TABLE I

pK_a's OF CORRESPONDING ANILINE AND 2-NITROANILINE DERIVATIVES IN WATER AT 25 ± 3°

No.	Substituent	Aniline pK_a	Aniline ref	2- (or 6-) Nitroaniline pK_a	Nitroaniline ref	ΔpK_a, exptl − calcd (eq 1)
1	Unsubstituted	4.60	*a*	−0.29	*b*	0.10
2	4-CH_3O–	5.34	*a*	0.77	*c*	−0.14
3	4-CH_3–	5.08	*a*	0.43	*c*	−0.09
4	4-F–	4.65	*a*	−0.44	*c*	0.30
5	4-Cl–	3.98	*a*	−1.03	*c*	0.14
6	4-Br–	3.86	*a*	−1.05	*c*	0.03
7	4-CF_3–	2.57	*d*	−2.25	*c*	−0.21
8	4-CH_3OCO–	2.46	*e*	−2.61	*c*	0.03
9	4-NO_2–	1.00	*b*	−4.27	*l*	0.06
10	4-CH_3CO–	2.19	*f*	−2.85	*c*	−0.03
11	4-HO–	5.60	*f*	1.20	*g*	−0.28
12	3-CH_3–	4.73	*a*	−0.09[h]	*i*	0.04
13	3-CH_3O–	4.23	*a*	−0.72[h]	*i*	0.11
14	3-Cl–	3.52	*a*	−1.48[h]	*i*	0.08
15	3-Br–	3.58	*a*	−1.48[h]	*i*	0.15
16	3-NO_2–	2.46	*a*	−2.49[h]	*i*	−0.09
17	3-HO–	4.25	*f*	−0.55[h]	*j*	−0.03
18	2-Cl–	2.65	*a*	−2.41	*b*	0.04
19	2-NO_2–	−0.29	*b*	−5.56	*b*	−0.09
20	2,4-Cl_2–	2.05	*k*	−3.16	*k*	0.12
21	4-CH_3-2-NO_2–	0.43	*c*	−4.45	*k*	−0.39
22	2,4-$(NO_2)_2$–	−4.27	*l*	−10.23	*b*	0.15

[a] A. I. Biggs and R. A. Robinson, *J. Chem. Soc.*, 388 (1961). [b] Reference 1. [c] J. O. Shreck, C. K. Hancock, and R. M. Hodges, *J. Org. Chem.*, **30**, 3504 (1965). [d] J. D. Roberts, R. L. Webb, and E. A. McElhill, *J. Amer. Chem. Soc.*, **72**, 408 (1950). [e] R. A. Robinson and A. I. Biggs, *Aust. J. Chem.*, **10**, 128 (1957). [f] J. M. Vandenbelt, C. Henrich, and S. G. Vanden Berg, *Anal. Chem.*, **25**, 726 (1954). [g] H. G. Hansson, *Acta Chem. Scand.*, **16**, 1956 (1962). [h] 3-Substituted 6-nitroanilines. [i] C. K. Hancock, R. A. Brown, and J. P. Idoux, *J. Org. Chem.*, **33**, 1947 (1968). [j] J. W. Eastes, M. H. Aldridge, and M. J. Kamlet, *J. Chem. Soc. B*, 922 (1969). [k] E. Hogfeldt and J. Bigeleisen, *J. Amer. Chem. Soc.*, **82**, 15 (1960). [l] Reference 5.

series A were in standard buffers and those in series B in H_0 solutions; at the lower pK_a's, the overlap indicator method was used to determine basicities in both series. The excellent linearity, extending from the buffer range completely through the H_0 range, therefore serves to confirm both the accuracy of the latter measurements and the validity of the method. Considering the diverse sources of the data, and the fact that determinations in the H_0 range involved hydrochloric, perchloric, and sulfuric acid solutions, it is significant that the measured pK_a for 2,4,6-trinitroaniline (22B of Table I), which involves the greatest H_0 extrapolation, fits the correlation equation to within a single standard deviation, and that only one value (a relatively older measurement for 21B) differs from the calculated by as much as two standard deviations.

It is also worth comment that the 1.11 slope in the correlation equation implies that the base-weakening effect of the 2-nitro group in series B is not quite constant (*i.e.*, no straightforward additivity of substituent effects) but rather increases slightly the greater the electron-withdrawing ability of additional substituents. We rationalize this on the basis that intramolecular amine → nitro hydrogen bonding in 2-nitroanilines serves toward stabilization of the free bases relative to the corresponding anilinium ions and that inductive or mesomeric electron withdrawal from the amine nitrogens tends toward an increase in the strength of these amine → nitro hydrogen bonds.[7]

It should be noted that the 2- (or 6-) nitro substituents in series B are always unhindered and most likely essentially coplanar. The correlation would probably break down in situations where the nitro were adjacent to a second ortho substituent which might tend to force it toward noncoplanarity, *e.g.*, in 3-substituted 2-nitroanilines.

(7) Jaffé's generalization[6] would have required a 1.00 slope in eq 1. The slightly higher observed value, attributable to the hydrogen-bonding effect, represents a refinement of the earlier statements but not a significant or inexplicable difference.

Synthesis and Cyclization of *S*-(2-Propynyl)-L-cysteine *S*-Oxide and *S*-Dioxide

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1-Alkenylcysteine *S*-oxides and *S*-dioxides in the presence of base undergo an internal addition of the amino function to the double bond to yield cyclic sulfoxides and sulfones.[1] It was of interest to determine if acetylenic cysteine *S*-oxides and *S*-dioxides would react in a similar manner. McDowell and Stirling[2] have shown that in the addition of a secondary amine to 1-alkynyl-, 2-alkynyl-, or the corresponding allenyl-*p*-tolyl sulfone, the same addition product is formed in each case with the double bond appearing α,β to the sulfur. These investigators also obtained evidence from kinetic studies that 2-alkynyl sulfones first isomerize to allenes which then add amine in a rate-determining step.

S-(2-Propynyl)-L-cysteine *S*-dioxide (**1**) was prepared by oxidation of *S*-(2-propynyl)-L-cysteine with hydrogen peroxide in acetic acid at 50°. Oxidation with the same reagent under milder conditions yielded a mixture of diastereomeric sulfoxides which were separated by fractional crystallization into (+)-*S*-(2-propynyl)-L-cysteine *S*-oxide, $[\alpha]^{26}D$ +72.5° (water), and the (−) *S*-oxide, $[\alpha]^{25}D$ −110° (water). With the expectation of comparing the cyclization of 1-propynyl and 2-propynyl derivatives, the oxidation of *S*-1-propynyl-L-cysteine[3] was attempted. Neither sulfoxide nor sulfone could be obtained by reaction with hydrogen peroxide in acetic acid or with aqueous sodium metaperiodate. Cystine and starting material were the only recoverable products. We have no explanation for the failure of 1-propynylcysteine to form sulfoxides or sulfones under conditions where the 1-propenyl and the 2-propynylcysteines oxidize.[4]

(1) J. F. Carson, L. E. Boggs, and R. E. Lundin, *J. Org. Chem.*, **33**, 3739 (1968); J. F. Carson, R. E. Lundin, and L. E. Boggs, *ibid.*, **34**, 1996 (1969).
(2) S. T. McDowell and C. J. M. Stirling, *J. Chem. Soc. B*, 351 (1967).
(3) J. F. Carson and L. E. Boggs, *J. Org. Chem.*, **30**, 895 (1965).
(4) Truce and Markley[5] have recently reported the preparation of aliphatic 1-propynyl sulfoxides and sulfones by oxidation of the corresponding sulfides with *m*-chloroperbenzoic acid in chloroform at 0° with no difficulty.
(5) W. E. Truce and L. D. Markley, *ibid.*, **35**, 3275 (1970).

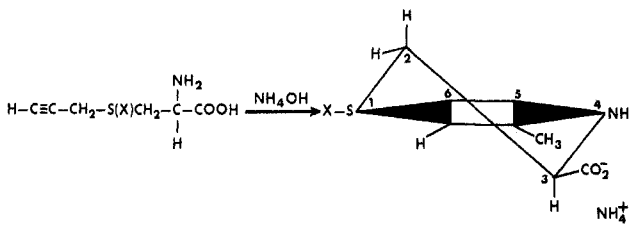
TABLE I

NMR SPECTRAL DATA FOR 3-(*R*)-CARBOXY-5-METHYL-2,3-DIHYDRO-4*H*-1,4-THIAZINE *S*-DIOXIDE (3) AND OXIDE (4) AT 100 MHz

Sulfone (3)[a]		CH_3	H-2 (a)	H-2 (e)	H-3 (a)	H-6	NH	NH_4^+
Dimethyl-d_6 sulfoxide, 60°	δ[b]	s[d] 1.87	t 2.72	d of t 3.22	q 3.92	s 4.81	s 6.32	s 6.78
	J[c]		$J_{22'}$ = 13.5 (g)	$J_{22'}$ = 13.0 (g)	J_{23} = 13.5 (aa)			
			J_{23} = 13.5 (aa)	J_{23} = 3.0 (ae)	J_{23} = 3.0 (ae)			
				J_{26} = 3.0 (LR)				
D_2O, 31°	δ'[b]	s 0.74	q 2.05	q 2.21	q 3.10			
	J		$J_{22'}$ = 13.3 (g)	$J_{22'}$ = 13.3 (g)	J_{23} = 11.7 (aa)			
			J_{23} = 11.7 (aa)	J_{23} = 3.6 (ae)	J_{23} = 3.6 (ae)			
D_2O + trifluoroacetic acid (D), 31°	δ'	s 1.12	q 2.73	q 2.92	q 3.50			
	J		$J_{22'}$ = 15.5 (g)	$J_{22'}$ = 15.5 (g)	J_{23} = 8.0 (aa)			
			J_{23} = 8.0 (aa)	J_{23} = 3.6 (ae)	J_{23} = 3.6 (ae)			
Sulfoxide (4)								
D_2O, 31°	δ'	s 0.78	t 1.15	q 1.97	q 2.75			
	J		$J_{22'}$ = 13.8 (g)	$J_{22'}$ = 13.8 (g)	J_{23} = 13.8 (aa)			
			J_{23} = 13.8 (aa)	J_{23} = 2.7 (ae)	J_{23} = 2.7 (ae)			

[a] Chemical shifts and coupling constants for the sulfone in dimethyl sulfoxide are first order; all other data were obtained by an ABX approximation. [b] Chemical shifts (δ) are in ppm from tetramethylsilane as internal standard; δ' refers to *tert*-butyl alcohol as internal standard. [c] Coupling constants (J) are in Hz. [d] s = singlet, t = triplet, q = quartet, d of t = doublet of triplets.

S-(2-Propynyl)-L-cysteine *S*-dioxide (1) and the corresponding (+) *S*-oxide (2) cyclize in dilute ammonium hydroxide solution to the ammonium salts of 3-(*R*)-carboxy-5-methyl-2,3-dihydro-4*H*-1,4-thiazine *S*-dioxide (3) and of the corresponding *S*-oxide (4), respectively. Cyclization of the sulfone was accomplished in ammonium hydroxide solution at 25° or in sodium hydroxide solution followed by absorption on a cation exchanger and elution with ammonium hydroxide. The (+) sulfoxide requires carefully controlled conditions for cyclization (0.5 *N* ammonium hydroxide at 0–5° for 18–24 hr) to avoid excessive resin formation. Attempts to cyclize the (−) sulfoxide or mixtures rich in the (−) isomer under the same conditions yielded only dark resinous materials from which no cyclic compound could be isolated. Apparently, only one cyclic sulfoxide with $[\alpha]^{25}D$ *ca.* +1° (water) with configuration undetermined at sulfur is produced and predominately from the (+) sulfoxide isomer. The compounds are unusual as amino acids in that they crystallize as stable ammonium salts. Attempts to prepare the free cyclic amino acids led to hygroscopic amorphous materials.



1. X=O2 SULFONE
2. X=O SULFOXIDE
3. X=O2
4. X=O

The structures of the cyclic sulfone (3) and of the sulfoxide (4) were established by elemental analysis and nmr spectra as shown in Table I. Integrations were consistent with the assignments. The coupling constants between the 2 and 3 protons of the sulfone (3) in dimethyl-d_6 sulfoxide (J_{23} = 13.5 and 3.0 Hz) and of the sulfoxide (4) in D_2O (J_{23} = 13.8 and 2.7 Hz) are consistent with a trans-diaxial relation between the 3 proton and one of the 2 protons. If the compounds are present in the half-chair form, they must have the conformation as shown with H-3 axial and carboxylate equatorial rather than the inverted one with H-3 equatorial and carboxylate axial.

J_{23}(aa) for the sulfone (Table I) decreases as solvent is changed from dimethyl sulfoxide to D_2O to D_2O + trifluoracetic acid (13.5, 11.7, and 8.0 Hz, respectively). The decrease of J_{23}(aa) in D_2O on acidification may be a consequence of changing carboxylate anion to unionized carboxyl. This is consistent with the general rule that vicinal coupling constants decrease with increasing electronegativity of substituents.[6] In the absence of appropriate models, however, the possibility of small conformational changes cannot be eliminated. The magnitude of J_{23}(aa) favors a half-chair rather than a boat conformation. In the latter case, a dihedral angle of approximately 120° between the diaxial 2 and 3 protons would be expected to produce a much smaller coupling constant.[7]

In the ir (KBr pellet) the sulfoxide stretching frequency of sulfoxide (4) occurs at the unusually low value 995 cm^{-1}. In thiane sulfoxides an equatorial sulfoxide usually absorbs at a higher frequency than the axial isomer. This rule is applicable to the 3-carboxy-1,4-thiazane *S*-oxides with equatorial sulfoxides absorbing at 1040–1060 cm^{-1} and axial sulfoxides at 1025–1040 cm^{-1} in the solid state.[8] If the rule applies in the present case, the low sulfoxide ir frequency suggests an axial or pseudoaxial conformation for the sulfoxide. This must be speculative since the conformation is now a half-chair with unsaturation in the ring; the other isomer is not available and hydrogen bonding to the sulfoxide may be important.

Experimental Section[9]

S-(2-Propynyl)-L-cysteine *S*-Dioxide (1).—A mixture of 21.0 g (0.132 mol) of *S*-propargyl-L-cysteine[3] in 750 ml of acetic acid

(6) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, New York, N. Y., 1969, p 283.

(7) Similar arguments were used to establish the conformation of shikimic acid as a half-chair in D_2O; see ref 6, pp 296–297, and L. D. Hall, *J. Org. Chem.*, **29**, 297 (1964).

(8) J. F. Carson, L. E. Boggs, and R. E. Lundin, *ibid.*, **35**, 1594 (9970).

(9) Infrared spectra were determined as potassium bromide disks with a Perkin-Elmer Model 237 spectrophotometer. Nmr spectra were taken on a Varian Associates HR-100 spectrometer to which had been added an internal

was stirred at 50° for 7 hr while 65 ml of 30% hydrogen peroxide was added in 10-ml portions per hour. The yellow-orange solution was held overnight at room temperature and then concentrated *in vacuo* to a yellow oil. Crystallization from 100 ml of water and 100 ml of ethanol yielded 9.62 g of sulfone. From the mother liquor there was obtained an additional 1.45 g (combined yield 44%). Treatment of an aqueous solution with carbon and recrystallization from 50% ethanol yielded pure *S*-(2-propynyl)-L-cystene *S*-dioxide (1): dec 152°; $[\alpha]^{25}D$ −0.98° (*c* 2.8, H_2O); ir 3270 (HC≡C–), 1605 (ionized carboxyl), and 1135 cm^{-1} (sulfone).

Anal. Calcd for $C_6H_9NO_4S$: C, 37.69; H, 4.74; N, 7.33. Found: C, 37.7; H, 4.67; N, 7.33.

***S*-(2-Propynyl)-L-cysteine *S*-Oxide (2).**—To a solution of 18 g (0.113 mol) of *S*-propargyl-L-cysteine in 1000 ml of acetic acid, there was added 13.0 ml of 32% hydrogen peroxide in 2-ml portions per hour, while the solution was stirred for 8 hr at 25°. The opalescent reaction solution was stirred overnight at room temperature, filtered from a trace of insoluble material, and concentrated *in vacuo* to an oil. Crystallization from 50 ml of water yielded 3.53 g, $[\alpha]^{26}D$ ~0° (water). Crystallization of the mother liquor from ethanol–water with increasing proportions of ethanol yielded the further fractions: 2.77 g, $[\alpha]^{26}D$ −16°; 6.65 g, $[\alpha]D$ −24.7°; 4.27 g, $[\alpha]D$ −41.0° (combined yield 87%). Several recrystallizations of the most levorotatory fraction from aqueous ethanol yielded 450 mg of (−)-*S*-(2-propynyl)-L-cysteine *S*-oxide as prismatic plates: dec 198° (colors 150°); $[\alpha]^{26}D$ −110.1° (*c* 2, water); ir 3190 (s) (HC≡C–), 1630 (s) (ionized carboxyl), and 1005 cm^{-1} (s) (sulfoxide).

Anal. Calcd for $C_6H_9NO_3S$: C, 41.12; H, 5.18; N, 7.99. Found: C, 40.9; H, 5.18; N, 8.03.

Five recrystallizations of the first fraction with $[\alpha]D$ ~0° from water–ethanol (1:4) or aqueous acetone yielded 590 mg of (+)-*S*-(2-propynyl)-L-cysteine *S*-oxide as soft fibrous needles: dec 189°; $[\alpha]^{26}D$ +72.5° (*c* 2, water); ir 3200 (m) (HC≡C–) 1660 (s), 1580 (s) (ionized carboxyl), and 1025 cm^{-1} (s) (sulfoxide).

Anal. Calcd for $C_6H_9NO_3S$: C, 41.12; H, 5.18; N, 7.99. Found: C, 40.7; H, 5.14; N, 7.94.

Cyclization of *S*-(2-Propynyl)-L-cysteine *S*-Dioxide (1).—A solution of 4.86 g (0.0254 mol) of **1** in 1 l. of 2 *N* ammonium hydroxide was kept at room temperature under nitrogen for 2 days. The pale yellow solution was concentrated *in vacuo* to a solid, redissolved in 100 ml of water, and passed through a column of Dowex 50 (H^+) (200 cm^3). The column was eluted with 1300 ml of 2 *N* ammonium hydroxide and the ammonical eluate concentrated *in vacuo* to a solid. Crystallization from 4 ml of water and 30 ml of ethanol yielded 3.39 g of crystalline product. An additional 1.12 g was obtained from the mother liquor (combined yield 85%). Recrystallization from the same solvent system yielded pure 3-(*R*)-carboxy-5-methyl-2,3-dihydro-4*H*-1,4-thiazine *S*-dioxide ammonium salt (**3**) as tiny crystals: dec 185°; $[\alpha]^{26}D$ −0.1° (*c* 4.5, water); ir 3360 (s), 3000–3200 (broad), 1580 (s) (ionized carboxyl), and 1125 cm^{-1} (s) (sulfone).

Anal. Calcd for $C_6H_{12}N_2O_4S$: C, 34.60; H, 5.89; N, 13.45; S, 15.40. Found: C, 34.6 ; H, 5.84; N, 13.2; S, 15.4.

Conversion of the Ammonium Salt (3) to the Hyrochloride.—The ammonium salt (**3**) (4.89 g, 0.0235 mol) was dissolved in 100 ml of cold 3 *N* hydrochloric acid and concentrated *in vacuo* to a solid. Ammonium chloride was removed by crystallization from cold acetone–H_2O (8:1). A yield of 1.12 g (89%) was obtained. The amino acid hydrochloride was obtained from the mother liquor by crystallization from ethanol–acetone (1:15). A yield of 3.86 g of crystalline 3-(*R*)-carboxy-5-methyl-2,3-dihydro-4*H*-1,4-thiazine *S*-dioxide hydrochloride was obtained: dec 173° (sharp); ir 1740 (un-ionized carboxyl) and 1125 cm^{-1} (sulfone).

Anal. Calcd for $C_6H_{10}NO_4SCl$: C, 31.65; H, 4.43; N, 6.15; Cl, 15.57. Found: C, 32.3; H, 4.67; N, 6.17; Cl, 15.3.

Cyclization of *S*-(2-Propynyl)-L-cysteine *S*-Oxide (2) to 4.—A solution of 3.56 g of the sulfoxide ($[\alpha]D$ +1.4°) containing 61% of the (+) isomer and 39% of the (−) isomer in 600 ml of water containing 6 ml of reagent ammonium hydroxide was kept at +3° for 18 hr. The pale amber solution was concentrated *in vacuo* (<20°) to *ca.* 100 ml, decolorized with carbon, and further concentrated *in vacuo* to a solid. Crystallization from 3 ml of water and 18 ml of ethanol yielded 1.50 g of prisms. An additional 0.61 g was obtained from the mother liquor.

The yield of crude product was 88% based on reaction of the (+) isomer. Recrystallization from ethanol–water (5:1) yielded pure 3-(*R*)-carboxy-5-methyl-2,3-dihydro-4*H*-1,4-thiazine *S*-oxide ammonium salt (**4**) as small colorless prisms: dec 182–184° (darkens, 177°); $[\alpha]^{25}D$ +1.0 (*c* 2.4, water); ir 3340 (m), 3000–3100 (broad), 1605 (s) (ionized carboxyl), and 992 cm^{-1} (s) (sulfoxide).

Anal. Calcd for $C_6H_{12}N_2O_3S$: C, 37.49; H, 6.29; N, 14.58; S, 16.68. Found: C, 37.5; H, 6.38; N, 14.6; S, 16.8.

Fractional crystallization from aqueous ethanol or aqueous acetone showed no variation in rotation at the D line and a second sulfoxide could not be obtained. A hydrochloride could not be prepared and addition of acid to the ammonium salt led to decomposition. When cyclization was attempted with pure (−) isomer, only dark resins were obtained.

Registry No.—**1**, 27199-03-7; (+)-**2**, 27199-04-8; (−)-**2**, 27199-05-9; **3**, 27199-06-0; **3** HCl, 27199-07-1; **4**, 27199-08-2.

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field-frequency lock built at this laboratory. Reference to a company or product name does not imply approval or recommendation of the product by the U. S. Department of Agriculture to the exclusion of others that may be suitable.

A Facile Quantitative Reduction of Sulfoxides

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The recent literature indicates an interest in finding an effective method for the reduction of sulfoxides to sulfides.[1] However, no general method is available which accomplishes the reduction in high yields under mild conditions with common laboratory reagents. A recent report[2] showing the effectiveness of sodium borohydride–transition metal salt systems in the reduction of nitro, amide, and nitrile groups has prompted us to report our findings in sulfoxide reductions.

In connection with our previous work[3] on the novel reduction–dehydration of thioxanthone sulfoxide to thioxanthone and thioxanthenol by sodium borohydride, we found that the same products resulted when the hydroxide ion was replaced by cobalt chloride.[4] However, it was not clear whether the latter reduction again proceeded through a dehydration step or occurred by a simple sulfoxide reduction. Thus, we began an investigation into the effect of this reducing system on sulfoxides.

As shown in Table I, the sodium borohydride–cobalt chloride system reduced dialkyl, arylalkyl, and diaryl sulfoxides, as well as the conformationally restricted[5]

(1) (a) I. Granoth, A. Kalir, and Z. Pelah, *J. Chem. Soc. C*, 2424 (1969), and references cited therein; (b) H. Alper and E. C. H. Keung, *Tetrahedron Lett.*, 53 (1970); (c) K. Naumann, G. Zon, and K. Mislow, *J. Amer. Chem. Soc.*, **91**, 2788 (1969); (d) G. V. Kaiser, R. D. G. Cooper, R. E. Koehler, C. F. Murphy, J. A. Webber, I. G. Wright, and E. M. Van Heynengen, *J. Org. Chem.*, **35**, 2430 (1970).

(2) T. Satoh, S. Suzuki, Y. Suzuki, Y. Miyaji, and Z. Imai, *Tetrahedron Lett.*, 4555 (1969).

(3) A. L. Ternay and D. W. Chasar, *J. Org. Chem.*, **32**, 3814 (1967).

(4) D. W. Chasar, Ph.D. Thesis, Case Western Reserve University, Cleveland, Ohio, 1968; *Diss. Abstr.*, **30**, 116B (1969).

(5) A. L. Ternay, L. Ens, J. Herrmann, and S. Evans, *J. Org. Chem.*, **34**, 940 (1969).