SYNTHESIS AND ANALGESIC AND PSYCHTROPIC PROPERTIES OF PIPERIDINE AND DECAHYDROQUINOLINE DERIVATIVES.

III. 1-(3-PHENYLPROPARGYL)-4-PHENYL-4-PROPIONYLOXYPIPERIDINE AND ITS DERIVATIVES

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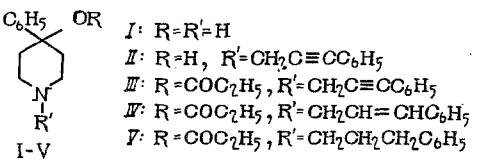
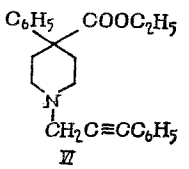
The introduction of pethidine [1] and prodine [2] into medical practice has led to the appearance of a large number of investigations into the synthesis and pharmacological activity of their analogs. A particularly large amount of work has been devoted to studying the dependence of analgesic activity on structure, particularly on the presence of various radicals in the 1 position of the piperidine ring. It has been shown to be possible to obtain preparations with a very broad range of analgesic action [3, 4]. Among the compounds of this type, the desmethyl analog of prodine containing a phenylpropargyl group attached to the nitrogen, which has not been prepared hitherto, is of potential interest.

In the present article, we will describe the synthesis of this acetylene-containing compound, its reactions, and its pharmacological properties.





The conversion of 4-phenyl-4-piperidol (I) [5] into 1-(3-phenylpropargyl)-4-phenyl-4-piperidol (II) is easily effected in the presence of paraformaldehyde and phenylacetylene (under Mannich reaction conditions). When heated with a mixture of propionic anhydride and propionic acid, II is esterified almost quantitatively to form the required 1-(3-phenylpropargyl)-4-phenyl-4-propionyloxypiperidine (III). The IR spectrum of the piperidol (II) has bands characteristic of the hydroxyl (3440 cm^{-1}) and acetylene (1960 cm^{-1}) groups, but no absorption band characteristic of the secondary amino group. In the IR absorption spectrum of III, the hydroxyl band disappears and an intense ester-carbonyl band appears (1740 cm^{-1}).

Partial hydrogenation of the triple bond in the hydrochloride of propionate III in the presence of palladium and its total saturation with hydrogen in the presence of Raney nickel give more than 90% yields of the known analgesics 1-cinnamyl-4-phenyl-4-propionyloxypiperidine (IV) and 1-(3-phenylpropyl)-4-phenyl-4-propionyloxypiperidine (V), respectively, which have been synthesized by other methods [6].

The purity of all the compounds was monitored by means of thin-layer chromatography on alumina.

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EXPERIMENTAL

Pharmacology

We determined the acute 24-hour toxicity of compounds III-V and investigated their analgesic activity in comparison with promedol and fentanyl. Their analgesic activity was assessed on the basis of their ability to increase the sensitivity threshold to mechanically stimulated pain in rats [7] and thermally and electrically stimulated pain in mice [8]. The compounds were administered intraperitoneally and subcutaneously. We calculated the mean effective dose (ED_{50}), the therapeutic index, and the duration of maximum analgesic action at doses close to the ED_{50} [9].

As can be seen from Table 1, compounds IV and V are more toxic than promedol but less toxic than fentanyl. For mice, compound III having a phenylpropargyl radical attached to the nitrogen is 2.5 times less toxic than promedol.

Compounds III-V possess pronounced analgesic properties. Thus, the minimum active dose in the case of electrically stimulated pain is 5.5, 0.32 and 0.23 mg/kg, respectively, which is 1/60, and 1/300 of the corresponding LD_{50} values. Promedol under these conditions increases the pain threshold only at a dose of 10 mg/kg (1/14 LD_{50}). Compound III has a similar analgesic activity and therapeutic index to promedol in the case of mechanical stimulation, but is considerably superior in the case of thermal stimulation (see Table 1).

In connection with this, it is interesting to note that 1-(3-phenylpropargyl)-4-phenyl-4-ethoxycarbonylpiperidine (VI), which is an isomer of propionate III with a "reversed" ester group (a pethidine derivative), has no analgesic activity at all [10].

In the case of mechanical and thermal stimulation, compounds IV and V are almost 10-30 times more active than promedol. These compounds are also significantly superior to promedol in their therapeutic index, while the therapeutic index of V approaches that of fentanyl (see Table 1).

As regards the duration of their analgesic effect, the test compounds are not significantly different from promedol, and only compound V is somewhat superior to fentanyl (thermal stimulation).

Thus, the compound synthesized by us (III) is less toxic than promedol, is superior to the latter in its analgesic activity in the case of electric and thermal stimulation, and approaches the analgesic activity of promedol in the case of mechanical stimulation. Saturation of the acetylenic bond in the radical attached to nitrogen, i.e. its conversion into an ethylenic (IV) or aliphatic (V) bond, leads to a sharp increase in analgesic activity, but the toxicity of IV and V increases simultaneously.

EXPERIMENTAL

Chemistry

1-(3-Phenylpropargyl)-4-phenyl-4-hydroxypiperidine (II). A mixture of 4 g I [5], 2.31 g phenylacetylene, 1.04 g paraformaldehyde and 0.23 g cuprous chloride in 650 ml of dry dioxane was heated on a boiling-water bath for 4 h. The cooled solution was filtered, evaporated down to 100 ml *in vacuo*, diluted with 100 ml of cold water, and the reaction product repeatedly extracted with ether and dried with potash. The solvent was removed to give 6.46 g (98.3%) of II as colorless crystals, mp 102-103° (from ether), R_f 0.61. Found, %: C 83.01, 82.62; H 7.18, 7.30; N 4.82, 4.50. $C_{20}H_{21}NO$. Calculated, %: C 82.43; H 7.26; N 4.80. The hydrochloride was obtained in the form of fine colorless crystals, mp 189-190° (from acetone). Found, %: C 73.24, 73.60; H 6.75, 6.98; N 4.50, 4.82; Cl 10.54, 10.86. $C_{20}H_{21}NO \cdot HCl$. Calculated, %: C 73.27; H 6.76; N 4.27; Cl 10.81.

Hydrochloride of 1-(3-Phenylpropargyl)-4-phenyl-4-propionyloxypiperidine (III). A mixture of 5.2 g II, 31.2 ml propionic anhydride and 10.4 ml propionic acid was heated at 85-90° for 10 h. The excess reagents were removed *in vacuo*, the residue dissolved in a mixture of 50 ml water and 30 ml ether, and the solution adjusted to pH 8.0 with 5% aqueous soda solution while cooling. The acylation product was taken up in ether and dried with anhydrous magnesium sulfate. After removing the solvent, the oily residue was dissolved in 150 ml of dry ether and made weakly acidic with an ether solution of hydrogen chloride at 0°.

TABLE 1. Analgesic Activity of N-Substituted 4-Phenyl-4-propionyloxypiperidine Derivatives

Compound	Administration route	ED_{50}, mg/kg (rat)	Mechanical stimulation			LD_{50}, mg/kg (mouse)	Thermal stimulation		
			ED_{50}, mg/kg	therapeutic index (LD_{50}/ED_{50})	duration of maximum action, min		ED_{50}, mg/kg	therapeutic index (LD_{50}/ED_{50})	duration of maximum action, min
III	Intraperitoneal	38,0 (21,1–68,4)	2,0 (,14–2,9)	19	18,7±3,7	330 (275–396)	6,4 (4,6–7,2)	52	42,0±7,3
	Subcutaneous	50,0 (14,7–170,0)	1,8 (1,2–2,6)	28	25,0±5,0	—	5,6 (4,0–7,7)	—	26,0±11,3
IV	Intraperitoneal	5,3 (3,5–7,9)	0,13 (0,08–0,19)	41	37,5±22,4	97,0 (77–151)	0,56 (0,40–0,78)	173	37,5±7,5
	Subcutaneous	3,1 (1,6–5,9)	0,06 (0,05–0,08)	52	30,0±15,0	—	0,31 (0,25–0,39)	—	27,5±2,6
V	Intraperitoneal	3,9 (3,1–5,0)	0,14 (0,11–0,18)	28	37,5±22,3	70,0 (54,5–93,8)	0,53 (0,45–0,63)	132	70,0±10,0
	Subcutaneous	6,1 (3,1–12,0)	0,05 (0,04–0,06)	120	30,0±15,0	—	0,28 (0,20–0,39)	—	66,0±21,6*
Promedol	Intraperitoneal	25,0 (13,0–44,5)	1,3 (0,9–1,8)	19	27,0±10,0	137 (123–152)	15,5 (11,6–20,6)	8,8	50,0±10,0
	Subcutaneous	38,0 (25,0–57,0)	0,9 (0,6–1,2)	42	39,9±9,0	200 (159–252)	—	—	38,6±7,0
Fentanyl	Intraperitoneal	—	0,07 (0,05–0,09)	—	39,0±6,0	76,0† (69,0–89,0)	0,38 (0,32–0,45)	200	55,0±21,9
	Subcutaneous	0,7 (0,51–1,2)	0,006 (0,004–0,01)	117	20,0±10,0	—	0,076 (0,045–0,13)	—	19,3±2,8

*Significant difference compared with fentanyl.
†Literature data [11].

The crystals were filtered off and recrystallized from a mixture of acetone and ether to give 6.55 g (94.93%) of the hydrochloride of propionate III in the form of a colorless powder, mp 132-133°, R_f 0.47. Found, %: C 71.86, 71.98; H 7.06, 6.92; N 3.74, 3.79; Cl 9.17, 9.03. $C_{23}H_{25}NO_2 \cdot HCl$. Calculated, %: C 71.96; H 6.83; N 3.65; Cl 9.23.

Hydrochloride of 1-Cinnamyl-4-phenyl-4-propionyloxypiperidine (IV). A solution of 2 g of the hydrochloride of III in 80 ml of anhydrous alcohol was added to 0.2 g of hydrogen-saturated palladium (5%) on calcium carbonate in 50 ml alcohol. The mixture was shaken under normal conditions until 1 mole of hydrogen was absorbed (20 min, 140 ml). The catalyst was filtered off, washed with hot alcohol, and the mother liquors evaporated. The residue was crystallized from a mixture of ethanol and ether to give 1.9 g (94.6%) of the hydrochloride of unsaturated ester IV, mp 168-169°, R_f 0.52. Found, %: C 71.44, 71.74; H 7.60, 7.80; N 3.45, 3.58; Cl 9.45, 9.28. $C_{23}H_{27}NO_2 \cdot HCl$. Calculated, %: C 71.58; H 7.31; N 3.63; Cl 9.19.

Hydrochloride of 1-(3-Phenylpropyl)-4-phenyl-4-propionyloxypiperidine (V). A mixture of 2 g III, 1 g Raney nickel and 200 ml absolute ethanol was shaken until 2 moles of hydrogen was absorbed (5 h, 280 ml). The product was worked up as above to give 1.83 g (90.1%) of the hydrochloride of V, mp 165.5-166° (from ethanol/ether), R_f 0.56. The mixed melting point of the hydrochlorides of V and IV was 160-163°. Found, %: C 71.25, 71.50; H 7.85, 7.88; N 3.66, 3.77; Cl 9.16, 9.33. $C_{23}H_{29}NO_2 \cdot HCl$. Calculated, %: C 71.20, H 7.80; N 3.61; Cl 9.14.

The compounds were subjected to thin-layer chromatography on alumina (activity III) using a 2:1 mixture of ether and petroleum ether as eluents; the spots were visualized with iodine vapor.

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