SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME FURYLPROPYLAMINES

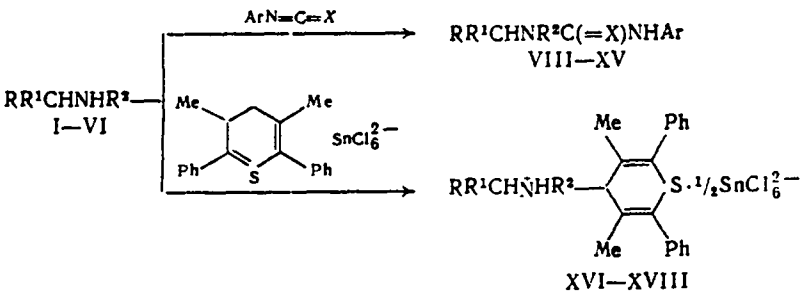
I. N. Klochkova, M. V. Noritsina,
L. K. Kulikova, M. K. Krasheninnikova,
and V. G. Kharchenko

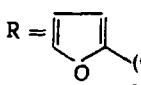
UDC 615.28:547.722.743].
012.1

We have previously reported the preparation of some N-R-furylalkylamines and their acyl derivatives, which are of interest in the synthesis of biologically active compounds [1-3].

Continuing these investigations, we have for the first time carried out nucleophilic reactions of the 3-(2-furyl)-1-propyl-amines (I-VI) with a variety of substrates, including aryl isocyanates and bisthiapyrylium hexachlorostannate, to give the N-aryl-N'-furylalkylureas (VII-XV) and γ-thiopyrans (XVI-XVIII), containing the furylalkylammonium substituent. Also obtained were the novel acid tartrates (XIX and XX) of (V) and (VI).

An examination of the reactions of the furylamines with aryliso(thio)-cyanates and thiapyrylium salts reveals the effect of the nucleophilic strength of the nitrogen in these compounds on their reactivity. For example, primary furylalkylamines give the appropriate derivatives with isocyanates at room temperature. Secondary aromatic furyfurylamines give substituted ureas on prolonged boiling in dioxane only with amines (III) and (IV), in which the aromatic ring contains electron-donor substituents.



R = 
(CH₂)₂ (I—XVIII); R¹ = H (I, III, IV, VII, XI, XII, XVII); Me (II, VIII—X, XVII), $CH_2CH(CH_3)_2$ (V, XVIII, XIV, XVIII). *tert*-Bu (VI, XV); R² = H (I, II, V—X, XIII—XVIII), C_6H_4OMe-p (III, XI), C_6H_4OEt-p (IV, XII); Ar = Ph (VII, VIII—XIII); $C_6H_3Cl_2$-2,4 (IX, XIV, XV); X = O (VII-IX, XI-XV), S (X).

The reaction of amines (I), (II), and (V) with bisthiapyrylium hexachloro-stannate is a nucleophilic addition with the formation of the ammonioalkyl-furyl substituted γ-thiopyrans (XVI-XVIII), which are insoluble under the experimental conditions. The N-arylfurylpropylamines (III) and (IV) failed to react with thiapyrylium salts. The structures of the products were confirmed by their elemental analyses and IR spectra. The IR spectra of (VII-XX) showed absorption at 3140-3120 cm^{-1}, and of (VII-XV), at 3040-3030 cm^{-1}, attributed to ν_{C-H} of the furan and aromatic rings respectively. Stretching vibrations of the methyl and methylene groups in (VII-XX) were seen as absorption at 2970-2950 cm^{-1} (ν_{as} CH_3, CH_2) and 2850-2870 cm^{-1} (ν_{as} CH_3, CH_2). The presence of ammonium nitrogen in (XIX), (XX), and (XVI-XVIII) was confirmed by strong absorption at 3380-3280 cm^{-1} ($\nu\overset{+}{N}H_3$) and medium absorption at 2700-220 cm^{-1} ($\nu\overset{+}{N}H_2$) respectively. The —C=C stretching vibrations in the γ-thiopyrans (XVI-XVIII) were manifested as medium absorption at 1650-1620 cm^{-1}.

Examination of the IR and UV spectra of the ureas (VII-XV) showed the presence of different isomeric forms of the latter both in the solid state, and in solvents of varying polarity. The enol forms of (VII-IX) and (XIII-XV) in the solid state were confirmed by strong absorption at 3400-3200 cm^{-1} (ν_{OH}) in the IR spectra, and medium intensity absorption

N. G. Chernyshevskii Saratov University. N. I. Vavilova Saratov Agricultural Institute.
Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 21, No. 6, pp. 696-699, June, 1987. Original article submitted December 29, 1985.

0091-150X/87/2106-0435$12.50

TABLE 1. Antimicrobial Activity of the Test Compounds

Compound	Minimum bacteriostatic concentration, μg/ml				
	Staphyloc. aureus 209 P	E. coli 675	Proteus vulgaris 38	Pseudomonas aeruginosa 165	Candida albicans 45
VII	100	50	100	100	100
VIII	100	50	50	50	100
IX	100	50	50	50	100
X	100	100	50	100	100
XI	100	50	50	50	100
XII	100	100	50	100	100
XIII	100	100	100	100	100
XIV	100	50	50	50	50
XV	50	50	50	50	50
XVI	6	50	25	25	12
XVII	3	50	25	25	6
XVIII	3	50	25	25	6
XIX	100	50	50	50	100
XX	50	50	50	50	50

TABLE 2. Antiphage Activity of the Test Compounds

Compound	% inactivation of phage			
	T_4		MS-2	
	dose of drug, μg/ml			
	1000	100	1000	100
VII	7	0	0	0
VIII	10	0	0	0
IX	10	0	0	0
X	20	10	0	0
XI	29	10	0	0
XII	40	37	0	0
XIII	10	0	0	0
XIV	15	14	0	0
XV	25	19	0	0
XVI	33	10	40	8
XVII	44	10	55	10
XVIII	60	41	65	10
XIX	23	19	5	3
XX	48	19	10	5

at 1630-1620 cm^{-1} ($\nu_{C=N}$). In the UV spectra of (VII-IX) and (XIII-XV), changing to a polar solvent resulted in a bathochromic shift of the long-wavelength band. The carbonyl form of (XI-XII) was characterized by a narrow absorption band at 3430-3410 cm^{-1} (amide ν_{NH}), and strong absorption with a maximum at 1680 cm^{-1} (urea $\nu_{C=O}$), together with the absence of hydroxyl absorption in the IR spectrum.

The results of tests for antimicrobial and antiviral activity are shown in Tables 1 and 2. Examination of these results shows that the furylalkylamine acid tartrates (XIX) and (XX), and furylalkylaminoureas and isoureas (VII-XV) possess moderate antimicrobial activity. The greatest antistaphylococcal activity is shown by the thiopyrans (XVI-XVIII). These compounds also show the highest antiphage activity. The antimicrobial and antiphage activity of (VII-XX) are virtually independent of the nature of the substitution in the aliphatic chain and the aromatic ring.

Thus, the antimicrobial activity which we have found in some furylalkylamines, together with their ability to inhibit phage reproduction, provide grounds for further study of this group of compounds as potential chemotherapeutic agents.

TABLE 3. Properties of Compounds Obtained

Compound	Yield, %	mp, °C	Found, %					Empirical formula	Calculated, %				
			C	H	Cl	N	S		C	H	Cl	N	S
VII	68	181—2	68,60	6,80	—	11,60	—	$C_{14}H_{16}N_2O_2$	68,85	6,55	—	11,47	—
VIII	76	124—5	70,00	6,77	—	10,70	—	$C_{15}H_{18}N_2O_2$	69,76	6,97	—	10,85	
IX	96	151—2	55,40	5,02	21,58	8,50	—	$C_{15}H_{16}Cl_2N_2O_2$	55,04	4,89	21,71	8,56	—
X	40	66—7	65,88	6,40	—	10,22	11,70	$C_{15}H_{16}N_2OS$	65,63	6,56	—	10,22	11,67
XI	65	176—7	71,92	6,30	—	8,31	—	$C_{21}H_{22}N_2O_2$	72,0	6,28	—	8,0	—
XII	54	76—8	72,44	6,39	—	7,40	—	$C_{22}H_{24}N_2O_2$	72,52	6,59	—	7,69	—
XIII	71	90—1	72,50	8,0	—	9,15	—	$C_{16}H_{24}N_2O_2$	72,0	8,0	—	9,33	—
XIV	96	114—5	58,38	6,00	19,42	7,28	—	$C_{15}H_{22}Cl_2N_2O$	58,53	5,96	19,24	7,58	—
XV	89	171—2	58,80	5,99	19,30	7,98	—	$C_{15}H_{22}Cl_2N_2O$	58,53	5,96	19,24	7,58	—
XVI	58	197—8	—	—	18,55	2,35	5,45	$C_{53}H_{54}N_2O_2S_2 \cdot H_2SnCl_6$	—	—	18,78	2,46	5,63
XVII	56	229—30	—	—	18,19	2,07	5,55	$C_{54}H_{58}N_2O_2S_2 \cdot H_2SnCl_6$	—	—	18,33	2,40	5,50
XVIII	45	289—90	—	—	17,08	2,05	5,50	$C_{60}H_{70}N_2O_2S_2 \cdot H_2SnCl_6$	—	—	17,07	2,24	5,13
XIX	97	133—4	54,40	7,34	—	4,28	—	$C_{11}H_{19}NO \cdot C_4H_6O_6$	54,33	7,55	—	4,23	—
XX	80	89—90	54,38	7,52	—	4,25	—	$C_{11}H_{19}NO \cdot C_4H_6O_6$	54,33	7,55	—	4,23	—

EXPERIMENTAL CHEMICAL PART

IR spectra were obtained on a UR-20 spectrometer (East Germany), in vaseline oil and hexachlorobutadiene.

UV spectra were obtained on an SF-4A spectrophotometer in absolute ethanol and a mixture of isooctane and dioxane (2:1), thickness of absorbing layer $0.6.10^{-2}$ cm, concentration of solutions 10^{-3} mole/liter.

Data for the compounds obtained are given in Table 3.

Furylalkylamines (I-IV) were obtained as described in [1, 3].

3-(2-Furyl)-1-isobutyl-1-propylamine hydrogen tartrate (XIX) and 3-(2-furyl)-1-tert-butyl-1-propylamine hydrogen tartrate (XX) were obtained by reacting equimolar amounts of the amine and tartaric acid in ethanol.

N-Aryl-N'3-(2-furyl)-1-alkylisoureas (VII-IX), (III-XV), N-phenyl-N'-3-(2-furyl)-1-methyl-1-propylthiourea (X), and N-phenyl-N'-3-(2-furyl)-1- propyl-N'-(p-alkoxyphenyl)ureas (XI), (XII) were obtained by reacting equimolar amounts of the amine (I-VI) with phenyl or 2,4-dichlorophenyl isocyanates, or phenyl isothiocyanate in a solvent at 20-80°C for 1-24 h, followed by isolation of the crystalline products.

Bis-(3,5-dimethyl-2,6-diphenyl-4-thiopyranyl)-N-3-(2-furyl) propylammonium hexachloro-stannates (XVI-XVIII) were obtained by reacting molar ratios of amines (I), (II), and (V) with bis-(3,5-dimethyl-2,6-diphenyl)thiapyrylium hexachloro-stannate in dry dioxane at room temperature for 4 h, followed by isolation of the crystalline products and recrystallization from DMF.

EXPERIMENTAL BIOLOGICAL PART

The antimicrobial activity of the test compounds was determined by the double serial dilution method in meat peptone broth at pH 7.2-7.4 against *Staph. aureus* 209p, *E. coli* 675. *Proteus vulgaris* 38, *Pseudomonas aeruginosa* 165 and *Candida albicans* 45 (Table 1). The antiphage activity of the compounds was examined using DNA- containing (T_6) and RNA-containing (MS-2) phages (Table 2). The indicator cultures were the *E. coli* strains B and Hfr C respectively. The numbers of surviving phage particles were determined by the Grazia agar layer method. Antiphage activity was expressed as the percentage inactivation using the formula $(1 - C_o/C_c) \times 100$, where C_o is the number of surviving phage particles in the test, and C_c the number surviving in the control.

The compounds were dissoved in DMF, then diluted with sterile distilled water.

LITERATURE CITED

1. I. N. Klochkova, M. V. Noritsina, and L. K. Kulikova, Khim.-farm. Zh., No. 9, 63-66 (1977).
2. I. N. Klochkova, L. K. Kulikova, M. K. Krasheninnikova, and M. V. Noritsina, Khim.-farm. Zh., No. 8, 931-934 (1983).
3. A. A. Ponomarev, M. V. Noritsina, and A. P. Kriven'ko, Khim. Geterotsikl. Soedin., No. 6, 923-931 (1966).