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REACTION OF AROMATIC DIAZO DERIVATIVES WITH GLYCINE AND GLYCINE METHYLAMIDE*

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UDC 615.277.3:547.236.1].012.1

We have previously shown [1, 3] that when the pH, temperature and ionic strength of the solution correspond to the biological values (pH 7.4, 37°C and μ = 0.178), free amino acids and also terminal basic amino groups of peptides can take part in the formation of unstable disubstituted triazenes with aryldiazo derivatives, which subsequently undergo rapid transformation into 1,3-diaryltriazenes.

In continuation of the investigations carried out in [3], the present work is devoted to a kinetic study of the reactivity of aryldiazo derivatives (I-III) in reaction with glycine and glycine methylamide, similar to the chemical model of the glycine target of natural proteins and peptides.

EXPERIMENTAL (CHEMICAL)

The course of the reactions, the composition of the reaction mixtures and the purity of the synthesized compounds were monitored chromatographically on "Silufol UV-254" plates in the systems of PrOH – 0.2 N ammonia (3:1), R_{f_1}, $CHCl_3$ – EtOH (6:1), R_{f_2} BuOH–AcOH–water (4:1:1) R_{f_3}. The UV spectra were taken on a "Beckman" spectrometer, model 26 "Kinetic" (USA), the IR spectra on a UR-20 spectrophotometer in KBr tablets, and the PMR spectra on a "Bruker" WH-80 spectrometer (90 MHz) with tetramethylsilane as internal standard.

The diazo derivatives I-III were synthesized according to [4]. The results of the elemental analyses corresponded to the calculated values.

*Communication IX; for VIII see [3].

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 0091-150X/90/2407-0510 $12.50

Glycine methylamide (IV) hydrochloride was obtained according to [2] in a yield of 82%, mp 148°C. $C_3H_8N_2OCl$.

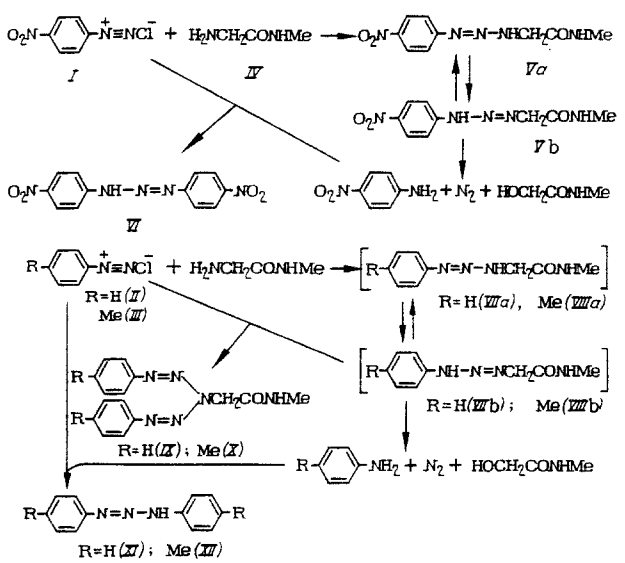
N-(4-Nitrophenylazo)glycine Methylamide (V). A freshly prepared solution of 0.6 g (0.003 mole) of 4-nitrophenyldiazonium chloride was added with stirring and cooling to 0-5°C to an aqueous solution of 1.24 g (0.01 mole) of glycine methylamide (IV), and a pH of 7-7.5 was maintained by addition of saturated sodium carbonate solution. The precipitate was filtered, washed with water and then was treated several times with 20 ml of acetone. Yield 35%, mp 163-165°C. R_{f_1} 0.78, R_{f_2} 0.48, R_{f_3} 0.74. $C_9H_{11}N_5O_3$. UV spectrum λ_{max}, (EtOH): 237, 271, 350 nm (log ε 3.8; 3.8; 4.2). IR spectrum ν_{max}, cm^{-1}: 1320, 1560 (NO_2), 1540, 1590 (NH), 1640 (CO), 2930, 2985 (CH-aliph), 3040, 3100 (CH-arom), 3270 (NH) PMR spectrum ($CDCl_3$), δ, ppm: 3.86 d (3H), 4.35 s (2H), 7.48 d (2H), 7.85 q (1H), 8.15 d (2H), 8.65 s (1H).

N-Bis(phenylazo)glycine methylamide (IX) was obtained in a similar way as V in a yield of 30%, mp 165°C (expl.). R_{f_1} 0.91, R_{f_2} 0.79, R_{f_3} 0.92. $C_{13}H_{16}N_5O$. UV spectrum, λ_{max} (EtOH): 230, 260, 357 nm (log ε 3.9; 3.8; 4.2). IR spectrum, ν_{max}, cm^{-1}: 1580 (NH), 1680 (CO), 2870, 2940 (CH-aliph), 3250, 3420 (NH). PMR spectrum ($CDCl_3$), δ, ppm: 2.82 d (3H), 5.25 s (2H), 5.60 s (1H), 7.4 m (5H), 7.8 m (5H).

N-Bis(4-methylphenylazo)glycine methylamide (IX) was obtained in a similar way as V in a yield of 32%, mp 167°C (expl.). R_{f_1} 0.69, R_{f_2} 0.57, R_{f_3} 0.88. $C_{17}H_{20}N_6O$. UV spectrum, λ_{max} (EtOH): 275, 360, nm (log ε 4.2; 4.1). PMR spectrum ($CDCl_3$), δ, ppm: 2.40 d (6H), 2.86 d (3H), 5.22 s (2H), 5.5 s (1H), 7.25 d (2H), 8.63 d (2H).

The determination of the rate constants of the reaction of the diazo derivatives I-III with glycine (XIII) and glycine methylamide (IV) was carried out according to [2].

The examination of the N-azo-coupling reaction of p-nitrophenyl diazonium chloride (I) with glycine methylamide (IV) in a neutral medium at 0 and 37°C showed that unlike the analogous reaction with glycine [1], the main end product of the reaction is a corresponding disubstituted triazene, which possibly exists in the most stable tautomeric form Vb and not Va, as confirmed by PMR spectroscopy data. Moreover, 1,3-bis(4-nitrophenyl)triazene (VI) was also isolated in an amount not exceeding 5%.



As the result of a TLC investigation of the reaction of the diazo derivatives II and III containing donor substituents with glycine methylamide (IV) at 0-5°C and at pH 7.4, the formation of three types of reaction products was recorded, presumably VII-XII, having cryptodiazonium properties. This is confirmed by a positive qualitative reaction of the compounds: the appearance of a color of the chromatographic spots characteristic for azo compounds, obtained on treating the plates with an aqueous alcoholic solution of m-phenylenediamine, HCl vapors and heating.

TABLE 1. Values of Rate Constants (K) and Half-Conversion Times ($\tau_{1/2}$) of Diazo Derivatives I-III in the Reaction with Glycine XIII and Glycine Methylamide IV at pH 7.4, 37°C, μ = 0.178

Compound	Nucleophilic target	Analytical wave length, nm	Order of reaction	$K \pm \Delta K$, min^{-1}	$K \pm \Delta K$, liter·$mole^{-1}$·min^{-1}	$\tau_{1/2}$, min
I	XIII	260	1	0,560±0,01	—	1,2
II	XIII	260	2	—	700,0±60,0	16,5
III	XIII	275	2	—	808,0±4,0	14,5
I	IV	260	1	0,2238±0,01	—	3,1
II	IV	260	1	0,0232±0,002	—	29,9
III	IV	275	2	—	444,0±40,0	20,0

TABLE 2. Values of Rate Constants (K) and Half-Conversion Times ($\tau_{1/2}$) of the Protolytic Decomposition Reaction of Triazene V and Pentazenes IX and X at pH 7.4, 37°C, and μ = 0.178.

Compound	Analytical wave length, nm	$K \pm \Delta K$, min^{-1}	$\tau_{1/2}$, min
V	355	0,0015±0,0001	458,9
IX	360	0,1380±0,007	5,0
X	360	0,1340±0,006	5,2

Compounds IX-XII which are less soluble and more stable could be isolated and identified as N-bis(phenylazo)glycine derivatives and 1,3-diaryltriazenes.

It should be noted that, unlike the analogous reaction of p-nitrophenyldiazonium chloride I, carrying out of the reaction of II and III with glycine methylamide in a phosphate buffer (pH 7.4) at a higher temperature (37°C) leads to the formation of 1,3-diaryltriazenes XI and XII as the only end products. The presence of the intermediate products VII-X in the reaction mixture can be detected only by chromatography.

The study of the quantitative regularities of the reaction of aryldiazo derivatives I-III with glycine and glycine methylamide (Table 1) showed that the kinetics of model reactions of p-nitrophenyldiazonium chloride I and phenyldiazonium chloride II with IV is governed by an equation of a first order reaction. In some cases there is a higher order of reaction (second with respect to the diazo derivative), which we have previously observed in reactions with other amino acids. It should be noted that the hydrolytic splitting of diazonium salts I-III, being a relatively slow process under the reaction conditions studied [3], does not affect their rate and the structure of the products formed.

The considerably higher stability of the disubstituted triazene V under protolytic decomposition conditions (Table 2) conforms well with the acceptor (passivating) influence of the NO_2 group of the aromatic ring on the reactivity of the triazene fragment with respect to electrophilic reagents. In particular, this may explain the absence of the corresponding pentazene among the products of model reactions with IV and XIII.

On the other hand, the low stability of pentazenes IX and X under the reaction conditions studied and their ability to generate the corresponding diazo derivatives explain the preferential formation of 1,3-diaryltriazenes XI and XII as more stable compounds in the reactions of diazo derivatives II and III with glycine and glycine methylamide at physiological values of pH and temperature [5].

The comparison of $\tau_{1/2}$ of model reactions (see Table 1) indicates that under close to physiological conditions, the NH_2 group of free glycine has a somewhat higher reactivity than the terminal amino group of the same amino acid included in the composition of natural

peptides. In the case of diazo derivatives containing acceptor substituents in the aromatic ring, the NH_2 group is capable of forming relatively stable disubstituted triazenes. These compounds having cryptodiazonium properties, as well as 1,3-diaryltriazene derivatives of phenylazopyrrolidinecarboxylic acid and thiadiazenes, should also be considered as possible transport depot forms of aryldiazo derivatives, as the active principles of the corresponding 3,3-dimethyltriazenes. The study of the biological properties of these cryptodiazonium compounds is the subject of investigations being carried out in the laboratory.

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ANTIRADICAL ACTIVITY OF SANTOQUIN AND INHIBITING PROPERTIES OF ITS MIXTURES WITH DIBUTYLHYDROXYTOLUENE

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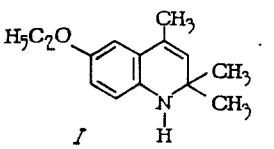
UDC 615.272-4.014.425.07

Santoquin (I) is used as an antioxidant for the stabilization of veterinary preparations of lipid nature and of powdered hay feed. Santoquin is highly effective in β- carotene preparations.

In [5-9] data are given on its antiradical activity and transformations at elevated temperatures in the absence and in the presence of oxygen. However, the action mechanism of santoquin has not been sufficiently investigated.

In the present work, under model reaction conditions of an initiated oxidation of cumene, an evaluation was carried out of the antiradical activity of santoquin and the characteristic features of its inhibiting action in mixtures with 3,5-dibutyl-4-hydroxytoluene (DBHT) were studied. According to the data in [2], this mixture has a synergistic effect during the oxidation of ethyl esters of fatty acids.



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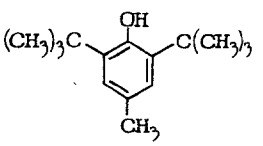

DBHT

Scientific-Industrial Association "Vitaminy," Moscow. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 24, No. 7, pp. 58-60, July, 1990. Original article submitted May 4, 1989.