TABLE IX

DETERMINATION OF THE EQUILIBRIUM CONSTANT FOR THE REACTION, $HI + I_2 \rightleftharpoons HI_3$, IN ACETIC ACID[a]

$[I_3^-]$, $M \times 10^4$	Dilution factor, V	A_{360}[d]	r	F	$K \times 10^7$	$1/K \times 10^{-6}$	$a_m \times 10^{-4}$
4.61[b]	1	1.097					
	2	0.538	2.039	0.959	8.10	1.23	2.48
	5	0.208	5.274	0.958	8.49	1.18	2.48
	10	0.099	11.058	0.954	10.2	1.02	2.49
5.51[c]	1	1.425					
	2	0.699	2.039	0.959	9.65	1.03	2.69
	5	0.270	5.276	0.957	10.6	0.94	2.70
	10	0.128	11.13	0.962	8.27	1.21	2.68

[a] For definitions of V, r, and F, and the rationale for the method, see Katzin and Gebert.[15] $K = [HI][I_2]/[HI_3]$ so that $1/K = K_5$ in this paper. [b] Sufficient acetic anhydride was introduced to consume the water introduced with hydrogen iodide. [c] Contained ~0.1% water. [d] Values obtained with Cary spectrophotometer, 1-mm path.

and 4,4′-dithiodibutyric acid, mp 108°, 2,2′-dithiodipropionic acid, mp 110°, and dithiodisuccinic acid, mp 171–173°, were prepared in exactly the same way. The other disulfides were purchased from Distillation Products Industries, Rochester, N. Y., with the exception of triphenylmethyl disulfide. This compound, originally prepared by Vorländer and Mittag[19] by the addition of sulfuryl chloride to an alkaline alcoholic solution of triphenylmethanethiol, has apparently never been prepared by direct oxidation of the latter. That it is not feasible to oxidize the latter to the corresponding disulfide by iodine in acetic acid is obvious from the data in Table IV. But the data in Table II provided the basis for a simple and effective procedure. Triphenylmethanethiol (0.281 g) was dissolved in 100 ml of acetic acid, 0.5 M in sodium acetate. This solution rapidly consumed 1 equiv of iodine (97 ml of 1.05 N iodine) when the latter was added from a buret. The bulk of the acetic acid was removed by flash evaporation *in vacuo*, water was added, and the mixture extracted with ethyl ether. Evaporation of the ether left 0.28 g of white solid which recrystallized from chloroform, mp 160°. The highest previously reported melting point was 158°.[20]

Acetic acid was purified by the method of Tomiček and Heyrovsky.[21]

Methods.—Both a Beckman DB-G spectrophotometer and a Cary recording spectrophotometer were used, with a 1-mm light path in each case. Stable absorbance values were attained in all cases as soon as solutions were prepared.

Registry No.—Iodine, 7553-56-2; hydrogen iodide, 10034-85-2; acetic acid, 64-19-7; 3-mercaptopropionic acid, 107-96-0; triphenylmethanethiol, 3695-77-0; 3,3′-dithiodipropionic acid, 1119-62-6; triphenylmethyl disulfide, 15446-31-8; hydrogen triiodide, 30228-79-6.

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(19) D. Vorländer and E. Mittag, *Ber.*, **46**, 3453 (1913).

(20) H. Rheinboldt, M. Dewald, and O. Diepenbruck, *J. Prakt. Chem.*, [2], **130**, 133 (1931).

(21) O. Tomiček and A. Heyrovsky, *Collect. Czech. Chem. Commun.*, **15**, 984 (1950).

The Oxidation of Organic Divalent Sulfur by Iodine. III. Further Evidence for Sulfenyl Iodides as Intermediates and for the Influence of Structure on the Occurrence of Cyclic Intermediates in the Oxidation of Thiols

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Further support for the view that the overoxidation of certain thiols by iodine in aqueous iodide proceeds *via* a cyclic intermediate formed by the intramolecular displacement of an iodide ion from a sulfenyl iodide by a carboxylate ion is provided by the study of the oxidation of 19 selected primary and secondary thiols. Only those thiols which have a free carboxyl group on a carbon atom β or γ to the thiol sulfur atom show the marked tendency to overoxidize with decreasing initial concentration of thiol and increasing pH previously reported. 2,5-Dimercaptoadipic acid and 3-mercapto-2-(mercaptomethyl)propionic acid, in which a second mercapto group can make an intramolecular attack on the sulfenyl iodide, show a minimal tendency to be overoxidized. The view that a sulfenyl iodide is the first product of the nucleophilic attack of a thiol on iodine is strengthened by observations on two tertiary thiols, 2-mercapto-2-methylpropanoic acid and penicillamine. Though each is oxidized only to the corresponding disulfide, the deep-orange sulfenyl iodide can be seen unless the iodine is added very slowly, and significantly higher I/SH ratios are observed when iodine is added rapidly. The sulfenyl iodide corresponding to 2-mercapto-2-methylpropanoic acid has been trapped at −40° with 4-chlorothiophenol. The product of trapping, 2-(4′-chlorophenyldithio)-2-methylpropanoic acid, has been characterized.

The question of the mechanism of the oxidation of thiols by iodine has recently been reexamined in conjunction with an attempt to explain the anomalous, excessive consumption of iodine by a few thiols.[2] It was suggested that in all cases the initiating event is the nucleophilic attack of thiol (or thiolate ion) on iodine to displace an iodide ion and to form a sulfenyl iodide,

(1) (a) Postdoctoral Research Associate, 1969–1970. (b) Undergraduate student, Indiana University, South Bend campus.

(2) J. P. Danehy and M. Y. Oester, *J. Org. Chem.*, **32**, 1491 (1967).

as originally suggested by Fraenkel-Conrat.[3] The fate of the latter depends upon its structure. In the great majority of cases an attack of thiol on sulfenyl iodide, which displaces iodide from sulfur and forms disulfide, completes the oxidation. But, in those cases in which thiols are sensitive to overoxidation, all of which have carboxyl groups on the carbon β to the sulfur, it was suggested that the carboxylate anion displaces iodide from the sulfenyl iodide and forms a cyclic, five-membered intermediate. Formation of a sulfenic acid by hydrolysis of the cyclic intermediate is followed by further uptake of iodine, which leads to higher oxidation products: sulfinic and sulfonic acids. Evidence in support of these views was obtained both by product analysis and elementary kinetic considerations.

The present paper offers further support for these views based on three groups of experimental data. First, a number of other thiols which do *not* undergo overoxidation, as well as three more β-mercaptocarboxylic acids which do, are reported. Second, the tendency for some γ- and δ-mercaptocarboxylic acids to be overoxidized by iodine has been measured. Third, the peculiar behavior of two water-soluble tertiary thiols toward iodine is interpreted as favoring the reality of a sulfenyl iodide as the first intermediate in the oxidation of thiols by iodine.

Since the alternative pathways are competitive, the second one, which leads to overoxidation, is favored over the first one, as the initial concentration of thiol is decreased. Over a wide range of concentration the following thiols show only that slight tendency to overoxidation which is always present: thiophenol, 2-mercaptophenol, 4-mercaptophenol, 4-mercaptobenzenesulfonic acid, 3-mercaptobenzoic acid, and 4-mercaptobenzoic acid. It is interesting to note that the favorably rigid structure of 2-mercaptobenzoic acid, which is extremely sensitive to overoxidation, is matched by the unfavorably rigid structures of the 3 and 4 isomers just reported. Because of solubility limitations, the titrations of these aromatic thiols were carried out only in acetate buffer (~pH 5.6). This fact does not in any way qualify the results, since lowering the pH value in the range of 6–2 almost always reduces any tendency to overoxidation. It has never been observed to increase the tendency.

Quantitative data are given in Table I for the extent of overoxidation, as a function of initial concentration of thiol and of pH, for eight β-mercaptocarboxylic acids. The compounds are arranged, very roughly, in the order of decreasing sensitivity to overoxidation. It must be remembered that in the case of cysteine (and perhaps *N*-acetylcysteine as well?) the maximal value for the I/SH ratio is four rather than six. The effect of structural variation on sensitivity is neither very marked nor subject to any rationalization that has occurred to us. In five cases there is at least some support for the generalization that sensitivity increases with the pH value of the medium, which was previously illustrated graphically.[2] The unique insensitivity to pH of cysteine has been shown previously.[2]

The last compound listed in Table I, a β-mercaptocarboxylic acid (doubly so, in fact) which exhibits negligible tendency to overoxidation, requires special

TABLE I

EXTENT OF OVEROXIDATION OF β-MERCAPTOCARBOXYLIC ACIDS BY AQUEOUS POTASSIUM TRIIODIDE AS A FUNCTION OF INITIAL CONCENTRATION OF THIOL AND OF pH

Compd	Registry no.	Initial [RSH]	I/SH at pH 3.0–3.5	I/SH at pH 5.6–6.0
o-HSC_6H_4COOH	147-93-3	0.20		1.85
		0.0001		5.90
$HSCH(CH_2COOH)$	70-49-5	0.100	1.10	
		0.001	4.50	5.21
$HSCH_2CH_2COOH$	107-96-0	0.100	1.00	
		0.001	4.21	4.55
$HSCH_2C(N^+H_3)HCOOH$	52-90-4	0.100	1.00	
		0.006	1.63	
		0.001		2.58
$HSCH_2CH(CH_2COOH)COOH$	28525-49-7	0.102		2.07
		0.056	1.04	
		0.006	1.87	3.06
		0.003	2.51	3.38
$HSCH_2CH(NHAc)COOH$	616-91-1	0.010	1.04	2.11
		0.005	1.09	2.45
$HSC(CH_3)HCH_2COOH$	26473-49-4	0.090		1.47
		0.024	1.00	1.71
		0.006		2.23
$(HSCH_2)_2CHCOOH$	7634-96-0	0.100		1.00
		0.009		1.01
		0.004		1.01

consideration. Jansen[4] isolated from concentrates of asparagus a disulfide which could not be crystallized because of its polymeric character although it was readily reduced to 3-mercapto-2-(mercaptomethyl)propionic acid, melting at 61–62°. Schotte and Ström[5] prepared the disulfide by aerial oxidation of the dithiol, successfully separated the 1,2-dithiolane-4-carboxylic acid component from the polymeric one by taking advantage of the solubility of the former one in benzene, and showed by recovery that the monomer constitutes at least 62% of the crude disulfide. We have now found that oxidation of the dithiol with potassium triiodide also gives a mixture of monomer and polymer. Quantitative data on the distribution will be reported elsewhere. Here our interest is limited to the extent of overoxidation observed. That it is negligible may be attributed to the facts that not only the carboxylate ion, but a second mercapto group as well, is in a position to make an intramolecular attack on the sulfenyl iodide moiety to give a five-membered ring, and that the mercapto group is more nucleophilic than the carboxylate ion. Since, as Schotte and Ström pointed out, the 1,2-dithiolane system readily undergoes spontaneous cleavage of sulfur–sulfur bonds and subsequent formation of polymer, it may be that all of the dithiol passes through the dithiolane form upon oxidation by iodine.

The possible overoxidation of γ- or δ-mercaptocarboxylic acids could be explained by an exactly analogous scheme, invoking a six- or seven-membered cyclic intermediate, respectively. Relevant experience in this area indicates that the formation of six-membered, and particularly seven-membered, cyclic intermediates is less facile than the formation of five-membered ones. Quantitative data for five compounds are found in Table II. γ-Mercaptobutyric acid and its substitution product, *N*-acetylhomocysteine, do fit this pattern; while their sensitivity to overoxidation is more than minimal, it is considerably less than that of any of the β-mercaptocarboxylic acids. But the data for homo-

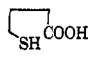
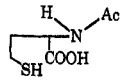
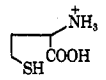
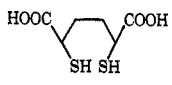
(3) H. Fraenkel-Conrat, *J. Biol. Chem.*, **217**, 373 (1955).

(4) E. F. Jansen, *ibid.*, **176**, 657 (1948).

(5) L. Schotte and H. Ström, *Acta Chem. Scand.*, **10**, 687 (1956).

TABLE II

EXTENT OF OVEROXIDATION OF γ- AND δ-MERCAPTOCARBOXYLIC ACIDS BY AQUEOUS POTASSIUM TRIIODIDE AS A FUNCTION OF INITIAL CONCENTRATION OF THIOL AND OF pH

Compd	Registry no.	Initial [RSH]	I/SH (pH)	I/SH (pH)
	13095-73-3	0.050	1.00 (2.4)	1.00 (5.18)
		0.0033	1.01 (2.4)	1.17 (5.18)
	7378-21-4	0.013	1.00 (2.00)	1.00 (5.4)
		0.0039	1.04 (2.0)	1.11 (5.4)
	454-28-4	0.058		2.12 (6.5)[a]
		0.015	1.00 (1.5)	2.51 (6.5)
		0.0044	1.03 (1.5)	2.79 (6.5)
		0.048		1.07 (6.0)
		0.029		1.09 (6.0)
δ-Mercapto valeric acid	30247-98-4	0.015		1.10 (6.0)
		0.0075		1.14 (6.0)
		0.0029		1.18 (6.0)
 meso	30318-69-5	0.0060	1.00 (1.9)	1.02 (6.0)

[a] Fleeting end points. In one case, I/SH = 2.81, direct analysis gave 0.26 mmol of RSSR and 0.53 mmol of RSO_2H. Since RSSR/RSO_2H = [4 − (I/SH)]/[2 (I/SH) − 2], 0.26/0.53 should equal (4 − 2.81)/[2(2.81) − 2]; actually, 0.49 = 0.33.

cysteine itself provides an anomaly for which we have not yet been able to account. While low pH (predominantly cationic species) effectively represses overoxidation, at higher pH (predominantly dipolar ionic species) the tendency to overoxidation is just as pronounced as with the β-mercaptocarboxylic acids. The I/SH ratios given for homocysteine are for fleeting end points which correspond to the disappearance of thiol and little oxidation beyond the sulfinic acid stage, so that the maximum value would be four rather than six. Comparison with the behavior of the *N*-acetyl derivative suggests that the positively charged nitrogen atom interacts with the carboxylate anion to produce a sterically favored conformation which potentiates the intramolecular attack. But examination of models has not yet revealed plausibly specific details.

The data for δ-mercaptovaleric acid reveal that its tendency to overoxidation is quite comparable to that of the two "normal" γ-mercaptocarboxylic acids. It is not surprising that the only other δ-mercaptocarboxylic acid investigated, 2,5-dimercaptoadipic acid, shows even less tendency to overoxidation for not only the carboxyl groups, but a second mercapto group as well, is in the δ position. Fredga[6] has shown that only cyclic disulfide, no trace of polymer, is formed by the oxidation of this dithiol with iodine. On the basis of relative nucleophilicity, carboxylate ion would not be expected to be competitive with thiol when both of them can participate in intramolecular attack.

Finally, it should be noted that glutathione is not overoxidized significantly over the pH range of 2–6. While this tripeptide, γ-glutamylcysteinylglycine, has two carboxyl groups, participation of one of them in an intramolecular reaction would involve an eight-membered cyclic intermediate and of the other one, a ten-membered ring.

During the titration of an aqueous solution of 2-mercapto-2-methylpropanoic acid, an orange color appears when little more than 5–10% of the equivalent amount of iodine has been added.[7] The color, which is quite different from that of aqueous triiodide, is neither intensified nor otherwise changed in the presence of starch. If the addition of iodine is stopped as soon as this color appears, the solution becomes colorless within a few moments. Further addition of iodine restores the color, which takes a little longer to disappear each time. If the titration is continued in this cautious fashion a stable, true iodine end point is eventually reached, and the I/SH ratio is 1.0, independent of the initial concentration of thiol. When, however, to a suitably dilute solution iodine is added as rapidly as possible from a buret, ignoring the orange color, no difficulty is encountered in seeing the starch-sensitized iodine end point, corresponding to an I/SH ratio of 1.15–1.20 at room temperature. Titrations carried out near 0° give I/SH ratios near 1.30. During the few minutes following the attainment of the end point the solution becomes much darker. Back-titration with standard thiosulfate after 15 min shows that the iodine which develops by "backing up" corresponds exactly to the observed excess of the I/SH ratio over 1.0. 2,2′-Dithiodiisobutyric acid is recovered quantitatively. More limited experiments carried out with penicillamine (2-amino-3-mercapto-3-methylbutanoic acid, another tertiary thiol) gave parallel results.

These observations can be reasonably interpreted in the following manner. The tertiary sulfenyl iodide, formed instantly by the reaction of iodine with thiol, is appreciably more resistant to attack by thiol than are primary or secondary sulfenyl iodides. This is consistent with the data and interpretation of Kolthoff and Harris[8] on the nonaqueous titration of tertiary thiols, and, less directly, with the relative stability of 2-methyl-2-propane sulfenyl iodide reported by Rheinboldt and Motzkus,[9] who prepared it by the reaction of silver or

(6) A. Fredga, *Ber. B*, **71**, 289 (1938).

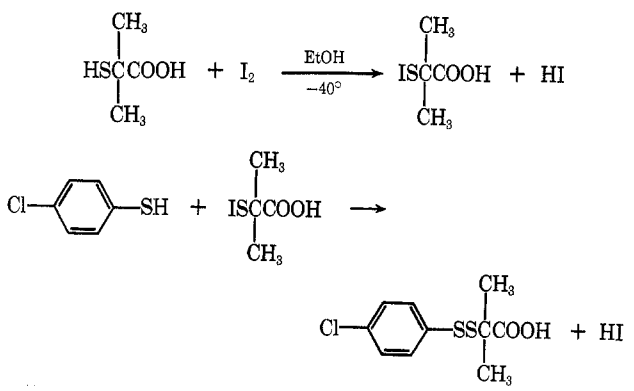
(7) It may be that the appearance of this color misled Schöberl into concluding that aqueous acidic solutions of this thiol cannot be titrated with iodine: A. Schöberl, *ibid.*, **70**, 1186 (1937).

(8) I. M. Kolthoff and W. E. Harris, *Anal. Chem.*, **21**, 963 (1949).

(9) H. Rheinboldt and E. Motzkus, *Ber.*, **72**, 657 (1939).

mercury *tert*-butyl mercaptide with iodine in ethyl ether. Nevertheless, the half-life of these tertiary sulfenyl iodides in the presence of thiols is only a few seconds, so that if iodine is added slowly enough sulfenyl iodide does not accumulate. But, if iodine is added as rapidly as possible, or tertiary thiol is added to iodine, formation of sulfenyl iodide is maximized. The facts shows that sulfenyl iodide (at least, tertiary sulfenyl iodide) does not undergo nucleophilic attack by water in the absence of thiol. Rather, dismutation takes place, with disulfide and iodine as the products.

The tertiary sulfenyl iodide corresponding to 2-mercapto-2-methylpropanoic acid has been trapped by the following sequence.



The mixed disulfide, 2-(4′-chlorophenyldithio)-2-methylpropanoic acid, was obtained in 36% yield, after separation from the corresponding symmetrical disulfides. In view of the demonstrated resistance of dithiodiisobutyric acid to alkaline hydrolysis[10] (nucleophilic displacement of sulfur from sulfur by hydroxide ion) and the fact that the 4-chlorophenylmercapto group is a good leaving group but a relatively poor nucleophile *vis-à-vis* the dithiodiisobutyric acid,[11] it is extremely unlikely that any of the mixed disulfide was formed by the reaction of 4-chlorothiophenol with the symmetrical disulfide.

Experimental Section

Materials.—*o*-Mercaptobenzoic acid, mercaptosuccinic acid, 3-mercaptopropionic acid, and L-cysteine were identified in paper I.[2] Mercaptomethylsuccinic acid and 3-mercaptobutanoic acid were prepared exactly as specified by Holmberg and Schjånberg.[12] Thiophenol and *N*-acetylcysteine were purchased from Distillation Products Industries, Rochester, N. Y. 4-Mercaptophenol, 3-mercaptobenzoic acid, and 4-mercaptobenzoic acid were identified in another paper.[11] 2-Mercaptophenol was a gift from Hooker Chemical Corp., Niagara Falls, N. Y. *meso*-2,5-Dimercaptoadipic acid was a gift from the Toni Co., Chicago, Ill. 2-Mercapto-2-methylpropanoic acid was purchased from Pierce Chemical Co., Rockford, Ill. γ-Butyrothiollactone, DL-homocysteinethiollactone, and *N*-acetyl-DL-homocysteinethiollactone were purchased from Aldrich Chemical Co., Milwaukee, Wis. 3-Mercapto-2-(mercaptomethyl)propanoic acid was a gift from Dr. Daniel L. Klayman, Walter Reed Army Medical Center, for whom it had been prepared by the Regis Chemical Co. 4-Mercaptobenzenesulfonic acid was prepared exactly as specified by Gorin.[13] Glutathione and penicillamine were purchased from California Biochemicals, Los Angeles, Calif.

(10) J. P. Danehy and W. E. Hunter, *J. Org. Chem.*, **32**, 2047 (1967).
(11) J. P. Danehy and K. N. Parameswaran, *ibid.*, **33**, 568 (1968).
(12) B. Holmberg and E. Schjånberg, *Ark. Kemi, Mineral. Geol.*, **14A** (7), 22 pp (1940).
(13) H. A. Smith, G. Doughty, and G. Gorin, *J. Org. Chem.*, **29**, 1484 (1964).

δ-Mercaptovaleric Acid.—δ-Bromovaleronitrile (10.0 g) was refluxed for 3 hr with 50 ml of 9 *N* H_2SO_4, the solution was cooled and extracted with ethyl ether, and the combined ethereal extracts were dried over $MgSO_4$ and evaporated to give 6.5 g of oil. The latter, without purification, was refluxed for 3 hr with 2.8 g of thiourea in 30 ml of ethanol. Then 25 ml of 4 *N* NaOH was added and refluxing was continued for another 2 hr. The solution was concentrated *in vacuo*, extracted with ether (ether extract discarded), acidified with 6 *N* HCl, and extracted with ether, the ethereal extract dried over $MgSO_4$, the ether evaporated, and the residue distilled *in vacuo* to give 4.7 g of δ-mercaptovaleric acid, 73% pure by determination of thiol content with Folin's reagent, and 74% pure by electrometric titration of the carboxyl group.

Alkaline Hydrolysis of γ-Thiollactones.—Since γ-mercaptobutyric acid undergoes lactonization spontaneously, it is not practical to obtain and store samples of this compound in the pure state. For our purpose it seemed reasonable to dissolve a known weight of γ-butyrothiollactone in a volume of standard aqueous alkali whose equivalence slightly exceeded that of the lactone. This procedure seemed justified by the statement of Schjånberg[14] that "· · · alkaline hydrolysis of the thiollactone is very rapid and complete," although he did not specify details. Only after we had collected a considerable quantity of confusing and misleading data did we realize that complete and rapid hydrolysis depends on a very substantial excess of alkali. The definitive data in Table II were obtained by dissolving 1.0201 g of γ-butyrothiollactone in 12 ml of water in which 5.0 g of NaOH had already been dissolved, holding 10 min before diluting to 25 ml with water, and mixing 2-ml aliquots with sufficient HCl and AcOH, or acetate buffer, to give the pH values shown, before titrating with standard potassium triiodide. From constant I/SH ratios at higher initial concentrations than those given in the table, the purity of the thiollactone was calculated to be 89%.

N-Acetyl-DL-homocysteinethiollactone (93% pure) was found to require the same treatment so that the data for *N*-acetyl-DL-homocysteine in Table II were obtained by the same procedure.

This resistance to hydrolysis by a thiollactone was recently quantified for DL-homocysteinethiollactone by Duerre and Miller,[15] who showed spectrophotometrically that 5 min of exposure at room temperature to 2 *N*, but not 1.5 *N*, NaOH was sufficient to cleave the ring quantitatively. Our experience has shown that 2-ml aliquots of 0.5 *M* homocysteinethiollactone (93% pure) must be mixed with 2-ml aliquots of 5 *N* NaOH and held for 5 min in order that, when neutralized, maximum iodine titers can be obtained.

Trapping of *S*-Iodo-2-mercapto-2-methylpropanoic Acid with 4-Chlorothiophenol.—In four separate experiments 2 equiv of iodine in ethanol at −40° was added to 0.5–1.0-g samples of 2-mercapto-2-methylpropanoic acid in ethanol at −40° in a darkened flask. In one of the cases inverse addition was employed. Within 5 min or less 1 equiv of 4-chlorothiophenol in ethanol at −40° was added and the solution was allowed to warm to room temperature. The slight excess of iodine was reduced by addition of aqueous sodium bisulfite dropwise, the solution was neutralized with sodium bicarbonate, evaporated to small volume, water was added, and the solution was acidified and filtered to yield a solid residue (80–90% of the weight of the initial thiols) A. Suspension of A in water with excess sodium bicarbonate and filtration gave an insoluble residue B which, after a single recrystallization from ethanol, was readily identified by melting point and ir spectrum as 4-chlorophenyl disulfide, corresponding to about 25% of the initial 4-chlorothiophenol. Acidification of the filtrate gave a precipitate C, mp 125–135°. Limited extraction of C with CCl_4 or $HCCl_3$ and evaporation of the extract gave D, mp 137–138°, an equivalent weight of 249. *Anal.* Calcd for $ClC_6H_4SSCMe_2CO_2H$ (263): C, 45.71; H, 4.23; Cl, 13.47; S, 24.40. Found: C, 46.82; H, 4.57; Cl, 13.01; S, 21.48. The ir spectrum of D closely resembled that of a superposition of those of authentic specimens of 2,2′-dithiodiisobutyric acid and 4-chlorophenyl disulfide. The simple nmr spectrum of D in $CDCl_3$ (TMS) shows a singlet (6 H) at δ 1.52 and a quartet (4 H) centering at δ 7.28. For reference, 2,2′-dithiodiisobutyric acid melts at 197° and has an equivalent weight of 119; 4-chlorophenyl disulfide melts at 72°. D appears

(14) E. Schjånberg, *Ber., B*, **75**, 468 (1942).
(15) J. A. Duerre and C. H. Miller, *Anal. Biochem.*, **17**, 310 (1966).

to be 2-(4′-chlorophenyldithio)-2-methylpropanoic acid contaminated with a small amount of 2,2′-dithiodiisobutyric acid.

Registry No.—4-$ClC_4H_4SSCMe_2CO_2H$, 30247-81-5; 4-chlorophenyl disulfide, 1142-19-4.

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Notes

Lithium Aluminum Hydride Reduction of Bridged Bicyclic Nitroso Chloride Dimers

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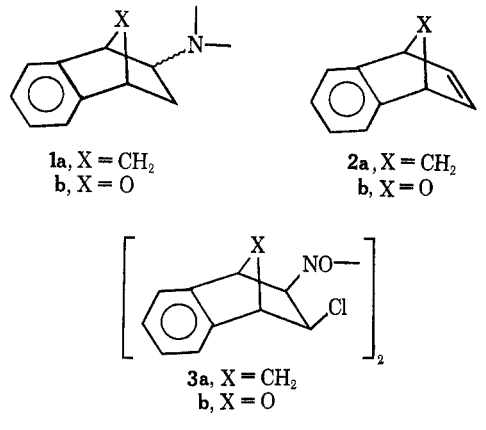
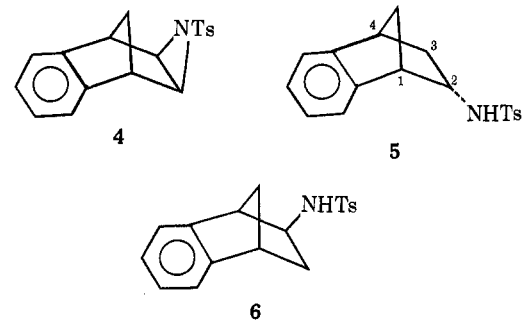
In connection with synthetic routes to amino compounds of type **1**, we have examined the $LiAlH_4$ reduction of the nitrosyl chloride adducts **3** derived from the olefins **2**. Thus, treatment of **2a** with nitrosyl chloride in chloroform followed by dilution with methanol afforded the white dimer **3a**[1] in 68% yield. Reaction of **3a** with $LiAlH_4$ in dioxane (heterogeneous mixture) followed by acylation with *p*-toluenesulfonyl chloride in pyridine provided a mixture from which two compounds could be isolated. The major product (*ca.* 45%), mp 153–154°, was shown to be the *exo*-aziridine **4** by comparison with authentic material prepared from **2a** and tosyl azide.[2] The minor product (*ca.* 5%), mp 142–144°, is assigned the endo structure **5** on the basis of its composition and the following nmr (100 MHz, C_6D_6) evidence: δ 1.82 (doublet of quartets, J = 12.3, 9.8, 4.0 Hz, H_3 exo), 2.73 (broad singlet, H_4), 3.11 (doublet of triplets, J = 1.0, 1.0, 4.0 Hz, H_1), 3.59 (broad doublet, J = 9.8, 4.0, and *ca.* 0.9 Hz, H_3 endo). The presence of a 4-Hz coupling between H_1 and H_2 dictates the exo configuration for H_2 (and thus the endo configuration for the *N*-tosyl group) since it is well established that coupling of significant magnitude between such protons in bicyclic systems is observed only when H_2 is exo.[3] Further, **5** is isomeric with **6**, mp 123–125°, which was prepared by treatment of **2a** with sodium azide–mercuric acetate–sodium borohydride in THF–H_2O,[4] followed by $LiAlH_4$ reduction of the azide and tosylation (60% overall yield). This sequence would be expected to lead to the exo product **6**; that this is indeed the case is supported by the apparent absence of coupling between H_1 and H_2 in the nmr spectrum (100 MHz, C_6D_6) of **6**. Careful comparison of the nmr spectra of **4**, **5**, and **6** with the spectrum of the mixture from reduction of **3a** showed the composition to be 60% **4**, 25% **5**, and 15% **6**.



1a, X = CH_2
b, X = O

2a, X = CH_2
b, X = O

3a, X = CH_2
b, X = O



Prior thermal isomerization of **3a** followed by $LiAlH_4$ reduction and tosylation, as before, led to a mixture of **4**, **5**, and **6** in approximately the same ratio. It thus seems reasonable to suppose that the reduction of **3a** occurs *via* a prior isomerization to a chloro oxime (which could not be isolated). Recent work has shown that $LiAlH_4$ reduction of bridged oximes gives predominantly aziridines.[5]

The 7-oxa analog **3b** behaved differently. Treatment of **2b** with nitrosyl chloride provided **3b** (61%).[1] Reduction of **3b** with $LiAlH_4$ (either directly or after thermal isomerization) followed by tosylation afforded a mixture from which two isomeric, chlorine-containing tosyl amides could be isolated by fractional crystallization from 2-propanol. The less soluble isomer, mp 185–187° (*ca.* 20% yield), is assigned the exo-cis structure **9**; the more soluble isomer, mp 196–198° (*ca.* 20% yield), was assigned the endo-trans structure **9**. Careful examination of the nmr spectrum of the crude mix-

(1) Exo-cis stereochemistry is based on analogy with other NOCl additions [*e.g.*, J. B. Miller, *J. Org. Chem.*, **26**, 4905 (1961); J. Meinwald, Y. C. Meinwald, and T. N. Baker, III, *J. Amer. Chem. Soc.*, **86**, 4074 (1964)] and subsequent transformations.

(2) M. M. Martin and R. A. Koster, *J. Org. Chem.*, **33**, 3428 (1968).

(3) F. A. L. Anet, *Can. J. Chem.*, **39**, 789 (1961).

(4) C. H. Heathcock, *Angew. Chem., Int. Ed. Engl.*, **8**, 134 (1969).

(5) For a recent summary, see K. Kotera and K. Kitahonoki, *Org. Prep. Proced.*, **1**, 305 (1969).