Synthesis and Rearrangement of *trans*- and *cis*-4-Acetamido-5-phenyl-3-isothiazolidinone 1,1-Dioxide[1]

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The title compounds (2 and 4, respectively) were synthesized from *N,S*-diacetyl-*erythro*-3-phenylcysteine ethyl ester (1) by aqueous chlorination and subsequent ammoniation. Both isomers rearranged with the elimination of the elements of aminosulfurous acid (NH_2SO_2H) to give 4-benzylidene-2-methyl-2-oxazolin-5-one (6) when treated with acetic anhydride–pyridine. A mechanism is suggested which involves acetylation of the ring nitrogen followed by nucleophilic attack by the oxygen of the 4-acetamido group and a base-catalyzed elimination of acetamidosulfurous acid.

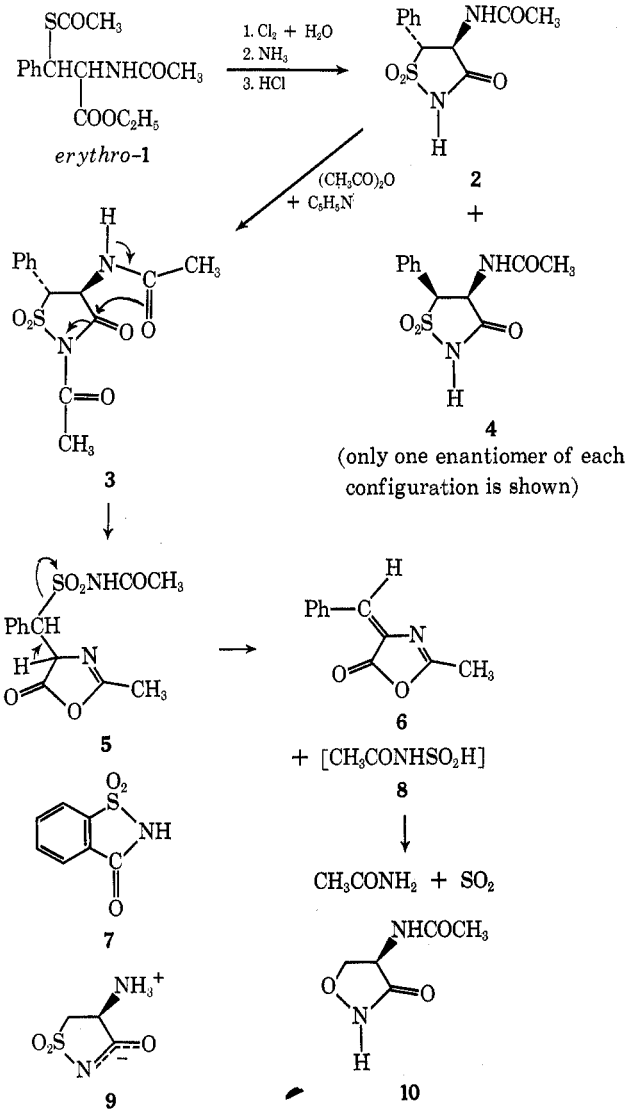
The 4-amino-3-isothiazolidinone 1,1-dioxides, *e.g.*, **9**, are of interest from the viewpoints of biological, medicinal, and organic chemistry. These heterocycles are literally α-amino acids in which the acidic function is the *N*-sulfonylcarboxamide group. Unlike the carboxylic acid group, which may rotate about the C_1–C_2 axis, the acidic function of these compounds is held in one configuration by the ring. In this respect they resemble the 4-amino-3-isoxazolidones which have been more extensively studied because the 5-unsubstituted compound is the antibiotic cycloserine. Apart from 4-amino-3-isothiazolidinone 1,1-dioxide (**9**), which was investigated[2] because of its relationship to cycloserine, this class of compounds has not been reported.

An interest in the acidic properties of a phenylalanine dipeptide which contained a C-terminal *N*-cyanocarboxamide function[3] led us to consider the synthesis of the title compounds (**2** and **4**). It was found that aqueous chlorination of *N,S*-diacetyl-*erythro*-3-phenylcysteine ethyl ester[4] (**1**) followed by treatment of the crude sulfonyl chloride product with aqueous ammonia and subsequent strong acidification gave a mixture of **2** and **4** in about 50% yield. Separation of the isomers was accomplished by fractional cystallization from ethanol. Characterization of **2** and **4** as 3-isothiazolidinone 1,1-dioxides was made on the basis of their elemental analyses, infrared spectra, and pK' values (**2** and **4**, like saccharin (**7**), are strongly acidic).

Construction of Dreiding models of each isomer indicated that the dihedral angles between the 4 and 5 protons were about 130° for the trans and 20° for the cis configuration. The nmr coupling constants ($J_{4,5}$) for **2** and **4** in pyridine-d_5 were 7.5 and 10.6 Hz, respectively. These values are consistent with the assignment of the trans configuration to **2** and the cis to **4** only in the absence of strong substituent electronegativity effects. Since these are unknown for **2** and **4**, the assignments are tentative.[5]

The formation of two isothiazolidones in this reaction probably results from the acidity of the 3 H in the intermediate sulfonyl chloride.

As part of the characterization of these compounds, their susceptibility to acetylation was investigated. Two heterocycles quite closely related to **2** and **4**, saccharin (**7**), and acetylcycloserine (4-acetamido-3-isoxazolidone, **10**) can be acetylated at the ring nitrogen by acetic anhydride in the presence of base (sodium acetate[6] with **7** and pyridine[7] with **10**). Acetylcycloserine acts as an acyl acceptor in its role as a catalyst in the hydrolysis of active esters such as *p*-nitrophenylacetate,[8] and similar behavior might be expected for **2** and **4**. When each of these compounds was treated overnight with pyridine and acetic anhydride, evaporation of the reagents and recrystallization of the residues gave identical products which contained *no* sulfur.



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Elemental analysis was consistent with the formula $C_{11}H_9NO_2$, corresponding to the loss of aminosulfurous acid (NH_2SO_2H). The infrared spectrum showed two strong bands in the carbonyl region, but no absorption characteristic of NH. These facts suggested that the product might be 4-benzylidene-2-methyl-2-oxazolin-5-one[9] (**6**) and comparison of its melting point and infrared spectrum with an authentic sample established their identity. Since both **2** and **4** could be recovered from solutions in pyridine–acetic acid after storage overnight, acetylation was obviously a necessary preliminary step in this elimination–rearrangement reaction. A possible mechanism (shown for the trans isomer) involves an intramolecular nucleophilic attack on the electron-deficient ring carbonyl of the 2-acetyl derivative (**3**) by the oxygen of the 4-acetamido group. This is followed (or accompanied) by a base-catalyzed elimination (**5**) of acetamidosulfurous acid (**8**), which would be expected to break down into acetamide (identified as a product) and sulfur dioxide. Several examples of nucleophilic attack by amide oxygen have been discussed by Cohen and Witkop.[10] Although this rearrangement does not occur with diacetylcycloserine, a similar opening of the isoxazolidone ring has been suggested[11] to explain the irreversible inhibition of pyridoxal phosphate dependent enzyme systems by cycloserine. In this case the nucleophile is thought to be an amino acid residue and the reaction is intramolecular only in the sense that it occurs within the enzyme–substrate complex.

Experimental Section

Elemental microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., and Clark Microanalytical Laboratory, Urbana, Ill. Melting points were taken on a calibrated Mel-Temp apparatus. The ir spectra were determined with a Perkin-Elmer 137-B spectrophotometer, and nmr spectra were determined by W. W. Simons of Sadtler Research Laboratories, Philadelphia, Pa., on a Varian A-60A spectrometer using TMS as an internal standard. Dissociation constants were measured with a Radiometer Titrator, Autoburette, and Titration Assembly (TTA 31) equipped with Radiometer glass and calomel electrodes, G 2222C and K 4112. Solutions in 50% ethanol (8.00 ml, *ca.* 5×10^{-3} *M*) were prepared from analytical samples or samples which were >99% pure by titration. Standardized 0.1 *N* NaOH was added in 0.05-ml or 0.100-ml increments with an equal volume of ethanol added before the pH was measured. Titrations were carried out in duplicate under N_2. The p*K'* values were calculated from five or six pH readings by the following equation. The quantity [HA] equals the total concentration of the heterocycle less the concentration of the base added. The latter is equal to [A^-]. The limit of acceptable spread of p*K'* values was 0.08. The authentic 4-benzylidene-2-methyl-2-oxazolin-5-one (**6**) was purchased from Aldrich as "α-acetamidocinnamic lactone."

$$pK' = pH + \log \frac{[HA] - (H^+)}{[A^-] + (H^+)}$$

cis- and *trans*-**4-Acetamido-5-phenyl-3-isothiazolidinone 1,1-Dioxide (4 and 2).**—Chlorine was introduced to 40.0 g (0.13 mol) of *N*,*S*-diacetyl-*erythro*-3-phenyl-DL-cysteine ethyl ester[4] (**1**) in 500 ml of water at 5° at a rate which kept the temperature at 11–14°. After 40 min Cl_2 addition was stopped and the mixture was filtered after 50 min. The colorless precipitate was washed with H_2O, sucked damp-dry with the aspirator, and added to 120 ml of concentrated NH_4OH with vigorous stirring. The cloudy solution was clarified (Darco) and added dropwise to 135 ml of concentrated HCl in an ice–salt bath with vigorous stirring. The strongly acidic mixture was stored overnight at 4°; the colorless solid was then collected and washed with two 25-ml portions of H_2O. The colorless solid was dried *in vacuo* at 25° and then at 80°. The product weighed 18.2 g (52%), mp 210–215° dec.

Separation of Trans Isomer 2.—The mixture of **2** and **4** was heated in 330 ml of ethanol, filtered from 1 g of a high melting point (>230°) solid, and stored at −10°. The crystals were collected and washed with 2 ml of ethanol, 4.74 g, mp 215–218° dec. After washing with 20 ml of H_2O, the melting point was 218–220° dec, 3.92 g (11.2%). Evaporation of the filtrate to 50 ml and subsequent crystallization gave 1.02 g, mp 217–219° dec. The total yield of **2** was 14.2%. Both fractions gave identical ir spectra (mineral oil): 3300, 3100 (NH), 1720 (ring C=O), 1650, 1550 (amide C=O), 1140 cm^{-1} (SO_2); nmr (pyridine-d_5) 1.84 ppm (s, 3, CH_3), 5.53 (d, 1, J_{4-5} = 7.7 Hz, H-5), 6.08 (q, 1, H-4), 7–7.6 (m, 5, aromatic protons); $pK'^{25°}_{50\%\ EtOH}$ 2.21.

Anal. Calcd for $C_{11}H_{12}N_2O_4S$: C, 49.25; H, 4.51; N, 10.44; S, 11.95. Found: C, 48.98; H, 4.58; N, 10.53; S, 12.19.

Separation of Cis Isomer 4.—The filtrate from the crystallization of **2** was evaporated to a pale yellow solid (9 g) which was triturated with ether, filtered, washed with 25 ml of H_2O, and dried at 80° *in vacuo*, 5.32 g, mp 218–220° dec. This was dissolved in 100 ml of CH_3NO_2, treated with Darco, filtered, added to 100 ml of CCl_4, and stored at 4°. The product weighed 4.19 g (12.0%), mp 223–225° dec. No evidence of **2** was detected in the ir spectrum (mineral oil): 3300, 3150 (NH), 1740 (ring C=O), 1670, 1650 (amide C=O); nmr (pyridine-d_5) 2.06 ppm (s, 3, CH_3) 5.61 (d, 1, $J_{4,5}$ = 5.61, H-5), 6.05 (q, 1, H-4), 7.1–8.0 (m, 5, aromatic protons); $pK'^{22°}_{50\%\ EtOH}$ 2.47.

Anal. Calcd for $C_{11}H_{12}N_2O_4S$: C, 49.25; H, 4.51; N, 10.44; S, 11.95. Found: C, 49.09; H, 4.47; N, 10.38; S, 12.10.

Rearrangement of *cis*-4-Acetamido-5-phenyl-3-isothiazolidinone 1,1-Dioxide (4).—To 0.50 g (1.86 mmol) of **4** were added 3 ml of pyridine and 2 ml of acetic anhydride. After storage overnight at room temperature the reagents were evaporated at reduced pressure, and the residue was washed with a little ethanol. After recrystallization from toluene–hexane, 0.268 g (77%) of pale yellow crystals was obtained, mp 157–158°. The ir spectrum, melting point, and mixture melting point were identical with those of 4-benzylidene-2-methyl-2-oxazolin-5-one[10] (**6**). Approximately the same yield of identical product was obtained under the same conditions with the trans isomer **2**.

Identification of Acetamide.—In one experiment the reaction mixture was added to 10 g of ice and filtered, and the filtrate clarified with Darco. This was treated with Dowex 50 (H^+) and evaporated. The residue was distilled (bp ~200°); the ir spectrum of the distillate (neat) was insignificantly different from liquid acetamide.

Registry No.—**2**, 27720-66-7; **4**, 27720-67-8.

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