8. Cyclic β-Diketones [in Russian], G. Ya. Vanag, ed., Riga (1961); A. V. Bogatskii, L. Ya. Glinskaya, and A. I. Gren', Zh. Obshch. Khim., 39, 25-28 (1969).
9. K. Nakanishi, Infrared Spectra and Structure of Organic Compounds [Russian translation], Moscow (1965), pp. 31-52.
10. H. Biltz, Ber. Dtsch. Chem. Ges., 45, 3659 (1912); E. Fischer, Justus Liebigs Ann. Chem., 215, 253 (1882); E. Fischer, Ber. Dtsch. Chem. Ges., 14, 1905 (1881).
11. J. N. Ashley, W. H. Perkin, and R. Robinson, J. Chem. Soc., 382-395 (1930); S. Gabriel, Ber. Dtsch. Chem. Ges., 51, 1508 (1918); H. Dahn and A. Donzel, Helv. Chim. Acta, 50, 1911-1917 (1967).
12. C. S. Marvel and G. S. Hiers, Organic Syntheses, Vol. 1 (1951), pp. 327-330.

SYNTHESIS AND ANTIVIRAL ACTIVITY OF 1-SUBSTITUTED DERIVATIVES OF BENZIMIDAZOLE AND 5,6-DIMETHYLBENZIMIDAZOLE

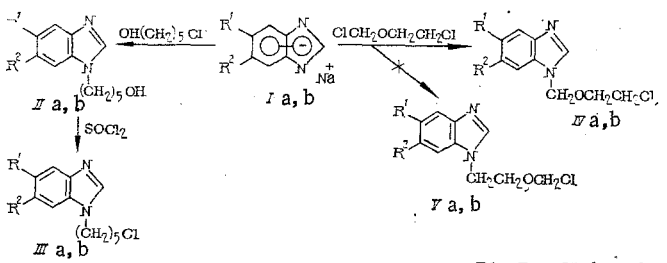
E. V. Belozerova, T. A. Pospelova I. P. Rudakova, and A. M. Yurkevich

UDC 615.281:547.785.5].012.1

In recent years several compounds were found in the benzimidazole series, having antiviral activity. In [1-3], the synthesis of 2-hydroxybenzimidazoles is described, which were found to be strong multiplication inhibitors of several small RNA-containing viruses, such as poliovirus 1, poliovirus 2, coxsackievirus A9, and many others. It was noted that the activity of the 1-alkyl derivatives of benzimidazole depends on the number of carbon atoms in the alkyl substituent, and reaches a maximum with propyl and butyl substituents. No literature data are available on benzimidazole derivatives containing the methoxyethyl substituent in the 1-position. However, the authors of [4, 5] reported that benzimidazole derivatives containing the ethyleneoxyethyl group have antiviral and antitumor activity. Derivatives of guanine with a methoxyethyl group show a strong action against the herpes virus type 1, and also against varicellazoster, cytomegalovirus, and B-virus [6].

The present work deals with the synthesis and confirmation of structure of the following substituted benzimidazoles: 1-(5'-hydroxypentyl)benzimidazole (IIa), 1-(5'-hydroxypentyl)-5,6-dimethylbenzimidazole (IIb), 1-(5'-chloropentyl)benzimidazole (IIIa), 1-(5'-chloropentyl)-5,6-dimethylbenzimidazole (IIIb), 1-(2'-chloroethoxymethyl)benzimidazole (IVa), and 1-(2'-chloroethoxymethyl)-5,6-dimethylbenzimidazole (IVb).

Compounds IIa,b and IVa,b were obtained by alkylation of sodium derivatives of benzimidazole (Ia) and 5,6-dimethylbenzimidazole (Ib), by a previously described method [7-11], with certain modifications.



a: $R^1=R^2=H$ b: $R^1=R^2=CH_3$.

As the alkylating agent in the synthesis of benzimidazoles, we used 5-chloro-1-pentanol. Compounds IIa, b serve as the starting materials in the synthesis of benzimidazoles IIIa,b, respectively. The structure of the compounds obtained was confirmed by physicochemical methods (UV, IR, and mass spectra)

Scientifc Industrial Association "Vitaminy," Moscow. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 16, No. 1, pp. 50-54, January, 1882. Original article submitted April 23, 1981.

 0091-150X/82/1601-0040$07.50

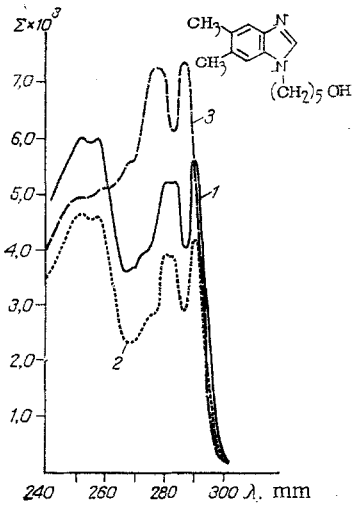


Fig. 1. UV Spectra of compounds IIa,b and IIIa,b. 1) In 96% EtOH; 2) in 1 N HCl in 96% EtOH; 3) in 1 N NaOH in 96% EtOH.

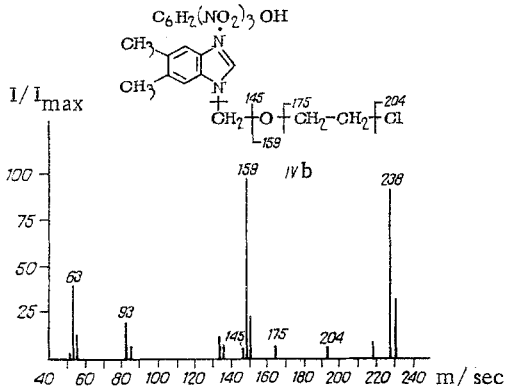


Fig. 2. Mass spectra and characteristic fragmentation of the compounds. IVb is 1-(2'-chloroethoxymethyl)-5,6-dimethylbenzimidazole.

In the IR spectra of the hydroxypentyl compounds IIa,b, there are absorption bands in the 1205-1255 cm^{-1} region, which are absent in the spectra of the initial benzimidazole and 5,6-dimethylbenzimidazole, and characterize the ν_{C-H} vibration in the polymethylene chain [12]. The presence of bands in the 1050-1075 cm^{-1} region, assigned to ν_{C-O} in the C—O—H group [13], confirms the introduction of the hydroxypentyl substituent. Compounds IIa,b were additionally characterized by UV absorption spectra at different pH values (Fig. 1). A similarity between the spectra obtained and the absorption spectra of N-methyl derivatives of benzimidazole, taken at different pH values [14] additionally confirms the entry of the substituents into the N-1 position of benzimidazoles Ia,b.

Chlorobenzimidazoles IIIa,b were obtained by reacting compounds IIa,b with thionyl chloride [15]. Introduction of the chlorine atom into compounds IIIa,b is confirmed by IR spectra, in which we observe the disappearance of bands in the 1050-1075 cm^{-1} region, assigned to ν_{C-O} in the C—O—H group, and appearance of bands at 720-760 cm^{-1}, characterizing the ν_{C-Cl} in the monochloro-substituted compounds [13].

The structure of compounds IIa,b and IIIa,b was also confirmed by mass spectra. Besides the presence of the corresponding molecular ions, peaks are observed of the characteristic fragments of the hydroxypentyl and chloropentyl groups. Moreover, in the mass spectra there are peaks characterizing fragments which remain after splitting of the above substituents (see Table 1 and Fig. 2).

TABLE 1. Relative Peak Intensity of Ions of (I) in % of I_{max}, Formed during Fragmentation of Side Chain of N-Substituted Compounds IIa,b IIIa,b, and IVa,b

Ion	Compound											
	IIa		IIb		IIIa		IIIb		IVa		IVb	
	m/e	I	m/e	I	m/e	I	m/e	I	m/e	I	m/e	I
M+	204	55,6	232	94,0	222	49,6	250	92,9	210	74,7	238	91,4
[M—OH]+	187	5,2	215	12,4	—	—	—	—	—	—	—	—
[M—CH_2OH]+	173	13,1	201	11,1	—	—	—	—	—	—	—	—
[M—C_2H_4OH]+	159	26,2	187	10,2	—	—	—	—	—	—	—	—
[M—C_3H_6OH]+	145	14,3	173	10,4	—	—	—	—	—	—	—	—
[M—C_4H_8OH]+	131	100	159	100	—	—	—	—	—	—	—	—
[M—$C_5H_{10}OH$]+	117	3,1	145	18,4	—	—	—	—	—	—	—	—
[M—Cl]+	—	—	—	—	187	18,7	215	32,8	175	5,3	203	4,1
[M—CH_2Cl]+	—	—	—	—	173	1,4	201	2,1	161	1,0	—	—
[M—C_2H_4Cl]+	—	—	—	—	159	5,1	187	3,7	147	3,6	175	4,9
[M—C_3H_6Cl]+	—	—	—	—	145	3,8	173	3,1	—	—	—	—
[M—C_4H_8Cl]+	—	—	—	—	131	100	159	100	—	—	—	—
[M—$C_5H_{10}Cl$]+	—	—	—	—	118	7,4	145	8,9	—	—	—	—
[M—C_2H_4OCl]+	—	—	—	—	—	—	—	—	131	100	159	100
[M—C_3H_6OCl]+	—	—	—	—	—	—	—	—	117	1,7	145	13,7
[$C_5H_{10}OH$]+	87	1,2	87	1,4	—	—	—	—	—	—	—	—
[$C_5H_{10}Cl$]+	—	—	—	—	105	1,3	105	3,2	—	—	—	—
[C_3H_6OCl]+	—	—	—	—	—	—	—	—	—	—	—	

In the synthesis of benzimidazoles IVa,b we used chloromethyl 2-chloroethyl ether as the chlorinating agent. The alkylating agent has two reactive chlorine atoms, and therefore the formation of a second compound with a structure of Va,b could be assumed. However, in the reaction only one compound was isolated, as confirmed by chromatography in different systems of solvents.

Compounds IVa,b were obtained in the form of oils, and therefore, to prove their structure, we isolated them in the form of picrates. The IR spectra of the picrates of compounds IVa,b contain ν_{C-O} bands in the 1060-1150 cm^{-1} region of the ether grouping [13], which confirms the introduction of the chloroethoxymethyl fragment in the molecules. The mass spectra unequivocally confirm the structure of the 2'-chloroethoxymethyl substituent in compounds IV,b. Together with the molecular ions, peaks are observed corresponding to the characteristic fragments of the chloroethoxymethyl group. Moreover, in the mass spectra there are peaks which remain after the splitting of the chloroethoxymethyl group (see Table 1 and Fig. 2).

Preliminary biological tests showed that in doses of 30-250 μg/ml, compounds Ia and IVa did not exhibit any activity in tests on a culture of chicken embryonic fibroblasts preliminarily (30 days before administration) infected by group A virus.

EXPERIMENTAL

The chromatography of the reaction products was carried out on the FN-11 paper in the following systems of solvents: isopropanol—n-butanol—glacial acetic acid—water, 70:100:1:100 (system A), and isopropanol—12 N hydrochloric acid—water, 170:44:36 (system B). For the TLC of the compounds obtained on the Silufol UV-254 plates, the following systems of solvents were used: isoamyl alcohol—glacial acetic acid—water, 4:3:3 (system C), and acetone—water, 1:1 (system D). The electrophoresis was carried out on the UEF apparatus in 1 N acetic acid at a potential gradient of 16 V/cm. The spectra in the UV region were recorded in 96% ethanol on the recording spectrophotometer Hitachi M-124 (Japan). The IR spectra were run on the UR-10 spectrophotometer (GDR) in mineral oil. The mass spectra were taken on the YMS-01-SG-2 apparatus (Japan), the temperature of the ionization chamber was 130°C, and the ionization voltage 75 eV.

1-(5'-Hydroxypentyl)benzimidazole (IIa). A mixture of 2 g of benzimidazole (Ia) and 0.5 g of sodium hydride in 35 ml of anhydrous DMFA is stirred for 1 h at room temperature. A 2.46 g portion of 5-chloro-1-pentanol is added dropwise to the suspension in the course of 20 min. The mixture is stirred at 60°C for 4 h, and left to stand overnight at room temperature. The precipitate formed is filtered off. The filtrate is evaporated to dryness, and the residue washed with a small amount of diethyl ether, and recrystallized to yield 2.25 g

(65%) of IIa, mp 75-76°C (from benzene). Found, %: C 69.18; H 7.83; N 13.52. $C_{12}H_{16}N_2O$. Calculated, %: C 70.59; H 7.80; N 13.70. Absorption spectrum, λ_{max}, nm (ε): 248 (6000), 254 (6100), 267 (4100), 275 (4600), 282 (4800). R_f 0.93 (A), 0.90 (B), 0.53 (C). E_{bza} = 0.67.

1-(5'-Hydroxypentyl)-5,6-dimethylbenzimidazole (IIb). A mixture of 1.7 g of 5,6-dimethylbenzimidazole (Ib) and 0.5 g of sodium hydride in 35 ml of anhydrous DMFA is stirred for 1 h at room temperature. Then, 2.30 g of 5-chloro-1-pentanol are added dropwise to the stirred solution in the course of 20 min. The mixture is stirred for 3 h at 60°C and left to stand overnight at room temperature. The precipitate is filtered, and the filtrate evaporated to dryness. The residue is washed with a small amount of diethyl ether, and recrystallized to yield 2.43 g (78%) of IIb, mp 102-103°C (from diethyl ether). Found, %: C 72.23; H 8.64; N 12.05. $C_{14}H_{20}N_2O$. Calculated, %: C 72.38; H 8.68; N 12.06. Absorption spectrum, λ_{max}, nm (ε): 252 (6000), 257 (6000), 273 (3900), 280-283 (5500), 290 (5700), R_f 0.97 (B), 0.59 (C). $E_{5,6bza}$ = 0.69.

1-(5'-Chloropentyl)benzimidazole (IIIa). Compound IIa (1 g) is added to 36 ml of thionyl chloride and the mixture obtained is heated for 40 min. The excess of thionyl chloride is distilled off in a rotary evaporator. The yellow precipitate obtained is washed with benzene, and recrystallized to yield 0.98 g (88%) of hydrochloride of IIIa, mp 162-163°C (from acetone). Found, %: C 54.73; H 6.22; N 10.71; Cl 27.33. $C_{12}H_{15}N_2Cl \cdot HCl$. Calculated, %: C 55.59; H 6.22; N 10.80; Cl 27.39. Absorption spectrum, λ_{max}, nm (ε): 249 (5000), 254 (5100), 267 (3800), 275 (4100), 182 (3700). R_f 0.95 (A), 0.93 (B), 0.65 (C).

1-(5'-Chloropentyl)-5,6-dimethylbenzimidazole (IIIb). The procedure of the preparation is similar to that described above, with IIb being the starting material. Yield, 0.38 g (36%) of hydrochloride of IIIb, mp 157-158°C (twice from acetone). Found, %: C 58.50; H 7.18; N 10.47; Cl 24.62. $C_{14}H_{19}N_2Cl \cdot HCl$. Calculated, %: C 58.52; H 7.02; N 9.75; Cl 24.71. Absorption spectrum, λ_{max}, nm (ε): 252 (4500), 257 (4500), 274 (2700), 280-283 (3500). R_f 0.96 (B), 0.66 (C).

1-(2'-Chloroethoxymethyl)benzimidazole (IVa). A 2.74 g portion of chloromethyl 2-chloroethyl ether is added dropwise, with stirring, to the sodium salt of benzimidazole, obtained from 2 g of benzimidazole, as described above, and the reaction mixture is kept for 1.5 h at 60°C. The precipitate formed is filtered, and the filtrate evaporated *in vacuo*. The oily residue is converted to the picrate, and recrystallized to yield 2.43 g (51%) of picrate of IVa, mp 154-155°C (from isopropanol). Found, %: C 44.04; H 3.18; N 15.23; Cl 8.06. $C_{16}H_{14}N_5O_8Cl$. Calculated, %: C 43.69; H 33.19; N 15.93; Cl 8.12. R_f 0.50 (C), 0.73 (D).

1-(2'-Chloroethoxymethyl)-5,6-dimethylbenzimidazole (IVb). A 1.32 g portion of chloromethyl 2-chloroethyl ether is added dropwise, with stirring, to the sodium salt prepared from 1 g of 5,6-dimethybenzimidazole, according to the above described procedure, and the reaction mixture is kept at 60°C for 2 h. The precipitate formed is filtered off, and the filtrate evaporated. The oily residue is converted to the picrate, and recrystallized to yield 1.90 g (60%) of picrate of IVb, mp 179-181°C (from absolute ethanol). Found, %: C 46.41; H 3.99; N 14.96; Cl 7.41. $C_{18}H_{18}N_5O_8Cl$. Calculated, %: C 46.50; H 3.91; N 15.07; Cl 7.63. R_f 0.66 (D).

The biological tests were carried out at the Chemotherapy Laboratory, Institute of Virology, Academy of Medical Sciences of the USSR, under the guidance of Prof. G. A. Galerov.

The authors wish to express their gratitute to Zh. K. Torosyan for taking the mass spectra.

LITERATURE CITED

1. D. G. O'Sullivan and A. K. Wallis, J. Med. Chem. 15, 103-104 (1972).
2. D. G. O'Sullivan and A. K. Wallis, Nature, 198, 1270-1273 (1963).
3. D. G. O'Sullivan, D. Pantic, and A. K. Wallis, Nature, 203, 433-444 (1964).
4. H. E. Kaufman, E. L. Martola, and C. Dohlman, Arch. Ophthalmol., 68, 235-239 (1962).
5. R. Papac, E. Jacobs, C. Wong, et al., Proc. Am. Assoc. Cancer Res., 3, 257-260 (1961).
6. H. J. Schaeffer, L. Beauchamp, P. de Miranda, et al., Nature, 272, 583-585 (1978).

7. T. A. Pospelova, I. P. Rudakova, S. Yu. Drizhova, et al., Bioorg. Khim., No. 6, 787-792 (1975).
8. T. Sieta, K. Yamauch, and M. Imoto, Bull. Chem. Soc. Jpn., 45, 926-928 (1972).
9. K. L. Carraway, P. C. Huang, and T. G. Scott, Synth. Proc. Nucleic Acid. Chem., 1, 3-5 (1968).
10. E. L. M. Pattison, W. C. Howell, A. J. McNamara, et al., J. Org. Chem., 21, 739-747 (1956).
11. J. W. Farren, H. R. Fife, F. E. Clark, et al., J. Am. Chem. Soc., 47, 2419-2423 (1925).
12. R. A. Meikeljohn, R. J. Meyer, S. M. Aronovic, et al., Anal. Chem., 29, 329-324 (1957).
13. L. Bellamy, Infrared Spectra of Complex Molecules [Russian translation], Moscow (1963).
14. G. H. Beaven, E. R. Holiday, and E. A. Johnson, Spectrochim. Acta, 4, 338-347 (1951).
15. J. K. Coward and W. D. Suced, J. Med. Chem., 15, 381-384 (1972).

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

V. A. Sedavkina, N. A. Morozova, V. F. Chulkov, and L. K. Kulikova

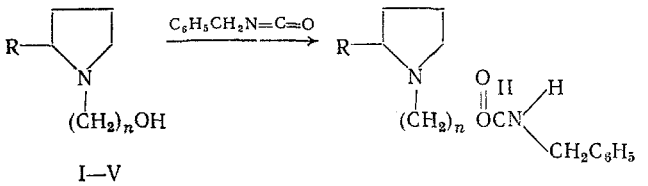
UDC 615.281:547.743.1/.012.1

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.

N. G. Chernyshevskii Saratov University. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 16, No. 1, pp. 54-58, January, 1982. Original article submitted May 26, 1981.

0091-150X/82/1601-0044$07.50