SYNTHESES BASED ON ARYLFURFURALS

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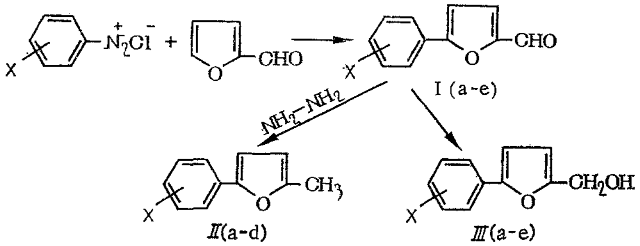
A series of physiologically active materials has recently been found among arylfuran derivatives [1, 2], which has stimulated interest in this class of compounds.

Meerwein arylation of furfural can be used to obtain arylfurans; in this case the aryl residue enters into position 5 of the furan ring [1-4]. However, in the majority of cases [1-3] the formed 5-arylfurfurals were not isolated in an individual state.

This research studied the arylation of furfural with phenyldiazonium salts having electron-accepting substituents in the benzene ring. All of the 5-arylfurfurals (Ia - e) obtained in this case were isolated individually and characterized in detail. Kishner reduction of arylfurfurals (Ia-d) gives the corresponding 2-methyl-5-arylfurans (IIa-d) in high yield; 5-(p-nitrophenyl)furfural (Ie) does not form the corresponding arylfuran upon Kishner reduction. Reduction of aldehydes Ia-e with sodium borohydride gave high yields of the corresponding 2-hydroxymethyl-5-arylfurans (IIIa-e), transformed further into their acetates and ethyl ethers.



X =a) P =F, b) m=F , c) P =Br, d) P =Cl, e) P =NO$_2$

TABLE 1. 5-Arylfurfurals

Compound	Yield (%)	Mp (deg)	Found (%)		Empirical Formula	Calc. (%)		IR spectrum ν (cm⁻¹) (CHO)	UV spectrum λ max (nm)	lg ε (ethanol)
			C	H		C	H			
1a	30	73—74 (from hexane)	69,53	3,59	$C_{11}H_7FO_2$	69,47	3,68	1 666	325, 224	4,37 4,17
1b	34	95—96 (from petroleum ether)	69,69	4,00	$C_{11}H_7FO_2$	69,47	3,68	1 679	322, 223	4,41 4,21
1c	30	153,5—154 (from benzene) †	52,77	3,00	$C_{11}H_7BrO_2$	52,46	2,80	1 690	328, 227	4,79 4,09

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*Thiosemicarbazone: mp 205-206° (from benzene). Found, %: C 54.87; H 4.03; N 15.79; S 12.33. $C_{12}H_{10}FN_3OS$. Calculated, %: C 54.75; H 3.80; N 15.97; S 12.17.

† Thiosemicarbazone: mp 205-206° (from chlorobenzene). Found, %: C 44.49; H 2.98; Br 24.50; N 13.14; S 9.99. $C_{12}H_{10}BrN_3OS$. Calculated, %: C 44.45; H 3.11; Br 24.65; N 12.96; S 9.89. Found, %: Br 32.21. Calculated, %: Br 31.74.

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TABLE 2. 2-Methyl-5-arylfurans

Compound	Yield (%)	Temperature (deg)		Found (in %)			Empirical formula	Calculated (%)			UV spectrum λmax (nm)	log ε ethanol
		boiling	melting	C	H	Br (Cl)		C	H	Br (Cl)		
IIa	58	80—81 (1 mm)	31—32	74,97	5,10		$C_{11}H_9FO$	75,00	5,12		283, 210	4,15 3,92
IIb	70	84 (1 mm) n_D^{20} 1,5726	—	75,39	5,20		$C_{11}H_9FO$	75,00	5,12		290, 225	4,00 3,91
IIc	80	—	70—71 (from hexane)	56,01	4,06	33,22	$C_{11}H_9BrO$	55,71	3,82	33,70	295, 226	3,91 3,81
IId	56	—	51—52 (from hexane)	69.00	4,90	18,21	$C_{11}H_9ClO$	68,57	4,67	18,44	293, 224	4,09 3,86

TABLE 3. 2-Hydroxymethyl-5-arylfurans

Compound	Yield (%)	Mp (deg)	Found (%)			Empirical formula	Calculated (%)			IR spectrum (cm⁻¹; OH)	UV spectrum (nm)	lg ε (ethanol)	Ethyl ether*		Acetate*	
													temperature (deg)			
			C	H	Br, Cl or N		C	H	Br, Cl or N				boiling	melting	boiling	melting
IIIa	57	62—63 (from hexane)	68,33	4,72		$C_{11}H_9O_2$	68,78	4,70		3 200— 3 300	282, 210	4,29 3,95	115 (2 mm) n_D^{20} 1,5480	—		140 (2 mm) 35—36
IIIb	92	76—77 (from hexane)	68,86	4,64		$C_{11}H_9O_2$	68,78	4,70		3 230— 3 270	285, 224	4,31 3,75	107 (1 mm) n_D^{20} 1,5496	—		124 (1 mm) 48—49
IIIc	95	107—108 (from hexane)	52,09	3,53	31,89	$C_{11}H_9BrO_2$	52,20	3,58	31,58	3 300— 3 350	293, 223	4,41 4,32		34—35(from petroleum ether)		61—62 (from petroleum ether)
IIId	93	88—89 (from ethyl acetate)	63,59	4,37	16,90	$C_{11}H_9ClO_2$	63,31	4,32	17,02	3 219— 3 290	291, 223	4,40 3,88	138—139 (1.5 mm) n_D^{20} 1,5840	—	—	46—47(from alcohol)
IIIe	87	139—140 (from benzene)	60,45	4,13	6,56	$C_{11}H_9NO_4$	60,27	4,12	6,39	3 120— 3 350	357, 243	4,28 3,99				72—73 (from hexane)

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*Elemental analysis data for C, H, Br(Cl) coincide with calculated data.

The synthesized compounds (I), (II), and (III), and also the ethyl ethers and acetates of compounds (III) were examined in the Chemotherapy Laboratory of the S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry on the spectrum of antibacterial effect and also in relation to the type A (strain PR-8) influenza virus. It was established that compound (IIIc) and also its acetate and ethyl ether display antiviral activity in vitro and neutralize ILD_{100} of influenza virus in a dilution of 1:1000; these same compounds display antitubercular activity in vitro and in a dilution of 1:250,000.

EXPERIMENTAL

p-Fluoroaniline was obtained by the known method [5], bp 65-66° (7 mm), n_D^{20} 1.5416. Literature data: n_D^{20} 1.5195 [6].* Found, %: C 64.76; H 5.50; N 12.40%. C_6H_6FN. Calculated, %: C 64.86; H 5.40; N 12.62%.

5-(p-Fluorophenyl)furfural (Ia). p-Fluoroaniline hydrochloride, obtained from 12.8 g of p-fluoroaniline, 25 ml of water, and 50 ml of concentrated hydrochloride acid, was diazotized with a solution of 8.2 g of sodium nitrite in 35 ml of water. The reaction mixture was stirred for 20 min at 5°, then 9.6 g of furfural in 10 ml of acetone and a solution of 2.3 g of copper chloride in 5 ml of water were added. The reaction mixture was stirred for 4 h at 20-25° and 500 ml of water was added. The precipitate was filtered and washed with water. Aldehydes (Ib-e) were obtained analogously. Yields, constants, and analytical data of the obtained 5-arylfurfurals (and their thiosemicarbazones) are presented in Table 1; for constants of compounds (Id, e) see the literature [4].

2-Methyl-5-(p-fluorophenyl)furan (IIa). We boiled 1.9 g of (Ia) and 4 ml of hydrazine hydrate in 20 ml of ethylene glycol for 15 min. To the reaction mixture cooled to 60° was added 4 g of powdered potassium hydroxide, the mixture was boiled with stirring for 30 min and cooled, and the precipitate was filtered. Constants of compounds (IIa-d) obtained by us are presented in Table 2.

2-Hydroxymethyl-5-(p-fluorophenyl)furan (IIIa). To 1.2 g of (Ia) in 20 ml of dioxane was added in drops a solution of 0.4 g of sodium borohydride in 5 ml of water. The mixture was boiled for 1 h and cooled, 2 ml of 10% sulfuric acid was added, and the mixture was poured into 100 ml of water. The precipitate was filtered. Constants of compounds (IIIa-e) obtained by us are presented in Table 3. Reaction of (III) with acetic anhydride in the presence of sodium acetate gave the corresponding acetates, and reaction of (III) with ethyl iodide in the presence of potassium hydroxide gave the ethyl ethers. Their constants are also presented in Table 3.

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*The refractive index indicated in the literature [6] is a result of error. We obtained the acetyl derivative of p-fluoroaniline, the constant of which was identical to literature data [6]. The PMR spectrum of p-fluoroaniline taken by us completely confirmed its structure.