SYNTHESIS OF PIPERIDINE AND DECAHYDROQUINOLINE DERIVATIVES, THEIR ANALGESTIC AND PSYCHOTROPIC PROPERTIES. XXI. 1-METHYL-4-VINYLETHYNYLPIPERIDIN-4-OL AND ITS ESTERS

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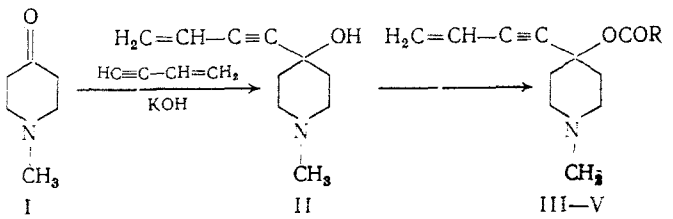
In the present work, we continue the synthetic studies based on the readily available 1-methyl piperidin-4-one (I) [5]. We have already synthesized from I a series of esters of 1-methyl-4-acetylpiperidin-4-ol, among which compounds were discovered with a broad spectrum of neurotropic activity [4]. To continue the search for new effective neurotropic agents in the series of 4-substituted piperidin-4-ol derivatives, and to find the influence of the char acter of the unsaturated substituents and acylating residues at C_4 on the toxicity and activity of the preparations, in the present work we synthesized and studied the pharmacological properties of 1-methyl-4-vinylethyhylpiperidin-4-ol (II) and its ester (III-V).



III: R = CH_3; IV: R = C_2H_5; V: R = C_6H_5.

In the reaction of piperidone I with vinylacetylene in a benzene solution in the presence of powdered potassium hydroxide, piperidol II is formed in a 75.7% yield. The compound is sparingly soluble in water, but when its acetone solution is treated by an ether solution of HCl, a water-soluble hydrochloride is isolated in a quantitative yield. The piperidol II synthesized served as a starting material for the preparation of a series of esters (III-V). The hydrochloride of the acetate ester III was obtained in a 96.3% yield by acylation of II with a mixture of AcCl and Ac_2O. Propionate IV was obtained in a 95.5% yield by treating II with a mixture of propionic acid and its anhydride. Benzoate V was obtained in a 83.1% yield by esterifying II with benzoyl chloride in boiling pyridine solution. All piperidin-4-ol derivatives (II-V) were identified and were tested in the form of water-soluble hydrochlorides for pharmacological activity.

The structure of the compound synthesized was confirmed by the data of elemental analysis and IR spectroscopy. The stretching vibrations of the hydroxylic group of II appear in the IR spectrum at 3060-3120 cm^{-1}. The presence of the ester carbonyl in compounds III-V is confirmed by characteristic intense bands at 1723-1755 cm^{-1} in the IR spectra.

It should be noted that because of the presence of a vinyl group in their molecules, compounds II-V can participate in homo- and copolymerization reactions to form water-soluble high-molecular-weight compounds with a prolonged pharmacological action.

EXPERIMENTAL (CHEMICAL SECTION)

The IR spectra were recorded on a "UR-20" spectrophotometer (GDR) in KBr or KCl tablets. The course of the reaction and the purity of compounds synthesized was controleld by the TLC

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TABLE 1. LD_{50} of Hydrochlorides of Compounds II-V Synthesized, Their Influence on Sleep-Producing Action of Narcotics, and Spasmodic Activity of Arecoline in Mice

Compound	LD_{50} mg/kg	Duration, min		
		of a hexenal-induced sleep	of a chloral hydrate-induced sleep	of an arecoline-induced tremor
II·HCl	1050,0 (1004,8—1097,3)	94,9 (50,8—139,0)	95,5 (48,3—142,7)	18,8 (15,0—22,6)
III·HCl	750,0 (641,0—877,5)	253,1 (196,2—310,0)	92,5 (45,3—139,7)	21,4 (19,0—23,8)
IV·HCl	650,0 (532,8—793,0)	242,5 (147,7—337,3)	146,6 (110,3—182,9)	20,9 (17,6—24,2)
V·HCl	450,0 (335,8—603,0)	269,4 (223,7—315,1)	371,0 (298,5—443,5)	Did not develop
Control	—	34,5 (25,7—43,3)	17,9 (11,5—24,3)	25,1 (23,0—27,2)

method on plates with Al_2O_3 with development of the spots by iodine vapors. The starting 1-methylpiperidin-4-one (I) was obtained by the method described in [7].

1-Methyl-4-vinylethynylpiperidin-4-ol (II). A 113.15 g portion (1 mole) of piperidone I is added, with vigorous stirring, to a cooled (from −5 to −10°C) mixture of 56 g (1 mole) of powdered KOH, 130 ml of dry benzene, and 52 g (1 mole) of freshly prepared vinylacetylene [6], stabilized by 1 g of hydroquinone, at such a rate that the temperature of the reaction mixture does not exceed 0°C. The temperature of the mixture is then raised to room temperature, the mixture is stirred for 1 h, and the thickened mass is treated with 100 ml of water. The precipitate that separates is filtered, washed with water and benzene, and dried. The benzene layer of the filtrate is separated, and the aqueous layer is extracted several times by benzene. The combined benzene solutions are evaporated and the remaining crystals are combined with the precipitate that separated after the neutralization by water. After recrystallization from a mixture of acetone with ether, 125 g (75.7%) of II are obtained, mp 105-106°C. Found, %: C 72.44; H 9.40; N 8.44. $C_{10}H_{15}NO$. Calculated, %: C 72.69; H 9.15; N 8.48. The hydrochloride of II is obtained in a quantitative yield by treating an acetone solution of II with an ether solution of hydrogen chloride; fine colorless crystals, mp 141-142°C (from alcohol with ether). Found, %: C 60.39; H 8.02; Cl 17.53; N 6.91. $C_{10}H_{16}ClNO$. Calculated, %: C 59.55; H 8.00; Cl 17.58; N 6.94.

1-Methyl-4-vinylethynyl-4-acetoxypiperidine hydrochloride. A mixture of 5 g (0.03 mole) of II, 23.55 g (0.3 mole) of a freshly distilled AcCl, and 30.63 g (0.3 mole) of Ac_2O is heated for 1 h at 90-95°C. After cooling, the crystals that separate are filtered, washed with ether and dried. Yield, 7.1 g (96.3%) of hydrochloride of III, mp 182-183°C (from acetone). Found %: C 58.93; H 7.40; Cl 14.83; N 5.83. $C_{12}H_{18}ClNO_2$. Calculated, %: C 59.13; H 7.44; Cl 14.55; N 5.75.

1-Methyl-4-vinylethynyl-4-propionyloxypiperidine (IV). A mixture of 10 g (0.061 mole) of II, 37 ml (0.488 mole) of propionic acid, and 110 ml (0.847 mole) of propionic anhydride is heated for 3 h at 100-110°C. After evaporation in a water jet pump vacuum, 15 ml of water are added to the residue and the mixture is neutralized in cold by a 5% aqueous solution of $NaHCO_3$ to pH 8.0. The acylation products are extracted by ether, the extract is dried, and after the removal of solvent, the oily residue is distilled. Yield 12.79 g (95.5%) of IV in the form of a transparent liquid, bp 106-108°C (3 mm), n_D^{20} 1.4910. Found. %: N 6.30, $C_{13}H_{19}NO_2$. Calculated, %: N 6.33. The hydrochloride of IV is obtained in a quantitative yield as described above; white powder, mp 202-203°C (from alcohol with ether). Found, %: C 60.69; H 7.87; Cl 14.01; N 5.48. $C_{13}H_{20}ClNO_2$. Calculated, %: C 60.57; H 7.82; Cl 13.75; N 5.43.

1-Methyl-4-vinylethynyl-4-benzoyloxypiperidine Hydrochloride. A mixture of 12 g (0.059 mole) of hydrochloride II, 120 ml of dry pyridine, and 25 ml (0.217 mole) of a freshly distilled benzoyl chloride is heated at 135-140°C for 1.5 h. After cooling, most of the pyridine is removed in a water-jet pump vacuum, the residue is dissolved in 100 ml of water, and the neutral products are extracted by ether. The aqueous solution is made alkali by dry potassium

hydroxide to pH 9.0, the benzoylation products are extracted by ether, the extract is dried, and after the removal of solvent, 13.32 g (83.14%) of an oil residue, which is compound V, are obtained. The latter is dissolved in ether, an ether solution of HCl is added and a hydrochloride is obtained, mp 206-207°C (from alcohol with ether). Found, %: C 66.82; H 6.65; Cl 11.73; N 4.55. $C_{17}H_{20}ClNO_2$. Calculated, %: C 66.75; H 6.59; Cl 11.59; N 4.58.

EXPERIMENTAL (PHARMACOLOGICAL SECTION)

The experiments were carried out on a noninbred white mice (6 or more animals in each group) and rabbits. Compounds II-IV in the form of water-soluble solutions of hydrochlorides were introduced to the mice subcutaneously in one signle dose, and to the rabbits into the conjunctive bag of an eye (0.15 ml).

The acute toxicity of the compounds was determined for mice [2]. Then, in doses equal to 1/5 LD_{50}, the analgesic activity was found from the increase in the threshold of pain sensitivity during thermal irritation [8], and antispasmodic action for spasms induced by nicotine (25 mg/kg, subcutaneously), Corazole (60 mg/ml, subcutaneously) and arecoline (15 mg/kg, subcutaneously). The influence of the compounds was determined on the duration of a hexenal (60 mg/kg, subcutaneously) and chloral hydrate (350 mg/kg, subcutaneously) induced sleep, central effects of phenamine (7.5 mg/kg, subcutaneously), motive excitation, recorded by acto meter [1] and hypothermia determined by a TPEM-1 electrothermometer, and on central effects of 5-hydroxytryptophan (50 mg/kg, intraperitoneally) – hypothermia and spasms (head shaking). The ability of the compounds to cause terminal anesthesia was tested on rabbits by the Renier–Vallette method [3]. The activity of the compounds was compared with the activity of dicaine and promedol.

DISCUSSION

The LD_{50} of the compounds listed in Table 1, indicates that the compounds studied have variable toxicity. The most toxic is the benzoate V. According to change in the LD_{50} values (see Table 1), the compounds can be arranged in the following series: V > IV > III > II. Vinylethynylpiperidin-4-ol (II) has a very low toxicity. In the acylated derivatives III-V the toxicity increases with increase in the molecular weight of the acyloxy groups. However, the compounds studied are less toxic than promedol: its LD_{50} value for mice (subcutaneously) is equal to 200 mg/kg (184.5 - 216.8).

Studies on the anesthetic activity of compounds II-V showed that they have a weak local-anasthetic action. The Renier–Valette index is equal to 33-41, compared with the index for dicaine (tetracaine hydrochloride), equal in equivalent concentration (1%). The compounds are 90-99 times inferior to dicaine with respect to the intensity of the terminal anesthesia. It was found that compounds II-IV have no analgesic activity. They do not change the threshold of pain sensitivity of mice in a 30 min-3 h range from the start of administration. Benzoate V is characterized by an analgesic action, which decreases the pain sensitivity of mice. However, the intensity of the analgesic action of V is lower than that of promedol by a factor of 7. This is indicated by the value of the latitude of the analgesic action: for V it is equal to 11.8 (10.2-13.7) and for promedol 80.0 (37.4-167.7).

The compounds synthesized do not change the spasmodic action of nicotine and Corazol. Compounds II-IV shorten the duration of an arecoline-induced tremor, and V prevents its development (see Table 1). The compounds studied, and in particular V, thus have a central M-cholinolytic action.

All the compounds regularly increase the sleep-producing effect of narcotics. The duration of the sleep-producing action of hexenal increases 2.7-7.8 times and that of chloral hydrate 5.2-20.7 times, compared with the control. Compound C gives the most pronounced effect (see Table 1).

Compounds II-V hinder the development of phenamine hyperthermia, II and IV do not change it, and III and V lower the phenamine-stimulated motive activity of mice. All the preparations have a statistically significant intensifying action on hypothermia induced by the administration of 5-hydroxytryptophan. The spasmodic activity of the latter is decreased by the action of the compounds studied.

Among the piperidin-4-ol derivatives studied, the benzoate ester V, which differs from other compounds by the presence of a benzoxyl group at the $C_{(4)}$ atom of the piperidine ring, has the highest pharmacological activity and the most acute toxicity (see Table 1).

All the data confirm expediency of further search for effective neurotropic preparations in the series of 4-substituted 1-methylpiperidin-4-ol derivatives.

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STUDY IN THE SERIES OF 4-QUINAZOLINONES.

XVII. SYNTHESIS AND BIOLOGICAL ACTIVITY OF 1,2-DISUBSTITUTED 4-QUINAZOLINONES

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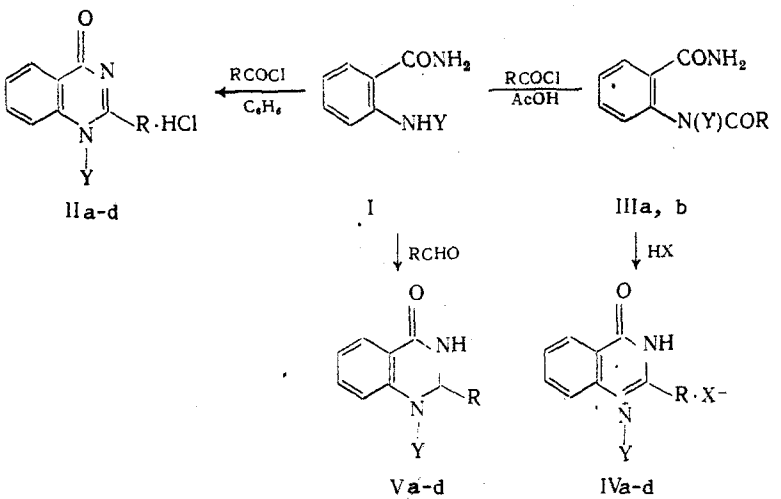
In order to search for biologically active compounds and to continue the studies in [8], derivatives of 4-quinazolinone substituted at the 1– and 2-positions of the quinazolinone ring were obtained from N-(2-methoxyphenyl) anthranylamide (I).



IIa: R = Me; IIb: R = Et; IIc: R = Ph; IId: R = CH_2Ph; IIIa: R = Me; IIIb: R = = Et; IVa, c: R = Me; IVb, d: R = Et; IVa, b: X = Br; IVc, d: X = ClO_4; Va: R = Pr; Vb: R = Ph; Vc; R = C_6H_4OMe-4; Vd: R = furyl-2; Y = 2-methoxyphenyl (IIa-d; I; IIIa, b; IVa-d; Va-d)

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