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

V.* SOME TRANSFORMATIONS IN THE IMIDAZO[4,5-d]-1,2,3-TRIAZINE SERIES

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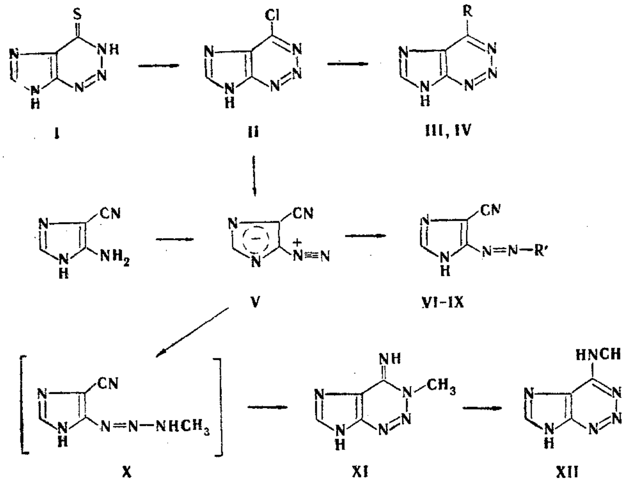
4-Chloroimidazo[4,5-d]-1,2,3-triazine was obtained by oxidative chlorination from imidazo[4,5-d]-1,2,3-triazine-4-thione, and its reaction with nucleophilic agents and cleavage of the triazine ring to give 5-diazoimidazole-4-carbonitrile were studied. The newly synthesized diazoimidazole was subjected to C- and N-diazo coupling. It was established that 3-methylimidazo[4,5-d]-1,2,3-triazine-4-imine, formed by reaction of the diazo compound with methylamine, is capable of recyclization to 4-methylaminoimidazo[4,5-d]-1,2,3-triazine.

The present paper is devoted to the synthesis of new compounds in the imidazo[4,5-d]-1,2,3-triazine series that are of interest as 2-aza analogs of purines.



III $R=N(CH_3)_2$; IV $R=NH-N(CH_3)_2$; VI $R'=p\text{-}N(CH_3)_2C_6H_4$; VII R'=2-hydroxynaphthyl; VIII $R'=N(CH_3)_2$; IX $R=(C_2H_5)_2$

Inasmuch as the triazine ring of condensed 1,2,3-triazine-4-ones is destroyed under the conditions of replacement of the hydroxyl group by a halogen atom [2], we attempted to synthesize 4-chloroimidazo[4,5-d]-1, 1,2,3-triazine (II) under milder conditions from the corresponding 4-thio derivative (I). We were able to obtain azapurine II by reaction of I with chlorine in 1 M hydrochloric acid at reduced temperature. Azapurine II readily undergoes nucleophilic substitution with dimethylamine and asymmetrical dimethylhydrazine to give, respectively, 4-dimethylamino- (III) and 4-(2,2-dimethylhydrazino)-imidazo[4,5-d]-1,2,3-triazine (IV). The introduction of a chlorine atom in the 4 position of the molecule leads to a considerable reduction in the sta-

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*See [1] for communication IV.

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TABLE 1. Characteristics of the Synthesized Compounds

Compound[a]	mp, °C	R'_f	R_f	Empirical formula	Found, %			Calculated, %			Electronic absorption spectra[b]		Yield, %
					C	H	N	C	H	N	λ_{max}, nm	lg ε	
II	105	0,51	—	$C_4H_2ClN_5 \cdot H_2O$[c]	27,0	2,4	39.8	26,7	2,3	40,4	209; 261	4,18; 3,70	41,0
III	225	0,28	0,59	$C_6H_8N_6$	44,2	5,1	51,5	43,9	4,1	51,2	214; 269; 316	4,15; 4,10; 3,84	70,3
IV	215	0,50	0,64	$C_6H_9N_7$	40,0	4,8	55,0	40,3	5,0	54,7	215; 269; 314	4,09; 4,02; 3,80	67,8
V	97—98	—	—	$C_4H_1N_5$	40,5	1,1	59,1	40,3	0,8	58,8	200; 268 (sh); 311	4,15; 3,65; 4,00	48,6
VI	230—231	0,87	—	$C_{12}H_{12}N_6$	60,5	4,9	34.5	60,0	5,0	35,0	275; 480	3,84; 4,55	69,6
VII	183—185	0,81	0,78	$C_{14}H_9N_5O$	63,3	3,6	26.8	63,9	3,4	26,5	279; 476	3,93; 4,24	73,1
VIII	189—190	0,70	0,86	$C_6H_8N_6$	44,4	4,9	50,5	44,0	4,9	51,1	224; 328	4,02; 4,11	92,5
IX	145—146	0,84	0,80	$C_8H_{12}N_6$	49,9	6,4	43.5	50,0	6,3	43,7	224; 333	4,01; 4,03	84,0
XI	240	0,17	0,47	$C_5H_6N_6$	40,4	4,2	55,7	40,0	4,0	56,0	227; 260; 302	4,33; 3,80; 3,62	95,3
XII	255	0,56	0,52	$C_5H_6N_6$	40,3	4,1	55.9	40,0	4,0	56,0	218; 264; 303	4,13; 3,96; 3,75	80,0

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[a] The physical constants of III and XII are in agreement with the data in [5].

[b] The spectra of aqueous solutions of II–V, XI, and XII and of ethanol solutions of VI–IX were recorded.

[c] Found: Cl 20.5%. Calculated: Cl 20.5%.

bility of the triazine ring. Because of this, II on gentle heating in water is converted to 5-diazoimidazole-4-carbonitrile (V), which was isolated in solid form as a zwitterion.

Like the spectrum of the 5-diazoimidazole-4-carboxamide zwitterion [3], the IR spectrum of diazoimidazole V contains intense absorption bands at 2190 and 1380 cm^{-1} corresponding to the vibrations of the diazo group. In addition, the characteristic band of stretching vibrations of a nitrile group appears at 2240 in the spectrum of V, along with a CH band at 3100 cm^{-1}, whereas imidazole NH absorption is absent. In order to identify the diazo compound we also accomplished its alternative synthesis from 5(4)-aminoimidazole-4(5)carbonitrile.

Diazoimidazole V undergoes C- and N-diazo coupling with dimethylaniline and 2-naphthol, as well as with aliphatic dimethylamine and diethylamine, to give the corresponding azo dyes VI, VII, and 5(4)-(3,3-dialkyl-1-triazeno)imidazole-4(5)-carbonitriles (VIII, IX). The nitrile group in the dyes absorbed at 2240 cm^{-1}, and the $C \equiv N$ absorption band in the triazenes is shifted slightly to the lower-frequency region (2225 cm^{-1}). Diazo compound V was subjected to reaction with methylamine to obtain 5(4)-(3-methyl-1-triazeno)imidazole-4(5)carbonitrile (X). However, this reaction gave a compound having an IR spectrum in which the $C \equiv N$ absorption band is absent, whereas there is a band of stretching vibrations of an exocyclic $C=N$ group at 1625 cm^{-1}. On the basis of the IR spectrum it can be concluded that triazene X is converted to 3-methylimidazo[4,5-d]-1,2,3-triazine-4-imine (XI) under the conditions of the diazo coupling reaction. It is known that o-benzonitriletriazenes of similar structure are cyclized to 3-substituted benzo-1,2,3-triazine-4-imines, which can be subjected to a reaction of the Dimroth rearrangement type to 4-alkyl(aryl)amino derivatives of benzotriazine [4]. Compound XI is also recyclized to 4-methylaminoimidazo[4,5-d]-1,2,3-triazine (XII) on heating in water; this product differs from the starting material with respect to its melting point, chromatographic mobilities in two systems, and IR and UV spectra but is identical to a sample of XII that we previously obtained by amination of 4-methylthioimidazo[4,5-d]-1,2,3-triazine [5].

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. Chromatography was carried out on Silufol UV-254 plates in the following systems: butanol–acetic acid–water (4 : 1 : 1) (R_f) and propanol-0.2 N NH_4OH (3 : 1) (R'_f). The physical constants, the yields, and the results of analysis of II-XII are presented in Table 1.

4-Chloroimidazo[4,5-d]-1,2,3-triazine (II). Chlorine was bubbled with stirring for 1 h through a cooled (to −4°) suspension of 1 g (5.95 mmole) of imidazo[4,5-d]-1,2,3-triazine-4-thione in 8 ml of 1 N HCl, and the resulting precipitate was removed by filtration, washed with water and alcohol, and dried over P_2O_5.

4-Dimethylaminoimidazo[4,5-d]-1,2,3-triazine (III). A 0.2-g (1.15 mmole) sample of II was added with stirring to 3 ml of a 33% aqueous solution of dimethylamine. The reaction mixture was vacuum evaporated to dryness, and the residue was crystallized from water.

4-(2,2-Dimethyl)hydrazinoimidazo[4,5-d]-1,2,3-triazine (IV). A 0.8-ml sample of 1,1-dimethylhydrazine was added to a suspension of 0.5 g (2.88 mmole) of II in 8 ml of methanol, and the mixture was refluxed for 30 min. It was then vacuum evaporated to dryness, and the residue was crystallized from water.

5-Diazoimidazole-4-carbonitrile (V). A) A 0.4-g (2.3 mmole) sample of II was heated to the boiling point, after which the mixture was cooled, and the diazoimidazole was extracted with chloroform (10 · 20-ml portions). The extract was dried with sodium sulfate and evaporated. The residue was suspended in 5 ml of ether, and the mixture was filtered. The light-yellow crystals were dried over P_2O_5 to give 0.1 g (30.5%) of product.

B) A solution of 1.2 g (17.4 mmole) of sodium nitrite in 5 ml of water was added dropwise with vigorous stirring at −2° to a solution of 1 g (6.92 mmole) of 5(4)-aminoimidazole-4(5)-carbonitrile [6] in 15 ml of 2 N HCl, after which the mixture was allowed to stand at this temperature for 30 min. The mixture was worked up as in the preparation of diazo compound V by method A to give 0.4 g (48%) of product. The compounds isolated by methods A and B were identical with respect to their melting points and UV and IR spectra.

5(4)-(4-Dimethylaminophenylazo)imidazole-4(5)-carbonitrile (VI). A 0.3-ml sample of dimethylaniline was added to a solution of 0.1 g (0.84 mmole) of diazo compound V in 10 ml of water, and the mixture was stirred for 30 min. The precipitated dye was removed by filtration and crystallized from 50% ethanol.

5(4)-(2-Hydroxy-1-naphthylazo)imidazole-4(5)-carbonitrile (VII). A solution of 0.13 g (0.90 mmole) of 2-naphthol in 11 ml of 0.01 N NaOH was added to a solution of 0.1 g (0.84 mmole) of diazoimidazole V in 10 ml of 0.01 N HCl, and the mixture was stirred for 30 min. It was then acidified to pH 4 with HCl, and the precipitated dye was removed by filtration and crystallized from 30% acetone.

5(4)-(3,3-Dialkyl-1-triazeno)imidazole-4(5)-carbonitriles (VIII, IX). A total of 20 ml of a 20% solution of dimethylamine or diethylamine in methanol was added dropwise in the dark at −2° to a solution of 0.4 g (3.36 mmole) of diazo compound V in 40 ml of chloroform. The mixture was vacuum evaporated to dryness, 8 ml of water was added to the residue, and the resulting crystals were removed by filtration, washed with ethanol and ether, and dried in the dark over P_2O_5.

3-Methylimidazo[4,5-d]-1,2,3-triazine-4-imine (XI). A total of 40 ml of a 20% solution of methylamine in methanol was added dropwise in the dark at −2° to a solution of 0.8g (6.72 mmole) of diazoimidazole V in 80 ml of chloroform, after which the mixture was allowed to stand for 30 min. The resulting precipitate was removed by filtration. Imine IX was reprecipitated from a solution of 0.1 N HCl by the addition of sodium acetate.

4-Methylaminoimidazo[4,5-d]-1,2,3-triazine (XII). A suspension of 0.3 g (2.0 mmole) of XI in 15 ml of water was refluxed for 30 min, after which it was cooled, and the precipitate was removed by filtration and crystallized from water.

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