247–248 °C); NMR ($CDCl_3$) 2.38 (s, ring CH_3), 2.98 (s) ppm.

Tetramethyl-1,4-benzenedithiol. The above *S,S'*-diester (11 g, 0.032 mol) was refluxed with 60 mL of pyridine, 11 mL of water, 60 mL of methanol, and 20 g (0.3 mol) of potassium hydroxide for 6.5 h under nitrogen with stirring. The volume was then reduced under nitrogen, the solution was diluted with water, and hydrochloric acid was added until precipitation of the dithiol was complete. The dithiol was filtered off, air-dried, and recrystallized from dichloromethane to give 5.8 g (91%) in two crops: mp 195–198.5 °C; NMR ($CDCl_3$) 2.37 (s, CH_3), 3.12 (s, SH) ppm; NMR (C_6D_6) 2.17 (s, CH_3) 2.84 (s, SH) ppm.

Anal. Calcd for $C_{10}H_{14}S_2$: C, 60.56; H, 7.11; S, 32.33. Found: C, 60.88; H, 7.25; S, 32.50.

2,5-Dimethoxy-1,4-benzenedithiol. 2,5-Dimethoxy-1,4-benzenedisulfonyl chloride[15] (40 g, 0.12 mol), 650 mL of ethanol, 200 g (2.9 mol) of 95% zinc dust, and 240 mL (2.86 mol) of hydrochloric acid were stirred and refluxed for 30 min. The mixture was poured into 2 L of water, and the product and excess zinc were filtered off. The air-dried mixture was extracted with cyclohexane, and the dithiol was crystallized from the cyclohexane to give 16.5 g (68%), mp 124–126 °C (lit.[16] mp 122 °C, prepared by another route).

1,4-Benzenedithiol. This dithiol was prepared by the hydrolysis of *p*-phenylene *S,S'*-bis(dimethylthiocarbamate)[11b] as described for the tetrafluoro derivative.

(15) Manecke, G.; Beyer, H. J. *Makromol. Chem.* **1968**, *116*, 26.
(16) Ariyan, Z. S.; Martin, R. L. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1687.

Acknowledgments. I am indebted to W. A. Sheppard and L. R. Melby for helpful discussions, to G. S. Reddy for calculation of the conformation energy barrier for **4**, to L. J. Guggenberger for the X-ray examination of **4**, to N. E. Schlichter and E. W. Matthews for IR, UV, and Raman spectra interpretations, and to P. J. Krusic for the ESR experiment.

Registry No. 4, 70470-78-9; **4** *N,N*-dimethyldihydrophenazine complex (1:1), 70470-79-0; **4** 1,3-diphenylisobenzofuran complex (1:4), 70470-80-3; tetrafluoro-*p*-phenylene *O,O'*-bis(dimethylthiocarbamate), 70470-81-4; tetrafluorohydroquinone, 771-63-1; dimethylthiocarbamoyl chloride, 16420-13-6; tetrafluoro-*p*-phenylene *S,S'*-bis(dimethylthiocarbamate), 70470-82-5; tetrafluoro-1,4-benzenedithiol, 3467-78-5; *N,N'*-dimethyldihydrophenazine, 15546-75-5; 1,3-diphenylisobenzofuran, 5471-63-6; tetrachloro-*p*-phenylene *O,O'*-bis(dimethylthiocarbamate), 70470-83-6; tetrachlorohydroquinone, 87-87-6; tetrachloro-*p*-phenylene *S,S'*-bis(dimethylthiocarbamate), 70470-84-7; tetrachloro-1,4-benzenedithiol, 67341-48-4; tetramethyl-*p*-phenylene *O,O'*-bis(dimethylthiocarbamate), 13522-73-1; tetramethylhydroquinone, 527-18-4; tetramethyl-*p*-phenylene *S,S'*-bis(dimethylthiocarbamate), 13512-07-7; tetramethyl-1,4-benzenedithiol, 70470-85-8; 2,5-dimethoxy-1,4-benzenedithiol, 30079-16-4; 2,5-dimethoxy-1,4-benzenedisulfonyl chloride, 19116-92-8; 1,4-benzenedithiol, 624-39-5; *p*-phenylene-*S,S'*-bis(dimethylthiocarbamate), 13512-06-6; 2,3,5,6-tetrachloro-1,4-benzenedithiol homopolymer, 70470-87-0; poly[dithio(2,3,5,6-tetrachloro-1,4-phenylene)], 70470-88-1.

Oxidative Cyclization of 3-(Amino)thioethers to Form S-Substituted Isothiazolidinium Salts[1]

David O. Lambeth* and Darrell W. Swank

Department of Biochemistry, School of Medicine, The University of North Dakota, Grand Forks, North Dakota 58202

Received May 23, 1978

The reaction in which methionine is cyclized to form dehydromethionine (*S*-methylisothiazolidinium-3-carboxylate) by iodinic oxidation at neutral pH[3] has now been shown to be a general one for compounds possessing an amine group γ to a thioether function. Thus, the reaction provides a convenient route to the preparation of N-protonated, cyclic sulfilimines. The S-substituted isothiazolidinium salts from ethionine, *S*-phenylhomocysteine, *S*-benzylhomocysteine, and 3-(methylthio)propylamine were prepared and characterized by elemental analyses and NMR spectra. Cyclization of L-methionine was shown to produce a mixture of diastereomers which are chiral at positions 1 (sulfur) and 3. Evidence was obtained that hydrolysis of each diastereomer to form the sulfoxide proceeds with inversion of configuration. Oxidative cyclization of 3-(amino)thioethers was found to also be induced by a variety of *N*-halo derivatives and by lead tetraacetate.

Substances containing an isothiazolidine ring unsubstituted at sulfur are unknown, presumably because of their instability. The only previous example of an S-substituted isothiazolidine is dehydromethionine (*S*-methylisothiazolidinium-3-carboxylate) which was isolated by Lavine as a stable intermediate on the pathway to sulfoxide when methionine was oxidized by iodine in neutral solution.[2-4] Lavine's proposed structure for dehydromethionine was confirmed by X-ray diffraction.[5] Additional studies of dehydromethionine have been concerned with reversibility of the formation reaction and hydrolysis to the sulfoxide[6] and with reduction by thiols to form methionine.[7] Evidence has also been presented that a sulfurane intermediate is on the pathway to dehydromethionine when methionine is oxidized by iodine.[8]

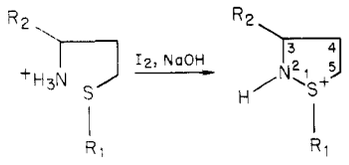
In this paper, we report our findings regarding the scope of the reaction resulting in formation of S-substituted isothiazolidinium salts. We find that iodine and several *N*-halo derivatives will induce ring closure of substances containing a 3-(amino)thioether moiety. Many of the substances cyclized by us are amino acid derivatives and the carboxyl group neither prevents nor interferes with the cyclization reaction. Ring closure introduces a chiral center at sulfur and the mixture of diastereomers resulting from L- and/or D-amino acids is separated by chromatography.

The S-substituted isothiazolidinium salts may be viewed as the conjugate acids of cyclic sulfilimines. The sulfilimine class has been the subject of a recent review[9] and in

(1) This work was supported by USPHS Grants GM 21539 and 25252. The work was initiated while D.O.L. was a member of the faculty of the Department of Chemistry, University of South Florida, Tampa, Fla.
(2) T. F. Lavine, *J. Biol. Chem.*, **151**, 281 (1943).
(3) T. F. Lavine, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **4**, 96 (1945).
(4) T. F. Lavine, U.S. Patent No. 2 465 461 (March 29, 1949).
(5) R. S. Glass and J. R. Duchek, *J. Am. Chem. Soc.*, **98**, 965 (1976).
(6) K.-H. Gensch and T. Higuchi, *J. Pharm. Sci.*, **56**, 177 (1967).
(7) D. O. Lambeth, *J. Am. Chem. Soc.*, **100**, 4808 (1978).
(8) P. R. Young and L.-S. Hsieh, *J. Am. Chem. Soc.*, **100**, 7121 (1978).
(9) T. L. Gilchrist and C. J. Moody, *Chem. Rev.*, **77**, 409 (1977).

0022-3263/79/1944-2632$01.00/0

Scheme I



compd	R_1	R_2
1	CH_3	COO^-
2	C_2H_5	COO^-
3	C_6H_5	COO^-
4	$C_6H_5CH_2$	COO^-
5	CH_3	H

comparison with previously reported sulfilimines, the S-substituted isothiazolidinium salts reported here are unique. They are N-protonated sulfilimines which are fairly stable in aqueous solution at neutral pH, even when both carbon substituents of sulfur are alkyl groups. In contrast, most of the previously reported sulfilimines have strong electron-withdrawing groups adjacent to the sulfilimine linkage.[9] The increased stability of the S-substituted isothiazolidinium salts may be due to their cyclic structure since enhanced stability of labile functional groups has often been observed for ring systems.

Results and Discussion

Synthesis of S-Substituted Isothiazolidinium Salts. Scheme I shows the general procedure for the synthesis of S-substituted isothiazolidinium salts and the structures of five members of this group isolated in sufficient quantity to permit characterization by elemental analyses and NMR spectroscopy. The numbering system for the ring is also shown.

The cyclization reactions take place in high yield. Purification of product mixtures was facilitated by using exactly stoichiometric amounts of reactants and by taking care to minimize side reactions. The latter was accomplished by slowly adding iodine and sodium hydroxide to the thioether, by efficiently stirring the reaction mixture, and by working rapidly through the purification procedure.

Our procedure for preparing 1 and 2 differs from previous procedures for 1 in that we used ion-retardation resin to remove NaI from the zwitterionic products. Our method is also more suitable for large quantities since it avoids the use of expensive silver oxide[3] and the inconvenience of working with sodium methoxide in strictly nonaqueous solvents.[5]

The reactions of *S*-phenyl- and *S*-benzylhomocysteine with iodine to form 3 and 4 were comparatively sluggish and were forced to completion by precipitating the iodide as the silver salt. Purification of 2–4 and separation of the diastereomeric mixtures were accomplished by column chromatography on silica columns, using methanol as the eluent.

Crystallization of dehydromethionine, 1, had previously been induced by permitting ether to diffuse through the vapor phase into a methanol solution of the substance.[5] Using this technique, we found that only one of the two diastereomers derived from L-methionine (see below) formed crystals, and attempts to use the vapor-diffusion technique for crystallization of 2–4 were unsuccessful. Substance 5 was easily purified as the nitrate salt by crystallization from ethanol.

Once purified, products 1–5 are white compounds which are very soluble in methanol and water to give colorless solutions. They hydrolyze slowly to give sulfoxides in neutral aqueous solution, but hydrolysis occurs within minutes in either 0.1 M HCl or 0.1 M NaOH. The substances are stable for at least several weeks when stored desiccated at 0 °C.

Characterization of Compounds 1–5. In analogy with sulfonium salts, the products of the cyclization reaction were expected to be chiral at sulfur. Since the parent compounds for 1–4 are amino acids with a chiral center at carbon 2, cyclization of each should result in a mixture of diastereomers. The product mixtures containing 1–4 each gave two well-resolved spots on thin-layer chromatograms which showed the properties of isothiazolidinium salts. The faster moving spots always contained 2–3 times more material than the slower spot.

The diastereomers of 1 were prepared from L-methionine, and elemental analyses of each indicated their empirical formulas were identical. The chemical shifts and integrated intensities of the proton NMR spectra of the diastereomers were consistent with an *S*-alkylisothiazolidine structure. The proton resonance of the *S*-methyl substitutent of 1 appeared as a singlet which was shifted downfield relative to methionine by 0.7 ppm which is the approximate shift observed for methionine sulfoxide and *S*-methylmethionine sulfonium chloride. The remaining proton resonances of the diastereomers of 1 gave a complex and not easily interpreted spectrum which is to be expected for a ring system in which none of the ring hydrogens are equivalent.

The diastereomeric relationship of the chromatographically separable components of 1 was further indicated by comparing the ^{13}C NMR spectrum of the faster migrating component with that of an approximately equimolar mixture of the diastereomers. The resonance of each carbon of the mixture was clearly resolved, and the signals of the corresponding carbons were closely paired as expected for diastereomers.

Data from the proton NMR spectra for 2–5 and the ^{13}C NMR spectra of 2 and 5 are listed in the Experimental Section. In each case, these data together with elemental analyses are consistent with the S-substituted isothiazolidinium structure.

On the basis of the following arguments, the absolute configurations of the diastereomers of 1 are tentatively assigned. In more than 10 crystallization attempts using the vapor-diffusion technique of Glass and Duchek,[5] only the faster migrating diastereomer (R_f 0.39) crystallized. Since Glass and Duchek used DL-methionine as the starting material for the synthesis of 1, we believe the crystal they chose for X-ray diffraction contained one or both of the enantiomers which would show an R_f of 0.39 in our thin-layer chromatography system. The structure depicted in their paper[5] shows the crystal originated from D-methionine and has the 3(*R*),*S*(*S*) configuration. However, their packing diagram for the crystal shows both the 3-(*S*),*S*(*R*) and 3(*R*),*S*(*S*) enantiomers. Regardless, since our synthesis started with L-methionine, we assign our crystallizable isomer the 3(*S*),*S*(*R*) configuration. The other diastereomer derived from L-methionine (R_f 0.27) is assigned the 3(*S*),*S*(*S*) configuration. This diastereomer precipitated from methanol as a seemingly amorphous solid regardless of the rate at which ether was added.

Hydrolysis of each diastereomer of 1 in 1 N HCl was found by TLC to give methionine sulfoxide. The sulfoxide resulting from the isomer of 1 assigned the 3(*S*),*S*(*R*) configuration showed an optical rotation, $[\alpha]^{25}_D$, of +126.5°. This rotation is in good agreement with the values of +127 and +131° reported for L-methionine *d*-sulfoxide,[10,11] which has been shown to have the 2(*S*),*S*(*S*) configuration.[11] The

(10) T. F. Lavine, *J. Biol. Chem.*, 169, 477 (1947).
(11) B. W. Christensen and A. Kjaer, *Chem. Commun.*, 225 (1965).

Table I. Reactions of 3-(Amino)thioethers and Related Compounds with Iodine[a]

compd	reacn time,[b] min	% reversibility[c]
L-methionine	<1	99.2
DL-ethionine	<1	99.6
S-phenyl-DL-homocysteine	9	97.8
S-benzyl-DL-homocysteine	28	56
3-(methylthio)propylamine	<1	96.8
α-methyl-DL-methionine	<1	99.9
L-methionine amide	<1	99.8
L-methionine methyl ester	<1	99.3
L-methionine hydroxamate	<1	40.6
L-methionylglycine	<1	99.6
DL-methioninol	<1	61
N-acetyl-DL-methionine	240	0
glycyl-L-methionine	110	0
DL-methionine *dl*-sulfoxide	nr[d]	
DL-methionine sulfone	nr	
S-methyl-DL-methionine	nr	
S-methyl-L-cysteine	44	<1
S-benzyl-L-cysteine	50	<1

[a] Approximately 100 mg of each compound was added to 50 mL of water containing 1 g of Na_3BO_3. A 90% stoichiometric amount of iodine was then added as 0.05 M I_2 dissolved in 0.24 M KI. [b] Approximate time required for color of iodine to disappear. [c] Reactions were reversed by adding 5 g of KI and 2 mL of 8 N HCl. The iodine produced was titrated with 0.1 N $Na_2S_2O_3$. Percent reversibility is (amount of iodine titrated)/(amount of iodine originally added) × 100. [d] No reaction.

product of the 3(*S*),*S*(*S*) isomer showed $[\alpha]^{25}_D$ of −54° compared with −57.6° for L-methionine *l*-sulfoxide[10] which has the 2(*S*),*S*(*R*) configuration. These data further support our conclusion that the cyclized products derived from L-methionine are indeed diastereomeric and that optically pure sulfoxides are formed upon hydrolysis. If our configurational assignments of the diastereomeric, cyclic products are correct, then hydrolysis of each diastereomer proceeds with inversion of configuration at sulfur.

We assume that our preparation of **5** is a racemic mixture chiral at sulfur. Since **2–4** were prepared from a racemic mixture of the D- and L-amino acids, the fast-migrating component of each is presumably a racemic mixture of the 3(*S*),*S*(*R*) and 3(*R*),*S*(*S*) enantiomers.

Scope of the Cyclization Reaction. Several methionine derivatives and analogues were studied to examine the requirements of an iodine-induced cyclization reaction. On the basis of the behavior of compounds **1–5**, cyclization was inferred by observation of the following: rapid reaction with iodine, nearly quantitative reversal of the reaction upon acidification, appearance of isothiazolidinium-positive spots on TLC, and formation of sulfoxide upon alkalinization of the product mixture. Sulfoxides of 3-(amino)thioethers were found not to be rapidly reduced to thioethers by iodide in acid solution.

Each of the first 11 substances listed in Table I generally conformed to the expected behavior. Thus, with the exception of **5**, products of iodine oxidation produced two isothiazolidinium-positive spots on TLC (color of iodine observed on spraying with acidified KI), and these spots were eliminated and replaced by a spot for sulfoxide when the product mixtures were pretreated with alkali. The product mixture derived from 3-(methylthio)propylamine showed only one isothiazolidinium-positive spot as expected. The three cases where excellent reversibility was not obtained may have been the result of competing reactions for iodine consumption and/or competition by hydrolysis in the reverse direction.

Table II. Yields of Isothiazolidinium Salts Induced by Various Oxidizing Agents[a]

	% yields			
	from L-methionine		from 3-(methylthio)-propylamine	
oxidizing agent	in CH_3OH	in H_2O	in CH_3OH	in H_2O
iodine	97	97	92	93
N-chlorosuccinimide	60	14	82	38
N-bromosuccinimide	66	25	97	56
N-iodosuccinimide	55		88	
chloramine-T	78	17	57	37
lead tetraacetate	87		70	

[a] Approximately 1 mmol of aminothioether was reacted for 30 min with an equimolar amount of oxidizing agent in either of the two solvents indicated. The apparent pH was kept near 7 by adding 0.2 N NaOH. Yields were determined by the iodometric titration procedure and were corrected for any unreacted *N*-halo derivative present (these reagents reacted with iodide to give iodine *before* the solution was acidified). No attempt was made to optimize the yields. Confirmation that both diastereomers of **1** were being formed from L-methionine and that **5** was being produced from 3-(methylthio)propylamine was obtained by TLC.

N-Acetylated methionine and *S*-alkylcysteine derivatives reacted slowly with iodine to form sulfoxides and no evidence of cyclic intermediates was obtained by TLC. Methionine sulfoxide, methionine sulfone, and *S*-methylmethionine failed to react with iodine. Derivitization of the carboxyl group did not prevent the cyclization reaction and the results with the two dipeptides of glycine and methionine indicate that only N-terminal methionyl residues of peptides will form a cyclic ring. The testing of secondary amines in the cyclization reaction awaits preparation of suitable starting compounds.

Cyclization Induced by Other Oxidizing Agents. Several oxidizing agents, particularly *N*-halo derivatives, have been used to prepare noncyclic sulfilimines.[9] Some of these reagents have also been used to prepare sulfoxides, to oxidize methionyl residues in proteins,[12] and to decarboxylate and deaminate amino acids.[13] A summary of our results with several of these agents is shown in Table II. Verification that the reactions produced the expected isothiazolidinium salts was obtained by TLC, and the apparent yields of the reactions were determined by iodometric titration.

The *N*-halo reagents each produced fair to good yields of the isothiazolidinium salts. However, sulfoxides were also produced with the amount being less when the reactions were carried out in methanol.

Lead tetraacetate has been used to prepare sulfilimines,[9] and we obtained significant yields of isothiazolidinium salts with this reagent.

We did not detect isothiazolidinium salts in the product mixtures resulting from reaction of methionine with peroxidation agents ($NaIO_4$ and H_2O_2), iodosobenzoic acid, or cyanogen bromide. The yields were very low when trichloromethanesulfonyl chloride was used.

Iodine has not been used widely, if at all, to prepare noncyclic sulfilimines. However, we find it to be more efficient than the other oxidative reagents we have tried.

(12) Y. Schechter, Y. Burstein, and A. Patchornik, *Biochemistry*, **14**, 4497 (1975).
(13) J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids", Vol. 2, Wiley, New York, N.Y., 1961.

The 3-(amino)thioethers, which can cyclize to form S-substituted isothiazolidinium salts, react much more rapidly with iodine than do simple thioethers which proceed directly to the sulfoxide. The reason appears to be related to a highly favorable intramolecular reaction in which amine displaces iodide from an iodosulfonium intermediate.[6]

Experimental Section

Ion-retardation resin, amino acids and derivatives, and *N*-halo derivatives were obtained from Sigma Chemical Co. The *N*-halo derivatives were recrystallized from water and dried just before use. Thin-layer cellulose sheets (No. 6064) and 3-(methylthio)propylamine were obtained from Eastman. SilicAR CC-7 for column chromatography was obtained from Mallinckrodt. Solvents and inorganic compounds were analytical reagent grade. Elemental analyses were performed by Galbraith Laboratories. Proton NMR spectra were generally obtained with a Varian EM-390 90-MHz NMR spectrometer. The ^{13}C NMR spectra were obtained at 15 MHz with a JEOL FX-60 Fourier transform NMR spectrometer. Samples were dissolved in D_2O at a concentration of about 5% and chemical shifts are reported relative to the methyl substituents of DSS. The multiplicity observed in partially decoupled spectra was used to assign some of the resonances. Positions of ring substituents are denoted by assigning sulfur and nitrogen as positions 1 and 2, respectively.

General Procedure for Synthesis. A stoichiometric amount of iodine in methanol was added in aliquots to a water or methanol–water solution (or suspension) of the aminothioether. The pH was kept between 7 and 8.5 by the dropwise addition of 5 M NaOH. Iodine reacted within 1 h, and the yields of product (iodometric titration) were usually greater than 90%.

***S*-Methylisothiazolidinium-3-carboxylate (1).** The reaction of equimolar amounts (0.1125 mol) of L-methionine (16.79 g) and iodine (28.55 g) required approximately 0.225 mol of NaOH for neutralization. The volume of the solution was reduced to 75 mL, using a rotary evaporator, and sodium iodide was then removed on a 500-mL column of ion-retardation resin. The product was eluted and the column was regenerated by continued passage of water. Fractions containing 1, but which were free of iodide ($AgNO_3$ test), were combined and evaporated to dryness on a rotary evaporator.[14]

The product mixture contained fast (R_f 0.39) and slow (R_f 0.27) components as detected by TLC in an approximate ratio of 2:1. As described in the text, these components are diastereomers which have been assigned the 3(*S*),*S*(*R*) and 3(*S*),*S*(*S*) configurations, respectively.

The R_f 0.39 isomer was purified[5] by dissolving crude 1 in methanol (1 g/60 mL), filtering, and placing the resultant solution in an Erlenmeyer flask inside a larger, tightly sealable vessel containing two volumes of absolute ether. After 1 week at 0 °C, the well-formed crystals (spike-shaped clusters of plates) were separated from the mother liquor and any amorphous precipitate present. These crystals were washed with a 2:1 mixture of ether–methanol and dried to afford approximately 8 g (50% yield) of the 3(*S*),*S*(*R*) isomer of 1: ^1H NMR (D_2O) δ 2.3–3.0 (m, 2 H), 2.82 (s, 3 H), 3.4–4.0 (m, 2 H), 4.2–4.5 (pair of doublets approximately a triplet, 1 H); ^{13}C NMR (D_2O) δ 178.3 (COO^-), 69.5 (C-3), 49.5 (C-5), 33.9 and 33.5 (C-4 and *S*-methyl). Anal. Calcd for $C_5H_9NO_2S$: C, 40.80; H, 6.16; N, 9.52; S, 21.78. Found: C, 40.71; H, 5.95; N, 9.49; S, 21.66.

The slow-migrating diastereomer of 1 was obtained pure as follows: A series of precipitates were collected from a solution of 1 in methanol by adding slowly and with stirring a total of 2.5 volumes of ether in 0.5-volume aliquots. Precipitates were collected (by vacuum filtration) immediately after each aliquot of ether had been added. Each precipitate was checked for composition by TLC and was often found to be predominantly one diastereomer. Precipitates which were mixtures of the two diastereomers were taken through the procedure again. Nearly pure fractions were repeatedly dissolved in methanol (60 mg/mL) and precipitated with two volumes of ether until satisfactorily pure by TLC. Small amounts of precipitates were collected by centrifugation. The yields of the 3(*S*),*S*(*R*) and 3(*S*),*S*(*S*) isomers of 1 were approximately 8 g (50%) and 1 g (6%), respectively. The ^1H NMR spectrum (D_2O) of the 3(*S*),*S*(*S*) isomer was nearly the same as for the 3(*S*),*S*(*R*) isomer (see above). ^{13}C NMR (D_2O) δ 180.0 (COO^-), 70.4 (C-3), 50.4 (C-5), 34.3 and 32.5 (C-4 and *S*-methyl). Anal. Calcd for 2(*S*),*S*(*S*) isomer: see above. Found: C, 40.63; H, 6.33; N, 9.38; S, 21.58.

A solvent dependency was observed for the methyl resonances of the diastereomers of 1. In D_2O, a sharp singlet with a chemical shift of δ 2.82 was observed for both diastereomers. However, in deuterated methanol, the methyl resonances of a mixture were separated by 4 Hz in a 60-MHz spectrum. Addition of aliquots of D_2O caused the peaks to move together, without changing the relative heights, until they coalesced when the solvent was predominantly D_2O. Coalescence was not due to rapid interconversion of configurations at sulfur since purified diastereomers maintained their configurations for several hours. The solvent effect may be due to differences in the solvation of the N–S group and/or rapid inversion of nitrogen in the aqueous environment.

***S*-Ethylisothiazolidinium-3-carboxylate (2).** Reaction of 5.04 g (30.88 mmol) of DL-ethionine with 7.76 g (30.57 mmol) of I_2 and removal of sodium iodide were carried out as described for 1. The eluate containing 4.32 g of 2 was taken to dryness and then dissolved in 20 mL of methanol. The filtered solution was chromatographed in methanol on a 2.5 × 28 cm column of silica gel. The first few fractions containing ethionine, ethionine sulfoxide, and colored impurities were discarded as were the fractions at the end of the column chromatography which were primarily the slow-migrating form of 2. Fractions enriched in the fast-migrating isomer of 2 were pooled and solvent was removed to yield 3 g of material. The bulk of the sample was dissolved in ethanol (25 mL), and insoluble material was removed by centrifugation. Three volumes of ether were added and the voluminous precipitate was collected by centrifugation. Precipitation was repeated four times to give 1 g (20% yield) of the fast-migrating isomers of 2: ^1H NMR (D_2O) δ 1.35 (t, 3 H), 2.1–3.2 (m, 2 H), 3.1 (q, 2 H), 3.4–4.0 (m, 2 H), 4.32 ("t", 1 H). Anal. Calcd for $C_6H_{11}NO_2S$: C, 44.70; H, 6.88; N, 8.69; S, 19.89. Found: C, 44.53; H, 7.00; N, 8.50; S, 19.63.

***S*-Phenylisothiazolidinium-3-carboxylate (3).** *S*-Phenyl-DL-homocysteine was prepared by the method of Armstrong and Lewis.[15] To 2.5 mmol (0.528 g) of *S*-phenyl-DL-homocysteine suspended in methanol, 2.5 mmol of iodine in methanol was added slowly while the pH was kept between 7 and 8 with 1 M KOH. Dropwise addition of 5 mmol of $AgNO_3$ in water forced the reaction to completion and precipitated the iodide. The resulting mixture containing 0.428 g of 3 (by titration) was filtered. Solvent was removed and the residue was extracted with a total of 9 mL of methanol. The volume of this solution was reduced to 1 mL. After removal of solid material, the solution was chromatographed in methanol on a 28 × 1.5 cm column of SilicAR CC-7. Fractions enriched in the fast-migrating component (R_f 0.61) were combined, taken to dryness, redissolved in 1 mL of methanol, and rechromatographed. The product recovered (0.105 g, 20% yield) was chromatographically pure and slightly off-white: ^1H NMR (D_2O) δ 2.4–2.8 (m, 2 H), 3.6–4.2 (m, 2 H), 4.4–4.7 ("t", 1 H), 7.73 (s, 5 H). Anal. Calcd for $C_{10}H_{11}NO_2S$: C, 57.40; H, 5.30; N, 6.69; S, 15.32. Found: C, 57.57; H, 5.52; N, 6.57; S, 15.12.

***S*-Benzylisothiazolidinium-3-carboxylate (4).** *S*-Benzyl-DL-homocysteine, obtained from Sigma, was purified by the procedure used for *S*-phenyl-DL-homocysteine.[15] Preparation of 4 from 2.5 mmol (0.563 g) of *S*-benzylhomocysteine was accomplished by the same procedure used for 3. The product recovered from the second chromatography on SilicAR CC-7 was dissolved in 1 mL of CH_3OH, precipitated with 3 mL of ether, and washed with ether. Substance 4 seemed to be the most unstable of the group 1–5, and the yield was low (20 mg) because of poor recovery during purification. The sample showed on TLC the fast-migrating product (R_f 0.70) contaminated with barely

(14) The isothiazolidinium salts are hygroscopic and typically formed oils during rotary evaporation. Crystallization and removal of water were induced by addition of small aliquots of absolute ethanol near the end of the evaporation procedure.

(15) M. D. Armstrong and J. D. Lewis, *J. Org. Chem.*, 17, 618 (1952).

detectable traces of the slow isomer (R_f 0.57) and two unknown, ninhydrin-positive compounds: ^{1}H NMR (D_2O) δ 2.2–2.9 (m, 2 H), 3.6–3.9 (m, 2 H), 4.1–4.6 (m, 3 H), 7.48 (s, 5 H). Anal. Calcd for $C_{11}H_{13}NO_2S$: C, 59.17; H, 5.87; N, 6.27; S, 14.36. Found: C, 59.22; H, 6.17; N, 6.05; S, 14.24.

S-Methylisothiazolidinium Nitrate (5). The reaction of 13.78 g (0.131 mol) of 3-(methylthio)propylamine with 31.73 g (0.125 mol) of iodine required 0.125 mol of NaOH. The product salts were converted to nitrates by use of Dowex-1 nitrate. Solvent was removed from the eluate and the residue was extracted with 100 mL of hot ethanol. Following decolorization with charcoal and filtration, the product readily crystallized to give 14.7 g (67% yield) of white needles which tested 96.5% pure. Crystallization was repeated until the sample was chromatographically and titrimetrically pure: ^{1}H NMR (D_2O) δ 1.9–2.9 (m, 2 H), 2.78 (s, 3 H), 3.4–4.1 (m, 4 H); ^{13}C NMR (D_2O) δ 53.7, 51.3, 32.9, 29.6. Anal. Calcd for $C_4H_{10}NSNO_3$: C, 28.90; H, 6.06; N, 16.86; S, 19.31. Found: C, 28.71; H, 6.00; N, 16.66; S, 19.09.

Titrimetric Assay for S-Substituted Isothiazolidinium Salts. To approximately 50 mg of compound dissolved in alcohol or water, 3 mL of 5 M KI and then 5 mL of 3 N HCl were added. The liberated iodine was titrated with standardized sodium thiosulfate. The best preparations of **1**, **2**, and **5** gave 99 ± 1% of the calculated amount of iodine in spite of the potentially competing hydrolysis reaction.

Thin-Layer Chromatography. Duplicate 20-μg samples were chromatographed on thin-layer cellulose plates, using acetonitrile–ethylene glycol–0.1 M ammonium acetate (70:15:15), pH 7.4, as the solvent. *S*-Alkylisothiazolidines were detected as brown spots formed immediately upon spraying with acidified potassium iodide. Duplicate chromatograms were sprayed with ninhydrin and developed at room temperature. Free amino acids gave purple spots within 1 h while the S-substituted isothiazolidinium salts gave purple spots after several days. Solvents containing acids or bases were avoided as they caused substantial decomposition of the *S*-alkylisothiazolidinium salts.

Optical Rotation Studies. Optical rotations were determined with 10 and 20 dm tubes, a Rudolph Model 325 polarimeter, and the D-line of sodium. The L-methionine as purchased had an $[\alpha]^{25}_D$ of +23.5° (5% solution in 1 N HCl) which is in satisfactory agreement with literature values. The diastereomers of **1** dissolved in water at a concentration of 2% gave $[\alpha]^{25}_D$ values of +86 and +18° for the 3(*S*),*S*(*R*) and 3(*S*),*S*(*S*) isomers, respectively. Rotations of the unhydrolyzed compounds were stable for at least 1 h. The samples were then diluted with an equal volume of 2 N HCl and the optical rotations of the resulting methionine sulfoxides gave the values reported in the text. Hydrolyses at room temperature were complete within 10 min.

Acknowledgments. We gratefully acknowledge the technical assistance of Dennis Lubahn, Angel DeCobo, and David Toman in the preliminary stages of this work, the Department of Chemistry, University of North Dakota, for the use of their NMR instruments, and Sylvia Farnum and Robert Zoellner for their assistance in obtaining and interpreting the NMR spectra. Preliminary NMR studies were conducted at the University of South Florida with the able assistance of Ron Federspiel.

Registry No. **1**, isomer 1, 70224-21-4; **1**, isomer 2, 70266-80-7; **2**, isomer 1, 70198-01-5; **2**, isomer 2, 70198-02-6; **3**, isomer 1, 70208-82-1; **3**, isomer 2, 70198-03-7; **4**, isomer 1, 70198-04-8; **4**, isomer 2, 70198-05-9; (±)-**5**, 70198-07-1; L-methionine, 63-68-3; DL-ethionine, 67-21-0; *S*-phenyl-DL-homocysteine, 52162-05-7; *S*-benzyl-DL-homocysteine, 1017-76-1; 3-(methylthio)propylamine, 4104-45-4; α-methyl-DL-methionine, 2749-07-7; L-methionine amide, 4510-08-1; L-methionine methyl ester, 10332-17-9; L-methionine hydroxamate, 19253-87-3; L-methionylglycine, 14486-03-4; DL-methioninol, 16720-80-2; *N*-acetyl-DL-methionine, 1115-47-5; glycyl-L-methionine, 554-94-9; DL-methionine *dl*-sulfoxide, 4241-59-2; DL-methionine sulfone, 820-10-0; DL-methionine, 59-51-8; *S*-methyl-L-cysteine, 1187-84-4; *S*-benzyl-L-cysteine, 3054-01-1.

Alkyl Thioether Activation of the Nitro Displacement by Alkanethiol Anions. A Useful Process for the Synthesis of Poly[(alkylthio)benzenes]

Pietro Cogolli, Lorenzo Testaferri, Marco Tingoli, and Marcello Tiecco*

Istituto di Chimica Organica, Facoltà di Farmacia, Università di Perugia, 06100 Perugia, Italy

Received February 13, 1979

The reactions of *o*- and *p*-dinitrobenzenes, 2,4-dinitro-1-chlorobenzene, picryl chloride, and other simple halogenonitrobenzenes, with an excess of the sodium salt of the isopropanethiol, in HMPA, afforded the products of complete displacement of all the chloro and the nitro groups present in the molecule. These results indicated that the thioether function in the ortho or para positions activates the substitution of the nitro group by the alkanethiolate anion. The effect of the structure of the thiolate was examined by effecting the same reactions, in HMPA, with MeSNa, EtSNa, Me_3CSNa, and PhSNa. Reactions with Me_2CHSNa were also carried out in DMF and Me_2SO. It was observed that the reduction of the nitro group competes with the displacement process and that the relative importance of the two reactions depends on the structure of the aromatic substrate and of the thiolate as well as on the solvent employed. Complete and clean substitution reactions were obtained only with Me_2CHSNa in HMPA.

In the course of our researches in the field of homolytic aromatic ipso substitution reactions by alkyl radicals,[1] it was necessary to synthesize some poly(sulfonylbenzenes) and nitrosulfonylbenzenes in order to investigate the alkyldesulfonylation process. For this purpose, we employed the procedure described by Kornblum and co-workers[2] consisting of the displacement of the nitro group in nitrobenzenes by the sodium salt of thiols in hexamethylphosphoramide (HMPA). While the reaction of *p*-dinitrobenzene with excess PhSNa afforded *p*-nitrophenyl phenyl sulfide, as reported in the literature,[2] the use of

(1) L. Testaferri, M. Tiecco, M. Tingoli, M. Fiorentino, and L. Troisi, *J. Chem. Soc., Chem. Commun.*, 93 (1978); L. Testaferri, M. Tiecco, and M. Tingoli, *J. Chem. Soc., Perkin Trans. 2*, in press.

(2) N. Kornblum, L. Cheng, R. C. Kerber, M. M. Kestner, B. N. Newton, H. W. Pinnick, R. G. Smith, and P. A. Wade, *J. Org. Chem.*, 41, 1560 (1976).

0022-3263/79/1944-2636$01.00/0