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

IV. * SYNTHESIS OF 5(4)-MERCAPOIMIDAZOLE-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 diazolimidazoles 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, ethoxy-carbonyl, 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 imidazolcarboxamide from diazolimidazole 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 mercaptoimidazolide 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. Mercaptoimidazolide II was also synthesized by another more convenient method — by reaction of diazolimidazole 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-diazolimidazole-4-carboxylate [6].

Assuming that the method that we successfully used for the synthesis of the previously inaccessible mercaptoimidazolide II and VI would also prove to be successful for the preparation of 5(4)-mercaptimidazole-4(5)-hydroxamic acid, we synthesized 5-diazolimidazole-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 · 10⁻⁵ and 26.5 · 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 · 10⁻⁵ and 56.6 · 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 Na₂S₂ is evidently the structural peculiarities 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 P₂S₅ 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) (Rf) and propanol-0.2 N NH₄OH (3:1) (Rf') 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-