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

13.* SYNTHESIS OF 5(or 4)-HYDRAZINOIMIDAZOLES AND THEIR DERIVATIVES

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A method for the synthesis of derivatives of 5(or 4)-hydrazinoimidazole-4(or 5)carboxylic acid by reducing the corresponding diazoimidazoles with stannous chloride has been developed, and a number of hydrazones and semicarbazides have been synthesized. It has been shown that under the reduction conditions selected imidazo[4,5-d]-1,2,3-triazinone does not have cryptodiazonium properties.

The derivatives of 5(or 4)-hydrazinoimidazole-4-(or 5)-carboxamide are of interest for biological tests as antagonists of one of the most important purine precursors, viz., 5(or 4)-aminoimidazole-4(or 5)-carboxamide (AICA) [2]. The known method for obtaining 5(or 4)-hydra-zinoimidazoles by replacing a halogen atom by a hydrazino group is not applicable for the synthesis of imidazoles without a substituent in the first ring position [3, 4].

In order to obtain 5(or 4)-hydrazinoimidazoles, we synthesized a number of derivatives of 5-diazoimidazole-4-carboxamide (I-VIII) and imidazo[4,5-d]-1,2,3-triazin-4-one (IX-XII) and studied the reduction of these compounds by stannous chloride.

The synthesis of 5-diazoimidazole-4-carboxamide (I), ethyl 5-diazoimidazole-4-carboxylate (III), and 5-diazoimidazole-4-hydroxamic acid (II) was carried out according to [5-7]. Ethyl 2-mercapto-5-diazoimidazole-4-carboxylate (IV), ethyl 2-methylmercapto-5-diazoimidazole-4-carboxylate (V), 2-phenyl-5-diazoimidazole-4-carboxamide (VI), 5-diazoimidazole-4-Nbenzylcarboxamide (VII), and 5-diazoimidazole-4-N-phenylcarboxamide (VIII) were obtained by diazotization of the corresponding aminoimidazoles. Their structures were confirmed by the IR-spectroscopic data. The IR spectra of compounds I-VIII contain absorption bands of the stretching vibrations of the diazo group at 2160-2180 cm⁻¹. The original 5(or 4)-aminoimidazole-4(or 5)-N-benzycarboxamide (XIII) and 5(or 4)-aminoimidazole-4(or 5)-N-phenylcarboxamide (XIV) were obtained by catalytic hydrogenation of the nitroimidazolecarboxamides. 2-Phenyl-5(or 4)-aminoimidazole-4(or 5)-carboxamide (XV) was synthesized according to [8]. Imidazo-[4,5-d]-1,2,3-triazines IX and X were obtained after [5, 6]. Diazoimidazoles VII and VIII are converted at pH 0-10, like diazo compound I, into imidazotriazinones XI and XII.

Unlike the 3,4-condensed 1,2,3-benzotriazines, whose reduction by stannous chloride in 5-10 N hydrochloric acid at room temperature results in the detection of the formation of hydrazines [9, 10], imidazo[4,5-d]-1,2,3-triazin-4-one (IX) is stable under similar conditions and is recovered from the reaction mass in an unaltered form. Compound I exists in 0.1 N hydrochloric acid in the form of a zwitterion, and in 5-11 N acid it exists in the form of a diazonium chloride [11]. In order to study the reactivity of the various forms of diazo compound I, we reduced it with stannous chloride in concentrated, 1 N, and 0.1 N hydrochloric acid. It was shown that regardless of the concentration of the acid, and, therefore, the structure of the diazo compound, 5 (or 4)-hydrazinoimidazole-4 (or 5) carboxamide (XVI) forms with a 40-50% yield in all cases.

The highest yield of hydrazinoimidazoles XXI-XXIII (30-50%) is achieved in the case of the reduction of diazo compounds VI-VIII by 2-3 mole of stannous chloride in concentrated hydrochloride acid at 0-10°C [4]. The conditions found were unacceptable for the reduction of diazoimidazole II, which is converted under all the conditions studied into 3-N-hydroxy-imidazo[4,5-d]-1,2,3-triazin-4-one (X). In the case of the reduction of 5-diazoimidazoles *For Report 12, see [1].

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I R¹=H; X=CONH₂; II R¹=H; X=CONHOH; III R¹=H; X=COOC₂H₅; IV R¹=SH; X=COOC₂H₅; V R¹=SCH₈; X=COOC₂H₅; VI R¹=Ph; X=CONH₂; VII R¹=H; X=CONHCH₂Ph; VII R¹=H; X=CONHPh; IX R¹=H; R²=CH; X R¹=H; R²=OH; XI R=Ph; R²=CH₂Ph; XII R¹=H; X=COOC₂H₅; XVI R¹=H; X=CONH₂; XVII R¹=H; X=CONHOH; XVIII R¹=H; X=COOC₂H₅; XX R¹=SCH₃; X=COOC₂H₅; XXI R¹=Ph; X=CONH₂; XXI R¹=H; X=CONHCH₂Ph; XXII R¹=SCH₃; X=CONHCH₂Ph; XXII R¹=H; X=CONHCH₂Ph; XXII R¹=SCH₃; X=CONHCH₂Ph; XXII R¹=H; X=CONHCH₂Ph; XXII R¹=SCH₃; X=CONHCH₂Ph; X=CONHCH₂Ph; XXII R¹=SCH₃; X=CONHCH

III-V, which have an esteric grouping in position 4 of the imidazole ring, it was discovered that the greatest yield is achieved when the reaction is carried out at room temperature in the concentrated acid. The application of dilute hydrochloric acid produces a complex mixture of several compounds. This mixture could not be separated into components due to their close chromatographic mobilities. It is noteworthy that 2-phenyl-5(or 4)-hydrazinoimidazole-4(or 5)-carboxamide (XXI) is readily oxidized in air; therefore, compound XXI was identified in the form of the p-nitrophenylhydrazone XXIV.

The method developed for obtaining 5(or 4)-hydrazinoimidazoles was employed to obtain analogs of AICA with hydrazone and semicarbazide groups. For this purpose we synthesized 4(or 5)-benzylcarbamoyl-(XXV) and 4(or 5)-N-phenylcarbamoyl-5(or 4)-(p-nitrobenzylidene)hydrazinoimidazole (XXVI) from hydrazines XXII and XXIII and p-nitrobenzaldehyde. Semicarbazides XXVII-XXIX were obtained from hydrazines XVI, XVIII, and XX by reacting them with potassium cyanate in hydrochloric acid. The IR spectra of these compounds show two bands of the stretching vibrations of the carbonyl group at 1640-1660 and 1680-1685 cm⁻¹, which attest to the addition of carbamoyl at the β -nitrogen atom of the hydrazino group, rather than at the N₁ and N₃ atoms in the imidazole ring [12].

EXPERIMENTAL

The individuality of the compounds was monitored with the aid of TLC on Silufol UV-254 plates in the following systems: 4:1:1 butanol-acetic acid-water, R_f (A); 9:1 chloroformethanol, R_f (B). The IR spectra were recorded on a UR-20 instrument in KBr tablets, and the UV spectra were recorded on a Beckman UV-26 spectrophotometer. The properties of the compounds synthesized are given in Table 1.

5(or 4)-Hydrazinoimidazole-4(or 5)-carboxamide Hydrochloride (XVI). A. A solution of 4.9 g (22 mmole) of SnCl \cdot 2H₂O in 43 ml (44 mmole) of l N HCl at -3° C is given a gradual addition of 1 g (7.3 mmole) of diazoimidazolecarboxamide I, the mixture is stirred for 30 min and diluted with water to 300 ml, and the tin ions are precipitated by hydrogen sulfide. The precipitate of tin sulfides is filtered out, the filtrate is evaporated to 5-10 ml, and the residue is filtered out and washed with ethanol and ether. The yield is 0.5 g (40%) (from water).

B. The reduction of l g (7.3 mmole) of compound I and 4.9 g (22 mmole) of $SnCl_2 \cdot 2H_2O$ in 440 ml (44 mmole) of 0.1 N HCl is carried out in analogy to method A. The yield is 0.65 g (51%).

C. The reduction of 1 g (7.3 mmole) of compound I and 4.9 g (22 mmole) of $SnCl_2 \cdot 2H_2O$ in 20 ml of 5 N and 11 N HCl is carried out in a similar manner. The yield is 0.67 g (52%).

<u>Hydrazinoimidazoles XVIII-XXIII</u> are obtained according to method C from the corresponding diazo compounds.

5(or 4)-Aminoimidazoles XIII and XIV. Raney Ni is added to a solution of 20 mmole of nitroimidazolecarboxamide in 250 ml of ethanol, and 20 ml of hydrazine hydrate are added over the course of 2 h at 70°C. The mixture is held for 2-3 h, the catalyst is filtered out, the

Com- pound	mp, deg C	Found, %			Empirical	Calculated, %			UV spectrum, nm		R _f		Yield,
		С	н	N	Iormula	с	н	N	λ _{max}	lg e	A	В	%
VII VIII XI XII ^a XIII XIV	$192 \\ 240 \\ 203 - 205 \\ 208 \\ 125 - 127 \\ 180$	57,9 56,1 58,6 57,0 60,9 58,9	3,9 3,5 4,1 3,1 5,7 5,2	30,9 32,5 30,7 32,5 25,7 28,1	C ₁₁ H ₉ N ₅ O C ₁₀ H ₇ N ₅ O C ₁₁ H ₉ N ₆ O C ₁₀ H ₇ N ₆ O C ₁₁ H ₁₂ N ₄ O C ₁₀ H ₁₀ N ₄ O	58,1 56,3 58,1 56,3 61,0 59,4	4,1 3,3 4,1 3,3 5,6 4,9	30,8 32,8 30,8 32,8 25,9 27,9	 224; 295 241; 267 247; 285	3,94; 4,40 4,10; 4,19 3,98; 4,23	0,60 0,65 0,60 0,65 —	0,70 0,70 0,65 0,77 0,80 0,60	86 85 90 95 65 68
XVI ^d XVIII	187—188 190—191	26,8 29,5	4,7 5,2	39,4 23,0	$C_4H_7N_5O \times HCl$ $C_6H_{10}N_4O_2 \times HCl$	27,0 29,6	4,5 4,9	39,4 23,0	$\frac{268}{266}$	4,00 4,01	0,37 0,70	0,60 0,46	$\frac{52}{46}$
XIX	149—150	30,0	4,4	23,6	$C_6H_{10}N_4O_2S \times 2HCl$	30,2	4,2	23,5	294	4,12	0,40	0,68	50
XX	171-172	33,4	4,7	22,5	$C_7H_{12}N_4O_2S \times 2HCl$	33,3	4,8	22,2	281	4,36	0,40	0,30	50
XXII	139-140	49,6	4,5	26,5	$C_{11}H_{13}N_5O \times HCl$	49,1	4,9	26,2	274	4,45	0,19		34
XXIII	186-187	40,4	4,1	26,9	$C_{10}H_{11}N_5OX$ XHCl	47,3	4,3	27,6	271	4,41	0,16	0,42	41 80
XXV XXVI XXVII XXVIII XXVIII	$\begin{array}{c} 100-187\\ 170-171\\ 193\\ 215-216\\ 190-191\end{array}$	59,3 58,1 32,4 36,4	3,8 4,6 4,0 4,8 5,4	23,9 22,8 23,8 45,4 30,6	$C_{17}T_{14}N_6O_3$ $C_{18}H_{16}N_6O_3$ $C_{17}H_{14}N_6O_3$ $C_5H_8N_6O_2$ $C_7H_{11}N_5O_3 \times$	59,5 58,3 32,6 36,9	4,0 4,7 4,0 4,4 5,6	23,0 22,2 45,7 30,5	 227; 265 223; 267	3,68; 4,10 3,55; 4,14	$0,07 \\ 0,48 \\ 0,44 \\ 0,26 \\ 0,30$	$0,20 \\ 0,24 \\ 0,20 \\ 0,20$	90 91 67 47
XXIX	210	36,9	5,0	27,0	$C_8H_{13}N_5O_3S$	36,9	5,2	27,5	215; 240 285	4,07; 3,96 4,32	0,45	0,20	62

TABLE 1. Characteristics of the Compounds Synthesized

^aThe yield of compound XII according to method A is given. ^bThe yield of compound XVI according to method B is given.

filtrate is evaporated in a vacuum, and the residue is crystallized from water with charcoal.

<u>5-Diazoimidazole-4-N-benzylcarboxanilide (VII)</u>. A suspension of l g (4.6 mmole) of compound VI in 50 ml of l N HCl is added in portions to a solution of 1.7 g (24.6 mmole) of sodium nitrite in 20 ml of water at -3° C with intense stirring. The mixture is held for 10 min, filtered, washed with water and ethanol, and dried in a vacuum. The yield is 0.9 g (86%). IR spectrum: 2195 cm⁻¹ (N₂).

<u>5(or 4)-(p-Nitrobenzylidene)hydrazinoimidazoles XXIV-XXVI.</u> A solution of 20 mmole of hydrazinoimidazoles XXI-XXIII in 100 ml of ethanol is given an addition of 20 mmole of p-nitrobenzaldehyde, boiled for 15 min, cooled, and filtered, and the product is crystallized from ethanol.

<u>5(or 4)-Semicarbazidoimidazoles XXVII-XXIX.</u> A solution of 2.8 mmole of hydrazinoimidazoles XXI-XXIII in 20 ml of water is given an addition of 5.7 mmole of potassium cyanate with stirring. The mixture is held for 5 h at room temperature, a pH of 5-6 being maintained by adding HCl. The mixture is cooled, and the precipitate is filtered out. The product is crystallized from ethanol. IR spectrum (vC=0): XXVII - 1660, 1680; XXVIII - 1640, 1685; XXIX - 1650, 1690 cm⁻¹.

<u>3-Phenylimidazo[4,5-d]-1,2,3-triazin-4-one (XII).</u> A. A solution of 8 ml of 2% ammonia is given an addition of 2 g (9.5 mmole) of compound VIII with stirring at 10-15°C. The mixture is held for 1 h and given an addition of 0.1 g of charcoal. The charcoal is filtered out, and the filtrate is acidified with HCl to pH 5-6, cooled, and filtered. The yield is 1.9 g (95%) (from water).

B. A 1-g portion (4.75 mmole) of diazo compound VIII is suspended in 100 ml of water or 0.1 N to 1 N HCl, and the suspension is left for 24 h at room temperature with stirring and filtered. The yield is 0.6 g (60%).

<u>3-Benzylimidazo[4,5-d]-1,2,3-triazin-4-one (XI).</u> This compound is obtained in analogy to XII according to method A.

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TETRAZOLES.

15.* ELECTRICAL CONDUCTIVITY OF 5-PHENYLTETRAZOLE AND ITS SALTS IN WATER

AND ORGANIC SOLVENTS

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The electrical conductivity of 5-phenyltetrazole and its potassium, cesium, and ammonium salts in water, acetone, acetonitrile, nitromethane, and dimethyl sulfoxide has been studied. 5-Phenyltetrazole and its ammonium salt exists in an associated state in organic solvents. The potassium and cesium salts of 5-phenyl-tetrazole are practically completely dissociated in water, acetonitrile, nitromethane, and dimethyl sulfoxide when the concentration is less than 10^{-3} M.

One of the widely used methods for obtaining 1,5- and 2,5-disubstituted tetrazoles is the alkylation of salts of 5-substituted tetrazoles $(T^{-}M^{+})$ [1]. On the basis of a study of the kinetics of this reaction it has been shown that the alkylation takes place according to a two-step mechanism [2, 3]:



However, the absence of quantitative information on the state of the salts of the 5substituted tetrazoles in the solvents used for alkylation prevents the further development of investigations in this area. For this reason we studied the electrical conductivity of 5-phenyltetrazole and its potassium, cesium, and ammonium salts in water, acetone, acetonitrile, nitromethane, and dimethyl sulfoxide. The experimental data from the conductometric measurements were treated according to the method in [4]. The values of the dissociation constants of 5-phenyltetrazole and its salts were calculated with the aid of the Bray-Kraus, Shedlovsky, and Ostwald equations. The thermodynamic values of the dissociation constants (K_d) were found according to the Debye-Hückel equation. The parameters obtained for the electrical conductivity are presented in Table 1.

The salts of the 5-substituted tetrazoles in organic solvents can be found in the form of various ionic species, viz., free ions, solvent-separated ion pairs, and contact ion pairs, as well as more complex agglomerates:

*For Report 14, see [3].

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