INTERACTION OF 3-AROYLMETHYLENE-1,2,3,4-TETRAHYDRO-QUINOXALIN-2-ONES WITH LAWESSON REAGENT AND THE BIOLOGICAL ACTIVITY OF THE REACTION PRODUCTS

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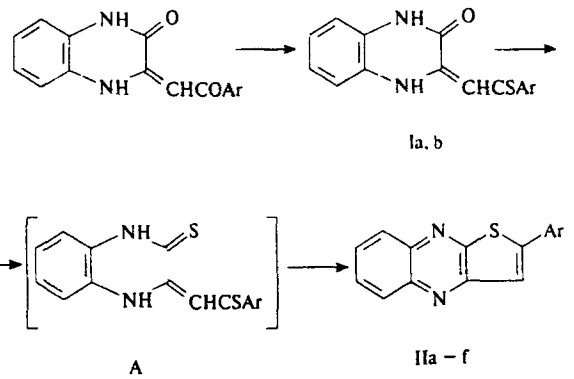
Earlier [1], we demonstrated that 3-aroylmethylene-1,2,3,4-tetrahydroquinoxalin-2-ones with a γ-dicarbonyl fragment readily enter into a cyclization reaction upon treatment with phosphorus chloroxide, with the formation of arylfuro[2,3-b]quinoxalines. Some of the latter products were found to exhibit high antiinflammatory activity [2]. At the same time, compounds with γ-dicarbonyl fragments may convert into thiophene derivatives [3, 4] upon reaction with thionating agents. It could be therefore expected that 3-aroylmethylene-1,2,3,4-tetrahydroquinoxalin-2-ones must be capable of entering into thionation and cyclization reactions with the formation of biologically active thiopheno[2,3-b]quinoxalines.

We have established that interaction between 3-aroylmethylene-1,2,3,4-tetrahydroquinoxalin-2-ones and 2,4-bis-(4-methoxyphenyl)-2,4-dithioxo-P^V, P^V-1,2,3,4-dithiophosphetan (an efficient thionating agent known as the Lawesson reagent), taken in a 2 : 1 ratio in boiling benzene, leads to the formation of of 3-thioaroylmethylene-1,2,3,4-tetrahydroquinoxalin-2-ones (Ia, b). The same reactants mixed in the equimolar ratio in boiling xylene yield 2-arylthiopheno[2,3-b]quinoxalines (IIa – f). However, prolonged boiling of quinoxalone Ia in xylene does not lead to the formation of thiopheno[2,3-b]quinoxaline (IIa). Apparently, interaction of the equimolar amounts of the initial reactants in boiling xylene leads to the formation of 3-thioaroylmethylene-1,2,3,4-tetrahydroquinoxalin-2-thiones (A) followed by cyclization of the latter under the experimental conditions studied. This conclusion is confirmed by the formation of compound IIa upon boiling of Ia and the Lawesson reagent in the ratio 2 : 1 in xylene.



Ar = Ph (Ia, IIa), 4-Me (Ib, IIb), 4-ClC_6H_4 (IIc), 4-BrC_6H_4 (IId), 4-IC_5H_4 (IIe), 2,4-$Me_2C_5H_3$ (IIf).

Quinoxalones Ia, b are red crystalline substances poorly soluble in hot DMF and DMSO. The IR absorption spectra show the bands due to stretching vibrations of the N–H bonds of heterocycles at 3140 cm^{-1} and vibrations of the amide carbonyl at 1682 and 1676 cm^{-1}, and a wide band due to superposition of stretching vibrations of the aromatic ring and the exo C=C bond at 1596 and 1610 cm^{-1} (in compounds Ia and Ib, respectively). The ^1H NMR spectrum of Ia contains a signal of the methine proton at 6.71 ppm, a group of signals centered at 7.30 ppm due to aromatic protons, and two broadened signals at 12.35 and 13.55 ppm due to protons of the N^1H and N^4H groups, respectively.

Quinoxalones are capable of prototropic tautomerism and, hence, may occur in several tautomeric forms similar to those observed earlier in 3-aroylmethylene-1,2,3,4-tetrahydroquinoxalin-2-ones [7, 8]. Intense coloration of quinoxalones Ia, Ib (with a longwave absorption maximum of the ethanol solution of Ia observed at 500 nm, $\log \varepsilon = 4.26$), suggesting the presence of a thioketone group [9], the absence of signals from methylene protons in the ^1H NMR spectrum, and the appearance of a broad weak-field signal due to the NH-group proton in the ^1H NMR spectrum, are indicative of

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TABLE 1. Physicochemical Characteristics and Antimicrobial Activity of Synthesized Compounds

Compound	Yield, %	M.p., °C	Empirical formula	MIC, μg/ml	
				St.aureus	*E.coli*
Ia	35	241 – 242	$C_{16}H_{12}N_2OS$	500	1000
Ib	42	223 – 224	$C_{17}H_{14}N_2OS$	500	1000
IIa	50	184 – 185	$C_{16}H_{10}N_2S$	125	500
IIb	60	214 – 215	$C_{17}H_{12}N_2S$	125	500
IIc	62	242 – 243	$C_{16}H_9ClN_2S$	125	500
IId	65	246 – 247	$C_{16}H_9BrN_2S$	125	500
IIe	63	255 – 256	$C_{16}H_9IN_2S$	250	1000
IIf	32	106 – 108	$C_{18}H_{14}N_2S$	–	–
Ethacridine lactate				50	2000
Mercury dichloride				1000	1000

the existence of compounds Ia, Ib in a thiophenacylidene form with high-molecular hydrogen bonds of the N^4–H...S=C type. This type is characteristic of the compounds with β-aminoethylenethiocarbonyl fragments [10].

2-Arylthiopheno[2,3-b]quinoxalines (IIa – f) have the form of light-yellow crystalline substances poorly soluble in usual organic solvents. The IR spectra of these compounds exhibit no absorption bands due to amide carbonyl groups and N–H bonds (observed for the initial quinoxalone system [7]). The UV spectrum of IIa measured in dioxane shows a longwave absorption maximum at 370 nm ($\log \varepsilon = 4.29$). The sharp hypsochromic shift of the longwave absorption maximum (against $\lambda_{max} = 420$ mm for the initial quinoxalones [1, 7]) is evidence of the loss of the conjugation system typical of the phenacylidene derivatives of quinioxalones.

EXPERIMENTAL CHEMICAL PART

The IR spectra were recorded on a UR-20 spectrophotometer (Germany) using the samples prepared as vaseline oil suspensions. The ^1H NMR spectra were obtained on a RYa-2310 spectrometer (Russia) (DMSO-d_6 solutions; HMDS internal standard). The UV spectra were measured on an SF-20 spectrophotometer (Russia).

3-Thioaroylmethylene-1,2,3,4-tetrahydroquinoxalin-2-ones (Ia, b). A mixture of 0.01 mole 3-aroylmethylene-1,2,3,4-tetrahydroquinoxalin-2-one and 0.005 mole Lawesson reagent in 50 ml benzene was boiled for 2 h. Then the product was separated by filtering from the hot solution and recrystallized from acetic acid (for compound Ia) or washed with hot toluene (Ib).

2-Arylthiopheno[2,3-b]quinoxalines (IIa – f). (a) A mixture of 0.01 mole 3-aroylmethylene-1,2,3,4-tetrahydroquinoxalin-2-one and 0.01 mole Lawesson reagent in 50 ml xylene was boiled for 5 h. Then the hot solution is decanted from the tar, the solvent is evaporated, and the residue is recrystallized from isopropanol (compounds IIa, b, f); alternatively, the solution is cooled, and the residue is filtered and recrystallized from dioxane (compounds IIc – e).

(b) Compound IIa is obtained by a similar method from a mixture of 0.01 mole 3-aroylmethylene-1,2,3,4-tetrahydroquinoxalin-2-one and 0.005 mole Lawesson reagent; yield, 41%.

EXPERIMENTAL BIOLOGICAL PART

Antimicrobial activity of compounds Ia, b, and IIa – d was determined with respect to the *E. coli* M_{17} and *St. aureus* P-209 standards by the method of consecutive double dilutions in a meat-infusion broth [11] upon loading 250 thousand microbe units per ml solution. The active dose was determined as the minimum inhibiting concentration (MIC) of the compound (maximum dilution), leading to complete growth suppression of the test microbe. The reference preparations were mercury dichloride [12, 13] and ethacridine lactate [12].

The antiinflammatory properties of compounds II and VIII were studied using a model of an acute inflammatory edema initiated by subplantar injection of 0.1 ml 1% carrageenan solution into the hind leg of 160 – 200 g white mice [14].

Data on the antimicrobial activity are presented in Table 1. It was found that 3-thioaroylmethylene-1,2,3,4-tetrahydro-2-quinoxalones exhibit a weak antimicrobial effect (MIC = 500 – 1000 μg/ml), but their cyclization into arylthiopheno[2,3-b]quinoxalines markedly increases the antimicrobial activity (maximum to MIC = 125 μg/ml). Substitution of sulfur for oxygen upon going from furo[2,3-b]quinoxalines [2] to thiopheno[2,3-b]quinoxalines leads to disappearance of the antiinflammatory activity.

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