SYNTHESIS OF PIPERIDINE AND DECAHYDROQUINOLINE DERIVATIVES: THEIR ANALGETIC AND PSYCHOTROPIC PROPERTIES. XVIII. 1-METHYL-4-ACETYLPIPERIDIN-4-OL AND ITS ESTERS

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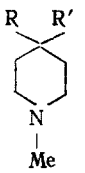
Substituted piperidin-4-ols and their esters occupy a prominent place among the various synthetically prepared biologically active compounds. In continuation of the search for compounds with neurotropic activity among the piperidine derivatives [4-6] it was interesting to investigate the newly prepared esters (IV-VI) of the known [8] 1-methyl-4-acetylpiperidin-4-ol (III), since 1,2,5-trimethyl-4-acetyl-4-acyloxypiperidines, which exhibit a local-anesthetic action, have been described in the literature [3]. The synthesis of IV-VI is based on 1-methyl-piperidin-4-one (I) which is being produced on an industrial scale.



II—VI

II:R=OH, R′ = ethynyl; III:R=OH; IV:R=AcO; V:R=EtCOO; VI:R=PhCOO; III—VI:R′=Ac; IV-VI – hydrochlorides.

According to the data in [8, 9], alcohol II was obtained in a yield of 48-64% by the condensation of I with acetylene in an ether solution in the presence of powdered KOH. We improved the method of synthesis of II by using liquid NH_3 as solvent for ethynylation reaction of I, and as a result the yield of II increased to 93.8%. We also succeeded in considerably increasing the yield of ketone III (up to 96% against 63% reported in [8]), which is probably due to the completeness of its extraction by $CHCl_3$ from the reaction medium. Acetic ester IV was obtained in a 95.6% yield by acetylation of III by a mixture of AcCl and Ac_2O. Propionic ester V was synthesized by the reaction between III and excess EtCoCl in an acetone solution at 50°C for 30 min. Benzoates VI was obtained in a yield of 85.7% by esterification of III with PhCoCl in a solution of boiling pyridine. All the esters IV-VI synthesized were isolated from the reaction medium in the form of pharmacologically acceptable hydrochlorides.

The IR spectrum of ketol III is characterized by the presence of characteristic frequencies: 3320 cm^{-1} (ν OH), 1715 (ν C=O of acetyl). The strong absorption band at 1715-1720 cm^{-1}, characteristic of the acetyl group carbonyl is retained in the IR spectra of esters IV-VI, and a more intense absorption band at 1740-1745 cm^{-1} appears, which we assigned to the stretching vibrations of the ester group carbonyl. The absorption band of the hydroxyl group is absent.

EXPERIMENTAL (CHEMISTRY)

The IR spectra of the compounds were run on the UR-20 spectrophotometer (GDR) in KBr or KCl tablets. The purity of the compounds obtained and the course of the reaction were controlled by chromatography in a nonstationary thin layer of aluminum oxide with grade III activity, using the ether–ethanol system (20:1) as eluent, and developing with iodine vapors. The initial 1-methylpiperidin-4-one (I) was prepared according to [10].

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1-Methyl-4-ethynylpiperidin-4-ol (II). A four liter portion of liquid NH_3 and 336 g (6 moles) of powdered KOH are placed in a 5 liter three-necked round bottomed flask, fitted with a mechanical stirrer, dropping funnel, and a tube for passing acetylene. The mixture is saturated, with vigorous stirring for 1.5 h, with acetylene, and then a solution of 279.69 g (2.47 moles) of I in 300 ml of dry ether is added in the course of 2.5 h. Stirring of the reaction mixture with a continuous current of acetylene is continued for 6 h, and the mixture is left to stand overnight, whereby a large part of NH_3 evaporates. On the following day, the residual NH_3 is removed from the highly thickened mixture, which is treated with 500 ml of water, and extracted several times by ether. The combined ether extracts are neutralized by carbon dioxide to slight turbidity, and then dried over $MgSO_4$. After removal of the solvent, 322.67 g (93.8%) of II, mp 122-123°C (from acetone), are obtained. IR spectrum, ν_{max}, cm^{-1}: 3310 (≡C–H), 2115 (C=C), 3600 (OH). According to the data in [8], mp 122-123°C.

1-Methyl-4-acetylpiperidin-4-ol (III). A 40 g portion of II is added, with stirring, to a solution of 13.34 g of $HgSO_4$ and 26.7 g of concentrated H_2SO_4 in 270 ml of water; the temperature of the mixture thus increases to 70°C. The solution is heated for 5 h on a boiling water bath, neutralized with potassium carbonate, and treated with zinc dust. The precipitate is filtered and washed with hot water, and after most of the water has been removed, the aqueous solution is extracted by $CHCl_3$ (9 × 50 ml). The combined extracts are evaporated, the residue is dried by azeotropic distillation of water with benzene, and after recrystallization from hexane, 43.36 g (95.98%) of III, mp 95-96°C, are obtained. According to the data in [8], mp 95-96°C.

Hydrochloride of III is obtained in a quantitative yield by treating the base with an ether solution of hydrogen chloride; fine colorless crystals, mp 168-169°C (ethanol–ether). Found %: C 49.82; 50.02; H 8.25; 8.21; N 7.53; 7.54; Cl 18.42; 18.28. $C_8H_{16}ClNO_2$. Calculated %:C 49.61; H 8.32; N 7.23; Cl 18.30.

1-Methyl-4-acetyl-4-acetoxypiperidine Hydrochloride (IV). A mixture of 10 g (0.064 mole) of III, 42.62 ml (0.6 mole) of AcCl and 56.61 ml (0.6 mole) of Ac_2O is heated for 1 h at 80-90°C. When cool, the crystals are filtered, washed with ether, and dried in a vacuum exciccator. Yield, 14.5 g (95.62%) of IV, mp 218-219°C (i-PrOH). Found %: C 50.69; 50.89; N 8.24; 8.02; N 5.86; 6.09; Cl 15.13; 15.01. $C_{10}H_{18}ClNO_3$. Calculated %: C 50.96; H 7.70; N 5.94; Cl 15.04.

1-Methyl-4-acetyl-4-propionyloxypiperidine Hydrochloride (V). A mixture of 1 g (0.006 mole) of III and 1.05 ml (0.012 mole) of EtCOCl and 10 ml of acetone is heated for 30 min at 50°C. When cool, the required product is precipitated by dry ether, filtered, washed with ether, and recrystallized from alcohol. Yield, 1.35 g (88.2%) of V, mp 193-194°C. Found %: C 53.14; 53.27; H 7.96; 7.87; N 5.72; 5.67; Cl 14.70; 14.53. $C_{11}H_{20}ClNO_3$. Calculated %: C 52.90; H 8.07; N 5.61; Cl 14.20.

1-Methyl-4-acetyl-4-benzoyloxypiperidine (VI). A mixture of 4 g (0.025 mole) of III, 50 ml of dry pyridine and 10.54 g (0.075 mole) of freshly distilled PhCOCl is heated at 120-125°C for 1 h; pyridine is distilled off in vacuo, and the residue is ground into a powder under dry ether, filtered, and dried in a vacuum exciccator. After recrystallization from alcohol, 6.49 g (85.7%) of VI, mp 224-225°C, are obtained. Found %: C 60.69; 60.84; H 6.93; 6.81; N 4.77; 4.82; Cl 12.01; 12.12. $C_{15}H_{20}ClNO_3$. Calculated %: C 60.50; H 6.77; N 4.70; Cl 11.90.

EXPERIMENTAL (PHARMACOLOGY)

The studies were carried out on 502 white mice and 6 rabbits of both sexes. The compounds were introduced in one single dose in the form of aqueous solutions, to the rabbits into the conjuctival eyebag (0.15 ml, 0.1% and 1%) and to the mice subcutaneously in doses: compounds III and IV – 50 mg/kg, V and VI – 1/5 of LD_{50} (35 and 3.7 mg/kg, respectively).

In the course of the investigations, the local anesthetic (terminal anesthesia), analgetic (narcotic), antispasmodic, and psychotropic activities of compounds III-VI were determined. The terminal anesthesia was determined on the eyes of rabbits, by the Renier–Balet method, the analgetic activity by the hot plate method [11], and the antispasmodic action by studying the influence of the compounds on spasms induced by arecoline and Corazol. The psychotropic activity was determined by studying the influence of the compounds on the sleep-producing effect of hexenal and chloral hydrate, the central effects of phenamine

TABLE 1. Acute Toxicity and Pharmacological Activity of Compounds III-VI (experiments on mice)

Parameter	Control	Compound			
		III	IV	V	VI
LD_{50}, mg/kg		>2000,0	>2000,0	175,0 (116,7±262,5)	18,5 (16,8—20,4)
Duration of hexenal-induced sleep, min	17,0 (7,0—26,2)	48,6 (22,1—75,1*)	74,5 (55,3—93,7)*	68,3 (40,1—96,5)*	54,3 (14,5—94,1)*
Duration of chloral hydrate-induced sleep, min	56,3 (26,5—86,1)	85,9 (20,0—151,8)	80,0 (18,9—141,1)	171,4 (67,8—275,0)*	93,9 (22,8—165,0)
Duration of arecoline-induced tremor, min	26,7 (23,6—29,8)	24,3 (16,2—32,4)	24,8 (18,6—31,0)	39,9 (26,9—52,9)*	34,1 (23,9—44,3)
Body temperature, °C					
initial background 30 min after introduction of phenamine:	37,3 (37,0—37,6)	36,5 (36,0—37,0)	37,0 (36,7—37,3)	36,0 (35,7—36,3)	35,8 (35,3—36,3)
distilled water + phenamine	38,3 (37,8—38,8)				
compound + phenamine		37,7 (36,9—38,5)	36,1 (35,8—36,4)*	34,4 (33,9—34,9)*	35,4 (34,4—36,4)*

*Statistically significant result.

(hyperthermia and motive excitation) and the central effects of 5-hydroxytryptophan (5-HTP) (hypothermia and spasms – head shaking). All these tests, except the determination of the local-anestetic activity, were carried out on mice. Thirty minutes after the mice had received compounds III-VI, arecoline (15 mg/kg), Corazol (80 mg/kg), hexenal (60 mg/kg), chloral hydrate (350 mg/kg), and phenamine (7.5 mg/kg) were administered subcutaneously in one single dose, and 5-HTP (50 mg/kg) intraperitoneally.

The motive activity was determined by actometer [1]. The rectal temperature was determined by electrothermometer TPEM-1. The numerical data were processed statistically [2]. Before the above experiments were carried out, the acute toxicity of the compounds was determined by a generally accepted method [2]. The activity of the compounds was compared with that of promedol and dicain.

The investigations showed that the LD_{50} value (subcutaneously) of promedol for mice is equal to 200 (184.5-216.8) mg/kg. The compounds synthesized have different toxicities (see Table 1). The compounds studied and promedol can be arranged into the following series according to the value of LD_{50}: VI > V, promedol > III, IV.

Compounds III-VI have a local anesthetic activity. By blocking the pain receptor apparatus of the eye cornea of rabbits, they cause terminal anesthesia. In this effect they are inferior to dicain by a factor of 86-99. The Renier–Balet index of compounds III-VI is equal to 33-44, while in dicain it is 1296 units (1% solutions).

Compounds III-VI do not change the pain sensitivity threshold to thermal irritant (55°C) for 30 min – 3 min after administration. Promedol in an equivalent dose considerably lowers the pain sensitivity threshold.

Compounds III-VI regularly increase the duration of hexenal-induced sleep (see Table 1), which increases 2.9, 4.4, 4.0, and 3.2 times, respectively, compared with that of the control. Compound V prolongs the chloral hydrate-induced sleep by a factor of 3. On the background of compounds III, IV, and VI, a tendency is observed to prolong the chloral hydrate induced sleep (see Table 1). Compounds III, IV, and VI do not change, while V regularly increases the spasmodic period of arecoline (see Table 1).

Ketol II, acetate IV, and propionate V do not change the spasmodic activity of Corazol. Benzoate VI increases the spasmodic action of Corazol: In the control group, 8 out of 14 mice died, and in the experimental group, 11 out of 12 ($P < 0.05$).

In the dose studied, phenamine causes a distinctly expressed hyperthermia after 30 min, and rectal temperature of the mice increases by 1°C (see Table 1). Compound II does not influence the phenamine-induced hyperthermia, while compounds IV-VI prevent its development (see Table 1). The compounds do not have the same time type of action on phenamine-induced motive excitation in mice. Compounds III-V do not change, while in compound VI there is a statistically significant decrease in intensity, and the number of movements (in the course of 10 min) decreases after 30 min by a factor of 2.7 (from 286.0 ± 39.9 to 104.8 ± 40.7) and after 60 min by a factor of 4.2 (from 547.2 ± 142.0 to 130.2 ± 57.3), compared with the control.

Ketol III and esters IV-VI do not change the spasmodic activity of 5-HTP. Compounds III, IV, and VI do not influence the development and the course of hypothermia, modeled by the introduction of 5-HTP. Propionate V intensifies the hypothermal effect of 5-HTP by a statistically significant amount.

The results of the above experiments show that compounds III-VI influence certain functions of the nervous system of animals. In the case of propionate V, the spectrum of the neurotropic action is somewhat broader than that in ketol III, acetate, IV, and benzoate VI. Propionate V is also more toxic than the other compounds (see Table 1).

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SYNTHESIS AND PHARMACOLOGICAL PROPERTIES OF N-β-[3-INDOLYL] ETHYLPROPANOLDIAMINES

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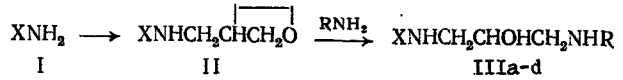
We showed earlier [3, 4] that the introduction of arylalkyl and arylalkenyl substituents into the aliphatic part of the tryptamine molecule gives compounds which act on the cardiovascular system.

In the present work, we have synthesized tryptamine derivatives substituted at the nitrogen atom with an aminopropanol group, a group found in substances acting on the adrenergic system [1].



$$\underset{\text{I}}{XNH_2} \longrightarrow \underset{\text{II}}{XNHCH_2\overline{CHCH_2O}} \xrightarrow{RNH_2} \underset{\text{IIIa-d}}{XNHCH_2CHOHCH_2NHR}$$

IIIa: R = *i*-Pr; IIIb: R = *t*-Bu; IIIc: R = $CHMeCH_2Ph$; IIId: R = $CHMe(CH_2)_2Ph$; X = 3-indolylethyl.

Epoxypropylamine (II) was obtained by the reaction of tryptamine (I) with epichlorhydrin in $CHCl_3$ in the presence of Et_3N. The latter was reacted with primary amines [6] in i-PrOH in the presence of catalytic amounts of water to give the diamines (IIIa-d), which were characterized as the dihydrochlorides.

The purity and structure of the compounds were confirmed by elemental analysis, infrared and mass spectrometry, and chromatography.

EXPERIMENTAL (CHEMISTRY)

TLC was carried out on alumina (activity II) in butanol—AcOH—water (4:1:3), using iodine vapor as a developer. IR spectra of the compounds in mineral oil were taken on a UR-20 (GDR) instrument, mass spectra on an MX-1303 with direct introduction of the sample into the ion beam. Melting points were determined on a "Boezius" micro hot stage (GDR).

N-β-(3-Indolyl)ethyl-2,3-epoxypropylamine (II). To 4.8 g (30 mmoles) of tryptamine I in 100 ml of $CHCl_3$ in the presence of 3.03 g (30 mmoles) of Et_3N at room temperature (20-25°C) was added dropwise 2.8 g (30 mmoles) of epichlorohydrin. The mixture was stirred for 2-3 hours, then heated at 50-55°C for 4-5 hours. The oily material formed was separated, heated in 100 ml of 40% NaOH at 60-65°C for 2-3 hours, filtered, washed three times with ice water and dried in a desiccator to give 5.4 g of II (77%), mp 126-127°C. Found %: C 72.32; H 7.31; N 12.62. $C_{13}H_{16}N_2O$. Calculated %: C 72.22; H 7.40; N 12.95. Rf 0.6. Mass spectrum, m/z (I rel.): 216 (12), 143 (25), 130 (75), 86 (100).

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