AMINO AND HYDROXYAMINO DERIVATIVES OF ARYLFURANS

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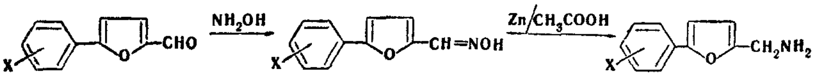
5-Aryl-2-aminomethylfurans, 5-aryl-2-(ω-aminoacetyl)furans, and (5-aryl-2-furyl)aminomethylcarbinols were synthesized.

Continuing our research on arylfurans, we have synthesized aminoalkyl- and hydroxyaminoalkylfurans from our previously synthesized 5-arylfurfurals [1] and 5-aryl-2-acetylfurans [2].

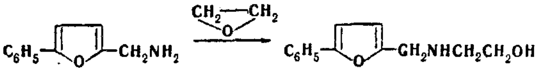
Oximes Ia-f were obtained from the corresponding 5-arylfurfurals and converted to primary amines IIa-f by reduction with zinc in acetic acid.



Ia-f IIa-f

a X=p-Br; b p-Cl; c m-F; d p-CH$_3$; e p-OCH$_3$; f H

The behavior of the 2-aminomethyl-5-arylfurans with respect to hydroxyethylation was studied. One of us and Yu. K. Yur'ev and I. G. Bolesov [3] have previously shown that furfurylamine readily undergoes reaction with ethylene oxide to give mono- and dihydroxyethylation products in high yields. It was found that the introduction of an aryl group into the 2-aminomethylfuran molecule considerably hinders hydroxyethylation. Arylaminoethylfurans IIa-e do not undergo this reaction under the conditions that we used, and only 5-phenyl-2-aminomethylfuran forms a monohydroxyethyl derivative (III) in low yield.



III

A study of the spectrum of antibacterial action of I, II, III carried out in the chemotherapy laboratory of the Ordzhonikidze All-Union Scientific-Research Pharmaceutical-Chemistry Institute demonstrated that some of them (Ic, IIb) display antitubercular activity in vitro in dilutions of 1 : 250,000 and 1 : 30,000, respectively. The activity of these compounds decreases in the presence of blood serum.

We synthesized hydroxyamino derivatives with a different structure — 2-(β -amino-α-hydroxy)ethyl-5-ethyfurans — from 5-aryl-2-acetylfurans [2]. Bromination of 5-aryl-2-acetylfurans with dioxane dibromide gives stable 5-aryl-2-(ω-bromoacetyl)furans IVa-c, from which amino ketones Va-f were synthesized by reaction with amines. We note that when the duration of the reaction of the bromo ketones with amines is increased, the yields of amino ketones decrease substantially due to the formation of a sparingly soluble high-melting substance which, according to the results of elementary analysis, is the product of the condensation of several molecules of the amino ketone.

The synthesized amino ketones (Va-f) were reduced to the corresponding amino alcohols (VIa-f) with sodium borohydride.

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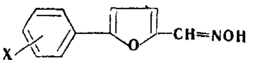
TABLE 1. 5-Arylfurfural Oximes



Comp.	X	mp., °C	Empirical formula	Found, %			Calc., %			Yield, %
				C	H	N	C	H	N	
Ia	p-Br	174—175 from alcohol	$C_{11}H_8BrNO_2$[a]	49,6	3,0	5,3	49,6	2,7	5,2	80
Ib	p-Cl	159—160 from ethyl acetate	$C_{11}H_8ClNO_2$[b]	59,9	3,8	6,2	59,6	3,6	6,3	91
Ic	m-F	140—141 from alcohol	$C_{11}H_8FNO_2$	64,4	4,1	6,6	64,4	4,0	6,8	85
Id	p-CH₃	171—171,5 from methanol	$C_{12}H_{11}NO_2$	71,5	5,9	6,7	71,6	5,5	7,0	82
Ie	p-OCH₃	168—169 from ethyl acetate	$C_{12}H_{11}NO_3$	66,0	5,0	6,6	66,4	5,1	6,4	86

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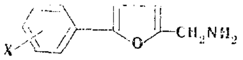
[a] Found: Br 30.0%. Calculated: Br 29.7%. [b] Found: Cl 16.2%. Calculated: Cl 16.0%.

TABLE 2. 5-Aryl-2-aminomethylfurans



Comp.	X	bp or mp, °C	Empirical formula	Found, %			Calc., %			Yield, %
				C	H	N	C	H	N	
IIa	p-Br	91—92 from hexane	$C_{11}H_{10}BrNO$	52,7	4,1	5,3	52,4	4,0	5,6	60
IIб	p-Cl	161 (3 mm), 37—38	$C_{11}H_{10}ClNO$[a]	63,4	4,9	6,4	63,6	4,8	6,8	58
IIв	m-F	96 (1 mm)[b]	$C_{11}H_{10}FNO$	69,2	5,3	7,5	69,0	5,3	7,3	59
IIг	p-CH₃	53—54 from petroleum ether	$C_{12}H_{13}NO$	76,9	6,9	7,6	77,0	7,0	7,5	62
IIд	p-OCH₃	77—78 from hexane	$C_{12}H_{13}NO_2$	71,2	6,6	7,2	70,9	6,4	6,9	60
IIe	H	136 (2mm), 32—33	$C_{11}H_{11}NO$	76,2	6,3	7,9	76,3	6,4	8,1	55
Picrate		177—178	$C_{17}H_{14}N_4O_8$	50,7	3,7	13,7	50,7	3,5	13,9	

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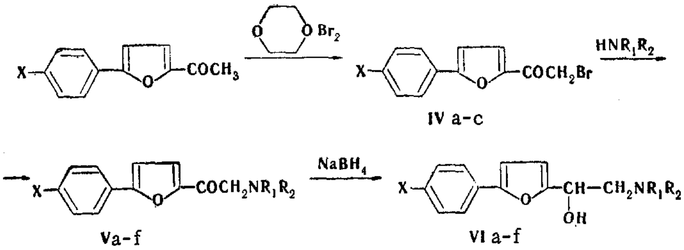
[a] Found: Cl 16.9%. Calculated: Cl 17.1%. [b] n_D^{20} 1.5945.

The structures of the amino ketones and amino alcohols were confirmed from the IR and UV spectra.



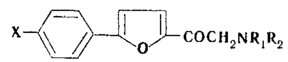
IVa X=Br, b Cl, c NO_2; V, VI a X=Br, $R_1R_2=(CH_2)_5$; b X=Br, $R_1=H$, $R_2=C_6H_5$; c X=Cl, $R_1R_2=(CH_2)_5$; d X=Cl, $R_1=H$, $R_2=C_6H_5$; e X=NO_2, $R_1=H$, $R_2=C_6H_5$; f X=NO_2, $R_1R_2=(CH_2)_5$

EXPERIMENTAL

5-(p-Bromophenyl)furfural Oxime (Ia). A mixture of 2.5 g (0.01 mole) of 5-(p-bromophenyl)furfural [1] in 15 ml of alcohol, 0.8 g (0.011 mole) of hydroxylamine hydrochloride, and 0.9 g (0.011 mole) of sodium acetate in 15 ml of water was heated on a boiling water bath for 4 h. The mixture was cooled, and the Ia was removed by filtration.

Oximes Ib-f were similarly obtained. The yields, physical constants, and results of analysis of 5-arylfurfural oximes Ia-e are presented in Table 1 (see [4] for the physical constants of 5-phenylfurfural oxime If).

TABLE 3. 5-Aryl-2-(ω-aminoacetyl)furans



Comp.	X	R_1	R_2	mp, °C	Empirical formula	Found, %			Calc., %			Yield, %	IR spec.,	UV spectrum	
						C	H	N	C	H	N			λ_{max}, nm	lg ε ethanol
V a	Br	$(CH_2)_5$		90—91 from benzene	$C_{17}H_{18}BrNO_2$[a]	58,6	5,1	3,7	58,6	5,2	4,0	85	1678	321, 224	4,46, 4,12
V b	Br	H	C_6H_5	150—151 from benzene	$C_{18}H_{14}BrNO_2$	60,3	3,8	3,6	60,7	4,0	3,9	63	1670	318, 244	4,54, 4,31
V c	Cl	$(CH_2)_5$		91,5—93,5 from alcohol	$C_{17}H_{18}ClNO_2$[b]	67,2	6,1		67,2	6,0		90	1680	327, 227	4,44, 4,15
V d	Cl	H	C_6H_5	150—151,5 from alcohol	$C_{18}H_{14}ClNO_2$[c]	69,3	4,5		69,3	4,5		32	1670	324, 230	4,45, 4,27
V e	NO_2	H	C_6H_5	175—177 from ethyl acetate	$C_{18}H_{14}N_2O_4$	67,1	4,2	8,4	67,1	4,4	8,7	42	1675	348, 238	4,45, 4,26
V f	NO_2	$(CH_2)_5$		170—171,5	$C_{17}H_{18}N_2O_4$	65,2	6,0	8,5	64,9	5,8	8,9	19	1660		

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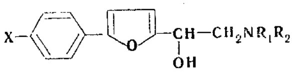
[a] Found: Br 22.8%. Calculated: Br 23.0%. [b] Found: Cl 11.4%. Calculated: Cl 11.7%. [c] Found: Cl 11.0%. Calculated: Cl 11.4%.

TABLE 4. (5-Aryl-2-furyl)aminomethylcarbinols



Comp.	X	R_1	R_2	mp, °C (from alcohol)	Empirical formula	Found, %			Calc., %			Yield, %	UV spectrum	
						C	H	N	C	H	N		λ_{max}, nm	lg ε (ethanol)
VI a	Br	$(CH_2)_5$		103—104	$C_{17}H_{20}BrNO_2$[a]	58,4	5,7	4,0	58,4	5,8	4,0	82	298	4,44
		Hydrochloride		193,5—194,5	$C_{17}H_{21}BrClNO_2$	52,4	5,4	3,6	52,8	5,5	3,7			
		Methiodide		186—187	$C_{18}H_{23}BrINO_2$[b]			2,6			2,8			
VI b	Br	H	C_6H_5	109—110	$C_{18}H_{16}BrNO_2$[c]	60,6	4,3	4,2	60,3	4,5	3,9	80	294, 247	4,50, 4,24
VI c	Cl	$(CH_2)_5$		101—102	$C_{17}H_{20}ClNO_2$[d]			4,9			4,6	70	292	4,42
		Methiodide		167—168,5	$C_{18}H_{23}ClINO_2$[e]			3,0			3,1			
VI d	Cl	H	C_6H_5	100,5—101,5	$C_{18}H_{16}ClNO_2$[f]	68,9	5,3		68,9	5,1		64	292, 248	4,44, 4,20
VI e	NO_2	H	C_6H_5	118—120	$C_{18}H_{16}ClN_2O_4$	66,5	5,3	8,5	66,7	5,0	8,6	14	362, 248	4,27, 4,34
VI f	NO_2	$(CH_2)_5$		119—121	$C_{17}H_{20}N_2O_4$	64,5	6,3	8,5	64,5	6,4	8,8	12	360, 245	4,30, 4,00

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[a] Found: Br 22.9%. Calculated: Br 22.8%. [b] Found: I 26.1%. Calculated: I 25.8%. [c] Found: Br 22.5%. Calculated: Br 22.3%. [d] Found: Cl 11.3%. Calculated: Cl 11.6%. [e] Found: I 28.4%. Calculated: I 28.3%. [f] Found: Cl 11.0%. Calculated: Cl 11.3%.

5-(p-Bromophenyl)-2-aminomethylfuran (IIa). Glacial acetic acid (7 ml) was added dropwise with stirring to a mixture of 2.4 g (0.01 mole) of Ia and 3.4 g of zinc dust in 8 ml of methanol, and the mixture was stirred on a boiling-water bath for 3 h. The mixture was cooled, and the zinc was removed by filtration and washed with methanol. The combined methanol filtrates were vacuum evaporated, and the residue was treated with concentrated sodium hydroxide solution. The resulting amine was removed by filtration and washed with water.

Amines IIb-f were similarly obtained. The yields, physical constants, and results of analysis of the 5-aryl-2-aminomethylfurans were presented in Table 2.

5-Phenyl-2-[N-(β-hydroxyethyl)aminomethyl]furan (III). A solution of 1.5 g of 5-phenyl-2-aminomethylfuran (IIf) in 10 ml of ethylene oxide was allowed to stand in a flask with a reflux condenser for 2 days. The resulting viscous liquid was vacuum distilled to give 0.7 g of starting IIf and 0.6 g (60%, based on the converted amine) of III with bp 198-200° (2 mm). Found: C 72.0; H 6.9; N 6.5%. $C_{13}H_{15}NO_2$. Calculated: C 71.9; H 6.4; N 6.5%. The picrate had mp 154-155° (from alcohol): Found: C 51.2; H 4.1; N 12.9%. $C_{19}H_{18}N_4O_9$. Calculated: C 51.1; H 4.1; N 12.5%.

5-(p-Bromophenyl)-2-(ω-bromoacetyl)furan (IVa). A 3.8-g sample of dioxane dibromide was added in portions to a solution of 4 g (0.015 mole) of 5-(p-bromophenyl)-2-acetylfuran [2] in a mixture of 80 ml of ether and 8 ml of dioxane, and the reaction mixture was stirred at room temperature for 2.5 h. It was then heated on a water bath for 15 min, cooled, and poured into 500 ml of water. The resulting crystals were removed by filtration and washed with water to give 4.4 g (85%) of IVa with mp 124.5-125° (from benzene). Found: C 41.9; H 2.3; Br 46.4%. $C_{12}H_8Br_2O_2$. Calculated: C 41.9; H 2.3; Br 46.5%.

Compounds IVb and IVc were similarly obtained.

5-(p-Chlorophenyl)-2-(ω-bromoacetyl)furan (IVb). This compound was obtained in 68% yield and had mp 112-113° (from benzene). Found: C 48.3; H 2.6%. $C_{12}H_8O_2ClBr$. Calculated: C 48.1; H 2.7%.

5-(p-Nitrophenyl)-2-(ω-bromoacetyl)furan (IVc). This compound was obtained in 60% yield and had mp 160-161° (from ethyl acetate). Found: C 46.7; H 2.6; Br 25.4%. $C_{12}H_8NO_4Br$. Calculated: C 46.5; H 2.6; Br 25.8%.

5-(p-Bromophenyl)-2-(ω-piperidinoacetyl)furan (Va). A saturated benzene solution of 5 g (0.01 mole) of IVa was added dropwise to 4 ml of piperidine, and the mixture was stirred at room temperature for 20 min. The precipitate was removed by filtration and washed with benzene. The combined benzene solutions were washed with water, dried with calcined magnesium sulfate, and concentrated in vacuo. The resulting precipitate was removed by filtration.

Amino ketones Vb-f were similarly obtained. The yields, physical constants, and results of analysis of the 5-aryl-2-(ω-aminoacetyl)furans are presented in Table 3.

[5-(p-Bromophenyl)-2-furyl]piperidinomethylcarbinol (VIa). A solution of 0.3 g of sodium borohydride in 6 ml of water was rapidly added dropwise to a saturated solution of 4.7 g of Va in dioxane, and the mixture was heated on a boiling-water bath for 30 min. The mixture was then cooled, acidified with 6 ml of 10% sulfuric acid, and poured into 300 ml of water. The aqueous solution was extracted with ether and treated with concentrated sodium hydroxide solution until it was weakly alkaline. The precipitate was removed by filtration and washed with water.

Amino alcohols VIb-f were similarly obtained. The yields, physical constants, and results of elementary analysis of the (5-aryl-2-furyl)aminomethylcarbinols are presented in Table 4.

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