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IMIDAZOLE DERIVATIVES.

XV. SYNTHESIS AND BIOLOGICAL ACTIVITY OF BENZOLINE DERIVATIVES

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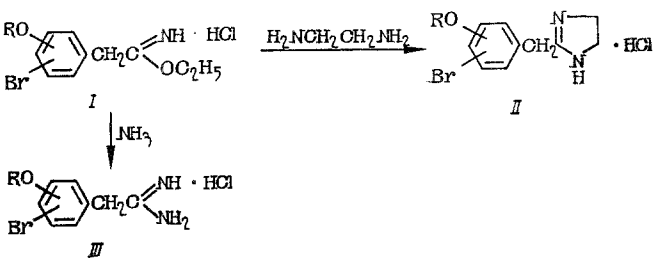
In the preceding publications we described the synthesis of substituted benzimidazolines, hydrazinoimidazoline hydrazones, and certain mercapto derivatives of 2-imidazoline [1-4].

In a continuation of these investigations, we prepared 2-benzyl-2-imidazolines containing bromine or an alkoxy group in positions 3,4 or 5,2 of the benzyl radical. We studied the possibility of synthesizing N-substituted imidazolines, and prepared 1-benzyl- and 1-(β-dialkylaminoethyl)-2-(4-chlorobenzyl)-2-imidazolines. Several α-(β-dialkylaminoethyl)-α-(phenyl)acetamidine hydrochlorides have been synthesized.

Benzylimidazolines (II) were prepared by cyclization of α-(alkoxy-bromophenyl)acetimidate ester hydrochlorides (I) with ethylenediamine; compounds I were also used in the synthesis of substituted α-(phenyl)-acetamidines (III).



It is known that N-substituted imidazolines can be obtained by intramolecular cyclization of amidines [5], cyclization of derivatives of carboxylic acids with N-substituted ethylenediamine [1, 6, 7], and alkylation of imidazolines with alkyl halides in the presence of sodium ethoxide [8, 9].

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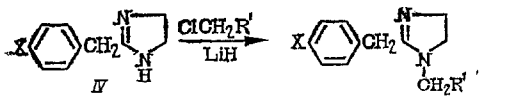
The reaction of 2-benzyl-2-imidazoline with benzyl chloride or diethylaminoethyl chloride was carried out in the presence of an equimolecular amount of lithium hydride in DMFA, according to the scheme:



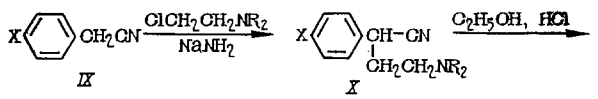
IV

V: X=H, R'=C_6H_5 VII: X=Cl, R'=$CH_2N(C_2H_5)_2$

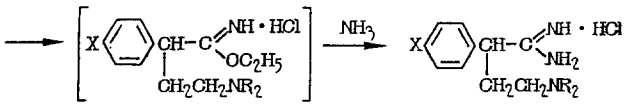
VI: X=H, R'=$CH_2N(C_2H_5)_2$

2-Benzyl-2-imidazoline (benzoline) was synthesized by cyclization of ethyl phenylacetimidate hydrochloride (VIII) with ethylenediamine.

The substituted phenylacetamidine hydrochlorides were prepared according to the scheme:



IX X



XI XII

where X=H, F, Cl, Br, C_2H_5O, C_3H_7O, R=CH_3, C_2H_5

It is possible that the yields of the acetimidate hydrochlorides XI are low due to steric hindrances. These hydrochlorides are obtained in a mixture with the hydrochloride of the initial aminonitrile in the form of an oil. At a later stage, after treatment of the ethanolic solution of the mixture of the hydrochlorides X and XI with ammonia, the amidine hydrochlorides XII and unreacted aminonitrile X were identified.

To prove the structure, mass spectra of some of the compounds were taken.

EXPERIMENTAL CHEMICAL PART

The mass spectra were run on the MX-1303 apparatus with direct introduction of the sample into the ionization region at an energy of ionizing electrons of 30 eV, at a temperature 20-30° below the melting point of the compound.

Ethyl α-(alkoxybromophenyl)acetimidate hydrochlorides (I). Dry hydrogen chloride is passed for 1 h through a mixture of 0.1 mole of the corresponding benzyl cyanide [10], 50 ml of absolute ether and 4.6 g (0.1 mole) of absolute alcohol. The reaction mixture is left to stand overnight. The precipitate is filtered and washed on the filter with absolute ether (Table 1).

2-Alkoxybromobenzyl-2-imidazoline hydrochlorides (II). A mixture of 0.05 mole of I, 3.3 g (0.055 mole) of anhydrous ethylene-diamine and 45 ml of absolute alcohol is heated for 8-10 h. The solvent is distilled off and the precipitate is recrystallized from a mixture of absolute ethanol and methyl ethyl ketone (Table 2).

α-(Alkoxybromophenyl)acetamidine hydrochlorides (III). A mixture of 0.01 mole of I in 20 ml of absolute ethanol is saturated with ammonia for 10-15 min, and left to stand overnight. The ethanol is distilled off, and absolute ether is added. The precipitate is filtered (see Table 2).

I, III; R = 4 = CH_3, 4 = C_2H_5, 4 = C_3H_7 have already been described [10].

1,2-Dibenzyl-2-imidazoline (V). A mixture of 3.2 g (0.02 mole) of IV (X = H), 20 ml of DMFA and 0.16 g (0.02 mole) of lithium hydride is stirred for 30 min. Then 2.5 g (0.02 mole) of benzyl chloride are added, and the mixture is heated at

TABLE 1. Alkoxybromophenyl-acetimidate and Amidine Hydrochlorides

Compound	R	Position of halogen atom	Yield, in %	Melting point, °C	Found, %			Empirical formula	Calculated, %		
					C	H	N		C	H	N
Ia	2-CH_3	5-Br	66,5	133—4 (dec.)	42,50	4,70	4,43	$C_{11}H_{14}BrNO_2 \cdot HCl$	42,80	4,90	4,54
Ib	2-C_2H_5	5-Br	64,1	132—3 (dec.)	44,50	5,37	4,35	$C_{12}H_{16}BrNO_2 \cdot HCl$	44,67	5,31	4,34
Ic	4-C_4H_9	3-Br	50,0	86—8 (dec.)	47,68	6,30	4,12	$C_{14}H_{20}BrNO_2 \cdot HCl$	47,95	6,04	3,99
IIIa	2-CH_3	5-Br	96,4	171—2	36,35	3,98	9,78	$C_9H_{11}BrN_2O \cdot HCl$	38,68	4,33	10,02
IIIb	2-C_2H_5	5-Br	94,6	168—9	40,72	4,56	9,26	$C_{10}H_{13}BrN_2O \cdot HCl$	40,91	4,81	9,54
IIIc	4-C_4H_9	3-Br	86,4	122—3	44,48	5,76	8,70	$C_{12}H_{17}BrN_2O \cdot HCl$	44,81	5,64	8,71

TABLE 2. 2-Alkoxy-bromobenzyl-2-imidazoline Hydrochlorides

Compound	R	Position of halogen atom	Yield, %	Melting point, °C	Found, %			Empirical formula	Calculated, %		
					C	H	N		C	H	N
IIa	4-CH_3	3-Br	87,8	229—30	42,96	4,90	9,13	$C_{11}H_{13}BrN_2O \cdot HCl$	43,23	4,62	9,17
IIb	4-C_2H_5	3-Br	90,6	195—6	44,36	4,85	8,49	$C_{12}H_{15}BrN_2O \cdot HCl$	45,09	5,05	8,76
IIIc	4-C_3H_7	3-Br	83,6	180—1	46,47	5,20	8,10	$C_{13}H_{17}BrN_2O \cdot HCl$	46,80	5,44	8,40
IId	4-C_4H_9	3-Br	75,5	162—3	48,22	6,13	7,90	$C_{14}H_{19}BrN_2O \cdot HCl$	48,36	5,80	8,06
IIe	2-CH_3	5-Br	80,0	162—3	42,90	4,80	9,03	$C_{11}H_{13}BrN_2O \cdot HCl$	43,23	4,62	9,17
IIf	2-C_2H_5	5-Br	78,8	173—4	44,80	5,25	8,79	$C_{12}H_{15}BrN_2O \cdot HCl$	45,09	5,05	8,76

100°C for 6-7 h. When cool, the mixture is poured into a beaker with ice, the oily precipitate is extracted with ether, and the ether extracts are dried over sodium sulfate. After distillation of the solvent, the residue is distilled in vacuo. The yield is 2.6 g (52%), bp 185-187°C (1 mm), d_4^{20} 1.0927, n_D^{20} 1.5928, mp of hydrochloride 108-109°C. Found, %: C 81.35, H 7.50, N 11.42. $C_{17}H_{18}N_2$. Calculated, %: C 81.56, H 7.25, N 11.19. Mass spectrum, m/e: 250 (75)* M^+, 249(62), 159(35), 157(38), 109(27), 105(26), 91(100), 81(8).

1-β-Diethylaminoethyl-2-benzyl-2-imidazoline (VI). A mixture of 3.2 g (0.02 mole) of IV (X = H), 20 ml of DMFA and 0.16 g (0.02 mole) of lithium hydride is stirred for 30 min. Then, 4.1 g (0.03 mole) of freshly distilled diethylaminoethyl chloride are added, and the mixture is heated at 100°C for 6-7 h. The solvent is distilled in vacuo (water-jet pump), and the residue is distilled in high vacuo. The yield is 2.2 g (42.3%), bp 163-165°C (1 mm), d_4^{20} 1.0204, n_D^{20} 1.5342, Found, %: C 74.42, H 9.70, N 16.40. $C_{16}H_{25}N_3$. Calculated, %: C 74.09, H 9.71, N 16.20. Mass spectrum, m/e: 259(13) M^+, 173(6), 172(11) 160(26), 159(56), 131(16), 91(63), 86(100).

1-β-Diethylaminoethyl-2-(4-chlorobenzyl)-2-imidazoline (VII) is obtained in the same way as VI from 3.9 g (0.02 mole) of IV (X = Cl) [1], 20 ml of DMFA, 0.16 g (0.02 mole) of lithium hydride and 4.1 g (0.03 mole) of diethylaminoethyl chloride. The yield is 2.5 g (42.6%), bp 195-197°C (1 mm), d_4^{20} 1.0418, n_D^{20} 1.5131. Found, %: C 65.62, H 8.48, N 14.51. $C_{16}H_{24}ClN_3$. Calculated, %: C 65.40, H 8.23, N 14.30.

Ethyl Phenylacetimidate Hydrochloride (VIII) is obtained in the same way as I, and its melting point (85-86°C) (with decomp.) is the same as that given in [11].

2-Benzyl-2-imidazoline (IV, X = H). A mixture of 20 g (0.1 mole) of VIII, 6 g (0.1 mole) of anhydrous ethylenediamine and 100 ml of absolute ethanol is heated on a water bath for 6-8 h. Ethanol is then distilled off, 100 ml of absolute ether are added, and the precipitate is filtered and dissolved in 80 ml of ethanol containing 5.6 g of potassium hydroxide. The potassium chloride precipitate is filtered, and the residue distilled in vacuo. The yield of 11.5 g (71.9%, bp 135-137°C (1 mm), mp 66°C, mp of hydrochloride (174-175°C)) is the same as that given in [11]. Mass spectrum, m/e: 160(44) M^+, 159(100), 132(5), 131(26), 130(4), 117(3), 104(4), 103(3), 91(63).

α-(β-Dialkylaminoethyl)-α-(4-halophenyl)acetonitriles (X). A 3.9-g portion (0.1 mole) of sodium amide is added with water cooling to a mixture of 0.1 mole of IX, 0.12 mole of dialkylaminoethyl chloride and 60 ml of absolute benzene, and the mixture is stirred for 1 h. It is then heated for 2 h on a water bath. After the addition of 40 moles of water, the benzene layer is separated and treated with a 10% hydrochloric acid to an acid reaction to Congo red. The hydrochloric acid solution is made alkaline by sodium carbonate and extracted with ether. The ether extracts are dried over sodium sulfate, and after distillation of the solvent, the residue is distilled in vacuo (Table 3). Compounds X (X = C_2H_5O, C_3H_7O) are described in [2].

Amidine Hydrochlorides XII. A mixture of 0.01 mole of X and 0.46 g (0.01 mole) of absolute ethanol in 25 ml of absolute chloroform is saturated with dry hydrogen chloride, and the mixture is left to stand overnight. The solvent is removed and absolute ether is added. The oily precipitate of XI is dissolved in absolute ethanol, and ammonia is passed through the solution for 20-25 min. The mixture is left to stand overnight. Ethanol is then distilled, and absolute ether is added. The precipitate of XII is filtered and boiled in methyl ethyl ketone (Table 4). Compounds X are obtained from the filtrate after removal of ether. Mass spectrum of XIIb, m/e: 234(25) $(M + 1)^+$, 205(22), 190(7), 188(12), 162(45), 161(15), 134(12), 117(20), 115(13), 106(25), 100(78), 91(60), 86(100), 72(50). Mass spectrum of XIIe, m/e: 270(8), 268(16), $(M + 1)^+$, 255(3), 253(8), 241(6), 239(12), 224(4), 222(8), 198(15), 196(37), 171(4), 169(10). 151(3), 142(5), 140(11), 127(7), 125(5), 117(5), 100(50), 86(100), 72(35).

EXPERIMENTAL PHARMACOLOGICAL PART

It is known that 2-benzyl-2-imidazoline (benzoline, tolazoline) has pronounced adrenoblocking and sympatholytic properties [13, 14].

*Here and forthwith, the numerals outside the brackets designate the mass of the ions, and the numerals in the brackets, the peak intensity in percent of the intensity of the maximum peak.

TABLE 3. α-(β-Dialkylaminoethyl)-α-(4-halophenyl)acetonitriles

Compound	X	R	Yield, %	Boiling point, °C	d_4^{20}	n_D^{20}	Found, %			Empirical formula	Calculated, %			R_f*
							C	H	N		C	H	N	
Xa	F	C_2H_5	51,8	113—5 (1 мм)	1,0218	1,4908	71,88	8,35	12,18	$C_{14}H_{19}FN_2$	71,76	8,17	11,96	0,75
Xb	Cl	CH_3	49,5	130—2 (1 мм)	1,0916	1,5048	64,80	6,91	12,22	$C_{12}H_{15}ClN_2$	64,71	6,79	12,58	0,70
Xc	Cl	C_2H_5	60,2	138—40 (1 мм)	1,0545	1,5131	67,28	7,42	11,15	$C_{14}H_{19}ClN_2$	67,05	7,64	11,17	0,78
Xd	Br	C_2H_5	50,1	140—2 (1 мм)	1,2435	1,5021	56,81	6,65	9,27	$C_{14}H_{19}BrN_2$	56,96	6,49	9,49	0,82

*Thin layer chromatography was carried out on aluminum oxide activity grade II, in an absolute ether—petroleum ether system.

TABLE 4. Substituted α-Phenyl-α-(β-dialkylaminoethyl)acetamidines

Compound	X	R	Yield, %	Melting point, °C	Found, %			Cl (ionic)	Empirical formula	Calculated, %			Cl (ionic)
					C	H	N			C	H	N	
XIIa	H	CH_3	79,5	200—201	52,10	7,79	14,81	25,40	$C_{12}H_{19}N_3 \cdot 2HCl$	51,80	7,61	15,10	25,48
XIIb	H	C_2H_5	81,3	183—4	62,51	8,71	15,25	12,69	$C_{14}H_{23}N_3 \cdot HCl$	62,33	8,97	15,58	13,14
XIIc	F	C_2H_5	68,3	179—80	58,70	8,19	14,30	12,30	$C_{14}H_{22}FN_3 \cdot HCl$	58,42	8,06	14,60	12,32
XIId	Cl	CH_3	65,7	226—7	46,20	6,08	13,26	22,35	$C_{12}H_{18}ClN_3 \cdot 2HCl$	46,10	6,45	13,44	22,68
XIIe	Cl	C_2H_5	80,5	148—50	55,20	7,74	13,56	12,50	$C_{14}H_{22}ClN_3 \cdot HCl$	55,26	7,62	13,81	11,65
XIIf	Br	C_2H_5	72,2	Oil	48,50	6,80	12,31	10,46	$C_{14}H_{22}BrN_3 \cdot HCl$	48,22	6,65	12,05	10,17
XIIg	C_2H_5O	C_2H_5	76,9	174—5	61,90	9,11	13,61	11,50	$C_{16}H_{27}N_3O \cdot HCl$	61,23	8,99	13,39	11,29
XIIh	C_3H_7O	CH_3	80,8	161—2	59,82	8,88	14,26	12,30	$C_{15}H_{25}N_3O \cdot HCl$	60,08	8,74	14,01	11,82

TABLE 5. Ability of Certain Compounds to Decrease the Resistance of the Cerebral Vessels of a Cat

Compound	Dose in mg/kg	Degree of decrease in resistance of vessels in % of initial level	
		intravenous administration	Intracarotid administration
IIa	10	11,2±1,3	14,1±1,7*
IIb	5	17,2±2,1*	24,5±1,9*
IIIc	10	12,4±2,1	19,6±1,2*
IV (X=H)	10	10,1±0,8	13,2±1,1

*P < 0.05.

Up to the present, several derivatives of benzoline with also an adrenolytic activity have been synthesized [15, 16].

The influence of benzoline and its derivatives on the arterial pressure stimulated the study of the action of alkoxybromobenzylimidazolines II and amidines III and XII on the cerebral blood circulation and systemic arterial pressure.

To record the tonus of the cerebral vessels, we used the perfusion method under the conditions of stabilization of the perfusional pressure. We used the resistograph suggested by Khayutin [17]. The systemic arterial pressure was measured at the same time.

The experiments were performed on cats weighing 2.5 — 4 kg each, the autoperfusion of the cerebral vessels was carried out through the internal maxillary artery under a general anesthesia (600 mg/kg of urethane with 60 mg/kg of chloramose, intraperitoneally). The animals were preliminarily treated with heparin (1300-1500 units). The experimental results indicate that the preparations unequally influence the resistogram of the cerebral vessels. In experiments with stabilized autoperfusion of the cat's brain, compounds IIa, e, IIIb and IV (X = H) show a tendency to decrease the resistance of the cerebral vessels (Table 5). Table 5 shows that of the synthesized compounds, 2-(2-methoxy-5-bromobenzyl)-2-imidazoline hydrochloride (IIe), whose application is accompanied by a distinct decrease in the resistance of the cerebral vessels, is the most active. The above effects are observed during both the intravenous and direct administration into the cerebral vessels. The decrease in the systemic arterial pressure is thus moderate in character, which indicates a selectivity of action of the preparation. A similar but a weaker action is displayed by 2-methoxy-5-bromophenylacetamidine hydrochloride (IIIb), which during intraarterial administration only causes a significant decrease in the resistance of the cerebral arteries. Preparations IIa and IV (X = H, benzoline) lead to a decrease in the cerebral vessels tonus, but these shifts are only statistically significant.

If we compare the effects of preparations IIe and IIIb with those of known agents, such as papaverine [18], and Gammalon [γ-aminobutyric acid] [19], it is clear that the derivatives 2-benzyl-2-imidazoline studied are inferior to the above compounds by a factor of 2 on the average.

The remaining derivatives of compounds listed in Table 5, as well as 4-chloro-4-bromo- and 4-alkoxy-(3-nitro)-benzyl-2-imidazolines [1, 2] do not have an appreciable action on the cerebral vessels tonus. Most of the compounds studied do not affect the systemic arterial pressure. 2-(4-Ethoxy-5-bromophenyl)-2-imidazoline hydrochloride, which inappreciably increases the arterial pressure, is an exception. The amidines XII have no activity at all. The influence of the synthesized compounds on the systemic arterial pressure was studied in rats. The preparations were administered into the femoral vein in a dose of 0.1 mg/kg. Clonidin [2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride], which in a dose of 0.1 mg/kg caused a pronounced long-term decrease in the arterial pressure, was used as a control. Imidazolines II and amidines III did not have any effect on the arterial pressure. 2-Ethoxy-5-bromobenzyl-2-imidazoline hydrochloride caused a short-term increase in the arterial pressure.

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