C3), 136.8 (C2), and 163.8 (C=O); IR (KBr) 1670, 1595 cm^{-1}. Anal. Calcd for $C_5H_6O_2S$: C, 46.14; H, 4.65; S, 24.63. Found: C, 46.42; H, 4.84; S, 24.73.

Methyl 2,5-Dihydro-2-thiophenecarboxylate (3a, R″ = CH_3). The mixture of esters (300 mg) derived from the reduction of **1a** with 3 equiv of lithium was separated via preparative TLC using a mixture of hexane/ethyl acetate (4:1 v/v). Isolation of the major fraction afforded **3a** (200 mg): ^1H NMR ($CDCl_3$) 3.70 (3 H, s), 3.83 (2 H, m), 4.78 (1 H, m), and 5.93 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 39.3 (C5), 52.5 (CH_3O), 55.4 (C2), 127.2 (C3), 131.7 (C4), and 172.2 (C=O) and [lit.[23] ^1H NMR 3.65 (3 H, s), 3.75 (2 H, m), 4.65 (1 H, m), and 5.86 (2 H, m)].

Methyl *cis*- and *trans*-2,5-Dihydro-5-methyl-2-thiophenecarboxylate (3b, R″ = CH_3). The cis/trans mixture of the ester **3b** (300 mg) was isolated as described above for **3a**, with a 7:1 ratio of the same solvent mixture: ^1H NMR ($CDCl_3$) δ 1.45 (3 H, d, J = 6.8 Hz), 3.76 (3 H, s), 4.42 (1 H, m), 4.83 (1 H, m), and 5.87 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 23.2 and 24.2 (C5–CH_3), 50.2 and 50.5 (C5), 52.5 (CH_3O), 55.4 and 55.7 (C2),

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125.6 (C3), 137.9 and 138.2 (C4), and 172.2 and 172.3 (C=O); IR (film) 1740, 1640 cm^{-1}; HRMS calcd for $C_7H_{10}O_2S$, 158.0401; found, 158.0396.

Methyl 2,5-Dihydro-3-methyl-2-thiophenecarboxylate (3c, R″ = CH_3). Acid **3c** (0.238 g, 1.66 mmol) was esterified with methyl iodide (0.244 g, 1.72 mmol) via the procedure of Rao.[24] Isolation of the product afforded 0.174 g (1.1 mmol) of **3c** (R″ = CH_3, 67%): bp 73–75 °C (1.8 mm); ^1H NMR ($CDCl_3$) δ 1.81 (3 H, br s); 3.73 (5 H, m), 4.50 (1 H, br s), and 5.65 (1 H, br s); IR (film) 1735, 1670 cm^{-1}. Anal. Calcd for $C_7H_{10}O_2S$: C, 53.14; H, 6.37; S, 20.27. Found: C, 53.38; H, 6.44; S, 20.01.

Dimethyl *cis*-2,5-Dihydro-3,4-dimethyl-2,5-thiophenedicarboxylate (3d). Dilithium 3,4-dimethyl-2,5-thiophenedicarboxylate was prepared as described.[1b] Reduction of the dilithium dicarboxylate salt (4.59 g, 23.0 mmol) was effected with lithium (0.330 g, 0.0476 mol) in 125 mL of ammonia. Isolation of the products afforded two fractions. The first was a solid, which precipitated upon acidification of the aqueous solution during workup. NMR spectroscopy indicated a 1:1 mixture of 3,4-dimethyl-2,5-thiophenedicarboxylic acid (**1d**) and **4d**. Extraction of the aqueous filtrate with 3 × 30 mL ether followed by magnesium sulfate drying and removal of the solvent in vacuo afforded a gummy solid. Esterification of this solid as previously described gave an oil that solidified on standing. Preparative TLC with 3:1 petroleum ether/ether afforded two bands. The upper band (R_f 0.40) was a mixture of dimethyl *trans*-2,5-dihydro-3,4-dimethyl-2,5-thiophenedicarboxylate (**3d**, ^1H NMR C2 and C5 δ 4.77) and dimethyl (*Z*)-2-mercapto-3,4-dimethyl-3-hexenedioate (**4d**). These two compounds were not separated. The lower band (R_f 0.28) afforded dimethyl *cis*-2,5-dihydro-3,4-dimethyl-2,5-thiophenedicarboxylate (**3d**): ^1H NMR ($CDCl_3$) δ 1.79 (6 H, s), 3.77 (6 H, s), and 4.58 (2 H, s); IR (film) 1740, 1680 cm^{-1}; HRMS calcd for $C_{10}H_{14}O_4S$, 230.0613; found, 230.0601.

(*Z*)-5-Mercapto-3-pentenoic Acid (4a). Acid **1a** (8.00 g, 62.5 mmol) was reduced with lithium (2.20 g, 0.313 mol) in ammonia (250 mL) in the presence of methanol (5.0 mL, 130 mmol). After 25 min, 10 mL of methanol was added. Isolation of the product as described previously afforded 7.57 g (57.3 mmol) of **4a** (92%): bp 80–83 °C (0.025 mm); ^1H NMR ($CDCl_3$) δ 1.50 (1 H, t, *J* = 7 Hz), 3.15 (4 H, m), 5.62 (2 H, m), and 11.27 (1 H, s); IR (film) 1710, 1650 cm^{-1}. Anal. Calcd for $C_5H_8O_2S$: C, 45.43; H, 6.10; S, 24.26. Found: C, 45.73; H, 6.16; S, 24.15.[5]

Methyl (*Z*)-5-Mercapto-3-pentenoate (4a, R″ = CH_3). Acid **4a** (2.20 g, 16.7 mmol) was esterified as previously described to afford 2.35 g (16.1 mmol) of **4a** R″ = CH_3 (96%): bp 100–101 °C (15 mm); ^1H NMR ($CDCl_3$) δ 1.50 (1 H, t, *J* = 7.5 Hz), 3.13 (4 H, m), 3.62 (3 H, s), and 5.63 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 21.1 (C5), 32.4 (C2), 51.9 (CH_3O), 122.1 (C3 or C4), 131.9 (C4 or C3), and 171.5 (C=O); IR (film) 2520, 1735, 1645 cm^{-1}. Anal. Calcd for $C_6H_{10}O_2S$: C, 49.29; H, 6.89; S, 21.93. Found: C, 49.47; H, 6.99; S, 21.96.

(*Z*)-5-Mercapto-3-hexenoic Acid (4b). Reduction of **1b** (7.10 g, 50.0 mmol) was carried out with lithium (1.71 g, 0.247 mol) in ammonia (200 mL) in the presence of methanol (4 mL, 100 mmol). After 35 min, 14 mL of methanol was added, and isolation of the product as described previously afforded 7.01 g (48 mmol) of **4b** (96%): bp 77–78 °C (0.025 mm); ^1H NMR ($CDCl_3$) δ 1.38 (3 H, d, *J* = 7 Hz), 1.79 (1 H, d, *J* = 4.5 Hz), 3.22 (2 H, m), 3.90 (1 H, m), 5.60 (2 H, m), and 11.81 (1 H, s); IR (film) 1720, 1650 cm^{-1}; HRMS calcd for $C_6H_{10}O_2S$, 146.0402; found, 146.0409. Anal. Calcd for $C_6H_{10}O_2S$: C, 49.29; H, 6.89; S, 21.93. Found: C, 49.27; H, 7.03; S, 21.75.

Methyl (*Z*)-5-Mercapto-3-hexenoate (4b, R″ = CH_3). Acid **4b** (0.822 g, 5.63 mmol) was esterified as previously described to afford 0.797 g (4.99 mmol) of **4b**, R″ = CH_3 (89%): bp 82–84 °C (3.3 mm); ^1H NMR ($CDCl_3$) δ 1.38 (3 H, d, *J* = 7 Hz), 1.78 (1 H, d, *J* = 5 Hz), 3.17 (2 H, d, *J* = 5.5 Hz), 3.72 (3 H, s), 3.92 (1 H, m), and 5.60 (2 H, m); IR (film) 2530, 1740, 1650 cm^{-1}. Anal. Calcd for $C_7H_{12}O_2S$: C, 52.47; H, 7.55; S, 20.01. Found: C, 52.56; H, 7.62; S, 19.83.

(*Z*)-5-Mercapto-3-methyl-3-pentenoic Acid (4c). Reduction of **1c** (7.01 g, 49.3 mmol) was carried out with lithium (1.70 g, 0.245 mol) in ammonia (200 mL) in the presence of methanol (4.0 mL, 100 mmol). Methanol (10 mL) was added, and isolation of the product as previously described afforded 6.60 g (45.2 mmol) of **3c** (92%): bp 87–90 °C (0.09 mm); ^1H NMR ($CDCl_3$) δ 1.50 (1 H, t, *J* = 7.2 Hz), 1.80 (3 H, s), 3.07 (4 H, m), 5.55 (1 H, t, *J* = 8 Hz), and 11.40 (1 H, s); IR (film) 1710, 1660 cm^{-1}; HRMS calcd for $C_6H_{10}O_2S$, 146.0402; found, 146.0392.

Methyl (*Z*)-5-Mercapto-3-methyl-3-pentenoate (4c, R″ = CH_3). Acid **4c** (0.516 g, 3.54 mmol) was esterified as previously described to afford 0.320 g (2.0 mmol) of **4c**, R″ = CH_3 (57%): bp 80–82 C, (3.3 mm); ^1H NMR ($CDCl_3$) δ 1.51 (1 H, t, *J* = 7 Hz), 1.85 (3 H, s), 3.17 (4 H, m), 3.71 (3 H, s), and 5.59 (1 H, t, *J* = 8 Hz); IR (film) 2520, 1740, 1660 cm^{-1}; HRMS calcd for $C_7H_{12}O_2S$, 160.0558; found, 160.0568.

3,6-Dihydro-2*H*-thiopyran-2-one (12a). Acid **4a** (3.26 g, 24.7 mmol) was heated with an oil bath at 150–160 °C for 1 h. A solution of the crude product in 30 mL of chloroform was washed with saturated aqueous sodium bicarbonate until no more carbon dioxide was released. The chloroform solution was dried over magnesium sulfate, and removal of the solvent in vacuo afforded 0.50 g (4.4 mmol) of **12a**: bp 83–86 °C (3 mm); ^1H NMR ($CDCl_3$) δ 3.10 (2 H, m), 3.67 (2 H, m), and 6.03 (2 H, m); IR (film) 1670 cm^{-1}; HRMS calcd for C_5H_6OS, 114.0140; found, 114.0134. Anal. Calcd for C_5H_6OS: C, 52.60; H, 5.30; S, 28.09. Found: C, 52.49; H, 5.39; S, 27.80.

3,6-Dihydro-6-methyl-2*H*-thiopyran-2-one (12b). Method A. The thiolactone **12b** (0.60 g, 4.7 mmol) was obtained from **4b** (2.00 g, 13.7 mmol) by the same procedure described for **12a**.

Method B. The procedure of Neises and Steglich for the preparation of thioesters was employed.[9] Mercapto acid **4b** (1.50 g, 10.3 mmol), 4-(dimethylamino)pyridine (46.5 mg, 0.381 mmol), and dicyclohexylcarbodiimide (1.92 g, 9.31 mmol) afforded 0.702 g (5.48 mmol) of **12b** (59%): bp 87–89 °C (3.3 mm); ^1H NMR ($CDCl_3$) 1.48 (3 H, d, *J* = 7 Hz), 3.08 (2 H, m), 4.12 (1 H, m), and 5.96 (2 H, m); IR (film) 1670 cm^{-1}. Anal. Calcd for C_6H_8OS: C, 56.22; H, 6.29; S, 25.01. Found: C, 55.95; H, 6.44; S, 24.88.

3,6-Dihydro-4-methyl-2*H*-thiopyran-2-one (12c) and 5,6-Dihydro-4-methyl-2*H*-thiopyran-2-one (13). Method A. Treatment of **4c** (1.5 g, 10 mmol) under the conditions of Method A afforded a 3:2 mixture of thiolactones **12c** and **13**. Preparative TLC (hexane/ethyl acetate 5:1) afforded **12c** (0.33 g) and **13** (0.22 g). **12c**: ^1H NMR ($CDCl_3$) δ 1.83 (3 H, m), 3.05 (2 H, m), 3.64 (2 H, m), and 5.86 (1 H, m); IR (film) 1665 cm^{-1}; HRMS calcd. for C_6H_8OS, 128.0296; found, 128.0303. **13**: ^1H NMR ($CDCl_3$) δ 1.98 (3 H, br s), 2.55 (2 H, m), 3.15 (2 H, m), and 5.92 (2 H, m); IR (film) 1645, 1625 cm^{-1}; HRMS calcd for C_6H_8OS, 128.0296; found, 128.0296.

Method B. Reaction of **4c** (0.652 g, 4.46 mmol), DMAP (24.3 mg, 0.199 mmol), and DCC (0.921 g, 4.47 mmol) under the conditions of method B afforded 0.50 g (3.9 mmol) of **12c** (87%): bp 78–80 °C (1.6 mm).

(*Z*)-5-(Ethylthio)-3-pentenoic Acid (15a). To a solution of **4a** (9.55 g, 72.4 mmol) in 40 mL of methanol at 0 °C was added a solution of sodium methoxide (3.44 g, 0.149 mol sodium) in 55 mL of methanol and ethyl iodide (11.34 g, 72.6 mmol). After 1 h water (200 mL) was added, and the aqueous solution was acidified at 0 °C with 9 N sulfuric acid, saturated with sodium chloride, and extracted with chloroform (3 × 50 mL). The combined chloroform layers were dried over magnesium sulfate. Removal of the solvent in vacuo afforded 8.99 g (56.2 mmol) of **15a** (78%): bp 100–102 °C (0.05 mm); ^1H NMR ($CDCl_3$) δ 1.23 (3 H, t, *J* = 7.5 Hz), 2.52 (2 H, q, *J* = 7.5 Hz), 3.18 (4 H, m), 5.70 (2 H, m), and 11.70 (1 H, s); IR (film) 1710, 1650 cm^{-1}; HRMS calcd for $C_7H_{12}O_2S$, 160.0558; found 160.0548.[5]

(*Z*)-5-(Ethylthio)-3-hexenoic Acid (15b). Treatment of mercapto acid **4b** (8.70 g, 59.6 mmol) with sodium methoxide (2.80 g, 0.122 mol sodium) and ethyl iodide (9.31 g, 59.7 mmol) as described above afforded 9.99 g (57.4 mmol) of **15b** (96%): bp 94–95 °C (0.025 mm); ^1H NMR ($CDCl_3$) δ 1.25 (6 H, m), 2.41 (2 H, q, *J* = 7 Hz), 3.15 (2 H, d, *J* = 6 Hz), 3.68 (1 H, m), 5.57 (2 H, m), and 11.02 (1 H, s); IR (film) 1720, 1650 cm^{-1}; HRMS calcd for $C_8H_{14}O_2S$, 174.0714; found, 174.0725.[5b]

(*Z*)-5-(Ethylthio)-3-methyl-3-pentenoic Acid (15c). Treatment of mercapto acid **4c** (4.93 g, 33.7 mmol) with sodium methoxide (1.55 g, 0.0676 mol sodium) and ethyl iodide (5.28 g, 33.8 mmol) as described above afforded 4.43 g (25.5 mmol) of **15c** (76%): bp 92–94 °C (0.025 mm); ^1H NMR ($CDCl_3$) δ 1.21 (3 H,

(24) Rao, C. G. *Org. Prep. Proceed Int.* **1980**, *12*, 225.

t, J = 7.3 Hz), 1.82 (3 H, br s), 2.50 (2 H, q, J = 7.3 Hz), 3.15 (4 H, m), 5.44 (1 H, t, J = 7 Hz), and 10.81 (1 H, s); IR (film) 1710, 1670 cm^{-1}. Anal. Calcd for $C_8H_{14}O_2S$: C,55.14; H, 8.10; S, 18.40. Found: C, 55.16; H, 8.21; S, 18.29.[5b]

(Z)-3-Pentenoic Acid (8a). The reductive cleavage of **15a** (8.01 g, 50.0 mmol) was effected with lithium (1.21 g, 0.174 mol) in 200 mL of ammonia. After 1 h ammonium chloride (4.75 g, 88.8 mmol) was added. Isolation of the product as previously described afforded 3.52 g (35.2 mmol) of **8a** (70%): bp 72–74 °C (3.2 mm) [lit.[25] bp 80.5 °C (15 mm)]; ^1H NMR ($CDCl_3$) δ 1.68 (3 H, d, J = 5 Hz), 3.15 (2 H, d, J = 5 Hz), 5.64 (2 H, m), and 11.47 (1 H, s); IR (film) 1710, 1660 cm^{-1}. The NMR spectrum indicated the presence of 8% 4-pentenoic acid (**9a**): δ 2.43 (2 CH_2), 4.9–5.3 (vinyl CH).

(Z)-3-Penten-1-ol (14a). To a suspension of lithium aluminum hydride (1.29 g, 34.1 mmol) in 75 mL of ether was added **8a** (3.52 g, 35.2 mmol) in 25 mL of ether. The mixture was stirred for 30 min and was then quenched by slowly adding 1.4 mL of water, 1.4 mL of 15% aqueous sodium hydroxide, and finally 4 mL of water. The aluminum salts were removed by filtration and washed with ether. The combined ether solutions were dried over magnesium sulfate, and the solvent was removed in vacuo to afford 2.54 g (29.5 mmol) of **14a** (84%): bp 70 °C (40 mm) [lit.[26] bp 140 °C]; ^1H NMR ($CDCl_3$) δ 1.67 (3 H, d, J = 5 Hz), 2.33 (2 H, m), 3.05 (1 H, br s), 3.64 (2 H, t, J = 6.5 Hz), and 5.53 (2 H, m); IR (film) 3250, 1050 cm^{-1}. Gas chromatographic analysis showed ~10% E isomer and ~5% 4-penten-1-ol.

Reductive Cleavage of (Z)-5-(Ethylthio)-3-hexenoic Acid (15b). The reductive cleavage of **15b** (5.75 g, 33.0 mmol) was effected with lithium (0.690 g, 0.0995 mol) in 100 mL of ammonia. After 30 min ammonium chloride (5.5 g, 103 mmol) was added. Isolation of the product as previously described afforded 2.98 g (26.1 mmol) of a mixture containing (Z)-3-hexenoic acid (**8b**, 23%) and (E)-4-hexenoic acid (**9b**, 77%) as determined by NMR spectroscopy: bp 79–83 °C (3.3 mm) [**8b**, lit.[27] bp 103 °C (11 mm); **9b**, lit.[27] bp 107 °C (16 mm)]. **8b**: ^1H NMR ($CDCl_3$) δ 1.00 (3 H, t, J = 7.0 Hz), 2.00 (2 H, m), 3.12 (2 H, m), 5.50 (2 H, m), and 11.45 (1 H, s). **9b**: ^1H NMR ($CDCl_3$) δ 1.63 (3 H, dd, J_1 = 3.5 Hz, J_2 = 1 Hz), 2.35 (4 H, d), 5.50 (2 H, m), and 11.45 (1 H, s).

Reduction of 8b and 9b with Lithium Aluminum Hydride. Reduction of the mixture of **8b** and **9b** with lithium aluminum hydride as previously described afforded a mixture of the corresponding hexenols. Analysis of the mixture by GC/MS showed (E)-3-hexen-1-ol (3%, major m/z 82, 41), (Z)-3-hexen-1-ol (20%, major m/z 82, 41), (E)-4-hexen-1-ol (77%, major m/z 82, 67, 41). Mass spectra and GC elution were in good agreement with published data.[12]

(Z)-3-Methyl-3-pentenoic Acid (8c). The reductive cleavage of **15c** (1.90 g, 10.9 mmol) was effected with lithium (0.234 g, 0.0334 mol) in 75 mL of ammonia. After 15 min ammonium chloride (2.0 g, 37 mmol) was added. Isolation of the product as previously described afforded 0.93 g (8.2 mmol) of **8c** (75%): bp 53–55 °C (0.55 mm) [lit.[28] bp 90–94 °C (7 mm)]; ^1H NMR ($CDCl_3$) δ 1.61 (3 H, d, J = 7 Hz), 1.77 (3 H, t, J = 1.5 Hz), 3.03 (2 H, br s), 5.43 (1 H, q, J = 7 Hz), and 11.30 (1 H, s); IR (film) 1700 cm^{-1}.

Methyl (Z)-3-Methyl-3-pentenoate (8c, R″ = CH_3). Acid **8c** (0.48 g, 4.2 mmol) was esterified as previously described to afford 0.391 g (2.5 mmol) of **8c**, R″ = CH_3 (59%): bp 61–63 °C (34 mm) [lit.[13] bp 43–44 °C (16 mm)]; ^1H NMR ($CDCl_3$) δ 1.60 (3 H, d, J = 7 Hz), 1.74 (3 H, t, J = 1.5 Hz), 3.01 (2 H, s), 3.62 (3 H, s), and 5.38 (1 H, q, J = 7 Hz); IR (film) 1740, 1660 cm^{-1}; n^{23}_D 1.4281 [lit.[13] n^{21}_D 1.4298].

Reduction of 2-Thiophenecarboxylic Acid (1a) Using Three Equivalents of Lithium. The general procedure used for all lithium/ammonia reductions has been described previously.[1a,b] To a suspension of 2-thiophenecarboxylic acid (10.0 g, 78 mmol) in 250 mL of ammonia at −78 °C was added lithium wire (1.65 g, 0.238 mol) over a period of 40 min. The reaction mixture was stirred an additional 20 min before quenching with ammonium chloride (12.7 g, 238 mmol). The mixture of carboxylic acids obtained after an aqueous workup was converted to the corresponding mixture of methyl esters. A methanol (75 mL) solution of the carboxylic acids (2.0 g) was acidified with 4 drops of concentrated sulfuric acid and stirred at ambient temperature for 24 h. Dilution with 200 mL of water caused the esters to separate as an oil, which was dissolved in chloroform. The aqueous layer was saturated with sodium chloride and extracted with chloroform (2 × 40 mL). The combined chloroform solutions were washed with aqueous sodium bicarbonate (25 mL) and dried over magnesium sulfate. Removal of solvent in vacuo afforded a mixture of methyl esters. Analysis by GC/MS showed the following compounds: **7a**, **5a**, **4a**, and **3a**. Identifications of this mixture and other mixtures were made by comparison with the individual components prepared or isolated as described in this article or in ref 1a, 1b, and 20. See Table I.

Reduction of 5-Methyl-2-thiophenecarboxylic Acid (1b) Using Three Equivalents of Lithium. The reduction of **1b** (7.10 g, 50 mmol) was effected as described above with lithium (1.05 g, 0.151 mol), ammonia (200 mL), and ammonium chloride (8.0 g, 150 mmol). The resulting mixture of carboxylic acids was esterified with methanol and sulfuric acid as described for **1a**. Analysis of the esters by GC/MS showed the following products: **9b**, **7b**, **6b**, **4b**, and *cis*- and *trans*-**3b**.

Reduction of 3-Methyl-2-thiophenecarboxylic Acid (1c) Using Three Equivalents of Lithium. The reduction of **1c** (3.63 g, 25.5 mmol) was effected as described above with lithium (0.525 g, 0.0756 mol), ammonia (125 mL), and ammonium chloride (4.3 g, 80.5 mmol). Esterification of the resulting mixture of carboxylic acids was carried out with methanol and sulfuric acid. Analysis of the mixture of esters by GC/MS showed the following compounds: **7c**, **4c**, **3c**, and an unidentified isomer of **3c** (2%, retention time 34.4 min).

Reduction of 2-Thiophenecarboxylic Acid (1a) Using Ten Equivalents of Lithium. The reduction of **1a** (3.22 g, 25.1 mmol) was carried out as described above with lithium (1.75 g, 0.253 mol) ammonia (125 mL), and ammonium chloride (13.5 g, 253 mmol). The resulting mixture of carboxylic acids was esterified with methanol and sulfuric acid. Analysis of the mixture of esters by GC/MS showed the following compounds: **9a**, **7a**, **8a**, **6a**, **4a**, and **3a**.

Reduction of 5-Methyl-2-thiophenecarboxylic Acid (1b) Using Ten Equivalents of Lithium. Acid **1b** (5.00 g, 35.2 mmol) was reduced with lithium (2.45 g, 0.354 mol), ammonia (250 mL), and ammonium chloride (19.0 g, 354 mmol) as described above. The resulting mixture of carboxylic acids was esterified with methanol and sulfuric acid. Analysis of the mixture of esters by GC/MS showed the following products: **9b**, **7b**, **6b**, an isomer of **6b** (<1%, retention time 25.0 min), **4b**, and *cis*- and *trans*-**3b**.

Reduction of 3-Methyl-2-thiophenecarboxylic Acid (1c) Using Ten Equivalents of Lithium. Acid **1c** (3.64 g, 25.6 mmol) was reduced with lithium (1.77 g, 0.256 mol), ammonia (125 mL), and ammonium chloride (13.7 g, 256 mmol). The resulting mixture of carboxylic acids was esterified with methanol and sulfuric acid. Analysis of the mixture of esters by GC/MS showed the following compounds: **9c** (tentative), **8c**, **7c**, unidentified isomer (2%, retention time 13.7 min), **4c**, and **3c**.

Methyl (E)-3-Pentenoate (7a, R″ = CH_3). (E)-2,4-Pentadienoic acid (2.00 g, 20.4 mmol) was reduced to **7a**, R″ = H (0.65 g, 6.5 mmol) as previously described.[20] Esterification of the crude pentenoic acid using the procedure described for the carboxylic acid mixtures afforded 0.50 g (4.4 mmol) (59%) of **7a** (R″ = CH_3): bp 55–58 °C (40 mm) [lit.[29] bp 128.1–128.3 °C (625 mm)]; ^1H NMR ($CDCl_3$) δ 1.67 (3 H, dd, J_1 = 3 Hz, J_2 = 1 Hz), 2.98 (2 H, m), 3.61 (3 H, s), and 5.50 (2 H, m); IR (film) 1735, 1660, 969 cm^{-1}.

Methyl (E)-3-Hexenoate (7b, R″ = CH_3). This compound was prepared using the same procedure as for **7a**. Sorbic acid (10.0 g, 89.3 mmol) afforded 9.25 g (81.2 mmol) (91%) of **7b**, R″ = H, bp 80–82 °C (2 mm) [lit.[30] bp 110 °C (15 mm)]. Esterification of the acid (1.27 g, 11.1 mmol) gave 0.57 g (4.5 mmol) (40%) of **7b**, R″ = CH_3: bp 75–78 °C (40 mm) [lit.[31] bp 57 °C (17 mm)];

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^{1}H NMR ($CDCl_3$) δ 0.99 (3 H, t, J = 7.2 Hz), 2.03 (2 H, m), 3.03 (2 H, m), 3.67 (3 H, s), and 5.67 (2 H, m).

(*E*)-4-Bromo-2-pentenoic Acid (10a). To a solution of (*E*)-2-pentenoic acid[32] (8.43 g, 84.2 mmol) in carbon tetrachloride (50 mL) was added *N*-bromosuccinimide (15.0 g, 84.3 mmol) and 3–4 mg AIBN. The mixture was refluxed for 30 min and then cooled with an ice bath. Removal of the succinimide by filtration and removal of the solvent in vacuo afforded an oil which solidified at 0 °C. Recrystallization from petroleum ether afforded 14.3 g of white solid (95%), mp 82–83 °C [lit.[15] mp 85 °C].

(*E*)-4-Mercapto-2-pentenoic Acid (5a). To a stirred solution of **10a** (16.9 g, 94.4 mmol) in 60 mL of chloroform was added a solution of potassium thioacetate (11.15 g, 97.8 mmol) in 125 mL of methanol and 50 mL of water. The mixture was stirred for 16 h at ambient temperature and then diluted with 400 mL of water. The aqueous layer was saturated with sodium chloride and extracted with 3 × 50 mL chloroform. The combined organic portions were washed with saturated aqueous sodium chloride and dried over magnesium sulfate. Removal of the solvent in vacuo afforded 13.25 g crude **11a**. To a solution of the crude thioester/acid **11a** (8.00 g) in 60 mL of methanol was added a solution of sodium methoxide in 60 mL of methanol (3.2 g sodium). This mixture was stirred for 45 min at ambient temperature and then diluted with 250 mL of water. The aqueous solution was acidified with 9 N sulfuric acid and was then extracted with 3 × 50 mL chloroform. After the combined organic portions were dried over magnesium sulfate, removal of the solvent in vacuo afforded crude **5a** (6.0 g).

Chromatography of one-half of this material on silica gel using a mixture of petroleum ether/ether/formic acid (70:59.2:0.8) as eluant followed by recrystallization from petroleum ether gave 1.6 g (12 mmol) of pure **5a** (42%): mp.p. 49–50 °C; ^{1}H NMR ($CDCl_3$) δ 1.48 (3 H, d, J = 7 Hz), 1.75 (1 H, d, J = 6.5 Hz), 3.68 (1 H, m), 5.83 (1 H, d, J = 16 Hz), 7.07 (1 H, dd, J_1 = 16 Hz, J_2 = 8 Hz), 11.36 (1 H, s); IR (KBr) 1690, 1640 cm^{-1}. Anal. Calcd for $C_5H_8O_2S$: C, 45.43; H, 6.10; S, 24.26. Found: C, 45.60; H, 6.31; S, 24.41.

Methyl (*E*)-4-Mercapto-2-pentenoate (5a, R″ = CH_3). Acid **5a** (0.631 g, 4.79 mmol) was esterified as previously described to afford 0.56 g (3.4 mmol) of **5a** R″ = CH_3 (80%): bp 74–77 °C (3 mm); ^{1}H NMR ($CDCl_3$) δ 1.48 (3 H, d, J = 7 Hz), 1.79 (1 H, d, J = 6.5 Hz), 3.70 (1 H, m), 3.72 (3 H, s), 5.88 (1 H, dd, J_1 = 15.5 Hz, J_2 = 1.3 Hz), and 7.02 (1 H, dd, J_1 = 15.5 Hz, J_3 = 7.5 Hz); IR (film) 2500, 1740, 1650 cm^{-1}. Anal. Calcd for $C_6H_{10}O_2S$: C, 49.29; H, 6.89; S, 21.93. Found: C, 49.31; H, 6.78; S, 21.75.

2-(4-Bromophenyl)-2-oxoethyl (*E*)-4-(Acetylthio)-2-pentenoate (17a). Crude **11a** (1.08 g, 6.2 mmol) was esterified with α,*p*-dibromoacetophenone (1.90 g, 6.85 mmol) using the procedure of Rao.[24] Chromatography of the crude product on silica gel using a mixture of 2:1 petroleum ether/ether afforded 0.673 g (1.8 mmol) of pure **17a**: mp 90–91 °C; ^{1}H NMR ($CDCl_3$) δ 1.40 (3 H, d, J = 7.5 Hz), 2.35 (3 H, s), 4.33 (1 H, m), 5.37 (2 H, s), 6.10 (1 H, dd, J_1 = 16.0 Hz, J_2 = 1.5 Hz), 7.03 (1 H, dd, J_1 = 16.0 Hz, J_3 = 7.0 Hz), and 7.73 (4 H, m); IR (KBr) 1725, 1690, 1580 cm^{-1}. Anal. Calcd for $C_{15}H_{15}BrO_4S$: C, 48.53; H, 4.07; S, 8.64. Found: C, 48.28; H, 4.31; S, 8.55.

(*E*)-4-Bromo-2-hexenoic Acid (10b). This acid was obtained from (*E*)-2-hexenoic acid[33] (21.7 g, 191 mmol) by using the same procedure employed for **10a**. The preparation afforded 22.8 g (118 mmol) (62%) of **10b**: bp 96–100 °C (0.40 mm) [lit.[34] bp 94–98 °C (0.40 mm)].

(*E*)-4-Mercapto-2-hexenoic Acid (5b). Treatment of **10b** to the same procedure previously described for the preparation of **5a** afforded **5b** as an oil (42% from **10b**): ^{1}H NMR ($CDCl_3$) δ 1.02 (3 H, t, J = 7 Hz), 1.70 (3 H, m, C5–CH_2 overlaps SH), 3.52 (1 H, m), 5.93 (1 H, d, J = 16 Hz), 7.12 (1 H, dd, J_1 = 16 Hz, J_2 = 9 Hz), and 12.33 (1 H, s); IR (film) 1705, 1655 cm^{-1}; HRMS calcd for $C_6H_{10}O_2S$, 146.0402; found, 146.0397.

Methyl (*E*)-4-Mercapto-2-hexenoate (5b, R″ = CH_3). Acid **5b** (1.0 g, 6.8 mmol) was esterified as previously described to afford 0.9 g (5.6 mmol) of **5b**, R″ = CH_3 (82%): ^{1}H NMR ($CDCl_3$) δ 1.00 (3 H, t, J = 7 Hz), 1.67 (3 H, m, C5–CH_2 overlaps SH), 3.45 (1 H, m), 3.75 (3 H, s), 5.97 (1 H, d, J = 16 Hz), and 6.91 (1 H, dd, J_1 = 16 Hz, J_2 = 9 Hz); IR (film) 2530, 1720, 1650 cm^{-1}; HRMS calcd for $C_7H_{12}O_2S$, 160.0558; found, 160.0553.

2-(4-Bromophenyl)-2-oxoethyl (*E*)-4-(Acetylthio)-2-hexenoate (17b). This derivative was prepared as previously described for **17a**. From 0.997 g of **11b** was obtained 0.51 g (1.3 mmol) of **17b**: mp 66–67 °C; ^{1}H NMR ($CDCl_3$) δ 1.01 (3 H, t, J = 7 Hz), 1.78 (2 H, m), 2.32 (3 H, s), 4.12 (1 H, q, J = 7 Hz), 5.30 (2 H, s), 6.17 (1 H, d, J = 15.5 Hz), 6.90 (1 H, dd, J_1 = 15.5 Hz, J_2 = 8 Hz), and 7.65 (4 H, m); IR (KBr) 1720, 1680, 1650, 1580 cm^{-1}. Anal. Calcd for $C_{16}H_{17}BrO_4S$: C, 49.88; H, 4.45; S, 8.32. Found: 50.04; H, 4.61; S, 8.50.

Registry No. **1a**, 527-72-0; **1b**, 1918-79-2; **1c**, 23806-24-8; **2a**, 59753-16-1; **3a**, 40033-24-7; **3a** (R″ = CH_3), 74373-07-2; *cis*-**3b**, 81292-74-2; *trans*-**3b**, 81292-77-5; *cis*-**3b** (R″ = CH_3), 86610-34-6; *trans*-**3b** (R″ = CH_3), 86610-35-7; **3c**, 81292-72-0; **3c** (R″ = CH_3), 86610-36-8; *cis*-**3d**, 86610-43-7; *trans*-**3d**, 86610-39-1; *cis*-**3d** (R″ = CH_3), 86610-42-6; *trans*-**3d** (R″ = CH_3), 86610-38-0; **4a**, 69962-06-7; **4a** (R″ = CH_3), 74373-08-3; **4b**, 86610-44-8; **4b** (R″ = CH_3), 86610-45-9; **4c**, 86610-46-0; **4c** (R″ = CH_3), 86610-47-1; **4d**, 86610-41-5; **4d** (R″ = CH_3), 86610-40-4; **5a**, 74373-06-1; **5a** (R″ = CH_3), 74373-09-4; **5b**, 86610-54-0; **5b** (R″ = CH_3), 86610-55-1; **6a**, 21651-12-7; **6a** (R″ = CH_3), 2409-87-2; **6b**, 110-44-1; **6b** (R″ = CH_3), 689-89-4; **7a**, 1617-32-9; **7a** (R″ = CH_3), 818-58-6; **7b**, 1577-18-0; **7b** (R″ = CH_3), 13894-61-6; **7c**, 41653-93-4; **7c** (R″ = CH_3), 41654-12-0; **8a**, 33698-87-2; **8a** (R″ = CH_3), 36781-66-5; **8b**, 1775-43-5; **8c**, 41653-94-5; **8c** (R″ = CH_3), 56728-17-7; **9a**, 591-80-0; **9a** (R″ = CH_3), 818-57-5; **9b**, 1577-20-4; **9b** (R″ = CH_3), 14017-81-3; **9c**, 1879-03-4; **9c** (R″ = CH_3), 20459-97-6; **10a**, 27652-18-2; **10b**, 86610-53-9; **11a**, 86610-51-7; **12a**, 74373-10-7; **12b**, 86610-48-2; **12c**, 86610-49-3; **13**, 86610-50-6; (*Z*)-**14a**, 764-38-5; (*E*)-**14a**, 764-37-4; **15a**, 69962-08-9; **15b**, 75988-40-8; **15c**, 75988-37-3; **16a**, 86610-33-5; **17a**, 86610-52-8; **17b**, 86610-56-2; dilithium 3,4-dimethyl-2,5-thiophenedicarboxylate, 86610-37-9; dicyclohexylcarbodiimide, 538-75-0; (*E*)-3-hexen-1-ol, 928-97-2; (*Z*)-3-hexen-1-ol, 928-96-1; (*E*)-4-hexen-1-ol, 928-92-7; sorbic acid, 110-44-1; (*E*)-2-pentenoic acid, 13991-37-2; α,*p*-dibromoacetophenone, 99-73-0.

Supplementary Material Available: Tables of mass spectral fragmentation data for all components of the methyl ester mixtures and for other new compounds (8 pages). Ordering information is given on any current masthead page.

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