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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF CERTAIN DERIVATIVES OF N-SUBSTITUTED PYRROLIDONES AND PYRROLIDINES

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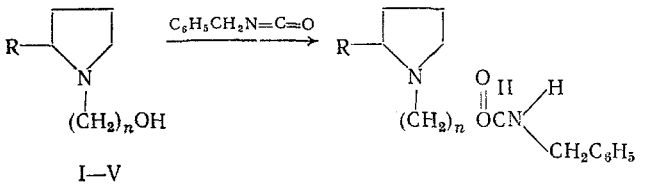
Pyrrolidones and pyrrolidines substituted at the nitrogen atom occupy a prominent place among the various biologically active compounds of both synthetic and natural origin.

We have already shown that 2-alkyl-1-(hydroxyalkyl)pyrrolidines and their esters exhibit antimicrobial activity [1]. In continuation of these investigations, we obtained new N-substituted derivatives of pyrrolidone and pyrrolidine, containing carbamic and sulfanilic acid fragments, and studied the influence of these structures on the antimicrobial activity.

The conditions of the synthesis of the initial 5-alkylpyrrolidones, 5-alkyl-1-(hydroxyalkyl)-pyrrolidones and 2-alkyl-1-(hydroxyalkyl)-pyrrolidines (I-V) are described in [1-4].

As a result of the reaction between 2-alkyl-2-(hydroxyalkyl)-pyrrolidines and benzylisocyanate in toluene, we obtained carbamates of pyrrolidinyl alcohols (VI-X):



I—V

VI: R = C_3H_7, n = 2
VII: R = C_5H_{11}, n = 2
VIII: R = C_5H_{11}, n = 3
IX: R = C_8H_{17}, n = 4
X: R = C_6H_5, n = 2

In a synthesis directed to find the active antimicrobial compounds containing a carbamoyl grouping, it was desirable to obtain also derivatives in which the carbamic acid residue is directly bound to the heterocyclic ring (XIII-XVI) and (XIX-XXII). For this purpose, we reacted pyrrolidones and pyrrolidines unsubstituted at the nitrogen atom (XI, XII, XVII, XVIII) with butyl and phenyl isocyanates.

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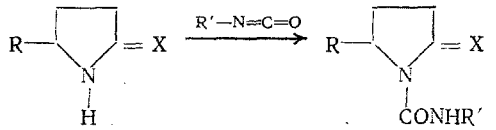


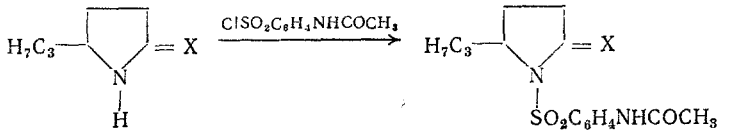
XI: X = O, R = C_3H_7
XII: X = O, R = C_4H_9

XIII: X = O, R = C_3H_7, R′ = C_4H_9
XIV: X = O, R = R′ = C_4H_9
XV: X = O, R = C_3H_7, R′ = C_6H_5
XVI: X = O, R = C_4H_9, R′ = C_6H_5

XII: X = H_2, R = C_3H_7
XVIII: X = H_2, R = C_4H_9

XIX: X = H_2, R = C_3H_7, R′ = C_4H_9
XX: X = H_2, R = R′ = C_4H_9
XXI: X = H_2, R = C_3H_7, R′ = C_6H_5
XXII: X = H_2, R = C_4H_9, R′ = C_6H_5

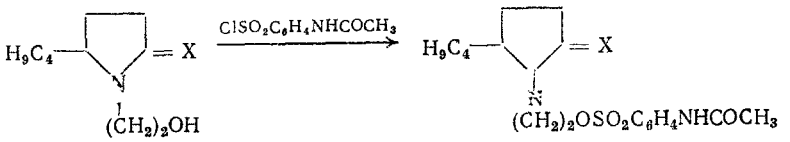
In the study of the sulfamide derivatives in the series of pyrrolidones and pyrrolidines, we prepared compounds with different distances between the ring nitrogen atom and the sulfamide fragment. Thus, acylation of 5-propylpyrrolidone (XI) and 2-propylpyrrolidine (XVII) with acetyl-sulfanilyl chloride in ethanol with cooling gave N-acetylsulfanilamidopyrrolidones (XXIII) and pyrrolidines (XXIV).



XI: X = O
XVII: X = H_2

XXIII: X = O
XXIV: X = H_2

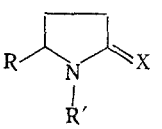
If 2-butyl-1-(β-hydroxyethyl)pyrrolidine (XXVI) and 5-butyl-1-(β-hydroxyethyl)pyrrolidone (XXV) are the substrates, their esters with N-acetylsulfanilic acid (XXVII, XXVIII) are obtained:



XXV: X = O
XXVI: X = H_2

XXVII: X = O
XXVIII: X = H_2

TABLE 1. Physicochemical Constants of N-Substituted Pyrrolidones and Pyrrolidines of type:



Compound	Yield, %	bp, °C (mm Hg) or mp, °C	n_D^{20}	Found, %				Empirical formula	Calculated, %			
				C	H	N	S		C	H	N	S
VI	70	149—1 (3)	1,4723	70,8	9,4	9,7	—	$C_{17}H_{26}N_2O_2$	70,4	9,0	9,6	—
VII	70	254—6 (3)	1,4730	71,9	9,6	9,1	—	$C_{19}H_{30}N_2O_2$	71,7	9,4	8,8	—
VIII	69	218—1 (1)	1,4751	72,5	10,2	8,7	—	$C_{20}H_{32}N_2O_2$	72,3	9,7	8,4	—
IX	69	262—4 (2)	1,4684	74,7	10,5	7,6	—	$C_{24}H_{40}N_2O_2$	74,3	10,4	7,2	—
X	70	189—1 (1)	1,4711	74,5	7,7	8,7	—	$C_{20}H_{24}N_2O_2$	74,2	7,5	8,6	—
XIII	73	139—1 (4)	1,4683	64,1	9,7	12,2	—	$C_{12}H_{22}N_2O_2$	63,7	9,7	12,5	—
XIV	73	145—7 (4)	1,4670	65,5	10,4	11,8	—	$C_{13}H_{24}N_2O_2$	65,0	10,0	11,6	—
XV	72	154—6 (3)	1,4567	68,4	7,9	11,4	—	$C_{14}H_{18}N_2O_2$	68,3	7,3	11,4	—
XVI	72	164—6 (3)	1,4573	69,4	7,8	10,6	—	$C_{15}H_{20}N_2O_2$	69,2	7,7	10,7	—
XIX	75	182—4 (3)	1,4712	68,2	11,3	13,3	—	$C_{12}H_{24}N_2O$	67,9	11,3	13,2	—
XX	75	187—9 (3)	1,4720	69,2	11,4	12,0	—	$C_{13}H_{26}N_2O$	69,1	11,6	12,4	—
XXI	76	130—2 (4)	1,4772	72,4	8,6	12,6	—	$C_{14}H_{20}N_2O$	72,4	8,6	12,0	—
XXII	76	139—1 (4)	1,4781	73,3	9,1	11,3	—	$C_{15}H_{22}N_2O$	73,2	9,0	11,4	—
XXIII	57	202—4	—	55,8	6,5	8,8	9,6	$C_{15}H_{20}N_2O_4S$	55,5	6,1	8,6	9,8
XXIV*	65	240—3	—	58,5	8,9	10,4	9,6	$C_{15}H_{23}N_2O_3SCl$	58,6	9,0	10,3	9,2
XXVII	64	251—3	—	56,4	7,2	7,5	8,1	$C_{18}H_{26}N_2O_5S$	56,0	7,0	7,5	8,6
XXVIII*	67	263—5	—	53,8	7,7	7,1	8,3	$C_{18}H_{29}N_2O_4SCl$	53,4	7,2	6,9	7,9

*Compounds XXIV, XXVIII were obtained as hydrochlorides.

TABLE 2. Antimicrobial Activity of Compounds Studied

Compound	Minimal bacteriostatic concentration, μg/ml				
	St. aureus	E. coli	Pr. vulgaris	Ps. aeruginosa	C. albicans
VI	12	25	100	100	25
VII	25	50	100	100	25
VIII	25	50	100	100	50
IX	100	100	100	100	100
X	50	50	50	100	100
XIII	50	50	100	50	100
XIV	50	50	100	50	100
XV	50	50	100	50	100
XVI	50	50	100	50	100
XIX	100	50	100	50	100
XX	100	50	100	50	100
XXI	100	50	100	50	100
XXII	100	50	100	50	100
XXIII	100	50	100	50	50
XXIV	50	50	100	50	50
XXVII	12	12	50	50	25
XXVIII	12	12	50	50	25

The structure of the compounds obtained was confirmed by elemental analysis and IR spectroscopy (Table 1). The IR spectra of the synthesized compounds were in accordance with the structure accepted for them. For the carbamates VI-X, the C=O absorption band in the 1715-1525 cm^{-1} region is the most pronounced. In compounds XIII-XXII, stretching vibrations appear in the 3330 cm^{-1} region for the NH group in secondary amides, 1690-1700 cm^{-1} for the carbonyl group, and deformational vibrations of the NH group at 1500 cm^{-1}. For compounds XIII-XVI, the vibrations of the C=O group of the pyrrolidone ring in the 1706 cm^{-1} region are characteristic, and the absence of this absorption in compounds XIX-XXII indicates the presence of pyrrolidine systems. For sulfamide compounds XXIII, XXIV, XXVII, XXVIII, NH-stretching vibrations are found at 3320 cm^{-2}, SO_2- asymmetric vibrations at 1130 cm^{-1}, SO_2-symmetric vibrations at 1140 cm^{-1}, and the amide carbonyl group vibrations in the 1670 cm^{-1} region.

EXPERIMENTAL BIOLOGICAL PART

The antimicrobial activity of the synthesized compounds was determined by the method of double serial dilutions in Hottinger's broth (pH 7.2) with respect to *St. aureus* 209 P, *E. coli* M-17, *Pr. vulgaris* 30, *Ps. aeruginosa* 165, and *C. albicans* 45.

All the compounds tested have antimicrobial activity, inhibiting the growth of the test cultures at a concentration of 12-100 μg/ml (Table 2).

Compounds XIII-XXII, in the which the carbamoyl group is bound directly to the heterocyclic ring, exhibit antimicrobial activity at a concentration of 50-100 μg/ml. The reduction of the carbonyl group in pyrrolidones to CH_2 and the substitution of the butyl in the carbamate part for phenyl do not influence the antimicrobial activity.

It was noted that increase in the chain length of the alkyl substituent in the 2-position of the heterocyclic ring of the carbamates of pyrrolidinyl alcohols does not appreciably influence the antimicrobial activity. When R = C_8H_{17} (IX) and the distance between the heterocyclic ring nitrogen atom and the carbamate group was increased to four methylene groups, the activity considerably decreased (up to 100 μg/ml). Substitution of the alkyl substituent in the pyrrolidine ring for phenyl also causes a decrease in the microbial action (VI, VII, VIII, X).

Introduction of sulfanilic acid fragment into the pyrrolidones and pyrrolidines studied leads to an increase in the activity of the compounds with respect to *St. aureus* and *E. coli* (XXVII, XXVIII). The most active among the compounds studied are the derivatives of N-(β-hydroethyl-2-pyrrolidone and N-(β-hydroxyethyl)pyrrolidine (VI, XXVII, XXVIII).

EXPERIMENTAL CHEMICAL PART

The IR spectra were run on the UR-20 spectrometer (GDR) in a microlayer for liquid compounds and in the form of a suspension in mineral oil for crystalline compounds.

The thin layer chromatography was carried out on Silufol UV-254 plates in a hexane–ethanol–chloroform system (50:25:10).

β-[1-(2-Propylpyrrolidino)]-ethyl-N-benzylcarbamate (VI). A 1.86-g portion (0.01 mole) of benzyl isocyanate in 20 ml of dry toluene is added with heating at 100°C to 2.4 g (0.01 mole) of 2-propyl-N-(β-hydroxyethyl)pyrrolidine in 30 ml of dry toluene. Heating is continued for 2 h, and the reaction mixture is brought to the boil. The cooled solution is extracted with 2 M hydrochloric acid. The aqueous solution is neutralized with alkali, extracted with chloroform, and dried over Na_2SO_4. Chloroform is distilled off and VI is isolated by distillation *in vacuo*. Yield, 2.8 g (70%). Compounds VII-X were obtained similarly (see Table 1).

5-Propyl-N-(butylcarbamoyl)-2-pyrrolidone (XIII). A 1.1 g-portion (0.01 mole) of butylisocyanate in 5 ml of absolute toluene is added, with heating, to 1.5 g (0.01 mole) of 5-propyl-2-pyrrolidone in 5 ml of absolute toluene. The reaction mixture is then refluxed for 2.5 h, and toluene is distilled off. Compound XIII is isolated by distillation *in vacuo*. Yield, 1.9 g (73%). Compounds XIV, XV, XVI were obtained similarly.

2-Propyl-N-(phenylcarbamoyl)pyrrolidine (XXI). A 2.2 g-portion (0.02 mole) of phenyl isocyanate in 7 ml of absolute toluene is added dropwise, with heating and stirring, to 2.3 g (0.02 mole) of 2-propylpyrrolidine in 15 ml of absolute toluene. The reaction mixture is refluxed for 2 h, toluene is distilled off, and XXI isolated by distillation *in vacuo*. Yield, 3.6 g (76%). Compounds XIX, XX, XXII were obtained similarly.

p-[1-(5-Propyl-2-pyrrolidonone)sulfonyl]-acetaminobenzene (XXIII). A solution of 2.6 g (0.01 mole) of acetylsulfanilyl chloride in 10 ml of absolute ether or alcohol is added with cooling to 0-7°C to 1.5 g (0.01 mole) of 5-propylpyrrolidone in 15 ml of absolute ether or alcohol. Light-yellow crystals precipitated. Yield, 2.1 g (57%), mp 202-204°C (from ethanol). Compound XXIV was obtained similarly.

β-1-(2-Butylpyrrolidino) ethyl Ester of N-Acetylsulfanilic Acid (XXVIII). A solution of 7 g (0.03 mole) of acetylsulfanilyl chloride in 15 ml of absolute ether is added with cooling to 4.7°C to 5g (0.03 mole) of 2-butyl-N-(β-hydroxyethyl)pyrrolidone in 15 ml absolute ether. Crystals of hydrochloride of XXVIII precipitate. Yield, 8.0 g (67%), mp 263-265°C (dec.) (from a mixture of alcohol and ether). Compound XXVII was obtained similarly.

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