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HIGHLY POLARIZED ENAMINES
1. SYNTHESIS AND SOME PROPERTIES OF β-TETRAZOLYLENAMINES

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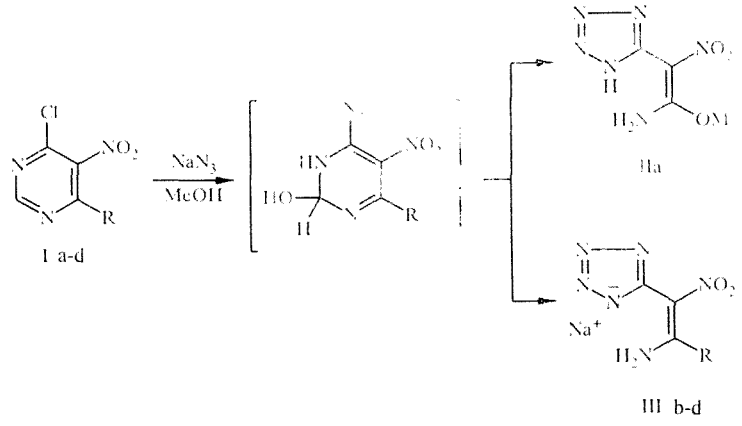
A method has been developed for the synthesis of some β-tetrazolyl-β-nitroenamines containing various alkoxy or amino substituents in the α position. It is based on the transformation of a pyrimidine ring by sodium azide.

We have investigated the reaction of derivatives of 4,6-dichloro-5-nitropyrimidine with sodium azide as a development of the study [1] of the special features of their nucleophilic substitution reactions.

It is known that the introduction of an azide group into the even-numbered positions of a pyrimidine ring may lead, depending on the character of the substituents in it and on the reaction conditions, directly to an azidopyrimidine and to a bicyclic tetrazolopyrimidine (depending on whether the tautomeric equilibrium is displaced toward the imidazide or tetrazole forms) [2]. In several cases, such as when 2,4-dimethoxy-5-nitropyrimidine is the starting material, the reaction products may be furoxanopyrimidines [3, 4] or monocyclic tetrazole derivatives [5, 6]. Interest in the synthesis of these compounds arose because substances have been discovered among the monocyclic tetrazoles which possess antitumor [7] and antiallergic [8] activity. Certain tetrazolylethylenes [9] and their reduced analogs [10] are used in agriculture as herbicides and in medicine as antiulcer preparations. Their mechanism of action is linked with their ability to block H_1 acid receptors.

We established that 4-chloro-6-methoxy-5-nitropyrimidine (Ia) reacts with sodium azide in boiling methanol to form the β-tetrazolylenamine (IIa). Under analogous conditions the 6-amino derivatives of 5-nitropyrimidine (Ib-d) are converted into the tetrazolylenamine sodium salts (IIIb-d).



I–III a R = OMe, b R = NMe_2, c R =  , d R = 

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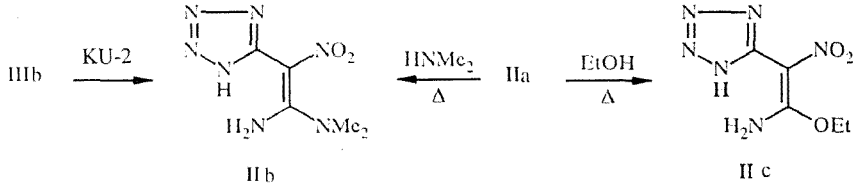
TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	mp, °C	IR spectrum, ν, cm^{-1}	UV spectrum, λ_{max} (log ε)	Yield, %
IIa	$C_4H_6N_6O_3$	188...189	3312, 3190, 1565, 1075, 762	213 (4,59), 323 (4,66)	55
IIb	$C_5H_9N_7O_2$	171...173	3400...3150, 1630, 1081, 752		47
IIc	$C_5H_8N_6O_3$	153...155	3318, 3168, 1634, 1064, 768		58
IIIb	$C_5H_8N_7O_2Na$	210...211	3400...3030, 1535, 1081, 755	208 (4,21), 292 (4,07)	45
IIIc	$C_7H_{10}N_7O_3Na$	208...210	3350...3200, 1602, 1070, 753	213 (4,19), 296 (4,00)	42
IIId	$C_8H_{12}N_7O_2Na$	220...221	3500...3100, 1560, 1085, 750	205 (4,08), 341 (3,99)	45
IIIe	$C_3H_4N_7O_2Na$	169...171	3500...3100, 1530, 1080, 753	221 (3,44), 334 (3,35)	67
IV	$C_5H_6N_4O_3$	242...243	3260, 1636, 1140, 1007		69
V	$C_4H_3N_7O_2$	178...179	3212, 3017, 1620, 1071, 760	210 (4,01), 305 (3,90)	19
VII	$C_{12}H_{14}N_{14}O_4$	280	3340...3050, 1564, 1080, 752	218 (4,51), 280 (4,47)	67

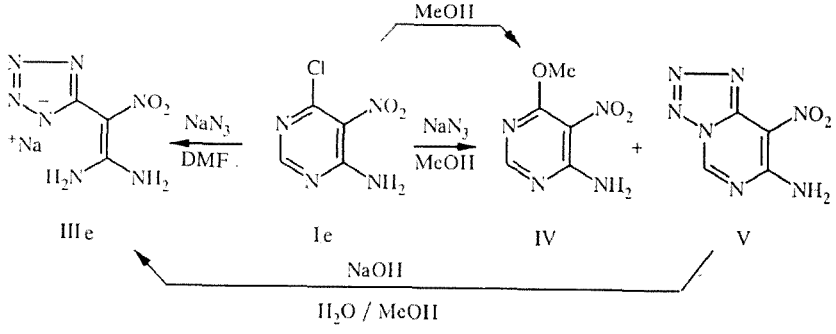
According to literature data, compounds containing a tetrazole ring are characterized by the presence in their IR spectra of intense absorption bands at 1500-1580, 1000-1100, and 710-780 cm^{-1} and two absorption maxima in the UV spectra at 205-215 and 290-310 nm [6, 11]. These data were used to identify the tetrazolylenamines. The bands indicated were observed in the spectra of products (II) and (III) (see Table 1).

Treatment of the sodium salt (IIIb) with KU-2 ion-exchange resin enabled the sodium cation to be removed and compound (IIb) to be isolated. It was not possible to achieve this by the action of acetic or hydrochloric acid on (IIIb). This is probably caused by hydrolysis of the amino group of the enamine in acid medium (see [12]) and formation of a complex mixture. Compound (IIb) was also obtained by the reaction of the tetrazolylenamine (IIa) with dimethylamine. It was established that the methoxy group in the α-position of enamine (IIa) is readily replaced not only by the NMe_2 group but also by an alkoxy group. For example, the ethoxy derivative (IIc) is formed even on recrystallizing compound (IIa) from ethanol.



IIb IIc

A special feature of the reaction of 6-amino-4-chloro-5-nitropyrimidine (Ie) with sodium azide in methanol is the formation of a mixture of two compounds (IV) and (V) in which the former predominates (69.1%).

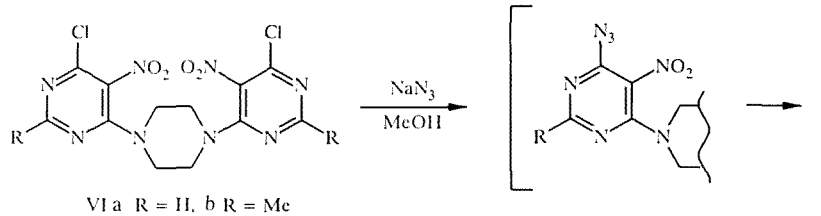


IIIe Ie IV V

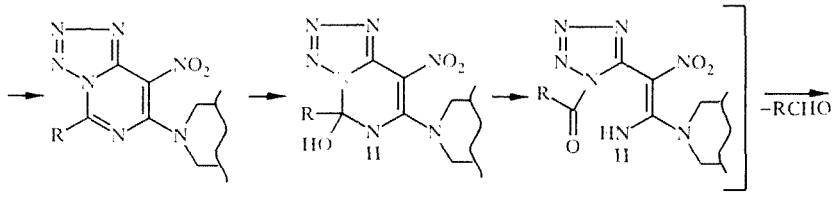
The structure of 6-amino-4-methoxy-5-nitropyrimidine (IV) was confirmed by its preparation on treating (Ie) with methanol. Choice of the bicyclic tetrazolo[1,5-c]pyrimidine structure for the minor product (V) (having a different elemental composition to 6-amino-4-azido-5-nitropyrimidine) was made on the basis of the absence from its IR spectrum of an absorption band at 2120-2160 cm^{-1} characteristic of the azide group [6], and the presence of absorption bands observed for compounds containing a tetrazole ring (see Table 1). There was a peak in the mass spectrum of compound (V) for the molecular ion $M^{+\cdot}$ = 181, corresponding to the calculated molecular mass, but the main decomposition was linked with elimination from the molecular ion of N_2 with subsequent fission of NO, NO_2, and HCN fragments.

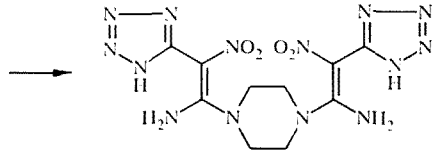
It was established that the sole product of the reaction of 6-amino-4-chloro-5-nitropyrimidine (Ie) with sodium azide in aqueous DMF was the sodium salt of α-amino-β-nitro-β-tetrazolylenamine (IIIe). The same compound was also obtained by the alkaline hydrolysis of compound (V) in aqueous methanol.

During the investigation of the reaction of 6-amino-4-chloro-5-nitropyrimidine with sodium azide it seemed of interest to study the application of this reaction to the bispyrimidinylamines (VIa, b) synthesized by us previously [13]. It was discovered that in both cases the product of their reaction with sodium azide in aqueous methanol was compound (VII). There were absorption bands in the IR spectrum at 1540, 1088, 1036, 1010, and 746 cm^{-1} belonging to a tetrazole ring and the absorption band of the azide group was absent. The structure of product (VII) was confirmed by the presence in its PMR spectrum of signals for piperazine ring protons as a sharp singlet at 3.75 ppm, a broad signal for the NH_2 group at 9.35, and also a low-field signal at 15.34 ppm assigned by us to a tetrazole ring NH fragment by analogy with data published previously in [14]. The formation of compound (VII), from literature analogies and data obtained by us previously, may be explained by covalent hydration of the intermediate tetrazolo[1,5-c]pyrimidine with subsequent fission of the pyrimidine ring. The $C_{(2)}$ atom of the pyrimidine ring is eliminated as a formyl [from (VIa)] or acetyl [from (VIb)] residue. The special feature of the reaction of the bis-pyrimidinylamines (VIa, b) with sodium azide, in comparison with the substituted pyrimidines (Ib-e), is the preparation of compound (VII) containing no sodium cation. This is probably explained by its separation from the reaction medium due to its poor solubility in methanol.



VI a R = H, b R = Me





VII

When studying the reaction of 4-chloro-5-nitropyrimidines with sodium azide we have discovered that derivatives of tetrazolo[1,5-c]pyrimidine and β-nitro-β-tetrazolylenamine may be formed depending on the substituent in the pyrimidine ring and on the reaction conditions. The formation of the latter compound is caused by hydration of the pyrimidine ring destabilized by the introduction of an azide group and its subsequent decomposition. The ethylenic bond in these compounds is the $C_{(5)}=C_{(6)}$ fragment of the pyrimidine ring.

EXPERIMENTAL

The IR spectra were taken on a Perkin–Elmer spectrophotometer as suspensions in nujol. The PMR spectra were taken on a Varian XL 200 spectrometer in DMSO-d_6. Internal standard was TMS. The mass spectra were obtained on a MAT 118 spectrometer with direct insertion of substances into the ion source. Purity and a check on the progress of reactions was effected chromatographically on Silufol UV 254 plates.

The data of elemental analysis for C, H, N, Cl, and S for all the compounds synthesized agreed with calculated values. The physicochemical characteristics of the compounds obtained are given in Table 1.

5-(2-Amino-2-methoxy-1-nitrovinyl)tetrazole (IIa). A solution of sodium azide (0.35 g: 5.30 mmole) in methanol (5 ml) and water (2 ml) was added to a solution of the pyrimidine (Ia) (1 g: 5.27 mmole) in methanol (50 ml) and the mixture obtained was boiled for 2 h. The reaction mixture was evaporated, the residue extracted with boiling methanol, the extract obtained was passed through a layer of activated carbon and aluminum oxide, and then evaporated under vacuum.

Sodium Salts of 5-(2-Amino-2-R-1-nitrovinyl)-tetrazoles (IIIb-d). A solution of sodium azide (0.34 g: 5.25 mmole) in water (2.5 ml) was added to a solution of the pyrimidine (Ib-d) (5.00 mmole) in methanol (50 ml) and the mixture obtained boiled for 5 h. The reaction mixture was evaporated to dryness, treated with boiling anhydrous methanol (40 ml), and the solid filtered off. The filtrate was evaporated to a volume of 20 ml and poured into ether (100 ml). The white solid precipitate of tetrazolylenamine salt was filtered off and purified by reprecipitation with ether from methanol. PMR spectrum of salt (IIIb): (6H, s, NMe_2), 8.82 ppm (2H, s, NH_2).

5-(2-Amino-2-dimethylamino-1-nitrovinyl)tetrazole (IIb). A. Ion exchange resin KU-2 (21 g) was added to a solution of salt (IIIb) (0.5 g: 1.94 mmole) in methanol (30 ml) and the mixture left for 72 h. The reaction mixture was filtered, the filtrate evaporated under vacuum, the residue treated with acetone (5 ml), and ether (75 ml) added. The precipitated solid was separated.

B. A 33% aqueous solution (0.67 ml) of dimethylamine (4.30 mmole) was added to a solution of enamine (IIa) (0.8 g: 4.30 mmole) in methanol (20 ml). The reaction mixture was boiled for 10 min then left for 16 h at room temperature, filtered, the filtrate was poured into a mixture of acetone (40 ml) and dioxan (40 ml), and the solid filtered off.

5-(2-Amino-2-ethoxy-1-nitrovinyl)tetrazone (IIc). A solution of enamine (IIa) (0.5 g: 2.68 mmole) in ethanol (10 ml) was boiled for 1.5 h, then cooled, and ether (50 ml) added. The precipitated solid was filtered off, and reprecipitated from absolute ethanol with ether.

7-Amino-6-nitrotetrazole[1,5-c]pyrimidine (V). Crystalline 6-amino-4-chloro-5-nitropyrimidine (Ve) (1.5 g: 8.59 mmole) was added with vigorous stirring to a solution of sodium azide (0.56 g: 8.61 mmole) in methanol (30 ml). After 2 h 4-amino-6-methoxy-5-nitropyrimidine (IV) was filtered off and the filtrate evaporated. The residue was treated with dioxan (20 ml), the tetrazolopyrimidine (V) which separated was filtered off, and was recrystallized from dioxan.

5-(2,2-Diamino-1-nitrovinyl)tetrazole Sodium Salt (IIIe). A. A solution of sodium azide (0.35 g: 5.53 mmole) in DMF (5 ml) and water (3 ml) was added to a solution of the pyrimidine (Ie) (1 g: 5.73 mmole) in DMF (20 ml). The reaction mixture was kept at 40°C for 5 h, evaporated, and the residue treated with a mixture (5:1) of ether–methanol. The solid which separated was filtered off, treated with boiling methanol (30 ml), and the mixture filtered. The filtrate was poured into ether (80 ml), the precipitated solid was filtered off, and reprecipitated from methanol with ether.

B. A solution of sodium hydroxide (0.12 g: 3.00 mmole) in water (5 ml) was added to a suspension of the tetrazolopyrimidine (V) (0.5 g: 2.70 mmole) in methanol (20 ml). The reaction mixture was heated to boiling for 1 h, and then evaporated. The dry residue was dissolved in cold methanol (20 ml), the solution was then poured into diethyl ether (100 ml), and the product which precipitated was filtered off.

N,N′-Bis[2-amino-1-nitro-1-(5-tetrazolyl)vinyl]-piperazine (VII). A. A solution of sodium azide (0.32 g: 5.00 mmole) in methanol (20 ml) and water (5 ml) was added to a suspension of compound (VIa) (1 g: 2.50 mmole) in methanol (30 ml) and the mixture obtained was boiled for 8 h. The reaction mixture was filtered, the solid was washed with water, with methanol, and with chloroform, and then reprecipitated from DMSO with acetone. PMR spectrum: 3.75 (2H, s, CH_2); 9.34 (2H, br s, NH_2); 15.34 ppm (1H, br s, NH).

B. A solution of sodium azide (0.3 g: 4.61 mmole) in methanol (20 ml) and water (5 ml) was added to a suspension of compound (VIb) (1 g: 2.32 mmole) in methanol (30 ml) and the mixture boiled for 5 h. The reaction mixture was filtered, and the solid washed with water and with methanol.

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