UNUSUAL AZO-COUPLING REACTION IN THE IMIDAZOLE SERIES: FORMATION OF A NEW HETEROCYCLIC SYSTEM—THAT OF IMIDAZOBENZO-1, 2, 4-TRIAZINE*

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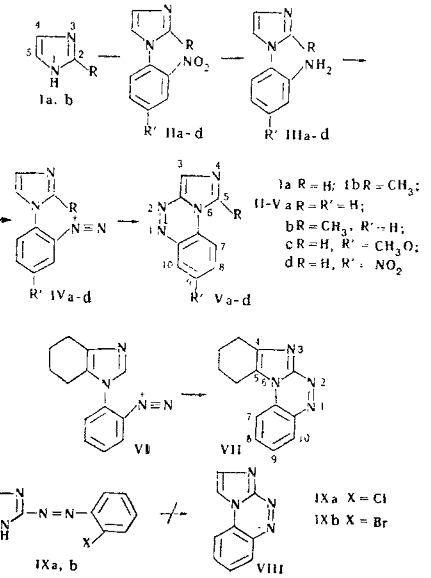
The intramolecular azo-coupling of diazotized N-o-aminophenylimidazoles forms derivatives of the new heterocyclic system of imidazo[5,1-c]benzo-1,2,4-triazine or, if position 5 of the imidazole ring is substituted, that of imidazo[1,2-c]benzo-1,2,4-triazine. This reaction is the first case of the azo-coupling of an imidazole ring in the nonanionic form. The spectral characteristics and basicities of the compounds obtained have been studied. Quantum-mechanical calculations by the MOH method have been performed.

Electrophilic substitution is one of the most complex questions of the chemistry of imidazoles**. It is known that the molecule of imidazole (I, R = H) may, according to the conditions, react with an electrophilic agent in the form of a cation, an anion, or the base. Thus, nitration and sulfonation in strongly acid media take place with the participation of the protonated form of imidazole and exclusively in position 4(5) [4]. Deuteration and azo-coupling in an alkaline medium lead primarily to 2-substituted imidazoles and involve attack by the electrophilic agents on the imidazole anion. If, however, position 2 is occupied, 4(5)-orientation is observed here, as well. There is extremely little information on electrophilic reactions of the neutral molecule of imidazole. It is assumed [5] that bromination in organic solvents, leading to 4(5)-bromoimidazole, takes place through the uncharged form of imidazole. Reactions of this type apparently also include the formation of 2-hydroxymethyl derivatives of imidazole by the reaction of N-substituted imidazoles with a number of aldehydes. However, this reaction is probably protophilic in nature, i.e., it depends on the acidity of a C—H bond of the substrate. The observed hydroxymethylation of 1-vinylbenzimidazole at position 2, for which nucleophilic reactions are characteristic appears to confirm this. The situation sketched is complicated still further by cases in which imidazole reacts even in the form of an anion predominantly in position 2 (deuteration) [6, 7]. All this indicates that the orientation of electrophilic substitution in the imidazole series depends not only on the form of the substrate but also on the nature of the reagent and the mechanism of the reaction. In addition to this, it is obvious that positions 2 and 4(5) in imidazole differ from one another in reactivity only slightly. This is also reflected in calculations by the molecular orbital method, which are partially contradictory and, moreover, do not always correlate with the observed reactivity.

Until now it has been considered that imidazole is incapable of coupling with diazonium salts in the form of a neutral molecule and, all the more, in the form of the cation, since 1-methyl- and 1-phenylimidazoles do not react with the usual diazonium salts. We have observed reactions forming an exception to this rule. It has been found that the o-(imidazol-1-yl)benzenediazonium salts (IV) formed in the diazotization of N-(o-aminophenyl)imidazoles (III) readily undergo intramolecular coupling in position 5 at pH 5–6. This leads to the formation of derivatives of a new heteroaromatic system—imidazo[5, 1-c]benzo-1, 2, 4-triazine (V). If position 4(5) is occupied, azo-coupling may be directed into position 2, as well. Thus, for example, compound VI gives, although with greater difficulty, the 4, 5-tetramethylene derivative of the isomeric heterocyclic system imidazo[1, 2-c]benzo-1, 2, 4-triazine (VII). This reaction does not take place in the benzimidazole series.



Ia R = H; Ib R = CH_3;
II–V a R = R' = H;
b R = CH_3, R' = H;
c R = H, R' = CH_3O;
d R = H, R' = NO_2

IXa X = Cl
IXb X = Br

Since in more strongly acid media (pH 1–4), compounds V and VII are not formed, it may be assumed that the form of the diazonium salt not protonated in the imidazole ring takes part in the reaction.

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*The subject-matter of the present paper was presented at the II-nd All-Union Conference on "The Chemistry of Five-Membered Nitrogen Heterocycles" [1].

**For a list of the publications on this question up to 1964, see [2, 3]. Subsequently, only references to more recent investigations are given in the text.

Calculations that we have carried out by the MOH method (Diagram 1) show that in IVa, as in other N-arylimidazoles [8], the π-electron density in position 5 is higher than in position 2 of the imidazole ring. The energy of electrophilic localization in the diazonium salt for positions 2 and 5 also indicates preferential 5-substitution (2.10 β^0 and 1.95 β^0, respectively).

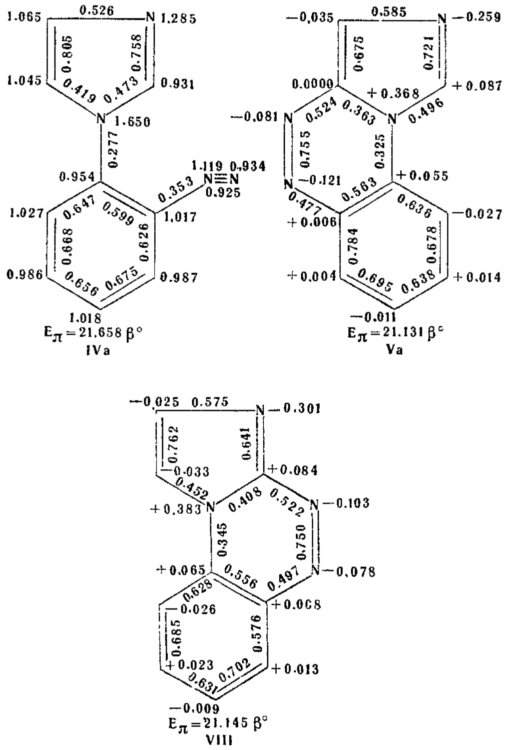

Diagram 1. π-Electronic densities, mobile bond orders, and π-electronic energies of the ground states of the o-(imidazol-1-yl)-benzenediazonium ion and the imidazo[5,1-c]benzo-1,2,4-triazine and imidazo[1,2-c]-benzo-1,2,4-triazine molecules.

At first sight, it is not absolutely clear why positions 5 and 2 in the imidazole ring of compounds IV and VI are more active with respect to the diazonium cation than, let us say, the corresponding positions in 1-methyl- and 1-phenylimidazoles. Since the N-imidazole group is apparently not a –E substitutent capable of causing pronounced activation of the diazonium group [9], it appears likely that the determining factor for the occurrence of intramolecular azo-coupling is the tendency to the formation of the new aromatic system of imidazobenzotriazine. Calculations performed in accordance with the formula

$$DE_\pi = E_\pi^{\mathrm{V}} \text{ or } {}^{\mathrm{VII}} - E_\pi \text{ 1-phenylimidazole}^{[7]} - E_\pi^{N=N},$$

show that such cyclization is accompanied by a substantial gain in energy: 1.064 β^0 in the formation of Va and 1.078 β^0 in the formation of VII.

It is an interesting fact that the nature of the substituent (cf. IVc and IVd) in the phenyl group of the diazonium salt exerts no substantial influence on the course of this reaction. Thus, the observed transformations show that, in contrast to the imidazole anion, the neutral form of the imidazole ring takes part in the azo-coupling reaction at position 5; if, however, the latter is blocked, the reaction may also take place at the $C_{(2)}$ atom. As is well known, the opposite phenomenon is observed for the imidazole anion.

Imidazobenzotriazines of types V and VII form yellow crystalline substances with extremely high melting points. They are sparingly soluble in water and more soluble in organic solvents. The imidazobenzotriazines have a lower basicity than the imidazoles. The pK_a values determined spectrophotometrically in water at 20° C for Va and Vb are, respectively, 1.84 and 2.66 (we were unable to determine the pK_a value of VII because its UV spectrum in hydrochloric acid solution changes with time). The melting points of the picrates are lower than those of the free bases, which is probably due to their molecular, and not ionic, nature.

In the determination of the ionization constants of Va and Vb, the question arose of the site of protonation of their molecules. The results of MO calculations (Diagram 1) predict that this should be the pyridine N-atom of the imidazole ring. This is confirmed by the change in the pK_a value on passing from Va to its 5-methyl derivative (Vb) ($\Delta pK_a = +0.82$), which is equal to the change in pK_a on passing from imidazole to 2-methylimidazole [10]. If the azo group were protonated, ΔpK_a would, of course, be considerably lower.

In view of the possible occurrence of intramolecular azo-coupling in both positions 2 and 5 of the imidazole ring, we found the direction of cyclization of compounds IV (a, c, d), on the basis of an analysis of their electronic absorption spectra (Table 1). All attempts to obtain the isomeric imidazo[1,2-c]benzo-1,2,4-triazines by the intramolecular arylation of the 2-(o-halogenophenylazo)imidazoles IX in nitrobenzene in the presence of K_2CO_3 and CuBr, in liquid ammonia in the presence of KNH_2, or in a melt with sodium acetate were unsuccessful.

The UV absorption spectra of the imidazobenzotriazines consist of four absorption bands, in the 220, 245, 260, and 380 nm regions. The long-wave absorption band is the most interesting for further discussion.

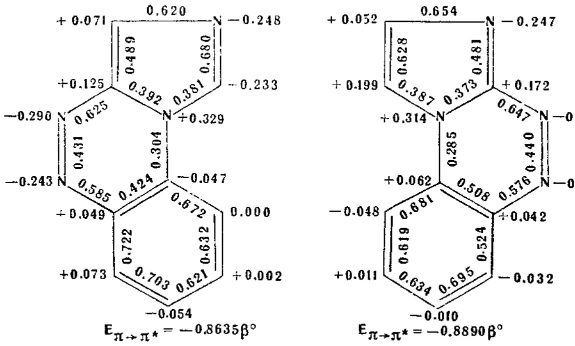

Diagram 2. π-Electronic densities, mobile bond orders, and energies of the $E_{\pi\to\pi^*}$ transitions for the first excited states of imidazobenzotriazine molecules.

Table 1

UV Spectra of the Imidazobenzo-1, 2, 4-triazines

Compound	Solvent	λ, nm					ε				
Va	5 *N* H_2SO_4	220	244	265*	325		15700	16700	—	6800	
	0.05 *N* NaOH	221	242	258**	388		18700	12700	10200	5280	
	Water	222	240	262	385		18200	13030	10520	5360	
	Methanol	—	244	261	378		—	12200	10450	4700	
	Octane;	—	233*	262	362		—	10350	7520	3000	
Vb	5 *N* H_2SO_4	217	245	270*	336		17600	14600	—	5780	
	0.05 *N* NaOH	—	235	264	393		—	12700	9430	5360	
	Methanol	—	233**	264	385		—	13460	10470	5530	
Vc	5 *N* H_2SO_4	—	240	263	330	387	—	—	26060	6800	3440
	Methanol	—	231	252	343	400	—	22400	19100	4800	4100
Vd	5 *N* H_2SO_4	—	233	277	337		—	14060	21380	5920	—
	Methanol	—	238	287	363		—	15200	20500	6270	—
VII	5 *N* H_2SO_4	218	249	289	380		22600	15450	2800	12470	—
	0.05 *N* NaOH	225	—	260	395		30000	—	8730	13100	—
	Methanol	225	—	262	385		43500	—	9100	16830	—

*inflection

**plateau

Since the energy of the first electronic transition, $E_{\pi\to\pi^*}$ is practically the same for the two isomeric imidazobenzotriazines (Diagram 2), it must be expected that their long-wave bands will be in approximately the same region. This is actually the case. Some increase in intensity and a bathochromic shift (~7 nm in methanol) of this absorption band for **VII** as compared with **Va** may be due to the electron-donating effect of the tetramethylene grouping.

A consideration of the first excited state of the molecules of imidazo-[5, 1-c]benzo-1, 2, 4-triazine and of imidazo[1, 2c]benzo-1, 2, 4-triazine shows that the $\pi\to\pi^*$ electronic transition corresponding to the long-wave band of these compounds is connected basically with a transfer of electron density from the imidazole ring to the azo group. In all the imidazo[5, 1-c]benzo-1, 2, 4-triazines, the formation of a cation is accompanied by a marked hypsochromic shift of the long-wave absorption band (Va, 53 nm; Vb, 49 nm; Vd, 27 nm)*.

In compound VII, the transition from the neutral molecule to the cation is accompanied by a considerably lower hypsochromic shift (15 nm). The observed difference can be explained by the fact that in the cation of imidazo[5, 1-c]-benzo-1, 2, 4-triazine the resultant electronic vector of the long-wave $\pi\to\pi^*$ transition and the vector directed to the quaternary nitrogen atom, counteracting this transition, are subtracted from one another more effectively than in the cation of imidazo-[1, 2-c]benzo-1, 2, 4-triazine (Diagram 3).

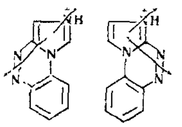

Diagram 3. Approximate interaction of the vector of the first electronic transition and the electric vector of the $\equiv\overset{+}{N}H$ group in the cations of the isomeric imidazobenzo-1, 2, 4-triazines.

EXPERIMENTAL

Quantum-mechanical calculations. All calculations by the MO LCAO method were performed in the simple Hückel approximation. The following magnitudes of the Coulomb and resonance integrals were taken [11]:

$$\alpha(C)=\alpha^0;\qquad \beta(C{=}C)=\beta(N{=}N)=\beta(C{=}N)=\beta^0;$$
$$\alpha(-N{=})=\alpha^0+0.5\beta^0;\qquad \beta(C{-}N)=0.8\beta^0.$$
$$\alpha(-\ddot{N}\langle)=\alpha^0+1.5\beta^0;$$

In the calculation of the diazonium cation, the parameters recommended by Schuster and Polansky [12] were taken for the diazonium group $C_{(1)}-N_{(2)}\equiv N_{(3)}$:

$$\alpha_{N_2}=\alpha^0+0.8\beta^0;\quad \alpha_{N_3}=\alpha^0+$$
$$+0.4\beta^0;\quad \beta_{C_1-N_2}=\beta^0;\quad \beta_{N_2-N_3}=1.5\beta^0.$$

The other details of the calculations are expounded in the paper of Staab et al. [7].

The solution of the secular determinants were obtained on a "Minsk-12" electronic computer.*

Measurement of pK_a values. The ionization constants were measured at 20° C in the pH range 1.3–2.4 for Va and 2.0–3.5 for Vb at analytical wavelengths of 326 and 330 nm, respectively. As the spectrum of the neutral molecules we took the spectrum of V in 0.05 N NaOH solution and as the spectrum of the cations its spectrum in 5 N H_2SO_4 solution. The accuracy of the measurements was ±0.05 pK_a unit.

1-(o-Nitrophenyl)tetrahydrobenzimidazole (X). A mixture of equimolecular amounts of tetrahydrobenzimidazole, o-chloronitrobenzene, and sodium acetate was heated at 175° C in the presence of a catalytic amount of cuprous bromide for 8 hr. After cooling, the melt was treated with chloroform and the insoluble residue was separated off. The compound X formed, together with the unchanged tetrahydrobenzimidazole, was extracted from the filtrate with 10% HCl. After neutralization with aqueous ammonia, the oil that had separated out was dissolved in chloroform, and the solution was passed through a column of alumina. The first fraction was collected. After the elimination of the solvent, the reaction product was purified by recrystallization.

1-(o-Nitrophenyl)imidazoles (IIa-c) were obtained by the direct arylation of imidazole with o-halogenonitrobenzenes by the procedure described previously [13] (Table 2).

1-(o-Aminophenyl)imidazoles (IIIa-c). Dilute HCl (1 : 1) (20% excess) was added in portions to a mixture of the appropriate compound II with a small (10–15%) excess of powdered tin. The mixture was heated for

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*It is difficult to come to any kind of conclusion on the nature of the shift of the long-wave band for Vc.

*The calculations were performed with the participation of E. Malysheva, RGU (Rostov-on-Don State University) Computing Center, to whom the authors express their deep gratitude.

Table 2

N-(o-Nitrophenyl)-and N-(o-Aminophenyl)imidazoles

Compound	1-Arylimidazoles	Mp, °C (solvent for crystallization)	Empirical formula	Found, %			Calculated, %			Yield, %
				C	H	N	C	H	N	
IIa	1-(o-Nitrophenyl)-imidazole	99—100 (benzene)*	$C_9H_7N_3O_2$	—	—	22.37	—	—	22.21	85
IIb	2-Methyl-1-(o-nitrophenyl)-imidazole	88—89 (carbon tetrachloride)**	$C_{10}H_9N_3O_2$	58.95	4.31	20.52	59.11	4.46	20.68	51
IIc	1-p-Methyl-o-nitrophenyl-imidazole	97—99 (aqueous ethanol)	$C_{10}H_9N_3O_3$	54.52	4.45	19.11	54.79	4.14	19.17	46
IIId	1-(o-Amino-p-nitrophenyl)-imidazole	218 (ethanol)	$C_9H_8N_4O_2$	52.89	4.11	27.02	52.94	3.95	27.40	33
IIIa	1-(o-Aminophenyl)-imidazole	106 (heptane)	$C_9H_9N_3$	67.77	5.53	26.56	67.90	5.70	26.40	85
IIIb	1-(o-Aminophenyl)-2-methyl-imidazole	135—136 (water)	$C_{10}H_{11}N_3$	68.96	6.30	24.66	69.34	6.40	24.26	90
IIIc	1-(o-Amino-p-methoxyphenyl)-imidazole	113 (water)	$C_{10}H_{11}N_3O$	63.37	5.95	22.31	63.48	5.86	22.31	66
	1-(o-Nitrophenyl)-tetrahydrobenzimidazole	103.5—104.5 (petroleum ether)	$C_{13}H_{13}N_3O_2$	64.46	5.29	16.93	64.18	5.39	17.28	37
	1-(o-Aminophenyl)-tetrahydrobenzimidazole	126.5—128 (petroleum ether)	$C_{13}H_{15}N_3$	73.09	7.06	19.41	73.21	7.09	19.70	87

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*According to the literature [8], 98-99° C.

**According to the literature [18], 88-89° C.

Table 3

Imidazobenzo-1, 2, 4-triazines

Compound	Mp, °C	Empirical formula	Found, %			Calculated, %			Yield, %
			C	H	N	C	H	N	
Va	210—211.5	$C_9H_6N_4$	63.16	3.45	33.00	63.52	3.55	32.93	70
Vb	229—230	$C_{10}H_8N_4$	64.97	4.20	30.55	65.21	4.38	30.42	85
Vc	251—252	$C_{10}H_8N_4O$	59.64	3.96	28.29	59.99	4.03	27.99	67
Vd	194—195	$C_9H_5N_5O_2$	50.45	2.64	32.22	50.24	2.34	32.55	59
VII	226—229	$C_{13}H_{12}N_4$	69.30	5.50	24.67	69.62	5.39	24.98	39

30 min. The cooled solution was diluted twofold with water, and hydrogen sulfide was passed through it until the tin sulfides had been completely precipitated. The filtrate from the precipitate was neutralized with 40% caustic soda solution and the amine formed was filtered off (Table 2).

1-(o-Nitrophenyl)benzimidazole was obtained by the arylation of benzimidazole with o-chloronitrobenzene [14]. Mp 80–81° C (according to the literature [15], mp 82.5° C).

1-(o-Aminophenyl)benzimidazole was obtained by the reduction of 1-(o-nitrophenyl)benzimidazole with tin in hydrochloric acid. Mp 112–114° C (according to the literature [15], mp 114–115° C).

1-(o-Amino-p-nitrophenyl)imidazole (IIId). A suspension of 1.17 g (0.005 mole) of 1-(2,4-dinitrophenyl)imidazole [15] in 10 ml of ethanol was added in portions to 5 ml of a boiling aqueous solution of 0.63 g (0.006 mole) of sodium disulfide. Heating was continued for 5 hr and then the reaction mixture was poured into water and the precipitate was filtered off and dissolved in chloroform. This solution was passed through a column of alumina and the second fraction was collected (the first fraction was unreduced 1-(2,4-dinitrophenyl)-imidazole).

Imidazobenzo-1,2,4-triazines (V, VII). With stirring, an aqueous solution of 0.01 mole of sodium nitrite was added dropwise to a solution of 0.01 mole of 1-(o-aminophenyl)imidazole in 15 ml of dil HCL (1:1) cooled to 0° C. Stirring was continued for 1.5 hr, the temperature of the mixture being kept at 0–5° C, and then it was slowly neutralized with a saturated aqueous solution of sodium carbonate. The precipitate that deposited was filtered off, dried in vacuum over P_2O_5, and purified first by chromatography on alumina (the fraction fluorescing in UV light was collected) and then by recrystallization from ethanol.

2-(o-Chlorophenyl)azoimidazole (IXa). This was obtained by coupling imidazole with an o-chlorobenzenediazonium salt [17] with a yield of 56%. Orange needles with mp 196.5° C (decomp.). Found, %: C 52.37; H 3.50; Cl 17.22. Calculated for $C_9H_7ClN_4$, %: C 52.31; H 3.41; Cl 17.16.

2-(o-Bromophenyl)azoimidazole (IXb) was obtained similarly with a yield of 61%. Golden orange plates with mp 202–203° C (decomp.) (from aqueous ethanol). Found, %: C 43.09; H 2.79; N 22.50; Br 31.64. Calculated for $C_9H_7BrN_4$, %: C 43.05; H 2.81; N 22.31; Br 31.83.

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