The physicochemical constants, results of elementary analysis, and yields of the compounds obtained are presented in Tables 1 and 2.

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

9.* PECULIARITIES OF THE REACTION OF 5(4)-AMINOIMIDAZOLE-4(5)-CARBOXHYDRAZIDE WITH NITROUS ACID AND OF 5-DIAZOIMIDAZOLE-4-CARBOXAZIDE WITH AMINES

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The reaction of 5(4)-aminoimidazole-4(5)-carboxhydrazide with nitrous acid was investigated. A mixture of four compounds, viz., 5-diazoimidazole-4-carboxazide, 5-diazoimidazole-4-carboxylic acid, 5(4)-aminoimidazole-4(5)-carboxazide, and 2-azahypoxanthine, is formed under all of the investigated conditions. 5(4)-Azidoimidazole-4(5)-carboxamide derivatives were obtained in the reaction of diazoimidazolecarboxazide with various amines in protic and aprotic solvents. 5-N-(Piperidyl)azoimidazole-4-carboxazide was isolated only in the reaction with piperidine in an aqueous medium.

5-Diazoimidazole derivatives are of great interest in the chemistry of heterocyclic diazo compounds. However, the available information on the diazotization of imidazole derivatives involves only compounds that have one substituent, viz., and amino group. that is reactive in this process [2-4].

In the present paper we examine the reaction of nitrous acid with 5(4)-aminoimidazole-4(5)-carboxhydrazide (I), which, as we have shown in [1], has approximately identically reactive groupings in the 4 and 5 positions of the imidazole ring.

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*See [1] for Communication 8.

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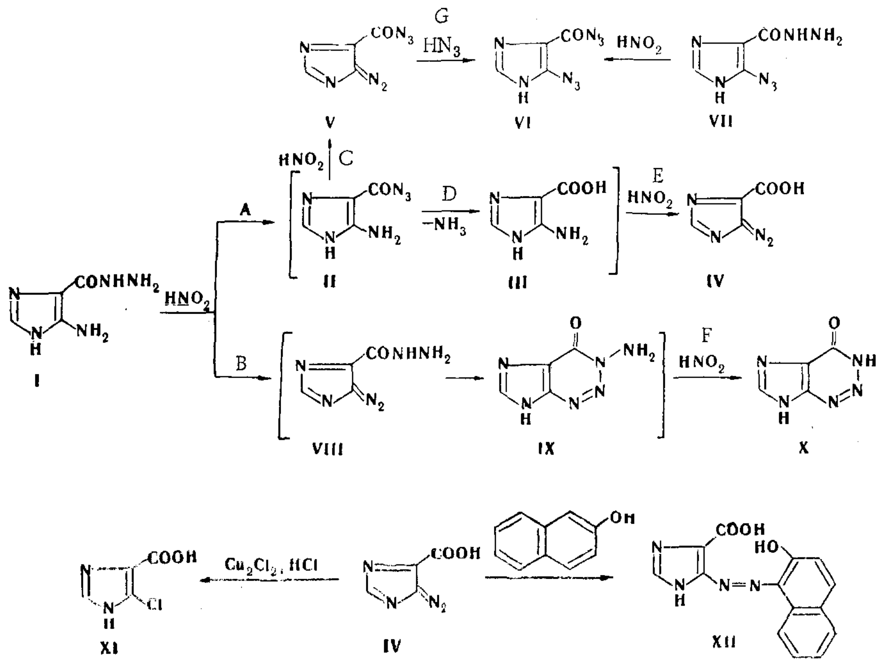
The literature contains data on the diazotization of anthranil hydrazide and pyridine and pyrazole o-aminocarboxhydrazides; only the carboxhydrazide group reacts with nitrous acid in the case of 2-amino-pyridine-3-carboxhydrazide and 3-aminopyridine-4-carboxhydrazide owing to the electron-acceptor effect of the pyridine ring, and the corresponding o-amino carboxy azides are formed [5]. The amino group in anthranil hydrazide and in 3-methyl-4-aminopyrazole-5-carboxhydrazide reacts with equimolar amounts of sodium nitrite and hydrochloric acid to give diazo compounds that undergo cyclization to 3-N-amino-1,2,3-triazin-4-one derivatives [6, 7]. When twofold molar amounts of sodium nitrite and hydrochloric acid were used, 3(H)-triazin-4-ones were isolated. Both the amino and carboxyhydrazido groups react in the case of diazotization of anthranil hydrazide with nitrous acid in aqueous acetic acid, and a mixture of anthranil azide and benzo-1,2,3-triazin-4-one is formed [6].

One might have expected that the reaction of imidazole I with nitrous acid would proceed in the same way as the reaction of the corresponding pyrazole and benzene derivatives. However, aminoimidazolecarboxylic acid hydrazide reacts with nitrous acid in a more complex manner. In contrast to anthranil hydrazide [6], a mixture of four compounds, viz., 5-diazoimidazole-4-carboxylic acid (IV), 5-diazoimidazole-4-carboxazide (V), 5(4)-azidoimidazole-4(5)-carboxazide (VI), and imidazo[4,5-d]-1,2,3-triazin-4-one (X), is formed with a twofold excess of sodium nitrite in both hydrochloric acid and acetic acid, as well as with isoamyl nitrite.

Only these compounds were recorded in the case of monitoring of the course of the reaction by means of thin-layer chromatography (TLC) in three systems of solvents during the entire reaction period. Unidentified azo compounds were obtained in addition to IV-VI and X in the case of diazotization of imidazole I with an equimolar amount of nitrous acid.

In addition to 5-diazoimidazole-4-carboxazide (V), the formation of which in the investigated reaction was established in [1], a new diazo derivative, viz., 5-diazoimidazole-4-carboxylic acid (IV), was isolated from the reaction mixture. The IR spectrum of diazocarboxylic acid IV contains bands of stretching vibrations that are characteristic for a carboxy C=O group at 1710 cm^{-1} and a diazo group at 2180 cm^{-1}. The structure of diazo derivative IV was confirmed by its conversion to 5(4)-chloroimidazole-4(5)-carboxylic acid (XI) and by azo coupling with 2-naphthol to give 5(4)-(2-hydroxyl-1-naphthylazo)imidazole-4(5)-carboxylic acid (XII).



In addition to diazoimidazoles IV and V, 5(4)-azidoimidazole-4(5)-carboxazide (VI) was isolated from the reaction mixture. An authentic sample of VI was obtained from the reaction mixture. An authentic sample of VI was obtained by alternative synthesis by reaction of

5(4)-azidoimidazole-4(5)-carboxhydrazide (VII) with sodium nitrite in hydrochloric acid. A fourth product of the investigated reaction is imidazo[4,5-d]-1,2,3-triazin-4-one (X), which is identical to a sample of X synthesized by the method described in [8].

Thus the principal process in the investigated reaction is, in our opinion, the reaction of the carboxhydrazido group of I with nitrous acid (reaction A). The resulting 5(4)-aminoimidazole-4(5)-carboxazide (II) then reacts with excess diazotizing agent to give diazoimidazolecarboxazide (reaction C) and is simultaneously hydrolyzed (reaction D) to 5(4)-aminoimidazole-4(5)-carboxylic acid (III), which is converted to diazo compound IV (reaction E) under the diazotization conditions. Azidoimidazolecarboxazide VI is formed (reaction G) as a result of reaction of the diazo group of V with the hydrazoic acid liberated in the hydrolysis of aminoimidazolecarboxazide II.

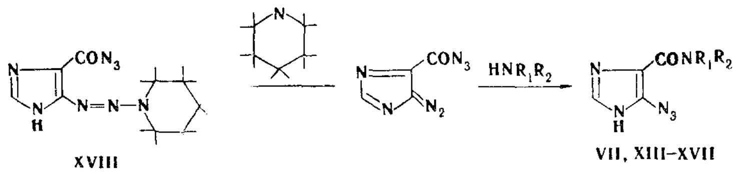
In contrast to o-amino carboxhydrazides of pyridine [5], the amino group of I also reacts with nitrous acid (reaction B) but to a lesser extent than the carboxhydrazido group; in this case one observes the formation of 3-N-aminoimidazo[4,5-d]-1,2,3-triazin-4-one (IX), which, as we have shown in the case of the individual product, again reacts with excess nitrous acid (reaction F) and is converted to imidazotriazinone X.

It might be assumed that diazoimidazolecarboxylic acid IV is formed as a consequence of hydrolysis of the carboxazido group of V. However, conversion of the carboxazido group does not occur not only under the conditions of diazotization of amino carboxhydrazide I but even in the case of prolonged heating of diazoimidazolecarboxazide V in hydrochloric acid, and V is isolated unchanged.

Thus new data on the reactivities of o-amino carboxhydrazides with respect to nitrous acid as a function of the peculiarities of the electronic character of the cyclic system and the ratio of the rates of the secondary reactions of the products of the transformation have been obtained.

One of the principal reaction products is carboxazide V. Since diazo compound may be the starting compounds in the synthesis of new imidazole derivatives, we studied the chemical properties and reactivities of diazoimidazolecarboxazide V. We observed that neither elimination of the diazo group nor conversion of the carboxazido substituent via the Curtius reaction occurs even when product V is refluxed in alcohol for a long time. In the case of the reaction of V with amines one might have expected nucleophilic substitution of the azido group, the formation of triazenes, or the simultaneous occurrence of these reactions. However, we found that 5(4)-azidoimidazole-4(5)-carboxamide derivatives (VII and XIII-XVII) are formed in high yields in the reaction of diazoimidazolecarboxazide V with various amines in both protic and aprotic solvents. The structures of the products isolated in this case were confirmed by the IR spectroscopic data and, in the case of 5(4)-azidoimidazole-4(5)-carboxamide (XIII), by alternative synthesis [9, 10].

Thus in the investigated reaction one observes the unusual fact of the successive occurrence of two processes, viz., nucleophilic substitution of the azido group and reaction of the resulting azide ion with the diazo group in the 5 position of the imidazole ring.



VII R_1=H, R_2=NH_2; XIII R_1=H, R_2=H; XIV R_1=H, R_2=CH_3; XV R_1=CH_3, R_2=CH_3;
XVI R_1= morpholino XVII R_1= piperidino

The reaction proceeds in a different way, depending on the conditions, only with piperidine, which has high nucleophilicity; specifically, the corresponding azide XVII is formed in absolute ether, whereas 5(4)-N-piperidylazoimidazole-4(5)-carboxazide (XVIII) is formed in the presence of water.

TABLE 1. 5(4)-Azidoimidazole-4(5)-carboxamide Derivatives (VII and XIV-XVII)

Compound	Decomposition temp. °C	UV spectra, λ max, nm (log ε)	Found, %			Empirical formula	Calc., %			Yield, %
			C	H	N		C	H	N	
VII	160	212 (4,00); 270 (4,16)	29,4	3,1	58,4	$C_4H_5N_7O$	28,7	3,0	58,7	84
XIV	146	212 (4,07); 267 (4,18)	36,8	3,8	50,2	$C_5H_6N_6O$	36,2	3,6	50,4	81
XV	136	220 (4,05); 263 (4,14)	40,3	4,6	46,6	$C_6H_8N_6O$	40,0	4,4	46,7	75
XVI	108	232 (4,05); 268 (4,10)	43,6	4,7	38,2	$C_8H_{10}N_6O_2$	43,2	4,5	37,8	78
XVII	163—164	230 (4,02); 267 (4,03)	49,0	5,8	37,7	$C_9H_{12}N_6O$	49,1	5,5	38,1	70

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds obtained were recorded with a UR-20 spectrometer. The UV spectra of solutions of the compounds in alcohol or water were obtained with a Beckmann UV-26 spectrophotometer. Thin-layer chromatography (TLC) on Silufol UV-254 plates in the following three systems of solvents was used to confirm the individuality of the substances: 1) butanol—acetic acid—water (4:1:1) (R_f); 2) n-propanol—0.2 N ammonium hydroxide (R'_f); 3) chloroform—methanol (3:1) (R''_f).

Reaction of 5(4)-aminoimidazole-4(5)-carboxhydrazide (I) with Nitrous Acid. A solution of 1 g (5.64 mmole) of amino carboxhydrazide I in 15 ml of 1 N hydrochloric acid was added gradually with stirring at −2°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. It was then made alkaline to pH 7-8 with sodium carbonate solution, and product V was extracted with ether. The extract was dried over Na_2SO_4 and evaporated to dryness *in vacuo* to give 0.3 g (33%) of product. The aqueous layer after extraction of V was evaporated to dryness in vacuo, and the residue was extracted with ether to give 0.03 g (3%) of 5(4)-azidoimidazole-4(5)-carboxazide (VI). Subsequent extraction of the residue with acetone yielded 0.05 g (6%) of imidazo[4,5-d]-1,2,3-triazin-4-one (X). The residue was a mixture of diazoimidazolecarboxylic acid IV with NaCl.

5(4)-Chloroimidazole-4(5)-carboxylic Acid (XI). The aqueous layer containing acid IV was added gradually with stirring to a freshly prepared and cooled (to 8°C) solution of 1.9 g (19.1 mmole) of CuCl in 25 ml of concentrated HCl, and the mixture was stirred at 20°C for 1 h. It was then heated briefly to 50°C, and hydrogen sulfide was passed through the reaction mixture. The precipitated copper sulfide was removed by filtration and washed with water. The filtrate was evaporated to dryness *in vacuo,* and the residue was treated with boiling absolute ethanol. The mixture was filtered, and the solvent was removed by vacuum evaporation to dryness to give 0.27 g (32%) of a product with mp 242-243°C (from water) and R_f 0.77, R'_f 0.68, and R''_f 0.33. IR spectrum: 1680 cm^{-1} (C=O). UV spectrum (in alcohol), λ_{max}(log ε): 238 nm (4.05). Found: C 33.0; H 2.2; Cl 24.4%. $C_4H_3N_2O_2Cl$. Calculated: C 32.8; H 2.1; Cl 24.2%.

Azo Coupling of Diazo Carboxylic Acid IV with 2-Naphthol. A solution of 0.6 g (4.2 mmole) of 2-naphthol in ethanol was added with stirring to the aqueous layer containing IV, and the mixture was maintained at 20°C for 2 h. The precipitate was removed by filtration and triturated in ether (five 30-ml portions) to give 0.3 g (17%) of a product with mp 229-230°C (from 1 N HCl) and R_f 0.49 and R'_f 0.55. IR spectrum: 1730 cm^{-1} (C=O). UV spectrum (in alcohol), λ_{max}(log ε): 207 sh (4.43), 225 (4.53), 301 (3.91), and 480 nm (4.19). Found: C 54.5; H 3.9; N 18.1%. $C_{14}H_{10}N_4O_3 \cdot 1.5\ H_2O$. Calculated: C 54.4; H 4.2; N 18.1%.

The yields of products V, VI, X, XI, and XII are the yields based on aminoimidazolecarboxhydrazide I.

5(4)-Azidoimidazole-4(5)-carboxazide (VI). A solution of 45.6 mg (0.66 mmole) of $NaNO_2$ in 15 ml of water was added dropwise with stirring to a cooled (to −2°C) solution of 0.1 g (0.6 mmole) of azidoimidazolecarboxhydrazide VII in 1.56 ml (1.32 mmole) of 1 N HCl, and the mixture was maintained at this temperature for 30 min. The precipitate was removed by filtration, washed with water, and dried *in vacuo* over P_2O_5 to give 0.075 g (70%) of a product with mp 141°C (decomposed explosively), R_f 0.89, R'_f 0.85, and R''_f 0.9. IR spectrum: 1660 (C=O) and 2140 cm^{-1} (N_3). UV spectrum (in alcohol), λ_{max}(log ε): 207 (3.79, 225 sh (3.75), and 298 nm (3.95). Found: C 28.0; H 1.4; N 63.2%. $C_4H_2N_8O$. Calculated C 27.0; H 1.1; N 63.0%.

Reaction of 3-N-Aminoimidazo[4,5-d]-1,2,3-triazin-4-one (IX) with Nitrous Acid. A suspension of 129 mg (0.847 mmole) of IX in 1.1 ml (1.08 mmole) of 1 N HCl was added gradually with vigorous stirring at –4°C to a solution of 76 mg (1.1 mmole) of $NaNO_2$ in 0.76 ml of water, and the mixture was maintained at this temperature for 10 min. The precipitate was removed by filtration, washed with water, and dried in vacuo over P_2O_5. Product X was identical to imidazo[4,5-d]-1,2,3-triazin-4-one [8] with respect to its melting point and IR and UV spectra. The yield was 0.1 g (86%).

Reaction of 5-Diazoimidazole-4-carboxazide (V) with Amines. A 4.5-9 mmole sample of the amine was added with stirring at 0°C to a solution of 0.15 g (0.9 mmole) of V in 150 ml of absolute ether, and the mixture was allowed to stand for 1 h. It was then filtered, and the filtrate was evaporated to dryness *in vacuo*. Compounds XIV-XVII were crystallized from benzene, while VII was crystallized from absolute methanol. The yields, decomposition temperatures, results of elementary analysis, and the data from the UV spectra of the compounds obtained are presented in Table 1.

5(4)-N-Piperidylazoimidazole-4(5)-carboxazide (XVIII). A 1.31-mmole sample of aqueous piperidine was added with stirring at 0°C to a solution of 0.15 g (0.9 mmole) of V in 150 ml of ether, and the mixture was filtered. The filtrate was evaporated to dryness *in vacuo* to give 0.07 g (46%) of a product with mp 145°C (dec.) and R''_f 0.69. IR spectrum: 1660 (C=O) and 2130 cm^{-1} (N_3). Found: C 43.6; H 5.0; N 45.9%. $C_8H_{12}N_8O$. Calculated: C 43.6; H 4.8; N 45.2%.

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