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SYNTHESIS OF 4-PIPERIDONE DERIVATIVES AND STUDY OF THEIR PHARMACOLOGICAL PROPERTIES

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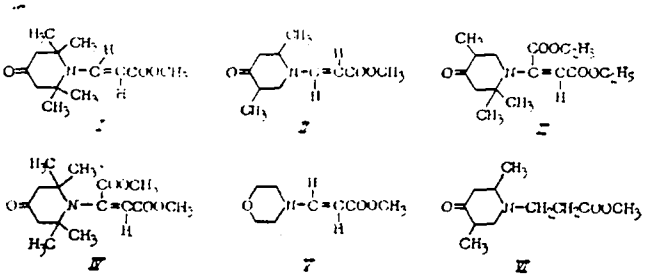
We synthesized a group of 4-piperidone derivatives (I-VI), and studied them with respect to certain pharmacological activity parameters.



EXPERIMENTAL CHEMICAL PART

The PMR spectra were run on a Bruker WM-400 spectrometer (^{1}H, 400 MHz, TMS), mass spectra on a M-80a Hitachi spectrometer (Japan) at a ionizing voltage of 12 and 70 eV, and IR spectra in $CHCl_3$ on a Specord 75 IR spectrophotometer in $CHCl_3$ in KBr cuvettes. The melting points were determined on a RNMX-05 apparatus. In the syntheses, absolute solvents and freshly prepared and freshly purified reagents were used.

Methyl Ester of trans-N-β-(2,2,6,6-Tetramethyl-4-oxo-1-piperidyl)acrylic Acid (I). A 1-g portion (12 mmoles) of methyl propiolate is added at 20°C to a solution of 1.7 g (11 mmoles) of 2,2,6,6-tetramethyl-4-oxopiperidine in 10 ml of MeOH. After 12 days, the crystals that separate are filtered, washed with CCl_4 (3 × 5 ml), and dried in vacuo. The yield of I is 1.03 g. Another 1.1 g of I are isolated from the mother liquor. The overall yield is 2.13 g of I (81%) of white needlelike crystals, mp 144-145°C. Found, %: C 65.47; H 8.80; N 5.64. $C_{13}H_{21}NO_3$. Calculated, %: C 65.22; H 8.86; N 5.85. M^+ m/z 239. IR spectrum (in CCl_4), ν, cm^{-1}: 1595 (C=C), 1690 and 1720 (C=O). PMR spectrum ($CDCl_3$), δ, ppm: 1.43 (Me), 2.60 (CH_2), 3.63 (MeO), 4.85 (H_α, $^3JH_\alpha H_\beta$ 14.0), 7.73 (H_β).

Methyl Ester of trans-N-β-(2e,5e-Dimethyl-4-oxo-1-piperidyl)-acrylic Acid (II). A solution of 1.66 g (13 mmoles) of 2.5-dimethyl-4-oxopiperidine in 5 ml of Et_2O is added at 20°C to a solution of 1.1 g (13 mmoles) of methyl propiolate in 10 ml of Et_2O. After 12 h, ether is evaporated, and the residue is distilled in vacuo. The yield of II is 1.7 g (80%), viscous liquid, bp 150-151°C (2 mm Hg). Found, %: N 6.72. $C_{11}H_{17}NO_3$. Calculated, %: N 6.63. IR spectrum (molecular layer), ν, cm^{-1}: 1605 (C=C), 1690 and 1715 (C=O). Mass spectrum at 70 eV, m/z (relative intensity in %) M^+ 211 (100), 196 (88.2), 180 (89.1), 168 (22.0), 152 (46.0), 141 (19.1), 140 (63.7), 112 (16.9), 110 (20.6), 82 (57.1). Mass spectrum at 12 eV: M^+ 211 (100), 196 (51.1), 180 (30.1), 168 (10.4), 152 (20.5), 141 (10.1), 140 (10.2), 112 (5.8) 84 (24.6). PMR spectrum ($CDCl_3$), δ, ppm: 1.14 (MeCN, $^3J_{MeCH}$ 7.08), 1.37 [MeCCO, $^3J_{MeCH}$ 6.59, 2.28 and 2.70 CH_2 (AB), $^2J_{H,H}$ 14.89, $^3JH_AHCMeCO$ 5.13 and $^3JH_BHCMe_{CO}$ 7.08, 2.60 ($HCMe_N$) 3.07 and 3.76 CH_2CO (AB), $^2J_{H,H}$ 13.67, $^3JH_AHCMe$ 8.79, 3.81 ($HCMe_{CO}$), 3.68 (MeO), 4.80 ($H_\alpha C=$, $^3J_{H,H}$ 13.18), 7.58 ($H_\beta C=$)].

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TABLE 1. Characteristics of Certain Pharmacological Effects of 4-Piperidone Derivatives

Compound	LD_{50}, mg/kg	Dose, mg/kg	Catalepsy, points	Ptosis, points	Hypothermia, °C	Decrease in the motor activity, %
I	200	50	1,0±0,05	1,5±0,05	1,5±0,2	10±0,8
		100	1,5±0,05	2,5±0,05	2,5±0,4	50±3,5
II	350	50	0,5±0,05	0,7±0,05	0,8±0,2	0
		100	1,0±0,05	0,7±0,05	1,2±0,2	25±2,0
III	300	60	1,0±0,05	0	0	10±0,5
IV	350	70	1,0±0,05	0	1,1±0,07	15±0,8
		100	1,3±0,05	0	2,1±0,4	25±0,9
V	600	100	1,0±0,05	0	0	20±0,4
		200	1,5±0,05	0	3,1±0,5	25±0,8
VI	300	60	1,0±0,05	0	0,7±0,08	30±0,8
Chlorpromazine	150	5	3,0±0,05	3,8±0,05	5,5±0,5	94±0,9
Sulfpyride		100	0	0	0	40±0,8

Diethyl Ester of (2,2,5-Trimethyl-4-oxo-1-piperidyl)maleic Acid (III). A solution of 1.25 g (7 mmoles) of diethyl acetylene-dicarboxylate in 10 ml of n-hexane is added at 20°C to a solution of 1 g (7 mmoles) of 2,2,5-triethyl-4-oxopiperidine in 10 ml of n-hexane. After 2 h, the solvent is removed, and the residue is crystallized from n-pentane. The yield of III is 1.88 g (78%), white crystals, mp 77-88°C. Found, %: C 62.01; H 8.72; N 4.77. $C_{16}H_{25}NO_5$. Calculated, %: C 61.52; H 8.39; N 4.75%. IR spectrum ($CHCl_3$), ν, cm^{-1}: 1572 (C=C), 1684 and 1715 (C=O). PMR spectrum ($CDCl_3$), δ, ppm: 1.42 (MeCH, $^3J_{MeCH}$ 7.08), 1.47 and 1.59 (Me_2C), 1.25 and 1.37 (MeEt, $^3J_{MeCH}$ 7.08), 2.46 and 2.87 [CH_2CO (AB), $^2J_{AB}$ 16.36 and $^{14}J_{HC.CHMe}$ 0.73], 2.38 and 2.77 (CH_2N), $^2J_{H,H}$ 18.07, $^3J_{CH,CH}$ 2.44 and $^3J_{CH,CH}$ 6.1), 4.03 (HCMe), 4.11 (quart, CH_2CH_3) and [4.38 (AB) - 4.37 and 4.39 $^2J_{H,H}$ 9.77%, 4.98 (=CH).

Dimethyl Ester of (2,2,6,6-Tetramethyl-4-oxo-1-piperidyl)-maleic Acid (IV). A solution of 1.45 g (10 mmoles) of dimethyl acetylenedicarboxylate in 5 ml of MeOH is added at 20°C to a solution of 1.6 g (10 mmoles) of 2,2,6,6-tetramethyl-4-oxopiperidine in 5 ml of MeOH. After 44 h, the solvent is removed in vacuo, and the residue is recrystallized from an n-hexane—CCl_4 mixture. The yield of IV is 1.57 g (51.5%), colorless needle-like crystals, mp 65°C. Found, %: C 60.62; H 7.91; N 4.65. $C_{15}H_{23}NO_5$. Calculated, %: C 60.60; H 7.74; N 4.71. M^+ M/z 297. IR spectrum (CCl_4), ν, cm^{-1}): 1600 (C=C), 1720 and 1740 (C=O). PMR spectrum ($CDCl_3$), δ, ppm: 1.33 (Me), 2.21 (CH_2), 3.67 and 3.80 (MeO), 5.67 (=CH).

Methyl Ester of trans-N-β-Morpholinoacrylic Acid (V). A solution of 1.51 g (17 mmoles) of morpholine in 10 ml of Et_2O is added at −10°C to a solution of 1.4 g (17 mmoles) of methyl propiolate in 20 ml of Et_2O. After 5 h, the crystals that separate are filtered, washed with n-pentane, and dried in vacuo. The yield of V is 2.35 g (81%), white flake-like crystals, mp 73-74°C (cf. [1]). Found, %: 56.46; H 7.63; N 8.46. $C_8H_{13}NO_3$. Calculated, %: C 56.14; H 7.60; N 8.19. IR spectrum (CCl_4), ν, cm^{-1} 1630 (C=C), 1710 (C=O). PMR spectrum $CDCl_3$), δ, ppm: 3.11 (H_2CNCH_2), 3.62 (H_2COCH_2), 3.52 (MeO), 4.52 (H_α, $^{13}J_{H\alpha H\beta}$ 13.5) 7.17 (H_β).

Methyl Ester of N-β- (2e,5e-Dimethyl-4-oxo-1-piperidyl)propionic Acid (VI). A mixture 1.5 g (12 mmoles) of 2,5-dimethyl-4-oxo-piperidine and 1.1 g (13 mmoles) of methyl acrylate is allowed to stand for 7 days at 20°C, and then is heated for 30 min at 100°C. The excess of methyl acrylate is evaporated, and the residue distilled in vacuo. The yield of VI is 2.2 g (87%) in the form of a viscous colorless liquid, bp 114-115°C (3 mm Hg). n_D^{20} 1.4720. Found, %: N 6.54, $C_{11}H_{19}NO_3$. Calculated, %: 6.57. IR spectrum ($CHCl_3$), ν, cm^{-1}: 1702 and 1720 (C=O). Mass spectrum at 70 eV m/z (relative intensity in %; M^+ 213 (19.1), 198 (97.1), 170 (4.2), 142 (71.2), 140 (100), 98 (20.2), 70 (29.5), 56 (25.5), 42 (39.7). Mass spectrum at 12 eV: M^+ 213 (28.5), 198 (100), 142 (10.1), 140 (31.3). PMR spectrum ($CDCl_3$) δ, ppm: 0.99 (MeCN, $^3J_{MeCH}$ 6.59), 1.18 (MeCCO, $^3J_{MeCH}$ 6.35), 2.22 [CH_2N_{CYCL}(AB), $^2J_{H,H}$ = $^3J_{HACMeCO}$ = 11.47 and $^3J_{HBHCMeCO}$ 6.35], 2.68 ($HCMe_N$), 2.53 and 3.16 [CH_2CO_{CYCL} (AB), $^2J_{H,H}$ 13.43, $^3J_{HB}$ HCMe 7.08 and $^3J_{HA}$HCMe 6.5], 2.89 ($HCMe_{CO}$), 2.84 and 3.13 [CH_2CO_{chain} (AB), $^2J_{H,H}$ 13.3, $^3J_{HA}CH_2$ 8.30 and 6.35 and $^3J_{HB}CH_2$ 6.35 and 4.15], 3.70 (MeO). Hydrochloride of VI, bright white lamellar crystals, mp 174-175°C. Found, %: C 52.73; H 8.40; N 5.87. $C_{11}H_{20}NO_3Cl$. Calculated, %: C 52.90; H 8.02; N 5.61.

TABLE 2. Effects of Interaction of Compound I-VI with Apomorphine and Hexenal

Compound	Dose, mg/kg	Effects of apomorphine, change in % with respect to control			Effects of hexenal, change in sleep duration in %
		stereotypy		hypothermia	
		duration	degree of expression		
I	50	—23	—50	—180 (blockade)	+130
	100	Total	Total	Total	+180
	150	blockade	blockade	blockade	+190
II	50	—28	—50	—50	+60
	100	—30	—50	—50	+70
III	60	—10	—50	—70	+150
IV	70	—20	—50	—90	+180
V	100	—20	—70	—30	0
VI	60	0	—25	—30	+40
Sulfpyride	5	Total blockade			+230
Blockade	100	Total blockade			+40

EXPERIMENTAL PHARMACOLOGICAL PART

A set of tests that has been developed at the psychopharmacology laboratory of the Scientific-Research Institute of Biological Testing of Chemical Compounds [2], was used for the experimental selection of psychotropic and antipasmodic preparations, including the determination of acute toxicity, evaluation of the influence of the behavior of animals, orientational motor activity, body temperature, vegetative symptoms, and effects of interaction with hexenal, apomorphine, phenamine, L-DOPA, reserpine, arecoline, and nicotine.

The experiments were carried out on male mice, each weighing 18-22 g. The preparations were administered intraperitoneally; the behavior of the animals was observed continuously, 4 h from the moment of the administration and on the following days. In the interaction tests, the administration was carried out 40 and 5 min before the test preparation. A comparison was made with a typical neuroleptic, chlorpromazine (aminazine) and an atypical neuroleptic, sulfpyride (Eglonil).

It was found that the compounds studied have moderate toxicity (Table 1). A two-phase effect is characteristic for all of them: in the first minutes after administration, a short term excitation is observed, with stereotypical movements and jumps, and this is followed by a prolonged period of restrainment with a cataleptic type disturbance of the muscle tonus, in the degree of expression of which the compounds studied are inferior to chlorpromazine. Even the most active of these compounds (I) causes catalepsy, which can be evaluated at only 1.5 points, despite the use of a high dose of 50 and 100 mg/kg. When chlorpromazine is introduced in a dose of 5 mg/kg, pronounced catalepsy is observed (4 points). Sulfpyride does not lead to catalepsy in doses of 100 and 200 mg/kg. The most active compounds also cause ptosis, hypothermia and weaken or completely block apomorphine-induced stereotypy and hypothermia, and intensify the effects of hexenal (Table 2). Anti-apomorphine activity is displayed only when apomorphine is introduced simultaneously or 5-10 min after the introduction of the compounds. When apomorphine was introduced after 30-40 min, the blocking action of the tested preparation was not observed. This indicates a relative short duration of the dopamine-blocking action. Chlorpromazine and sulfpyride lead to a total and stable blockade of the apomorphine effects. The ability of the tested compounds to cause at the beginning a stimulation with the stereotypy elements may indicate a dopamine-stimulating action in the first minute after administration.

Thus, the compounds studied are inferior to chlorpromazine and sulfpyride in the intensity of major pharmacological activities.

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