ANALOGS OF DESMETHYLPRODINE SYNTHESIZED FROM 1-(4-PHENOXYBUTINE-2-YL)-4-PHENYL-OXYPIPERIDINE

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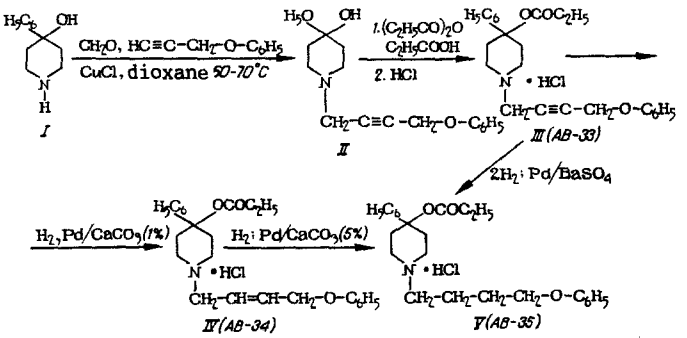
The N-analogs of desmethylprodine with a butoxybutinyl and butoxybutenyl [1, 4] radical on the nitrogen atom exhibit pronounced analgesic activity that is markedly enhanced in proportion to the saturation of the radical's acetylene bond.

As a continuation of our search for analgesic substances in the series and for the purpose of clarifying structure-action relationships, we describe in this work the synthesis of compounds (III-V) containing a phenoxy group (instead of a butoxy group as in earlier compounds [1, 4]) and we examine their pharmacological properties.

4-Phenyl-4-oxypiperidine (I) [2, 5] condenses with paraformaldehyde and 3-phenoxypropine-1 in dioxane in the presence of cuprous chloride.



The resultant 1-(4-phenoxybutine-2yl)-4-oxypiperidine (II) is esterfied by propionic anhydride in the presence of propionic acid to 1-(4-phenoxybutine-2-yl)-4-phenyl-4-propionyloxypiperidine which is converted to the hydrochloride salt (III). Upon partial hydrogenation of the latter in ethanol on a palladium catalyst placed on calcium carbonate (containing 1% of the active metal) the salt III is converted to 1-(4-phenoxybutene-2-yl)-4-phenyl-4-propionyloxypiperidine HCl (IV) at a 86.8% yield of the theoretical. Complete hydrogenation of the amino-ester hydrochloride (III) in ethanol at room temperature on a palladium catalyst applied on barium sulfate (containing 6% of the active metal) results in the formation of 1-(4-phenoxybutyl(-4-phenyl-4-propionyloxypiperidine hydrochloride (V) at a yield of 84.2% [3]. The latter is also obtained by hydrogenation of the double bond of compound IV on a palladium catalyst applied on calcium carbonate (containing 5% of the active metal), in ethanol at a yield of 88.1%

The individuality and structure of the synthesized compounds II-V were confirmed by TLC on aluminum oxide, element analysis, and IR-spectroscopy.

The molecular ions in the mass spectra of the hydrochloride compounds (II-IV) correspond to the mol. wt. of the bases (II, mol. wt. =321; III, mol. wt. = 377; IV, and mol. wt. = 379).

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TABLE 1. Analgesic Activity of 4-Phenyl-4-propionyloxypiperidine Derivatives III-V as Tested by Electropain Stimulation of Mice

Compound	LD_{50}, mg/kg (ip)	Dose, mg/kg (ip)	Initial pain sensitivity threshold, mA	Change in pain sensitivity threshold, mA			
				after 15 min	after 30 min	after 60 min	after 120 min
III(AB-33)	800	160	2,3	+1,7±0,25*	+1,0±0,08*	+0,57±0,17	+0,7±0,17
IV(AB—34)	200	10	2,7	>5*	>5*	+1,45±0,31*	+0,85±0,37
		5	2,4	+1,56+0,33*	+1,32±0,43	+0,74±0,41	+0,3±0,16
V(AB—35)	100	5	2,5	>5*	>5*	+1,81±0,34*	+0,52±0,28
		2,5	2,5	+2,1±0,37*	+1,0±0,46	+0,47+0,43	+0,25+0,42
Promedol	138	7	2,6	+4,3±0,50*	+2,19±0,63*	+1,19±0,63	+0,38±0,29
		3,5	2,05	+2,6±0,27*	+1,23±0,11*	+0,9±0,18*	+0,63±0,06
Control	—	—	2,6	—0,07±0,07	+0,18±0,15	0	+0,27±0,19

*Difference statistically reliable in comparison to the control.

EXPERIMENTAL (CHEMICAL)

IR-spectra were recorded on a UR-20 double beam spectrometer (GDR) in KBr pellets (bases) or KCl (hydrochlorides). TLC with second degree Al_2O_3 activity was employed for the tested compounds with spot development by iodine vapors. The eluent was ethyl ether/petroleum ether, 5:1. Mass spectra were recorded on a MX-1320 mass spectrometer at an accelerated voltage of 2500 W and ionization voltage of 70 W. Element analysis data satisfied the calculated values.

1-(4-Phenoxybutine-2-yl)-4-phenyl-4-oxypiperidine (II). A 5.32 g (0.03 mole) portion of 4-phenyl-4-oxypiperidine I in 100 ml of dioxane together with 3.96 g (0.04 mole) of 3-phenoxypropine-1 in 100 ml of dioxane, 1.35 g (0.045 mole) of paraformaldehyde in 100 ml of dioxane, and 0.45 g of freshly prepared CuCl was place into a three-necked flask fitted with a mechanical stirrer, reflux condenser, and thermometer. The reaction mixture was heated with stirring for 24 h at 65°C. The catalyst was filtered off, washed with dioxane, and the filtrate was vacuum-evaporated to a volume of 50 ml to which 75 ml of water was added. The solution was extracted with ethyl ether and the extract was dried with potash. The drier was filtered off, the ether was distilled off, and the soiled residue was recrystallized from abs. ether. The yield of 5.3 g (55% of the theoretical) of compound II, mp 91-92°C (from ether). R_f 0.7 (eluent – ethyl ether/petroleum ether, 5:1). $C_{21}H_{23}NO_2$.

IR-spectrum: ν_{max}, cm^{-1}: 1130 and 1180 (C—O—C); 3270 (O—H). Hydrochloride II, mp 108-109°C (from a 1:2 mixture of ethanol and ethyl ether). $C_{21}H_{23}NO_2 \cdot HCl$. IR-spectrum, ν_{max}, cm^{-1}: 1134, 1210 (C—O—C), 3420 (O—H).

1-(4-Phenoxybutine-2-yl)-4-phenyl-4-propionyloxpiperidine Hydrochloride (III). A 5 g (0.015 mole) portion of II, 28 ml (0.215 mole) of pripionic anhydride, and 9.2 ml (0.124 mole) of propionic acid was placed into a round-bottom flask fitted with a reflux condenser with a calcium chloride tube and a mechanical stirrer. The mixture was stirred for 19 h at 100°C. TLC was used to control the reaction. The excess of reagents was vacuum-distilled and the residue was dissolved in 30 ml of water and neutralized with a 5% aq. solution of sodium bicarbonate. The weak alkaline solution was extracted with ethyl ether and the ether extract was dried with magnesium sulfate. The drier was separated, the ether was distilled-off, and the oily residue was dissolved in 100 ml of ether to which an ether solution of HCl was added until a weak acid reaction was obtained. The resultant hydrochloride precipitate was recrystallized from ethyl acetate with an addition of abs. alcohol. Yield was 5.5 g (85.30% of the theoretical, mp 172-173°C, R_f 0.52. $C_{24}H_{27}NO_3 \cdot HCl$. IR-spectrum, ν_{max}, cm^{-1}: 1185 (C—O—C), 1740 (C=O).

1-(4-Phenoxybutene-2-yl)-4-phenyl-4-propionyloxypiperidine HCl (IV). A 0.2 g portion of $Pd/CaCO_3$ (1% active metal) in 50 ml of abs. ethanol was placed in a long-necked hydrogenation flask. By passing 1 liter of hydrogen through the system the catalyst became saturated with hydrogen within 1 h. Then a 0.85 g (0.0021 mole) portion of II in 100 ml of ethanol in a hydrogen stream was placed into the flask. Hydrogenation was interrupted 4 h after absorption of the calculated quantity (0.0021 mole) of hydrogen (53 ml). The catalyst was filtered off, carefully washed with hot ethanol, and the filtrate was evaporated. Crystallization of the residue from a 1:1 mixture of ethyl acetate and ethanol resulted in a yield of 0.75 g (87.8% of the theoretical) of compound IV, mp 165-166°C, R_f 0.65 (eluent – ethyl ether/petroleum ether, 5:1). IR-spectrum, ν_{max}, cm^{-1}: 1180, 1200 (C—O—C), 1730 (C=O).

TABLE 2. Analgesic Activity of Compounds IV and V in Comparison to Promedol during Heat and Mechanical Stimulation

Compound	LD_{50}, mg/kg (subcutaneously)		Heat stimulation (mice)			Mechanical stimulation (rats)		
	mice	rats	ED_{50}, mg/kg (subcutaneously)		range of pharmacological activity (LD_{50}/ED_{50})	ED_{50}, mg/kg (subcutaneously)		LD_{50}/ED_{50}
			"sufficient analgesia"	"complete analgesia"		"sufficient analgestia"	"complete analgesia"	
IV(AB—34)	1000	68,0 (46,0—101,0)	1,2 (0,6—2,3)	5,2 (3,1—8,6)	192,3	0,9 (0,6—1,4)	2,5* (1,7—3,6)	27,2
V(AB—35)	287,0 (168,0—487,9)	24,5 (12,6—47,8)	0,3* (0,18—0,5)	1,35* (1,60—1,7)	212,6	0,23 (0,13—0,41)	0,27* (0,16—0,47)	90,7
Promedol	200,0 (159,0—292,0)	48,0 (35,3—65,3)	3,2 (2,6—3,8)	5,9 (5,0—7,0)	33,9	0,55 (0,45—0,67)	0,88 (0,69—1,2)	54,5

*Difference reliable in comparison to promedol.

1-(4-Phenoxybutyl)-4-phenyl-4-propionyloxypiperidine HCl (V). A. A 0.4 g portion of $Pd/BaSO_4$ in 50 ml of abs. ethanol was placed into a long-necked flask for hydrogenation. The catalyst was activated by 1 liter of hydrogen for a period of 5 h. Then a 2.2 g (0.005 mole) portion of III in 200 ml of abs. alcohol in a hydrogen stream was placed into the flask. After washing the flask with 0.5 liter of hydrogen, the mixture was hydrogenated until the absorption of the calculated quantity (280 ml) of hydrogen over a period of 2.5 h. The catalyst was filtered off and washed with ethanol. The ethanol solution was evaporated to dryness and the solid residue was crystallized from ethyl acetate to yield 1.87 g (84.2% of the theoretical) of compound V, mp 153-154°C, R_f 0.8. $C_{24}H_{31}NO_3 \cdot HCl$. IR-spectrum, ν_{max}, cm^{-1}: 1190 (C—O—C), 1740 (C=O).

B. Compound V was also synthesized by the hydrogenation of 0.41 g (0.001 mole) of IV on $Pd/CaCO_3$ (5% active metal) upon the absorption of the calculated quantity (0.001 mole) of hydrogen (27 ml) under similar conditions for a period of 30 min. After the hydrogenation product was crystallized from ethyl acetate the yield was 0.37 g (88.1% of the theoretical), mp 153-154°C. A tested mix of the synthesized product with the earlier obtained product (experiment A) did not depress the melting point.

EXPERIMENTAL (PHARMACOLOGICAL)

The acute toxicity and neurotropic activity (psychotropic, anticonvulsant, analgesic activity) of the synthesized compounds III-V was examined. The measurement of acute daily toxicity showed that the LD_{50} for compounds III-V when injected subcutaneously was >1000, 1000 and 287 mg/kg respectively, and 800, 200, and 100 mg/kg when administered ip. The LD_{50} for compound IV was 68 mg/kg when administered subcutaneously to rats, and 24 mg/kg for compound V.

Our examination of neurotropic activity demonstrated that the compounds under study exhibit a CNS depressant action upon ip administration. Thus, when administered at doses that were $^1/_5$ of the LD_{50}, all of the compounds lowered body temperature of the mice by 2-3°C. Compounds III and V impeded the animals' ability to hold on the rotating piston and doubled their chloral hydrate-induced sleep time. Compounds III and IV exhibit anticonvulsant activity in the maximum electric shock test.

Our investigation of the analgesic activity of compounds III, IV, and V in ip administration and electric pain stimulation tests on mice showed that all of the examined compounds exhibit analgesic activity (Table 1). There was no significant difference between the analgesic activity of compounds IV and V and that of promedol. Thus, analgesic effect of compounds IV and V as well as promedol is manifested when the dose is lowered to $^1/_{40}$ of the LD_{50}. Compound III increases the pain sensitivity threshold at a dose $^1/_5$ of the LD_{50}.

An expanded study was undertaken of the indicated preparations' analgesic activity in thermal stimulation tests on mice [7] and in mechanical stimulation experiments on rats [6]. These tests showed that compound III has only very slight analgesic properties. Only during mechanical stimulation did it raise the pain sensitivity threshold at a dose equal to $^1/_5$ of the LD_{50}. Compounds IV and V exhibited pronounced analgesic activity. These compounds were analyzed for their ED_{50} of analgesic activity with respect to "sufficient" analgesia (doubling the pain sensitivity threshold) and "complete analgesia" (the absence of any response to a near-injurious strong painful stimulation) (Table 2). Compound IV did not differ from

promedol in the heat stimulation test, but was weaker than promedol only in the "complete" analgesia test. Compound V was 10.7 and 4.4 times more active than promedol in the "sufficient" analgesia and "complete" analgesia heat stimulation tests respectively, and was 2.4 and 3.5 times more active in those tests respectively, in the mechanical stimulation study. Compound V significantly exceeds promedol in the range of pharmacological activity. It does so by 6.3 times in heat stimulation and by 1.7 times in the mechanical stimulation tests. Compound IV was weaker than promedol in the mechanical stimulation test.

Thus, our experiment demonstrates that compounds IV and V exhibit pronounced analgesic activity. Furthermore, compound V significantly exceeds the activity of promedol. Moreover, the analgesic activity of compounds III-V with a phenoxy group is directly proportional to the degree of the radical's acetylene bond on the nitrogen of the piperidine ring, and even exceeds the activity of the desmethylprodine analogs that have a butoxy group in the nitrogen radical [1, 4].

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ANTIHEPARIN ACTIVITY OF POLYCATIONS BASED ON 1-VINYLAZOLES

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In this report we present the results of examination of antiheparin activity and acute toxicity of poly-1-vinylbenzimidazole hydrochloride (I) and methiodide (II) and of poly-1-vinylimidazole hydrochloride (III) and methiodide (IV).

The starting compounds poly-1-vinylbenzimidazole and poly-1-vinylimidazole were obtained by polymerization of 1-vinlybenzimidazole (VBI) and 1-vinlyimidazole (VI), respectively, under conditions of free radical initiation on exposure to azobisisobutyronitrile (ABI) in bulk or in solvents (Table 1). Varying the conditions of monomer polymerization allows us to obtain polymer products with different molecular weights (M_w). Carrying out polymerization in a chain transfer medium (CCl_4) results in a significant decrease of polymer mol. wt.

Spectral investigations of the polymers showed that polymerization proceeds via vinyl group multiple bonds and does not affect the azole ring. Vinly group proton signals are absent in the PMR spectra: 7.05, 5.44 and 4.96 ppm for the polymer of VI and 6.96, 5.32 and 4.83 ppm for the polymer of VBI. However, signals for protons of the imidazole and benzimidazole rings are present, having chemical shifts in the region of 7-8 ppm. Signals for hydrocarbon protons of the polymer chain are poorly resolved in the PMR spectra and appear in the form of a broad peak in the region of 2.1-2.4 ppm. Data from IR spectroscopy also indicate the preservation of side substituent structures: the polymer spectra maintain absorption bands for vibtation of C=C and C=N bonds of the imidazole ring at 1493, 1510, 3010, and 3100 cm^{-1} and 745 and 3000 cm^{-1} for C—H bonds of the benzene ring.

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