INVESTIGATIONS IN THE 4-ARYL-5-ARYLAMINO-1,2,4-

## TRIAZOLINE-3-THIONE SERIES

S- AND N-SUBSTITUTED DERIVATIVES OF SUBSTITUTED 4-PHENYL-5-PHENYLAMINO-1,2,4-TRIAZOLINE-3-THIONES

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Cyanoethylation of 4-aryl-5-arylamino-1,2,4-triazoline-3-thiones proceeds at the nitrogen atom of the thioamide group. Alkylation of 4-aryl-5-arylamino-1,2,3-triazoline-3-thiones with chloroacetonitrile, monochloroacetic acid and its ester,  $\beta$ -chloropropionic acid, and methyl iodide proceeds at the sulfur atom. The acidity constants of substituted 4-phenyl-5-phenylamino-1,2,4-triazoline-3-thiones differ by two orders of magnitude from the acidity constants of the more acidic substituted 4-phenyl-1,2,4-triazoline-3-thiones.

It was shown in [1] that replacement of one CH group in the 4-phenyl-1,2,4-triazoline-3-thione (A) series by a nitrogen atom [transition to 1-phenyltetrazoline-5-thione (B)] leads to intensification of the acidity and to a change in the chemical properties of the compounds. The transition from A to C (replacement of phenyl by  $\alpha$ -pyridyl) brings the triazole derivative (C) obtained close to 1-phenyltetrazoline-5-thione (B) because of the presence of conjugation between the rings [2].



It was of interest to elucidate the effect of replacement of a hydrogen atom by an arylamino group in the 5 position of the ring of A (transition to 4-aryl-5-arylamino-1,2,4-triazoline-3-thiones previously synthesized by us [3]) on the chemical properties and acidity of the triazole derivatives.

According to our data (Table 1), the replacement of hydrogen in the 5 position of the 1,2,4-triazoline-3-thione ring by an arylamino group leads to a decrease in the acidity by two orders of magnitude as compared with 4-aryl-1,2,4-triazoline-3-thiones [1].

R	$p - RC_6H_4NH - C_NC = S$	
	Ka	K <sub>a</sub>
H Cl H₅O	$\begin{array}{c} 4,12\cdot 10^{-9} \\ 3,39\cdot 10^{-9} \\ 7,08\cdot 10^{-10} \end{array}$	$1,58 \cdot 10^{-71} \\ 2,51 \cdot 10^{-71} \\ 6,31 \cdot 10^{-81}$

TABLE 1. Acidity Constants of 1,2,4-Triazoline-3-thione Derivatives

Institute of Organic Chemistry, Academy of Sciences of the Ukrainian SSR, Kiev. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 129-132, January, 1971. Original article submitted November 18, 1969.

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UDC 547.792

As seen from Table 1, the chlorine atom in the 4 position of the phenyl ring displays an electronaccepting effect and increases the acidity of the compound, while the electron-donating ethoxy group lowers the acidity of the triazole derivatives; these results are in agreement with those in [1].

The 4-aryl-5-arylamino-1,2,4-triazoline-3-thiones (I) have the thione structure, as confirmed by the IR spectra (the presence of bands at 1330 cm<sup>-1</sup> for the C=S group and at 1548 cm<sup>-1</sup>, assigned to the NHC=S group) and by a qualitative reaction for the thione group [4].

Cyanoethylation of Ia with acrylonitrile in absolute dioxane with sodium ethoxide yielded IIa, the UV spectrum of which in alcohol was similar to the UV spectrum of Ia  $(\lambda_{max} 260 \text{ nm})$ , while the IR spectrum contained bands at 1552 cm<sup>-1</sup> (>N-C=S) and at 2270 cm<sup>-1</sup> (CN). These results indicate that cyanoethylation proceeds at the nitrogen atom of the thioamide group, as is the case for A [5].

The corresponding acids (III), esters (IV), and hydrazides (V), which are of interest as physiologically active substances, were obtained by saponification of II.

The corresponding S-substituted derivatives (VI-X) were obtained by alkylation of I with methyl iodide, chloroacetonitrile, monochloroacetic acid and its ester, and  $\beta$ -chloropropionic acid. The absorption curves of the alkylation products in alcohol were similar ( $\lambda_{max}$  255 nm) and differed from the absorption curves of the starting thione I and nitrile II.

Acid IXa, obtained by the reaction of Ia with  $\beta$ -chloropropionic acid, differs from isomeric acid IIIa, obtained by saponification of nitrile IIa.



The absorption curve of IIIa is similar to the absorption curve of starting thione Ia, while the absorption curve of IXa recalls the spectrum of sulfide VI, the thiol structure of which is confirmed by a positive test for a methylmercapto group [6].

The reaction of Ia with chloroacetonitrile in alkaline medium yielded nitrile VIIa, the hydrolysis of which gave acid VIIIa, which is identical to the acid obtained by the reaction of Ia with monochloroacetic acid.

Amides XI and hydrazides XII were obtained from esters X; XII were condensed with any isothiocyanates to give substituted 1-acetyl-4-arylthiosemicarbazides (XIII), which, on cyclization under the influence of alkali, form substituted 4-phenyl-5-phenylamino-3-(5-arylamino-1,3,4-thiodiazolyl-2)methylmercapto-1,2,4-triazoles (XIV) and, with  $\omega$ -bromoacetophenone, 2-(4-phenyl-5-phenylamino-1,2,4-triazolyl-3-mercaptoacetylhydrazino)-3-aryl-4-phenylthiazolium bromides (XV).

Com- pound	Mp, °C	Empirical formula	Ele- ment	Found <sub>*</sub> %	Calcu- lated, %	Yield, %
IIa IIb IIIc IIId III a III b IV c IV c VI v VI v VI v VI v VI v VI v VI v VI v	$\begin{array}{c} 150 - 151, \\ 174 - 175 \\ 156 - 157 \\ 224 - 225 \\ 221 - 222 \\ 171 - 172 \\ 88 - 89 \\ 169 - 170 \\ 132 - 133 \\ 132 - 133 \\ 132 - 133 \\ 132 - 133 \\ 132 - 133 \\ 132 - 133 \\ 132 - 133 \\ 132 - 133 \\ 132 - 132 \\ 196 - 197 \\ 163 - 164 \\ 142 - 143 \\ 93 - 94 \\ 179 - 180 \\ 188 - 183 \\ 221 - 222 \\ 206 - 207 \\ 223 - 224 \\ 202 - 203 \\ 142 - 143 \\ 221 - 222 \\ 206 - 207 \\ 223 - 224 \\ 202 - 203 \\ 142 - 143 \\ 218 - 219 \\ 211 - 212 \\ 206 - 207 \\ 223 - 224 \\ 200 - 203 \\ 142 - 143 \\ 218 - 219 \\ 211 - 212 \\ 210 - 203 \\ 142 - 143 \\ 218 - 219 \\ 210 - 203 \\ 142 - 143 \\ 218 - 219 \\ 210 - 203 \\ 142 - 143 \\ 218 - 219 \\ 210 - 203 \\ 142 - 143 \\ 218 - 219 \\ 212 - 213 \\ 186 - 187 \\ 204 - 205 \\ 182 - 183 \\ 207 - 208 \\ 162 - 163 \\ 184 - 185 \\ 158 - 159 \\ 174 - 175 \\ 143 - 144 \\ 149 - 151 \\ 129 - 130 \\ 152 - 153 \\ 212 - 213 \\ 183 - 184 \\ 179 - 180 \\ 130 - 131 \\ \end{array}$	$ \begin{array}{c} C_{17}H_{15}N_5S\\ C_{19}H_{19}N_5S\\ C_{21}H_{23}N_5O_2S\\ C_{17}H_{13}C_{12}N_5S\\ C_{17}H_{13}C_{12}N_5S\\ C_{17}H_{13}C_{12}N_4O_2S\\ C_{21}H_{22}N_4O_2S\\ C_{21}H_{22}N_4O_2S\\ C_{19}H_{20}N_4O_2S\\ C_{21}H_{24}N_4O_2S\\ C_{21}H_{24}N_4O_2S\\ C_{21}H_{24}N_4O_2S\\ C_{21}H_{24}N_4O_2S\\ C_{21}H_{24}N_4O_2S\\ C_{21}H_{26}N_6OS\\ C_{19}H_{22}N_6OS\\ C_{17}H_{16}C_{12}N_6OS\\ C_{17}H_{16}C_{12}N_6OS\\ C_{17}H_{16}C_{12}N_6OS\\ C_{17}H_{16}C_{12}N_6OS\\ C_{17}H_{16}N_4O_2S\\ C_{18}H_{12}C_{12}N_6OS\\ C_{17}H_{16}N_4O_2S\\ C_{16}H_{12}C_{12}N_6OS\\ C_{17}H_{16}N_4O_2S\\ C_{16}H_{13}N_5S\\ C_{16}H_{14}N_4O_2S\\ C_{20}H_{22}N_4O_2S\\ C_{16}H_{16}C_{12}N_4O_2S\\ C_{20}H_{22}N_4O_2S\\ C_{16}H_{16}C_{12}N_4O_2S\\ C_{18}H_{16}K_{10}O_2S\\ C_{18}H_{18}N_4O_2S\\ C_{20}H_{22}N_4O_2S\\ C_{18}H_{16}K_{10}O_2S\\ C_{18}H_{19}N_6OS\\ C_{18}H_{19}N_6OS\\ C_{18}H_{20}N_6OS\\ C_{16}H_{14}C_{12}N_6OS\\ C_{18}H_{20}N_6OS\\ C_{16}H_{16}C_{12}N_4O_2S\\ C_{21}H_{22}N_7OS_2\\ C_{22}H_{22}N_7OS_2\\ C_{23}H_{20}C_{1N}OS_2\\ C_{23}H_{20}C_{1N}OS_2\\ C_{23}H_{20}N_7OS_2\\ C_{23}H_{20}N_7$	N N N U N N U N N U N N U N N U N N U N N U N N U N N U N N U N N U N N U N N U N N N N N N N N N N N N N N N N	$\begin{array}{c} 21,6\\ 19,8\\ 16,7\\ 18,6\\ 16,3\\ 15,2\\ 13,0\\ 17,6\\ 15,2\\ 14,1\\ 12,1\\ 16,3\\ 23,6\\ 8,0\\ 19,0\\ 16,8\\ 10,4\\ 15,3\\ 20,6\\ 22,8\\ 17,0\\ 15,8\\ 10,4\\ 15,3\\ 20,6\\ 22,8\\ 17,0\\ 15,8\\ 10,4\\ 15,3\\ 20,6\\ 22,8\\ 17,0\\ 15,8\\ 13,3\\ 17,8\\ 16,5\\ 22,6\\ 22,7\\ 12,8\\ 13,8\\ 13,7\\ 12,2\\ 12,8\\ 13,8\\ 13,7\\ 12,2\\ 12,8\\ 13,8\\ 13,7\\ 12,2\\ 12,8\\ 13,8\\ 13,7\\ 12,2\\ 12,8\\ 14,8\\ 13,9\\ 14,1\\ $	$\begin{array}{c} 21,8\\ 20,0\\ 17,1\\ 18,2\\ 16,5\\ 15,2\\ 13,0\\ 17,3\\ 15,2\\ 14,1\\ 12,3\\ 16,2\\ 23,7\\ 8,4\\ 18,9\\ 16,8\\ 10,3\\ 15,1\\ 20,2\\ 22,8\\ 17,2\\ 16,8\\ 10,3\\ 15,1\\ 20,2\\ 22,8\\ 17,2\\ 15,8\\ 17,9\\ 16,5\\ 15,7\\ 14,6\\ 12,7\\ 16,8\\ 21,5\\ 19,8\\ 7,7\\ 18,0\\ 24,7\\ 22,8\\ 19,6\\ 20,0\\ 12,3\\ 12,6\\ 14,0\\ 13,5\\ 12,7\\ 13,0\\ 14,9\\ 14,3\\ 13,9\\ 14,2\\ \end{array}$	76 59 49 81 65 70 63 85 80 80 80 80 80 80 80 80 80 80

TABLE 2. Characteristics of the Compounds Obtained

Thus, replacement of a hydrogen atom by an arylamino group in the 5 position of the triazoline-3thione ring leads only to a decrease in the acidity and does not substantially affect the chemical properties.

## EXPERIMENTAL

 $2-\beta$ -Carbethoxyethyl-4-phenyl-5-phenylamino-1,2,4-triazoline-3-thione (IVa). Alcohol (15 ml) and several drops of concentrated H<sub>2</sub>SO<sub>4</sub> were added to 3.4 g (10 mmole) of IIIa. The mixture was refluxed for 1 h, cooled, and the resulting sticky mass of crystals was filtered and washed with water, alcohol, and ether to give 3.13 g (85%) of a product with mp 132-133° (from alcohol).

IVb-d (Table 2) were obtained under similar conditions.

<u>Hydrazide of  $2-\beta$ -Carboxyethyl-4-phenyl-5-phenylamino-1,2,4-triazoline-3-thione (Va).</u> A total of 0.7 ml (7 mmole) of 50% hydrazine hydrate was added to a suspension of 2.58 g (7 mmole) of IVa in alcohol, and the mixture was heated for 30 min. It was then cooled, filtered, and the precipitate was washed with water, alcohol, and ether to give 2.11 g (85%) of a product with mp 163-164° (from alcohol).

Vb-d (Table 2) were obtained under similar conditions.

The substituted VI were obtained via the method in [7].

 $\frac{3-\text{Cyanomethylmercapto-4-phenyl-5-phenylamino-1,2,4-triazole (VIIa).}}{(2 \text{ N})], 2.5 \text{ ml of alcohol, and 0.33 g (5 mmole) of chloroacetonitrile were added to 1.34 g (5 mmole) of Ia,}$ 

and the mixture was heated for 40 min. It was then cooled, diluted with water, and the resulting crystalline precipitate was filtered and washed with water, alcohol, and ether to give 0.85 g (56%) of a product with mp 206-207° (from alcohol).

<u>Amide of 3-Carboxymethylmercapto-4-phenyl-5-phenylamino-1,2,4-triazole (XIa)</u>. Ammonia was bubbled for 2 h with heating through a solution of 1.34 g (3.8 mmole) of Xa in 20 ml of methanol. The resulting precipitate was filtered and washed with water, alcohol, and ether to give 0.93 g (74%) of a product with mp  $179-180^{\circ}$  (from alcohol).

XIb-d (Table 2) were synthesized under similar conditions.

 $\frac{1-[4'-phenyl-5'-phenylamino-3'(1',2',4'-triazolyl)]mercaptoacetyl-4-phenylthiosemicarbazide (XIIIa).}{Phenyl isothiocyanate [0.4 g (3 mmole)] was added to 1.02 g (3 mmole) of XIIa in alcohol, and the mixture was heated on a water bath for 10-15 min. It was then cooled, and the resulting precipitate was filtered and washed with alcohol and ether to give 1.11 g (79%) of a product with mp 162-163° (from alcohol).$ 

XIIIb-d (Table 2) were obtained under similar conditions.

 $\frac{4-\text{Phenyl-5-phenylamino-3-[5'-(p-chl orophenylamino)-2'(1',3',4'-thiadiazolyl)]\text{methylmercapto-1,2,4-}}{\text{triazole (XIVd)}}.$  Sodium hydroxide [10 ml (2 N)] was added to 0.51 g (1 mmole) of XIIId, and the mixture was refluxed for 1 h. It was then cooled, acidified with hydrochloric acid, and the resulting precipitate was filtered and washed with water and aqueous alcohol to give 0.32 g (70%) of a product with mp 152-153° (from aqueous alcohol).

XIVa-c (Table 2) were similarly obtained.

 $\frac{2-[4'-Phenyl-5'-phenylamino-3'(1',2',4'-triazolyl)]mercaptoacetylhydrazino-3-aryl-4-phenylthiazolium}{Bromide (XVa). XIIIa [0.95 g (2 mmole)] was thoroughly triturated with 0.4 g (2 mmole) of <math>\omega$ -bromoaceto-phenone, the minimum amount of alcohol was added, and the mixture was heated on a water bath for 1 h. It was then cooled, and the resulting precipitate was filtered and washed with alcohol and ether to give 0.84 g (64%) of a product with mp 212-213° (from alcohol).

XVb-d (Table 2) were synthesized under similar conditions.

The acidity constants were determined by potentiometric titration (with 0.02 N sodium hydroxide) of aqueous alcohol solutions with a glass electrode counter to a chlorine-silver LPU-01 pH meter.

## LITERATURE CITED

- 1. I. L. Shegal, V. L. Nirenburg, V. F. Degtyarev, and I. Ya. Postovskii, Khim. Geterotsikl. Soedin., 580 (1965).
- 2. I. Ya. Postovskii and I. L. Shegal, Khim. Geterotsikl. Soedin., 443 (1966).
- 3. R. G. Dubenko and P. S. Pel'kis, Zh. Obshch. Khim., 33, 2220 (1963).
- 4. F. Feigl, Spot Analysis of Organic Substances [Russian translation], GNTIKhP (1962), p. 310.
- 5. I. Ya. Postovskii and I. L. Shegal, Khim. Geterotsikl. Soedin., 443 (1965).
- 6. E. Ochiai, Ber., 69, 1650 (1936).
- 7. M. Busch and T. Ulmer, Ber., 35, 1713 (1902).