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UNUSUAL HYDROXYMETHYLATION OF 2-AMINO-4-THIAZOLINONE

S. M. Ramsh[1] and A. G. Ivanenko[2]

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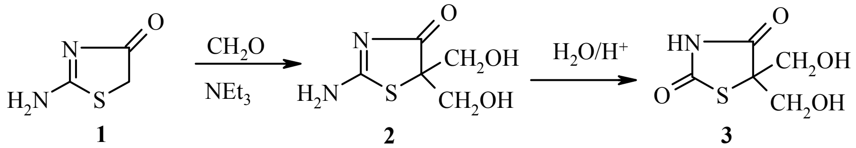
2-Amino-4-thiazolinone (pseudothiohydantoin, **1**) when treated with formalin in ethanol adds formaldehyde at the exocyclic nitrogen atom, forming 2-(hydroxymethyl)amino-4-thiazolinone [1]. Under similar conditions, its aza analog 2-amino-1-methyl-4-imidazolinone (creatinine) forms the product of addition at the methylene carbon atom of the heterocycle, 2-amino-5,5-bis(hydroxymethyl)-1-methyl-4-imidazolinone [2].



Assuming that the facile aldol condensation in the case of creatinine is due mainly to autocatalysis (p*K*a of the conjugate acid is ~4.8 [3]), we hypothesized that pseudothiohydantoin **1**, which itself has practically no basic properties (p*K*a of the conjugate acid is ~2.1 [4]), in the presence of a base of sufficient strength would also undergo aldol condensation with formaldehyde. In fact, treatment of pseudothiohydantoin **1** with formalin in the presence of a catalytic amount of triethylamine led to 2-amino-5,5-bis(hydroxymethyl)-4-thiazolinone **2** in ~50% yield.

Acid hydrolysis of compound **2** leads to its oxo analog: 5,5-bis(hydroxymethyl)-2,4-thiazolidinedione (**3**).

In the ^1H NMR spectra (200 MHz, D_2O) of compounds **2** and **3**, the diastereotopic methylene protons resonate as geminal AB quadruplets with spin-spin coupling constant 12-13 Hz.

2-Amino-5,5-bis(hydroxymethyl)-4-thiazolinone (2). Formalin (71 ml, 887 mmol) was added to pseudothiohydantoin **1** (22.7 g, 195 mmol), and triethylamine (3.2 ml) was added in 0.05 ml portions with stirring to the mixture obtained over a 1.5 h period, while maintaining pH 9. $(NH_4)_2CO_3$ monohydrate (38.0 g, 330 mmol) was added in portions to the solution obtained. After gas formation stopped, the reaction mixture was held for a few minutes at 40°C and allowed to stand overnight. The precipitated crystals were filtered out the next day, washed three times with ice water, and dried in air. Yield 17.3 g (46% based on the monohydrate). It was crystallized from water and dried at 105°C for 5 h; mp 186-188°C. IR spectrum (KBr), ν, cm^{-1}: 1700 (C=O), 1660 (C=N). ^1H NMR spectrum, δ, ppm (*J*, Hz): 3.9 (2H, d, J^{gem}_{AB} = 12, 5-H_A); 3.8 (2H, d, J^{gem}_{AB} = 12, 5-H_B). Found, %: C 34.01; H 4.63; N 15.98. $C_5H_8N_2O_3S$. Calculated, %: C 34.09; H 4.58; N 15.90.

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[1] St. Petersburg Technical University, St. Petersburg 198013, Russia; e-mail: gsramsh@mail.wplus.net.
[2] Institute of Toxicology, Ministry of Health, Russian Federation, St. Petersburg 193019; e-mail: drugs@mail.lanck.net. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1743-1744, November, 2003. Original article submitted September 18, 2003.

5,5-Bis(hydroxymethyl)-2,4-thiazolidinedione (3). Monohydrate of compound **2** (2.3 g, 12 mmol) was dissolved in water (5.3 ml); sulfuric acid (1.6 ml) was added and the reaction mixture was refluxed for 5 h. The material precipitating after cooling was washed twice with ice water and dried in air. Yield 1.5 g (70%). It was crystallized from water or ethanol and dried in air until the weight remained constant; mp 177-179°C (water). IR spectrum (KBr), ν, cm^{-1}: 1700 (C=O), 1660 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.0 (2H, d, J^{gem}_{AB} = 13, 5-H$_A$); 3.8 (2H, d, J^{gem}_{AB} = 13, 5-H$_B$). Found, %: C 33.72; H 3.94; N 8.01. $C_5H_7NO_4S$. Calculated, %: C 33.90.

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