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SALTS OF N,N'-BIS-[β-2-ALKYLPYRROLIDINO)ETHYL]PHTHALAMIDES AND THEIR BIOLOGICAL ACTION

I. V. Lizak, V. A. Sedavkina, and L. I. Kulikova

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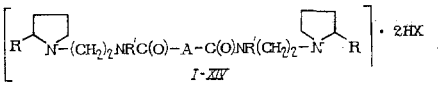
It was established by us previously in [1, 3] that 2-alkyl-1-aminoethylpyrrolidines and certain of their derivatives possess moderate antimicrobial and antiphage activity.

With the aim of studying the biological action of salts of the bisamides obtained by reacting phthalic acid chlorides with 2-alkyl-1-aminoethylpyrrolidines and also the influence of the acid and base fragments and of the character of the anions of their salts on antimicrobial and antiphage activity, we synthesized the dihydrochlorides and dihydrobromides of amides of phthalic, isophthalic, and terephthalic aicds of the following form.



I-XIV

I: R=C_3H_7, R′=H, A=C_6H_4-1,4, X=Br; II: R=iso-C_4H_9, R′-H, A=C_6H_4-1,4, X=Br; IIIa: R=C_3H_7, R′=H, A=C_6H_4-1,4, X=Cl; IV: R=iso-C_4H_9, R′=H, A=C_6H_4-1,4, X=Cl; V: R=C_3H_7, R′=H, A=C_6H_4-1,3, X=Cl; VI: R=iso-C_4H_9, R′-H, A=C_6H_4-1,3, X=Cl; VII: R=C_4H_9, R′=H, A=2,4-$(NO_2)_2C_6H_2$-1,3, X=Cl; VIII: R=iso-C_4H_9, R′=H, A=2,4-$NO_2C_6H_2$-1,3, X=Cl; IX: R=C_3H_7, R′=H, A=C_6H_4- 1,2, X=Cl; X: R=iso-C_4H_9, R′=H, A=C_6H_4-1,2, X=Cl; XI: R=C_3H_7, R′=$(CH_2)_2CN$, A=C_6H_4-1,4, X=Cl; XII: R=iso-C_4H_9, R′=$(CH_2)_2CN$, A=C_6H_4-1,4, X=Cl; XIII: R=C_3H_7, R′=$(CH_2)_2CN$, A=C_6H_4-1,2, X=Cl; XIV: R=iso-C_4H_9, R′=$(CH_2)_2CN$, A=C_6H_4-1,2, X=Cl.

Their physical constants, data of elemental analysis, and yields are given in Table 1.

The structures of the obtained compounds were confirmed by data of elemental analysis and IR spectroscopy.

Intense absorption of the amide carbonyl in the 1700-1650-cm^{-1} region was observed in the IR spectra of compounds (I-XIV). Absorption bands in the 3060-3030- and 2700-2250-cm^{-1}. region correspond to C–H of aromatic rings and N–H.

For all compounds except (XI-XIV) an intense absorption band was observed in the 3340-3320-cm^{-1} region corresponding to NH in amides. Absorption at 1550-1540 and 870-860 cm^{-1} was a characteristic of compounds (VII) and (VIII) and corresponds to NO_2 (as) and NO_2 (s) similarly absorption at 2260-2230 cm^{-1} characteristic of C=N was observed for compounds (XI-XIV).

The initial 2-alkyl-N-(β-aminoethyl)pyrrolidines have been described previously. Cyanoethylation of them under mild conditions gave the previously undescribed β-[1-(2-alkylpyrrolidino)ethyl-β-cyanoethylamines (XV-XVII) (Table 2).

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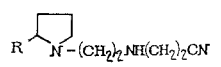
TABLE 1. Salts of N,N'-Bis-[β-(2-alkylpyrrolidino)ethyl] ethyl]-phthalamides (I-XIV)

Compound	Yield, %	mp, °C	Found, %		Empirical formula	Calculated, %	
			N	halogen		N	halogen
I	76	56—8	9,15	26,46	$C_{26}H_{44}N_4O_2Br_2$	9,26	26,4
II	80	69—70	9,07	25,19	$C_{28}H_{48}N_4O_2Br_2$	8,82	25,37
III	77	95—7	10,52	13,48	$C_{26}H_{44}N_4O_2Cl_2$	10,88	13,77
IV	84	78—9	10,06	13,22	$C_{28}H_{48}N_4O_2Cl_2$	10,32	13,26
V	76	82—4	10,96	13,81	$C_{26}H_{44}N_4O_2Cl_2$	10,88	13,77
VI	75	86—7	10,02	12,68	$C_{28}H_{48}N_4O_2Cl_2$	10,32	13,06
VII	82	132—4	13,12	10,87	$C_{28}H_{46}N_6O_6Cl_2$	13,34	11,17
VIII	78	137—9	12,93	11,13	$C_{28}H_{46}N_6O_6Cl_2$	13,34	11,17
IX	78	68—9	10,54	13,42	$C_{26}H_{14}N_4O_2Cl_2$	10,88	13,77
X	78	72—3	9,98	12,87	$C_{28}H_{48}N_4O_2Cl_2$	10,32	13,06
XI	78	72—3	15,20	12,70	$C_{32}H_{48}N_6O_2Cl_2$	15,34	12,94
XII	80	78—80	14,50	12,11	$C_{34}H_{52}N_6O_2Cl_2$	14,62	12,31
XIII	82	61—3	15,11	12,71	$C_{32}H_{48}N_6O_2Cl_2$	15,34	12,94
XIV	80	68—9	14,40	12,00	$C_{34}H_{52}N_6O_2Cl_2$	14,62	12,31

TABLE 2. β-[1-(2-Alkylpyrrolidino)ethyl]-β-cyanoethylamines (XV-XVII)

Compound	Yield, %	Bp, °C (mm Hg)	n_D^{20}	Found, %			Empirical formula	Calculated, %		
				C	H	N		C	H	N
XV	68	150—2 (4)	1,4950	68,77	10,80	20,3	$C_{12}H_{23}N_3$	68,89	11,04	20,07
XVI	63	158—9 (4)	1,4940	70,03	11,35	18,90	$C_{13}H_{25}N_3$	69,95	11,29	18,83
XVII	63	163—5 (4)	1,4920	70,71	11,42	17,65	$C_{14}H_{27}N_3$	70,89	11,39	17,92



XV-XVII

XV: R=C_3H_7; XVI: R=iso-C_4H_9; XVII: R=C_5H_{11}.

Intense absorption with maxima at 3400 and 1630 cm^{-1} was observed in the IR spectra of (XV-XVII) and corresponded to the stretching and deformation vibrations of a secondary amino group. There was also an absorption for C=N in the 2260-2230-cm^{-1} region.

Results of the investigation of antiphage and antimicrobial activity of the synthesized compounds are given in Table 3. It was established that all the investigated compounds displayed marked antiphage activity exceeding appreciably the activity of the initial N-aminoalkylpyrrolidines. Phage MS-2 was the most sensitive to the action of the investigated compounds.

Compounds (VII) and (VIII), containing a 2-nitro group in the acid fragment, displayed the greatest activity. An increase in activity in relation to phage MS-2 and the DNA-containing phage T_6 was also observed on replacing the hydrogen atom on the amide group by a cyanoethyl group (XI-XIV). Replacement of bromide ion by chloride ion led to some strengthening of the antiphage action (I and III, II and IV).

On studying the bacteriostatic action of salts (III-XIV) it was established that the mutual disposition of the amide groups in the aromatic fragment proved to have no influence on antimicrobial activity (III-VI, IX-X). Introduction of a 2-nitro group afforded an increase in antimicrobial action in relation to *Staphylococcus* and *Candida* mold (VII-VIII). The presence of a cyanoethyl substituent in the basic fragment also strengthened the bacteriostatic effect (XI-XIV) while the anions of the salts Br^- (I, II) and Cl^- (III, IV) proved to have practically no influence on antimicrobial activity.

TABLE 3. Biological Activity of Compounds (I-XIV, XVI, XVIII)

Compound	Minimum bacteriostatic concentration, μg/ml								
	microorganisms					% -inactivation of phage			
						phage T_6		phage MS-2	
	St. aureus	E. coli	Pr. vulgaris	Ps. aeruginosa	C. albicans	1000	100	1000	100
I	100	100	100	100	50	57	29	61	29
II	50	100	100	100	50	59	37	63	40
III	100	100	100	100	100	63	37	69	41
IV	50	100	100	100	50	63	34	71	37
V	100	50	100	50	100	66	40	61	33
VI	50	50	100	100	50	67	47	67	39
VII	25	50	50	50	25	63	50	84	51
VIII	25	50	50	50	25	61	43	77	54
IX	100	100	100	50	100	59	38	60	34
X	100	100	100	50	50	58	37	69	37
XI	25	50	50	50	25	68	47	73	43
XII	25	50	50	50	25	69	47	77	50
XIII	25	50	50	50	25	68	47	73	43
XIV	25	50	50	50	25	69	47	77	50
XVI	50	50	100	100	100	50	45	48	43
XVIII	100	50	100	100	100	47	43	40	35

EXPERIMENTAL CHEMISTRY

IR spectra were taken on a UR-20 (East Germany) spectrometer in a capillary layer. Silufol UV-254 plates were used for TLC in the system benzene—ethyl acetate (9:1).

Cyanoethylation of 2-Alkyl-N-(β-aminoethyl)pyrrolidines. Acrylonitrile)0.06 mole) was added dropwise with stirring to the 2-alkyl-N-(β-aminoethyl)pyrrolidine (0.06 mole). The mixture was heated to 40°C for 2 h (until complete disappearance of the initial pyrrolidine, check by TLC). The product was isolated by fractionation in vacuum. The physical constants and yields of the obtained compounds (XV-XVII) are given in Table 2.

Acylation of 2-Alkyl-N-(β-aminoethyl)pyrrolidines and β-[1-(2-Alkylpyrrolidino)ethyl]-cyanoethylamines. The condensation of phthalic acid chlorides with 2-alkyl-N-(β-aminoethyl)-pyrrolidine and β-[1-(2-alkylpyrrolidino)ethyl]-β-cyanoethylamine was effected in a medium of absolute ether or tetrahydrofuran (THF) at a reactant ratio of 2:1. The reaction went at room temperature. The obtained crystalline salts were filtered off and washed three times with absolute ether of THF. The physical constants of the synthesized compounds (I-XIV) are given in Table 1.

EXPERIMENTAL BIOLOGY

The antiphage activity of substances was studied in phage—bacteria systems. The DNA-containing phage T_6 and *E. coli* B, and the RNA-containing phage MS-2 and *E. coli* Hfrc served as systems. The antiphage effect was assessed by comparing the number of resulting negative spots in the experiment and in controls (without substance) by the agar layer method of Gracia. Antiphage activity was expressed in percentage inactivation from the formula $A = (1 - N_e/N_c) \times 100\%$, where N_e is the number of living phage corpuscles in the experimental and N_c the number of living phage corpuscles in the control.

Antibacterial and antifungal activity of compounds was determined by twofold serial dilutions in Cottinger bouillion pH 7.2 in relation to the standard test microbes *St. aureus* 209, *E. coli* 675, *Pr. vulgaris* 38, *Ps. aeruginosa* 165, and *C. albicans* 45.

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