CHEMISTRY OF AZOBENZAZOLE SYSTEMS. 1. SYNTHESIS AND STRUCTURE OF OXAZOLO[4,5-b]-PYRIDINE-2(3H)-THIONE AND ITS OXYGEN ANALOG

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We have synthesized oxazolo[4,5-b]pyridine-2(3H)-thione by reaction of 2-hydroxy-3-aminopyridine with potassium ethylxanthogenate. The structure has been confirmed by PMR, IR, and mass spectra. The thione form was established with the help of x-ray diffraction and PMR spectroscopy.

An interesting group of physiologically active compounds is benzoxazolinone (I) and related compounds. Benzoxazolinone itself and its mono- and dimethoxy derivatives are substances of plant origin, the content of which in rye and corn seedlings is responsible for the resistance of these plants to a number of diseases [1]. According to the data in [2], 6-methoxybenzoxazolinone was isolated from dry powdered *Scoparia dilcus* root. This plant was used long ago in treatment of diabetes (in India) and hypertension (in Taiwan).

Drugs having antipyretic, anticonvulsive, and tuberculostatic action have been created today on the basis of compounds in the indicated group. Analgesics and spasmolytics have also been found. Some halo- and methoxy-substituted derivatives have been patented as hypotensive drugs [3].

The sulfur analog of benzoxazolinone, benzoxazolinethione (II), also has diverse biological activity. For example, it exhibits the properties of a plant growth regulator [4], and a number of its derivatives have been proposed as insecticides [5].

As an outgrowth of our investigations of the chemical and biological properties of derivatives of compounds I and II [6, 7], in this paper we have obtained their aza analogs: oxazolopyridinone (III) and oxazolopyridinethione (IV) respectively, which are of interest for directed synthesis of compounds with potential biological effect, and the latter is also of interest as a new ambident system for theoretical studies. Compounds III and IV were synthesized by reaction -of 2-amino-3-hydroxypyridine (V) with urea or potassium ethylxanthogenate respectively.



Compounds III and IV were obtained in low yield, but when using freshly prepared xanthogenate the yield of thione IV could be increased up to 40%. Earlier, compound III was obtained in good yield from aminohydroxypyridine V and 1,1'-carbonyldiimidazole [8]. The structure of the synthesized compounds was confirmed by spectral data. Thus in the IR spectrum of oxazolopyridinone III, there are absorption bands in the 3000-2900 cm⁻¹ region and 1750 cm⁻¹, and also absorption bands from out-of-plane bending vibrations of the CH groups of the pyridine ring in the 1500 and 1610 cm⁻¹ region. The mass spectrum of compound III is characterized by a maximum M⁺ ion peak, the fragmentation of which occurs

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TABLE 1. PMR Data for Compounds III and IV, δ , ppm (spin-spin coupling constants, Hz)

Com-		here a second se		
pound	α-н. d.d	<i>β-</i> н d.d	у-н d.d	
111	8,05 (5,1, 1,0)	7,13 (8,2; 5,1)	7,63 (8,2; 1,0)	11,90
IV*	8,18 (5,2; 1,4)	7,12 (8,2; 5,2)	7,51 (8,2; 1,4)	3,08

*Solvent CDCl₃ with small CD₃OD additive.

TABLE 2. Charges (electron units) and Bond Lengths (Å) of Tautomeric Forms A and B of Compound IV

Bond	Form A		Form B		Х-гау	
j—k	charge j	bond j-+	charge j	bond j*	diffraction data, A	
1-2	-0,056	1,400	-0,061	1,402	1,380(7)	
23	-0,077	1,412	-0,022	1,331	1,38(1)	
33a	-0,101	1,423	0,204	1,426	1,423(9)	
3a-4	-0,066	1,354	-0,145	1,358	1,37(1)	
4-5	0,013	1,356	-0,029	1,349	1,352(9)	
5-6	-0,079	1,404	-0,057	1,410	1,38(1)	
6-7	-0,134	1,396	-0,140	1,390	1,45(1)	
7—7a	-0,042	1,388	-0,026	1,392	1,37(1)	
7a—1	-0,056	1,389	-0,039	1,386	1,448(9)	
3a—7a		1,411	-	1,410	1,39(1)	
8-2	0,196	1,615	-0,188	1,755	1,708(7)	

TABLE 3. Coordinates ($\times10^4$) of Nonhydrogen Atoms and Temperature Factors (Å 2 \times 10^3) of IVA Molecule

Atom	x	у	Z	U _{eq}
O(1)	10924(4)	9851 (3)	3415(5)	56(2)
C(2)	10852(13)	9354(5)	2105(8)	69(3)
N(3)	12644(10)	9685(4)	1273(6)	60(2)
C(3a)	13991(13)	10398(5)	2024(8)	61 (3)
N(4)	15885(11)	10893(4)	1558(7)	65(2)
C(5)	16726(16)	11544(5)	2533(9)	76(3)
C(6)	15753(16)	11693(9)	3880(9)	80(3)
C(7)	13733(16)	11165(5)	4334(8)	84(3)
C(7a)	12868(14)	10502(5)	3345(7)	68(3)
S(8)	8756(4)	8513(1)	1749(2)	53(1)

mainly according to the benzoxazolinone decomposition type [9]. In the mass spectrum, thione IV has an intense M⁺ ion peak, the decomposition of which occurs with ejection of fragments of the oxazole ring: COS and SCN fragments (ions with n/z 93 and 94). In addition, ejection of the fragments HC=O, C=O, HCN, H₂CN occurs, and accordingly in the spectrum we observe intense ion peaks with m/z 125, 124, 123.

In the PMR spectra of compounds III and IV (Table 1), there are three signals from protons of the pyridine ring in the form of doublets and a broad one-proton singlet at 3.08 ppm. In the case of compound IV, we assigned the latter signal to the proton of the NH group of the thione tautomeric form A, since in formation of the thiol form B the signal from the SH group should appear upfield. In the spectrum we took of the known benzo analog of compound IVb, such a signal resonates at 1.55 ppm.

In order to resolve the thiol-thione tautomerism question, we performed quantum chemical calculations for the tautomeric forms IVA and IVB and also x-ray diffraction of compound IV. The charges on the atoms and the bond lengths for the tautomeric forms IVA and IVB are given in Table 2. The calculations were done by the PM3 method in the AMPAK pro-

gram. According to the data presented in Tables 2 and 3, in molecule IV the condensed bicyclic system has a planar structure. Comparative analysis of the distances $S_{(8)}-C_{(2)}$ (1.708 Å), $C_{(2)}-N_{(3)}$ (1.383 Å), $C_{(2)}-O_{(1)}$ (1.380 Å) and the distances observed in related compounds [9, 10] is evidence in favor of the thione tautomeric form A. Differences between the computational data and the x-ray diffraction parameters (for example, for the $C_{(7a)}-O_{(1)}$ and $C_{(2)}-S_{(8)}$, bonds) are probably connected with somewhat inadequate allowance for delocalization of the double bonds in the semiempirical PM3 method. The computational data show a bond order of 1.530 for the thione bond $C_{(2)}-S_{(8)}$ and 0.615 for the ρ bond. In crystalline form, the order of this bond is probably even lower. The error in the calculated $C_{(2)}-N_{(3)}$, bond length in the opposite direction supports this hypothesis.

EXPERIMENTAL

The IR spectra were recorded on an UR-20 spectrometer in KBr pellets. The mass spectra were obtained on an MS25-RF (Kratos) instrument with direct injection of the sample into the ion source, electron ionizing energy 70 eV, ion source temperature 250°C, temperature of the sample injection system 150°C. The PMR spectra were taken on a Tesla-567A instrument in CDCl₃, operating frequency 100 MHz, internal standard HMDS.

The course of the reaction and the purity of the synthesized compounds were monitored by TLC on Silufol UV-254 plates in the solvent system benzene-ethanol, 21:2, visualized using 1 g KMnO₄ + 4 ml H₂SO₄ + 96 ml H₂O.

X-Ray Diffraction Analysis of Compound IV. The unit cell parameters and space groups were determined and refined on a Syntex-P2₁ diffractometer: a = 5.515(3), b = 14.827(3), c = 8.932(4) Å, $\beta = 95.60(2)^{\circ}$, $d_{calc} = 1.463$ g/cm³, space group P2₁/c, Z = 4.

The three-dimensional set of intensities was obtained on the same diffractometer: $\theta/2\theta$ scanning method using CuK α radiation (graphite monochromator), $\sin\theta/\lambda < 0.29$, scanning rate 10 deg/min, number of independent and nonzero reflections with $I > 2\sigma(I)$ 1445.

The structures were determined in the direct method using the program SHELXS-93 [12] (PC DOS version), where a model for the molecule could be found automatically. Subsequent Fourier syntheses made it possible to locate all the nonhydrogen atoms. The structure was refined by the least-squares method in a successively isotropic—anisotropic approximation using the program SHELX-76 [13]. The coordinates of the H atoms bonded to the carbon atoms were calculated geometrically and refined isotropically. The final value of the reliability factor was R = 0.046. The coordinates of the nonhydrogen atom from the last step of the least-squares method are given in Table 3.

Oxalol[4,5-b]pyridin-2(3H)-one (III). A mixture of 4.4 g (0.04 moles) 3-hydroxy-2-aminopyridine and 4.8 g (0.08 moles) urea were held at a temperature of 135-140°C under a stream of nitrogen for 4 h. The reaction mass obtained was poured into a 5% HCl solution, held for ~16 h, then alkalized up to pH 5-6; the precipitate was filtered off, washed with water, and dried. Obtained: 1.2 g (22%) product III with mp 203°C. After recrystallization, mp 210°C. Lit.: mp 211-212°C [8].

Oxazolo]4,5-b]pyridine-2(3H)-thione (IV). A mixture of 11.0 g (0.1 moles) 3-hydroxy-2-aminopyridine and 15.95 g (0.11 moles) freshly prepared potassium ethylxanthogenate was dissolved in 100 ml 95% ethanol and 20 ml water. The reaction mixture was boiled for 3 h in a water bath. Activated carbon (2.0 g) was added to it and this was heated for 10 min and then the carbon was filtered off. The filtrate was heated up to 60-70°C, then hot water (60-70°C) was added to it; then 12 ml acetic acid in 20 ml water was added with vigorous stirring. The solution obtained was cooled, the precipitated crystals were filtered off and dried. Obtained: 6.1 g (40%) product IVa. mp 235-237°C. After recrystallization from alcohol, mp 240°C. R_f 0.32. Found, %: N 18.39; S 21.32. $C_6H_4N_2OS$. Calculated, %: N 18.42; S 21.05.

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