The LD_{50} for white mice on intraperitoneal administration (in mg/kg) was 712.5 for (IX), 850 for (XIIa), and greater than 1000 for the rest of the compounds.

Among the studied compounds the most marked GABA-ergic component of the action (in the model of spasm using TCS) was displayed by compounds (XIXa, c) which contain urea or thiourea in the molecule. Other compounds were less active, (XIIa, b) and (XVIII), or did not possess activity in relation to convulsions caused by TCS, (VII), (IX), (XVI), and (XIXb).

The results of the experiments conducted indicate the expediency of further search for antihypoxic, potentially nootropic and neurotropic substances in the series of pyrrolid-2-one derivatives.

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

XVI. NEW N-ANALOGS OF DESMETHYLPRODINE

K. D. Praliev, N. A. Belikova,
V. M. Kurilenko, Zh. N. Khlienko,
L. M. Moiseeva, and D. V. Sokolov

UDC 615.211+615.214/:547.823].012.1

We have shown earlier [1, 4] that some N-substituted analogs of desmethylprodine possess high analgesic activity. In the present work, as part of a search for effective substitutes for morphine, new derivatives of 4-phenyl-4-propionyloxypiperidine were synthesized from 4-phenylpiperidine-4-ol (I) [10], and their pharmacological activity was studied.

Aminomethylation of the corresponding alkyne (II, β, VI) with piperidine and $(CH_2O)_n$ in the presence of a catalytic amount of freshly-prepared Cu_2Cl_2 in dioxane under individually selected conditions gave the corresponding N-substituted 4-phenylpiperidin-4-ols III and VII in high yield.

Alkylation of I in acetone with propargyl bromide (IX) in the presence of anhydrous potassium carbonate at 70°C gave 1-propargyl-4-phenylpiperidin-4-ol (X). Interaction of the latter with bromophenylacetylene (XI) [3] under Khodkevich–Kado reaction conditions [6] formed the diacetylenic alcohol (XII) in 76.2% yield.

The piperidinols III, VII, and XII were heated with $(EtCO)_2O$ in EtCOOH to give esterification to the corresponding mono- and diesters which were obtained in the form of the crystalline, water-soluble hydrochlorides (IV, VIII, XIII). Selective hydrogenation of the triple bond in diester IV in the presence of Pd on $CaCO_3$ gave the dihydrochloride V.

The purity and structure of the synthesized compounds were established by TLC, elemental analysis, and IR spectra data (cf. Table 1).

Institute of Chemical Science, Academy of Sciences of the Kazakh SSR, Alma-Ata. Novokuznetsk Pharmaceutical Chemistry Research Institute.

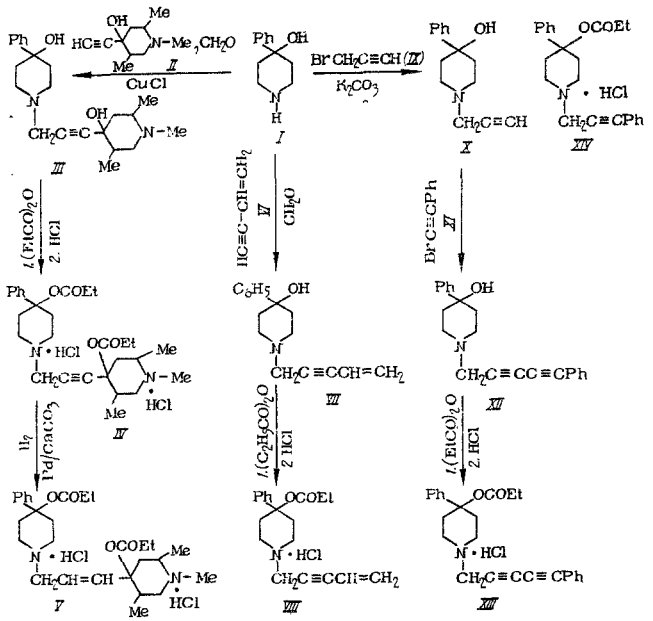
Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 18, No. 10, pp. 1203-1208, October, 1984. Original article submitted February 6, 1984.

0091-150X/84/1810- 0697$08.50

TABLE 1. Properties of 1-R-4-Phenylpiperidin-4-ols and Their Esters

Compound	Yield, %	mp, °C	R_f	Found, %				Empirical formula	Calculated, %				IR spectrum, ν_{max}, cm^{-1}
				C	H	Cl	N		C	H	Cl	N	
III	85,4	135—6,5	0,80	74,06	9,19	—	7,70	$C_{22}H_{32}N_2O_2$	74,12	9,05	—	7,86	3310 (OH)
IV	73,3	188—9	0,62	62,43	7,82	13,33	5,38	$C_{28}H_{40}N_2O_4 \cdot 2$ HCl	62,10	7,82	13,12	5,17	1743 (C=O)
V	72,5	215—6	0,55	61,40	8,23	...	5,55	$C_{28}H_{42}N_2O_4 \cdot 2$ HCl	61,86	8,16	13,08	5,15	1742 (C=O)
VII	91,8	90—1,5	0,35	79,62	8,14	—	6,07	$C_{16}H_{19}NO$	79,63	7,94	—	5,80	3200 (OH) 1610 (C=C)
VIII	70,0	166—7	0,74	68,37	7,42	10,72	4,19	$C_{19}H_{23}NO_2 \cdot HCl$	68,36	7,25	10,62	4,19	1740 (C=O) 1610 (C=C)
X	65,0	113—4	0,56	78,13	7,97	—	6,17	$C_{14}H_{17}NO$	78,10	7,95	—	6,50	3250 (≡C) 2220 (C≡C)
XII	76,2	118,5—9	0,40	84,16	6,34	—	4,59	$C_{22}H_{21}NO$	83,77	6,71	—	4,44	2260 (C≡C) 3440 (OH)
XIII	84,1	198—9	0,61	73,78	6,61	8,87	2,93	$C_{25}H_{25}NO \cdot HCl$	73,61	6,42	8,69	3,43	1736 (C=O) 2260 (C≡C)

Note. Recrystallization solvents were: acetone for III, VII, and X; alcohol for V and VIII; ethanol-ether for IV and XIII; and ether for XII. Eluents were: ether-ethanol (3:1) for III-V; ether for VII and VIII; and ether-petroleum ether (3:2) for X-XIII.



EXPERIMENTAL CHEMISTRY

IR spectra were recorded on a UR-20 (GDR) instrument in pellets of KBr (for bases) or KCl (for hydrochlorides). The compounds were chromatographed on a thin layer of Al_2O_3, activity grade III, with visualization by I_2 vapor.

1-[3'-(1,2,5-Trimethyl-4-hydroxypiperidyl-4)propyn-2'-yl]-4-phenylpiperidin-4-ol (III). A mixture of 1.06 g (6 mmoles) of I, 1.04 g (6 mmoles) of the β-isomer of 1,2,5-trimethyl-4-ethynylpiperidin-4-ol (II) [2], 0.3 g (10 mmoles) of $(CH_2O)_n$ and 0.7 g of freshly-prepared Cu_2Cl_2 in 200 ml of dry dioxane was heated at 90-97°C for 2.5 h. The precipitate was filtered off, washed with dioxane, and the filtrate was concentrated to 50 ml. The residue was diluted with 100 ml of water and extracted many times with ether. The combined ether extracts were dried with potassium carbonate, filtered, and concentrated to give III. The hydrochloride was colorless crystals, mp 227-228°C (from ethanol). Found, %: C 61.53; H 8.19; Cl 16.81; N 6.36. $C_{22}H_{32}N_2O_2HCl$. Calculated, %: C 61.53; H 7.98; Cl 16.51; N. 6.52.

Dihydrochloride of 1-[3'-(1,2,5-Trimethyl-4-proionyloxypiperidyl-4)propyn-2'-yl]-phenyl-4-propionyloxypiperidine (IV). A mixture of 1 g (3 mmoles) of III, 10 ml (84 mmoles) of $(EtCO)_2O$ in 3.6 ml (48 mmoles) of EtCOOH was heated at 80-95°C for 16.5 h. The reaction mixture was concentrated under aspiriator vacuum, 15 ml of water was added to the residue and the pH was adjusted to 8.0 by addition of 5% aqueous sodium bicarbonate. The acylation product was extracted with ether, dried and concentrated to give the free base of IV as an oily residue, which was dissolved in ether and treated with ethereal hydrogen chloride to form the hydrochloride IV.

Dihydrochloride of 1-[3'-(1,2,5-Trimethyl-4-propionyloxypiperidyl-4)propen-2'-yl]-4-phenyl-4-propionyloxypiperidine (V). To a hydrogenation flask containing 150 ml of absolute ethanol and 0.4 g of Pd on $CaCO_3$ (1% active metal) saturated with hydrogen was added a solution of 2 g of IV in 20 ml of absolute ethanol and the hydrogenation was carried out at 21°C and atmospheric pressure with vigorous shaking. After consumption of the calculated amount of hydrogen (98 ml), the hydrogenation was interrupted, the catalyst was filtered off, and V was isolated from the filtrate.

1-(Pentyn-2'-en-4'-yl)-4-phenylpiperidin-4-ol (VII). A 100-ml steel flask containing 3.6 g (20 mmoles) of I and 0.89 g (30 mmoles) of $(CH_2O)_n$ in 50 ml of dry dioxane was cooled to −15°C, and a suspension of 0.2 g of freshly prepared Cu_2Cl_2 and 1.14 g (22 moles) of vinylacetylene (VI) in 40 ml of dry dioxane was added. The flask was sealed and heated at 110-115°C for 14.5 h, cooled, and the catalyst was filtered off and washed with ether. The filtrate was concentrated under aspirator vacuum to a volume of ~40 ml, and the residue was diluted with 40 ml of water, extracted with ether, dried with potassium carbonate, filtered and concentrated to give VII.

TABLE 2. Toxicity and Pharmacological Activity of the Subject Compounds

Compound	LD_{50} for mice, mg/kg	Dose, mg/kg	Prolongation of chloralhydrate narcosis, min		Analgesic activity				
			control	test	electrical pain stimulation (mice) (change of pain threshold sensitivity, sec)	thermal stimulation (mice)		mechanical stimulation (rats)	
						change in pain threshold sensitivity, sec	ED_{50}, mg/kg	change in pain threshold sensitivity (mm Hg)	ED_{50}, mg/kg
IV	350	70	80,5±12,2	153±13,9*	+0,49±0,27	+3,8±1,02	...	...	...
V	260	52	80,0±10,4	72,0±6,7	+0,09±0,5	+3,3±4,4	...	+57,3±10,5*	...
		26	...	...	...	...	...	+5,5±2,4	...
VIII	180	36	...	...	+0,65±0,11*	+21,2±3,3*	...	...	...
		18	65,3±12,9	175,3±26,9*	+0,40±0,07*	+5,5±1,7*	43,0	+82,7±10,7*	12,0
		9	...	...	...	+2,9±0,9	(33,8±54,6)	+62,3±12,3*	(8,8±16,3)
		4	...	...	...	...	...	+13,0±3,0*	...
XIII	>1000	200	103,7±6,8	155,3±30,7	+0,47±0,08*	+8,1±1,7	...	...	...
Promedol	137	20	...	...	...	>30*	...	...	...
		10	...	...	...	+13,3±4,4*	15,5	...	1,3
		3,5	...	...	+2,6±0,27*	...	(11,6±20,6)	...	(0,94±1,8)
		2	...	...	...	...	...	+84,0±10,8*	...
		1	...	...	...	...	...	52,2±3,93*	...

*Statistically significant difference from the control.

Hydrochloride of 1-(Pentyn-2'-en-4'-yl)-4-phenyl-4-propionyloxypiperidine (VIII). A mixture of 2 g (8.2 mmoles) of VII, 5 ml (66 mmoles) of EtCOOH and 14.9 ml (115 mmoles) of freshly distilled $(EtCO)_2O$ was heated at 60-70°C for 7 h. The reaction mixture was worked up as described above for IV to give VIII.

1-(Propyn-2'-yl)-4-phenylpiperidin-4-ol (X). To a mixture of 10.64 g (60 mmoles) of I, 16.6 g (120 mmoles) of anhydrous potassium carbonate and 300 ml of dry acetone was stirred vigorously while adding dropwise over 40 min a solution of 7.9 g (66 moles) of 3-bromopropyne-1 (IX) in 60 ml of dry acetone. The reaction mixture was heated for 11 h at 60-70°C, cooled, filtered, and the solid was washed with acetone. Concentration of the filtrate gave X.

1-(5'-Phenylpentadiyn-2',4'-yl)-4-phenylpiperidin-4-ol (XII). To a methanolic solution of 2.15 g (10 mmoles) of X, 0.2 g Cu_2Cl_2, a small amount of $H_2NOH \cdot HCl$ and 3.2 ml of n-butylamine under argon was added dropwise with stirring 1.82 g (10 mmoles) of XI in 16 ml of MeOH over 30 min. The mixture was stirred for 3.5 h while cooling in an ice bath, diluted with water, and the condensation product was extracted with ether and dried with $MgSO_4$. The product XII was isolated by crystallization.

Hydrochloride of 1-(5'-Phenylpentadiyn-2',4'-yl)-4-phenyl-4-propionyloxypiperidine (XIII). A mixture of 1.58 g (50 mmoles) of XII, 3 ml (40 mmoles) of EtCOOH and 9 ml (70 mmoles) of $(EtCO)_2O$ was heated for 27 h at 80-90°C. The usual workup (v.s.) gave the oily free base, which was converted with ethereal HCl to XIII.

EXPERIMENTAL PHARMACOLOGY

The toxicity and neurotropic properties of IV, V, VIII, and XIII were studied in experiments on white mice. The studies included their influence on body temperature, movement coordinaton on a rotating rod, orientation reactions, and prolongation of chloralhydrate-induced narcosis. Antagonism to reserpine was determined according to the ability of the substance to diminish the reserpine ptosis. Antispasmodic activity was evaluated by Corazole (pentylene tetrazole) titration tests, and maximal electroshock. The analgesic effect of the compounds was indicated by the increase of the pain threshold sensitivity to electrical [7], thermal [8], and mechanical [5] stimulation. The latter tests were carried out on rats. The studies were compared with promedol as standard. For the active compounds, the ED_{50} for the analgesic effect was calculated [9], taking into account for each dose the number of animals in the group not reacting to the supramaximal pain sensitivity.

It was shown that the desmethylprodine derivatives IV, V, VIII, and XIII have different toxicities (cf. Table 2). The lowest toxicity was shown by the diacetylenic derivative (LD_{50} > 1000 mg/kg). These compounds did not show an influence on the CNS, except for prolongation of chloralhydrate narcosis (compounds IV and VIII).

Analgesic activity under all three forms of pain sensitivity was shown by VIII. However, with approximately equal toxicity to promedol, its analgesic activity is significantly lower, particularly under thermal and mechanical stimulation. The dipiperidino- (IV and V) and diacetylenic (XIII) derivatives are practically devoid of analgesic properties: Only V and XIII at a dose comprising one-fifth of the LD_{50} increases the pain threshold sensitivity under mechanical or electrical stimulation. Decreasing the dose leads to the disappearance of these effects (cf. Table 2).

Thus, these studies show that the diacetylenic compound XIII is three times less toxic (LD_{50} > 1000 mg/kg) than the monoacetylenic XIV (LD_{50} = 330 mg/kg) [1]. The analgesic activity of XIII is significantly less than promedol and XIV. Consequently, the introduction into the molecule of XIV of still another triple bond in the radical attached to nitrogen leads to a sharp decrease of the analgesic activity (at significantly decreased toxicity). Replacing the phenyl ring in XIV by a promedol fragment (compound IV) strongly decreases the analgesic activity.

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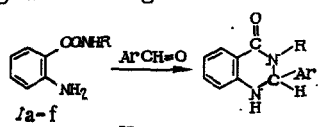
SYNTHESIS AND BIOLOGICAL ACTIVITY OF NEW DERIVATIVES OF 1,2,3,4-TETRAHYDROQUINAZOLIN-4-ONE

O. E. Sattarova, Yu. V. Kozhevnikov, V. S. Zalesov, and S. N. Nikulina

UDC 615.2:547.856

In the development of work in [1] and in a search for biologically active compounds, we prepared new derivatives of 1,2,3,4-tetrahydroquinazolin-4-one, substituted at the 2- and 3-positions of the quinazolone ring according to the following scheme:



Ia-f IIa-e, IIIa-e, IVa-f; Va-d, VIb

For I — VI: R = C_6H_5 (a), 2-$CH_3C_6H_4$ (b), 4-BrC_6H_4 (c), 4-$CH_3OC_6H_4$ (d), 2-pyridyl (e), 5-Br-2-pyridyl (f); Ar = 4-HOC_6H_4 (IIa-c), 3-CH_3O-4-HOC_6H_3 (IIIa-e), 3,4-$(CH_3O)_2C_6H_3$ (IVa-f), $CH{=}CHC_6H_5$ (Va-d), 2-HOC_6H_4 (VIb).

In the reaction of N-aryl anthranilamides (Ia-f) [3] with p-hydrobenzaldehyde, salicylaldehyde, veratraldehyde, cinnamaldehyde, and vanillin, 2,3-disubstituted 1,2,3,4-tetrahydroquinazolin-4-ones (II-VI) were obtained. In the acylation of Vd by acetic anhydride, the corresponding N-acetyl derivative (VIId) was obtained.

Compounds II-VI (Table 1) are crystalline compounds, slightly basic in character, which are insoluble in water, but soluble in ethanol, acetone, and dioxane. The composition and structure of the compounds were confirmed by UV, IR spectra, and the data of elemental analysis. It is known [1] that 3-(4'-bromophenyl)-1,2,3,4-tetrahydroquinazolin-4-one is characterized by two absorption maxima for alcoholic solutions: λ, nm (log ε): 228 (4.65) and 282 (3.92). The introduction of electron-donating substituents into the 2-position of the ring (compound IIIe) is accompanied by a bathochromic shift of the absorption maxima, while substitution of bromine by a methoxyl group at the 3-position of the phenyl radical does not influence UV absorption. In the IR spectra there are quinazolone bands in the 1630-1650, 1600-1610, and 1490-1530 cm^{-1} regions [4], and an intense absorption band in the 1680-1690 cm^{-1} region due to the Ar—C=O group. For compounds IIa-c, IIIa-e, IVa-f, and Va-d, there is a characteristic band in the 3300-3320 cm^{-1} region due to stretching vibrations of the NH group.

EXPERIMENTAL CHEMISTRY

The IR spectra were recorded on the UR-20 apparatus (GDR) in the form of a suspension in mineral oil, UV spectra on the SF-16 spectrophotometer for $1 \cdot 10^{-5}$ M solutions, solvent — 96% ethanol.

2-(4-Hydroxyphenyl)-3-phenyl-1,2,3,4-tetrahydroquinazolin-4-one (IIa). A 0.61-g portion (5 mmoles) of p-hydroxybenzaldehyde in 5 ml of 96% ethanol is added to 1.06 g (5 mmoles) of Ia in 15 ml of 96% ethanol; the mixture is heated on a water bath for 1 h, and cooled. The white precipitate is filtered, dried, and crystallized. Compounds IIb-c, IIIa-e, Va-d, and VIb are

Perm Pharmaceutical Institute. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 18, No. 10, pp. 1208-1210, October, 1984. Original article submitted November 14, 1983.

 0091-150X/84/1810-0702$08.50