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NITROAZINES 11.*

STRUCTURE OF PRODUCTS OF TRANSFORMATION OF 6-NITROAZOLO-[1,5-*a*]PYRIMIDINES UNDER THE INFLUENCE OF CYANOACETIC ESTER

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UDC 547.859.3.04'792: 737:543.422.25

The interaction of 6-nitroazolo[1,5-a]pyrimidines with ethyl cyanoacetate is accompanied by transformation of the pyrimidine ring, forming derivatives of 2-azolylaminopyrimidine. The structure of the transformation products has been investigated in crystals and in solution.

In an earlier communication [2], we described briefly the transformation of 6-nitroazolo[1,5-*a*]pyrimidines under the influence of ethyl cyanoacetate.

The present work has been aimed at determining the limits of applicability of this reaction by varying the type of ring annelated to the pyrimidine ring; the work was further aimed at following the influence of substituents and establishing the structure of the transformation products.

Upon interaction with ethyl cyanoacetate, the 2-R-6-nitro-1,2,4-triazolo- and 3-R-6-nitropyrazolo[1,5-*a*]pyrimidines Ia-i are converted to the 2-(5-azolylamino)-3-carbethoxy-5-nitropyridines IIa-i. The reaction proceeds without any additional activation by charging the reagent and substrate.

The capability of the azolo[1,5-*a*]pyridimines Ia-k to participate in reaction depends on the degree of π-deficiency of the system. The triazolylaminopyridines IIa-e are readily formed by 30-min refluxing of compounds Ia-e with cyanoacetic ester in alcohol. The introduction of donor substituents such as CH_3 or SCH_3 into the azole part does not hinder the reaction. However, groups having a significant +M-effect, such as $N(CH_3)_2$ or NH_2, deactivate the substrate; and the transformation products can be obtained only by heating to 100°C in DMSO.

A different sort of behavior in these conversions is exhibited by the desaza analogs of compounds Ia-g, i.e., the pyrazolo[1,5-*a*]-pyrimidines in Ih-k. They can be made capable of reacting with cyanoacetic ester by introducing acceptor substituents such as NO_2 or $COOC_2H_5$ into the pyrazole fragment. The 6-nitropyrazolo[1,5-*a*]pyrimidine itself (Ij), and all the more the 2-methyl-6-nitropyrazolo[1,5-*a*]pyrimidine (Ik) are incapable of such conversion (see scheme on page 1359).

With the aim of establishing the molecular-crystal structure of the transformation products, we carried out an x-ray structural study of compound IIb (Table 1 and Fig. 1).

*For Communication 10, see [1].

S. M. Kirov Ural Polytechnic Institute, Sverdlovsk, 620002. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1631-1637, December, 1990. Original article submitted April 24, 1989; revision submitted November 29, 1989.

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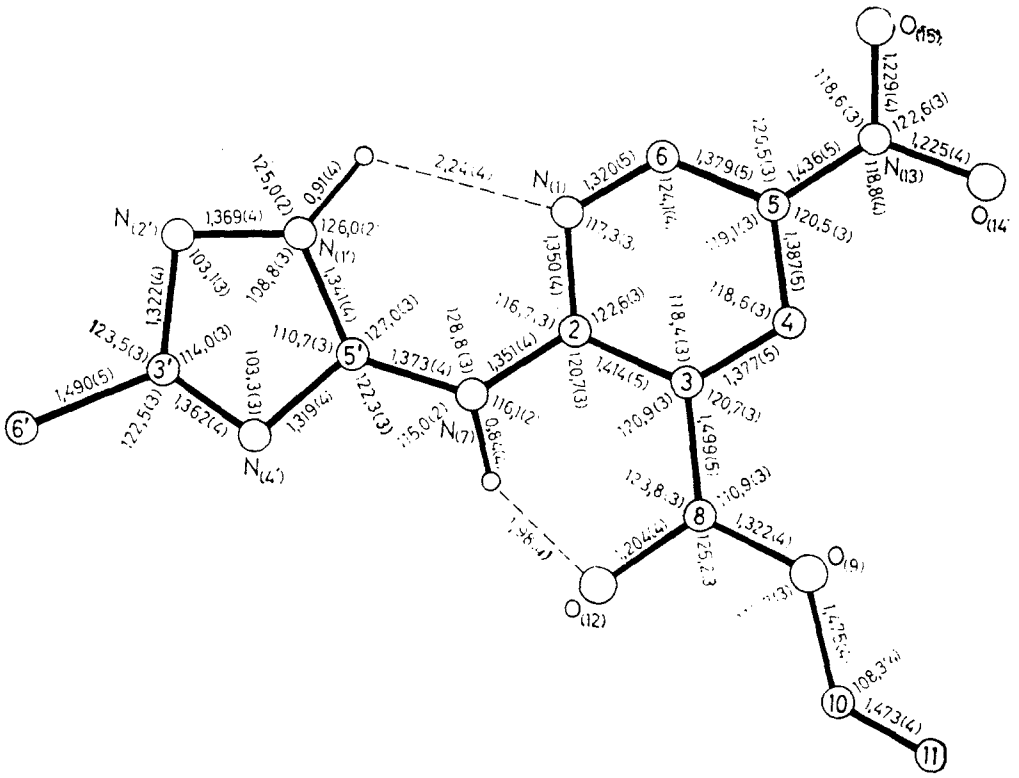
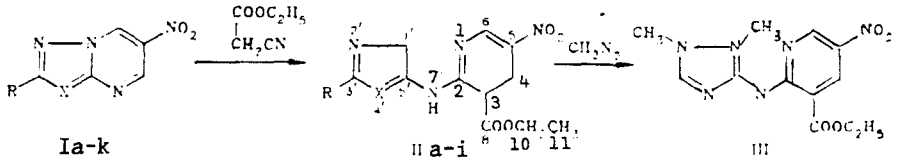


Fig. 1. Bond lengths and angles in molecule of compound IIb.

TABLE 1. Coordinates of Atoms in Structure of Compound IIb ($\times 10^4$; for H atoms, $\times 10^4$)*

Atom	x	y	z	Atom	x	y	z
$O_{(9)}$	18583(5)	−2774(3)	7117(2)	$C_{(6)}$	12181(7)	−2790(4)	10686(4)
$O_{(12)}$	15365(5)	−1591(3)	6310(2)	$C_{(6')}$	3902(9)	2046(6)	6669(5)
$O_{(14)}$	17842(6)	−4803(4)	11329(3)	$C_{(8)}$	16257(7)	−2223(4)	7162(3)
$O_{(15)}$	14380(6)	−4464(3)	12521(3)	$C_{(3')}$	5661(7)	1114(4)	7419(3)
$N_{(1')}$	7230(5)	−121(3)	8894(3)	$C_{(5')}$	8896(6)	−188(4)	7892(3)
$N_{(1)}$	11069(5)	−1976(3)	9815(3)	$C_{(10)}$	20226(8)	−2597(5)	5931(4)
$N_{(2')}$	5110(5)	717(3)	8596(3)	$C_{(11)}$	20350(9)	−3794(6)	5534(5)
$N_{(4')}$	7992(5)	587(3)	6945(3)	$H_{(N_{1'})}$	743(6)	−59(4)	965(3)
$N_{(7)}$	11240(5)	−939(3)	7806(3)	$H_{(N_7)}$	1206(7)	−85(4)	711(4)
$N_{(13)}$	15674(7)	−4284(4)	11513(3)	$H_{(16')}$	209(9)	195(5)	707(4)
$C_{(2)}$	12390(6)	−1792(4)	8689(3)	$H_{(26')}$	389(8)	166(5)	594(5)
$C_{(3)}$	14864(6)	−2435(4)	8426(3)	$H_{(36')}$	407(8)	288(5)	643(4)
$C_{(4)}$	15968(7)	−3259(3)	9359(3)	$H_{(4)}$	1766(8)	−361(4)	921(3)
$C_{(5)}$	14597(7)	−3436(4)	10513(3)	$H_{(6)}$	1131(8)	−290(4)	1139(4)

*Coordinates of H atoms of ethyl group are not listed. Values of the temperature factors of the atoms can be obtained from the authors.



I, IIa R=H, b R=CH_3, c R=SCH_3, d R=CF_3, e R=Cl, f R=NH_2, g R=$N(CH_3)_2$, h—j R=H, k R=CH_3; a—g X=N, h X=$CCOOC_2H_5$, g X=CNO_2, j,k X=CH

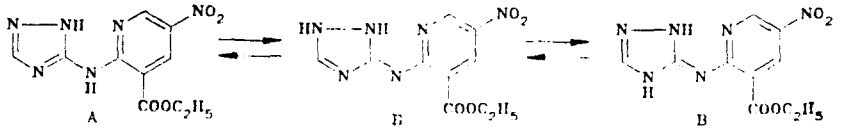
Significant conjugation in the molecule of compound IIb leads to a shortening of the $C_{(5)}$–$N_{(7)}$ bond length to 1.373(4) Å, and of the $C_{(2)}$–$N_{(7)}$ bond length to 1.351(4) Å, in comparison with the standard bond length of 1.44 Å [3]. The bond lengths in the nitro and ethoxycarbonyl groups are normal. The molecule is practically planar: The dihedral angle between the planes of the pyridine and triazole rings is 2.8°. The rotations of the nitro and ethoxycarbonyl groups relative to the plane of the pyridine ring around the $C_{(5)}$–$N_{(13)}$ and $C_{(3)}$–$C_{(8)}$ axes amount to 3.0 and 6.2°, respectively. The planarity of the molecule is due to the presence of two intramolecular hydrogen bonds $N_{(1')}$–H···$N_{(1)}$ and $N_{(7)}$–H···$O_{12)}$ [$N_{(1')}$···$N_{(1)}$ 2.24(4), $N_{(7)}$···O 1.98(4) Å, N–H···N angle 115°, N–H···O angle 137°]. Apart from the intramolecular bond $N_{(1')}$–H···$N_{(1)}$, this proton participates in the formation of an intermolecular hydrogen bond $N_{(1')}$–H···$N_{(2')}$ [$N_{(1')}$···$N_{(2')}$ 2.90(4) Å].

In the IR spectra of compounds IIk-i (Table 2*), recorded on crystals, there are absorption bands corresponding to stretching vibrations of the nitro group (1330-1350 and 1570-1595 cm^{-1}), the carbonyl group (1700-1710 cm^{-1}), and the amino group (3100-3300 cm^{-1}). The position of the band corresponding to vibrations of the C=O bond is consistent with the presence of an intramolecular hydrogen bond [4].

Thus, the compounds II in the crystalline form have the structure of 2-(5-azolylamino)-3-carbethoxy-5-nitropyridine, stabilized by two intramolecular hydrogen bonds.

In order to pinpoint the question of the form in which the transformation products exist in solution, let us examine the NMR spectroscopic data. The character and multiplicity of the ^1H and ^{13}C NMR spectra, recorded in DMSO-D_6 at 40° (Tables 2-4), are in good agreement with the structure II. In the spectrum of compound IIa, recorded in DMSO-D_6 at 25°C, the signal of the proton in position 3' is broadened; however, when the temperature is raised, the signal becomes considerably narrower, with a slight downfield shift. The same sort of spectral behavior is observed in hexamethylenephosphamide (HMPA-D_{18}). In DMSO-D_6 and DMFA-D_7, the line of the $H_{(3')}$ atom remains narrow even at 25°C. By cooling a solution of compound IIa in a mixture of HMPA-D_{18} and $CDCl_3$ to –50°C, we were able to obtain a double set of signals of protons with a 7:3 ratio of integral intensities (Fig. 2).

This sort of phenomenon can be explained by the existence of amino–imino tautomerism in solution:



The replacement of hydrogen by deuterium in the NH fragment of compound IIa, accomplished by synthesizing the compound in C_2H_5OD, leads to a considerable retardation of the exchange processes. In this case, even at 25°C, we can register two signals of the $H_{(3')}$ atom. Conditions of rapid exchange, expressed in an averaging of the signals in the ^1H NMR spectrum, are achieved at a temperature above 100°C.

Alkylation of compound IIa with diazomethane leads to the formation of only one substance: 2-(1,2-dimethyl-1,2,4-ditriazolyl-5-amino)-3-carbethoxy-5-nitropyridine (III). The position of the N-methyl groups was established on the basis of ^{13}C NMR spectroscopic data. Thus, the signal of the $C_{(3')}$ atom is registered in the form of a doublet of quartets with constants ^1J = 219.7 Hz and ^3J = 3.7 Hz; the signal of the $C_{(5')}$ is registered in the form of a doublet of quartets with constants ^3J = 6.1 Hz and ^3J = 3.7 Hz.† The signal of the $C_{(2)}$ atom in the pyridine ring, the same as in the nonalkylated compound IIa, is registered in the form of a doublet of doublets; this does not eliminate the possibility that the methyl groups may be found on the $N_{(4')}$ atom of the triazole fragment or on the exocyclic amino group. In the ^1H NMR spectrum of the dimethyl derivative of III, the chemical shift of the proton in position 3' is equal in magnitude to the chemical shift of the analogous signal of one of the forms of compound IIa.

*As in Russian original; no IR data given in Table 2; also compounds identified as IIk-i should probably be IIa-i – Translator.

†As in Russian original – Translator.

TABLE 2. Characteristics of Compounds IIa-i

Compound	Empirical formula	T_{mp}, °C	R_f	UV spectrum, λ_{max}, nm (log ε) ethanol	^{1}H NMR spectrum, δ, ppm (DMSO·D_6)					Yield, %
					OCH_2 2H, q	C–CH_3 3H, t	6-H 1H, d	4-H 1H, d.	R, s	
IIa	$C_{10}H_{10}N_6O_4$	275...278	0,50	214 (4,13), 233 (4,03), 335 (4,18)	4,46	1,41	9,15	8,81	8,03 (1H)	54
IIб	$C_{11}H_{12}N_6O_4$	300	0,43	215 (4,18), 238 (4,06), 336 (4,27)	4,43	1,38	9,18	8,83	2,29 (3H)	60
IIв	$C_{11}H_{12}N_6O_4$	300	0,46	216 (4,27), 241 (4,10), 339 (4,24)	4,43	1,38	9,15	8,85	2,55 (3H)	71
IIг	$C_{11}H_9F_3N_6O_4$	242...243	0,62	212 (4,18), 234 (4,10), 329 (4,31)	4,37	1,39	9,18	8,84	—	64
IIд	$C_{10}H_9ClN_6O_4$	232...233	0,52	214 (4,19), 240 (4,13), 333 (4,30)	4,38	1,48	9,08	8,88	—	35
IIe	$C_{10}H_{11}N_7O_4$	272...273	0,38		4,38	1,35	9,15	8,80	6,43 (2H, br.s.)	58
IIж	$C_{12}H_{15}H_7O_4$	273...275	0,40		4,40	1,40	9,18	8,80	2,90 (6H)	49
IIз	$C_{14}H_{15}N_5O_6$	232...233	0,57		4,40; 4,28*	1,40; 1,28*	9,18	8,85	8,30 (1H)	48
IIи	$C_{11}H_{10}N_6O_6 \cdot H_2O$	256...257	0,54		4,38	1,40	9,20	8,86	8,23 (1H)	65

*Signals of protons of carbethoxy group in position 4'.

TABLE 3. ^{13}C NMR Spectra of Compounds IIa-d

Compound	Chemical shift, δ, ppm (DMSO-D_6)										
	$C_{(3')}$	$C_{(5')}$	$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	$C_{(8)}$	$C_{(10)}$	$C_{(11)}$	$C_{(R)}$
IIa	148,5	150,7	156,2	108,3	135,7	137,9	149,3	166,1	63,3	14,2	—
IIb	149,1	150,1	155,3	107,2	135,0	136,6	148,9	165,0	62,3	13,8	12,6
IIc	150,0	150,6	155,8	108,7	135,8	138,2	149,2	166,0	63,4	14,2	14,0
IId	151,2	150,7	155,4	109,4	135,9	138,8	148,9	165,9	63,6	14,2	120,6

TABLE 4. SSC Constants of Compounds of IIa-d

Compound	SSCC, $J_{(C-H)}$, Hz																	
	R-3'	5'–3'	2–6	2–4	3–4	3–6	4–4	4–6	5–4	5–6	6–6	6–4	8–4	8–10	10–10	10–11	11–11	11–10
IIa	206,9	9,8	12,8	7,3	1,5	1,5	172,1	4,3	3,4	3,4	190,4	4,3	4,9	3,8	149,5	4,7	127,0	2,4
IIb	7,3	—	12,8	7,3	1,5	1,5	172,3	4,0	3,4	3,4	190,4	4,3	4,9	3,7	149,5	4,3	127,1	2,4
IIc**	3,7	—	12,8	7,6	—*	—*	172,4	4,0	3,4	3,4	190,4	4,3	4,9	3,1	149,5	4,3	127,0	2,4
IId**	39,2	—*	12,5	7,6	—*	—*	172,7	4,3	3,4	3,4	191,3	4,6	4,3	3,4	149,5	4,3	127,6	2,4

*Constant not resolved.

**J_{SCH_3} = 129.1 Hz; J_{C-F} = 269.4 Hz.

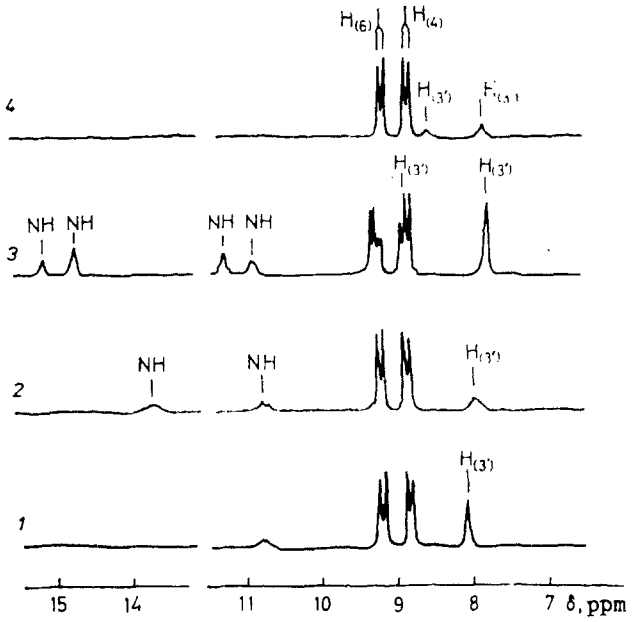


Fig. 2. ^{1}H NMR spectra of 2-(5-triazolylamino)-3-carbethoxy-5-nitropyridine IIa, recorded under the following conditions: 1) in DMSO-D_6 at 40°C; 2) in DMSO-D_6 at 25°C; 3) in mixture of HMPA-D_{18} and $CDCl_3$ at –50°C; 4) spectrum of deuterated sample, obtained in DMSO-D_6 at 25°C.

The rate constants of the exchange process, as determined from the temperature dependence of the half-width of the line corresponding to the $H_{(3')}$ signal in the ^{1}H NMR spectrum of compound IIa in the HMPA-D_{18}/$CDCl_3$ mixture at 310 K, are as follows (in sec^{-1}): 1049.92 at 310 K, 1626.80 at 320 K, 3289.76 at 330 K, 4260.12 at 340 K, and 7640.74 at 350 K. The activation energy is 45 kJ/mole.

These facts can serve as an argument in favor of the existence of the tautomers A and B in solutions at low temperatures.

EXPERIMENTAL

The IR spectra were recorded in a UR-20 instrument on KBr tablets; the UV spectra of alcohol solutions were recorded in a Specord UV-Vis instrument. The NMR spectra were obtained in a Bruker 80WP spectrometer with a roking frequency of 80.13 MHz (for ^{1}H) and 20.13 MHz (for ^{13}C), internal standard TMS. The thin-layer chromatography was performed don Silufol UV-254 plates in a chloroform–ethanol system (10:1), development in UV light.

X-ray structure study: The crystals of IIb are triclinic, a = 5.950(3), b = 10.366(5), c = 12.425(6) Å, α - 67.81(3)°, β - 72.02(3)°, γ = 72.62(3)°, V = 660.7 Å^3, Z = 2, space group R1. The structure was deciphered by the direct method and refined by the least-squares method in the full-matrix anisotropic approximation, down to R = 0.0-6 (R_w = 0.064) for 1336 reflections with $F^2 \geq 2\sigma$ (Syntex-P1 diffractometer, Ni filter, θ/2θ scanning, 3° ≤ 2θ ≤ 120°).

The 6-nitroazolo[1,5-*a*] pyrimidines were obtained in accordance with [5].

2-(Azolylamino)-3-carbethoxy-5-nitropyridines (IIa-e, h, i). A 2-mmole quantity of the appropriate 6-nitroazolo[1,5-*a*]pyridimine and 0.3 ml (2.5 mmoles) of cyanoacetic ester was refluxed in 10 ml of ethanol for 30 min. After cooling, the precipitate was filtered off and recrystallized from ethanol.

2-(5-Amino-1,2,4-triazolylamino)-3-carbethoxy-5-nitropyridines (IIf, g). A mixture of 2 mmoles of 2-dimethylamino- or 2-amino-6-nitro-1,2,4-triazolo[1,5-*a*]pyrimidine and 0.3 ml (2.5 mmoles) of cyanoacetic ester in 6 ml of DMSO was heated for 30 min at 100°C. The mixture was cooled and diluted with 50 ml of cold water; the precipitate was filtered off and recrystallized from ethanol.

2-(1,2-Dimethyl-1,2,4-triazolyl-5-imino)-3-carbethoxy-5-nitropyridine (III, $C_{12}H_{14}N_6O_4$). A suspension was prepared from 0.55 g (2 mmoles) of compound IIa in 20 ml of acetone; this suspension was cooled to 0°C, and a solution of 0.17 g (4 mmoles) of diazomethane in ether was added dropwise with mixing; the reaction mixture was held for 30 min at 0-5°C, after which the solvent was driven off. Yield 0.6 g (98%), mp 231-232°C (from a 2:1 mixture of ether and acetone). IR spectrum: 1345, 1570 (NO_2), 1770 cm^{-1} (C=O). ^{1}H NMR spectrum (DMSO-D_6): 1.40 (3H, t, CH_3); 4.40

(2H, q, CH_2); 3.44 (3H, s, NCH_3); 3.52 (3H, s, NCH_3); 8.42 (1H, d, 4-H); 8.53 (1H, s, 3'-H); 8.93 ppm (1H, d, 6-H). ^{13}C NMR spectrum (DMSO-D_6): 14.06 ($C_{(11)}$, $^1J_{(11\text{-}11)}$ = 126.9, $^2J_{(11\text{-}10)}$ = 2.5 Hz); 31.62 (NCH_3, ^1J = 147.7 Hz); 35.87 (NCH_3, ^1J = 147.7 Hz); 60.52 ($C_{(10)}$, $^1J_{(10\text{-}10)}$ = 148.9, $^2J_{(10\text{-}11)}$ = 4.9 Hz; 114.44 ($C_{(3)}$); 132.68 ($C_{(5)}$, $^2J_{(5\text{-}4)}$ = 3.7; $^2J_{(5\text{-}6)}$ = 3.7 Hz); 133.53 ($C_{(4)}$, $^1J_{(4\text{-}4)}$ = 172.1, $^3J_{(4\text{-}6)}$ = 4.9 Hz); 140.79 ($C_{(3')}$, $^1J_{(3'\text{-}3')}$ = 219.7, $^3J_{3'\text{-}NCH_3)}$ = 3.7 Hz); 148.01 ($C_{(6)}$, $^1J_{(6\text{-}6)}$ = 185.5; $^3J_{(6\text{-}4)}$ = 3.7 Hz); 152.00 ($C_{(5')}$, $^3J_{(5'\text{-}3')}$ = 6.1, , $^3J_{(5'\text{-}NCH_3)}$ = 3.7 Hz); 161.09 ($C_{(2)}$, $^3J_{(2\text{-}4)}$ = 7.3; $^3J_{(2\text{-}6)}$ = 12.2 Hz); 165.03 ppm ($C_{(8)}$, $^3J_{(8\text{-}4)}$ = 6.1; $^3J_{(8\text{-}10)}$ = 3.1 Hz).

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CHEMICAL CONVERSIONS OF 5,7-DISUBSTITUTED DIHYDRO-1,2,4-TRIAZOLO[1,5-*a*]PYRIMIDINES

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UDC 547.859.1.04:542.958.-2'943'942:543.422

Hydrolysis, oxidation, reduction, alkylation, and nitrosation of aromatic-substituted dihydro-1,2,4-triazolo-[1,5-a]pyrimidines have been studied.

We have studied the chemical properties of dihydrotriazolo[1,5-*a*]pyrimidines as exemplified by 5,7-diphenyl-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine (Ia), previously described by us [1], and its 5-methyl analog (Ib), which was obtained by condensation of 3-amino-1,2,4-triazole (IIa) with benzalacetone (IIIb). The chemical conversions of (Ia, b) are shown in the scheme shown on page 1363.

We studied the behavior of dihydroazolopyrimidines in acid and alkaline media. When solutions of (Ia, b) in 1:1 HCl are heated for 1 h, the compounds are practically completely hydrolyzed to amine (II) and the respective unsaturated ketones (IIIa, b). Compounds (Ia, b) are insoluble in aqueous alkali. In alcoholic KOH they are ionized, as shown in the electron absorption spectra of their solutions by the bands with λ_{max} at 341 and 307 nm, respectively, which disappear upon neutralization. The ionization of (Ia, b), which are quite stable in neutral medium, facilitates their heteroaromatization by atmospheric oxygen. Holding an alcoholic alkali solution of (Ib) in air forms only 5-methyl-7-phenyl-1,2,4-triazolo[1,5-*a*]pyrimidine (IVb)

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1638-1642, December, 1990. Original article submitted April 14, 1989.

0009-3122/90/2612-1362$12.50