54. E. I. Levkoeva, E. S. Nikitskaya, I. M. Sharapov, et al., Khim.-Farm. Zh., No. 9, 16 (1971).
55. E. I. Levkoeva and L. N. Yakhontov, Khim. Geterotsikl. Soedin., 927 (1976).
56. E. S. Nikitskaya, I. M. Sharapov, M. D. Mashkovskii, et al., Khim.-Farm. Zh., No. 8, 59 (1974).
57. E. E. Mikhlina, V. Ya. Vorob'eva, N. A. Komarova, et al., Khim.-Farm. Zh., No. 11, 56 (1976).
58. E. E. Mikhlina, V. Ya. Vorob'eva, T. K. Trubitsyna, et al., Khim.-Farm. Zh., No. 12, 23 (1973).
59. V. A. Bondarenko, K. A. Zaitseva, E. E. Mikhlina, et al., Khim.-Farm. Zh., No. 11, 56 (1978).
60. M. E. Kaminka, E. E. Mikhlina, V. Ya. Vorob'eva, et al., Khim.-Farm. Zh., No. 6, 48 (1976).
61. M. D. Mashkovskii, E. S. Mutina, and M. E. Kaminka, Klin. Med., No. 11, 22 (1978).
62. M. E. Kaminka, N. P. Voitsekhovskaya, and M. D. Mashkovskii, Khim.-Farm. Zh., No. 7, 32 (1979).
63. E. E. Mikhlina, A. D. Yanina, V. Ya. Vorob'eva, et al., Khim. Geterotsikl. Soedin., 935 (1976).
64. M. D. Krasnokutskaya, A. S. Morkovnik, B. A. Tertov, et al., Khim. Geterotsikl. Soedin., 1527 (1977).
65. L. I. Mastafanova, L. F. Linberg, T. Ya. Filipenko, et al., Khim. Geterotsikl. Soedin., 368 (1978).
66. M. E. Kaminka, Farmakol. Toksikol., 40, 158 (1977).
67. M. E. Kaminka, V. Ya. Vorob'eva, E. A. Golovanova, et al., in: Pharmacokinetics and Metabolism of Medicinal Preparations [in Russian], Moscow (1978), p. 109.
68. L. P. Firsova, A. V. Krasnyanskii, S. M. Svetlikin, et al., Zh. Org. Khim., 12, 2249 (1976).
69. A. V. Krasnyanskii, N. Yu. Kremlyakova, S. M. Svetlikin, et al., Radiokhimiya, No. 1, 35 (1978).
70. M. E. Kaminka, E. E. Mikhlina, V. Ya. Vorob'eva, et al., Khim.-Farm. Zh. No. 9, 22 (1976).
71. M. E. Kaminka, E. E. Mikhlina, V. Ya. Vorob'eva, et al., Khim.-Farm. Zh., No. 2, 24 (1977).

SYNTHESIS OF PIPERIDINE AND DECAHYDROQUINOLINE DERIVATIVES, THEIR ANALGESIC AND PSYCHOTROPIC PROPERTIES

IX. 1-(4'-n-BUTOXYBUTYN-2'-YL)-4-PHENYL-4-PROPIONYLOXYPIPERIDINE AND ITS HYDROGENATION PRODUCTS

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The aim of our synthetic investigations is to search for esters of different mono- and bicyclic 4-hydroxypiperidines with an analgesic activity. In one of the earlier articles [1] of the present series, we described the synthesis and pharmacological properties of propionic acid esters of 4-phenyl-4-hydroxypiperidines with γ-phenylpropargyl, cinnamyl, and γ-phenylpropyl residues as the N-substituent. These esters included analgesics with an activity of one order of magnitude or more greater than that of promedol.

In the present work, we describe the synthesis and pharmacological properties of unknown propionic acid esters with butoxybutynyl and butoxybutenyl residues at the nitrogen atom of the piperidine ring.

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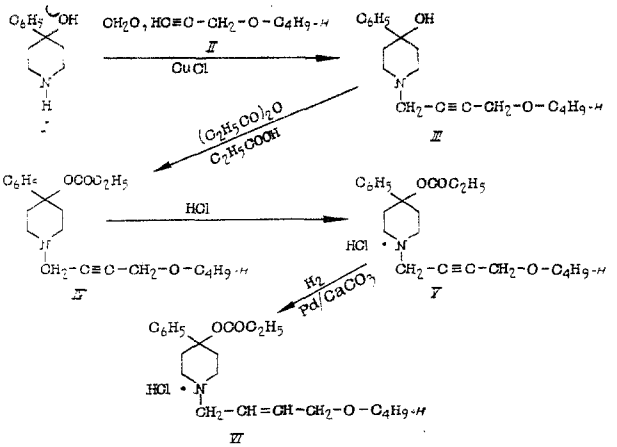
TABLE 1. LD_{50}, ED_{50} Values, Scope and Duration of Analgesic Action of the Synthesized Compounds

Compound	Mode of administration	Thermal stimulation of pain (mice)					Mechanical stimulation of pain (rats)				
		LD_{50}, mg/kg	ED_{50}, mg/kg	scope of pharmacological action (LD_{50}/ED_{50})	dose, mg/kg	duration of analgesic action, min	LD_{50}, mg/kg	ED_{50}, mg/kg	scope of pharmacological action (LD_{50}/ED_{50})	dose, mg/kg	duration of analgesic action, min
V	Intraperitoneally	350	34,0* (25,0—46,2)	10	50.0	27.0±9.0	—	—	—	—	—
	Subcutaneously	—	—	—	—	—	—	15,5* (17.4—20 4)	—	15,0	25,0±5,0
VI	Subcutaneously	200	0,90* (0,41—1.99)	220	1,0	22,5±4,3	50	0,20* (0,11—0.38)	250	0,2	26,2±7.2
Promedol	Intraperitoneally	137	9,80 (6,4—14.9)	14	—	—	—	—	—	—	—
	Subcutaneously	200	3,2 (2,6—3,8)	63	3.3	40.0±10,0	38	0.55 (0,45—0,67)	69	0.7	39,0±5.8

Note. Asterisk designates a statistically reliable difference with respect to promedol.

1-(4'-n-Butoxybutyn-2'-yl)-4-phenyl-4-hydroxypiperidine (III) is obtained in a high yield by the reaction of 4-phenyl-4-hydroxypiperidine (I) [2] with paraform and n-butyl propargyl ether (II) [3] in the presence of a catalytic amount of freshly prepared cuprous chloride, at 80-100°C, in anhydrous dioxane. When heated with propionic anhydride in the



presence of propionic acid, compound III produces a 92% yield of 1-(4'-n-butoxybutyn-2'-yl)-4-phenyl-4-propionyloxypiperidine (IV), characterized as a crystalline hydrochloride (V). The hydrochloride of propionate VI was obtained in a 93% yield by selective hydrogenation of the triple bond of the butoxybutynyl substituent at the nitrogen atom of compound V in the presence of palladium catalyst on calcium carbonate.

The identity and structure of compounds III-VI were confirmed by thin-layer chromatography, elemental analysis, and the data of IR spectroscopy [see experimental section (chemical)].

EXPERIMENTAL (PHARMACOLOGICAL)

The acute daily toxicity of the synthesized compounds V, VI was studied in experiments on white mice and rats, and the analgesic activity was studied in comparison with promedol for different types of pain stimulation: electric [4], thermal [5] on mice, and mechanical on rats [6]. The compounds were administered intraperitoneally and subcutaneously. We calculated the ED_{50}, the scope of the pharmacological action, and also the duration of the maximal analgesic action of doses close to ED_{50} [7].

The results of our studies showed that compound V with the acetylenic bond is less toxic than promedol, while VI has a toxicity nearly similar to that of promedol (Table 1).

Compounds V and VI have a pronounced analgesic activity for all three types of pain stimulation. During electric stimulation, compound V is inferior in activity to promedol, while VI exceeds it. Thus, if the minimal active dose of promedol for this type of pain stimulation is equal to 10 mg/kg, the analgesic action of V is manifested in a dose of 70 mg/kg, while compound VI considerably increases the pain sensitivity threshold, even in a dose of 2.5 mg/kg. Table 1 shows the ED_{50} values (which represent the doses leading to a twofold increase in the pain sensitivity threshold in 50% of the animals) of compounds V and VI for thermal and mechanical stimulation of pain. Table 1 shows that compound V is considerably inferior in activity to promedol, while VI has a 3-3.5-fold higher activity than promedol with respect to both the absolute values of the active doses and the scope of the pharmacological action.

In the duration of action, compounds V and VI in doses close to ED_{50} do not differ appreciably from promedol. The data obtained indicate that compounds V and VI, the new N-analogs of desmethylprodine synthesized, have a strong analgesic action.

A comparison of the structure with the activity of the derivatives of 4-phenyl-4-propionyloxypiperidine V, VI studied shows that the toxicity, the analgesic effect and scope of the pharmacological action increase on saturation of the triple bond of the butoxybutynyl substituent of compound V. We had already observed a similar regularity [1] in the study of 1-γ-phenylpropargyl-4-phenyl-4-propionyloxypiperidine and the products of its total and partial hydrogenation.

EXPERIMENTAL (CHEMICAL)

The IR spectra were recorded on a double-beam UR-20 spectrometer (DDR) in KBr. The thin layer chromatography of the compounds was carried out on aluminum oxide, grade III activity, with elution by a 50:1 mixture of ether and ethanol, and development of spots by iodine vapors.

The starting compounds I and II were prepared by known methods [2, 3].

1-(4'-n-Butoxybutyn-2'-yl)-4-phenyl-4-hydroxypiperidine (III). A mixture of 5.4 g (0.03 mole) of I, 4.03 g (0.03 mole) of 3-n-butoxy-1-propyne (II), 1.35 g of paraform, and 0.4 g of freshly prepared cuprous chloride in 100 ml of dry dioxane is heated at 100°C for 4 h, and cooled. The precipitate is filtered, and the filtrate is evaporated *in vacuo* to a volume of ∿50 ml, diluted with cold water, and extracted with diethyl ether (3 times with 75 ml). The combined ethereal extracts are dried over potassium carbonate and filtered to yield, after removal of ether, 7.5 g (82.4%) of III in the form of colorless crystals, mp 82-83.5°C (from ether), R_f 0.77. IR spectrum: 3420 cm^{-1} (OH group), 2265 cm^{-1} (triple bond) and 1100 cm^{-1} (stretching vibrations of C—O—C grouping); absorption band of secondary amino group is absent. Found, %: N 4.58, 4.76. $C_9H_{27}NO_2$. Calculated, %: N 4.65. Hydrochloride — fine colorless crystals, mp 98-99°C (from acetone). Found, %: N 3.96, 4.15. $C_{19}H_{28}ClNO_1$. Calculated, %: N 4.14.

1-(4'-n-Butoxybutyn-2'-yl)-4-phenyl-4-propionyloxypiperidine (IV) and Hydrochloride (V). A mixture of 1.51 g (0.005 mole) of III, 8.34 ml (0.07 mole) of propionic anhydride and 3 ml (0.04 mole) of propionic acid is heated for 3.5 h at 95°C. After evaporation *in vacuo*, 20 ml of water and 20 ml of ether are added to the residue, and the mixture is neutralized in the cold with 5% aqueous sodium bicarbonate to pH 8.0. The acylation products are extracted by ether and dried over anhydrous magnesium sulfate. After removal of solvent, the oily residue consisting of base IV is dissolved in ether, and with cooling to 0°C, an ethereal solution of hydrogen chloride is added to an acid reaction. The crystals which precipitate are filtered to yield 1.8 g (92.3%) of V in the form of a powder, mp 152-153°C (from absolute ethanol), R_f 0.87. In the IR spectrum, the absorption band characteristic of the hydroxyl group is absent, and intense narrow band (1743 cm^{-2}) characteristic of the ester carbonyl appears. Found, %: C 66.99, 66.83; H 8.19, 8.24; N 3.44, 3.65; Cl 9.35, 9.48. $C_{22}H_{32}ClNO_3$. Calculated, %: C 67.07; H 8.19; N 3.56; Cl 9.00.

1-(4'-n-Butoxybuten-2'-yl)-4-phenyl-4-propionyloxypiperidine Hydrochloride (VI). A 1.7 g portion of salt V in absolute ethanol is introduced to a long-necked hydrogenation flask, in which 0.15 g of palladium catalyst deposited on calcium carbonate (5% of active metal) in 100 ml of absolute ethanol was first saturated with hydrogen, and the hydrogenation is carried out at 21°C at atmospheric pressure with vigorous shaking. After absorption of the calculated amount of hydrogen (117 ml during 7 min), the hydrogenation is discontinued, and the catalyst is filtered and washed twice with hot ethanol. The alcoholic solution is evaporated to yield 1.6 g (93.4%) of VI, mp 136-137°C (from a mixture of ethanol and ether), R_f 0.79. In the IR spectrum, the intense absorption band characteristic of the ester carbonyl (1743 cm^{-1}) is retained, while the absorption band characteristic of the acetylenic bond disappears. Found, %: C 66.61, 66.64; H 8.92, 8.94; N 4.00, 4.09; Cl 9.16, 8.87. $C_{22}H_{34}ClNO_3$. Calculated, %: C 66.73; H 8.66; N 3.54; Cl 8.95.

LITERATURE CITED

1. V. M. Kurilenko, Zh. N. Khlienko, L. M. Moiseeva, et al., Khim.-Farm. Zh., No. 9, 60-64 (1976).
2. G. J. Schmidle and R. C. Mansfield, J. Am. Chem. Soc., 78, 1702-1705 (1956).
3. R. S. Vartanyan, Zh. V. Kazaryan, and V. F. Kucherov, Arm. Khim. Zh., 27, No. 4, 295-303 (1974).
4. R. A. Turner, Screening Methods in Pharmacology, New York (1965), pp. 104-106; 117.
5. N. B. Eddy and D. Zeimbach, J. Pharmacol. Exp. Ther., 107, 385-393 (1953).
6. A. K. Sangailo, N. D. Den'china, and N. P. Gorbacheva, Farmakol. Toksikol., No. 3, 10-12 (1958).
7. M. L. Belen'kii, Elements of Quantitative Estimation of Pharmacological Effect [in Russian], 2nd edn., Leningrad (1963).