

CYCLIZATION OF 5-DIAZOIMIDAZOLE-4-THIOAMIDE  
SYNTHESIS OF 2-AZAPURINES\*

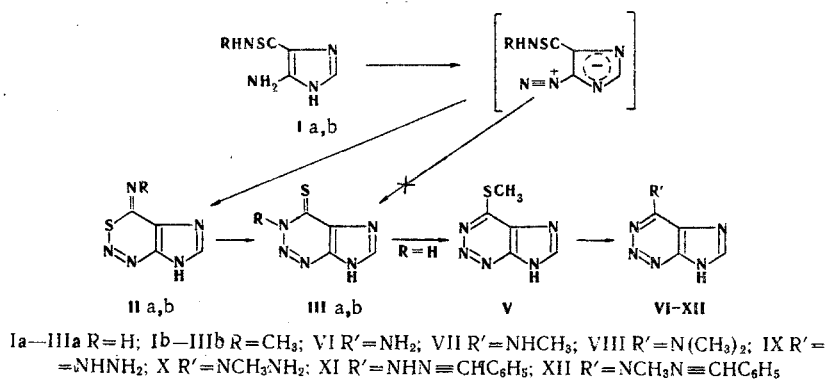
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Cyclization of 5-diazoimidazole-4-thioamide and -4-methylthioamide gives derivatives of a new heterocyclic system - imidazo[4,5-e]-2,3,4-thiadiazine - which are readily recycled to 2-azapurines. 4-Methylthioimidazo[4,5-d]-1,2,3-triazine was synthesized, and its reactions with amines and hydrazines were studied.

Of the imidazo[4,5-d]-1,2,3-triazine derivatives, which are of interest as 2-aza analogs of purines, only the 4-amino and 4-oxo derivatives have been described [2,3]. The present paper is devoted to the synthesis of 4-thio derivatives of imidazo[4,5-d]-1,2,3-triazine and to a study of their reaction with aliphatic amines and hydrazines.

As the starting compound for the synthesis of the azapurines we used 5(4)-aminoimidazole-4(5)-thioamide (Ia) obtained by thionation of 5(4)-aminoimidazole-4(5)-carboxamide with  $P_4S_{10}$  in dioxane, which enabled us to raise the yield considerably as compared with known methods [4,5]. Reaction of Ia with nitrous acid gave a crystalline substance (IIa), which in alkaline solutions is irreversibly converted to IIIa, which has the same elementary composition as IIa but differs from it with respect to its IR, UV, and PMR spectra (Table 1). The absence in the IR spectra of IIa and IIIa of an absorption band in the region of stretching vibrations of the diazo group and the absence in the PMR spectra of signals of protons of amino and thioamide groups indicate that the two compounds are different products of intramolecular cyclization of 5-diazoimidazole-4-thioamide. In this case, the formation of only two heterocyclic systems - imidazotriazine and imidazothiadiazine - is possible. A comparison of the spectra of IIa, IIIa, and imidazo[4,5-d]-1,2,3-triazin-4-one (IV), synthesized by the method in [2], made it possible to establish that IIIa is imidazo[4,5-d]-1,2,3-triazin-4-thione.



The IR spectra of IIIa and IV contain bands of stretching vibrations of N = N and C = N groups (endocyclic) at 1610-1630  $\text{cm}^{-1}$  and of the NH group of the imidazotriazine ring at 3480-3490  $\text{cm}^{-1}$ . The imidazotriazine

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TABLE 1. Data from the IR, UV, and PMR Spectra of Imidazo[4, 5-e]-2,3,4-thiadiazine and Imidazo[4,5-d]-1,2,3-triazine Derivatives

Compound	UV spectrum in 0.1 N HCl		IR spectrum, $\text{cm}^{-1}$	PMR spectrum ( $\text{CF}_3\text{COOH}$ ), $\delta$ , ppm
	$\lambda_{\text{max}}$ , nm	$\lg \epsilon$		
IIa	220; 253; 280; 327	4.18; 4.12; 3.63; 3.58	1585, 1660, 3110	9.00 (6H)
IIb	226; 256; 283; 325	4.13; 4.06; 3.72; 3.47	1620, 1650, 3135	3.51 (NCH <sub>3</sub> ); 8.94 (6H)
IIIa	237; 315	3.87; 4.18	1610, 3120, 3480	9.40 (6H)
IIIb	240; 313	4.01; 4.22	1608, 3130	4.42 (NCH <sub>3</sub> ); 9.43 (6H)
IV	247; 273	3.58; 3.67	1630, 1695, 3160 3490	—

structure of IIIa was also proved by chemical reactions. The establishment of the structure of IIIa made it possible to conclude that IIa is imidazo[4,5-e]-2,3,4-thiadiazine-1-imine. This is confirmed by the fact that the IR spectrum of the latter contains bands of stretching vibrations of ring N = N and C = N groups and of an exocyclic C = N group at 1585 and 1660  $\text{cm}^{-1}$ .

Inasmuch as the intramolecular cyclization of the diazoimidazolethioamide proceeds unusually and the resulting unstable heterocycle (IIa) has not been previously described, we synthesized the closest analog of Ia - 5(4)-aminoimidazole-4(5)-[N-methyl]thioamide (Ib) - in order to investigate yet another example of the cyclization. Compound Ib was obtained by reaction of ethyl 5(4)-nitroimidazole-4(5)-carboxylate [6] with methylamine, reduction of the resulting 5(4)-nitroimidazole-4(5)-carboxylate [6] with methylamine, reduction of the resulting 5(4)-nitroimidazole-4(5)-(N-methyl)carboxamide with stannous chloride, and subsequent thioanation of 5(4)-aminoimidazole-4(5)-(N-methyl)carboxamide with  $\text{P}_4\text{S}_{10}$  in dioxane. Under conditions similar to those in the synthesis of thiadiazine IIa, thioamide Ib gave 1-methyliminoimidazo[4, 5-e]-2,3,4-thiadiazine (IIb), the UV spectra of which practically coincides with the spectrum of IIa. The IR spectrum of thiadiazine IIb contains bands of N = N and C = N groups at 1620 and 1650  $\text{cm}^{-1}$ . In alkaline solution, IIb is converted to 3-methylimidazo[4,5-d]-1,2,3-triazine-4-thione (IIIb), the UV spectrum of which is similar to the spectrum of imidazotriazine IIIa, whereas its IR spectrum contains a band of stretching vibrations of the N = N group at 1608  $\text{cm}^{-1}$  but does not contain a band at 3480-3490  $\text{cm}^{-1}$  corresponding to vibrations of the NH group in the triazine ring of IIIa and IV.

In order to study some chemical properties of the new heterocyclic imidazothiadiazine system we made a comparative investigation of the reactivities of IIa and IIIa. The formation of a dye is not observed when thiadiazine IIa is heated in trifluoroacetic acid with 2-naphthol, and the final product is imidazotriazine IIIa. The triazine ring of IIIa is not opened under the conditions of the Sandmeyer reaction, while IIa reacts with  $\text{Cu}_2\text{Cl}_2$  in HCl to give 5(4)-chloroimidazole-4(5)-thioamide. The results of these reactions show that thiadiazine IIa has cryptodiazonium properties. This is apparently responsible for the fact that IIa, b are irreversibly cyclized to triazines IIIa, b in both acidic and alkaline media.

In order to obtain new 2-azapurine derivatives, we attempted to replace the thione group in IIIa by alkylamino and hydrazino groups. However, in contrast to benzo-1,2,3-triazine-[7], IIIa does not undergo nucleophilic substitution reactions even under severe conditions. 4-Methylthioimidazo[4,5-d]-1, 2,3-triazine (V), obtained by methylation of IIIa with methyl iodide in a methanol solution of sodium methoxide, is a more reactive compound. Methyl mercaptan is evolved in the reaction of V with ammonium hydroxide, and the known [2, 8] 4-aminoimidazo[4,5-d]-1,2,3-triazine (VI) is formed. New 2-azapurine derivatives - 4-methylamino- (VII), 4-dimethylamino- (VIII), 4-hydrazino- (IX), and 4-(1-methyl)hydrazinoimidazo[4,5-d]-1,2,3-triazine (X) - were synthesized by reaction of V with the appropriate amines and hydrazines. Hydrazines IX and X react with benzaldehyde to give easily crystallized benzylidene derivatives XI and XII.

#### EXPERIMENTAL METHOD

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The UV spectra were recorded with a Perkin-Elmer 402 spectrophotometer. The PMR spectra were recorded with a Jeol JNMR-MH-100 spectrometer at 100 MHz with tetramethylsilane as the internal standard. Chromatography was carried out on Silufol plates in the following systems: the  $R_f$  values were determined with butanol-acetic acid-water (4:1:1), and the  $R'_f$  values were determined with propanol-0.2 M  $\text{NH}_4\text{OH}$  (3:1).

TABLE 2. Imidazo[4,5-d]-1,2,3-triazines

Com- pound	mp, °C	R <sub>f</sub>	R' <sub>f</sub>	Empiric- al for- mula	Found, %			Calc., %			UV spectrum in water		Yield, %
					C	H	N	C	H	N	$\lambda_{max}$ , nm	$\epsilon$	
V	230	0,68	0,67	C <sub>5</sub> H <sub>5</sub> N <sub>5</sub> S	35,9	3,0	41,8	35,9	3,0	41,8	234; 290	4,11; 3,92	71,0
VI	>350*	0,51	0,59	C <sub>4</sub> H <sub>4</sub> N <sub>6</sub>	35,1	3,1	61,0	35,3	2,9	61,7	214; 258 279—290†	4,22; 3,87; 3,69	63,0
VII	255	0,56	0,52	C <sub>5</sub> H <sub>6</sub> N <sub>6</sub>	40,3	4,1	55,9	40,0	4,0	56,0	218; 264; 303	4,13; 3,96; 3,75	93,0
VIII	225	0,29	0,59	C <sub>6</sub> H <sub>8</sub> N <sub>6</sub>	44,3	5,1	51,6	43,9	4,9	51,2	214; 269; 316	4,15; 4,10; 3,84	81,5
IX	198— —200	0,18	0,53	C <sub>4</sub> H <sub>5</sub> N <sub>7</sub> · H <sub>2</sub> O	28,7	4,0	57,9	28,4	4,2	58,0	218; 268	4,19; 3,91	59,8
X	228— —230	0,47	0,40	C <sub>5</sub> H <sub>7</sub> N <sub>7</sub>	36,5	4,1	59,2	36,3	4,3	59,4	218; 275	4,12; 3,98	81,0
XI	240	0,57	0,50	C <sub>11</sub> H <sub>9</sub> N <sub>7</sub>	55,6	4,0	40,7	55,2	3,8	41,0	224; 249; 329	4,30; 4,08; 4,41	96,0
XII	254— —255	0,58	0,80	C <sub>12</sub> H <sub>11</sub> N <sub>7</sub>	56,6	4,4	38,6	56,9	4,3	38,7	225; 251	4,26; 4,20; 4,40	91,0

\*The melting point and UV spectrum were in agreement with the data in [8].

† Shoulder.

**5(4)-Nitroimidazole 4(5)-(N-Methyl)carboxamide.** A solution of 3 g (16.2 mmole) of ethyl 5(4)-nitroimidazole-4(5)-carboxylate [6] in 25 ml of 22% aqueous methylamine was held at room temperature for 72 h, after which it was vacuum-evaporated to dryness. The residue was dissolved in 15 ml of water, and the solution was acidified to pH 3 with concentrated HCl. The resulting precipitate was removed by filtration and crystallized from water to give 2.4 g (85%) of a product with mp 273°, R<sub>f</sub> 0.53, and R'<sub>f</sub> 0.46. Found: C 35.4; H 3.8%. C<sub>5</sub>H<sub>6</sub>N<sub>4</sub>O<sub>3</sub>. Calculated: C 35.3; H 3.5%.

**5(4)-Aminoimidazole-4(5)-(N-methyl)carboxamide Hydrochloride.** An 8-g (48 mmole) sample of 5(4)-nitroimidazole-4(5)-(N-methyl)carboxamide was added with stirring at 5° to a solution of 32 g (142 mmole) of stannous chloride in 60 ml of concentrated HCl, after which the mixture was held at 10° for 2 h and at 0–5° for 12 h. The resulting precipitate was removed by filtration and dissolved in 150 ml of water, and hydrogen sulfide was passed through the solution until the tin had been completely precipitated. The precipitated tin sulfide was removed by filtration, the filtrate was vacuum evaporated to dryness, and the residue was crystallized from ethanol to give 5 g (60.5%) of a product with mp 252–253° and R<sub>f</sub> 0.16. Found: Cl 19.9; N 31.6%. C<sub>5</sub>H<sub>8</sub>N<sub>4</sub>O·HCl. Calculated: Cl 20.1; N 31.8%.

**5(4)-Aminoimidazole-4(5)-thioamide Hydrochloride (Ia).** A 72-g (325 mmole) sample of P<sub>4</sub>S<sub>10</sub> was added with stirring at 70° to a suspension of 40 g (246 mmole) of 5(4)-aminoimidazole-4(5)-carboxamide hydrochloride [9] in 400 ml of dioxane, after which the mixture was refluxed with constant stirring for 4 h. It was then cooled, and the resulting precipitate was removed by filtration and dissolved in 1 liter of boiling 1 N HCl. The solution was decolorized with charcoal and vacuum evaporated to 40 ml. The concentrated solution was cooled, and the resulting precipitate was removed by filtration and washed with ethanol and ether to give 25 g (57%) of a product with mp 260° (from water) (mp 260° [4]).

**5(4)-Aminoimidazole-4(5)-(N-methyl)thioamide Hydrochloride (Ib).** This compound, with mp 244–246° (from water) and R<sub>f</sub> 0.38, was similarly obtained in 43% yield. Found: C 29.9; H 4.4; Cl 18.7%. C<sub>5</sub>H<sub>8</sub>N<sub>4</sub>S·HCl. Calculated: C 30.2; H 4.7; Cl 18.4%.

**Imidazo[4,5-e]-2,3,4-thiadiazine-1-imine (IIa).** A suspension of 2 g (14.1 mmole) of base Ia and 1.18 g (17.6 mmole) of sodium nitrite in 20 ml of water was added gradually with stirring at –1° to 25 ml of 3 N HCl, after which the mixture was stirred for 15 min and filtered. The filtrate was made alkaline to pH 4–5 with saturated sodium acetate solution, and the resulting precipitate was removed by filtration and reprecipitated from 0.1 N HCl by the addition of sodium acetate to give 1.48 g (69.5%) of a product with mp 183° (dec. explosively). Found: C 31.6; H 2.1; N 45.4; S 20.6%. C<sub>4</sub>H<sub>3</sub>N<sub>5</sub>S. Calculated: C 31.3; H 2.0; N 45.7; S 20.9%.

**1-Methyliminoimidazo[4,5-e]-2,3,4-thiadiazine (IIb).** This compounds, with mp 258° (dec. explosively) and R<sub>f</sub> 0.39, was obtained by the method used to prepare IIa. Found: C 35.9; H 3.0; N 41.9; S 19.4%. C<sub>5</sub>H<sub>5</sub>N<sub>5</sub>S. Calculated: C 35.9; H 3.0; N 41.9; S 19.1%.

**Imidazo[4,5-d]-1,2,3-triazine-4-thione (IIIa).** A solution of 1 g (6.54 mmole) of thiadiazine IIa in 20 ml of 5% NH<sub>4</sub>OH was vacuum-evaporated to dryness, and the residue was crystallized from water to give

0.85 g (76%) of a product with mp 190° (dec. explosively) and  $R_f$  0.78. Found: C 28.3; H 2.9; N 41.1; S 18.7%  $C_4H_3N_5S \cdot H_2O$ . Calculated: C 28.1; H 2.9; N 40.9; S 18.7%.

3-Methylimidazo[4,5-d]-1,2,3-triazine-4-thione (IIIb). This compound, with mp 239° (from water) and  $R_f$  0.79, was obtained in 85% yield from thiazine IIb as described above. Found: C 36.3; H 3.3; N 41.9; S 19.2%.  $C_6H_5N_5S$ . Calculated: C 36.9; H 3.1; N 41.9; S 19.2%.

4-Methylthioimidazo[4,5-d]-1,2,3-triazine (V). A 4-g (25.8 mmole) sample of triazine IIIa and 3.8 g (26.8 mmole) of methyl iodide were added at 10° to a solution of sodium methoxide, obtained by dissolving 0.6 g (25.8 mmole) of sodium in 150 ml of methanol at 10°, after which the mixture was held at 10–18° for 18 h. It was then vacuum-evaporated to dryness, and the residue was dissolved in 25 ml of water. The solution was acidified to pH 3 with concentrated HCl and cooled, and the resulting precipitate was removed by filtration and crystallized from water. PMR spectrum (in  $CD_3OD$ ),  $\delta$ , ppm: 2.94 ( $SCH_3$ ) and 8.80 (6H).

4-Aminoimidazo[4,5-d]-1,2,3-triazines (VI-VIII, Table 2). A solution of 3.59 mmole of V in 30 ml of 22% ammonium hydroxide, aqueous methylamine, or 33% aqueous dimethylamine, respectively, was heated in a sealed tube at 140° for 14 h, after which it was vacuum-evaporated to dryness, and the residual VII and VIII were crystallized from water; VI was reprecipitated from sodium carbonate solution by the addition of hydrochloric acid.

4-Hydrazinoimidazo[4,5-d]-1,2,3-triazines (IX and X, Table 2). A solution of 3 mmole of V in 5 ml of hydrazine hydrate or methylhydrazine was heated at 100° for 15 h, after which it was vacuum-evaporated to dryness, and the residue was crystallized from water.

4-Benzylidenehydrazino-(XI) and 4-Benzylidene(1-methyl)hydrazinoimidazo-[4,5-d]-1,2,3-triazine (XII). A 0.7-mmole sample of benzaldehyde was added to a solution of 0.6 mmole of the appropriate hydrazine (IX or X) in 25 ml of 50% aqueous ethanol, and the mixture was refluxed for 1 h. It was then vacuum-evaporated to dryness, and the residue was crystallized from water (XI) or from ethanol (XII).

5(4)-Chloroimidazole-4(5)-thioamide. A 1-g (6.54 mmole) sample of thiadiazine IIa was added gradually with stirring at 60° to a solution of 0.72 g (7.2 mmole) of  $Cu_2Cl_2$  in 20 ml of concentrated HCl, after which the mixture was held under these conditions for 2 h. It was then diluted to 200 ml with water, and hydrogen sulfide was passed through the mixture until copper had completely precipitated. The precipitate was removed by filtration and extracted with three 40-ml portions of boiling water. The combined filtrates were vacuum-evaporated to dryness, and the residue was dissolved in 80 ml of water. The solution was made alkaline to pH 5 with sodium carbonate, and the resulting precipitate was removed by filtration and crystallized from water to give 0.46 g (43%) of a product with mp 237°,  $R_f$  0.72, and  $R_f^1$  0.84. UV spectrum (in water),  $\lambda_{max}$ , nm (log  $\epsilon$ ), 200 (4.08), 280 (4.00), and 307 (4.16). Found: C 29.5; H 2.7; Cl 21.8; N 26.1%  $C_4H_4ClN_3$ . Calculated: C 29.7; H 2.5; Cl 22.0; N 26.0%.

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