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

12.* INVESTIGATION OF THE INTERACTION OF 4-CHLOROIMIDAZO[4,5-d]-1,2,3-TRIAZINE WITH NUCLEOPHILES

V. S. Mokrushin, T. A. Pospelova, and Yu. M. Shafran

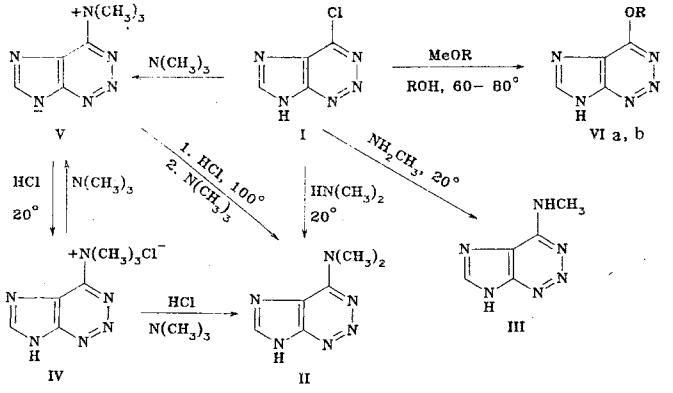
UDC 547.785.5'859.1.07:543.422

The reactions of 4-chloroimidazo[4,5-d]-1,2,3-triazine with a number of nucleophilic reagents have been studied. Either replacement of the chlorine atom in position 4 of the 1,2,3-triazine ring or opening of the triazine ring with the formation of products of the interaction of the intermediate 5-diazoimidazole-4-carbonitrile with these nucleophiles occurs, depending on the nucleophilicity of the reagent.

The higher mobility of the chlorine atom in 4-chloroimidazo[4,5-d]-1,2,3-triazine (I) in nucleophilic substitution reactions [2] in comparison to the methylmercapto group was previously demonstrated and is in good agreement with the data for condensed 4-chloro-1,2,3-triazines [3].

The purpose of the present work was to investigate the features of the reactivity of I with respect to nucleophiles, those used being methylamine, trimethylamine, sodium methoxide, sodium ethoxide, ammonia, hydrazine hydrate, hydroxylamine, the sulfide ion, and the cyanide ion.

Triazine I reacts with methylamine and dimethylamine to room temperature to form 2-azaadenines II and III. The reaction of compound I with trimethylamine is similar to the reaction with dimethylamine. In this case, either imidazo[4,5-d]-1,2,3-triazine-4-trimethylammonium chloride (IV) or zwitter ion V were obtained from the reaction mass, depending on the isolation conditions. The PMR spectrum of V shows a singlet signal of the fine equivalent protons in the three methyl groups at 3.89 ppm and a signal of the $C_{(5)}H$ proton at 8.78 ppm. When boiled in alcoholic trimethylamine or hydrochloric acid, triazines IV and V are converted into dimethylaminoimidazotriazine II, which is identical with respect to all its physicochemical properties to a sample known to have this structure [2].



a R=CH_3; b R=C_2H_5

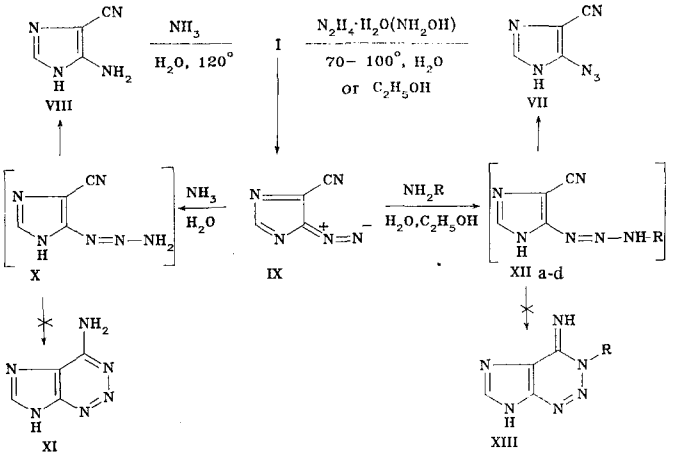
*For Report 11, see [1].

S. M. Kirov Ural Polytechnic Institute, Sverdlovsk 620002. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1548-1551, November, 1983. Original article submitted July 1, 1982; revision submitted May 19, 1983.

0009-3122/83/1911-1231$07.50

Unlike the reaction with alkylamines, chlorotriazine I does not react at room temperature with an equimolar quantity of sodium ethoxide or sodium methoxide. Furthermore, 4-methoxy- and 4-ethoxyimidazo[4,5-d]-1,2,3-triazines (VIa and b) form only as a result of prolonged boiling in ethanol with a fivefold excess of sodium alkoxide.

Compound I likewise does not react with hydrazine hydrate, hydroxylamine, and ammonia in water or ethanol at room temperature but at 70-100°C the reactions with hydrazine hydrate and hydroxylamine unexpectedly produced the same product 5(or 4)-azidoimidazole-4(or 5)-carbonitrile (VII), whose IR spectrum contains bands of the stretching vibrations of the azide and nitrile groups at 2130 and 2230 cm^{-1}, respectively. The heating of compounds I with ammonia to 120-130°C in an autoclave results in the formation of 5(or 4)-aminoinidazole-4-(or 5)-carbonitrile (VIII), which is identical with respect to all of its physicochemical properties to a sample known to have this structure [4]. It is noteworthy that even traces of 2-azaadenine (XI) could not be detected in the reaction mass with the aid of TLC. Therefore, in the reactions of chlorotriazine I with ammonia, hydrazine hydrate, and hydroxylamine, the only process is the elimination of the 1,2,3-triazine ring with the formation of diazoimidazolecarbonitrile IX, which is converted under the conditions of the experiment into triazene X or XII, and the latter, in turn, rapidly decompose to imidazoles VII and VIII. However, this conclusion cannot be considered sufficiently rigorous, since compounds X and XII can be converted with equal probability into imidazotriazines XI and XIII, in analogy to 5-(3-methyl-1-triazeno)imidazole-4-carbonitrile, which is cyclized to 3-methylimidazo[4,5-d]-1,2,3-triazin-4-imine [2]. In addition, tetrazene XIIb can be converted into aminoimidazole VIII with the release of HN_3. In order to confirm that the reaction proceeds with the intermediate formation of diazoimidazole IX, we studied its reaction with hydrazine hydrate, hydroxylamine, 1,1-dimethylhydrazine, and p-nitrophenylhydrazine. In all cases, only azimidimidazole VII was recovered. When diazo compound IX is treated with ammonia, aminoimidazole VIII is obtained. The absence of imidazotriazines as products of these reactions supports the conclusion that diazoimidazolecarbonitrile IX is found on the reaction coordinate. Triazine I splits to form diazoimidazole IX upon heating to 50-100°C in water or ethanol without a reagent. This is also evidence in support of the conclusion drawn.



XII a R=OH; b R=NH_2; c R=$N(CH_3)_2$; d R=$C_6H_4NO_2$

Thus, when reacted with nucleophilic reagents, compound I undergoes one of the following competitive reactions: either nucleophilic substitution or opening of the 1,2,3-triazine ring.

On the scale of "hard and soft acids and bases," the reagents which we used occupy a middle position. In order to ascertain the laws governing the reactions of triazine I with nucleophiles, we investigated the reaction of this compound with hydroxyl, sulfide, and cyanide ions, i.e., with some of the "hardest" and "softest" reagents, respectively.

At room temperature chlorotriazine I remains unchanged in 0.1 N NaOH over the course of 48 h, but extensive decomposition of the original substance is observed when the reaction mass is boiled. Compound I does not react with sodium sulfide in water at room temperature, and after boiling for 12 h, 80% of the original substance is recovered from the reaction mass. The boiling of an ethanolic solution of imidazotriazine I with sodium cyanide results in the production of a mixture of two or three azo compounds of undetermined structure and the original compound.

TABLE 1. Properties of the Compounds Synthesized

Compound	mp, Deg C	UV spectrum, nm		PMR spectrum, δ, ppm	R_f	R'_f	Found, %			Empirical formula	Calculated, %			Yield, %
		λ_{max}	lg ε				C	H	N		C	H	N	
III	255	218, 264, 303	4,13; 3,96; 3,75	—	0,50	—	39,8	4,1	—	$C_5H_6N_6$	40,0	4,0	56,0	65
IV	225	—	—	—	—	—	39,4	5,7	38,7	$C_7H_{12}N_6Cl$	39,2	5,2	39,1	41
V	193—194	220, 270	4,40; 3,54	8,78 (CH, s); 3,89 (CH_3, 9H, s)	—	—	47,6	5,7	46,7	$C_7H_{10}N_6$	47,2	5,7	47,2	48
VIa	177—178	203, 253	4,37; 3,78	8,93 (CH, s); 4,38 (CH_3, s)	0,32	0,6	39,5	3,4	46,0	$C_5H_5N_5O$	39,3	3,3	46,3	55
VIb	176—177	202, 243	4,37; 3,79	8,25 (CH, s); 3,34 (CH_2, q); 1,55 (CH_3, t, J=6,65Hz)	—	0,4	44,0	4,3	42,6	$C_6H_7N_5O$	43,6	4,3	42,4	64
VII	120	213, 258	3,97; 4,05	—	0,75	0,5	35,6	1,7	62,4	$C_4H_2N_6$	35,8	1,5	62,6	75 (a) 46 (b)

Therefore, the reaction of triazine I with sodium hydroxide, sodium sulfide, and sodium cyanide does not occur under the conditions for the replacement of the halogen in triazine I by an alkylamino group, and upon heating, in contrast to the reactions with the sodium alkoxides, the completing process of splitting of the triazine ring takes place. The varying behavior of triazine I with nucleophiles cannot be attributed to the fact that the anion of I reacts in some cases, while the neutral molecule of I reacts in others, since the value pK_a 6.90 ± 0.06 has been found spectrophotometrically for chloroimidazotriazine I.

An examination of the reasons for the varying behavior of triazine I with amines and hydrazine will be the subject of a special discussion.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 instrument in KBr tablets, the UV spectra were recorded on a Beckman UV-26 spectrophotometer, and the PMR spectra were recorded on a Perkin—Elmer 12B instrument (60 MHz). The chemical shifts are given on the δ scale relative to TMS as an internal reference. The chromatography was carried out on Silufol UV-254 plates in 4:1:1:1 n-butanol—acetic acid—water—ethyl acetate and 9:1 chloroform—ethanol systems. The pK_a was determined spectrophotometrically at 252 and 283 nm. The properties of the compounds synthesized are given in Table 1.

4-Methylaminoimidazo[4,5-d]-1,2,3-triazine (III). A 0.10-g portion (0.64 mmole) of compound I is dissolved in 10 ml of 33% aqueous methylamine. The mixture is stirred at room temperature for 1 h. The reaction mass is evaporated in a vacuum to dryness. The product is crystallized from water. According to the data from the UV spectrum, the melting point, and the chromatographic mobility, it is identical to compound III obtained according to [5].

Imidazo[4,5-d]-1,2,3-triazine-4-trimethylammonium Chloride (IV). A 40-ml portion of a 20% solution of trimethylamine in ethanol is given an addition with stirring of 1.00 g (6.43 mmole) of compound I. The reaction mass is stirred for 15 min, and 5 ml of concentrated hydrochloric acid are added. The mixture is evaporated in a vacuum, and the residue is crystallized from ethanol.

Imidazo[4,5-d]-1,2,3-triazine-4-trimethylammonium Hydroxide Inner Salt (V). A 30-ml portion of a 20% solution of trimethylamine in ethanol is given an addition of 0.50 g (2.33 mmole) of compound IV. The mixture is stirred for 24 h at room temperature, and the solvent is evaporated in a vacuum. The product is crystallized from ethanol.

Reaction of IV with Trimethylamine. A 30-ml portion of a 20% solution of trimethylamine in ethanol is given an addition of 0.40 g (2.24 mmole) of compound IV. The mixture is boiled for 2 h. The solvent is evaporated in a vacuum, and the product is crystallized from water. The product isolated is identical with respect to its melting point, chromatographic mobility, and UV spectrum to compound II obtained by a back synthesis [2]. The yield is 0.30 g (46%). PMR spectrum: 7.62 (CH, s); 3.15 (CH_3, s); 2.91 ppm (CH_3, s).

4-Alkoxyimidazo[4,5-d]-1,2,3-triazines (IVa, b). A 0.50-g portion (3.22 mmole) of I is added to a solution of 16.51 mmole of the sodium alkoxide in 50 ml of absolute ethanol. The

mixture is boiled for 30 min to 3 h. After cooling, dry hydrogen chloride is passed to pH 5-3. The suspension is treated with activated charcoal and filtered. The filtrate is adjusted to pH ∿ 7.25% with an NH_4OH solution, and the solvent is evaporated in a vacuum to dryness. The product is crystallized from water.

5(or 4)-Azidoimidazole-4-(or 5)-carbonitrile (VII). A. A 3-mmole portion of hydrazine hydrate or hydroxylamine is added to 0.16 g (0.92 mmole) of compound I in 5 ml of water of ethanol. The mixture is boiled for 30 min. The solvent is evaporated in a vacuum and extracted by ether. The ether is evaporated in a vacuum. IR spectrum: 2130 (N_3), 2230 cm^{-1} (C≡N).

B. A solution of 7 mmole of a compound with the formula NH_2R [R = OH, NH_2, $N(CH_3)_2$, p-NO_2—Ph] in 3 ml of ethanol at 0°C is given an addition of 0.25 g (2.1 mmole) of compound IX. The mixture is stirred for 1 h at room temperature. The solvent is evaporated in a vacuum to dryness. The residue is extracted with ether. The ether is evaporated in a vacuum.

5(or 4)-Aminoimidazole-4(or 5)-carbonitrile (VIII). A. A solution of 0.10 g (0.64 mmole) of compound I in 10 ml of NH_4OH is heated for 2 h at 120-130°C in an autoclave. The solvent is evaporated in a vacuum. The residue is extracted by ethanol. The latter is evaporated in a vacuum to dryness. The yield is 0.034 g (55%), and the mp is 120°C.

B. A mixture of 1 ml of 25% NH_4OH and 1 ml of ethanol at 0°C is given an addition with stirring of a solution of 0.30 g (2.5 mmole) of compound IX. The mixture is stirred at room temperature for 1 h and then filtered. The filtrate is evaporated, and the residue is extracted by 2 ml of ether. The ether is evaporated in a vacuum. The yield is 0.12 g (45%), and the mp is 120°C. The product isolated is identical with respect to its melting point, chromatographic mobility, and IR spectrum to compound VIII obtained by method A, as well as by a back synthesis [4].

LITERATURE CITED

1. V. A. Bakulev, V. S. Mokrushin, A. N. Grishakov, and Z. V. Pushkareva, Khim. Geterotsikl. Soedin., No. 7, 957 (1982).
2. V. S. Mokrushin, V. I. Ofitserov, T. V. Rapakova, A. G. Tsaur, and Z. V. Pushkareva, Khim. Geterotsikl. Soedin., No. 4, 556 (1976).
3. B. M. Adger, S. Bradbury, M. Keating, C. W. Rees, R. C. Storr, and M. T. Williams, J. Chem. Soc., Perkin I, No. 1, 31 (1975).
4. G. Shaw and D. N. Butler, J. Chem. Soc., No. 12, 4040 (1959).
5. Z. V. Pushkareva, V. I. Ofitserov, V. S. Mokrushin, and K. V. Aglitskaya, Khim. Geterotsikl. Soedin., No. 8, 1141 (1975).