SYNTHESIS, ANTI-AGGREGATION, AND ANTI-ARRHYTHMIC ACTIVITY OF DERIVATIVES OF PHENANTHRIDINE

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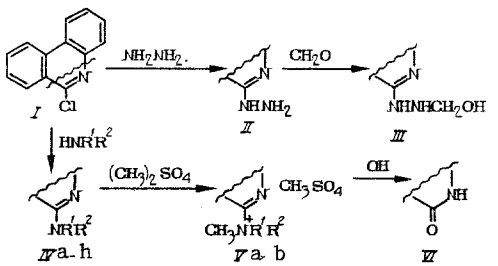
Antiarrhythmic activity has not been described until the present time in the series of phenanthridine derivatives, but this type of activity is characteristic of amidines [6, 9]. Therefore, interest is presented by the investigation of phenanthridine derivatives having the amidine fragment in the structure. A successful addition to the antiarrhythmic action would be the anti-aggregation activity in relation to platelets. The present work undertakes to seek such compounds combining simultaneously both these types of activity.

For the purpose of pharmacological screening, we accomplished the synthesis of the compounds (II)-(V) [4, 5]. The atom of chlorine in the initial compound (I) is substituted by N-nucleophiles with a varying degree of readiness. The reaction proceeds most readily with hydrazine hydrate; the reaction product is the amidrazone (II), which forms the alcohol (III) with formaldehyde. The boiling of the iminochloride (I) with the corresponding amines gives the amidines (IVa-h). The alkylation of the N-alkylamidines (IVa, b) with dimethyl sulfate gives the quaternary amidinium salts (Va, b). The regiospecificity of the methylation at the exocyclic nitrogen atom in this reaction was shown in the work [5]. The cleavage of the salts (Va, b) to 6-phenanthridone (VI) in an alkaline medium confirms the structure presented by us.



IV, V: NR^1R^2=piperidino (a), morpholino (c); R^1+R^2= $=(CH_2)_6$ (b); R^1=H (d-h); R^2= cyclohexyl (d), o-tolyl (e), 2,5-xylyl-1 (f), 2,4-xylyl-1 (g), mesityl (h).

The characteristics of the substances previously undescribed are presented in Table 1. For the compounds previously known in the form of bases, the melting temperatures of the hydrochlorides are given. The PMR spectra of the previously undescribed amidines are given for the bases with the exception of the compound (Vb), for which the spectrum of the methyl sulfate is presented, since its quaternary base is very hygroscopic and unstable. In the spectra of the N-arylamidines (IVe-h), the signal of the NH proton is shielded by the aromatic multiplet; this is confirmed by the total integral intensity. In the spectrum of the N-alkylamidine (IVd), the signal of the NH proton is observed at 4.30 ppm. The absorption band of the NH group in the IR spectra of the amidine bases (IVd-h) is observed in the region of 3400-3480 cm^{-1}.

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TABLE 1. Characteristics of the Compounds Synthesized

Compound	Yield, %	mp, °C	Empirical formula	PMR spectrum, δ, ppm
II	93	227—228	$C_{13}H_{11}N_3 \cdot HCl$	—
IVa	78	201—202	$C_{18}H_{18}N_2 \cdot HCl$	—
IVb	57	148—150	$C_{19}H_{20}N_2 \cdot HCl$	1,40—2,30, $(CH_2)_4$—C broad m; 3,25, $2CH_2$—N broad s 7,27—8,78 (m), Ar
IVc	63	218—219	$C_{17}H_{16}N_2O \cdot HCl$	—
IVd	68	280—282	$C_{19}H_{20}N_2 \cdot HCl$	0,93—2,26, $(CH_2)_5$—C broad m; 3,47, CH—N broad t; 4,30 (s), NH; 7,00—8,73)m), Ar
IVe	63	250—251	$C_{20}H_{16}N_2 \cdot HCl$	—
IVf	57	264—265	$C_{21}H_{18}N_2 \cdot HCl$	2,18 (s)—$2CH_3$; 6,60—8,57 (m), Ar
IVg	43	198—200	$C_{21}H_{18}N_2 \cdot HCl$	2,22 (s)—$2CH_3$; 6,35—8,42 (m), Ar
IVh	48	233—235	$C_{22}H_{20}N_2 \cdot HCl$	2,23 (s)—$3CH_3$; 6,30—8,63 (m), Ar
Vb	72	153—154	$C_{21}H_{26}N_2O_4S$	1,33—2,24, $(CH_2)_4$—C broad m; 4,03 broad s CH_3—N and CH_3O; 7,15—8,80 (m), Ar

EXPERIMENTAL (CHEMICAL)

The IR spectra were taken on the UR-20 spectrometer (Germany) in $CHCl_3$. The PMR spectra were recorded on the RYa-2310 (60 MHz) instrument in DMSO-d_6 for the compounds (IVd) and (Vb), and in $CDCl_3$ for the remaining substances. The internal standard was HMDS.

The chloroimine (I) was obtained by the method of [7]. The bases of the compounds (II) and (IVa, c, e), the hydrochloride (III), and the methyl sulfate (Va) were obtained in the works [4, 5, 8]. The salts of the corresponding bases (II) and (IVa, c, e) were obtained in ethyl acetate by the passage of gaseous HCl. All the salts were recrystallized from isopropyl alcohol. The values of the elemental analyses found for C, H, N, Cl, and S correspond with the calculated values.

The conditions of the cleavage of the salts (Va, b) to the lactam (VI) are also presented in the work [5].

Hydrochlorides of 6-N-R^1R^2-Aminophenanthridine (IVb, d, f, g, h). To 2.15 g (0.01 mole) of 6-chlorophenanthridine are added 3-4 drops of $POCl_3$, and the mixture is boiled in 10-12 ml of the corresponding amine for 4 h [the amidines (IVa-d)] or 7 h [the compounds (IVe-h)]. The resin-forming mass resulting from the reaction is dissolved in 20 ml of hot DMF; the solution is cooled and poured into 100 ml of water. The precipitated residue is filtered off and carefully washed with water [compound (IVb)] and then pentane [the amidines (IVd, f, g, h)] until the disappearance of the initial amine from the filtrate was achieved using the monitoring by TLC. The washed residue is dried and dissolved in ethyl acetate; the corresponding hydrochloride is obtained by the passage of gaseous HCl. The salt obtained is filtered off, dried, and recrystallized.

N-Methyl-N-(phenanthridinyl-6)hexamethyleniminium Methylsulfate (Vb). The solution of 2.76 g (0.01 mole) of the base (IVb) in 30 ml of abs. benzene is boiled with 2.23 ml (0.015 mole) of freshly distilled dimethyl sulfate in the course of 2 h; the mixture is cooled. The precipitated residue is filtered off, dried, and recrystallized.

EXPERIMENTAL (PHARMACOLOGICAL)

The pharmacological testing was only performed with the water-soluble salts (Table 2) since the methods utilized assume their direct introduction into the blood plasma.

The biological activity of the compounds was evaluated according to the data of the acute toxicity, anti-aggregation activity, and antiarrhythmic activity.

The acute toxicity was determined in white mice of both sexes, and having the mass of 16-20 g, by the iv method of application [1].

The anti-aggregation activity was investigated by the photometric method of Born [3] in relation to platelets of dog plasma, and was evaluated as the percentage decrease of the optical density. Platelet aggregation was induced by ADP at the dose of 0.05 mg/ml of plasma. All compounds were tested at the same concentration of 0.2 mg/ml of plasma.

The antiarrhythmic activity was studied using the model of arrhythmia induced by the iv injection of calcium chloride into white mice at the dose of 280 mg/kg [2].

TABLE 2. Acute Toxicity and Anti-Aggregation Activity of the Compounds Synthesized

Compound	Acute toxicity (LD_{50}, mg/kg)	Inhibition of platelet aggregation, %
II	78,3 (63,3—96,9)	90,9
III	50,0 (33,9—73,8)	7,5
IVa	50,0 (40,0—60,5)	38,8
IVb	65,3 (49,9—92,0)	30,9
IVc	125,0 (105,0—159,0)	45,0
IVe	135,0 (107,0—171,0)	62,5
Va	89,5 (70,2—114,2)	34,5
Vb	111,2 (99,6—124,2)	30,4

Note. Limits of variations are given in the brackets.

RESULTS

The study of the acute toxicity (Table 2) shows that the LD_{50} varies in the range of 50.0-135.0 mg/kg. All compounds show anti-aggregation action, suppressing the aggregation of the platelets by 7.5-90.9%. Not one of the substances studied showed antiarrhythmic activity with the exclusion of the amidine (IVe) for which the ED_{50} comprises 19.4 mg/kg, and the antiarrhythmic index (LD_{50}/ED_{50}) comprises 7.0.

It can be seen from the data obtained that the structure of the fragment at the position 6 of the phenanthridine ring does not exert a direct influence on the anti-aggregation properties. That provides the justification to propose that this form of action is associated with the presence of the phenanthridine ring. The absence of antiarrhythmic activity for seven out of eight compounds indicates that steric hindrance and the presence of the phenanthridine ring. The absence of antiarrhythmic activity for seven out of eight compounds indicates that steric hindrance and the presence of the amidine grouping [6] in the given case do not have roles. This can be explained by the fact that, in contrast to known amidines possessing antiarrhythmic action, one of the nitrogen atoms in the amidine group of the structure of our compounds is included in the planar heteroaromatic ring. The compound (IVe) exhibits high anti-aggregation activity with a clearly marked antiarrhythmic effect. Therefore, the search for compounds possessing the two named forms of activity simultaneously had a positive outcome. That means that the further investigations of the antiarrhythmic and anti-aggregation activity in the phenanthridine series are very promising.

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