Furan derivatives. LXV. Preparation and ultraviolet spectra of 5-arylthio- and 5-heteroarylthio-2-furaldehydes

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By a reaction of salts of 4-substituted benzenethiols (X = H, CH_3, OCH_3, $NHCOCH_3$, Cl, Br, NO_2) and heterocyclic thiols (2-mercaptobenzimidazole, 2-mercaptobenzothiazole, 2-mercaptobenzoxazole, 2-mercaptobenzoselenazole, and 2-mercaptopyrimidine) with 5-halo-2-furaldehydes in appropriate solvents the corresponding 5-(4-X-phenylthio)- and 5-heteroarylthio-2-furaldehydes have been prepared and their ultraviolet spectra have been interpreted.

Реакцией солей 4-замещенных бензолтиолов (X = H, CH_3, OCH_3, $NHCOCH_3$, Cl, Br, NO_2) и гетероциклических тиолов (2-меркаптобензимидазол, 2-меркаптобензоксазол, 2-меркаптобензтиазол, 2-меркаптобензселеназол и 2-меркаптопиримидин) с 5-галоген-2-фурфуролми в подходящем растворителе были получены соответствующие 5-(4-X-фенилтио)- и 5-гетероарилтио-2-фурфуролы. Разбираются ультрафиолетовые спектры полученных веществ.

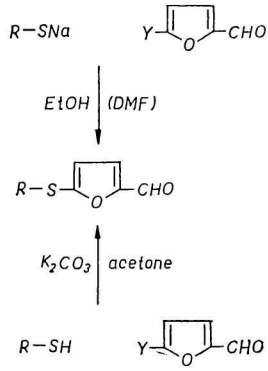
In course of the study of synthesis as well as of the physicochemical and biological properties of furan derivatives, 5-phenylthio- and 5-heteroarylthio-2-furaldehydes were synthesized by reaction of the corresponding thiophenols with 5-halo-2-furaldehydes in suitable solvents. *Carro et al.* [1] prepared 5-phenylthio- and 5-(4-acetamidophenylthio)-2-furaldehydes by reaction of the appropriate thiolates with 5-bromo-2-furaldehyde in diluted ethanol. Other authors [2, 3] prepared 5-(4-nitrophenylthio)-2-furaldehyde in a similar way. Lately *Lieb* and *Eiter* [4] have found that also 5-nitro-2-furaldehyde entered into S_N reactions with various nucleophiles. By the reaction of this aldehyde with sodium thiolates, they obtained 5-phenylthio-5-(4-chlorophenylthio)-2-furaldehydes.

In this work, the above-mentioned aldehydes were prepared by the reaction shown in Scheme 1.

Experimental

Physical constants, results of elemental analysis, and u.v. spectral data of the synthesized 5-(4-X-phenylthio)- and 5-heteroarylthio-2-furaldehydes as well as of the corresponding thiosemicarbazones are presented in Tables 1—3.

The u.v. spectra of the synthesized compounds were recorded using a Specord UV VIS recording spectrophotometer in the region of 200—800 nm; concentration $2-5\times10^{-5}$ M in methanol.



Y = Br, I.

R = 4-X-C_6H_4, where X = H, CH_3, CH_3O, $NHCOCH_3$, Cl, Br, NO_2, 2-benzimidazolyl, 2-benzoxazolyl, 2-benzothiazolyl, 2-benzoselenazolyl, and 2-pyrimidinyl.

Scheme 1

5-(4-X-Phenylthio)-2-furaldehydes (I—VII)

For the synthesis, two methods were used:

Method A

The mixture containing the sodium salt of the appropriate 4-X-thiophenol (0.05 mole) (prepared in advance by evaporation of equimolar amounts of thiophenol and of aqueous solution of sodium hydroxide and the ethanolic solution of sodium ethoxide, respectively), 5-bromo- and 5-iodo-2-furaldehydes, respectively (0.05 mole), and ethanol (50—70 ml) was refluxed on a water bath for 2.5—4 hrs under stirring. Then the reaction mixture was cooled to laboratory temperature and poured into cold water (200 ml). The precipitate was sucked, washed with a small amount of cold water, air-dried, and crystallized from ethanol. When on pouring the reaction mixture into cold water an oil was obtained instead of a solid, *e.g.* with 5-phenylthio-2-furaldehyde, this was extracted with ether and the extract was dried with anhydrous sodium sulfate. Then ether was distilled off and the residue was crystallized.

Method B

4-Substituted thiophenol (0.01 mole) and potassium carbonate (0.01 mole) were put into dry acetone (methyl ethyl ketone, dimethylformamide, dimethyl sulfoxide) (20 ml) and the solution of 5-bromo-2-furaldehyde (0.01 mole) in dry acetone (10 ml) was added to the reaction mixture under stirring. The reaction mixture was stirred at room temperature for 3 hrs. After the reaction was finished, the produced potassium bromide was sucked. The filtrate was boiled with charcoal, filtered, and diluted with water under stirring. The formed sulfide was sucked, washed with ether, and crystallized from ethanol.

Table 1

Characterization and u.v. spectral data of the synthesized 5-(4-X-phenylthio)-2-furaldehydes

No.	X	Formula	*M*	Calculated/found % C	% H	% S	Yield %	M.p. °C	λ_{max}, nm log ε				
I	H	$C_{11}H_8O_2S$	204.2	—	—	—	83.6	36	212		242	256–274	320
									4.10		4.02	3.85	3.84
II	CH_3	$C_{12}H_{10}O_2S$	218.3	66.02	4.62	14.69	90.4	58–60	212;	223 sh	243	274–276	322
				65.87	4.54	14.48			4.26;	4.21	4.13	3.99	4.10
III	CH_3O	$C_{12}H_{10}O_3S$	234.3	61.52	4.30	13.68	95.7	74–75	211		233	284	323
				61.45	4.19	13.56			4.04		4.09	3.85	4.02
IV	CH_3CONH	$C_{13}H_{11}NO_3S$	261.3	—	—	—	71.5	107–108	211		—	263	323
									4.26			4.28	4.00
V	Cl	$C_{11}H_7ClO_2S$	238.7	—	—	—	78.5	65–66	212–213;	221–224	249	270 sh	317
									4.18	4.17	4.21	4.05	3.93
VI	Br	$C_{11}H_7BrO_2S$	283.1	46.67	2.49	11.33	78	78–79	211	250		—	312–1
				46.48	2.37	11.18			4.22	4.24			3.77
VII	NO_2	$C_{11}H_7NO_4S$	249.2	—	—	—	90	95–96	211–229	—		263	315
									4.13			3.99	4.19

Table 2

Characterization and u.v. spectral data of the synthesized 5-heteroarylthio-2-furaldehydes

No.	Hetero-aryl	Formula	*M*	Calculated/found % C	% H	% N	% S	Yield %	M.p. °C	λ_{max}, nm log ε				
VIII	BI[a]	$C_{12}H_8N_2O_2S$	244.2	59.01	3.30	11.47	13.13	72	162–163	216			284	291
				58.86	3.22	11.38	13.16			4.19			4.28	4.28
IX	BO[b]	$C_{12}H_7NO_3S$	245.2	58.77	2.88	5.71	13.08	92	102–104	245		278;	283	—
				58.69	2.71	5.64	12.90			4.36		4.31	4.32	
X	BT[c]	$C_{12}H_7NO_2S_2$	261.3	55.15	2.70	5.36	24.54	74	86–87	226;	241 sh		275	—
				54.88	2.66	5.19	24.51			4.46;	4.33		4.39	
XI	BS[d]	$C_{12}H_7NO_2SSe$	308.2	46.76	2.29	4.54	10.40	50	103–105	232			280	—
				46.54	2.21	4.41	10.18			4.31			4.18	
XII	PY[e]	$C_9H_6N_2O_2S$	206.2	52.38	2.93	13.58	15.55	85.2	98–99	236			283	—
				52.34	2.88	13.42	15.61			4.24			4.17	

a) BI = 2-benzimidazolyl; *b*) BO = 2-benzoxazolyl; *c*) BT = 2-benzothiazolyl; *d*) BS = 2-benzoselenazolyl; *e*) PY = 2-pyrimidinyl.

5-Heteroarylthio-2-furaldehydes (VIII—XII)

The mixture containing potassium salt of heterocyclic thiol (prepared in advance) (0.02 mole), 5-bromo- and 5-iodo-2-furaldehydes (0.02 mole), respectively and purified dimethylformamide (50—70 ml) was stirred at 40—50°C for 10—12 hrs. Then it was poured into cold water (150—200 ml) under stirring. The formed solid was sucked, air-dried, and crystallized from the suitable solvent.

5-Phenylseleno-2-furaldehyde

The mixture containing dry acetone (20 ml), selenophenol (prepared according to [7]; 3.14 g; 0.02 mole), and anhydrous potassium carbonate (1.38 g; 0.01 mole) was stirred vigorously for 30 min and then the solution of 5-bromo-2-furaldehyde (3.5 g; 0.02 mole) in dry acetone (15 ml) was added continuously under stirring. The reaction was finished within 3 hrs. The formed potassium bromide was sucked and the filtrate was poured into cold water (100 ml). A dark oil was obtained and extracted with ether. The extract was dried with anhydrous sodium sulfate and filtered. Then ether was distilled off and the oily residue was crystallized. The crude 5-phenylseleno-2-furaldehyde was crystallized from ethanol. Yield 3.2 g, *i.e.* 64%; m.p. 58—60°C.

For $C_{11}H_8O_2Se$ (251.13) calculated: 52.61% C, 3.21% H; found: 52.48% C, 3.14% H.

Thiosemicarbazones (XIII—XXIV)

To the solution of thiosemicarbazide hydrochloride (0.7 g; 0.005 mole) in ethanol (25 ml) the equivalent amount of sodium hydroxide was added. The solution was boiled and then the solution of the appropriate aldehyde (0.005 mole) in ethanol (20 ml) was added continuously. After the total amount was added, the reaction mixture was refluxed for another 2 hrs and then cooled to laboratory temperature. The formed crystalline solid was sucked, washed with water, dried, and crystallized from a suitable solvent.

Results and discussion

The reaction of sodium salts of 4-substituted thiophenols (prepared in advance) with 5-bromo- and 5-iodo-2-furaldehydes, respectively, in ethanol at boiling (method *A*), or the reaction of 4-substituted thiophenols with the above-mentioned aldehydes in anhydrous acetone in the presence of anhydrous potassium carbonate (method *B*) was used to prepare 5-(4-X-phenylthio)-2-furaldehydes. In the first case, the prolonged reaction time, *i.e.* 2.5—4 hrs instead of 30—60 min as proposed in [2] made it possible to obtain considerably higher yields, *e.g.* 22% with 5-phenyl derivative and 35—40% with 5-(4-nitrophenyl) derivative. The yields obtained were higher than those in the reaction of 5-nitro-2-furaldehyde with thiolates in alcohol [4]. High yields of sulfides were obtained also by the method *B*. The advantage of this method was that the reaction proceeded at room temperature. 5-Phenylseleno-2-furaldehyde was obtained in a good yield by the reaction of selenophenol with 5-bromo-2-furaldehyde in anhydrous acetone in the presence of anhydrous potassium carbonate.

Alkali salts of heterocyclic thiols with 5-bromo- and 5-iodo-2-furaldehydes, respectively, in purified dimethylformamide gave 5-heteroarylthio-2-furaldehydes (in ethanol low yields were obtained). The reaction proceeded at 40—50°C for

Table 3

Characterization and u.v. spectral data of thiosemicarbazones of

No.	X	R	Formula	*M*	Calculated/found			
					% C	% H	% N	% S
XIII	H	—	$C_{12}H_{11}N_3OS_2$	277.3	51.98	4.00	15.15	23.13
					51.76	3.88	15.21	22.78
XIV	CH_3	—	$C_{13}H_{13}N_3OS_2$	291.3	53.60	4.50	14.42	22.02
					53.48	4.37	14.37	21.76
XV	CH_3O	—	$C_{13}H_{13}N_3O_2S_2$	307.3	50.81	4.26	13.67	20.87
					50.68	4.08	13.47	20.64
XVI	CH_3CONH	—	$C_{14}H_{14}N_4O_2S_2$	334.4	50.29	4.22	16.75	19.18
					50.04	4.07	16.48	19.22
XVII	Cl	—	$C_{12}H_{10}ClN_3OS_2$	311.8	46.23	3.23	13.48	20.57
					46.09	3.07	13.37	20.38
XVIII	Br	—	$C_{12}H_{10}BrN_3OS_2$	356.2	40.46	2.83	11.80	18.00
					40.28	2.67	11.56	17.84
XIX	NO_2	—	$C_{12}H_{10}N_4O_3S_2$	322.3	44.72	3.13	17.38	19.90
					44.61	2.84	17.21	19.96
XX	—	BI	$C_{13}H_{11}N_5OS_2$	317.3	49.21	3.49	22.07	20.21
					49.06	3.37	21.76	20.05
XXI	—	BO	$C_{13}H_{10}N_4O_2S_2$	318.3	49.06	3.17	17.60	20.15
					48.81	3.08	17.51	20.08
XXII	—	BT	$C_{13}H_{10}N_4OS_3$	334.4	46.69	3.01	16.75	28.77
					46.55	2.88	16.57	28.52
XXIII	—	BS	$C_{13}H_{10}N_4OS_2Se$	381.3	40.95	2.64	14.69	16.82
					40.76	2.51	14.58	16.77
XXIV	—	PY	$C_{10}H_9N_5OS_2$	279.3	43.00	3.25	25.07	22.96
					42.85	3.18	24.71	22.75

a) Crystallized from ethanol; *b*) crystallized from acetic acid.

10—12 hrs; shorter reaction time resulted in lower yields. From these aldehydes, 5-(2-benzimidazolylthio)- and 5-(2-benzothiazolylthio)-2-furaldehydes were prepared by reaction of 5-nitro-2-furaldehyde with sodium salt of 2-mercaptobenzimidazole and 2-mercaptobenzothiazole, respectively, in ethanol [4]. However, the yields of sulfides obtained in this way were lower (22 and 58%) than those obtained in dimethylformamide (72 and 74%). The prepared 5-heteroarylthio-2-furaldehydes were stable yellowish compounds well soluble in polar solvents except the benzoxazole derivative which underwent spontaneous decomposition within some time giving indefinable bituminous products.

In agreement with *Mangini* [5, 6], it was confirmed that the sulfur atom of 5-(4-X-phenylthio)-2-furaldehydes was conjugated with the 4-substituted phenyl residue on one side and with the carbonyl group of 2-furaldehyde on the other side by its free electron pairs. The possibility of an interaction with 4-X-substituted phenyl residue and the effect of substituents on this interaction was evident from the fact that the electron-donating substituents shifted the last absorption maximum of these derivatives bathochromically and the electron-accepting ones hypsochromically. This shift was only about 10 nm, however, it must be taken into consideration that in the case of electron-accepting substituents, the two effects acting each against the other on the sulfide sulfur atom (the —M effect of the furaldehyde carbonyl group from one side and the —I and —M effects of the electron-accepting group on the benzene ring from the other side) were partially compensated. The

Table 3 (Continued)

5-(4-X-phenylthio)- and 5-(R-thio)-2-furaldehydes

Yield %	M.p. °C	λ_{max}, nm log ε							
87.5	138–140[a]	205 4.43		241 4.15		338; 4.57	345 sh 4.56		
86.8	144–146[a]	205 4.42		222; 4.31;	242 sh 4.25	338–343 4.60			
87.8	168–169[a]	205 4.54		236 4.49		344; 4.73;	335 sh 4.72		
92.7	218–220[a]	206 4.57		262 4.40		343; 4.58	337 sh 4.59		
91.5	156–158[a]	206 4.47		239–243 4.31		344; 4.61;	343 sh 4.60		
93.4	164–165[a]	205 4.45		241 4.23		338; 4.54;	343 sh 4.53		
95.5	180–182[b]	211 4.23		— 		335; 4.55	345 sh 4.53		
81.2	238–240[a]	212; 4.29;	248 3.99	281 sh; 4.05	288 4.13	307 4.20	335; 4.42	343 sh 4.41	
83.4	205–206[b]	235 4.33		276 4.29		283 4.30	334; 4.44;	342 sh 4.47	
93.7	235–236[b]	220–223 4.36		243 sh 4.11		273 4.13	337; 4.57;	345 sh 4.56	
77.3	237–238[b]	230; 4.30	249 sh 4.13	230–237 sh 4.13		— 	337; 4.57;	345 sh 4.55	
79.5	204–205[b]	232 4.25		— 			334; 4.58;	343 sh 4.56	

possibility of conjugation through the sulfur atom was evident also from a comparison of *K* bands in the u.v. spectra of 5-phenylthio-2-furaldehyde (320 nm), 5-phenyl-2--furaldehyde (326 nm), 5-phenylseleno-2-furaldehyde (325 nm), and 5-phenylsulfonyl-2-furaldehyde (254 nm).

All the synthesized aldehydes were treated with thiosemicarbazide to give the appropriate thiosemicarbazones which were supposed to possess antitubercular activity. With thiosemicarbazones of 5-(4-X-phenylthio)-2-furaldehydes the last absorption maximum was shifted bathochromically by 20–25 nm in average.

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