IR spectra were obtained with a UR-20 instrument in mineral oil mulls. UV spectra were taken with a "Specord UVvis" spectrometer at a sample concentration of $10^{-4}$M in ethanol.

5-Phenacylidenyl-1,3-imidazole-2,4-dione (II). Method A. A mixture of equivalent quantities of benzoylpyruvic acid and urea was mixed at 130°C for 1 h in a paraffin oil bath with subsequent recrystallization of the product from acetic acid (1:1).

Method B. A mixture of equivalent quantities of 5-arylfuran-2,3-dione and urea was stirred in a paraffin oil bath at 100-110°C for 20 min.

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# AZACYCLOALKANES

## XXII. SYNTHESIS AND ANTIANGINAL PROPERTIES OF NONACHLAZINE AND NONAPHTAZINE


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One of the pressing problems of modern pharmacology is the search for antianginal agents with a new type of action that can influence the main regulatory processes responsible for blood supply, metabolism, and cardiac function.

It has already been shown in the preceding communication that many of the diazabicycloalkyl derivatives of N-acylphenothiazines can improve the blood supply to the heart. Two of them, 10-[β-N-(1,4-diazabicyclo-[4,3,0]nonanyl)propionyl]-2-trifluoromethylphenothiazine (IVa) and 10-[β-N-(1,3-diazabicyclo[4,3,0]nonanyl)-propionyl]-2-chlorophenothiazine (IVb) dihydrochlorides, named respectively nonaphtazine and nonachlazine, were found to be especially promising; the present paper describes their synthesis and pharmacological study.

These compounds were obtained according to the reaction scheme on the following page.

1,4-Diazabicyclo[4,3,0]nonan-5-one (I) was reduced by lithium aluminum hydride in dry triethylamine (cf. [1]) to 1,4-diazabicyclo[4,3,0]nonane (II). The reaction of the amine II with 2-substituted β-chloropropionyl-phenothiazines (IIIa, b) in toluene with an equimolecular ratio of the reagents and with triethylamine as the

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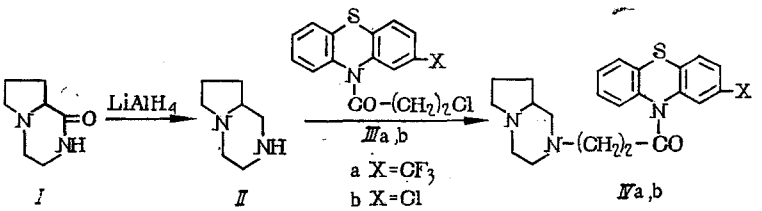


hydrogen chloride acceptor [2] gave the phenothiazines IVa, b. The reaction products IV, which are viscous high-boiling oils, were converted without purification into dihydrochlorides, disulfates, or salts with organic acids (maleic, fumaric). These salts are crystalline substances, white or pale-cream in color, soluble in water, aqueous alcohol, and physiological solution, slightly soluble in absolute alcohol, and practically insoluble in ether.

Comparative physiological study of nonachlazine and nonaphtazine in doses of 5-7 mg/kg (see experimental part) showed that the effects of the preparations in the experiment differ little. Nonachlazine considerably increases coronary blood flow (by 69 ± 4.5%), and its action lasts for 20-40 min after intravenous administration. Nonaphtazine increases the coronary blood flow to a lesser extent than nonachlazine, but the effect of the preparation lasts 1.5 h. The preparations did not differ much in the spectrum of their activity and toxicity. But the results of clinical study made it possible to conclude that nonachlazine is more effective than nonaphtazine for treating patients with ischemic heart disease. Establishment of the high effectiveness of nonachlazine as an antianginal agent served as the basis for a detailed study of the mechanism of its positive effect. It was shown that simultaneously with increase in the coronary blood flow, the difference in blood oxygen between arteries and veins decreases under the influence of nonachlazine as the result of an increase in the content of oxyhemoglobin in coronary vein blood. Thus, with increase in blood flow by 69 ± 4.5% on the average the absorption of oxygen by the myocardium increases by 13 ± 1.9% only.

Thus, it can be assumed that nonachlazine creates favorable conditions when the supply of oxygen to the heart exceeds its absorption, i.e., an additional oxygen reserve is provided (Fig. 1). At the same time, in the intensity of its action on coronary blood flow, nonachlazine does not surpass other antianginal agents (for example, persantine), whose clinical effectiveness is appreciably inferior. These facts make it possible to assume that the use of the aerobic path of oxidation is not the only mechanism determining the effectiveness of the preparation under the conditions of ischemia of the myocardium [3].

During intravenous administration, nonachlazine has a two-phased effect on the arterial pressure. The short-term decrease in the arterial pressure during the first 2-3 min (by 19 ± 2% on an average) changes to hypertension, amounting to 23 ± 1.1%, on the average, of the initial level, which lasts for 15-20 min. During oral administration of the preparation, no substantial changes in the arterial pressure were observed. The

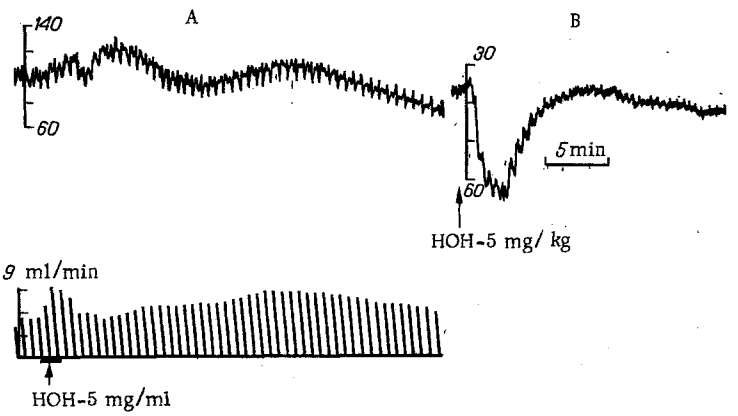


Fig. 1. Influence of nonachlazine on the volumetric rate of coronary blood flow (A) and the absorption of oxygen by the heart (B). A: top) arterial pressure in femoral artery; bottom) outflow of blood from coronary sinus of heart (measurements were carried out every 30 sec). B: content of oxyhemoglobin in venous blood of coronary sinus (in %). Introduction of the preparation is designated by an arrow.

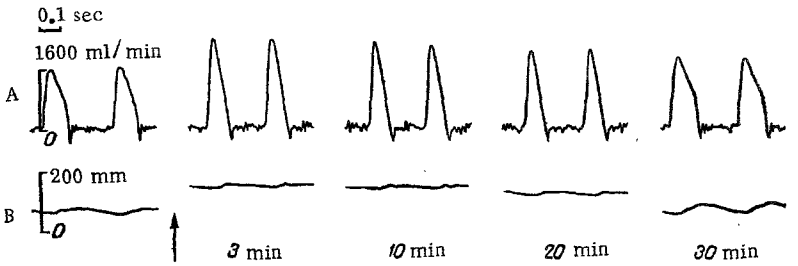


Fig. 2. Influence of nonachlazine (5 mg/kg intravenously) on the contractile function of the heart. A) Phased blood flow in the aorta; B) arterial pressure in the femoral artery. From left to right, background and curves taken at various periods of time after administration of preparation.

changes in the resistance of the peripheral vessels to blood circulation caused by nonachlazine coincide in their dynamics with the changes in the arterial pressure, and also have a two-phased character. In contrast to the peripheral vessels, the tone of the coronary arteries continuously decreases under the action of the preparation (by 21 ± 0.9%, on the average), while the phase of the increased resistance is absent. Under the conditions of preliminary application of practolol, a selective blocker of $\beta_1$-adrenergic structures of the myocardium, nonachlazine does not cause a decrease in the resistance of the coronary vessels. These experiments prove that the main role in the nonachlazine-induced increase of blood supply to the heart is played by extravascular factors of resistance.

Nonachlazine exhibits a two-phased influence on the activity of the heart. Immediately after the administration of the preparation, a small decrease in the cardiac output and the contractile capacity of the myocardium, lasting 3-5 min, is observed. Then there follows a prolonged (25-36 min) and a marked (28 ± 7.5%) increase in both the systolic output and in the instantaneous volume, which is accompanied by an increase in the contractile function of the heart (Fig. 2). It is important to note that the frequency of the heart contractions does not substantially change. An important role in the development of the first suppressing phase of action of the preparation in the intact organism is played by the direct influence of nonachlazine on the myocardial function. Also the absence of tachycardia under the influence of nonachlazine should be clearly explained by the predominating direct negative chronotropic action. The second phase, the intensification of heart activity, does not develop if practolol, a selective blocker of $\beta_1$-adrenergic structures, is preliminarily introduced. Hence, the increase in the systolic output and the contractile function of the heart are due to the stimulating influence of nonachlazine on the $\beta_1$-adrenergic structures. In nonnarcotized, wide-awake animals, the suppressing phase of nonachalazine action is manifested only in very few experiments, while the activating phase is very distinctly expressed.

It was shown that by affecting the adrenergic processes, nonachlazine increases the concentration of norepinephrine in the cardiac muscle and in the synaptic space, and also increases the activity of phosphorylase "a" in the myocardium of rats (in percent): control (physiological solution), 14.41 ± 3.49; nonachlazine (10 mg/kg), 32.4 ± 5.25; propranolol (5 mg/kg), 13.00 ± 2.89; nonachlazine against a background of propranolol (5 mg/kg), 17.23 ± 3.30. ($P = 0.05$. The samples were taken 15 min after the administration of the compounds.) In the same period of time, the coronary blood flow, the cardiac output, and the contractile function of the heart increase under the influence of the preparation.

We can thus assume that by increasing the concentration of free norepinephrine, nonachlazine leads to stimulation of the $\beta$-adrenergic structures of the myocardium, activation of adenyl cyclase, and accumulation of cyclic adenosine monophosphate. As a result of these processes, a positive ionotropic effect develops with acceleration of the glycogen decomposition [4].

From the correlation proved between the biochemical and functional effects of nonachlazine, we can assume that its effectiveness during the treatment of ischemic heart disease is to a great extent related to its effect on the processes of adrenergic regulation of glycogenolysis, i.e., the ability of the preparation to utilize the energy reserves of the myocardium by switching over to the anaerobic pathway. This view is confirmed by observations showing a decrease in the difference in the blood oxygen between the aorta and the veins, and the relatively small increase in the oxygen absorption by the myocardium compared with that of coronary blood flow.

In the present article we demonstrated the principal mechanisms to which the effectiveness of nonachlazine during the treatment of ischemic heart disease can be related. Among other properties specific for the preparation, it is important to mention the mild antiarrhythmic effect, the rather wide scope of therapeutic action, and the low toxicity.

Nonachlazine has successfully undergone clinical tests, and now has been introduced into medical practice.

## EXPERIMENTAL CHEMICAL PART

1,4-Diazabicyclo[4,3,0]nonane (II). A warm solution (40-50°C) of 21.2 g of the lactam I in 160 ml of dry triethylamine is added dropwise in the course of 1 h to a suspension of 7.6 g of lithium aluminum hydride in 80 ml of dry triethylamine. The mixture is then boiled, with stirring, for 15 h. At the end of the heating period, the reaction mixture is cooled, and the excess of lithium aluminum hydride is decomposed by successively adding dropwise, with stirring, 7.6 ml of water, 5.6 ml of 40% aqueous solution of sodium hydroxide, and 26.4 ml of water. The mixture is stirred for 1 h at 20°C, boiled for 30 min under reflux, and, filtered when cool. After the distillation of triethylamine, 12.6 g of II (65.6%) is obtained, bp 62-64°C (8 mm), $n_D^{20}$ 1.4930 (literature data, see [2]).

10-[β-N-(1,4-diazabicyclo[4,3,0]nonanyl)propionyl]-2-trifluoromethylphenothiazine (Nonaphtazine) (IVa). A solution of 5.04 g of amine II and 4.04 g of triethylamine in 20 ml of dry toluene are added to a solution of 14.3 g of the 2-trifluoromethylphenothiazine derivative IIIa in 70 ml of dry toluene, and the mixture is boiled for 3 h. When cool, the reaction mixture is filtered, and the toluene solution is washed with water and treated with a dilute solution of hydrochloric acid to pH 1.0. The aqueous solution is separated and made alkaline with a 10% solution of sodium hydroxide, and compound IVa is extracted with ether.

Dihydrochloride of IVa is obtained by mixing an ethereal solution of the base and an ethereal solution of hydrogen chloride. After recrystallization from absolute alcohol, the product melts at 222-223°C. Yield 84%. Found, %: C 52.68; H 5.28; N 8.18; Cl 13.32. $C_{23}H_{24}F_3N_3OS \cdot 2HCl$. Calculated, %: C 53.08; H 5.04; N 8.07; Cl 13.62.

In a similar way, from 1,4-diazabicyclo[4,3,0]nonane and β-chloropropionyl-2-chlorophenothiazine IIIb, 10-[β-N-(1,4-diazabicyclo[4,3,0]nonanyl)propionyl]-2-chlorophenothiazine (nonachlazine) (IVb) is obtained.

Dihydrochloride of IVb is obtained from ethereal solutions of base IVb and hydrogen chloride. Melting point 215-216°C (from absolute alcohol). Yield 78.8%. Found, %: C 53.89; H 5.48; N 8.75; Cl 21.99; Cl' 14.32. $C_{22}H_{24}ClN_3OS \cdot 2HCl$. Calculated, %: C 54.26; H 5.38; N 8.63; Cl 21.85; Cl' 14.56.

Disulfate of IVb was obtained from an alcoholic solution of 2.7 g of base IVb and a solution of 1.2 g of 94% sulfuric acid in absolute ether. Melting point 158-161°C. Yield 3 g (81%). Found, %: C 43.25; H 5.04; N 6.85; S 15.50. $C_{22}H_{24}ClN_3OS \cdot 2H_2SO_4$. Calculated, %: C 43.31; H 4.73; N 6.89; S 15.76. Difumarate of IVb was obtained by mixing an ethereal solution of 3.4 g of base IVb and a solution of 1.9 g of fumaric acid in 40 ml of absolute alcohol. Melting point 157-159°C. Yield, 4.9 g (94%). Found, %: C 55.78; H 5.32; N 6.21. $C_{22}H_{24}ClN_3O \cdot 2C_4H_4O_4$. Calculated, %: C 55.77; H 4.99; N 6.50. Dimaleate of IVb was obtained by mixing an ethereal solution of 4.5 g of base IVb with a solution of 2.5 g of maleic acid in 30 ml of absolute alcohol. Melting point 169-170°C. Yield, 5.1 g (72.8%). Found, %: C 55.60; H 4.99; N 6.71. $C_{22}H_{24}ClN_3O \cdot 2C_4H_4O_4$. Calculated, %: C 55.77; H 4.99; N 6.50.

## EXPERIMENTAL PHARMACOLOGICAL PART

In series I of the experiments we studied the influence of nonachlazine (in a dose of 5-7 mg/kg) on the blood supply and activity of the heart. The experiments were carried out on narcotized (urethane, 400 mg/kg; chloralose, 300 mg/kg) cats. The coronary blood flow was evaluated from the blood outflow from the coronary sinus. The content of oxyhemoglobin in the coronary venous blood was recorded photometrically by an oxyhemograph. The resistance of the coronary vessels to the circulation of blood was recorded by the resistography method. The activity of the heart and the principal hemodynamic factors were calculated from the curve of the phased blood flow in the aorta, which was recorded by an electromagnetic method. The systolic output, the instantaneous volume, and the contractile capacity of the myocardium were determined.

In series II of the experiments we determined the content of phosphorylase "a" in the myocardium of rats by the Diamond method [5].

In series III of the experiments, we determined the content of norepinephrine and epinephrine in the myocardium by the method of Euler [6].

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# INFLUENCE OF MOLECULAR WEIGHT AND COMPOSITION OF COPOLYMERS OF ACRYLIC ACID WITH MALEIC ANHYDRIDE ON THEIR ANTIVIRAL ACTIVITY


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It is known that the study of structural-functional features of synthetic interferonogens (polycarboxylates, polyphosphates, polysulfates) makes it possible to obtain information necessary for the directed synthesis of highly effective and promising antiviral compounds [1]. The antiviral activity of polycarboxylates is influenced by factors such as the content of the carboxylic groups and the molecular weight of the polymers [2]. The nature of the monomers forming the polymer is also of great importance. For example, many polycarboxylates with interferonogenic properties are copolymers with maleic anhydride [1, 3-7].

The aim of the present work was to study the process of radical copolymerization of acrylic acid (AA) with maleic anhydride (MA) and to test the copolymers obtained for their interferonogenic and antiviral activity in mice using as a model tick encephalitis virus.

Despite the fact that in the literature the manifestation of antiviral activity by the copolymers of AA with MA in animals is known, it was interesting to study certain relationships between the antiviral activity and the dimensions and structure of synthetic interferonogens such as the copolymer of AA with MA [8].

## EXPERIMENTAL CHEMICAL PART

The copolymerization reaction was carried out in ampuls at a residual pressure of $10^{-4}$ mm Hg and at 60°C. Typical initiators of radical polymerization used were benzoyl peroxide and azo(bis)isobutyronitrile. The polymerization was carried out in organic solvents, which were previously purified by conventional methods [9]. The copolymers obtained (white powders) were reprecipitated from acetone into ether and dried in vacuo at 35°C.

The molecular weights of the samples obtained were determined by the method of high-speed sedimentation (the Archibald method) on a 317OV ultracentrifuge [10].

The composition of the copolymers was calculated from the data of elementary analysis.

It is known that the direction of the polymerization processes of acrylic acid in organic solvents depends on the nature of the solvent, and, in particular, on its ability to form hydrogen bonds with AA [11]. We therefore selected solvents of different basicity (Table 1). For a quantitative evaluation of the nature of the solvent, Table 1 shows the values of the mixed association constants ($K_{mix.ass.}$) between AA and the solvent during


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