triphenylnitrone[16] in 5 ml. of dioxane was irradiated for 2 days. Removal of the solvent afforded a white solid, m.p. 178–180°, identical with N,N-diphenylbenzamide, in essentially quantitative yield.

(16) H. Rupe and R. Wittwer, *Helv. Chim. Acta*, **5**, 220 (1922).

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The Synthesis of L-1,4-Thiazane-3-carboxylic Acid 1-Oxide[1]

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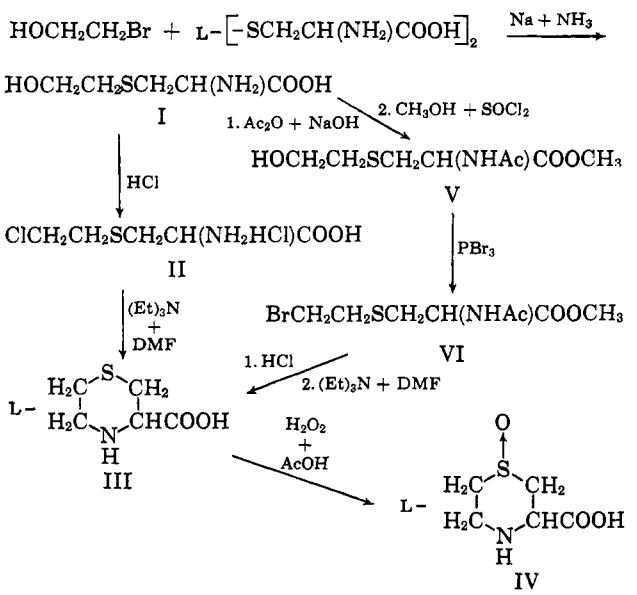
S-(2-Hydroxyethyl)-L-cysteine (I) has been converted to S-(2-chloroethyl)-L-cysteine hydrochloride (II). Cyclization of this compound in dimethylformamide containing triethylamine yielded L-1,4-thiazane-3-carboxylic acid (III, reduced "chondrine"). Oxidation yielded a mixture of diastereoisomeric sulfoxides from which (+)-L-1,4-thiazane-3-carboxylic acid 1-oxide (IV, "chondrine") was obtained.

Kuriyama, *et al.*,[3] isolated the sulfoxide amino acid "chondrine" (L-1,4-thiazane-3-carboxylic acid 1-oxide, IV) from the red alga *Chondria crassicaulis*. More recently, this compound has been isolated from a brown alga *Undaria pinnatifida*.[4] This compound was of interest to us because of its relation to the other known cyclic sulfoxide amino acid "cycloalliin" (L-5-methyl-1,4-thiazane-3-carboxylic acid 1-oxide) obtained from onions.[5] We have synthesized L-1,4-thiazane-3-carboxylic acid (III), which Kuriyama[3] obtained by hydriodic acid reduction of "chondrine." The DL-amino acid was also synthesized. Oxidation of III with hydrogen peroxide in acetic acid yielded a mixture of diastereoisomeric sulfoxides from which the dextrorotatory isomer was obtained by fractional crystallization, $[\alpha]^{26}D$ +19.0.



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(2) A laboratory of the Western Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

(3) M. Kuriyama, M. Takagi, and K. Murata, *Hokkaido Daigaku Suisan Gakubu Kenkyu Iho (Faculty of Fisheries Bulletin, Hokkaido University)*, **11**, 58 (1960).

(4) F. Tominaga and K. Oka, *J. Biochem.* (Tokyo), **54**, 222 (1963).

(5) A. I. Virtanen and E. J. Matikkala, *Acta Chem. Scand.*, **13**, 623 (1959).

The identity of the intermediate (III) with the reduced "chondrine" obtained by Kuriyama was established by analysis and specific rotation; the structure was confirmed for the DL-compound by Raney nickel desulfurization which yielded the expected N-ethyl-DL-alanine. Reduced "chondrine" (III) was also characterized by the preparation of a crystalline hydrochloride and a cyclohexylamine salt of the N-2,4-dinitrophenyl derivative.

Bromoethanol and L-cystine were condensed with sodium in liquid ammonia to give S-(2-hydroxyethyl)-L-cysteine (I, 94%). This compound on heating in reagent hydrochloric acid (38%) gave S-(2-chloroethyl)-L-cysteine hydrochloride (II, 70–90%). Finally, the chloride was cyclized in dimethylformamide–triethylamine to give III in an 80% yield. The corresponding DL-compound was also prepared in a similar manner from S-(2-chloroethyl)-D,L-cysteine hydrochloride. This intermediate was prepared by addition of β-mercaptoethanol to α-acetamidoacrylic acid[6] to give S-(2-hydroxyethyl)-N-acetyl-DL-cysteine as an oil which, on heating with 38% hydrochloric acid, yielded the DL-chloride (II).

In a modification of this general procedure, I was acetylated and methylated to yield the crystalline S-(2-hydroxyethyl)-N-acetyl-L-cysteine methyl ester (V) which was converted to the bromide (VI). When VI was hydrolyzed with 38% hydrochloric acid at 90–95° and cyclized as before, III was obtained in good yield. However, when VI was hydrolyzed by refluxing in 2.5–3.0 *N* hydrochloric acid for 18 hr., extensive decomposition occurred and further reaction with triethylamine–dimethylformamide produced a complex mixture of products. The thiazane carboxylic acid could then be obtained in maximum yields of only 7% by ion-exchange chromatography. These results are similar to the findings of Welti and Whittaker[7] who observed that refluxing β-hydroxyethyl sulfides in dilute hydrochloric acid yielded a mixture of decomposition products in contrast with heating in concentrated acid, in which case high yields of β-chloroethyl sulfides were obtained.

When cyclization was attempted in aqueous base (barium hydroxide or sodium carbonate at pH 8–10), no

(6) A. Schöberl and A. Wagner, *Chem. Ber.*, **80**, 379 (1947); D. McHale, P. Mamalis, and J. Green, *J. Chem. Soc.*, 2847 (1960).

(7) D. Welti and D. Whittaker, *ibid.*, 3955 (1962).

thiazane derivative could be detected and the major product was 2-hydroxyethyl cysteine. Ogston, *et al.*,[8] found that the hydroxyl ion is more nucleophilic toward the intermediate ethylene–sulfonium ion of mustard gas than methylamine. The competition factors in water at 25° for β,β′-dichloroethyl sulfide were found to be 8000 for OH^- as compared with 390 for methylamine. Apparently, in our cyclization reaction the entropy advantage of cyclization over reaction with a second molecule is not sufficient to enable the amino group to compete successfully with hydroxyl ion in attacking the presumed intermediate sulfonium ion.

Experimental

S-(2-Hydroxyethyl)-L-cysteine (I).—To a solution of 10.4 g. of sodium in 1000 ml. of liquid ammonia, 24 g. (0.1 mole) of L-cystine was added in small portions to the first permanent discharge of blue. Bromoethanol (35.0 g., 0.28 mole) was added cautiously, in very small portions, over a period of an hour. After spontaneous evaporation of the ammonia, the solid was dissolved in 300 ml. of water and passed through a column of Dowex 50 (H^+) (56 × 300 mm.). The resin was washed with 3.5 l. of water and the amino acid was then eluted with 3 l. of normal ammonium hydroxide. Concentration *in vacuo* yielded a crystalline solid which, upon solution in 50 ml. of water and addition of 500 ml. of ethanol, yielded 31 g. (94%) of product free of cystine. Recrystallization from 440 ml. of 92% ethanol yielded 29 g. (88%) of the pure compound, m.p. 189–189.5°,[9] $[\alpha]^{20}D$ −53.3 (*c* 2, water).

Anal. Calcd. for $C_5H_{11}NO_3S$: C, 36.35; H, 6.71; S, 19.41. Found: C, 36.4; H, 6.61; S, 19.7.

S-(2-Chloroethyl)-L-cysteine Hydrochloride (II).—A solution of 5.0 g. (0.030 mole) of I in 200 ml. of 38% reagent hydrochloric acid was heated for 7 hr. in a hot water bath at 92–95° and then concentrated *in vacuo* to a white solid. Crystallization from 175 ml. of isopropyl alcohol at 0° yielded 5.3 g. of white micaceous plates. Additional material was obtained from the mother liquor to give a total yield of 6.19 g. (91%). Recrystallization from isopropyl alcohol yielded the pure compound (70%), m.p. 181.5–182° dec. (preheat 170°).[10]

Anal. Calcd. for $C_5H_{11}Cl_2NO_2S$: C, 27.28; H, 5.04; Cl, 32.21; N, 6.36. Found: C, 27.6; H, 5.05; Cl, 32.07; N, 6.40.

L-2,4-Thiazane-3-carboxylic Acid (III).—To a solution of 6.0 g. (0.0273 mole) of S-(2-chloroethyl)-L-cysteine hydrochloride in 450 ml. of anhydrous dimethylformamide, there was added 50 ml. of anhydrous triethylamine. A white solid precipitated. The mixture was stirred and heated, under anhydrous conditions, for 2.5 hr. in a water bath at 90–94° and was then concentrated *in vacuo* to a light brown solid. This was dissolved in 75 ml. of water and passed through a column of Dowex 50 (H^+) (260 cm.³) which was then washed with 2 l. of water and finally with 1.5 l. of 1.5 *N* ammonium hydroxide. The ammoniacal eluate was concentrated *in vacuo* to 400 ml. and added to 100 ml. of Amberlite IRC-50 (H^+) and allowed to stand overnight. This treatment removed most of the color. On concentration to 30 ml. and refrigeration, the solution yielded 1.91 g. of white crystalline product. An additional 1.31 g. was obtained when the mother liquor was reduced to 5 ml., and 15 ml. of acetone was added (combined yield 80%). Both fractions were chromatographically homogeneous with butanol–acetic acid–water (52:13:35) and collidine–lutidine (1:3) saturated with water. Recrystallization from 30 parts of water–acetone (1:2) yielded the pure amino acid as tiny white needles, m.p. 270–271° dec. (sealed tube), $[\alpha]^{25.5}D$ −54.03 (*c* 1.6, water) and −31.18 (*c* 1.5, 2 *N* HCl). Kuriyama,[3] *et al.*, report the values $[\alpha]^{13}D$ −52.94 (water) and −26.38 (6 *N* HCl) and a decomposition point of 262–263° (sealed tube).

The compound had a relative R_f with respect to alanine at 25° of 1.23 in butanol–acetic acid–water (52:13:35) and 1.42 in collidine–lutidine (1:3) saturated with water.

Anal. Calcd. for $C_5H_9NO_2S$: C, 40.80; H, 6.16; N, 9.52. Found: C, 40.8; H, 6.15; N, 9.47.

The hydrochloride was prepared by dissolving 1 g. of the amino acid in 50 ml. of normal hydrochloric acid and concentration *in vacuo* to a crystalline solid. Recrystallization from 1.5 ml. water to which was added 30 ml. of acetone yielded 0.95 g. of the hydrochloride as tiny dense needles, m.p. 201–204° dec.

Anal. Calcd. for $C_5H_{10}ClNO_2S$: C, 32.70; H, 5.49; Cl, 19.30; N, 7.63. Found: C, 32.7; H, 5.42; Cl, 19.3; N, 7.76.

S-(2-Chloroethyl)-DL-cysteine Hydrochloride (II).—A solution of 8.5 g. (0.066 mole) of acetamidoacrylic acid, 7.0 g. (0.09 mole) of β-mercaptoethanol, and 7.0 g. of potassium carbonate in 250 ml. of water was stirred for 3.5 hr., under nitrogen, in a water bath at 90 ± 3°. The cooled solution was freed of potassium ion by passing through a column of Dowex 50 (H^+) and the solution was then concentrated *in vacuo* to yield 12 g. of S-(2-hydroxyethyl) N-acetyl-DL-cysteine as a pale yellow oil.

The oil was heated with 350 ml. of reagent concentrated hydrochloric acid in a water bath at 95–97° for 9 hr. Concentration *in vacuo* to a dry solid and crystallization from isopropyl alcohol yielded 8.8 g. (61% based on acetamidoacrylic acid) of S-(2-chloroethyl)-DL-cysteine hydrochloride, m.p. 157° dec. (preheat 150°). This compound was more difficult to crystallize than the corresponding L-compound and tended to separate as a gel on recrystallization. Elemental analyses were generally unsatisfactory with low values for chloride.

Anal. Calcd. for $C_5H_{11}Cl_2NO_2S$: C, 27.28; H, 5.04; Cl, 32.21. Found: C, 27.1; H, 5.19; Cl, 31.5.

DL-1,4-Thiazane-3-carboxylic Acid.—S-(2-Chloroethyl)-DL-cysteine hydrochloride was cyclized and the product was isolated by the same procedure as for the corresponding L-compound. Crystallization from aqueous acetone yielded the substance as small prisms (63%), m.p. 263–264° dec. (sealed tube).

Anal. Calcd. for $C_5H_9NO_2S$: C, 40.80; H, 6.16; N, 9.52. Found: C, 40.8; H, 6.15; N, 9.47.

S-(2-Hydroxyethyl)-N-acetyl-L-cysteine Methyl Ester (V).—To a solution of 21.5 g. (0.130 mole) of III in 100 ml. of 1.5 *N* sodium hydroxide at 0° there was added 27 g. (0.27 mole) of acetic anhyride and 325 ml. of 1.5 *N* sodium hydroxide in small portions over a 3-hr. period. Sodium ion was removed by passage through Dowex 50 (H^+) and the filtrate was concentrated *in vacuo* to give a quantitative yield of the N-acetyl derivative as a colorless oil.

To prepare the methyl ester, the N-acetyl amino acid (39.4 g., 0.19 mole) was dissolved in 750 ml. of absolute methanol at −5° to which 10 ml. of thionyl chloride was added dropwise with continuous stirring over a 1-hr. period. The solution was kept at −20° for 20 hr. and at 0° for an additional 20 hr. and it was then concentrated *in vacuo* to 200 ml. The solution was diluted with methanol to 500 ml., stirred for 4 hr. with 350 ml. of a weak acid exchanger [Duolite A-4 (NH_2)], and filtered; the resin was washed with 800 ml. of methanol. The filtrate was concentrated *in vacuo* to a pale amber oil. Crystallization from ethyl acetate yielded 31.9 g. (75.6%) of coarse, sugar-like granular crystals, m.p. 49–50°, $[\alpha]^{25}D$ −75.3 (*c* 1, methanol).

Anal. Calcd. for $C_8H_{15}NO_4S$: C, 43.42; H, 6.83; N, 6.33. Found: C, 43.2; H, 6.84; N, 6.32.

S-(2-Bromoethyl)-N-acetyl-L-cysteine Methyl Ester (VI).—To a solution of 14 g. (0.063 mole) of V in 300 ml. of dry methylene chloride, there was added dropwise over a 2-hr. period a solution of 8 g. (0.030 mole) of phosphorus tribromide in 300 ml. of methylene chloride. During the addition, the solution was stirred at room temperature under anhydrous conditions. After standing overnight, the solution was washed with 150 ml. of water, dried with sodium sulfate, and concentrated *in vacuo* to 100 ml. Addition of 500 ml. of hexane precipitated an oil which crystallized at 0°. The crude product was obtained as fibrous needles, 16.8 g. (93%). Recrystallization from methylene chloride–hexane yielded the pure compound, 15.3 g. (85%), m.p. 72–73°.

Anal. Calcd. for $C_8H_{14}NO_3BrS$: C, 33.81; H, 4.97; Br, 28.12; S, 11.28. Found: C, 34.0; H, 5.0; Br, 28.5; S, 11.4.

L-1,4-Thiazane-3-carboxylic Acid (III). Alternate Synthesis.—A solution of 6.0 g. (0.021 mole) of bromide VI in 225 ml. of 37% reagent hydrochloric acid was heated under reflux for 8 hr. in a water bath kept at 100°. Removal of solvent *in vacuo* yielded a white crystalline solid which was cyclized in dimethylformamide–triethylamine as previously described to yield 2.09 g. (67% based on VI) of the cyclic amino acid (III) identical with the previous preparation.

(8) A. G. Ogston, E. R. Holiday, J. S. L. Philpot, and L. A. Stocken, *Trans. Faraday Soc.*, **44**, 45 (1948).

(9) A. Zilkha and S. Rappoport [*J. Org. Chem.*, **28**, 1105 (1963)] report the synthesis of this compound with m.p. 210° by reaction of ethylene oxide with cysteine in the presence of triethylamine.

(10) T. A. Connors and W. C. Ross [*Chem. Ind.* (London), 366 (1958)] report a melting point of 186–188° for this compound.

Raney Nickel Desulfurization of DL-III.—A solution of 0.80 g. of DL-1,4-thiazane-3-carboxylic acid in 250 ml. of 80% ethanol containing 20 ml. of Raney nickel suspension[11] was refluxed for 6 hr. It was then filtered through a layer of filter aid and the filter cake was washed with 600 ml. of 1:10 aqueous ammonia. After removal of ammonia *in vacuo* and precipitation of nickel with hydrogen sulfide, the final solution was concentrated *in vacuo* to an oil which was dissolved in 85% ethanol. Evaporation of the solution yielded 100 mg. of N-ethyl-D,L-alanine as small plates. Paper chromatography with butanol–acetic acid–water and collidine–lutidine gave the same R_f as for the authentic synthetic compound. The infrared spectrum (potassium bromide disk) was identical with that of a synthetic specimen.

Cyclohexylamine Salt of N-2,4-Dinitrophenyl-L-1,4-thiazane-3-carboxylic Acid.—The dinitrophenyl derivative was prepared as previously described[12] from 0.5 g. of the amino acid. After abortive attempts to crystallize, the compound was converted to the cyclohexylamine salt[12] which was crystallized from acetone as long yellow needles (0.98 g.), m.p. 185° dec., $[\alpha]^{25}D$ −135.8 (*c* 2, acetic acid).

Anal. Calcd. for $C_{17}H_{24}N_4O_6S$: C, 49.50; H, 5.86; S, 7.77. Found: C, 49.2; H, 5.83; S, 7.89.

(+)-L-1,4-Thiazane-3-carboxylic Acid 1-Oxide (Chondrine, IV).—To a suspension of 2.344 g. (0.0159 mole) of L-1,4-thiazane-3-carboxylic acid (III) in 35 ml. of acetic acid, 1.2 ml. of 30% hydrogen peroxide was added in 0.2-ml. portions over a period of 3 hr. with continuous stirring at 25°. The solution was allowed to stand overnight at room temperature and was then concentrated *in vacuo* to an oil. Crystallization from a mixture of 40 ml. of water and 140 ml. of acetone yielded 1.78 g. of product, $[\alpha]^{25}D$ +9.57. A second crop was obtained, 0.656 g., $[\alpha]^{15}D$ +2.35. Infrared (potassium bromide disk) showed typical sulfoxide absorption at 9.7–9.8 μ and no sulfone absorption for each fraction. Paper chromatography with two solvent systems showed only one ninhydrin-active spot. Five recrystallizations of the more dextrorotatory fraction from a combination of 20 parts of water and 40–50 parts of ethanol at 0° yielded 160 mg. (least soluble fraction) of (+)-L-1,4-thiazane-3-carboxylic acid 1-oxide, m.p. 252° dec. (sealed capillary), $[\alpha]^{26}D$ +19.0 (*c* 1, water).[13]

Anal. Calcd. for $C_5H_9NO_3S$: C, 36.81; H, 5.52; N, 8.59; S, 19.63. Found: C, 36.5; H, 5.64; N, 8.45; S, 19.6.

Paper chromatography with collidine–lutidine (1:3, saturated with water) at 25° gave the relative R_f with respect to alanine of 1.36. With butanol–acetic acid–water (52:13:35), the relative R_f was 0.80.

Acknowledgment.—We are indebted to L. M. White and Geraldine Secor for elemental analyses.

(11) R. Mozingo, *Org. Syn.*, **21**, 15 (1941).

(12) J. F. Carson and F. F. Wong, *J. Org. Chem.*, **26**, 4997 (1961).

(13) Kuriyama, *et al.* (ref. 3), report $[\alpha]^{16}D$ +20.91 (water) for the naturally occurring sulfoxide "chondrine."

The Multicentered Reactivity of Pseudoxazolones

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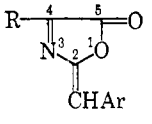
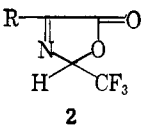
2-Arylidene pseudoxazolones possess several reactive sites for nucleophilic attack. The hydrolysis, aminolysis, and catalytic hydrogenation of these compounds are discussed and their behavior toward lithium aluminum hydride, phenylmagnesium bromide, and benzene under Friedel–Crafts conditions is reported. The attempted preparation of the linearly conjugated 2-benzylidene-4-benzyl-5(2H)-oxazolone gives instead the cross-conjugated 2-benzyl-4-benzylidene-5(4H)-oxazolone.

In recent years, there has been considerable impetus in the study of pseudoxazolones,[2] the 5(2H) isomers of the familiar 5(4H)-oxazolones or azlactones. Two classes of pseudoxazolones have been investigated,[3] the 2-arylidene type (**1**), the subject of this paper, and the 2-trifluoromethyl compounds (**2**), which Weygand and co-workers[4] have examined for the synthesis of α-keto acids and peptides.

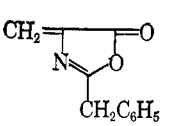


1



2

The only member of the 2-arylidene series to receive much attention has been 2-benzylidene-4-methyl-5-(2H)-oxazolone (**1a**, R = CH_3; Ar = C_6H_5). It is conveniently prepared by ring closure of either 2-phenylacetamido-3-bromopropionic acid[5] or N-(α-halophenylacetyl)alanine.[6,7] Recently, we have shown[8] that this pseudoxazolone, when exposed to light, slowly forms a dimer having a cyclobutane structure. Although the ultraviolet spectrum of **1a** supports the 5(2H) formulation rather than the isomeric 5(4H) form (**3**), the chemical evidence has been indecisive.[7] The formation of the photodimer now provides support for the 5(2H) structure.



3

Since the pseudoxazolones possess several potential sites for chemical attack, we have explored the chemistry of these compounds in order to shed further light on their reactivity.

Discussion and Results

While the 2-arylidene linkage is the reactive center for photodimerization and for attack by weak nucleo-

(1) Abstracted from the Ph.D. Thesis of E. J. Piasek, June, 1962.

(2) The *Chemical Abstracts* nomenclature for this system is 3-oxazolin-5-one.

(3) For a detailed discussion of pseudoxazolones, see R. Filler, "Advances in Heterocyclic Chemistry," Vol. IV, A. R. Katritzky, Ed., Academic Press, New York, N. Y., 1964, in press.

(4) F. Weygand and U. Glockler, *Chem. Ber.*, **89**, 653 (1956); F. Weygand and W. Steglich, *Angew. Chem.*, **73**, 433 (1961); F. Weygand, W. Steglich, and H. Tanner, *Ann.*, **658**, 128 (1962); F. Weygand, A. Prox, L. Schmidhammer, and W. Konig, *Angew. Chem., Intern. Ed. Engl.*, **2**, 183 (1963).

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(8) R. Filler and E. J. Piasek, *J. Org. Chem.*, **28**, 221 (1963).