Acute toxicity of compounds XI-XIII was assayed by the standard method [1] on white mice (males and females) weighing from 18 to 22 g, by means of an im injection of an emulsion of the preparations at various concentrations. Animal deaths were counted 24 h after the injections.

The toxicity of XI-XIII was greater than 1000 mg/ml.

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SYNTHESIS AND PHARMACOLOGICAL PROPERTIES OF THE ALKALOID KOMAROVININE AND ITS TETRAHYDRO DERIVATIVE

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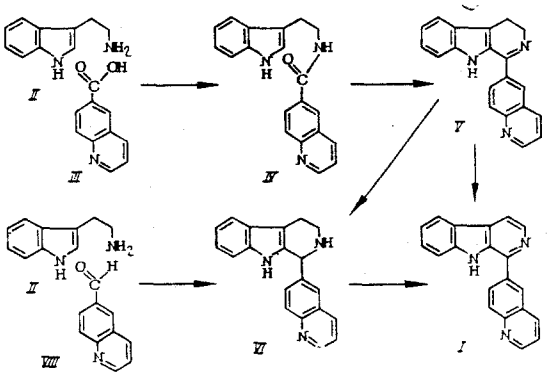
It was shown earlier [2, 4] that alkaloids of *Nitraria* L. plants and certain of their synthetic analogs possess spasmolytic, hypotensive, and hypertensive activity. The goal of the present work was the synthesis and pharmacological study of komarovinine (I) and 1,2,3,4-tetrahydrokomarovinine (VI). The isolation and establishment of the structure of I have been described earlier [3].



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Fusion of tryptamine (II) and quinoline-6-carboxylic acid (III) gave the amide (IV), the cyclization of which by the Bischler–Napieralski method led to 3,4-dihydro-1-(quinoline-6'-yl)-β-carboline (V). Dehydrogenation of V gave I, and reduction of V with sodium borohydride gave compound VI, which also was prepared by condensation of tryptamine hydrochloride with quinoline-6-carboxaldehyde (VII) in acid. The conversion of VI to I [3] took place analogously with the conversion of V to I.

Pharmacological studies showed that I possessed significant hypertensive properties, which were preceeded, however, by a temporary lowering of arterial pressure. The hypertensive action of VI was observed to be without the corresponding pressure decrease, and thus is more stable. Increasing the dose of VI simultaneously disclosed antiarrhythmic properties.

EXPERIMENTAL CHEMICAL PART

Spectral instrumentation and parameters were given earlier [4].

Quinoline-6-carboxylic Acid (III) was prepared by oxidation of quinoline-6-carboxaldehyde (VII) [3] with hydrogen peroxide, mp 290-291°C.

3-[β-(6'-Quinolinecarboxamido)ethyl]indole (IV). A mixture of 1.4 g (9 mmoles) of II and 1.9 g (11 mmoles) of III was heated in a sand bath for 2 h at 210-220°C. After cooling, the fused mass was worked up with acetone and then ethyl acetate. The resulting residue of IV was crystallized from methylene chloride to give 1.72 g (62.5%), mp 182-184°C.

3,4-Dihydro-1-(quinoline-6'-yl)-β-carboline (V). A mixture of 1.72 g of IV and 5 ml of $POCl_3$ was boiled under reflux for 2 h. After cooling, the excess reagent was cautiously decomposed with ice water and the mixture was made alkaline with 15% aqueous NaOH. The product was extracted with ether and then chloroform to give 0.7 g (43%) of V, mp 231-232°C.

1-(Quinolin-6'-yl)-β-carboline (I). A mixture of 57 mg of V and 40 mg of Pd-black was heated for 45 min at 180-200°C. The cooled mass was dissolved in a mixture of chloroform and methanol (1:1), the catalyst was removed, the filtrate was concentrated, the residue was dissolved in 5% sulfuric acid, and the solution was washed with ether. Decomposition with KOH solution and extraction with chloroform gave 30 mg (53%) of I, mp. 238-240°C (methylene chloride) PMR spectrum ($CDCl_3 + CD_3OD$), δ, ppm: 8.75; 8.34; 8.11; 7.55; 7.43. IR spectrum: ν_{max}, cm^{-1}: 750 (o-disubstituted benzene ring); 1460, 1505, 1575, 1630 (indole nucleus), 3150, 3210 (N-H). Found, %: C 79.50; H 4.89; N 13.96. Calculated for $C_{20}H_{13}N_3 \cdot 0.5H_2O$, %: C 78.95; H 4.61; N 13.81.

1,2,3,4-Tetrahydro-1-(quinoline-6'-yl)-β-carboline (VI). To a solution of 46 mg of V in 5 ml of ethanol was added 174 mg of sodium borohydride in portions. The mixture was stirred at room temperature for 1 h, the solvent was distilled, the excess reagent in the residue was destroyed with water, and the reaction product was extracted with chloroform to give 24 mg (52%) of VI, mp 251-252°C. M^+ 299. IR spectrum, ν_{max}, cm^{-1}:750 (o-disubstituted benzene ring), 1455, 1505, 1580, 1625 (indole nucleus), 2850, 2970 (C–H), 3290, 3320 (N–H). UV spectrum, λ_{max}, nm (log ε) ethanol: 226, 232 (shoulder), 275-283, 292, 318 (4.85, 4.80, 4.23, 4.17, 3.92); (ethanol, pH < 7.0): 221, 237, 266-274, 291, 319 (shoulder). PMR spectrum ($CDCl_3 + CD_3OD$), δ, ppm, 8.60 q (1H); 8.04; 7.93; 7.86; 7.76; 7.56; 7.45; 7.36; 7.21; 7.11; 6.96 m (1 OH); 5.22 s (1H); 2.96 m (4H).

EXPERIMENTAL PHARMACOLOGICAL PART

Acute toxicity was determined on white mice weighing 18-22 g by intravenous injection, followed by statistical treatment of the results by the method of Litchfield and Wilcoxon [1]. The effect upon arterial pressure, respiration, and the vegetative stage of the nervous system were studied with narcotized cats, and the influence on smooth muscle was determined on isolated rat small intestines. Antiarrythmic activity was studied in its effect on the arrhythm in rats induced by intravenous injection of aconitine.

RESULTS AND DISCUSSION

It was shown that the LD_{50}) of I for rats is equal to 146.5 (126.3-169.94) mg/kg. In doses of 5-10 mg/kg. I increases the arterial pressure by 15-35% for 2-4 h preceeded by a transient (1-3 min) pressure decrease of 35-45%. The introduction of I had essentially no effect on rat brain EKG tests. Activity also was not observed on the H-choline-reactive system in experiments on muscle directly isolated from frogs.

By comparison with I, VI increased arterial pressure without the sharp decrease. With intravenous introduction, beginning with doses of 0.5 mg/kg, VI increased the arterial pressure by 30-35% within 2-3 min. With a dose of 1-2 mg/kg, the arterial pressure increased by 45-70% over 4-5 min. The hypertensive effect on narcotized animals was observed upon subcutaneous injection of the preparation. In this case, their activity began 10-15 min after injection, slowly developed and slowly reduced. For example, with a dose of 3 mg/kg of VI the arterial pressure increased 20-25% and reduces to the initial value within 60-90 min. Simultaneously with increasing arterial pressure, a temporary respiratory depression was noted in all experiments with intravenous injection of VI.

Experiments on cats showed that intravenous injection of 1-2 mg/kg of VI did not exhibit stimulation of inter-neural transmission of impulses through the upper cervical symphathetic ganglia and the cardiac ganglia of the circulating nerves. Preliminary atropinization (1 mg/kg, intravenously) and bilateral severance of both circulating nerves did not substantially influence the degree and duration of the hypertensive activity of VI. Consequently, no substantial influence on the sympathetic innervation and the M-cholinoreactive systems of the organism was found for doses of VI in our studies. An appreciable effect on the EKG of rats upon intravenous injection of doses of 0.5-2 mg/kg also was not observed. In experiments on isolated rabbit ears, VI, at an initial concentration of 1×10^{-6} g/ml, narrowed down the blood vessel by 10-10.5%, and at a concentration of 1×10^{-5} g/ml, by 20-24%.

Certain resemblances of VI to serotonin (VIII) also have been discovered. Thus, VIII (in a dose of 1×10^{-8} g/ml) and VI (in a dose of 1×10^{-6}-1×10^{-5} g/ml) increase the tonus of isolated small intestines and isolated rat uterus horn. Compounds VIII (in a dose of 5-10 µg/kg) and VI (in a dose of 0.5-1 mg/kg) lowered the tonus of the small intestine of cats. Since VIII has the innate property of liberating catecholamines [5] which may play a positive role in the regulation of heart rhythms, the presence of certain antiarrhythmic properties of VI may possibly depend upon analogous activity. The LD_{50} of VI by intravenous injection in white mice was 67 (61.63-72.829) mg/kg.

Thus compound VI exhibits hypertensive and certain antiarrhythmic activity. The hypertensive effect depends upon its vessel-constricting properties. The data obtained indicate that in the series of *Nitraria* L. plant alkaloids and synthetic analogs studied, it is advisable to search for materials with hypotensive and hypertensive types of activities in combination with antiarrhythmic and other properties.

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