CHEMISTRY OF sym-TETRAZINE

IV.* AZIDO-TETRAZOLE TAUTOMERISM OF sym-TETRAZINE MONOAZIDES

V. A. Ershov and I. Ya. Postovskii

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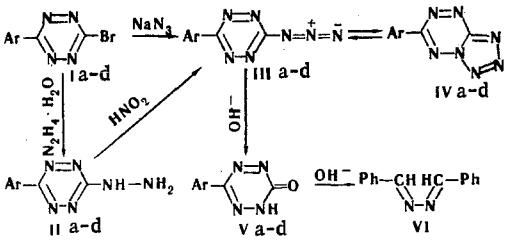
Previously undescribed sym-tetrazine monoazides were synthesized in order to study azido-tetrazole tautomerism. It is shown that polar solvents shift the equilibrium to favor the formation of the tetrazole form. The effect of annelation on the electronic structure of the sym-tetrazine ring was examined using the Hückel MO method. The results of the calculation of the comparative stabilities in the order pyridine < pyridazine < 1,2,4-triazine < sym-tetrazine explain the peculiarities of the azide ⇌ tetrazole tautomeric equilibrium in the sym-tetrazine series.

In the course of an investigation of the azido-tetrazole transformation in a number of aromatic N-heterocycles, it was of interest to study the structures of sym-tetrazine azides. The diazide of this heterocycle is described as a compound which decomposes explosively [2]. The IR spectrum of this compound has the absorption band of an azide group at 2130 cm^{-1}. The tetrazole form could not be detected.

Using the recently described methods for the preparation of unsymmetrically substituted sym-tetrazines [3, 4], we were able to obtain the until-now unknown sym-tetrazine monoazides and study the effect of substituents on the azido-tetrazole equilibrium. The starting materials for this were 3-bromo-6-aryl-sym-tetrazines (Ia-d). These compounds were obtained by the reaction of 1-formamidino-3-aryl-5-tetrazolylformazans with bromine in acetic acid [3]. The bromotetrazines were converted to hydrazines by reaction with hydrazine hydrate in alcohol, and the azides were then isolated by reaction of the hydrazines with nitrous acid. However, they were also obtained by the direct reaction of I with sodium azide in alcohol. 6-Methyl-3-azido-sym-tetrazine (IIIe) was also synthesized. For this, 3-hydrazino-6-methyl-sym-tetrazine [5] was obtained by hydrazinolysis of 3-amino-6-methyl-sym-tetrazine [4] and converted to the azide by reaction with nitrous acid.



I-V a Ar = Ph; b Ar = C_6H_4Cl-*p*; c Ar = $C_6H_4NO_2$-*m*; d Ar = $C_6H_4NO_2$-*p*

A study of the compounds by thin-layer chromatography (TLC) showed that IIIa gives two spots on aluminum oxide (chloroform containing 0.5% methanol) which are phosphorescent in near-UV light: a red spot with R_f 0.82 and a yellow spot with R_f 0.68. On standing for 24 h in light, the yellow spot again is converted to a red spot. Crystallization of IIIa from absolute alcohol gave a chromatographically pure red substance with empirical formula $C_8H_5N_7$, the IR spectrum of which contains a distinct group of bands in the azide region: 2139 (very sharp), 2180, and 2248 cm^{-1}. This made it possible to assign the azide form

*See [1] for communication III.

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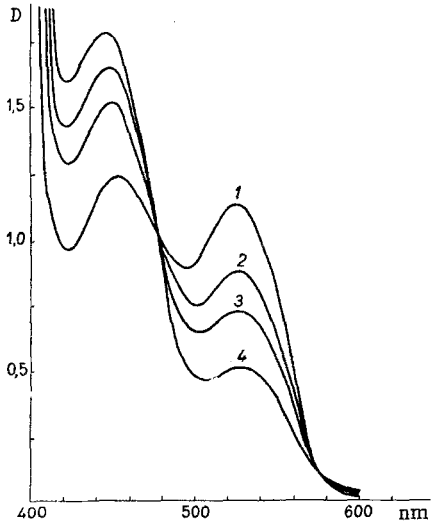


Fig. 1. Absorption spectra of 3-azido-6-phenyl-sym-tetrazine (IIIa) in dimethylformamide: 1) 5 min after dissolving; 2) after 1 h; 3) after 2 h; 4) after 5 h (c 2 · 10^{-3} M).

(III) to the red substance. In contrast to the diazide, azides IIIa-e, which are red substances, do not explode on heating but only slowly decompose at the melting point. A preponderant amount of yellow substance remained in the mother liquor from the crystallization. It could not be isolated in the chromatographically pure state even by preparative TLC because of the ease of conversion to the azide form even during elution from the plate with a solvent. The yellow azide-containing substance, which was isolated from the mother liquor by chromatography, had the same elementary composition ($C_8H_5N_7$) as IIIa. This made it possible to assume the tetrazole form (IVa) for the yellow substance. The data obtained attest to the higher stability of the azide form and to its lower polarity than is explained the large R_f value. The absorption maximum of IVa in alcohol (460 nm) coincides with λ_{max} of the previously obtained analog of IVa, 6-phenyl-sym-triazolo-[4,3-b]-sym-tetrazine [460 nm (log ε 2.64)] [6]. At the same time, λ_{max} for IIIa is 535 nm, as compared with 530 nm (log ε 2.71) for Ia.

A study of the effect of solvents on the azido-tetrazole equilibrium of IIIa indicated that only one absorption peak of the azide form is detected in n-heptane, viz., λ_{max} 545 nm (log ε 2.77). For IIIa in alcohol, the amount of the azide form, calculated from a comparison of the optical densities and extinctions of both forms, is ~50%; in benzene, pyridine, and dimethylformamide, the azide content is ~60%, ~50%, and ~20%, respectively. For IIIb, the amount of azide form in the above solvents is higher than for IIIa. These results indicate that the stability of the azide form is higher when acceptor substituents are present; polar solvents promote closing of the azide to tetrazolotetrazine. This sort of behavior of the azides in solvents of different polarity could provide a reason to expect the appearance of an isosbestic point in the spectra. However, because of the high lability of the n → π* transition of sym-tetrazine under the influence of polar agents, the isosbestic point in the visible region of the spectrum is washed out, since an increase in the amount of polar solvent, in addition to a shift in the equilibrium, also produces a hypsochromic shift of the n → π* transition with λ_{max} from 460 nm (alcohol) to 450 nm (dimethylformamide, IIIa). The isosbestic point is also diffuse in the UV region of the spectrum because of the superimposition of the electronic transitions of both forms. A distinct isosbestic point in the spectra of the visible region was obtained in a study of the azide-tetrazole conversion with time in one solvent. Thus, for IIIa in dimethylformamide, equilibrium is established in 8 h, in the course of which the maximum accumulation of tetrazole form IVa (up to 80%) occurs (Fig. 1).

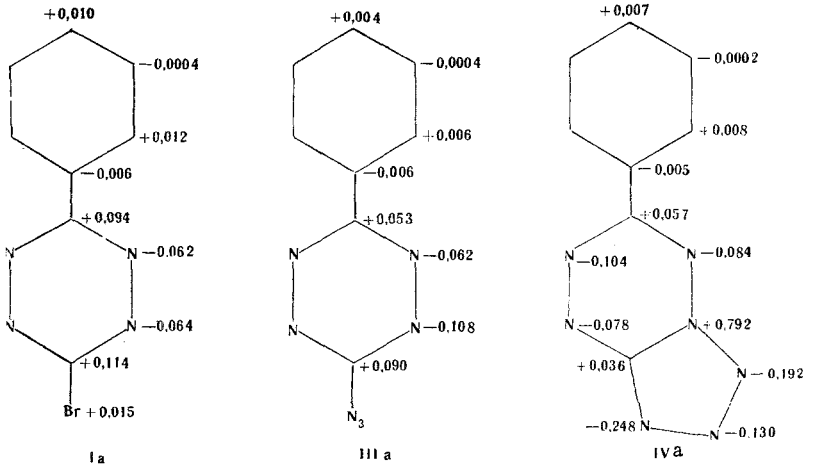
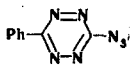
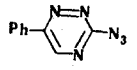
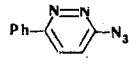
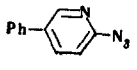


TABLE 1. Charge (q) on $N_{(2)}$ in Azides of the Phenylazine Series

Compound	q
	−0,108
	−0,146 for (N(4) −0,177
	−0,150
	−0,212

Quantum-chemical calculations of both forms (IIIa and IVa) and of Ia and tetrazine analogs were made by the Hückel MO LCAO method using Pullman's parameters [7, 8] to obtain information regarding the electronic structures of the azide and tetrazole forms, to study the relative stabilities of the azide forms in a number of azines and sym-tetrazine analogs, and to study the effect of the nature of the substituent on the azide-tetrazole equilibrium.

It is apparent from the calculated charge distribution that the azide group, being a mesomeric donor, increases somewhat the electron density in the ortho and para positions of the phenyl ring, as compared with unsubstituted C-phenyl-sym-tetrazine, for which the charges on $C_{(o)}$, $C_{(m)}$, and $C_{(p)}$ are +0.016, −0.0005, and +0.014. However, like halogen, the azide group cannot overcome the acceptor effect of the sym-tetrazine ring: the electron density remains higher in the meta position of the phenyl ring. From a comparison of the charges of IIIa and IVa it is apparent that the tetrazole form (IVa) is more of an acceptor than the azide form with respect to its own effect on the phenyl ring. This probably also affects the dipole moment which, judging from the R_f values, is higher for the tetrazole form than for the azide form (IIIa).

It is interesting that $C_{(3)}$ in Ia and IIIa have higher positive charges than $C_{(6)}$ which, for the azides of sym-tetrazine, should lead to the possibility of nucleophilic reactions at this carbon atom, as in the case of Ia. In fact, hydrolytic cleavage indicated that IIIa is destroyed to form benzalazine VI. If attack by the hydroxyl ion proceeds at $C_{(3)}$, 6-phenyl-sym-tetrazin-3-one (V) should be formed intermediately from the azide; V was, in fact, obtained when the reaction was carried out with potassium hydroxide in absolute alcohol. *

Calculation of the azide forms of a number of phenylazines for a study of the stabilities of the azide forms on replacement of the ring CH group by a nitrogen atom indicated that the π-electron density on $N_{(2)}$ decreases in the case of transition from the pyridine ring to the sym-tetrazine ring in the azides (Table 1). Since $N_{(2)}$ is converted to the donor state with two electrons in the π system on conversion to the tetrazole during ring closing, the increase in the electron density on $N_{(2)}$ should reduce the energy for conversion to the tetrazole form and stabilize the tetrazoles or, on the other hand, facilitate electrophilic attack at $N_{(2)}$ by the terminal nitrogen atom of the azide group, which has a low π-electron density. This is observed for a number of aromatic N-heterocycles, in which the most stable form in the case of azido-tetrazole tautomerism is the tetrazole form. Thus, according to spectroscopic data, tetrazolopyridine and its amino and hydroxy derivatives do not have the azide structure [9, 10]. The most stable form of sym-tetrazine is the azide form, as compared with other azine monoazides with fewer nitrogen atoms.

In varying the donor and acceptor substituents in the phenyl ring of IIIa, donor substituents should stabilize the tetrazole form somewhat more; as compared with acceptor substituents, the electron density on $N_{(2)}$ increases but remains lower than in unsubstituted IIIa. This effect is small for substituents in the para position and does not affect the electron density, as compared with unsubstituted azide, in the case of meta substituents. Calculations indicate that the charge on $N_{(2)}$ for the $p\text{-}CH_2^+$, $p\text{-}CH_2^-$, and $m\text{-}CH_2^-$ hypothetical substituents are, respectively, −0.097, −0.107, −0.108, and −0.108. When the CH_2 group is connected directly to the tetrazine ring, the electron density on $N_{(2)}$ is somewhat higher for donor substituents than in unsubstituted azides. The calculated data are experimentally confirmed for sym-tetrazine. Thus, the percentage of tetrazole forms in alcohol solutions for Cl and NO_2 in the para position (IIIb, d) decreases. (The electron density on $N_{(2)}$ is lower than in the unsubstituted azide.) Donor substituents facilitate cyclization of the azides to tetrazoles. Thus, sym-tetrazine diazide exists only in the azide form, while phenyl-sym-tetrazine azide exists as about 50% of the tetrazole form in alcohol.

*Nucleophilic reaction at $C_{(3)}$ occurs even during recrystallization of the azides from 96% alcohol, and this results in the appearance of V as an impurity.

The calculations indicate that there is a sharp lowering of the energy level of the lower antibonding orbital during annelation of the tetrazole ring: from $\alpha = -0.5967\beta$ for IIIa to $\alpha = -0.3045\beta$ for IVa. This leads to an increase in the first half-wave potential for polarographic reduction [11]. When the azides are reduced in dimethylformamide, in which the percentage of tetrazole forms is a maximum (~80%), it is observed that $E_{1/2}$ is shifted by 0.5 V toward the positive side, as compared with $E_{1/2}$ of the nonannelated phenyl-sym-tetrazine. Thus, $E_{1/2}$ was found to be −0.45 V for phenyl-sym-tetrazine in dimethylformamide, as compared with −0.07 V, −0.06 V, −0.03 V, and −0.025 V, respectively, for IIIa, IIIb, IIId, and IIIe. It is interesting that $E_{1/2}$ is −0.03 V for 6-phenyl-sym-triazolo[4,3-b]-sym-tetrazine – an analog of IVa – which also confirms that the investigated azides (III) exist in solution as the tautomeric tetrazole form (IV).

EXPERIMENTAL

6-Phenyl-3-azido-sym-tetrazine (IIIa). A. A solution of 0.09 g (1.30 mmole) of sodium nitrite in 5 ml of water was added to a solution of 0.25 g (1.33 mmole) of IIa in 200 ml of 6 N HCl. The red, flocculent precipitate that formed on standing was filtered and crystallized from absolute alcohol–benzene (1 : 1) to give 0.2 g (76%) of a product with mp 131° (decomp.). Found %: C 48.6; H 2.8; N 49.4. $C_8H_5N_7$. Calculated %: C 48.2; H 2.5; N 49.2.

B. A solution of 0.1 g (1.54 mmole) of sodium azide in 1 ml of water was added to a solution of 0.35 g (1.48 mmole) of 3-bromo-6-phenyl-sym-tetrazine (Ia) in 10 ml of hot alcohol, and the mixture was refluxed for 5 min to give 80% of a product that was quite soluble in benzene and somewhat less soluble in alcohol.

6-(m-Nitrophenyl)-3-azido-sym-tetrazine (IIIc). This was obtained in 75% yield by method B and had mp 149° (decomp.). Found %: N 45.6. $C_8H_4N_8O_2$. Calculated %: N 45.9. IR spectrum: 2145 (s), 2238, 2265, and 2317 cm^{-1}.

6-(p-Chlorophenyl)-3-azido-sym-tetrazine (IIIb). This was obtained in 82% yield by method B and had mp 154°. IR spectrum: 2139 (s), 2226, and 2303 cm^{-1}. Found %: N 42.4. $C_8H_4N_6Cl$. Calculated %: N 42.0.

6-Methyl-3-azido-sym-tetrazine. This was obtained in 50% yield from 3-hydrazino-6-methyl-sym-tetrazine [5] and had mp 60° (decomp.).* IR spectrum: 2142, 2154, 2225, and 2300 cm^{-1}.

6-(p-Nitrophenyl)-3-azido-sym-tetrazine (IIId). This was obtained in 80% yield by method A and had mp 159° [from alcohol–benzene (5 : 1); explosive decomposition]. IR spectrum: 2145 (s), 2238, and 2317 cm^{-1}. *

Hydrolysis of IIIa. A total of 0.06 g (1.07 mmole) of potassium hydroxide was added to 0.2 g (1.0 mmole) of IIIa in 6 ml of absolute alcohol, and the mixture was heated at 50° for 15 min, neutralized with hydrochloric acid, and the alcohol was vacuum distilled to give 0.1 g (57%) of 6-phenyl-sym-tetrazin-3-one with mp 185°. Benzalazine with mp 92-93° was obtained in 81% yield by hydrolysis of IIIa in aqueous alcohol under the conditions described in [12].

The IR spectra of mineral oil suspensions were obtained with a UR-20 spectrometer.

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*The compound decomposed violently during combustion, as a result of which the analyses for nitrogen gave high results.