ALIPHATIC AND AROMATIC 5-NITRO-2-FURYLAMINES AND AROMATIC 5-NITROFURFURYL ETHERS

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Tertiary 5-nitrofurylamines were prepared by a nucleophilic substitution of 5-nitro-2-furfuryl bromide (*I*) with aliphatic secondary amines. According to reaction conditions N-(5-nitro-2-furfuryl)-X-phenylamines or their mixture with N,N-di(5-nitro-2-furfuryl)-X-phenylamines were obtained from the reaction of *I* with substituted primary aromatic amines. Compound *I* gave with 2-aminophenol a mixture of O- and N-mono- and disubstituted derivatives, and with ethyl salicylate ethyl 2-(5-nitro-2-furfuryloxy)benzoate.

In continuation of the investigation of 5-nitrofurfuryl derivatives with an anticipated biological effect we prepared a series of amino derivatives by ammonolysis of 5-nitro-2-furfuryl bromide (*I*) with substituted primary aromatic and secondary aliphatic amines and investigated the alternative reaction leading to aromatic 5-nitrofurfuryl ethers.

As known, reaction of 5-nitrofurfuryl halides with secondary amines (dimethylamine, dibutylamine, methylaniline, and piperidine[1]), and especially with tertiary amines and aromatic nitrogen-containing heterocycles have already been reported[2-4]. Reaction of *I* with aliphatic primary amines produces tarry products; it was not succeded to isolate, besides of the starting material, any compound. Reaction of *I* with 2-aminopropane afforded at the same conditions bis(5-nitro-2-furyl)ethane in low yield[5]. Aromatic 5-nitrofurfuryl ethers have not been investigated as yet.

Considering the low yields of ammonolysis of 5-nitrofurfuryl halides with some secondary amines so far reported[1], we payed attention to conditions improving the reaction; thus, that with dimethylamine proceeded in the same yield as published, nevertheless that with piperidine afforded the product in a much higher yield (Table I). Ammonolysis with primary aliphatic amines[5], were even at a low temperature unsuccessful giving tarry products. Ammonolysis of *I* with less basic primary aromatic amines with electron-donating and also with electron-accepting substituents at the aromatic ring were, therefore, investigated in more detail. Reaction of *I* with anilines without electron-accepting substituent at the aromatic ring was carried out in benzene

TABLE I

Substituted 5-nitrofurfurylamines *II*—*VI* and 5-nitrofurfurylethers *VII*—*IX*

Compound	Formula (M_r)	M.p., °C (yield, %)	Calculated/Found		
			% C	% H	% N
IIa[a]	—	—	—	—	—
	—	(85·7)	—	—	—
IIb	$C_9H_{12}N_2O_4$	84—86	50·94	5·70	13·20
	(212·2)	(69·3)	51·19	5·91	13·27
III[a]	—	—	—	—	—
	—	(64·5)			
IVa	$C_{11}H_{10}N_2O_3$	53—56	60·55	4·58	12·85
	(218·2)	(46·6)	60·85	4·90	12·51
IVb	$C_{12}H_{12}N_2O_3$	62—65	62·07	5·17	12·08
	(232·2)	(36·4)	62·26	5·42	12·31
IVc	$C_{12}H_{12}N_2O_3$	95—98	62·07	5·17	12·08
	(232·2)	(32·3)	62·40	5·50	12·04
IVd	$C_{12}H_{12}N_2O_3$	81—84	62·07	5·17	12·08
	(232·2)	(30·4)	62·16	5·46	11·94
IVe	$C_{12}H_{12}N_2O_4$	81—83	58·06	4·84	11·29
	(248·2)	(42·1)	58·32	5·14	12·12
IVf	$C_{12}H_9N_2ClO_3$	90—93	52·27	3·56	11·11
	(252·7)	(33·0)	52·59	3·84	11·24
Va	$C_{11}H_{10}N_2O_4$	164—167	56·40	4·20	11·96
	(234·2)	(38·5)	56·76	4·31	11·86
Vb	$C_{11}H_{10}N_2O_4$	93—96	56·40	4·20	11·96
	(234·2)	(33·9)	56·80	4·51	11·86
Vc	$C_{11}H_{10}N_2O_4$	90—92	56·40	4·20	11·96
	(234·2)	(42·7)	56·72	4·48	11·78
VIa	$C_{12}H_{10}N_2O_5$	136—166	54·96	3·81	10·68
	(262·2)	(73·8)	54·62	3·60	10·52
VIb	$C_{12}H_{10}N_2O_5$	173—175	54·96	3·81	10·68
	(262·2)	(72·1)	55·21	4·10	10·50
VIc	$C_{14}H_{14}N_2O_5$	108—110	57·93	4·82	9·36
	(290·2)	(80·3)	57·72	4·50	9·72
VId	$C_{14}H_{14}N_2O_5$	69·71	57·93	4·82	9·65
	(290·2)	(60·3)	57·82	4·63	9·78
VII	$C_{11}H_{10}N_2O_4$	136—137	56·41	4·27	11·96
	(234·2)	(30·4)	56·74	4·59	11·88

TABLE I
(*Continued*)

Compound	Formula (M_r)	M.p., °C (yield, %)	Calculated/Found		
			% C	% H	% N
VIII	$C_{14}H_{13}NO_6$ (291·2)	70—76 (23·4)	57·73 57·42	4·46 4·28	4·81 5·35
IX	$C_{12}H_9NO_6$ (263·2)	115—117 (85·1)	54·75 54·35	3·42 3·22	5·32 5·50

[a] Ref.[1].

or dimethylformamide at room temperature; the yield did not exceed 50% and a part of the unreacted material could be recoved. An almost pure secondary amine was obtained at low temperature and a 1 : 2 ratio of reacting components proved the anticipation that the 5-nitrofurfuryl group with lowe nucleophility of the nitrogen atom of the secondary amine formed, which, only in polar solvent or at higher temperature reacts with *I* to give a N,N-bis(5-nitro-2-furfuryl)aniline derivative. The amount of the tertiary amine formed was temperature and time depended *e.g.* at 0°C and 3 h it was no more seen in the reaction mixture by thin-layer chromatography. A preparative separation of secondary and tertiary 5-nitrofurfurylamines was achieved by column chromatography.

Due to the lowered basicity of the amino group, reactions of *I* with aniline derivatives having a deactivation substituent at the benzene ring were carried out in methanol or ethanol at reflux temperature in the same molar ratio as in the preceding case. Yields of these reactions were higher (60—80%); however, a mixture of mono- and disubstituted aniline in a 2 : 1 to 4 : 1 ratio was obtained. Not any substitution at the aromatic ring of aniline was found under these reaction conditions. In non-planar solvents and at room temperature the O-substitution did not occur; compound *I* furnished with 2-aminophenol in methanol under catalysis with pyridine three products as a result of the reaction at two centres. Isolated were: N-(5-nitro-2-furfuryl)-2-aminophenol, N,N-bis(5-nitro-2-furfuryl)-2-aminophenol and 2-(5-nitrofurfuryloxy)aniline. The substitution at nitrogen was preferred in a 1 : 2 ratio in accordance with the lower nucleophility of phenols in relation with anilines.

The lower reactivity of the OH group was corroborated through reaction of *I* with ethyl salicylate, where, even at an enhanced temperature and prolonged reaction time to 24 h, the substitution did not take place. The substitution proceeded with sodium salicylate only, the nucleophility of which was considerably greater, but at the

same time its basicity increased stimulating thus resination of *I*, and consequently, causing decrease of yields. The free 5-nitrofurfuryl ether of salicylic acid was obtained by an acid hydrolysis of the corresponding ester.

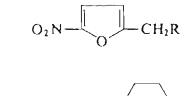
All products were characterized by IR, UV and ^{1}H NMR spectra, and other data (Tables II–V). The electron absorption spectra of secondary and tertiary amines revealed three or two absorption bands indicative of $\pi\rightarrow\pi^*$ or $n\rightarrow\pi^*$ transitions in the aromatic or furan rings and different for non-aromatic and aromatic amino derivatives. The non-aromatic tertiary amines showed the first absorption maximum at 213–215, the second one at 227–230 and the third one at 311–313 nm. Aromatic substituents displayed the maximum shifts according to the character of substituents. Thus, anilines with an electron-donating substituent had the first absorption maxima at 204–208, the second ones at 240–245 and the third ones at 312–318 nm, the position of the substituent being of little effect on the absorption maximum shift.

Similarly, tertiary aromatic amines with a deactivation substituent at benzene ring little influenced positions of absorption maxima, which appeared at 220–231 293–294 nm with a shoulder at 209 nm. Spectra of secondary amines obtained from aminobenzene acids considerably differ: *para* derivatives had two absorption maxima at 221–222 and 292–294 nm with a shoulder at 208 nm, *ortho* derivatives had three maxima at 220–222, 250–252 and 322–323 nm. The 5-nitrofurfuryl

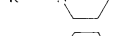
TABLE II
Substituted N,N'-di-(5-nitrofurfuryl)phenylamines *X*

Compound	Formula (M_r)	M.p., °C (yield, %)	Calculated/Found		
			% C	% H	% N
Xa	$C_{16}H_{13}N_3O_7$ (359·2)	156–159 (10·7)	53·48 53·77	3·62 3·87	11·69 11·80
Xb	$C_{17}H_{13}N_3O_8$ (387·3)	222–226 (21·6)	52·72 53·01	3·38 3·60	10·84 10·70
Xc	$C_{17}H_{13}N_3O_8$ (387·3)	185–187 (18·4)	52·72 53·03	3·38 3·61	10·84 10·76
Xd	$C_{19}H_{17}N_3O_8$ (415·3)	79–81 (37·4)	54·94 54·50	4·09 4·32	10·12 9·86
Xe	$C_{19}H_{17}N_3O_8$ (415·3)	178–182 (18·5)	54·94 54·52	4·09 3·99	10·12 9·96

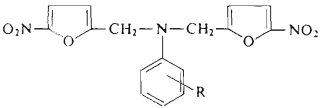
phenyl ethers are characteristic of three absorption bands at 219–218, 232–235 and 306–315 nm.



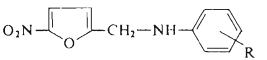
IIa, R =

IIb, R = 

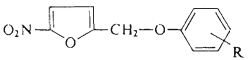
III, R = $-N(CH_3)_2$



Xa, R = 2-OH
Xb, R = 4-COOH
Xc, R = 2-COOH
Xd, R = 4-$COOC_2H_5$
Xe, R = 2-$COOC_2H_5$



IVa, R = H
IVb, R = 4-CH_3
IVc, R = 2-CH_3
IVd, R = 3-CH_3
IVe, R = 4-OCH_3
IVf, R = 4-Cl
Va, R = 4-OH
Vb, R = 3-OH
Vc, R = 2-OH



VIa, R = 4-COOH
VIb, R = 2-COOH
VIc, R = 4-$COOC_2H_5$
VId, R = 2-$COOC_2H_5$
VII, R = 2-NH_2
VIII, R = 2-$COOC_2H_5$
IX, R = 2-COOH

The IR spectral data of compounds *IV–X* (Table III) showed that the character and position of the substituent at benzene ring of the substituted aniline influenced quite significantly the shift of the $\nu_s(CH_2)$ absorption band of the furfuryl group, as well as the ν(NH) of these secondary amines. Substituents at nitrogen influenced the ν(CH) and ν(C—O—C) of the furan ring only feebly and deviations are within the limits of measurement errors (ν_s(C—O—C) = 1 025 ± 3 cm^{-1}, ν(C—O—C) = = 1 218 ± 3 cm^{-1}). Shift of the $\nu(NO_2)$ absorption bands at furan ring, on the other hand, are probably due to intermolecular interactions. The shift of the ν(OH) band of compounds *Vc* and *Va* indicated the N···HO hydrogen bonding.

The ^{1}H NMR data (Table V) are in favour of their proposed structure. The signal of CH_2 protons of the 5-nitrofurfuryl group with an aliphatic, or cyclic amine residue resonated at about 3·6 ppm, that of an aromatic amine residue at about 4·5 ppm. Protons of the furan ring of all amines and phenoxide derivatives gave a characteristic

doublet with coupling constant 3·3 Hz. The substituent at aromatic ring is virtually without effect on the chemical shifts of those signals (δ, ppm H_4 for the OH (*Va*) and COOH (*VIa*) derivatives is at 7·59 and 7·58, respectively). The H_3 signal for all secondary amines was not influenced by the NH proton thus evidencing the O,N-*cis* conformation of the synthesized amines.

TABLE III
Infrared (cm^{-1}) spectra of compounds *I*—*X*

Compound	$\nu_s(CH_2)$	$\delta(CH_2)$	$\nu_{as}(NO_2)$	$\nu_s(NO_2)$	ν(NH)	ν(CH)	ν(CH)	Other vibrations
I	2 940	1 375	1 520	1 344		3 070	978	
IIa	2 945	1 360	1 530	1 345		3 145	970	
IIb	2 945	1 380	1 520	1 342		3 142	975	
III	2 947	1 355	1 518	1 350		3 070	977	2 965, 1 460[a]
IVa	2 937	1 395	1 535	1 355	3 445	3 120	975	
IVb	2 940	1 398	1 540	1 363	3 439	3 125	980	2 859, 1 450[a]
IVc	2 935	1 392	1 543	1 363	3 430	3 110	975	2 899, 1 452[a]
IVd	2 935	1 389	1 545	1 360	3 440	3 120	980	2 925, 1 445[a]
IVe	2 960	1 385	1 520	1 350	3 425	3 120	977	2 920, 1 455[a]
IVf	2 936	1 352	1 550	1 352	3 420	3 120	979	
Va	2 960	1 386	1 530	1 350	3 400	3 120	975	3 320[b]
Vb	2 976	1 398	1 530	1 352	3 420	3 126	977	3 330[b]
Vc	2 960	1 380	1 542	1 352	3 410	3 120	978	3 280[b]
VIa	2 910	1 385	1 525	1 345	3 380	3 090	980	3 200[b], 1 685[c]
VIb	2 965	1 384	1 510	1 350	3 395	3 090	977	3 200[b], 1 697[c]
VIc	2 960	1 375	1 505	1 342	3 395	3 160	979	2 910, 1 435[a] 1 687[c]
VId	2 998	1 895	1 510	1 332	3 385	3 120	978	2 873, 1 430[a] 1 698[c]
VII	2 970	1 390	1 505	1 339	3 320 3 400	3 080	975	
VIII	2 980	1 375	1 509	1 342		3 120	978	2 890, 1 440[a]
IX	2 970	1 376	1 595	1 349		3 090	977	2 894, 1 439[a] 3 150[b]
Xa	2 958	1 382	1 536	1 348		3 098	978	3 245[b]
Xb	2 940	1 390	1 539	1 353		3 060	978	3 210[b]
Xc	2 980	1 387	1 545	1 340		3 070	976	3 330[b]
Xd	2 980	1 380	1 510	1 345		3 080	980	2 897, 1 445[a]
Xe	2 998	1 387	1 510	1 330		3 097	978	2 883, 1 430[a]

[a] $\nu_{as}(CH_3)$ and $\delta_{as}(CH_3)$; [b] ν(OH); [c] ν(C=O).

Although references[2] report those substances as inactive, three compounds were tentatively antimicrobially tested; results are listed in Table VI. The magnitude of the inhibition zones indicate selective antibacterial effect of this group of 5-nitrofurfuryl compounds on the strains of bacteria tested.

TABLE IV
Ultraviolet (λ_{max}, nm) spectra of compounds *I*—*X*

Compound	λ_{max}	log ε	λ_{max}	log ε	λ_{max}	log ε
I	203	4·04	—	—	304	4·05
IIa	213	3·91	229	3·72	311	4·15
IIb	215	3·95	230	3·77	313	4·19
III	214	3·90	227	3·71	312	4·13
IVa	204	4·35	242	4·15	314	4·60
IVb	206	4·43	244	4·16	315	4·11
IVc	207	4·43	240	2·10	314	4·01
IVd	205	4·56	245	4·20	313	4·16
IVe	204	4·36	242	4·18	316	4·17
IVf	205	4·49	253	4·46	314	4·36
Va	204	4·29	242	4·07	317	4·13
Vb	207	4·57	243	4·14	318	4·14
Vc	208	4·61	242	4·14	312	4·33
VIa	211	2·41	—	—	292	4·90
	208 s	1·50				
VIb	220	7·63	250	2·42	322	2·98
VIc	222	2·27	—	—	294	5·26
	208 s	1·66				
VId	222	9·44	252	3·72	323	4·84
VII	211	3·20	238	1·26	315	2·72
VIII	211	2·92	232	1·92	308	2·41
IX	210	3·66	233	2·42	306	2·60
Xa	211	5·21	235	2·97	288	1·48
Xb	220	4·03	—	—	294	8·19
Xc	220	3·66	—	—	294	7·57
	209 s	1·09				
Xd	221	2·73	—	—	294	5·84
Xe	221	4·22	—	—	293	7·87
	229 s	2·60				

s shoulder.

TABLE V

^{1}H NMR chemical shifts (δ, ppm) of compounds *I*—*X*

Compound[a]	Furan			Furfuryl CH_2	Benzene protons	NH
	H_3	H_4	$J_{3,4}$			
I	6·66	7·26	6·3	4·44	—	—
IIa	6·42	7·23	3·2	3·54	—	—
IIb	6·43	7·20	3·3	3·57	—	—
III	6·43	7·22	3·2	3·61	—	—
IVa	6·43	7·20	3·3	4·41	6·59—6·84 (m) 7·10—7·23 (m)	4·21
IVb	6·43	7·21	3·2	4·39	6·53 (d); 7·07 (d)	4·20
IVc	6·43	7·21	3·2	4·47	6·51—6·80 (m) 7·02—7·11 (m)	5·18
IVd	6·43	7·21	3·3	4·40	6·42—6·57 (m) 7·00—7·11 (m)	4·20
IVe	6·44	7·23	3·2	4·38	6·55 (d); 6·79 (d)	4·18
IVf	6·44	7·21	3·2	4·40	6·54 (d); 7·11 (d)	4·18
Va	6·64	7·59	3·3	4·30	6·53 (s)	5·40
Vb	6·62	7·57	3·3	4·46	6·38—7·00 (m)	5·51
Vc	6·65	7·60	3·3	4·34	5·90—6·30 (m) 6·70—7·00 (m)	5·41
VIa	6·66	7·58	3·4	4·33	6·80, 7·58 (d)	5·38
VIb	6·63	7·57	3·3	4·48	6·45—7·20 (m)	5·50
VIc	6·43	7·23	3·3	4·52	6·58—6·76 (m) 7·20—7·73 (m)	4·90
VId	6·42	7·20	3·3	4·48	6·61 (d); 7·86 (d)	4·58
VII	6·63 w	7·37	3·3	4·50	6·50—7·25 (m)	
VIII	6·45	7·23	3·3	4·52	5·45—7·00 (m)	
IX	6·63	7·56	3·3	4·63	6·55—7·30 (m)	
Xa	6·63	7·58	3·3	4·47	6·40—7·25 (m)	
Xb	6·67	7·56	4·44	4·34	6·82(d); 7·56 (d)	
Xc	6·63	7·56	3·3	4·47	6·53—7·35 (m)	
Xd	6·43	7·26	3·4	4·51	6·56—6·77 (m) 7·20—7·73 (m)	
Xe	6·43	7·22	3·3	4·49	6·64 (d); 7·84 (d)	

[a] Other signals: *IIa* (CH_2 1·44—1·65 (m), N—CH_2 2·33—2·44 (m); *IIb* N—CH_2 2·40—2·56 (m), O—CH_2 3·56—3·72 (m); *III* NÙCH_3 2·33 (s); *IVb*—*IVd* Ar—CH_3 2·22 (s); *IVe* O—CH_3 3·71 (s); *Va* OH 6·70 (s); *Vb* OH 6·74 (s); *Vc* OH 6·72 (s); *VIc* O—CH_2 4·28 (dd), CH_3 1·37 (t); *VId* O—CH 4·28 (dd), CH_3 1·33 (t); *VII* NH_2 5·38 (s); *VIII* OCH_2 4·27 (dd), CH_3 1·36 (t); *Xa* OH 6·74 (s); *Xd* O—CH_2 4·27 (d); CH_3 1·38 (t); *Xe* O—CH_2 4·26 (dd), CH_3 1·35.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage, the ^{1}H NMR spectra of compounds *I*—*IV*, *VIc*, *VId*, *VIII*, *Xd*, and *Xe* in deuteriochloroform and of compounds *Va*—*Vc*, *VIa*, *VIb*, *VII*, *IX*, and *Xa*—*Xc* in hexadeuteriodimethyl sulfoxide with tetramethylsilane as internal reference were measured with Tesla BS 487 B apparatus operating at 80 MHz. IR spectra were recorded in a 0·6 mm NaCl cell with a UR-20 (Zeiss, Jena) instrument as follows: compounds *I*—*V*, *VIc*, *VId*, *VIII*, *Xa*, *Xd*, and *Xe* in chloroform at $2 \cdot 10^{-2}$ mol l^{-1} concentration, *VIa*, *VIb*, *IX*, *Xb*, and *Xc* in KBr pellets. UV spectra of methanolic solutions were taken with a UV VIS (Zeiss, Jena) spectrophotometer in 1 cm cell at 3 to $5 \cdot 10^{-1}$ concentration.

N-(5-Nitrofurfuryl)piperidine (*IIa*), N-(5-Nitrofurfuryl)morpholine (*IIb*) and N-(5-Nitrofurfuryl)anilides *IVa*—*IVd* and *IVf*

Compound *I* (2·05 g, 0·01 mol) in benzene (50 ml) was dropwise added to the amine (0·02 mol) in benzene (50 ml at 5°C and stirred at room temperature for 2 h. The mixture was allowed to stand overnight in a refrigerator, the product was filtered off and washed with benzene (4 ×

TABLE VI
Biological activity

Solvent	Compound	Inhibition zone (in mm) of the microorganism[a]				
		1	2	3	4	5
Acetone	*IVd*	11	19	15	—	12
Acetone	*IVe*	13	22	15	11	12
Acetone	*Vb*	9	11	16	9	—
Acetone	—	9	9	13	—	—
Diethyl ether	*IVd*	12	18	16	10	12
Diethyl ether	*IVe*	12	19	—	12	11
Diethyl ether	*Vb*	9	—	9	9	—
Diethyl ether	—	9	9	—	10	—
Ethanol	*IVd*	10	17	15	10	12
Ethanol	*IVe*	11	12	11	10	10
Ethanol	*Vb*	9	13	10	9	—
Ethanol	—	9	9	10	10	—
H_2O	*IVd*	10	13	12	—	12
H_2O	*IVe*	—	14	—	—	—
H_2O	*Vb*	10	13	10	—	12
H_2O	—	—	—	—	—	—

[a] 1 *Staphylococcus aureus*, 2 *S. epidermis*, 3 *Bacillus subtilis*, 4 *Escherichia coli*, 5 *Klebsiella pneumoniae*.

× 100 ml). Benzene from the Na_2SO_4-dried filtrate was distilled off and ether (50 ml) and concentrated hydrochloric acid (5 ml) were added to the residue. The amine hydrochloride was suction-filtered, washed with ether (2 × 25 ml), dissolved in 5%-aqueous K_2CO_3, and the separated amine filtered off and recrystallized from ethanol. For compound *IVf* the reaction mixture was refluxed for 2 h.

N-(5-Nitrofurfuryl)dimethylamine (*III*)

Compound *I* (2·05 g, 0·01 mol) in benzene (50 ml) was dropwise added to dimethylamine (9 g, 0·02 mol) in benzene (50 ml) at 5°C. The solid was filtered off, the filtrate washed with 5%-aqueous K_2CO_3, the organic layer was separated, dried with Na_2SO_4, benzene was removed, and ether (50 ml) and charcoal were added to the residue. The mixture was heated for 10 min, the solvent distilled off and the product was purified through a silica gel column (eluent chloroform), and finally it was distilled *in vacuo*.

N-(5-Nitrofurfuryl)aminophenols *Va*—*Vc*

A solution of *I* (9·8 g, 48 mmol) in dimethylformamide (50 ml) was dropwise added to aminophenol (10·5 g, 96 mmol) dissolved in the same solvent (60 ml). The mixture was stirred at room temperature for 1 h, poured into ice-cold water (400 ml), and the separated oil was extracted with ether. The solvent was dried with Na_2SO_4, charcoal was added, the solution was heated, filtered and evaporated to dryness. The product was purified through a silica gel column (eluent benzene–chloroform 1 : 1) and the resulting compounds were crystallized from ethanol.

N-(5-Nitrofurfuryl)-2-aminophenol (*Vc*), N,N′-bis(5-Nitrofurfuryl)-2-aminophenol (*Xa*), and 2-(5-Nitrofurfuryloxy)aniline (*VII*)

A solution of *I* (2·5 g, 12 mmol) in methanol (40 ml) was dropwise added during 30 min to a solution of 2-aminophenol (24 mmol) in pyridine (1·5 ml). The mixture was stirred at 25°C for 1 h, the separated compound was filtered off, the filtrate was dried with $CaCl_2$ and concentrated under diminished pressure, the residue was separated on a silica gel column (eluent benzene–chloroform 1 : 1, then methanol) to afford *Vc*, *VII* and *Xa*. The products were crystallized from methanol–ether.

N-(5-Nitrofurfuryl)aminobenzoic Acids and Esters *VIa*—*VId*, N,N′-Bis(5-nitrofurfuryl)aminobenzoic Acids and Esters *Xb*—*Xe*

Compound *I* (2·5 g, 12 mmol) in methanol (30 ml) was dropwise added to a solution of aminobenzoic acid or its ethyl ester (24 mmol) in methanol (40 ml) at room temperature. The mixture was refluxed for 1 h, cooled, filtered, and the filtrate was dried with $CaCl_2$, concentrated and and worked up as in the preceding case.

O-(5-Nitrofurfuryl)salicylic Acid (*IX*) and Ethyl Ester (*VIII*)

Ethyl salicylate (6·26 g, 38 mmol) in tetrahydrofuran (30 ml) was added to sodium hydride (1·2 g, 50 mmol) in tetrahydrofuran (50 ml) at 15°C. The excess of NaH was filtered off after 1 h and a solution of *I* (7·85 g, 38 mmol) in the same solvent (60 ml) was added at room temperature. The solvent was removed under reduced pressure after 30min and the product was extracted with ether, dried with $CaCl_2$, concentrated until oily and purified through a silica gel column (eluent benzene–chloroform 1 : 1). The ester *VIII* was crystallized from ethanol–ether.

Dispersion of *VIII* (0·8 g) in water (40 ml) and concentrated hydrochloric acid (10 ml) was refluxed until the turbidity disappeared (6 h), the solution was cooled and left to crystalize at 5°C, the crystals were suction-filtered, washed with ice-cold water and crystallized from hot water.

Biologic Activity

Compounds *IVd*, *IVe*, and *Vb* were biologically tested against *Staphylococcus aureus*, *S. epidermitis*, *Bacillus subtillis*, *Escherichia coli*, and *Klebsiella pneumoniae*. The microbial culture was prepared on agar by an 18 h growth. Filtration-paper discs were soaked with 0·01 ml of 1%-solution of the respective compound and placed into the pre-prepared culture. After 48 h of cultivation at 37°C the inhibition zones were read (*cf.* Table VI). The inhibition zone of the solvent was monitored in the same way.

REFERENCES

1. Novitskii K. Y., Khachaturova G. T., Yurev Y. K.: Zh. Obsch. Khim. *34*, 1807 (1964).
2. Hook W. H., Howarth G. A., Hoyle W., Roberts G. P.: Chem. Ind. (London) *18*, 1630 (1965).
3. Štetinová J., Dandárová M., Knoppová V., Kováč J.: This Journal *43*, 2041 (1978).
4. Štetinová J., Dandárová M., Kováč J., Mesárošová D., Leško J.: This Journal *47*, 1738 (1982).
5. Mocelo R., Kováč J.: Collection of papers p. 221. 3rd International Symposition on Furan Chemistry, Smolenice 1979.

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