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Transthiazolination: The Rearrangement of 2-(2′-Aminoethylthio)-2-thiazoline

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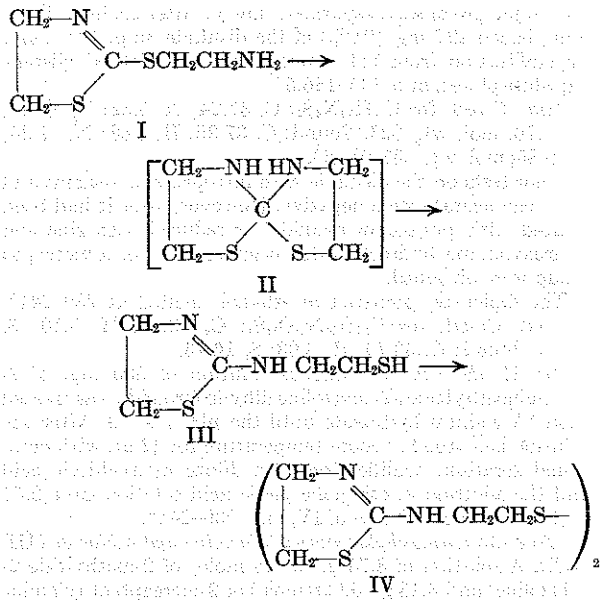
S-(2-Aminoethyl)isothiourea has been shown by Doherty *et al.*,[1] to undergo rearrangement to 2 mercaptoethylguanidine in neutral aqueous solution, and a cyclic intermediate has been postulated for the reaction. The rearrangement of a number of aminoalkylisothioureas to mercaptoalkylguanidines by this transguanylation reaction has been studied by ion exchange analysis.[2,3] In addition, it was demonstrated by ion exchange analysis that 2-(2′-aminoethylthio)-2-imidazoline underwent transimidazolination to 2-(2′-mercaptoethylamino)-2-imidazoline rapidly at *p*H 7.0; the properties of the compounds involved were not described.

We have found that 2-(2′-aminoethylthio)-2-thiazoline (I) undergoes a similar type of rearrangement, for which a symmetrical bicyclic intermediate can be postulated. The dihydrobromide of I was prepared by the reaction of 2-thiazolidinethione and 2-bromoethylamine hydrobromide in refluxing isopropyl alcohol. When an aqueous solution of I dihydrobromide was neutralized or made weakly alkaline, rearrangement to 2-(2′-mercaptoethylamino)-2-thiazoline (III) occurred. The latter compound readily underwent oxidation in air to the disulfide IV. Color tests on IV, its analytical data, and its infrared spectrum were consistent with its formulation as bis[2-(2′-thiazolinyl-2′-amino)ethyl] disulfide. Proof of this structure was obtained by alternate synthesis.

2-Methylthio-2-thiazoline and 2-mercaptoethylamine hydrochloride in refluxing methanol[4] afforded 2-(2′-mercaptoethylamino)-2-thiazoline hydrochloride (III, HCl). The disulfide obtained from the air oxidation of this mercaptan in alkaline solution proved to be identical to the sample of IV obtained from the rearrangement.

The high yield obtained and the low basicity required indicate that an intratransthiazolination is involved in the rearrangement.[5] The postulated cyclic intermediate for the rearrangement in this case is represented by formula II. In this instance, in which the bicyclic intermediate is composed



of similar rings, only one product was obtained. Rearrangements of this kind involving unsymmetrical bicyclic intermediates are being investigated.

EXPERIMENTAL

2-(2′-Aminoethylthio)-2-thiazoline dihydrobromide (I, 2HBr). A solution of 4.76 g. (0.04 mole) of 2-thiazolidinethione and 8.20 g. (0.04 mole) of 2-bromoethylamine hydrobromide in 60 ml. of isopropyl alcohol was refluxed for 4 hr. A solid precipitate began to separate during the refluxing. The cooled mixture yielded 3.50 g. (27%) of colorless product, m.p. 216° dec. Recrystallization from methanol afforded colorless crystals, m.p. 222° dec.

Anal. Calcd. for $C_5H_{12}Br_2N_2S_2$: C, 18.53; H, 3.73; S, 19.78; Br, 49.31. Found: C, 18.61; H, 3.71; S, 19.80; Br, 49.16.

There appeared to be some loss of material during the recrystallization from methanol; the recoveries obtained were low and erratic. The reaction product also gave satisfactory analyses before recrystallization.

When a solution of the dihydrobromide in aqueous ethanol was treated with alcoholic picric acid solution, a yellow crystalline dipicrate, m.p. 132–134°, was obtained.

Anal. Calcd. for $C_{17}H_{16}N_8S_2O_{14}$: C, 32.90; H, 2.60; S, 10.33. Found: C, 33.07; H, 2.65; S, 10.67.

On attempted recrystallization of this picrate from aqueous alcohol rearrangement occurred.[6] The picrate obtained from the recrystallization melted at 191–192° and was identical, by mixed melting point and infrared spectra, to the picrate of 2-(2′-mercaptoethylamino)-2-thiazoline (III).

Bis[2-(2′-thiazolinyl-2′-amino)ethyl]disulfide (IV) *from rearrangement of* I. (a) *At pH 9.1.* To a solution of 500 mg. (1.54 mmoles) of 2-(2′-aminoethylthio)-2-thiazoline dihydrobromide in 7 ml. of water was added two equivalents (3.1 ml.) of 1*N* sodium hydroxide. The resulting solution (*p*H 9.1) was allowed to stand at room temperature for 5 hr., and air was intermittently bubbled through it. A white

(1) D. G. Doherty, R. Shapira, and W. T. Burnett, Jr., *J. Am. Chem. Soc.*, **79**, 5667 (1957).

(2) J. X. Khym, R. Shapira, and D. G. Doherty, *J. Am. Chem. Soc.*, **79**, 5663 (1957).

(3) J. X. Khym, D. G. Doherty, and R. Shapira, *J. Am. Chem. Soc.*, **80**, 3342 (1958).

(4) A. F. McKay, D. J. Whittingham, and M.-E. Kreling [*J. Am. Chem. Soc.*, **80**, 3339 (1958)] have reported the reaction of 2-methylthio-2-thiazoline with various amines and amino acids.

(5) *Cf.* Refs. 1–3.

(6) It was shown by Doherty, *et al.*, (Refs. 1–3) that although *S*-(2-aminoethyl)isothiourea and related compounds were stable in strongly acidic solution (0.2*N* hydrochloric acid), the rearrangement began to take place under more weakly acidic conditions.

(7) I. W. Grote, *J. Biol. Chem.*, **93**, 25 (1931).

(8) N. D. Cheronis and J. B. Entrikin, *Semimicro Qualitative Organic Analysis*, 2nd Ed., Interscience, New York, 1957, p. 274.

crystalline precipitate separated slowly. After cooling, filtration yielded 227 mg. (91%) of the disulfide, m.p. 141–143°. Crystallization from 1:1 aqueous ethanol afforded glistening white plates, m.p. 145–146.5°.

Anal. Calcd. for $C_{10}H_{18}N_4S_4$: C, 37.24; H, 5.62; N, 17.37; S, 39.76; mol. wt., 323. Found: C, 37.35; H, 5.68; N, 17.25; S, 39.85; mol. wt., 337 (Rast).

Color tests on the disulfide with nitroprusside reagent and with lead acetate were negative. However, after it had been treated with potassium cyanide[7] or reduced with zinc and hydroxylamine hydrochloride,[8] positive tests for a mercapto group were obtained.

The dipicrate, prepared in ethanol, melted at 239–241°.

Anal. Calcd. for $C_{22}H_{24}N_{10}O_{14}S_4$: C, 33.84; H, 3.10; S, 16.43. Found: C, 33.79; H, 3.03; S, 16.73.

(b) *At pH 7.0.* An aqueous solution of 500 mg. of 2-(2′-aminoethylthio)-2-thiazoline dihydrobromide was treated with 1*N* sodium hydroxide until the *p*H was 7.0. After the solution had stood at room temperature for 42 hr. with occasional aeration, acidification with dilute hydrochloric acid and the addition of ethanolic picric acid solution gave 0.54 g. (90%) of the dipicrate of IV, m.p. 239–241°.

2-(2′-Mercaptoethylamino)-2-thiazoline hydrochloride (III, HCl). A solution of 3.73 g. (0.028 mole) of 2-methylthio-2-thiazoline[4] and 3.18 g. (0.028 mole) of 2-mercaptoethylamine hydrochloride in 75 ml. of methanol was refluxed for 4 hr. The solvent was removed under reduced pressure, and the remaining 6.40 g. of viscous oil was stored under nitrogen at 0–5°.

The ready oxidation of the mercaptan to the disulfide made crystallization difficult. Ultimately, in an atmosphere of nitrogen, a 2.35-g. portion of the 6.40 g. of oil separated from 8.5 ml. of absolute ethanol in clumps of fine white crystals; 1.20 g. (59%), m.p. 99–101°. These were filtered under nitrogen and washed on the filter with acetone. An analytical sample melted at 99.5–101.5°.

Anal. Calcd. for $C_6H_{11}ClN_2S_2$: C, 30.22; H, 5.58; S, 32.26. Found: C, 30.35; H, 5.50; S, 32.47.

This compound gave the usual tests for a mercaptan with nitroprusside reagent and with lead acetate. In addition, the infrared spectra of both this compound and its picrate showed a mercaptan band at 3.9 μ.

The picrate crystallized from ethanol as yellow needles, m.p. 191–192°. From a 0.51-g. portion of the 6.40 g. of concentrate from the reaction there was obtained 0.84 g. (96% yield from 2-methylthio-2-thiazoline) of the picrate.

Anal. Calcd. for $C_{11}H_{13}N_5O_7S_2$: C, 33.76; H, 3.35; S, 16.38. Found: C, 33.75; H, 3.37; S, 16.77.

Bis[2-(2′-thiazolinyl-2′-amino)ethyl] disulfide (IV) *from oxidation of* III. A 0.46-g. portion of the 6.40 g. of viscous concentrate obtained from 2-methylthio-2-thiazoline and 2-mercaptoethylamine hydrochloride was dissolved in 15 ml. of water, and sodium hydroxide was added dropwise until the solution was strongly alkaline (*p*H 10). A precipitate began to separate in a few minutes. After the mixture had stood at room temperature for about 20 hr. with occasional aeration, filtration afforded 0.30 g. (93% yield from 2-methylthio-2-thiazoline) of fine white crystals, m.p. 144–145.5°. Recrystallization from 1:1 aqueous ethanol gave glistening plates, m.p. 145–146.5°. The infrared spectra of this product and of the disulfide from the rearrangement were identical; there was no mixed melting point depression.

The dihydroiodide of the disulfide, m.p. 244.5–246°, was isolated from an attempted preparation of the mercaptan (III) from 2-methylthio-2-thiazoline hydroiodide[4] and 2-mercaptoethylamine in refluxing methanol. The same compound was obtained from IV and hydrogen iodide.

Anal. Calcd. for $C_{10}H_{20}I_2N_4S_4$: C, 20.76; H, 3.49; S, 22.17. Found: C, 20.88; H, 3.57; S, 22.41.

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