SYNTHESIS AND ANTIMICROBIC EFFECT OF FURYL-SUBSTITUTED INDOLIZINE, IMIDAZO[1,2-a]PYRIDINE, AND IMIDAZO[2,1-b]THIAZOLE

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In continuing investigations of the synthesis and antimicrobic properties of furyl-substituted heterocyclic condensed systems containing a nodal nitrogen atom [1,2], (5-R-furyl-2)-substituted indolizine (VIa, VId), imidazo[1,2-a]pyridine (VIIa, VIIb, VIId), and imidazo[2,1-b]thiazole (VIIIa-VIIIc) and (IXa, IXc) (R =H, Br, NO_2) have been synthesized and data on their antimicrobic effects are presented.

The synthesis of these compounds was carried out by the Chichibabin method [3, 4] based on bromoethyl (furyl-2) ketone (Ia), its 5-bromo and 5-nitro derivatives (Ib and Ic), and also α-bromoethyl (furyl-2) ketone (Id). The method of ketone bromination in a mixture of dioxane and ether [5] was used for the synthesis of (Id), described for the first time by us.

Reactions of the bromoketones with 2-picoline, 2-aminopyridine, 2-aminothiazole, and its 4-methyl derivative result in the formation of the ketoammonium salts (II-V), of which (IIa) [6], (IIc) [7], (IVa), (IVc) [8], and (Va) (Vc) [2] were described earlier. In contrast to other ketoammonium salts, the ketoammonium salts (IIIa), IIIb, IIId) obtained from 2-aminopyridine had a tar-like consistency and were used for further cyclization without isolation in pure form.

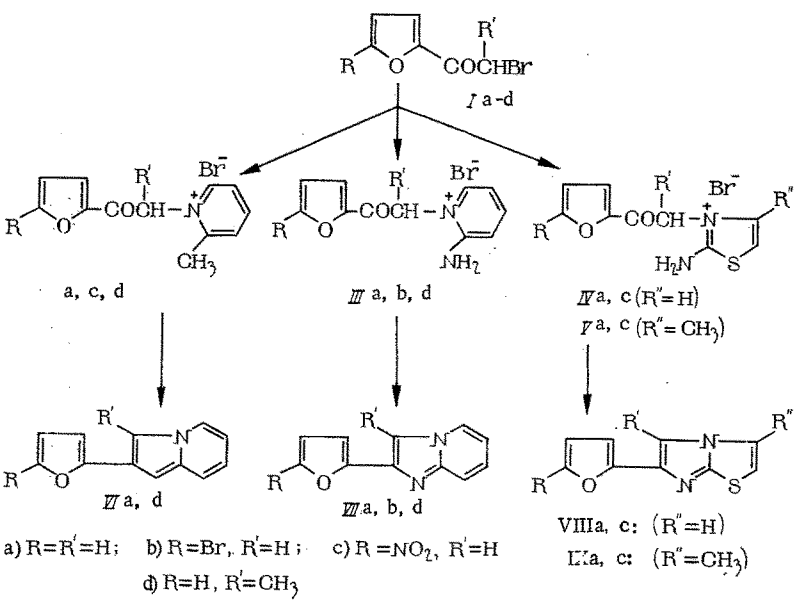

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TABLE 1. Furylazabicyclic Compounds

Compound	Method of preparation	Yield, %	Mp, °C	Found, %			Empirical formula	Calculated, %			UV spectrum in alcohol; λ_{max} (nm), log ε (in parentheses)
				C	H	N		C	H	N	
VIa	A	73	142—3[2,3]	78,67	4,95	7,66	$C_{12}H_9NO$	78,56	5,01	7,64	255, 340 (4,60, 3,56)
	B	45	140—3[4]	—	—	—		—	—	—	254, 339 (4,59, 3,54)
VI[d]	A	39	42—4[4]	79,60	5,90	7,32	$C_{13}H_{11}NO$	79,19	5,62	7,10	250, 263, 351 (4,60, 4,60, 3,54)
VIIa	B	53	110[2,5,6]	71,86	4,58	15,13	$C_{11}H_8N_2O$	71,73	4,34	15,21	250, 317 (4,47, 3,99)
	C	46	110—1[3,4]	—	—	—		—	—	—	251, 319 (4,43, 3,93)
perchlorate			173—5[7]	41,78	3,60	10,65	$C_{11}H_8N_2O \cdot HClO_4$	41,46	3,48	10,74	250, 307 (4,21, 4,06)
picrate			179—80[2]	49,61	2,78	17,09	$C_{11}H_8N_2O \cdot C_6H_2(NO_2)_3OH$	49,61	2,78	17,01	
VII[b]	D	26	155—6[2]	49,92	2,78	11,06	$C_{11}H_7BrN_2O$	50,22	2,68	10,65	258, 320 (4,47, 4,10)
hydrobromide			216—8	36,36	2,92	7,80	$C_{11}H_7BrN_2O \cdot HBr \cdot H_2O$	36,49	2,78	7,74	
picrate			195—200	41,28	2,32	14,76	$C_{11}H_7BrN_2O \cdot C_6H_2(NO_2)_3OH$	41,48	2,20	14,30	
VII[c]	[1]		253—5[4]	57,98	3,09	18,49	$C_{11}H_7N_3O_3$	57,64	3,08	18,34	232, 275, 290, 365 (4,54, 3,66, 3,65, 4,30)
hydrobromide			234—5[8]	—	—	13,72	$C_{11}H_7N_3O_3 \cdot HBr$	—	—	13,55	
hydrochloride			222—5[8]	49,45	3,06	15,62	$C_{11}H_7N_3O_3 \cdot HCl$	49,73	3,04	15,82	
VII[d]	B	37	85—8[2]	72,20	5,38	14,29	$C_{12}H_{10}N_2O$	72,71	5,08	14,11	249, 329 (4,39, 3,91)
			184—6	48,08	3,38	9,45	$C_{12}H_{10}N_2O \cdot HClO_4$	48,25	3,71	9,38	255 (4,36)
VIIIa	C	65	102—3[3,9]	—	—	16,70	$C_9H_6N_2OS$	—	—	16,84	258 (4,17)
hydrobromide			165—70[7]	—	—	10,12	$C_9H_6N_2OS \cdot HBr$	—	—	10,33	256 (4,30)
hydrochloride			160—5[7]	—	—	12,10	$C_9H_6N_2OS \cdot HCl$	—	—	12,36	258 (4,30)
perchlorate			193—5[7]	36,91	2,58	9,40	$C_9H_6N_2OS \cdot HClO_4$	37,19	2,43	9,63	
picrate			190—3[2]	—	—	17,02	$C_9H_6N_2OS \cdot C_6H_2(NO_2)_3OH$	—	—	16,70	
VIIIb	D	40	159—60[2]	—	—	10,32	$C_9H_5BBrN_2OS$	—	—	10,44	
VIIIc	E	40	215—18[4]	—	—	18,02	$C_9H_5N_3O_3S$	—	—	17,87	240, 370 (3,90, 3,91)
IXa	C	70	111—3[2,11]	—	—	—	$C_{10}H_8N_2OS$	—	—	—	257 (4,42)
hydrobromide			223—4	42,39	3,11	9,67	$C_{10}H_8N_2OS \cdot HBr$	42,12	3,18	9,82	255 (4,20)
hydrochloride			207—10[7]	—	—	—	$C_{10}H_8N_2OS \cdot HCl$	—	—	—	255 (4,35)
perchlorate			202—4[7]	—	—	9,07	$C_{10}H_8N_2OS \cdot HClO_4$	—	—	9,19	255 (4,28)
picrate			190—1[2]	44,21	2,70	16,40	$C_{10}H_8N_2OS \cdot C_6H_2(NO_2)_3OH$	44,34	2,55	16,16	
IXc	D	30	210—2[4]	—	—	16,92	$C_{10}H_7N_3O_3S$	—	—	16,86	241, 370 (3,99, 3,97)
hydrochloride			205—10[8]	—	—	14,42	$C_{10}H_7N_3O_0 \cdot HCl$	—	—	14,70	

1 See Experimental.
2 From aqueous alcohol.
3 From n-octane.
4 Vacuum sublimation (3 mm).
5 Bp 170° (4 mm).
6 Extraction with petroleum ether.
7 From a mixture of alcohol and ether.
8 With decomposition
9 Literature data [2]: mp 96-98°
10 With participation of G. Ya. Zarin'.
11 Literature data [2]: mm 112-113°

TABLE 2. Antimicrobic Effect of Furylazabicyclic Compounds in vitro (μg/ml)*

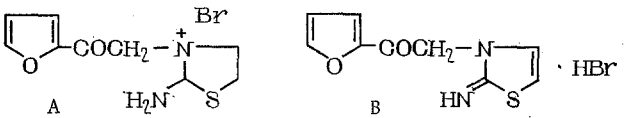
Compound	St. aureus № 209	Bac. mycoides № 537	E. coli № 675	Sh. sonnei № 5063	Salm. paratyphi «B» № 493	Salm. typhi № 4446	Salm.typhi murium № 4867	Proteus vulgaris № 1
VIa	≥133,3	≥133,3	>100	100	100	>100	>100	>100
VIIa	≥133,3	≥133,3	>100	100	100	100	>100	>100
VIIc	16,6	0,5	1,04	<0,0019	0,7	2,08	1,04	>100
VIIIa	6,6	≥133,3	100	100	100	100	>100	>100
VIIIc	—	—	—	2,5	2,5	1,66	—	>20
IXa	>66,6	>66,6	>100	100	100	100	>100	>100
IXc	—	—	33	8,3	6,25	12,5	—	>100
X	>33	<33	>100	100	100	100	>100	>100

*Determined by the dilution method in a liquid nourishment medium (Hottinger solution); results considered after 24 h.

The IR spectra* of (IVa) and (Va) contain broad bands of intense absorption in the 3200-2900 cm^{-1} region, which can be assigned to ν of associated N–H. These bands have weakly projecting peaks correspondingly at 3130, 3080, 3040, 3020, and 3123, 3090, and 3015 cm^{-1}, which correspond to superposition of ν of ring CH, since IR spectra of 1-(2-furoylmethyl)2-picolinium bromide (IIa) and 1-(2-furoylmethyl)-pyridinium iodide contain narrow bands at approximately these same frequencies (3120, 3090, 3040, and 3010 cm^{-1}). Compounds (IIa), (IVa), (Va), and (X) have intense absorption bands at 1690-1685 cm^{-1} (C = O) and 1570 cm^{-1} (vibrations of 2-carbonyl furan derivatives), which are absent in the subsequent cyclization products and also a band at 1640-1635 cm^{-1}, which can be assigned to $C = N^+$ or C = N [9]. In the case of (IIa) and (X) the latter band has average intensity and in the case of (IVa) and (Va), possibly because of superposition of ν of NH, it becomes very intense and more broad.

UV spectra† of (IIa), (IVa), and (Va) have an identical character (λ_{max} 270 nm, log ε 4.21, 4.32, and 4.25, respectively) and are similar to spectra of (X) (λ_{max} 270 nm, log ε 4.21), 1-(2-furoylmethyl)piperdine (λ_{max} 272 nm, log ε 4.20), and its hydrobromide (λ_{max} 273 nm, log ε 4.23).

On the basis of UV and IR spectroscopic data for the reaction products of (Ia) with 2-aminothiazole or its 4-methyl derivative (IVa and Va) it is not possible to show a preference for structure A or B [10]:



Cyclization of ketoammonium salts not having a substituent in position 5 of the furan ring or having bromine as a substitutent occurs upon heating with an aqueous solution of sodium bicarbonate, while cyclization of the nitrofuracyl derivatives (IIIc) [1], (IVc), and (Vc) [2] occurs merely upon heating with water or organic solvents (alcohol, dimethylformamide, acetic acid).

In addition, an attempt to obtain 2-(5-nitrofuryl-2)indolizine (VIc) cyclization of 1-(5-nitro-2-furoylmethyl)-2-picolinium bromide (IIc) [7] by heating in dimethylformamide, by reaction with aqueous solutions of sodium bicarbonate or acetate, and also by analogy with construction of other condensed systems having a nodal nitrogen (reaction with triethylamine in methanol [11], reaction with sodium acetate and acetic anhydride and subsequent cleavage of the acetyl group [12], boiling with concentrated hydrobromic acid [13,14]) did not give positive results.

Data on furyl-substituted azabicyclic compounds are presented in Table 1.

(Furyl-2)- and (5-bromofuryl-2)-substituted azabicyclic compounds are colorless crystalline materials, darkening upon storing. Compounds not containing the nitro group in the furan ring are very soluble in alcohol, ether, benzene, chloroform, acetic acid, dioxane, and dimethylformamide, insoluble in water, and poorly soluble in cold petroleum ether. Furyl- and bromofuryl-substituted imidazopyridine and

*Taken on a UR-10 instrument in hexachlorobutadiene (3600–2000 cm^{-1} region) and in mineral oil (2000-800 cm^{-1} region).

†Taken on an SF-4 spectrophotometer in alcohol solution.

imidazothiazole give stable salts with picric and mineral acids. Furylindolizine (VIa) and its methyl derivative (VId) darken upon reaction with mineral acids and form yellow-brown precipitates with picric acids, which decompose upon attempts to recrystallize them from alcohol.

Nitrofurylazabicyclic compounds are yellow crystalline materials, soluble in dimethylformamide, hot dioxane, and acetic acid, and insoluble in water. Their salts, like salts of other nitrofuryl-substituted nitrogen-containing heterocyclic compounds, can be obtained by reaction with acid in anhydrous solvents; they easily undergo hydrolysis.

All of the obtained azabicyclic compounds give an intense red or crimson-red color with concentrated sulfuric acid which disappears upon dilution with water, and all of them sublime in vacuum.

An absorption maximum in the 249-258 nm region is characteristic for UV spectra of furyl- and bromofurylazaindenes, while second maxima of low-intensity absorption appears at 320-340 nm in the case of indolizine and imidazopyridine derivatives (VIa, VId, and VIIa, VIIb, VIId). Two bands of strong absorption (235-245 and 370 nm) appear in all cases after introduction of a nitro group into the furan ring.

The results of a study of the antimicrobic effect of furylazabicyclic compounds and their substituted derivatives in vitro in relation to gram-positive and gram-negative bacteria are presented in Table 2. The minimal concentration of furylazabicyclic compounds retarding growth of the microorganisms amounts to 100 μg/ml, while it increases sharply for phenyl analogs: e.g., for 6-phenylimidazo[2,1-b]thiazole and its p-nitro derivative it is equal to 7800 μg/ml [5] in relation to Staphylococcus aureaus, Salmonella typhi, and Escherichia coli. Thus, substitution of the phenyl group with a furyl group leads to a strong increase of antimicrobic effect which increases even more in the nitrofurylazabicyclic compounds (VIIc, VIIIc, and IXc). The strongest bacteriostatic effect is shown by nitrofurylimidazopyridine (VIIc), while its aromatic analog, 2-p-nitrophenylimidazo[1,2-a]pyridine (X) [16], was found to be of low activity.

EXPERIMENTAL

α-Bromoethyl(furyl-2)ketone (Id). To a solution of 24.8 g of 2-propionylfuran in 40 ml of dioxane and 80 ml of ether with ice-water cooling and intense stirring was added 0.4 ml of bromine; after 15 min, when the mixture had lightened, the remaining 10 ml of bromine was added over 30 min and the mixture was diluted with 40 ml of ether and 120 ml of water. The ether layer was separated, washed with 40 ml of water, 40 ml of a saturated aqueous solution of sodium bicarbonate, again with water, and dried with sodium sulfate. The ether was distilled and the residue was distilled in vacuum using a rod-and-disk type fractionating column. Yield was 19.4 g (48%). It is an oily, straw-yellow, rapidly darkening liquid, having a sharp smell, and is a strong lachrymator. Bp 82-84° (3mm), n_D^{20} 1.5537, d_4^{20} 1.5268. Found %: C 40.91; H 3.20; Br 38.96. $C_7H_7BrO_2$. Calculated %: C 41.41; H 3.48; Br 39.35.

1-[α-(2-Furoyl)ethyl]-2-picolinium Bromide (IId). To a solution of 10.2 g of freshly distilled (Id) in 20 ml of ether was added 4.2 g of 2-picoline and the mixture was left for 4 days; the precipitate was separated and washed with ether. Yield 5 g (33.8%), mp 178-182° (from a mixture of absolute alcohol and ether). Found %: C 52.82; H 4.68; N 5.02. $C_{13}H_{14}BrNO_2$. Calculated %: C 52.72; H 4.76; N 4.73. λ_{max} (in alcohol) 255 nm, log ε 4.36.

3-(2-Furoylmethyl)-2-amino-4-methylthiazolinium Bromide (Va). The compound was obtained analogously by mixing an ether-dioxane solution of technical (Ia) and an acetone solution of 2-amino-4-methylthiazole. Yield 79%, mp 192-194° (from a mixture of alcohol and ether); literature data [2]: mp 174°. Found %: C 39.48; H 3.78. $C_{10}H_{11}BrN_2O_2$. Calculated %: C 39.61; 3.66.

Azabicyclic Compounds. Method A. We heated 70 mmoles of the α-ketoammonium bromide to boiling with 70 ml of water and 10 g of sodium bicarbonate, and upon cooling filtered the precipitate and washed it with water.

Method B. We dissolved 0.3 mole of bromomethyl(furyl-2)ketone in 100 ml of ether of acetone, added 0.3 mole of 2-picoline or 2-aminopyridine, respectively, after 2 days poured the liquid from the viscous ketoammonium bromide precipitate, washed it with 50 ml of ether, heated it with 250 ml of water and 25 g of sodium bicarbonate to boiling, and upon cooling filtered the precipitate.

Method C. We brominated 0.3 mole of methyl(furyl-2)ketone in a mixture of 60 ml of dioxane and 120 ml of ether with 15.2 ml of bromine [5] and poured the mixture into 120 ml of water and 120 ml of ether. The ether layer was separated, washed two times with 50 ml of water, dried with sodium sulfate,

filtered, and mixed with 0.27 mole of the corresponding methyl- or aminoheterocyclic compound. After 2 days the precipitate was separated and heated with 25 g of sodium bicarbonate and 250 ml of water; upon cooling the precipitate was separated.

Method D. To an ether solution of diazomethane, prepared from 0.4 mole of nitrosomethylurea, at 0-5° was added a solution of 0.1 mole of 5-bromo-2-furoyl chloride and the mixture was left for 1 h at room temperature. A solution of the diazo ketone was obtained [17]. To it was added 100 ml of a 40% solution of hydrobromic acid and the mixture was heated for 1 h on a water bath and poured into 1 liter of water. The ether layer was washed with a solution of sodium bicarbonate and water and dried with sodium sulfate. To the obtained solution of bromomethyl(5-bromofuryl-2)ketone was added 0.085 mole of 2-aminopyridine or 2-aminothiazole, respectively, and operations were carried out further as described in method B.

Method E. We mixed 0.04 mole of bromomethyl(5-nitrofuryl-2)ketone in 40 ml of dimethylformamide with 0.04 mole of the aminoheterocyclic compound in 40 ml of alcohol and heated the mixture on a water bath for 3 h, diluted it with two volumes of water, and filtered the precipitate.

Azabicyclic Salts. These were prepared in the following way: picrates, by reaction of an alcohol solution of picric acid; hydrochlorides, by reaction of an alcohol solution of hydrogen chloride, precipitate washed with ether; hydrobromides, by addition of a 40% solution of hydrobromic acid to an acetone solution of base, precipitate recrystallized from alcohol; perchlorates, by reaction with a 57% solution of perchloric acid.

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