

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

## 8.\* SOME REACTIONS OF 5(4)-AMINOIMIDAZOLE-4(5)-CARBOXYHYDRAZIDE

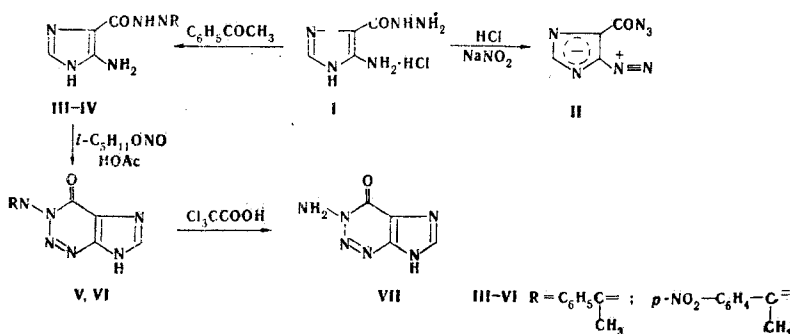
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5-Diazoimidazole-4-carboxazide was isolated in the diazotization of 5(4)-aminoimidazole-4(5)-carboxyhydrazide. The diazotization of N-substituted hydrazides of 5(4)-aminoimidazole-4(5)-carboxylic acid was studied. It is shown that the resulting diazo derivatives undergo cyclization to 3-arylideneaminoimidazo[4,5-d]-1,2,3-triazin-4-ones.

This paper is devoted to the preparation of new analogs of 2-azapurine by diazotization of 5(4)-aminoimidazole-4(5)-carboxyhydrazide (I) and its derivatives. In contrast to 5(4)-aminotriazole-4(5)-carboxyhydrazide [2], only 5-diazoimidazole-4-carboxazide (II), the IR spectrum of which contains bands of the stretching vibrations of azido and diazo groups at, respectively, 2135 and 2180  $\text{cm}^{-1}$ , was isolated in the diazotization of I under various conditions. Compound II does not undergo the Curtius reaction even when it is refluxed for a long time in alcohol.

For selective protection of the carboxyhydrazide group we subjected I to reaction with acetophenone and p-nitroacetophenone; pure compounds that are the only products of the investigated reaction were isolated in both cases. In analogy with o-aminobenzhydrazide [3], one might have assumed that the phenylethylidene- (III) and p-nitrophenylethylidenehydrazide (IV) of 5(4)-aminoimidazole-4(5)-carboxylic acid are formed in this case.



To prove the structure of III and IV we carried out the diazotization under conditions that exclude the hydrolysis of the protective group, viz., with isoamyl nitrite in a solution of absolute dioxane and glacial acetic acid; we were unable to establish the formation of diazo compounds, and isolated products with cyclic structures, viz., 3-(p-nitrophenyl-1-ethylideneamino)- (V) and 3-(phenyl-1-ethylideneamino)-4-oxoimidazo[4,5-d]-1,2,3-triazine (VI), in both cases. These results confirm our assumption regarding the structure of III and IV.

3-Aminoimidazo[4,5-d]-1,2,3-triazin-4-one (VII) was isolated when V and VI were treated with an aqueous solution of trifluoroacetic acid.

Compound VII displayed weak activity in tests of its cytostatic activity in vitro.

\* See [1] for communication 7.

## EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The UV spectra were recorded with a Beckmann 26 UV-vis spectrophotometer. Chromatography was carried out on Silufol UV-254 plates in butanol-acetic acid-water (4:1:1) ( $R_f$ ), propanol-0.2 N  $\text{NH}_4\text{OH}$  (3:1) ( $R_f'$ ), and chloroform-methanol (3:1) ( $R_f''$ ) systems.

**5-Diazoimidazole-4-carboxazide (II).** A solution of 1 g (5.64 mmole) of I in 15 ml of 1 N HCl was added gradually with stirring at  $-2^\circ\text{C}$  to a solution of 0.98 g (14.2 mmole) of sodium nitrite in 10 ml of water, and the mixture was maintained at this temperature for 10 min, after which it was made alkaline to pH 7-8 with sodium carbonate solution. The alkaline mixture was extracted with ether, and the extract was evaporated to dryness in vacuo. The residue was dried in vacuo over  $\text{P}_2\text{O}_5$  to give 0.3 g (34.1%) of a product with mp  $149^\circ\text{C}$  (decomposed explosively) and  $R_f$  0.91,  $R_f'$  0.80, and  $R_f''$  0.75. IR spectrum:  $1680\text{ cm}^{-1}$  ( $\text{C}=\text{O}$ ),  $2180\text{ cm}^{-1}$  ( $\text{N}\equiv\text{N}$ ), and  $2135\text{ cm}^{-1}$  ( $\text{N}_3$ ). Found: C 29.2; H 1.4; N 60.0%.  $\text{C}_4\text{HN}_7\text{O}$ . Calculated: C 29.4; H 0.6; N 60.1%.

**5(4)-Aminoimidazole-4(5)carboxylic Acid Phenylethylidenehydrazide (III).** A 0.687-g (5.7 mmole) sample of acetophenone in 6 ml of absolute ethanol was added to a solution of 1 g (5.6 mmole) of 5(4)-aminoimidazole-4(5)-carboxhydrazide hydrochloride in 104 ml of absolute ethanol and 0.64 ml of triethylamine, and the mixture was stirred at room temperature for 24 h. The precipitate was removed by filtration and washed with ether to give 0.55 g (40%) of a product with mp  $238-239^\circ\text{C}$  (from ethanol),  $R_f$  0.49, and  $R_f''$  0.73. IR spectrum:  $1650\text{ cm}^{-1}$  ( $\text{C}=\text{O}$ ). UV spectrum (in ethanol),  $\lambda_{\text{max}}$  (log  $\epsilon$ ): 218 (4.12) and 310 nm (4.45). Found: C 58.9; H 5.5; N 29.1%.  $\text{C}_{12}\text{H}_{13}\text{N}_5\text{O}$ . Calculated: C 59.2; H 5.4; N 28.8%.

**5(4)-Aminoimidazole-4(5)-carboxylic Acid p-Nitrophenylethylidenehydrazide (IV).** A 1-g (6 mmole) sample of p-nitroacetophenone was added to a solution of 1 g (5.6 mmole) of I in 200 ml of absolute ethanol and 0.64 ml of triethylamine, and the mixture was refluxed for 48 h. It was then evaporated to dryness in vacuo, and the residue was crystallized from dimethylformamide (DMF)-water to give 0.9 g (55.5%) of a product with mp  $245^\circ\text{C}$ ,  $R_f$  0.24,  $R_f'$  0.67,  $R_f''$  0.64. IR spectrum:  $1670\text{ cm}^{-1}$  ( $\text{C}=\text{O}$ ). UV spectrum (in ethanol),  $\lambda_{\text{max}}$  (log  $\epsilon$ ): 230 (4.05), 280 (4.15), and 350 nm (4.24). Found: C 49.8; H 4.7; N 29.1%.  $\text{C}_{12}\text{H}_{12}\text{N}_6\text{O}_3$ . Calculated: C 50.0; H 4.2; N 29.2%.

**3-(p-Nitrophenyl-1-ethylideneamino)-4-oxoimidazo[4,5-d]-1,2,3-triazine (V).** A 65-ml sample of absolute dioxane was added with stirring at  $-5^\circ\text{C}$  to a solution of 0.31 g (1.08 mmole) of IV in 65 ml of glacial acetic acid, 0.14 g of isoamyl nitrite was added, and the mixture was maintained at this temperature for 12 h. It was then evaporated to dryness in vacuo to give 0.3 g (93%) of a product with mp  $230^\circ\text{C}$  (from ethanol),  $R_f$  0.69,  $R_f'$  0.75, and  $R_f''$  0.59. IR spectrum:  $1730\text{ cm}^{-1}$  ( $\text{C}=\text{O}$ ). UV spectrum (in ethanol),  $\lambda_{\text{max}}$  (log  $\epsilon$ ): 202 (4.41), 270 (4.16), and 310 nm (3.92). Found: C 47.8; H 3.3; N 32.4%.  $\text{C}_{12}\text{H}_9\text{N}_7\text{O}_3$ . Calculated: C 48.2; H 3.0; N 32.8%.

**3-(Phenyl-1-ethylideneamino)-4-oxoimidazo[4,5-d]-1,2,3-triazine (VI).** Isoamyl nitrite was added dropwise with stirring at  $-4^\circ\text{C}$  to a solution of 0.18 g (0.74 mmole) sample of III in 3.3 ml of a mixture of glacial acetic acid and absolute dioxane (1:1), and the resulting precipitate was removed by filtration, washed with ether, and dried in vacuo over  $\text{P}_2\text{O}_5$  to give 0.175 g (93%) of a product with mp  $204^\circ\text{C}$  (from ethanol),  $R_f$  0.79,  $R_f'$  0.76, and  $R_f''$  0.70. IR spectrum:  $1700\text{ cm}^{-1}$  ( $\text{C}=\text{O}$ ). UV spectrum (in ethanol),  $\lambda_{\text{max}}$  (log  $\epsilon$ ): 205 (4.54) and 300 nm (3.91). Found: C 56.8; H 4.5; N 33.3%.  $\text{C}_{12}\text{H}_{10}\text{N}_6\text{O}$ . Calculated: C 56.7; H 3.9; N 33.1%.

**3-Aminoimidazo[4,5-d]-1,2,3-triazin-4-one (VII).** A 1.2-g (4 mmole) sample of V was added to 67.2 ml of a 33% solution of trichloroacetic acid, the mixture was filtered, and the filtrate was extracted with ether (six 50 ml portions). The aqueous layer was evaporated to dryness in vacuo in an argon atmosphere to give 0.38 g (62.3%) of a product with mp  $197^\circ\text{C}$ ,  $R_f$  0.39,  $R_f'$  0.41, and  $R_f''$  0.28. IR spectrum:  $1720\text{ cm}^{-1}$  ( $\text{C}=\text{O}$ ). UV spectrum (in water),  $\lambda_{\text{max}}$  (log  $\epsilon$ ): 233 (3.93) and 297 nm (3.63). Found: C 29.9; H 3.3; N 51.6%.  $\text{C}_4\text{H}_4\text{N}_6\text{O}\cdot 0.5\text{H}_2\text{O}$ . Calculated: C 29.8; H 3.1; N 52.2%.

## LITERATURE CITED

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