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NITROAZINES

25.* SPECTRAL STUDY OF THE REACTION OF THE TRANSFORMATION OF 6-NITROAZOLO[1,5-a]PYRIMIDINES BY CH-ACTIVE NITRILES

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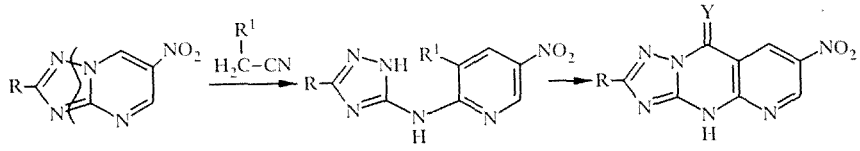
The methods of ^1H and ^{13}C NMR and UV spectroscopy were utilized to investigate the structure of products of the transformation of 6-nitroazolo[1,5-a]pyrimidines by CH-active nitriles. The mechanism of the reactions is discussed.

We previously reported [2] the transformation of 6-nitroazolo[1,5-a]pyrimidines by ethyl cyanacetate, cyanacetamide, cyanacetothioamide, and benzoylacetonitrile with the formation of derivatives of 2-azolylamino-5-nitropyridine. When the last were heated or treated with an alcoholic solution of sodium carbonate, as well as when the reaction of the azolylpyrimidines with the acetonitriles under consideration was performed in an alkaline medium, 7-nitroazolo[1,5-a]pyrido[2,3-d]pyrimidines were obtained [3, 4].



I II III

$R^1 = COOC_2H_5$, CN, $CONH_2$, $CSNH_2$, COC_6H_5; Y = O, NH

The novelty and unusual character of conversions of 6-nitroazolo[1,5-a]pyrimidines by CH-active derivatives of acetonitrile determined interest in the study of its mechanism. The reaction between 6-nitro-1,2,4-triazolo[1,5-a]pyrimidine and cyanacetic ester, containing the ^{13}C and ^{15}N isotopic labels in the nitrile group, was carried out to clarify the position of the nitrile fragment of the dinucleophile in the molecule of the transformation product.

Analysis of the ^{13}C and ^1H NMR spectra of the compound obtained showed that the bond in the pyrimidine nucleus of the 2-(1,2,4-triazolyl-5-ylamino)-3-ethoxycarbonyl-5-nitropyridine molecule is formed exclusively on account of the C–N fragment of cyanacetic ester [4, 5], which is unexpected. In known transformations of 5-nitropyrimidine [6], pteridine [7], and azapurine [8] by the action of cyanacetic ester or malonodinitrile, leading to 2-aminopyridine derivatives, a part of the pyrimidine nucleus is replaced by the C–C fragment of acetonitrile.

Results of spectral observations on the course of the reaction of 6-nitroazolo[1,5-a]pyrimidines with cyanacetic ester in the cell of the PMR and UV spectrometer are presented in the given work.

*For Communication 24, see [1].

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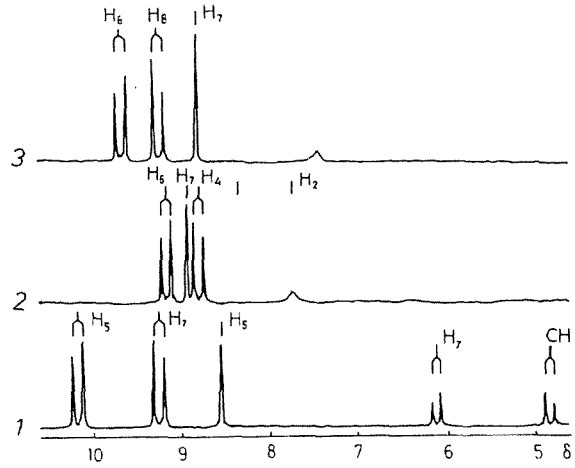
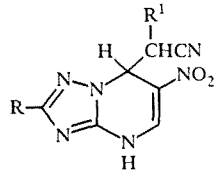
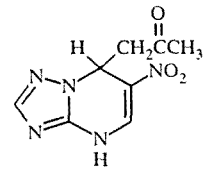


Fig. 1. NMR and PMR spectra of the reaction mass of 2-dimethylamino-6-nitro-1,2,4-triazolo[1,5-a]pyrimidine and cyanacetic ester in DMSO-D_6. 1) At 25°C; 2) after 15 min of heating at 60°C; 3) after 30 min of heating at 100°C.

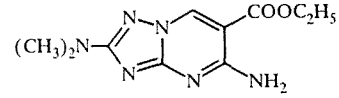
In all cases, signals having equal integral intensity appear in the PMR spectrum in the form of doublets at the δ 4.9 and 6.2-6.5 ppm and in the form of a singlet at the δ 8.55-8.75 ppm together with the signals of the initial compounds after the mixing of the reagents. The comparison with the characteristics of the spectra of the σ-adducts of 6-nitroazolo[1,5-a]pyrimidines with indoles and pyrroles [9, 10], as well as 7-acetonyl-4,7-dihydro-6-nitro-1,2,4-triazolo[1,5-a]pyrimidine (IV) [11], allows these signals to be assigned to the resonance of the CH, 7-H, and 5-H protons of the products of the addition of cyanacetic ester to the substrate (V).



V



IV



VI

The preparative isolation of the σ-adducts from the reaction mass was not managed since their further conversion to the corresponding transformation products thereby occurs. If it is taken into account that the compounds of the structure (IV) and analogous derivatives of indole and pyrrole do not dissociate under the reaction conditions, and that the final products of the transformation of the 6-nitroazolo[1,5-a]pyrimidines (I) by CH-active acetonitriles have high yields, then it is entirely probable to propose that the σ-adducts (V) participate in this conversion.

In order to investigate further conversions of the compounds (V), the spectral analysis of the interaction of cyanacetic ester with 2-dimethylamino-6-nitro-1,2,4-triazolo[1,5-a]pyrimidine was conducted in DMSO-D_6 at different temperatures. The triazolopyrimidine selected is convenient since it does not form covalent hydrates with water present in the DMSO-D_6, which simplifies the spectral picture, and also gives the most stable σ-adduct with the dinucleophile.

The initial PMR spectrum (Fig. 1) of the mixture of reagents at 25°C represents the superposition of the signals of the starting substances and the adduct (V): R = $N(CH_3)_2$, R^1 = $COOC_2H_5$ (1.40 t, 2.95 s, 4.30 q, 5.00 d, 6.35 d, and 8.65 s). After 15 min of the heating of the reaction mass at 60°C, the decrease in the intensity of the signals of the σ-adduct (V) occurs with the appearance of signals corresponding to 2-azolylamino-5-nitropyridine [R = $N(CH_3)_2$], as well as the singlet with the δ 9.00 and 8.75 ppm (Fig. 1). In the course of time, the intensity of the last two signals reaches a maximal value and is subsequently unchanged. The signals of the σ-adduct (V) and the 2-azolylamino-5-nitropyridine (II) disappear from the spectrum of the reaction mass after it has been held for 30 min at 100°C, and signals corresponding to the resonance of protons of 2-dimethylamino-7-nitroazolo[1,5-a]pyrido[2,3-d]pyrimidine appear. Compound (VI), responsible for the appearance of the

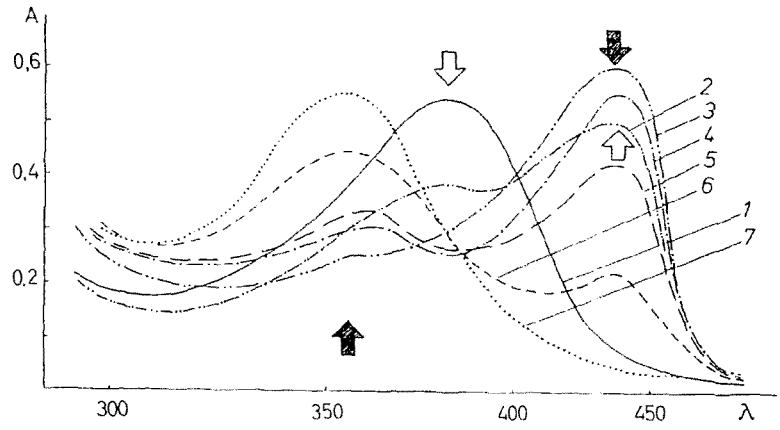


Fig. 2. Electronic spectra of the mixture of equimolar amounts of the compounds (I) [R = $N(CH_3)$, X = N] and cyanacetic ester in alcohol. 1) After mixing; 2) after 48 h; 3) after 168 h; 4) after 240 h; 5) after 480 h; 6) after 720 h; 7) after 788 h.

TABLE 1. Characteristics of the Electronic Spectra of the Adducts (IV) and Azolylaminopyrimidines (II) and the Time of Their Formation in the Reaction of 6-Nitro-1,2,4-triazolopyrimidines with Derivatives of Acetonitrile

R	R^1	λ_{max} of compound (IV)	Time to reach the maximum concentration of compound (IV), h	λ_{max} of compound (II)	Time to reach the maximum concentration of compound (II), h
NH_2	$COOC_2H_5$	266, 434	24	229	456
NH_2	$CONH_2$	353, 443	96	354	240
NH_2	$CSNH_2$	333, 448	6	347	96
NH_2	PhC=O	417	120	417	720
NH_2	CN	322, 396	6	322	168
H	$COOC_2H_5$	285, 430	6	366	432
H	$CONH_2$	285, 342, 440	24	342	200
H	$CSNH_2$	334, 447	6	350	96
H	PhC=O	410	24	436	360
H	CN	284, 354, 413	24	285	264
CF_3	$COOC_2H_5$	333, 430	96	328	168
CF_3	$CONH_2$	333, 445	240		

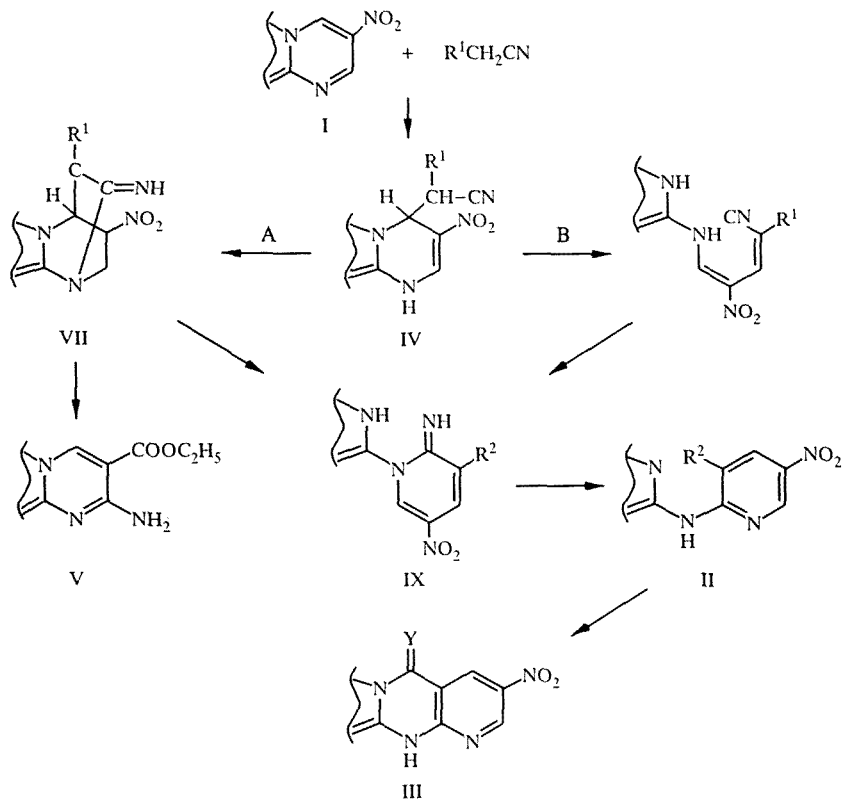
signals with the δ 8.75 and 9.00 ppm in the spectrum, was successfully isolated using preparative thin layer chromatography and identified as 2-dimethylamino-5-amino-6-ethoxycarbonyl-1,2,4-[1,5-a]pyrimidine.

When the reaction of 2-dimethylamino-6-nitroazolo[1,5-a]pyrimidine with malonodinitrile is performed in the cell of the PMR spectrometer, it gives the indication that it proceeds by analogy to the reaction with cyanacetic ester.

The observation of the course of the transformation of the 6-nitroazolo[1,5-a]pyrimidines by CH-active acetonitriles using UV spectroscopy was conducted at 20°C with the 1:100 substrate:nucleophile ratio in an alcoholic solution. Under these conditions, the reaction proceeds significantly more slowly. However, the result obtained allows an evaluation of the influence of substituents in the azole fragment of the nitropyrimidine and the nature of the CH-active acetonitrile utilized on the course of the transformation.

The UV spectrum of the mixture of reagents is characterized by the appearance of a band, changing with time, at 400-460 nm, which can be explained by the formation of the σ-adducts (V). The character of the changes in the spectrum (Fig. 2, Table 1) is typical of sequential reactions. It can be seen from the data presented in Table 1 that the most reactive in the series of dinucleophiles are malonodinitrile and thiocyanacetamide. In this case, the time taken to achieve the maximal concentration of the σ-adducts (V) comprises 1-4 h, and the time taken for the complete process comprises 96-264 h. The longest duration of the reaction occurs for cyanacetamide and benzoylacetonitrile.

We proposed the following reaction scheme on the basis of the set of experimental and published data. The initial attack of the nucleophile at the position 7 of the 6-nitroazolo[1,5-a]pyrimidine (I) leads to the formation of the adduct (IV), which is converted to 1,2-dihydro-1-azolyl-2-imino-3-R-5-nitropyridine (IX) via the cyclic intermediate (VII) (path A) or the open-chain intermediate (VIII) (path B).



It should be noted that the participation of an open-chain intermediate was postulated in the discussion of schemes for the transformation of monocyclic nitropyrimidines by dinucleophiles [6, 12].

Compound (IX) undergoes the Dimroth rearrangement with the formation of 2-azolylamino-3-nitro-5-R-pyridines (II). The conversion, for example, of 1-methyl-2-imino-1,2-dihydro-3-nitropyridines to the 2-methylamino derivative proceeds similarly [13]. The formation of 5-amino-6-ethoxycarbonyltriazolo[1,5-a]pyrimidine (V) may be presented as the elimination of the $C_{(5)}-C_{(6)}$ fragment (possibly in the form of nitroacetylene) from the cyclic intermediate (VII). The detection of the compounds (VII) is more probable in transformations of 6-nitroazolo[1,5-a]pyrimidines (I) to the nitropyridines (II) by the path A.

EXPERIMENTAL

The IR spectra were taken on the UR-20 instrument in mineral oil. The PMR spectra were taken on a Bruker WP spectrometer (80 MHz) in DMSO-D_6 using TMS as the internal standard. The UV spectra were recorded on a Specord UV-vis spectrometer in ethanol.

2-Dimethylamino-5-amino-6-ethoxycarbonyl-1,2,4-triazolo[1,5-a]pyridine (VI) ($C_{10}H_{14}N_6O_2$). The 2-dimethylamino-6-nitro-1,2,4-triazolo[1,5-a]pyrimidine (2.1 g, 0.01 mole) and 1.68 ml (0.015 mole) of cyanacetic ester are heated in 15 ml of DMSO at 90°C for 30 min. Separation is performed using chromatography on silica gel with the 10:1 mixture of chloroform–ethanol. The yield of 0.37 g (15%) is obtained. The mp is 181-183°C (from ethanol). The ^1H NMR spectrum is as follows: 1.36 ppm (3H, t, $C-CH_3$), 3.04 ppm [6H, s, $N(CH_3)_2$], 4.35 ppm (2H, q, $O-CH_2$), 7.75 ppm (2H, br.s, NH_2), and 9.00 ppm (1H, s, 7H). The ^{13}C NMR spectrum is as follows: 14.30 ppm $C_{(10)}$, 37.38 ppm C(NCH), 61.61 ppm $C_{(9)}$, 96.87

ppm $C_{(6)}$, 157.43 ppm $C_{(3a)}$, 159.90 ppm $C_{(5)}$, 165.19 ppm $C_{(8)}$, and [3]170.00 ppm $C_{(2)}$; J_{67} = 3.7 Hz, J_{67} = 3.1 Hz, J_{89} = 3.5 Hz, J_{99} = 148.9 Hz, J_{57} = 5.5 Hz, J_{77} = 186.99 Hz, and J_{109} = 3.7 Hz.

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