Syntheses and Properties of 2-Oxothiazolidine-4-carboxylic Acid and Its Derivatives[*1]

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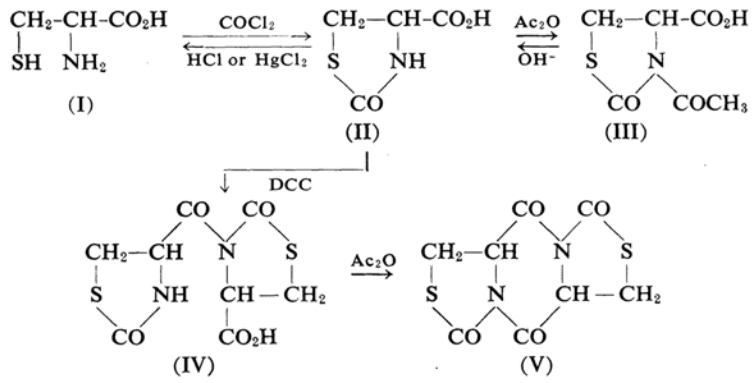
It has been shown that DL- or L-threonine is easily cyclized with phosgene to DL- or L-*trans*-5-methyl-2-oxo-oxazolidine-4-carboxylic acid in an alkaline solution without any configurational change at the either asymmetric center.[1] Cysteine may be similarly cyclized to 2-oxothiazolidine-4-carboxylic acid with phosgene beacause of the expected reactivity of the thiol group. Cook et al. have reported that the penicillamine methyl ester was also cyclized to the corresponding thiazolidone derivative with phosgene in the presence of sodium hydrogen carbonate.[2] This paper deals with the cyclization of L-cysteine with phosgene and with the properties of the cyclization product.

The cyclization of L-cysteine (I) to L-2-oxothiazolidine-4-carboxylic acid (II) with phosgene occured by means of the modified method as carried out in the cyclization of threonine.[1] The cyclized product II melted at 171~172.5°C and gave a strongly acidic aqueous solution. The racemic form of II (m. p. 155°C) was obtained from *S*-benzylthiocarbonyl-DL-cysteine by means of the action of alkali by Crawhall et al.[3] On hydrolysis in 6 N hydrochloric acid or treatment with mercuric chloride, the starting L-cysteine (I) was recovered in its pure state. During this cyclization reaction, no configurational change took place.

When II was heated in acetic anhydride, L-3-acetyl-2-oxothiazolidine-4-carboxylic acid (III) and two other by-products were obtained. One of the two by-products, which was also obtained by the dehydration of the other with acetic anhydride, melted at 259~260°C and had the empirical formula $C_4H_3NO_2S$. The other (m. p. 215°C) possessed the empirical formula $C_8H_8N_2O_5S_2$ and was identified with the dehydration product of II by *N*, *N'*-dicyclohexyl carbodiimide (DCC). This second compound is probably 2-oxo-3-(2'-oxothiazolidine-4'-carbonyl-)-thiazolidine-4-carboxylic acid (IV), while the former seems to be the diketopiperazine-type compound, 1, 4, 5, 8-tetraoxo-2, 6-dithia-4a, 8a-diazaperhydro-*s*-indacene (V).

Therefore, if *N*-acetyl-L-cysteine[4] is similarly cyclized with phosgene, III will be obtained directly. The cyclization of *N*-acetyl-L-cysteine, however, was unsuccessful. The *N*-benzoyl-L-cysteine ethyl ester (VII) obtained by the reduction of the *N*, *N'*-dibenzoyl-L-cystine diethyl ester (VI) with zinc and hydro-



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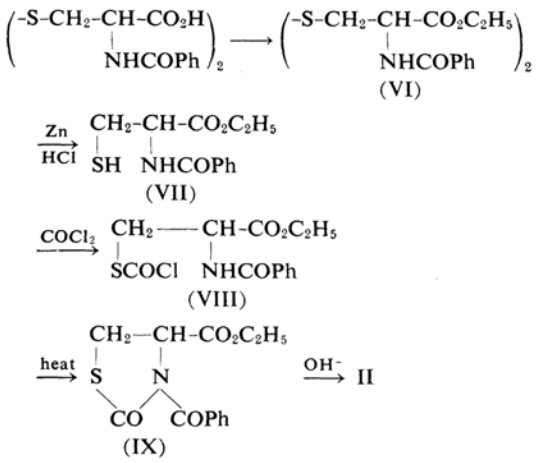
1) T. Kaneko and T. Inui, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **82**, 1075 (1961); T. Inui and T. Kaneko, ibid., **82**, 1078 (1961).

2) A. H. Cook, J. A. Elvidge and G. Shaw, *J. Chem. Soc.*, **1949**, 2367.

3) J. C. Crawhall and D. F. Elliott, ibid., **1951**, 2071.

4) N. W. Pirie and T. S. Helo, *Biochem. J.*, **27**, 1716 (1933).

chloric acid was used. According to the method employed in the reaction of the *N*-benzyloxycarbonyl-DL-serine benzyl ester with phosgene by Bergel,[5] VII was treated with phosgene in benzene and thereby an expected *S*-chlorocarbonyl intermediate VIII was obtained. This intermediate was cyclized to 3-benzoyl-4-ethoxycarbonyl-2-oxothiazolidine (IX) when refluxed in xylene for 6 hr. by applying the method of Ben-Ishai.[6]



When III was treated in an aqueous solution with dilute sodium hydroxide, the separation of the acetyl group took place and II was recovered without any racemization. In a similar way, IX yielded II and benzoic acid under the same conditions.

It is expected that these results will be of use in discussing the synthetic and structural problems of cysteine peptides.

Experimental

L-2-Oxothiazolidine-4-carboxylic Acid (II).—To a cold solution of 24.2 g. (0.200 mol.) of L-cysteine ($[\alpha]_D$ +7.9° (1 N hydrochloric acid)) in 350 ml. of water, 50 ml. of 40% potassium hydroxide was added and cooled below −5°C in an ice-salt bath. A solution of 26.0 g. (0.262 mol.) of phosgene in 100 ml. of toluene and 100 ml. of 40% potassium hydroxide were simultaneously vigolously stirred into the solution over a 10~15 min. period. After the solution had been stirred for a half hour, the toluene layer was separated. The aqueous layer was extracted twice with ether and acidified to Congo red with concentrated hydrochloric acid. The acidic solution concentrated to dryness in vacuo, and the residue was extracted three times with 250 ml. of ethanol while hot. The extract was concentrated to dryness in vacuo, and residual oil was dissolved in 10 ml. of hot water. A crude II (23.2 g.) crystallized out after the solution had been left standing for several hours. After two recrystallizations from hot water, the pure substance was obtained. Yield, 14.5 g. (49%); m. p. 171~172.5°C, $[\alpha]_D^{16}$ −57.3° (*c* 2.7, water).

IR (Nujol mull): 3260 (amide), 2600, 1740, 1225 (carboxylic acid), 1625 (cyclic amide) cm^{-1}.

Found: C, 32.91; H, 3.47; N, 9.52; S, 21.40. Calcd. for $C_4H_5NO_3S$: C, 32.64; H, 3.42; N, 9.52; S, 21.79%.

L-3-Acetyl-2-oxothiazolidine-4-carboxylic Acid (III).—Eight and eight-tenth grams (0.06 mol.) of II was heated in 50 ml. of acetic anhydride until the II had been dissolved. After cooling at room temperature, the V which had separated was filtered off (0.55 g.) To a filtrate, 30 ml. of water was added and heated several times in order to effect the decomposition of the excess acetic anhydride. The solution was then concentrated to a half volume in vacuo, and the crystallized IV was filtered (2.4 g.) When the filtrate was again evaporated to dryness in vacuo, III crystallized out. The yield was 5.9 g. (52.1%). It melted at 152~154°C after recrystallization from ethyl acetate and light petroleum, and it gave $[\alpha]_D^{20}$ −136.4° (*c* 1.8, water-acetone (1 : 1)).

IR (Nujol mull): 2600, 1710 (carboxylic acid), 1730 (acetyl), 1650 (cyclic amide) cm^{-1}.

Found: C, 38.30; H, 3.59; N, 7.42. Calcd. for $C_6H_7NO_4S$: C, 38.08; H, 3.74; N, 7.40%.

2-Oxo-3-(2'-oxothiazolidine-4'-carbonyl-)-thiazolidine-4-carboxylic Acid (IV).—To a cold solution of 1.47 g. (0.01 mol.) of II in 40 ml. of *N*,*N*-dimethylformamide, 1.1 g. (0.005 mol.) of DCC was added drop by drop. After the mixture had been left standing overnight, the precipitated *N*,*N'*-dicyclohexyl urea was removed. The filtrate was acidified with 10 ml. of 6 N hydrochloric acid and extracted five times with 50 ml. of ethyl acetate. The extract was concentrated to dryness in vacuo, and when water was added to the residue, IV crystallized out. Yield, 0.9 g. (65%); m. p. 215°C (decomp.).

IR (Nujol mull): 3260 (amide), 2500, 1710 (carboxylic acid), 1625 (cyclic amide) cm^{-1}.

Found: C, 34.98; H, 3.08; N, 10.14. Calcd. for $C_8H_8N_2O_5S_2$: C, 34.77; H, 2.91; N, 10.13%.

1,4,5,8-Tetraoxo-2,6-dithia-4a,8a-diaza-perhydro-*s*-indacene (V).—A solution of 0.10 g. (0.0004 mol.) of IV in 10 ml. of acetic anhydride was heated under reflux for about 3 hr., when V began to appear. When it had then been cooled at room temperature for a few hours, V filtered off. Yield, 0.085 g. (91%); m. p. 259~260°C (decomp.)

IR (Nujol mull): 1747, 1675 (cyclic amide) cm^{-1}.

Found: C, 37.60; H, 2.50; N, 10.81. Cacld. for $C_8H_6N_2O_4S_2$: C, 37.20; H, 2.34; N, 10.84%.

L-Cysteine (I). — *By Hydrolysis with Hydrochloric Acid.*—A solution of 3.0 g. (0.02 mol.) of II in 20 ml. of 6 N hydrochloric acid was heated on steam-bath for 20 hr. I was isolated from the hydrolizate in the usual way. Yield, 1.0 g. (40%). All the properties of this sample were identical with those of an authentic sample.

Treatment with Mercuric Chloride.—To a suspension of 3.0 g. (0.02 mol.) of II in 50 ml. of water, a solution of 10.0 g. (0.037 mol.) of mercuric chloride in 80 ml. of water was added. After it had been shaken at 75°C for 15 min., this mixture was

5) F. Bergel and R. Wade, *J. Chem. Soc.*, **1959**, 941.
6) D. Ben-Ishai, *J. Am. Chem. Soc.*, **78**, 4962 (1956).

allowed to stand at room temperature for 40 hr. A mercaptide which was precipitated was filtered and I was isolated from the mercaptide in the usual way. Yield, 0.8 g. (32%).

***N,N'*-Dibenzoyl-L-cystine Diethyl Ester (VI).**—Thirty grams (0.067 mol.) of *N,N'*-dibenzoyl-L-cystine[7] was esterified with hydrogen chloride in absolute ethanol in the usual way. Yield, 31.3 g. (78%). It melted at 183~185.5°C after recrystallization from absolute ethanol and gave $[\alpha]_D^{30}$ +13.3° (*c* 0.5, 99% ethanol).

Found: C, 56.96; H, 5.50; N, 5.33; S, 12.35. Calcd. for $C_{24}H_{28}N_2O_6S_2$: C, 57.14; H, 5.59; N, 5.55; S, 12.71%.

***N*-Benzoyl-L-cysteine Ethyl Ester (VII).**—To a suspension of 20 g. (0.037 mol.) of VI in 300 ml. of 50% ethanol, 20 g. of zinc dust and 50 ml. of acetic acid were added and heated with occasional shaking at 50~60°C for about 1 hr., or until the VI had been dissolved. After it had stood overnight at room temperature, the solution was evaporated to a small volume in vacuo under an atmosphere of nitrogen and extracted with benzene. The extract was evaporated to dryness in vacuo, and the residue was recrystallized from ethanol. Yield, 15 g. (70%); m. p. 85~89°C, $[\alpha]_D^{30}$ −30.6° (*c* 1.6, 99% ethanol).

Found: C, 56.38; H, 5.86; N, 5.32; S, 12.77. Calcd. for $C_{12}H_{15}NO_3S$: C, 56.91; H, 5.97; N, 5.53; S, 12.66%.

***N*-Benzoyl-*S*-chlorocarbonyl-L-cysteine Ethyl Ester (VIII).**—Phosgene was passed into a stirred suspension of 10 g. (0.036 mol.) of VII in 160 ml. of benzene at 5~10°C for 1 hr. VII was dissolved into a solution by additional stirring at room temperature for 2~3 hr. The next day, carbon dioxide was passed through the solution to remove the excess phosgene and the organic layer was evaporated to dryness in vacuo. The residue obtained was recrystallized from benzene. Yield, 10 g. (80%); m. p. 119~122°C (decomp.)

L-3-Benzoyl-4-ethoxycarbonyl-2-oxothiazolidine (IX). — Five grams (0.016 mol.) of VIII was refluxed in 100 ml. of xylene for about 6 hr., or until no hydrogen chloride had been evolved. After the removal of the solvent, the residue was recrystallized from benzene or xylene. Yield, 3.5 g. (79%); m. p. 130~132°C, $[\alpha]_D^{15}$ +18.0° (*c* 0.5, benzene).

IR (Nujol mull): 1735 (ester), 1710 (benzoyl), 1695 (cyclic amide) cm^{-1}.

Found: C, 55.94; H, 4.91; N, 4.88; S, 11.16. Calcd. for $C_{13}H_{13}NO_4S$: C, 55.91; H, 4.70; N, 5.02; S, 11.48%.

The Treatment of *N*-Acyl-thiazolidone Derivatives with Alkali. — a) To a solution of 0.38 g. (0.002 mol.) of III in 10 ml. of acetone and 10 ml. of water, 5 ml. (0.006 mol) of 1.25 N sodium hydroxide was added. After it had stood (and occationally been shaken) at room temperature for 1 hr., the mixture was acidified with 6 N hydrochloric acid and concentrated to drynes in vacuo. The residue was extracted with ethanol, and II was obtained from this ethanol extract. Yield, 0.24 g., (82%); m. p. 171~172°C (decomp.), $[\alpha]_D^{15}$ −57.8° (*c* 2.1, water). Its infrared absorption spectra were identical with those of the cyclized product of L-cysteine.

b) In a similar way, 3 g. (0.011 mol.) of IX were hydrolyzed with 1.2 g. (0.022 mol.) of potassium hydroxide in 40 ml. of 70% ethanol. After the removal of the benzoic acid, II was obtained. Yield, 0.9 g. (57%); m. p. 171~172.5°C (decomp.), $[\alpha]_D^{19}$ −56° (*c* 3.0, water).

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7) E. M. Fry, *J. Org. Chem.*, **15**, 438 (1950).