SYNTHESIS OF ANALOGS OF 5(4)-AMINOIMIDAZOLE-4(5)-CARBOXAMIDE AND PURINES

IV.* SYNTHESIS OF 5(4)-MERCAPTOIMIDAZOLE-4(5)-CARBOXYLIC ACID DERIVATIVES

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The corresponding 5(4)-mercaptoimidazoles, from which various 5(4)-mercaptoimidazole-4(5)-carboxylic acid derivatives were synthesized, were obtained from the amide and ethyl ester of 5-diazoimidazole-4-carboxylic acid by substitution of the diazo group. 5-Diazoimidazole-4-hydroxamic acid does not undergo substitution with sodium disulfide but does undergo cyclization to 3-N-hydroxyimidazo[4,5-d]-1,2,3-triazin-4-one under these conditions. The kinetics of the cyclization of diazoimidazoles were studied, and the interrelationship between the structure and reactivity of the latter was examined.

The present communication is devoted to the synthesis of new analogs of 5(4)-aminoimidazole-4(5)-carboxamide containing a mercapto group in the 5(4) position of the imidazole ring and carboxamide, ethoxycarbonyl, carboxyl, and thioamide groups in the 4(5) position. Of the methods for the preparation of imidazoles [2], no data on the synthesis of 5(4)-mercaptoimidazoles from the appropriate diazo compounds are available. We attempted to use 5-diazoimidazole-4-carboxamide (I) for the preparation of 5(4)-mercaptoimidazole-4(5)-carboxamide (II). A distinctive feature of o-diazocarboxamides of the aromatic series is their tendency to undergo intramolecular cyclization to give condensed 1,2,3-triazines [3]. Thus in acidic, neutral, and particularly rapidly in alkaline media I is irreversibly converted to imidazo[4,5-d]-1,2,3-triazin-4-one (III) [4]. In this connection, one might have assumed that the synthesis of 5(4)-thio derivatives of imidazolecarboxamide from diazoimidazole I would not be feasible. However, we have shown that I undergoes substitution in alkaline media to give the corresponding thio derivatives. 5(4)-Ethylxanthatoimidazole-4(5)-carboxamide (IV) is formed in small amounts along with the intramolecular cyclization product in the reaction of amide I with potassium ethylxanthate at 60°. The yield of IV increases to 43% when the reaction temperature is lowered. A mixture of mercaptoimidazole II and bis[4(5)-carbamoylimidazol-5(4)-yl] disulfide (V) is formed by saponification of IV with alkali. Chromatographically individual II was obtained by reduction of a mixture of II and V in alcohol with hydrazine hydrate, whereas disulfide V was obtained by oxidation of this same mixture with alcoholic iodine solution. Mercaptoimidazole II was also synthesized by another more convenient method – by reaction of diazoimidazole I with sodium disulfide [5] and reduction of the resulting mixture of II and V with hydrazine hydrate. Similarly, ethyl 5(4)-mercaptoimidazole-4(5)-carboxylate (VII) was obtained from ethyl 5-diazoimidazole-4-carboxylate [6].

Assuming that the method that we successfully used for the synthesis of the previously inaccessible mercaptoimidazole II and VI would also prove to be successful for the preparation of 5(4)-mercaptoimidazole-4(5)-hydroxamic acid, we synthesized 5-diazoimidazole-4-hydroxamic acid (VII) by diazotization of the corresponding amine [7]. Compound VII was isolated in the solid zwitterion form, the IR spectrum of which contains a band of stretching vibrations of a diazo group at 2210-2240 cm^{-1} (doublet).

*See [1] for communication III.

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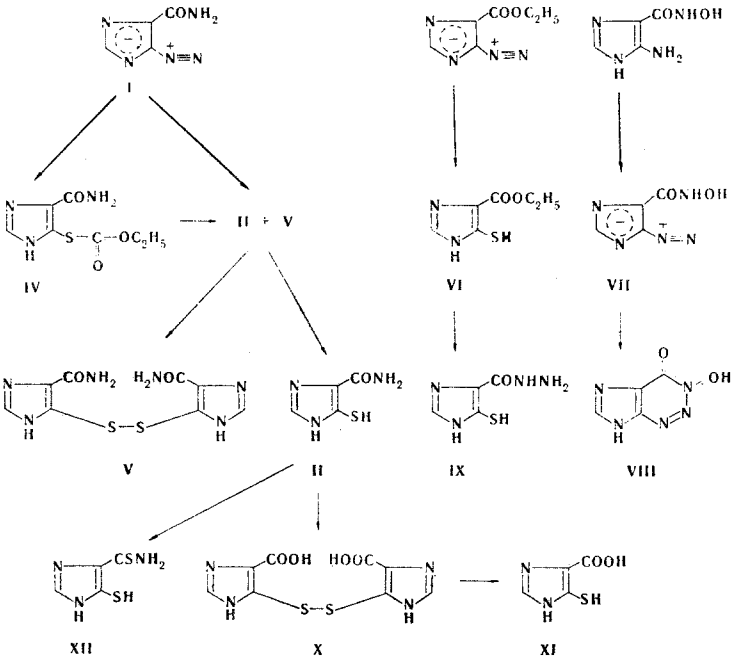

Like diazoimidazole I, VII in acidic, neutral, and alkaline media is converted to the corresponding cyclic derivative – 3-N-hydroxyimidazo[4,5-d]-1,2,3-triazin-4-one (VIII) – but does not react with sodium disulfide.

It might have been expected that the reason for the different reactivities of diazoimidazole I and VII is the higher rate of intramolecular cyclization of VII as compared with I. A comparative study of the rate of cyclization of diazoimidazoles I and VII was made spectrophotometrically at 21° in 0.1 N HCl, a phosphate–borate buffer (pH 7), and 0.1 N NaOH. The rate of cyclization is described by a first-order equation. As a result of a study of the kinetics of the reaction it was established that VII undergoes cyclization instantaneously on dissolving in acidic media, and the rate constant could not be determined. Cyclization proceeds slowly in neutral and alkaline media ($1.1 \cdot 10^{-5}$ and $26.5 \cdot 10^{-5}$ sec^{-1}, respectively). A different mechanism is observed for diazoimidazole I: in acid and neutral media it is slowly converted to cyclic compound III ($49.1 \cdot 10^{-5}$ and $56.6 \cdot 10^{-5}$ sec^{-1}, respectively) and undergoes practically instantaneous conversion in alkaline media. Thus the decisive factor in the ability of the diazo compound to undergo reaction with Na_2S_2 is evidently the structural pecularities of diazoimidazoles I and VII rather than the rate of intramolecular cyclization. Compound VII apparently exists in neutral and alkaline media in the zwitterion form, for which the formation of a reactive complex with sodium disulfide is difficult.

We used mercaptoimidazoles II and VI for the synthesis of various derivatives involving the carboxyl group. Thus 5(4)-mercaptoimidazole-4(5)-carboxyhydrazide (IX) is formed on refluxing VI in hydrazine hydrate. 5(4)-Mercaptoimidazole-4(5)-carboxylic acid (XI) was obtained by saponification of mercaptoimidazole II with nitrosylsulfuric acid and reduction of the resulting bis[4(5)carboxyimidazole-5(4)-yl]disulfide (X) with hydrazine hydrate in ethanol. 5(4)-mercaptoimidazol-4(5)-thioamide (XII) was synthesized by reaction of II with P_2S_5 in dioxane.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The UV spectra of the compounds were recorded with a Perkin–Elmer-402 spectrophotometer. Chromatography was carried out on Silufol UV-254 in butanol–acetic acid–water (4 : 1 : 1) (R_f) and propanol–0.2 N NH_4OH (3 : 1) (R'_f) systems. The kinetic cyclization curves of I were obtained at λ 315 nm (pH 7) and 300 nm (in 0.1 N HCl) (at λ 275 nm for diazoimidazole VII). The reaction rate constants were found by the method of least squares with an accuracy of 5%.

5(4)-Ethylxanthatoimidazole-4(5)-carboxamide (IV). A 2.05-g (15 mmole) sample of 5-diazoimidazole-4-carboxamide was added in portions with stirring at 15° to a solution of 3.2 g (20 mmole) of potassium ethylxanthate in 25 ml of water, after which the mixture was allowed to stand for 2 h. It was then acidified to pH 4 with concentrated HCl and cooled. The resulting precipitate was suspended in 30 ml of refluxing THF, and the insoluble portion was removed by filtration. The filtrate was vacuum evaporated to a mini-

mum volume, and the resulting precipitate was removed by filtration and dried over P_2O_5 to give 1.5 g (43%) of a product with mp 155° (from THF), R_f 0.84, and R'_f 0.75. Found: C 36.8; H 4.2; N 18.5; S 27.5%. $C_7H_9N_3O_2S_2$. Calculated: C 36.4; H 3.9; N 18.2; S 27.7%.

The THF-insoluble precipitate was crystallized from water to give a product with mp 210° and R'_f 0.20. This product was identical to the imidazo[4,5-d]-1,2,3-triazin-4-one obtained by the method in [4].

5(4)-Mercaptoimidazole-4(5)-carboxamide (II). A) A solution of 0.3 g (1.3 mmole) of IV in 5 ml of 10% NaOH was refluxed for 1 h, after which it was cooled and acidified to pH 3 with concentrated HCl. The resulting precipitate was removed by filtration to give a mixture of II and disulfide V. The mixture was suspended in 5 ml of absolute ethanol, 0.1 ml of hydrazine hydrate was added, and the mixture was refluxed for 30 min. It was then cooled, and the precipitated light-yellow crystals of II were removed by filtration to give 0.08 g (43%) of a product with mp 310°, R_f 0.39, and R'_f 0.62. Found: C 33.7; H 3.7; N 29.6; S 22.4%. $C_4H_5N_3OS$. Calculated: C 33.6; H 3.5; N 29.4; S 22.4%. UV spectrum (in water), λ_{max}, nm (log ε): 265 (3.86) and 293 (3.93).

B) A 1.33-g (9.3 mmole) sample of diazoimidazole I was added with stirring at 13° to a freshly prepared solution of 2.68 g (10.3 mmole) of $Na_2S_2 \cdot 9H_2O$ and 0.33 g (10.3 mmole) of sulfur in 10.6 ml of water, after which the reaction mixture was allowed to stand for 2 h. It was then acidified to pH 3 with concentrated HCl, and the resulting precipitate was removed by filtration and crystallized from water to give a mixture of II and V. The mixture was reduced with hydrazine hydrate to give a compound indentical to that described in experiment A. The yield was 0.75 g (53%).

Bis[4(5)-carbamoyl-5(4)imidazolyl] Disulfide (V). A 10% ethanol solution of iodine was added dropwise with stirring to a suspension of 0.4 g of a mixture of II and V in 30 ml of ethanol until the added iodine solution was no longer decolorized, after which the mixture was allowed to stand at room temperature for 12 h. The resulting precipitate was removed by filtration and washed successively with water, alcohol, and ether to give 0.38 g (95%) of a product with mp 300°, R_f 0.13, and R'_f 0.55. Found: C 33.5; H 2.9; S 22.2%. $C_8H_8N_6O_2S_2$. Calculated: C 33.8; H 2.8; S 22.5%. UV spectrum (in water), λ_{max}, nm (log ε): 202 (4.26) and 250 (4.04).

Ethyl 5(4)-Mercaptoimidazole-4(5)-carboxylate (VI). Method B for the preparation of II was used to obtain this compound from ethyl 5-diazoimidazole-4-carboxylate, which was synthesized by the method in [6]. The yield of product with mp 138-139° (from water), R_f 0.59, and R'_f 0.57, was 45%. Found: N 16.3; S 18.6%. $C_6H_8N_2O_2S$. Calculated: N 16.3; S 18.6%. UV spectrum (in water), λ_{max}, nm (log ε): 270 (3.73) and 300 (3.90).

5(4)-Mercaptoimidazole-4(5)-carboxyhydrazide (IX). A 0.4-g (2.32 mmole) sample of VI was refluxed in 4 ml of hydrazine hydrate for 3 h, after which the mixture was vacuum evaporated to dryness, and the residue was dissolved in 5 ml of water. The aqueous solution was acidified to pH 4 with concentrated HCl, and the resulting precipitate was removed by filtration to give 0.3 g (82%) of a product with mp 250-253° (from water), R_f 0.43, and R'_f 0.60. Found: C 30.6; H 4.1; N 35.5; S 20.5%. $C_4H_6N_4OS$. Calculated: C 30.4; H 3.8; N 35.5; S 20.2%. UV spectrum (in water), λ_{max}, nm (log ε): 263 (3.71) and 295 (3.92).

Bis[4(5)carboxy-5(4)imidazolyl] Disulfide (X). A solution of 3 g (43.5 mmole) of $NaNO_2$ in 10 ml of water, was added in portions with vigorous stirring at 20° (under the layer of the reaction mixture) to a solution of 4.65 g (32.5 mmole) of mercaptoimidazole II in 26.8 ml of concentrated H_2SO_4. After all of the nitrate had been added, the mixture was heated on a boiling-water bath for 2 h. It was then cooled and poured over 130 g of ice. The resulting precipitate was removed by filtration and washed with water and alcohol to give 4.45 g (96%) of a product with mp 190-191° (from water), R_f 0.12, and R'_f 0.28. Found: C 33.7; H 2.4; N 19.5; S 22.2%. $C_8H_6N_4O_4S_2$. Calculated: C 33.6; H 2.1; N 19.6; S 22.2%. UV spectrum (in water), λ_{max}, nm (log ε): 206 (4.22) and 246 (3.89).

5(4)-Mercaptoimidazole-4(5)-carboxylic Acid (XI). A 2.3-g (8 mmole) sample of disulfide X was added in portions at 30° to a solution of 3 ml of hydrazine hydrate in 5 ml of ethanol, after which the mixture was allowed to stand for 4 h. Ethanol (30 ml) was added, and the mixture was cooled to 0°. The resulting resin was triturated with absolute ethanol, and the solid material was removed by filtration and crystallized from water acidified to pH 5 to give 1.5 g (65%) of product with mp 115°, R_f 0.20 and R'_f 0.89. Found: C 33.5; H 3.0; N 19.7; S 22.4%. $C_4H_4N_2O_2S$. Calculated: C 33.3; H 2.8; N 19.5; S 22.2%. UV spectrum (in water), λ_{max}, nm (log ε): 266 (3.88) and 295 (3.89).

5(4)-Mercaptoimidazole-4(5)-thioamide (XII). A 2.33-g (10.5 mmole) sample of P_2S_5 was added with vigorous stirring at 60° to a suspension of 1 g (7 mmole) of II in 50 ml of dioxane, after which the mixture was refluxed with stirring for 4 h. It was then vacuum evaporated to a minimum volume, and the residue was dissolved in 200 ml of boiling water. The solution was decolorized with charcoal and vacuum evaporated to a volume of 15 ml. The precipitate that formed on cooling of the solution was removed by filtration and crystallized from water to give 0.48 g (43%) of a product with mp 248-249°, R_f 0.82 and R'_f 0.90. Found %: C 29.9; H 3.2; N 26.5; S 40.4%. $C_4H_5N_3S_2$. Calculated: C 30.2; H 3.1; N 26.4; S 40.3%. UV spectrum (in water), λ_{max}, nm (log ε): 214 (4.22), 273 (3.87), and 352 (4.30).

5-Diazoimidazole-4-hydroxamic Acid (VII). A solution of 1.60 g (8.95 mmole) of 5(4)-aminoimidazole-4(5)-hydroxamic acid hydrochloride [7] in 11.1 ml of 1 N HCl was added gradually with stirring at −3° to a solution of 1.11 g (15.4 mmole) of sodium nitrite in 18 ml of water, after which the mixture was allowed to stand for 15 min. It was then cooled, and the resulting precipitate was removed by filtration and washed successively with water, a small amount of ethanol, and ether to give 1 g (69%) of a product with mp 261° (dec. explosively). Found: C 30.0; H 2.3; N 43.1%. $C_4H_3N_5O_2 \cdot 0.5H_2O$. Calculated: C 29.7; H 2.5; N 43.2%. IR spectrum, cm^{-1}: 1729 (C=O); 2210, 2240 ($N^{+}\equiv N$). UV spectrum (in water), λ_{max}, nm (log ε): 224 (4.24) and 323 (3.67).

3-N-Hydroxyimidazo[4,5-d]-1,2,3-triazin-4-one (VIII). A) A 0.5-g (3.27 mmole) sample of diazoimidazole VII was added with stirring to 40 ml of 1 N HCl, after which the mixture was allowed to stand at room temperature for 2 h. Concentrated HCl (30 ml) was added, and the resulting precipitate was removed by filtration and washed successively with water, alcohol, and ether to give 0.2 g (42.3%) of a product with mp 270° (dec. explosively) and R_f 0.20. Found: C 31.2; H 2.0; N 46.0%. $C_4H_3N_5O_2$. Calculated: C 31.4; H 2.0; N 45.8%. IR spectrum: 1742 cm^{-1} (C=O). UV spectrum (in water), λ_{max}, nm (log ε): 224 (4.29), 275 (3.52), and 332 (3.63).

B) A 1-g (6.54 mmole) sample of diazoimidazole VII was added with stirring at 15° to a freshly prepared solution of 1.82 g (7 mmole) of sodium sulfide and 0.224 g (7 mmole) of sulfur in 8 ml of water, after which the mixture was allowed to stand for 1 h. It was then heated to 50°, acidified to pH 7 with concentrated HCl, and cooled. The resulting precipitate was removed by filtration and crystallized from water to give 0.5 g (53%) of product. The product was identical to the product described in experiment A.

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