30 min, after which it was cooled, diluted with water, and neutralized with 10% hydrochloric acid. The precipitate was filtered off and crystallized from an appropriate solvent (see Table 2).

LITERATURE CITED

1. M. P. LaMontagne, J. Med. Chem., 16, 68-72 (1973).
2. E. F. Elslager and D. F. Worth, US Patent No. 2925417 (1960); Ref. Zh. Khim., No. 5L285 (1962).
3. W. C. Austin, W. Courtney, J. C. Danilewicz, et al., Nature, 212, 1273-1274 (1966).
4. W. J. Ross, W. B. Jamieson, and M. C. McCowen, J. Med. Chem., 15, 1035-1040 (1972).
5. R. B. Burrows, and A. P. Phillips, US Patent No. 3772287 (1973); Ref. Zh. Khim., , No. 21H381P (1974).
6. V. A. Anisimov and A. F. Pozharskii, Khim. Geterotsikl. Soedin., 137-138 (1974).
7. L. Bellamy, New Data on the Infrared Spectra of Complex Molecules [Russian translation], Moscow (1971).
8. A. F. Pozharskii, I. S. Kashparov, P. Dzh. Kholls, et al., Khim. Geterotsikl. Soedin., 543-552 (1971).
9. E. Reimann, Justus Liebigs Ann. Chem., 750, 109-114 (1971).
10. W. West (editor), Chemical Applications of Spectroscopy, New York (1956), p. 787.
11. Tukumi Katsumoto, Bull. Chem. Soc. Japan, 33, 242-250 (1960).
12. A. I. Krotov, Bases of Experimental Therapy of Helminthosis [in Russian], Moscow (1973).

SYNTHESIS AND BIOLOGICAL PROPERTIES OF ARYLOXYFURAN DERIVATIVES

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In works which we have previously published [1, 2], it was shown that among the 5-aryl-2-acylfuran derivatives there is a large number of substances which have biological activity.

The object of the present work was the synthesis and study of analogous derivatives of an aryloxyfuran, to follow the effect of replacing the aryl residue by an aryloxy group on the biological activity of the synthesized substances.

We prepared the aryloxyfurans by the following scheme, which is described in the literature [3]:

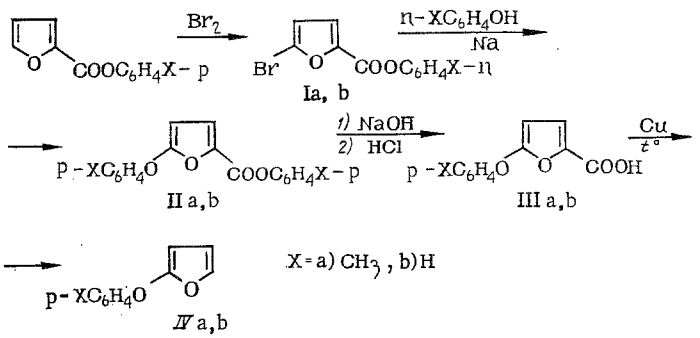

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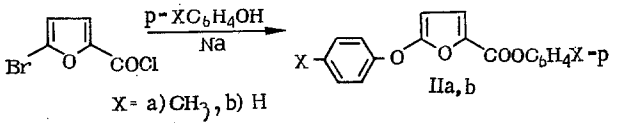
TABLE 1. Minimum Bacterio- and Fungistatic Concentrations of Arylfuran and Aryloxyfuran Derivatives (in μg/ml)

Compound	Form of microorganism			
	A	B	C	D
Thiosemicarbazone of Va	>1000	>1000	125	1000
Thiosemicarbazone of Vb	>1000	>1000	62	1000
Oxime of Va	>1000	>1000	32	32
Oxime of Vb	>1000	>1000	>1000	>1000
III a	>1000	>1000	250	>1000
III b	>1000	>1000	1000	5000
II a	>1000	>1000	>1000	>1000
II b	>1000	>1000	>1000	>1000
VII a	>1000	>1000	>1000	>1000
VII b	>1000	>1000	250	>1000
VIII a	>1000	>1000	>1000	>1000
VIII b	>1000	>1000	0,25	>1000
IX a	>1000	>1000	62	500
IX b	500	>1000	125	1000
X a	>1000	>1000	1,6	16
X b	>1000	>1000	0,06	16

Note. A) *St. aureus, Str. haemolyticus, C. diphteriae, B. ant-racoides*; B) *E. coli, S. typhi* abdominalis, *Sh. dysenteriae* Flexneri, *Proteus vulgaris, B. pyocyaneum*; C) *Mycobacterium tuberculosis* typus humanus (H-37); D) *Microsporon lanosum, Trichophyton gypseum, Achorion Schönleini.*

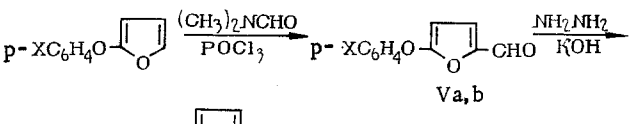
We also worked out another route for synthesis of the aryloxyfurans, which made it possible to cut down the number of stages and increase the yield of final product. In the scheme which we propose, aryl esters of 5-aryloxypyromucic acids are prepared by the direct reaction of 5-bromopyromucyl chloride with phenol or cresol.



X = a) CH_3, b) H

IIa,b

By Vilsmeier formylation of the aryloxyfurans we prepared the corresponding 5-aryloxyfurfurals (Va, b) and their carbonyl group derivatives (oximes and thiosemicarbazones). Kishner reduction of the 5-aryloxyfurfurals led to the 5-aryloxy-2-methylfurans (VIa, b).



Va,b

X = a) CH_3; b) H

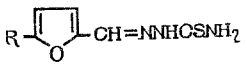
VI a,b

The biological activity of the compounds synthesized was investigated in several directions.

Antimicrobial activity was studied by the serial dilution method on Höttinger bouillion (for bacteria), on Soton medium (for mycobacteria), or on Saburo medium (for molds).

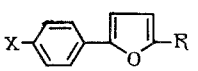
The tests performed showed that the bacterio- and fungistatic activity of the aryloxyfurans is close to that of the arylfurans.

TABLE 2. Antiblastic Effect and Toxicity of 5-Aryloxy- and 5-Arylfurfural Thiosemicarbazones



Compound	R	Means of introduction	Max. tolerable dose (mg/kg)		Antitumor effect	
			mice (6 injections)	rats (8 injections)	Sarcoma-45 rats	Sarcoma-180 mice
VIIa	C_6H_5	Intraperitoneally	125	200	±	Up to +
VIIb	p- $CH_3C_6H_4$	By mouth	50	>200	±	+ in toxic dose
VIIc	p- ClC_6H_4	Intraperitoneally	25	150	—	—
		By mouth	30	--	—	±
VIId	p- BrC_6H_4	Intraperitoneally	—	>100	+	—
		By mouth	~100	>300	+	0
		Intraperitoneally	25	>100	—	± to + in toxic dose
VIIe	p- $O_2NC_6H_4$	By mouth	375	—	0	+
		Intraperitoneally	250	200	0	+
Thiosemicarbazone of Va (etc.)	C_6H_5O	By mouth	~50	~50	—	±
	p- $CH_3C_6H_4O$	" "	~75	~75	0	+

Note: ±) Up to 30% retardation of tumor growth; +) tumor growth retardation from 30 to 59%.



IIIa-e; III-IVa,b

IIIa-e: R = CH=NNHCSNH$_2$

IIIa,b: R = CH=NOH

IVa,b: R = COOH

Va,b: R = $COOC_2H_5$

X = a) CH_3, b) H, c) Cl, d) Br, e) NO_2

The esters of the arylpyromucic acids (X) are an exception; these have a high tuberculostatic (0.06-1.6 μg/ml) and fungistatic (16 μg/ml) activity with respect to dermatophytes, while the esters of the aryloxypyromucic acids (II) do not exert this action (Table 1).

In the present work we also studied the antiblastic activity of the thiosemicarbazones of 5-aryloxyfurfurals and 5-arylfurfurals [1].

The antiblastic activity and toxicity of the thiosemicarbazones upon repeated injection was studied in 70 experiments on mice with sarcoma-180 and rats with sarcoma-45 (900 animals).

All the thiosemicarbazones studied, on injection in tolerable doses, caused retardation in the growth of tumors in the range from 30 to 70%. The antiblastic effect and toxicity of the aryloxyfurfural thiosemicarbazones (Va, b) and arylfurfural thiosemicarbazones (VIIa-e) differed little from one another. Introduction of various substituents into the benzene ring of the arylfurfural thiosemicarbazones (VIIb-e) did not lead to obtaining more active compounds in the antitumor respect (Table 2).

In the process of the investigation it was ascertained that on peroral introduction these substances have an appreciable toxicity, which was expressed more strongly in compound VIIb and in the thiosemicarbazone of Va (see Table 2).

As a study of the antitumor activity of other representatives of the arylfuran series showed (5-aryl-2-methylfurans [1], 5-aryl-2-ethoxymethylfurans [1], 5-arylfurfural oximes [4], and 5-aryl-2-(ω-bromoacetyl)furans [2]), an antiblastic effect is completely lacking in these compounds. On the basis of this fact, it may be assumed that the inhibition of tumor growth has been brought about by the presence of the thiosemicarbazone group in the structure of the molecule.

EXPERIMENTAL

p-Tolyl 5-Bromopyromucate (Ia). To a solution of 99.5 g (0.5 mole) of p-tolyl pyromucate [5] in 430 ml of dry dichloroethane, with boiling and stirring, was added, dropwise, a solution of 80.6 g (0.5 mole) of bromine in 30 ml of dry dichloroethane. Then the mixture was boiled, with stirring, for 1 h and was evaporated under vacuum; the residue which crystallized on cooling was collected on a suction filter and recrystallized from petroleum ether. The yield of Ia was 55.6 g (40%), mp. 84-85°. Found, %: C 50.8; H 3.3. $C_{12}H_9BrO_3$. Calculated, %: C 51.3; H 3.2.

p-Tolyl 5-(p-Tolyloxy)pyromucate (IIa). Method A. To 85 g of p-cresol at 70° was added 1.3 g of metallic sodium, gradually, with stirring. To the solution of sodium p-cresoxide in p-cresol so obtained was gradually added 14.5 g of p-tolyl 5-bromopyromucate. The reaction mixture was heated at 150° for 2 h; the excess cresol was distilled off under vacuum, and the residue was treated with 300 ml of water. The organic layer was separated and the water was extracted with ether (four portions of 50 ml each). The ether extract, combined with the organic layer, was dried with sodium sulfate; the dried solution was evaporated under vacuum, and the residue was distilled. The yield of IIa was 6.1 g (39%), bp. 218-220° (1 mm), mp. 92-93° (from hexane). Found, %: C 74.0; H 5.2. $C_{19}H_{16}O_4$. Calculated, %: C 74.0; H 5.2.

Method B. To the sodium cresolate prepared from 400 g of p-cresol and 10.3 g of sodium, with heating to 70° and stirring, was gradually added 33.5 g (0.16 mole) of 5-bromopyromucyl chloride [3].

The reaction mixture was heated with stirring at 150° for 8 h. The excess cresol was distilled off under vacuum, and the residue was treated with 250 ml of water. The organic layer was separated and the water layer was extracted with benzene. The benzene extract, combined with the organic layer, was washed with 2 N hydrochloric acid to a neutral reaction, dried with sodium sulfate, evaporated under vacuum, and the residue was distilled. The yield of IIa was 31.4 g (64%). The phenyl ester of 5-phenoxypymucate acid (IIb) was prepared similarly in 62% yield, mp. 54-56°; literature data [3]: mp. 52-53°.

5-(p-Tolyloxy)pyromucic acid (IIIa). Compound IIa (54.8 g) was boiled for 2 h with 150 ml of 20% sodium hydroxide solution, with stirring. Water (300 ml) was added to the reaction mixture. The water solution was filtered, and the filtrate was acidified with concentrated hydrochloric acid. The precipitate which fell was collected on a suction filter, washed with water to a neutral reaction, and dried in a vacuum desiccator. The yield of IIIa was 38.8 g (99%), mp. 140-142° (from benzene). Found, %: C 65.6; H 5.0. $C_{12}H_{10}O_4$. Calculated, %: C 66.0; H 4.6. 5-Phenoxypyromucic acid (IIIb) was prepared similarly in 93% yield, mp. 122-123°. According to [3], it has mp. 122-123°.

2-(p-Tolyloxy)furan (IVa). Compound IIa (58.2 g) and 0.05 g of copper powder were heated in a distilling flask under a vacuum of 8 mm. Thereupon compound IVa passed over into the receiver, yield 39.3 g (85%), bp. 101-104° (8 mm). Found, %: C 75.7; H 5.9. $C_{11}H_{10}O_2$. Calculated, %: C 75.8; H 5.8. 2-Phenoxyfuran (IVb) was prepared similarly in 86% yield, bp. 116° (30 mm). According to the literature [3], it has bp. 105-106° (18 mm).

5-(p-Tolyloxy)furfural (Va). To a mixture of 10 ml of dimethylformamide and 15.3 g (0.1 mole) of phosphorus oxychloride, kept at room temperature for 30 min, was added 17.4 g (0.1 mole) of IVa, at such a rate that the reaction temperature did not rise above 40°. The mixture was then stirred for 0.5 h at 35-40°. The contents of the flask were poured onto ice, the aqueous solution so obtained was neutralized with sodium carbonate, and it was extracted with benzene. The combined benzene extracts were dried with ignited potassium carbonate. The yield of Va was 14.3 g (71%), bp. 154-160° (2 mm), mp. 51-52° (from alcohol). Found, %: C 71.3; H 5.0. $C_{12}H_{10}O_3$. Calculated, %: C 71.3; H 5.0. Thiosemicarbazone: mp. 147-148° (from alcohol). Found, %: C 56.8; H 4.7. $C_{13}H_{13}N_3O_2$. Calculated, %: C 56.7; H 4.7. Oxime: mp. 150° (from alcohol). Found, %: C 66.3; H 5.2; N 6.7. $C_{12}H_{11}NO_3$. Calculated, %: C 66.3; H 5.1, N 6.4.

5-Phenoxyfurfural (Vb) was prepared similarly in 64% yield, bp. 140-144° (2 mm); the compound was not analyzed, since it rapidly discolors and decomposes in the air. Thiosemicarbazone: mp. 146° (from 50% alcohol). Found, %: C 55.2; H 4.2; N 16.2. $C_{12}H_{11}N_3O_2$. Calculated, %: C 55.2; H 4.2; N 16.1. Oxime: mp. 137-138° (from 50% alcohol). Found, %: C 65.1; H 4.3; N 6.7. $C_{11}H_9NO_3$. Calculated, %: C 65.0; H 4.5; N 6.9.

2-Methyl-5-(p-tolyloxy)furan (VIa). Compound Va (4.7 g, 0.02 mole) and 5 ml of hydrazine in 25 ml of ethylene glycol were boiled for 15 min. To the reaction mixture, cooled to 50°, was added 4 g of potassium hydroxide, the mixture was boiled for 30 min; it was cooled, 25 ml of water was added, and the mixture was extracted with benzene. The benzene extract was dried with ignited potassium carbonate. The yield of IVa was 3.4 g (90%), bp. 122-123° (9 mm), n_D^{20} 1.5303. Found, %: C 76.6; H 6.3. $C_{12}H_{12}O_2$. Calculated, %: C 76.6; H 6.4.

2-Methyl-5-phenoxyfuran (VIb) was prepared analogously in 78% yield bp. 80-81° (2 mm); n_D^{20} 1.5320. Found, %: C 76.2; H 6.0. $C_{11}H_{10}O_2$. Calculated, %: C 75.8; H 5.8.

LITERATURE DATA

1. A. F. Oleinik, T. I. Vozyakova, and K. Yu. Novitskii, Khim.-Farm. Zh., No. 7, 19-22 (1971).
2. A. F. Oleinik, G. A. Modnikova, K. Yu. Novitskii, et al., Khim.-Farm. Zh., No. 5, 7-13 (1974).
3. D. Manly and E. Amstutz, J. Org. Chem., 21, 516-519 (1956).
4. A. F. Oleinik, T. I. Vozyakova, G. A. Modnikova, et al., Khim. Geterotsikl. Soedin., No. 11, 1448-1452 (1972).
5. N. Eiji, A. Hiroo, T. Hiroshi, et al., Chem. Abstr., 68, 49377w (1968).

PREDICTION OF DRUGS HAVING THE HIGHEST ACTIVITY WITHIN A SERIES*

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UDC 615.015.07

The ever-increasing flow of synthetic drugs has in recent years made it clear that there is a need to systematize these drugs into classes according to the nature of their pharmacological effects. Furthermore, with the object of economizing in time and materials in the search for new drugs, increasingly sophisticated methods for the prediction of compounds having the desired biological activity have been proposed [1].

In order to clarify the relationships within a series of drugs having similar effects, it is necessary (in contrast to the "screening" stage) to take into account in great detail specific physicochemical information and any previously established relationships. Thus, at the present time it is very important to be able to predict the drug within a given series which possesses the highest activity. This is of importance for two reasons. First, it is necessary to test only some 20-30 compounds instead of an experimental selection of the whole family of compounds with a given range of substituents. Secondly, quantitative relationships expressed in a clear form enable the volume of information to be stored in the computer memory, and hence the time spent in searching, to be reduced. It is also possible to calculate the values of properties which correspond to the type of activity under consideration for any given compound in a series.

Two very effective approaches of this sort are known, namely, the Hansch correlation [2], and the Free-Wilson structure-additivity calculation [3]. The principles on which these methods are based are empirical and intuitive. Furthermore, "the time factor in the interaction of the drug with the body has been neglected" [4]. It is therefore of interest to examine in detail the chemical kinetics of this process, and to compare the results with correlations already found. We shall not concern ourselves with the kinetic curves themselves; the mathematical apparatus of chemical kinetics will be utilized for the derivation, and as a basis for correlations of the property—property type.

*Presented in the form of a discussion.

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