of ice and water. After recrystallization from alcohol 8.4 g of compound XIII (100%), mp 138-140°, is obtained.

1-Methyl-6-mercapto-8-nitro-2,3,4,5-tetrahydroazepino[2,3-b]quinoline (XIV). To 3.3 g of phosphorus pentasulfide in 30 ml of dry pyridine at 20° is added slowly (over a period of 50 min) 1.5 g of compound XIII in 20 ml of dry pyridine (exothermic reaction). The reaction mixture is kept at room temperature for 30 min and then refluxed for 3 h. The pyridine is evaporated and the residue cooled and dissolved in 2 N sodium hydroxide. The solution is filtered and acidified to pH 5.0 with 2N hydrochloric acid to give 0.9 g of compound XIV (62%), mp > 170° (with decomposition). Mass spectrum: M^+ 289. Found, %: C 57.7; H 5.3; N 14.4; S 11.1. $C_{14}H_{15}N_3O_2$. Calculated, %: C 58.1; H. 5.2; N 14.5; S 11.0.

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SYNTHESIS AND ANTILEISHMANIASIS ACTIVITY OF ARYLFURYLQUINOXALINES

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In previous works we have shown that 5-aryl-2-acylfurans having a chlorine or bromine substituent at the benzene ring exhibit germostatic activity *in vitro* [1]. In the present work, we have synthesized 5-aryl-2-acetyl-, 5-aryl-2-bromoacetylfurans and 5-aryl-2-furylglyoxals having dichloro, carbethoxy, or acetylamino substituents at the benzene ring. The 5-aryl-2-furylquinoxalines were obtained from 5-aryl-2-furylglyoxals. The biological activity was studied for all of the synthesized compounds.

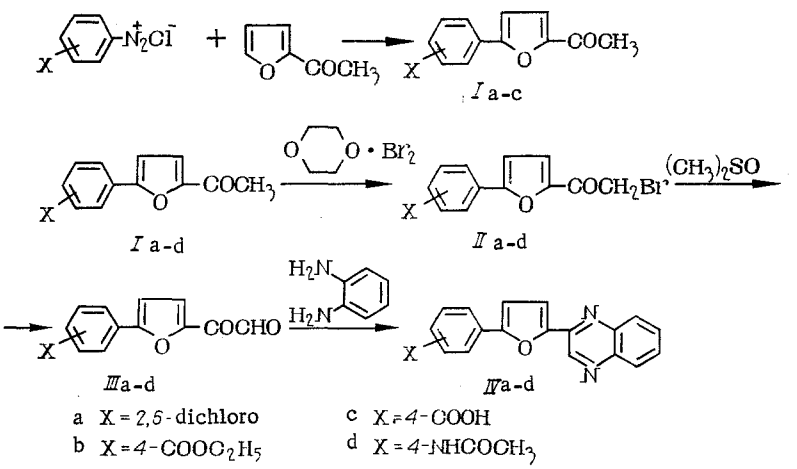

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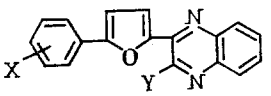
TABLE 1. Chemical Shifts of Protons* in Compounds III-VI (δ, ppm)

Compound	H_3, furan ring	H_4, furan ring	H, hydrate	H_3, quinoxaline	H, aryl substituent	NH
IIIa, IIIb	7,68 d	6,89 d	5,52c	—	7,45—7,60	—
IVa, IVd	7,59 d	6,91 d	—	9,29c	7,70—8,15	—
V	7,83 d	7,00 d	—	—	7,45—7,60	—
VI	7,96 d	6,88 d	—	—	7,20—8,00	12,69 Broadened

*The spectra were taken on a JNM4H-100 spectrometer with internal standard tetramethylsilane and solvent deuterochloroform.

Note. s) singlet, d) doublet.

TABLE 2. Antileishmaniasis Activity of 5-Arylfuryl-2-quinoxalines*



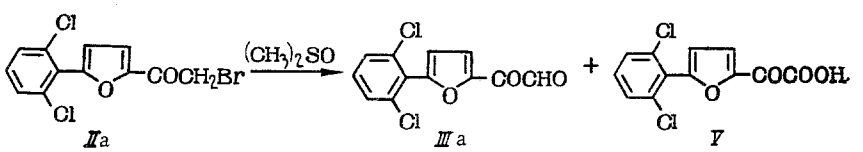
X	Y	Dose, mg/kg	Degree of local leishmaniasis infection	P	Effectiveness, %
4-Br	H	400	0,5±0,1	<0,05	58
4-Cl	H	300	0,5±0,2	<0,02	58
4-NO_2	H	150	1,2±0,3	<0,001	45
4-Br	OH	200	1,8±0,2	<0,02	22
4-Cl	OH	200	1,5±0,2	<0,01	35
4-$COOC_2H_5$	H	400	0,7±0,1	<0,01	22
4-COOH	H	400	0,9±0,3	—	0
2,6-dichloro	H	500	0,7±0,05	<0,01	30

*The activity of the studied compounds was compared with the activity of monomycin giving 100% effectiveness.

The arylfurylquinoxalines were synthesized by the following scheme: 5-aryl-2-acetylfurans (Ia-c) were obtained via the Meerwein reaction, during which we used as the diazonium components previously unused diazonium salts having 2,6-dichloro, 4-carboxy, and 4-carbethoxy groups on the benzene ring. 5-(p-Acetylaminophenyl)-2-acetylfuran (Id) was obtained by acetylation of 5-(p-aminophenyl)-2-acetylfuran (Ie), synthesized via reduction of 5-(p-nitrophenyl)-2-acetylfuran with hydrazine hydrate in the presence of Raney nickel. 5-Aryl-2-acetylfurans (Ia-d) on bromination with dioxane dibromide gave 5-aryl-2-bromoacetylfurans (IIa-d), which were oxidized with dimethyl sulfoxide to the corresponding glyoxals (IIIa-d).

5-Aryl-2-furylglyoxals, having 2,6-dichloro (IIIa) and carbethoxy (IIIb) substitutents at the benzene ring, were isolated and characterized as the hydrates; the remaining glyoxals (IIIc-d) were converted without isolation to the corresponding quinoxalines by treatment with o-phenylenediamine.

Oxidation of 5-(2',6'-dichlorophenyl)-2-bromoacetylfuran (IIa) with dimethyl sulfoxide led to the formation of a mixture of [5-(2',6'-dichlorophenyl)-2]furylglyoxal (IIIa) and [5-(2',6'-dichlorophenyl)-2]furylglycolic acid (V), which was separated by repeated recrystallization from ethyl acetate.*



*Formation of arylfurylglyoxalic acids during oxidation of 5-aryl-2-bromopropionyl- and 2-bromobutyrylfurans with DMSO was observed by us earlier [2].

TABLE 3. 5-Aryl-2-acetylfurans (Ia-e)

Compound	X	Yield, %	mp, °C*	Found, %				Empirical formula	Calc., %			
				C	H	Cl	N		C	H	Cl	N
Ia	2,6-dichloro	44	101—2	56,6	3,1	28,1	—	$C_{12}H_8Cl_2O_2$	56,5	3,2	27,8	—
Ib	4-$COOC_2H_5$	24	100—1,5	70,3	5,4	—	—	$C_{15}H_{14}O_4$	69,8	5,5	—	—
Ic	4-COOH	47	241—3 [7]	67,5	4,3	—	—	$C_{13}H_{10}O_4$	67,8	4,4	—	—
Id	4-$NHCOCH_3$	91	212,5—4,5	69,3	5,4	—	5,8	$C_{14}H_{13}NO_3$	69,1	5,4	—	5,8
Ie	4-NH_2	85	157—9	71,7	5,5	—	6,9	$C_{12}H_{11}NO_2$	71,6	5,5	—	6,9
Ie hydrochloride			180 (decomposition)	60,4	5,2	15,0	—	$C_{12}H_{11}NO_2 \cdot HCl$	60,6	5,1	14,9	—

*Compounds Ia, Id, and Ie were crystallized from ethanol, Ib from petroleum ether, and Ic from ethyl acetate.

TABLE 4. 5-Aryl-2-bromoacetylfurans (IIa-d)

Compound	Yield, %	mp, °C*	Found, %			Empirical formula	Calc., %		
			C	H	halogen		C	H	halogen
IIa	91	85,5—8	43,6	2,3	24,0 (Br) 21,3 (Cl)	$C_{12}H_7BrCl_2O_2$	43,2	2,1	23,9 (Br) 21,2 (Cl)
IIb	84	154—7	53,2	3,9	23,9	$C_{15}H_{13}BrO_4$	53,4	3,9	23,7
IIc	97	198—200	50,5	3,0	26,0	$C_{13}H_9BrO_4$	50,5	2,9	25,9
IId	96	182—4	52,4	3,9	24,6	$C_{14}H_{12}BrNO_3$	52,2	3,8	24,8

*From alcohol

TABLE 5. 2-(5'-Aryl-2'-furyl)quinoxalines

Compound	Yield, %	mp, °C*	Found, %				Empirical formula	Calc., %			
			C	H	halogen	N		C	H	halogen	N
IVa		150—1	61,8	2,7	20,2	8,2	$C_{18}H_{10}Cl_2N_2O \times H_2O$	61,7	3,1	20,3	8,0
IVb	96	165—6	73,2	4,7	—	7,9	$C_{21}H_{16}N_2O_3$	73,2	4,7	—	8,1
IVc	83	290—1	70,5	4,1	—	8,8	$C_{19}H_{12}N_2O_3 \times {}^1/_2H_2O$	70,2	4,3	—	8,6
IVd	52	262—4	72,5	4,5	—	12,7	$C_{20}H_{15}N_3O_2$	72,9	4,6	—	12,8
VI		318—20	60,1	3,0	20,1	—	$C_{18}H_{10}Cl_2N_2O_2$	60,5	2,8	19,9	—

*Compounds IVa-IVc and VI were crystallized from dioxane; IVd, from dimethylformamide.

Since a significant portion of the substance is lost during repeated recrystallization of the mixture, the ratio IIIa and V formed was determined from PMR spectra by comparing the intensity of the signals for H_3 and H_4 of the furan ring of both compounds. The IIIa and V ratio was 63 to 37%.

The arylfuryglyoxals were in the hydrated form, according to elemental analysis and PMR spectra (Table 1). The structure for the 5-aryl-2-furylquinoxalines (IVa-d) was supported by their spectra (see Table 1 and the Experimental Chemical Part).

Since the separation of the jointly formed IIIa and V was rather difficult, we used the mixture of these compounds in the reaction with o-phenylenediamine. The reaction of IIIa-V mixture with o-phenylenediamine gave the quinoxaline IVa and the corresponding 3-hydroxyquinoxaline VI, which are easily separated by virtue of their different solubilities in alcohol. The structure of the obtained hydroxyquinoxaline VI was supported by spectral data (Table 1 and Experimental Chemical Part).

EXPERIMENTAL BIOLOGICAL PART

Study of the bacterio- and fungistatic activity of the synthesized compounds was conducted by *in vitro* testing by the method of serial cultures [3] with respect to gram-positive (*Staphylococcus aureus, Streptococcus hemolyticus, C. diptheriae, B. antracoides*) and gram-negative bacteria (*E. coli, S. typhiabdominalis, Sh. dysenteria Flexneri, P. aeruginosa, Pr. vulgaris*) and pathogenic fungi (*Microsporon canosum, Trichophyton gypseum, Achorion schoenleini, Actinomyces albus, Candida albicans*). The test results show greatest antibacterial and antifungal activity for the furylglyoxal IIIa and the bromoacetylfuran IIa having two chlorine atoms on the benzene ring. Of special note is compound IIa, which has a minimum inhibiting concentration of 8 μg/ml for gram-positive bacteria, 64 μg/ml for gram-negative bacteria, and 4 μg/ml for pathogenic fungi.

In vivo study of activity was conducted for arylfurylquinoxalines IVa-d, presented in this work, and arylfurylquinoxalines, described by us previously [1] on the model of experimental dermal leishmaniasis of white mice [4]. The highest chemotherapeutic activity was noted for arylfurylquinoxalines containing a bromine or chlorine atom in the para position on the benzene ring. In tolerable doses (300-400 mg/kg), these compounds suppress the infectious process in 58% of the cases (Table 2).

Thus, among the arylfuran derivatives, the highest antibacterial, antifungal, and antileishmaniasis activity is observed for compounds having halogen substitutents on the benzene ring, which agrees with data obtained by us previously [2].

In continuation of work on elucidation of the relationship between chemical structure, antimicrobial activity, and inhibiting effect on enzymes, the effect of the synthesized compounds on the activity of bacterial DNAse-1 was studied (by the Bening modification of the Zeidel method [5]). The greatest activity with respect to DNAse was observed for compound IId, which in concentrations of 0.1-0.01% suppressed the activity of the enzyme by 80-85%.

The studied compounds do not suppress the activity of pyridoxalium enzymes, i.e., they do not disrupt the biosynthesis of essential amino acids. Apparently, the chemotherapeutic effect of the studied series of compounds is associated with a disruption of other enzymatic processes.

EXPERIMENTAL CHEMICAL PART

The IR spectra were taken on a Perkin-Elmer 457 spectrophotometer in mineral oil and the mass spectra on a Varian MAT 112 instrument with an ionizing voltage of 80 eV. Thin-layer chromatography was conducted on Silufol UV-254 with UV light as the developer.

5-(2',6'-Dichlorophenyl)-2-acetylfuran (Ia). Hydrochloric acid (105 ml, 10% solution) was heated to boiling and 8.3 g (0.05 mole) 2,6-dichloroaniline added. The reaction mixture was heated at boiling until the major portion of the precipitate was not dissolved. It was cooled to 10°C and 3.5 g (0.05 mole) sodium nitrite in 6 ml water was added. The solution was mixed for 10 min at 10°C, filtered, and then a solution of 5.5 g (0.05 mole) 2-acetylfuran in 4 ml acetone and a solution of 2.1 g copper chloride in 3 ml water were added. The reaction mixture was stirred for 4 h at 40-45°C, cooled to room temperature, and 20 ml water added. The precipitate was filtered off. The yields and elemental analysis data for the 5-aryl-2-actylfurans Ia-d are given in Table 3.

5-(p-Carboxyphenyl)-2-acetylfuran (Ic). p-Aminobenzoic acid hydrochloride, obtained from 27.4 g (0.2 mole) p-aminobenzoic acid, 42 ml water, and 96 ml concentrated hydrochloric acid, was diazotized with a solution of 13.8 g (0.2 mole) sodium nitrate in 60 ml water at 0-5 °C. The reaction mixture was stirred for 10 min at 10°C, then 22 g (0.2 mole) 1-acetylfuran in 20 ml acetone and 4 g copper chloride in 8 ml water were added. The reaction mixture was stirred for 4 h at 25°C and 150 ml water added. The precipitate was filtered off and washed with water. R_f 0.58 (chloroform—methanol, 5:1). IR spectrum, cm^{-1}: ν_{COOH} 3120, 2660, 2550, 1700; ν_{CO} 1640.

5-(p-Carboethoxyphenyl)-2-acetylfuran (Ib) was obtained in the same conditions described above, at pH 4.0.*

5-(p-Aminophenyl)-2-acetylfuran (Ie). Hydrazine hydrate (10 ml, 99.5% solution) and 8.4 g Raney nickel were added to a solution of 6.2 g (0.03 mole) 5-(p-nitrophenyl)-2-acetylfuran [6] in 370 ml absolute ethanol. The solution was heated at boiling for 2.5 h. After cooling the catalyst, it was filtered off and the solvent was distilled off in vacuum. The residue was recrystallized from ethanol. R_f 0.31 (ether—chloroform, 1:1). IR spectrum, cm^{-1}: ν_{NH_2} 3460, 3350, 3220; δ_{NH_2} 1610, ν_{CO} 1640.

5-(p-Acetylaminophenyl)-2-acetylfuran (Id). A mixture of 2.0 g (0.01 mole) Ie, 6 ml acetic anhydride, and 15 ml benzene were boiled for 30 min. After cooling, the precipitate was filtered off and washed with water.

5-(2',6'-Dichlorophenyl)-2-bromoacetylfuran (IIa). Dioxane dibromide (2.2 g) was added portionwise to a solution of 2.3 g (0.009 mole) Ia in 50 ml ether. The reaction mixture was stirred for 4 h at room temperature, boiled for 15 min, and decanted into 250 ml water after cooling. The precipitate formed was filtered off, washed with water, and recrystallized. IIb-IIe† were obtained analogously. Yields, constants, and elemental analysis data are given in Table 4.

[5-(4-Carboethoxyphenyl)-2-furyl]glyoxal hydrate (IIIb). A solution of 6.9 g (0.02 mole) IIb in 35 ml DMSO was heated for 2 h in a hot water bath and allowed to stand overnight. On the following day, 100 ml ice water was added and the IIIb precipitate formed was filtered off, washed with petroleum ether, and recrystallized from 50% ethanol. IIIb was obtained in 4.0 g (67%) yield, mp 148-150°C. IR spectrum, cm^{-1}: ν_{OH} 3540-3150; ν_{CO} 1720, 1680, 1650. Found, %: C 62.0; H 4.8. $C_{15}H_{12}O_5 \cdot H_2O$. Calculated, %: C 62.0; H 4.9.

[5-(2',6'-Dichlorophenyl)-2-glyoxal Hydrate (IIIa) and [5-(2',6'-dichlorophenyl)-2-furyl]-glycolic Acid Hydrate (V). A solution of 17.5 g (0.05 mole) IIa in 90 ml DMSO was heated for 2 h in a water bath and allowed to stand overnight. On the following day, 200 ml ice water was added and the precipitate formed was filtered off and treated with hot water. The precipitate IIIa formed on cooling the aqueous solution was filtered off. Yield, 5.5 g (36%) IIIa, mp 95-97°C, R_f 0.71 (chloroform—ether, 2:1). IR spectrum, cm^{-1}: ν_{OH} 3380, 3120; ν_{CO} 1670. Found, %: C 49.8; H 2.8; Cl. 24.7. $C_{12}H_6Cl_2O_3 \cdot H_2O$. Calculated, %: C 50.2; H 2.8; Cl 24.7. The water-insoluble residue was repeatedly recrystallized from ethyl acetate. Yield, 2.9 g (18%) V, mp 153-155°C. Found, %: C 47.8; H 2.7; Cl 23.4. $C_{12}H_6Cl_2O_4 \cdot H_2O$. Calculated, %: C 47.5; H 2.7; Cl 23.4.

2-[5'-p-Carboethoxyphenyl)-2'-furyl]quinoxaline (IVb). Sodium bisulfite (17 ml, 48% solution) was added to a solution of 1.5 g (0.005 mole) IIIb in 200 ml ethanol. The precipitate formed was filtered off, washed with ethyl acetate, dissolved in 100 ml boiling water, and added to a solution of 0.4 g o-phenylenediamine in 5 ml water. The reaction mixture was heated at 70°C for 30 min, then cooled to room temperature. The precipitate formed was filtered off. IR spectrum, cm^{-1}: ν_{COOEt} 1710, 1610, 1280. Yields, constants, and elemental analysis data for compounds IVa-d and VI are given in Table 5.

2-[5'-(p-Carboxyphenyl)-2'-furyl]quinoxaline (IVc). A solution of 1.5 g (0.005 mole) IIc in 10 ml DMSO was heated for 2 h in a hot water bath and allowed to stand overnight. On the following day, 100 ml ice water was added and the precipitate formed filtered off and dissolved in 60 ml 60% ethanol. Sodium bisulfite (5 ml, 48% solution) was added to the alcohol solution. The precipitate formed was filtered off, washed with acetone, dissolved in 100 ml

*The pH of the diazonium salt solution was adjusted to 4.0 by adding a saturated solution of sodium acetate.

†Compounds IIc, IId were obtained in saturated dioxane solution.

boiling water, and added to a solution of 0.4 g o-phenylenediamine in 5 ml water. The reaction mixture was heated at 70°C for 30 min and cooled to room temperature. The precipitate was filtered off. IR spectrum, cm^{-1}: ν_{OH} 3600-3440 (broad); ν_{COOH} 3120, 2660, 2550, 1700-1670.

2-[5'-(p-Acetylaminophenyl)-2'-furyl]quinoxaline (IVd). A solution of 2.6 g (0.008 mole) IId in 13 ml DMSO was heated for 2 h on a hot water bath and allowed to stand overnight. On the following day, 100 ml ice water was added and the precipitate formed was filtered off and dissolved in 70 ml 50% ethanol. o-Phenylenediamine (0.9 g, 0.008 mole) in 12 ml water was added with stirring to the obtained solution. The reaction mixture was heated at 70°C for 30 min and cooled to room temperature. The precipitate formed was filtered off. IR spectrum, cm^{-1}: ν_{NH} 3300-3040; ν_{CO} 1680.

2-[5-(2',6'-Dichlorophenyl)-2-furyl]quinoxaline (IVa) and 3-Hydroxy-2-]5-(2',6'-dichlorophenyl)-2-furyl]quinoxaline (VI). o-Phenylenediamine (4.8 g in 58 ml water) was added with stirring to a solution of 15.7 g mixture of compound IIIa and V in 700 ml 60% ethanol. The reaction mixture was heated at 70°C for 30 min and cooled to room temperature. The precipitate formed was filtered off. R_f 0.14 (chloroform, yellow spot). IR spectrum, cm^{-1}: ν_{CO} 1670. UV spectrum, nm: λ_{max}, nm (log ε): 384 (4.41); 218 (4.30). Mass spectrum of quinoxaline VI: M^+ 356 (358/360). The distribution of peak intensities indicated the presence of two chlorine atoms in the compound. After precipitation of VI, the mother liquor was evaporated *in vacuo* to half the volume. The precipitate formed after cooling was filtered off. R_f 0.36 (chloroform, yellow spot). IR spectrum, cm^{-1}: ν_{OH} 3130-3060. UV spectrum, nm: λ_{max}, (log ε) 372 (4.29); 290 (4.30).

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