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CYCLIZATION REACTIONS OF NITRILS.

29.* REGIOSELECTIVE SYNTHESIS OF 6-ARYL-3-CYANO-2(1H)-PYRIDINETHIONES AND THE CORRESPONDING SELENONES AND THEIR CHARACTERISTICS

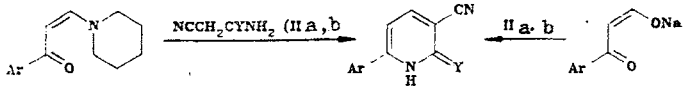
L. A. Rodinovskaya, Yu. A. Sharanin, A. M. Shestopalov, and V. P. Litvinov

UDC 547.829'735'789.6'538.1'298.4:543.422:51

The condensation of cyanothio- and cyanoselenoacetamide with 3-aryl-3-oxo-1-piperidino-1-propene or sodium 3-aryl-3-oxo-1-propen-1-olate takes place regioselectively with the formation of the 6-aryl-3-cyano-2(1H)-pyridinethiones or the corresponding selenones. Thieno[2,3-b]pyridines, thiazolo[3,2-a]pyridinium salts, and other annellated heterocycles were obtained from the 6-aryl-3-cyano-2(1H)-pyridinethiones.

The regioselectivity in the reactions of enamines of the unsymmetrical 1,3-diketone series (benzoylacetone, benzoyltrifluoroacetone, 2-acylcyclopentanone, 2-acylcyclohexanone) with cyanothioacetamide is due to the different electrophilicities of the sp^2-hybridized $C_{(1)}$ and $C_{(3)}$ atoms in the $O{=}C_{(3)}{-}C_{(2)}{=}C_{(1)}{-}N$ pentad of the β-enamino ketones [2-5]. In enamino ketones there is a larger difference in the electrophilic character of the $C_{(1)}$ and $C_{(3)}$ atoms than in 1,3-diketones. As a result of this the reactions of the β-enamines of benzoylacetone with cyanothioacetamide take place with the formation of only 4-methyl-6-phenyl-3-cyano-2(1H)-pyridinethione, whereas the analogous reaction of benzoylacetone leads to the formation of a mixture of 4-methyl-6-phenyl- and 4-phenyl-6-methyl-3-cyano-2(1H)-pyridinethiones [2].

While continuing an investigation into the reactions of β-enaminocarbonyl compounds with derivatives of cyanoacetic acid [2-7], in the present work we studied the reactions of the enamines of β-ketoaldehydes (Ia-f) with cyanothio- and cyanoselenoacetamides (IIa, b) and demonstrated the possibility of using the obtained pyridinethiones for the synthesis of difficultly obtainable annellated heterocycles. The reactions of the β-enamino ketones (Ia-f) with the amides (IIa, b) take place regioselectively with the formation of 6-aryl-3-cyano-2(1H)-pyridinethiones (IIIa-f) or the corresponding selenone (IIIg), respectively. Here the introduction of electron-withdrawing or electron-donating substituents into the benzene ring of the enamino ketones (Ia-e) does not change the direction of the reaction. Regioselectivity of the reaction is also observed in the case of the condensation of 3-(3-pyridyl)-3-oxo-1-piperidino-1-propene (If) with cyanothioacetamide (IIa). The largest yield of (IIIa-g) is obtained when the reaction is carried out in ethanol in the presence of acetic acid as catalyst. We note that the use of bases (sodium ethoxide, piperidine) as catalytic agents leads to resinification of the reaction mixture. Acid catalysis is a distinguishing feature of the reactions of β-enamino ketones (Ia-f), in contrast to the base catalysis of the reactions of the β-enamines of benzoylacetone and acylcyclopentanones and acylcyclohexanones [2-4] with cyanothioacetamide. We also obtained the 6-aryl-3-cyano-2(1H)-pyridinethiones and the corresponding selenone (IIIa-g) from sodium 3-aryl-3-oxo-1-propen-1-olates (IVa-f) and cyanothio(seleno)acetamides (IIa, b). However, their yields were somewhat lower in this method (Table 1).



I a-f III a-g IV a-g

I, IV a Ar=C_6H_5; b Ar=4-ClC_6H_4; c Ar=4-BrC_6H_4; d Ar=4-$CH_3OC_6H_4$; e Ar=3,4-$Cl_2C_6H_3$; f Ar=3-C_5H_4N; II a Y=S; b Y=Se; III a Ar=C_6H_5, Y=S; b Ar=4-ClC_6H_4, Y=S; c Ar=4-BrC_6H_4, Y=S; d Ar=4-$CH_3OC_6H_4$, Y=S; e Ar=3,4-$Cl_2C_6H_3$, Y=S; f Ar=3-C_5H_4N, Y=S; g Ar=C_6H_5, Y=Se

*For Communication 28, see [1].

T. G. Shevchenko Voroshilovgrad State Pedagogical Institute. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 805-812, June, 1988. Original article submitted December 25, 1986; revision submitted July 20, 1987.

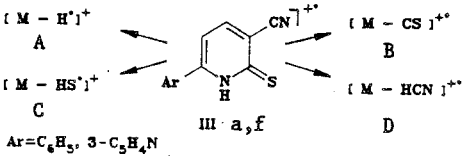
0009-3127/88/2406-0658$12.50

TABLE 1. Characteristics of 6-Aryl-3-Cyano-2(1H)-pyridinethiones and Corresponding Selenones (IIIa-g)

Compound	mp, °C (solvent)	IR spectrum, ν, cm^{-1}		PMR spectrum, δ, ppm, J, Hz					Found, %				Molecular formula	Calculated, %				Yield, %	
		C=S	C≡N	NH (s)	$C_{(4)}H$ (d)	$C_{(5)}H$ (d)	$^3J_{H_4H_5}$	Ar (m)	C	H	N	S or Se		C	H	N	S or Se	method A	method B
IIIa	254–255 decomp. (AcOH)	1208	2224	14,02	8,06	7,07	7,5	7,4; 7,8	67,8	3,9	13,1	14,9	$C_{12}H_8N_2S$	67,9	3,8	13,2	14,6	74	57
IIIb	203–204 (AcOH)	1205	2226	14,09	8,10	7,13	7,8	7,54 d; 7,80 d $^3J=5,4$	58,7	3,0	11,1	12,9	$C_{12}H_7ClN_2S$	58,4	2,9	11,4	13,0	67	38
IIIc	246 decomp. (AcOH)	1207	2228	13,96	8,12	7,12	7,7	7,62 d; 7,74 d $^3J=5,2$	49,4	2,3	9,5	11,3	$C_{12}H_7BrN_2S$	49,5	2,4	9,6	11,0	70	57
IIId	224–225 (AcOH)	1200	2221	13,94	8,04	7,03	7,6	7,08 d; 7,49 d $^3J=5,5$; 3,84 s	64,3	4,0	11,6	13,1	$C_{13}H_{10}N_2OS$	64,4	4,2	11,6	13,2	74	58
IIIe	220–221 (AcOH)	1208	2224	14,08	8,14	7,08	7,5	7,54; 7,89	51,0	2,0	9,7	11,2	$C_{12}H_6Cl_2N_2S$	51,3	2,2	10,0	11,4	79	76
IIIf	230–231* n-butanol	1207	2227	14,11	8,16	7,13	7,9	7,54 ($C_{(5)}H$) 8,16 q ($C_{(4)}H$) 8,70 q ($C_{(6)}H$) 8,90 s ($C_{(2)}H$)	62,1	3,2	19,9	15,2	$C_{11}H_7N_3S$	62,0	3,3	19,7	15,0	80	79
IIIg	216–217 decomp. ethanol	—	2226	14,12	8,12	7,18	7,5	7,42–7,83	55,7	3,3	10,9	30,3	$C_{12}H_8N_2Se$	55,6	3,1	10,8	30,5	63	50

*UV spectrum of (IIIf) in ethanol, λ_{max}, nm (log ε): 227 (4.1); 270 (3.9); 294 (3.6); 333 (3.4).

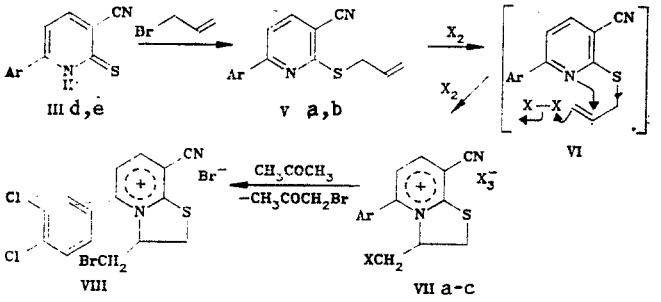
In the solid state or in solution compounds (IIIa-g) exist in the thione or selenone form. Their IR spectra contain absorption bands for the C≡N and C=S groups in the regions of 2221-2228 and 1200-1208 cm^{-1}, respectively. In the UV spectrum of (IIIf) there is an absorption maximum (λ_{max} 333 nm) characteristic of compounds containing the HNC=S fragment. In the PMR spectra of the pyridines (IIIa-g) there is a broadened singlet for the proton of the NH group in the region of δ 13.94-14.12 ppm. The signals for the protons of the $C_{(4)}$—H and $C_{(5)}$—H bonds in the pyridines (IIIa-g) appear in the form of doublets in the regions of δ 8.04-8.16 ppm and 7.03-7.18 ppm with $^3J_{H,H}$ 7.5-7.9 Hz, characteristic of the protons of the $C_{(4)}$—H and $C_{(5)}$—H bonds of pyridine [8]. In addition, we studied the mass spectra of the pyridinethiones (IIIa, f). The mass spectra of these compounds are characterized by the presence of molecular ion peaks $M^{+\bullet}$ with m/z 212 and 213, respectively, the intensities of which are maximum, and the stability to electron impact is high: W_M 44.1 and 51.5%. The main directions in the dissociation of the $M^{+\bullet}$ ions of the pyridinethiones (IIIa, f) involve elimination of the H•, CS, HS• and HCN particles and are similar to the dissociation of the $M^{+\bullet}$ ions of 4,6-disubstituted 3-cyano-2(1H)-pyridinethiones [9] with the formation of the fragments A-D. A feature which distinguishes the dissociation of the $M^{+\bullet}$ ions of compounds (IIIa, f) from 4,6-diaryl-3-cyano-2(1H)-pyridinethiones [9] is the elimination of HCN (fragment D). This is typical of the mass spectrum of pyridine itself [10] and of 3-cyano-3,4-dihydro-2(1H)-pyridinethiones [11].



The presence of the HN—C(S)—C—C≡N group in the compounds makes them suitable for the synthesis of difficultly obtainable annellated pyridines. In view of the fact that substances suitable for practical use have been found among the annellated pyridines [12, 13], we studied the reactions of compounds (IIId-f) leading to the substituted salts of thiazolo[3, 2-a]pyridinium, thieno[2,3-b]pyridines, and other annellated heterocycles.

The pyridinethiones (IIId, e) are alkylated regioselectively by allyl bromide in DMFA in the presence of potassium hydroxide with the formation of 2-allylthiopyridines (Va, b).

The action of a twofold excess of bromine or iodine on solutions of compounds (Va, b) in chloroform gave the thiazolo[3,2-a]pyridinium trihalides (VIIa-c). The tribromides (VIIa, b) were more labile than the triiodides (VIIc) and entered into reaction with acetone.



V a) Ar=4-$CH_3OC_6H_4$; b) Ar=3,4-$Cl_2C_6H_3$; VII a) Ar=4-$CH_3OC_6H_4$, X=Br; b) Ar=3,4-$Cl_2C_6H_3$, X=Br; c) Ar=4-$CH_3OC_6H_4$, X=I

Thiazolo[3,2-a]pyridinium bromide (VIII) and bromoacetone are formed here, i.e., bromination of the acetone occurs. According to the data from IR and PMR spectroscopy, the quaternization of compounds (Va, b) to (VIIa-c) takes place regioselectively with the formation of only the thiazole ring.

In the IR spectra of compounds (VIIa-c, VIII) the absorption band of the CN group is shifted toward the high-frequency region to 2240-2247 cm^{-1} compared with compounds (Va, b). This is due to the delocalization of the positive charge in the pyridine ring of the molecules of compounds (VIIa-c, VIII). In the PMR spectra the signals for the protons of the pyridine $C_{(6)}$—H and $C_{(7)}$—H bonds of compounds (VIIa-c, VIII) lie in the regions of $\delta_{C_{(6)}H}$

TABLE 2. Characteristics of 2-Alkylthio-6-(3-pyridyl)-3-cyanopyridines (Xa-f)

Compound	mp, °C (solvent)	UV spectrum λ_{max}, nm (log ε)	IR-spectrum ν, cm^{-1}		PMR spectrum, δ, ppm, $^3J_{H,H}$, Hz						Found, %				Molecular formula	Calculated, %				Yield, %
			C≡N	Z	$C_{(4)}H$ (d)	$C_{(5)}H$ (d)	$^3J_{H,H}$	CH_2 (s)	Z (s)	Py (m)	C	H	N	S		C	H	N	S	
Xa	177—178 (ethanol)	—	2220	—	8,29	7,95	8,4	—	3,83	7,5—9,2	63,2	3,8	18,3	14,3	$C_{12}H_9N_3S$	63,4	4,0	18,5	14,1	79
Xb	237—239 (ethanol—dioxane)	270 (4,2) 340 (4,0)	2218	1648	8,33	7,92	8,5	4,03	7,10	7,5—9,3	57,7	3,7	20,7	11,8	$C_{13}H_{10}N_4OS$	57,8	3,4	20,7	11,9	89
Xc	200 (dioxane)	325 (3,8) 357 (4,1)	2229	2251	8,38	7,97	8,6	4,54	—	7,5—9,3	61,9	3,1	22,2	12,7	$C_{13}H_8N_4S$	61,9	3,2	22,2	12,7	95
Xd	122—123 (ethanol—hexane 1 : 1)	262 (4,2) 335 (3,1)	2224	1722	8,30	7,95	8,4	4,22	4,05 q 1,14 t	7,56—9,26	60,2	4,4	14,0	10,7	$C_{15}H_{13}N_3O_2S$	60,2	4,4	14,0	10,7	99
Xe	249—250 (n-butanol)	242 (4,2) 266 (4,4) 334 (4,0)	2228	1708	8,31	7,95	8,4	4,11	—	7,4—9,2	57,5	3,3	15,5	11,8	$C_{13}H_9N_3O_2S$	57,6	3,3	15,5	11,8	93
Xf	142—143 (ethanol)	248 (4,3) 270 (4,3)	2220	1689	8,37*	7,96*	8,5	4,99	*	7,2—9,3	68,8	3,9	12,6	9,6	$C_{19}H_{13}N_3OS$	68,9	4,0	12,7	9,7	98

*The signals overlap.

TABLE 3. Characteristics of 3-Amino-6-(3-pyridyl)-2-Z-thieno[2,3-b]pyridines (XIa-e)

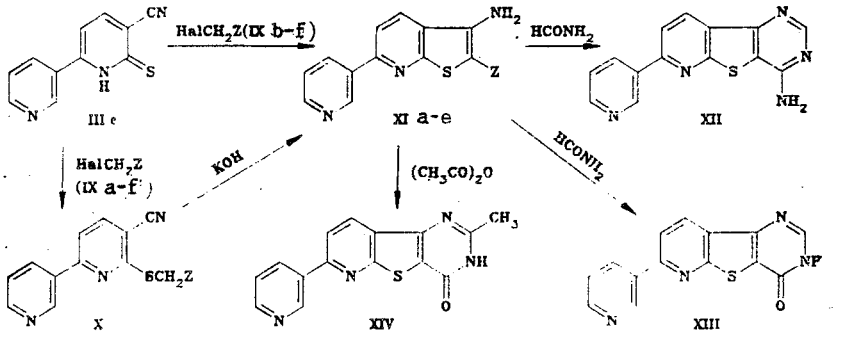
Compound	mp, °C (solvent)	UV spectrum, λ_{max}, nm (log ε)	IR spectrum ν, cm^{-1}		PMR spectrum, δ, ppm., J, Hz						Found, %				Molecular formula	Calculated, %				Yield, %
			NH_2	Z	$C_{(4)}H$ (d)	$C_{(5)}H$ (d)	$^3J_{H_4H_5}$	Py (m)	NH_2 (s)	Z	C	H	N	S		C	H	N	S	
XIa	294—295 (n-butanol)	256 (4,2) 313 (4,5)	1642 1660 3168 3235 3360	—	8,65	7,88	7,5	7,1—9,2	6,12	6,29	57,4	3,5	20,9	11,8	$C_{13}H_{10}N_4OS$	57,8	3,7	20,7	11,9	85
XIb	293—294 (n-butanol)	253 (4,1) 300 (4,4)	1640 3187 3265 3348	2218	8,71	7,98	7,8	7,40 8,43 8,61 q 9,28 q	6,93	—	62,2	3,0	22,4	13,0	$C_{13}H_8N_4S$	61,9	3,2	22,0	12,7	83
XIc	223 (n-butanol)	255 (4,1) 300 (4,6)	1638 3142 3345	1718	8,39	7,55	7,3	8,39 8,43 8,61 q 9,27 q	7,22	1,31 t 4,27 q	60,0	4,3	14,3	10,6	$C_{15}H_{13}N_3O_2S$	60,2	4,4	14,0	10,7	99
XId	303 (AcOH)	240 (4,2) 295 (3,4)	3194 3295	1705	8,66	7,95	7,8	7,95 8,66 8,77 q 9,49 q	7,26	—	57,4	3,6	15,3	12,0	$C_{13}H_9N_3O_2S$	57,5	3,3	15,5	11,8	63
XIe	227—228 (ethanol)	202 (4,7) 244 (4,1) 306 (4,5) 333 (4,5) 413 (4,0)	1605* 3155 3265 3363	*	8,69	7,85	7,5	7,1—9,3**	7,30	**	69,1	3,8	12,4	9,9	$C_{19}H_{13}N_3OS$	68,9	4,0	12,7	9,7	99

*The δ_{NH_2} and $\nu_{C=O}$ absorption bands overlap.
**The signals of the 3-C_5H_4N and C_6H_5 protons overlap.

7.93-7.98 ppm and $\delta_{C(7)H}$ 8.95-9.03 ppm, while the multiplets of the protons of the XCH_2 and CH_2 groups lie at δ 3.92-4.18 ppm. The multiplet of the proton of the NCH group is shifted downfield to δ 5.92-6.02 ppm.

The high regioselectivity in the quaternization of 2-allylthiopyridines (Va, b) to the thiazolo[3, 2-a]pyridinium salts (VIIa-c) is probably secured in the transition state (VI) by the simultaneous action of the electron acceptor (the halogen molecule Br_2, I_2) and donor (the pyridine nitrogen atom) on the double bond of the allyl fragment. The subsequent processes, i.e., cleavage of the double bond and the intramolecular quaternization, take place synchronously with the formation of the thiazolo[3,2-a]pyridinium salts (VIIa-c). These data agree with published data [14, 15] on the mechanism of the heterocyclization of unsaturated carboxylic acids, 2-allyloxy(amino)azines, and azoles.

6-(3-Pyridyl)-3-cyano-2(1H)-pyridinethione (IIIf) is also alkylated regioselectively by the halogenoalkanes (IXa-f) with the formation of the 2-alkylthiopyridines (Xa-f). According to the data from PMR spectroscopy, the position of the signal for the protons of the SCH_2Z groups of compounds (Xa-f) depends on the polarization of the C—H bond and varies with the substituent in the following order: C_6H_5—CO > CN > $COOC_2H_5$ > COOH > $CONH_2$ > H (Table 2). We used these data to predict the conditions for the cyclization of 2-alkylpyridines (Xa-f) to the thieno[2,3-b]pyridines (XIa-e).



IV, X a Z=H; b Z=$CONH_2$; c Z=CN; d Z=$COOC_2H_5$; e Z=COOH; f Z=COC_6H_5;
XI a Z=$CONH_2$; b Z=CN; c Z=$COOC_2H_5$; d Z=COOH; e Z=COC_6H_5

The cyclization of compounds (Xa-f) to the thienopyridines (XIa-e) was conducted in DMFA in the presence of an aqueous solution of potassium hydroxide at 25°C. In the case of Z = COC_6H_5 and CN complete cyclization required 15-20 min; with Z = $COOC_2H_5$ and $CONH_2$ this time was increased to 4-6 h. More rigorous conditions are required for the cyclization of 2-pyridylthioacetic acid (Xe, Z = COOH) to 3-amino-2-carboxythieno[2,3-b]pyridine (XId). This reaction was conducted by boiling in ethanol in the presence of a twofold excess of sodium ethoxide. It was not possible to obtain 3-aminothieno[2,3-b]pyridine from compound (Xa) (Z = H) under such conditions. The structures of the obtained compounds (XIa-e) were confirmed by the data from physicochemical analysis and also by single-stage synthesis from the pyridinethione (IIIf) and halogenoalkanes (IXb-f) in the presence of an excess of potassium hydroxide (Table 3). A characteristic feature of compounds (XIa-e) is the presence of absorption bands for the amino group in the IR spectra at 3142-3365 cm^{-1} and the presence of a signal for the protons of the NH_2 group at δ 6.93-7.38 ppm in the PMR spectrum. In addition, the structures of compounds (XIa-c) were confirmed by characteristic reactions. Thus, the heating of compounds (XIb, c) in formamide and of thienopyridine (XIa) in acetic anhydride leads to the formation of substituted pyrido[2,3:2',3']thieno[4,5-d]pyrimidines (XIII-XIV) respectively.

EXPERIMENTAL

The UV spectra were recorded in ethanol on a Specord UV-vis instrument. The IR spectra were recorded in tablets with potassium bromide on a UR-20 instrument. The PMR spectra were obtained on a Varian FT-80A instrument at 80 MHz in DMSO-d_6 with reference to TMS. The mass spectra were recorded on a MX-1310 instrument with direct injection (ionization chamber 150°C, ionizing potential 70 eV, emission current 100 μA). The individualities of the compounds were confirmed by TLC on Silufol UV-254 plates in the 3:5 acetone—hexane system.

6-Aryl-3-cyano-2(1H)-pyridinethiones and Selenone (IIIa-g). A. To a suspension of 10 mmole of the enamino ketone (Ia-f) in 25-30 ml of ethanol we added 0.4 ml of acetic acid and 11 mmole of cyanothio(seleno)acetamide (IIb). The mixture was heated to boiling and was then acidified with 0.2 ml of acetic acid. After 5 h the precipitate was filtered off and washed with ethanol and hexane. In the case of the selenone all the operations were carried out under argon. The data on compounds (IIIa-g) are given in Table 1.

B. The reaction of the salts (IVa-f) with cyanothio(seleno)acetamide (IIa, b) was conducted similarly to method A (Table 1).

Mass spectrum of 6-phenyl-3-cyano-2(1H)-pyridinethione (IIIa). Ion peaks (intensity, %):* 212 (100) M, 211 (13), 179 (8), 168 (23), 153 (5), 152 (7), 140 (7), 106 (5), 77 (7), 51 (5), 44 (9). W_M 44.1%.

Mass spectrum of 6-(3-pyridyl)-3-cyano-2(1H)-pyridinethione (IIIf). Ion peaks (intensity, %): 213 (100) M, 212 (19), 186 (5), 185 (8), 180 (9), 169 (18), 142 (5). W_M 51.5%.

2-Allylthio-6-aryl-3-cyanopyridines (Va, b). To a suspension of 10 mmole of the pyridinethione (IIId, e) in 20 ml of DMFA, while stirring, we added successively 5.6 ml of a 10% solution of potassium hydroxide in water and 10 mmole of allyl bromide. The reaction mixture was stirred at 25°C for 2 h, diluted with 10 ml of water, and cooled to 0°C, and the precipitate was separated. The yield of (Va) was 53% (from methanol); mp 69°C. IR spectrum: 2219 cm^{-1} (C≡N). PMR spectrum: 3.84 (3H, s, CH_3); 3.89 (2H, d, CH_2); 5.12 (1H, d, cis-CH_2=C, ^3J = 10 Hz); 5.32 (1H, d, trans-CH_2=C, ^3J = 18 Hz); 5.88 (1H, m, CH=C); 7.08 (1H, d, $C_{(5)}H$, ^3J = 8 Hz); 8.18 (1H, d $C_{(4)}H$); 7.09, 7.47 ppm (4H, d, C_6H_4, ^3J = 5.5 Hz). Found %: C 67.9; H 4.8; N 9.7; S 10.2%. $C_{16}H_{14}N_2OS$. Calculated %: C 68.1; H 5.0; N 9.9; S 10.4%.

The yield of (Vb) was 69%; mp 131-134°C. IR spectrum: 2223 cm^{-1} (C≡N). PMR spectrum: 3.92 (2H, d, CH_2); 5.09 (1H, d, cis-CH_2=C, ^3J = 10 Hz); 5.33 (1H, d, trans-CH_2=C, ^3J = 18 Hz); 5.89 (1H, m, CH=C); 7.07 (1H, d, $C_{(5)}H$, ^3J = 8 Hz); 8.21 (1H, d, $C_{(4)}H$); 7.55 ppm (3H, m, C_6H_3). Found: C 55.8; H 3.1; N 8.6; S 9.9%. $C_{15}H_{10}Cl_2N_2S$. Calculated %: C 56.1; H 3.1; N 8.7; S 10.0.

5-Aryl-3-halogenomethyl-8-cyanothiazolo[3,2-a]pyridinium Trihalides (VIIa-c). To 3 mmole of the compound (Va, b) in 5 ml of chloroform while stirring, we added dropwise a solution of 6 mmole of bromine in 5 ml of chloroform or of iodine in 30 ml of chloroform over 10-20 min. The mixture was kept at 0°C for 2 h, and the precipitate was filtered off and washed with chloroform and ether. The yield of (VIIa) amounted to 70%; mp 99-102°C (decomp.). IR spectrum: 2244 cm^{-1} (C≡N). PMR spectrum: 3.96 (3H, s, CH_3); 4.07, 4.18 (4H, m, SCH_2, $BrCH_2$); 5.92 (1H, m, NCH); 7.93 (1H, d, $C_{(6)}H$, ^3J = 8 Hz); 8.96 (1H, d, $C_{(7)}H$); 7.16, 7.53 ppm (4H, d, C_6H_4, ^3J = 5.5 Hz). Found %: C 31.7; H 2.2; Br 52.8; N 4.4; S 5.2. $C_{16}H_{14}Br_4N_2OS$. Calculated: C 31.9; H 2.3; Br 53.1; N 4.7; S 5.3%.

The yield of (VIIb) was 47%; mp 128-132°C (decomp.). IR spectrum: 2240 cm^{-1} (C≡N). PMR spectrum: 3.93; 4.09 (4H, m, SCH_2, $BrCH_2$); 6.02 (1H, m, NCH); 7.98 (1H, d, $C_{(6)}H$, ^3J = 8 Hz); 9.00 (1H, d, $C_{(7)}H$); 7.62, 7.74 ppm (3H, m, C_6H_3). Found %: C 27.9; H 1.4; Br 49.7; N 4.3; S 5.2. $C_{15}H_{10}Cl_2Br_4N_2S$. Calculated %: C 28.1; H 17.6; Br 49.9; N 4.4; S 5.0.

The yield of (VIIc) was 81%; mp 112-114°C (from nitromethane). IR spectrum: 2247 cm^{-1} (C≡N). PMR spectrum: 3.92 (3H, s, CH_3); 3.68, 3.92 (4H, m, SCH_2, ICH_2); 5.92 (1H, m, NCH); 7.93 (1H, d, $C_{(6)}H$, ^3J = 8 Hz); 8.95 (1H, d, $C_{(7)}H$); 7.14, 7.51 ppm (4H, d, C_6H_4, J = 5.5 Hz). Found %: C 24.1; H 1.6; I 63.9; N 3.4; S 3.9. $C_{16}H_{14}I_4N_2OS$. Calculated %: C 24.3; H 1.8; I 64.3; N 3.6; S 4.1%.

3-Bromomethyl-5-(3,4-dichlorophenyl)-8-cyanothiazolo[3,2-a]pyridinium Bromide (VIII). A 5-mmole sample of the tribromide (VIII) was stirred in 10 ml of acetone at 25°C for 1 h. The precipitate was filtered off and washed with acetone. The yield was 89%; mp 209°C (from nitromethane). IR spectrum: 2245 cm^{-1} (C≡N). PMR spectrum: 4.12, 4.20 (4H, m, SCH_2, $BrCH_2$); 6.02 (1H, m, NCH); 7.94 (1H, d, $C_{(6)}H$, ^3J = 8 Hz); 9.03 (1H, $C_{(7)}H$); 7.58 ppm (3H, m, C_6H_3). Found %: C 37.4; H 1.9; Br 66.2; N 6.2; S 6.4. $C_{15}H_{10}Cl_2Br_2N_2S$. Calculated: C 37.5; H 2.1; Br 66.4; N 5.8; S 6.7.

2-Alkylthio-6-(3-pyridyl)-3-cyanopyridines (Xa-f). To a suspension of 10 mmole of the pyridinethione (IIIf) in 20 ml of DMFA, while stirring, we gradually added 5.6 ml of a 10% solution of potassium hydroxide in water and 10 mmole of the corresponding alkyl halide. The

*Here and subsequently the ion peaks with intensities of ≥5% are given.

reaction mixture was stirred for 15-30 min and diluted with 10 ml of water. The precipitate was filtered off, washed with water, and dried (Table 2).

3-Amino-6-(3-pyridyl)-2-Z-thieno[2,3-b]pyridines (XIa-c, e). A. To a suspension of 10 mmole of the compound (Xb-d, f) in 20-25 ml of DMFA we added 5-6 ml of a 10% solution of potassium hydroxide. The mixture was stirred at 25°C for 18 min to 6 h and diluted with 10-15 ml of water. The precipitate was filtered off (Table 3).

B. To a suspension of 10 mmole of the pyridinethione (IIIf) in 20-25 ml of DMFA we added successively 5-6 ml of a 10% solution of potassium hydroxide in water, 10 mmole of the alkyl halide (IXb-d, f), and a further 5-6 ml of a 10% solution of potassium hydroxide. The reaction mixture was stirred at 25°C for 0.5-6 h and diluted with 5-10 ml of water. The precipitate was separated. The yield of the thieno[2,3-b]pyridines obtained by this method was 10-15% lower than by method A.

3-Amino-2-carboxy-6-(3-pyridyl)thieno[2,3-b]pyridine (XIg). To the sodium alkoxide prepared from 10 mmole of sodium and 40 ml of ethanol we added 5 mmole of compound (Xe). The mixture was boiled for 2 h and cooled to 25°C. After acidification with 10 ml of 10% hydrochloric acid the precipitate was separated (Table 3).

8-Amino-2-(3-pyridyl)pyrido[2,3:2',3']thieno[4,5-d]pyrimidine (XII). A 5-mmole sample of (XIb) was heated in 25 ml of formamide at 150°C for 2 h. The mixture was cooled to 0°C, and the precipitate was filtered off and washed with ethanol and hexane. The yield was 90%; mp 325°C (from acetic acid). UV spectrum, λ_{max} (log ε): 208 (2.9), 264 (3.2), 313 nm (3.1). IR spectrum: 1690 (δNH_2), 3070, 3400 cm^{-1} (NH_2). PMR spectrum: 7.4-8.0 (4H, 3-C_5H_4N); 7.61 (2H, s, NH_2 overlaps with 3-C_5H_4N); 8.16 (1H, d, $C_{(3)}H$); 8.6 (1H, d, $C_{(4)}H$, ^3J = 8 Hz); 8.54 ppm (1H, s, $C_{(6)}H$). Found %: C 60.1; H 3.5; N 25.2; S 11.4. $C_{14}H_9N_5S$. Calculated %: C 60.9; H 3.3; N 25.1; S 11.5.

2-(3-Pyridyl)pyrido[2,3:2',3']thieno[4,5-d]pyrimidin-8(7H)-one (XIII). A 5-mmole sample of (XIc) was heated in 15 ml of formamide at 150-160°C for 3 h. The mixture was cooled, and the precipitate was separated and washed with ethanol and hexane. The yield was 98%; mp >350°C (from acetic acid). UV spectrum λ_{max} (log ε): 260 (4.3), 322 nm (4.1). IR spectrum: 1680 (CONH), 3054 cm^{-1} (NH). Found %: C 60.1; H 2.9; N 20.2; S 11.2. $C_{14}H_8N_4OS$. Calculated % C 55.3; H 2.9; N 20.0; S 11.4.

6-Methyl-2-(3-pyridyl)pyrido[2,3:2',3']thieno[4,5-d]pyrimidin-8(7H)-one (XIV). A mixture of 5 mmole of (XIa) in 20 ml of acetic anhydride was boiled for 1 h 30 min. After cooling the precipitate was filtered off and washed with ethanol and hexane. The yield was 74%; mp 250°C (from acetic acid). IR spectrum: 1670, 1710 (CONH), 3225, 3267 cm^{-1} (NH). PMR spectrum: 2.32 (3H, s, CH_3); 7.4-8.1 (4H, 3-C_5H_4N); 8.12 (1H, d, $C_{(3)}H$); 8.35 ppm (1H, d, $C_{(4)}H$, ^3J = 8 Hz). Found %: C 61.3; H 3.2; N 19.2; S 10.8. $C_{15}H_{10}N_4OS$. Calculated %: C 61.2; H 3.4; N 19.0; S 10.9.

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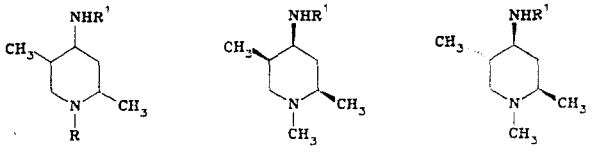
MASS SPECTRA AND THREE-DIMENSIONAL STRUCTURES OF γ-N-ARYL(ALKYL)AMINOPIPERIDINES

E. E. Stashenko, P. I. Zakharov,
V. V. Kuznetsov, L. A. Gaivoronskaya,
B. S. Subbotin, and N. S. Prostakov

UDC 547.822.3:545.51

The fragmentation of the investigated compounds proceeds with both retention and cleavage of the piperidine ring and makes it possible to distinguish the spatial orientation of the methyl group in the $C_{(5)}$ position of the ring in the analysis of the geometrical isomers of this series.

Compounds with high specific physiological activity have been found among N-substituted γ-aminopiperidines. Some of them are used as medicinal preparations [1]. We have accomplished the mass-spectrometric analysis of I-XI, which were described in [2, 3]. Compounds I-VIII were studied in the form of mixtures of two geometrical isomers, while γ-aminopiperidines, cis-IX-cis-XI and trans-IX-trans-XI were the individual cis and trans isomers, the structures of which were previously established [4]. The 1,2e,5a-trimethyl-4e-arylaminopiperidines are the cis isomers, while the 1,2e-5e,-trimethyl-4e-arylaminopiperidines are the trans isomers.



I-VIII cis-IX-cis-XI trans-IX-trans-XI

I—VII R=CH_3, VIII R=$CH_2C_6H_5$; I R^1=CH_2CH_2OH, II R^1=$CH_2CH_2CH_2OH$, III R^1= =C_6H_{11}, IV R^1=$CH_2C_6H_5$, V R^1=$CH_2CH_2C_6H_5$, VI R^1=$C_6H_4OCH_3$-*o*, VII R^1=C_6H_4Br-*o*, VIII, IX R^1=C_6H_5, X R^1=$C_6H_4OCH_3$-*p*; XI R^1= α-pyridyl

It has been previously shown that the fragmentation of piperidine and its alkyl and acyl derivatives, as well as γ-piperidols, proceeds with localization of the positive charge primarily on the piperidine nitrogen atom [5-8]. The introduction of a carbonyl or amino group leads to the development of new pathways of dissociative ionization due to partial localization of the positive charge on these substituents [9-11]. Interest in a study of the effect of substituents attached to the endocyclic and exocyclic nitrogen atoms on the fragmentation of I-XI under the influence of electron impact and under chemical-ionization conditions was generated by these properties. It was also necessary to establish the possibilities of the mass-spectrometric method for determining the spatial orientation of the methyl group in the $C_{(5)}$ position of the cis-IX-cis-XI and trans-IX-trans-XI geometrical isomers. This problem cannot be solved in the 1,2,5-trimethyl-4-hydroxypiperidine series [8].

Molecular-ion peaks (M^+) of high and medium intensity are observed in the mass spectra of I-XI (Table 1). Their stabilities (W_M) (Table 2) are determined by the nature of substituent R^1 attached to the exocyclic nitrogen atom. In the case of the presence of an aromatic R^1 radical in the molecules of IV-XI the W_M value increases by a factor of two to seven as compared with the W_M values for I-V. According to the data from the mass spectra of I-XI,

Patrice Lumumba Peoples' Friendship University, Moscow 117923. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 813-818, June, 1988. Original article submitted December 22, 1986; revision submitted August 25, 1987.

