The predicted accumulation of ^{14}C-I and its metabolites in the internal medium of the body and the GI tract occurred in agreement with [2, 6]. The computed data obtained from analyzing the results of a single administration demonstrate that the daily fluctuations of radioactive material in the GI tract are higher than in the body's internal medium and are equal to 1.19-0.4 Q and 0.46-0.25 Q respectively.

The data here presented indicate that the ^{14}C-preparation is rapidly eliminated and that there is no accumulation of ^{14}C-I and its metabolites in the experimental animals.

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SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF 2- AND 6-SUBSTITUTED (PYRIDE-3-ILOXY)ACETIC ACID DERIVATIVES

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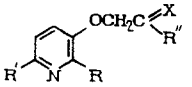
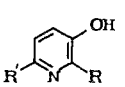
Acephen (meclofenoxate), a representative of the aryloxyacetic acid class [5, 9], along with piracetam and its analogs (derivatives of 2-oxopyrrolidinylacetic acid) is classified as a nootropic agent.

Compounds that activate the cognitive activity of animals have been identified in the O-substituted 3-oxypyridine series [7]. The most active of those compounds is 3-phenoxypyridine (CI-844). In that connection, we felt it would be of interest to look for psychotropic agents among the O-derivatives of 3-oxypyridine that are structurally related to meclofenoxate.

With this purpose in mind we synthesized esters, amides, and amidoximes of 2- and 6-substituted pyride-3-iloxyacetic acids (Ia-r).



Ia-r



IIa-c

R=Et(a), tert -Bu(b) Me(c)

R' = Me(a,c), H(b)

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TABLE 1. Derivatives of 1- and 6-Substituted Pyride-3-iloxyacetic Acids

Compound	R	R′	R″	X	Yield,% (method)	mp, °C (solvent), or bp, °C/mm	Empirical formula
Ia	Et	Me	OEt	O	87,0 (A)	129—30/4 159—60/12	$C_{12}H_{17}NO_3$
Ib	Tert-Bu	H	OEt	O	89,0 (A)	130—1/4	$C_{13}H_{13}NO_3$
Ic·$2C_2H_2O_4$	Et	Me	$O(CH_2)_2NMe_2$	O	55,0 (B)	131 (decomp., abs. ethanol)	$C_{14}H_{22}N_2O_3 \cdot 2C_2H_2O_4$
Id·2HCl	Et	Me	$O(CH_2)_3NMe_2$	O	61,8	168—70	$C_{15}H_{24}N_2O_3 \cdot 2HCl$
Ie·$2C_2H_2O_4$	Et	Me	$O(CH_2)_2NEt_2$	O	31,0 (B)	119—20 (abs. ethanol)	$C_{16}H_{26}N_2O_3 \cdot 2C_2H_2O_4$
If·$C_2H_2O_4$	Tert-Bu	H	$O(CH_2)_2NMe_2$	O	54,0 (B)	176 (decomp. abs., ethanol)	$C_{15}H_{24}N_2O_3 \cdot C_2H_2O_4$
Ig·$2C_2H_2O_4$	Et	Me	$NH(CH_2)_2NMe_2$	O	64,0 (C)	151—2 (ethanol)	$C_{14}H_{23}N_3O_2 \cdot 2C_2H_2O_4$
Ih·2HCl	Et	Me	$NH(CH_2)_2NEt_2$	O	73,0	164—8 (*i*-PrOH (acetone)	$C_{16}H_{27}N_3O_2 \cdot 2HCl$
Ii·$2C_2H_2O_4$	Et	Me	$NH(CH_2)_3NMe_2$	O	41,3 (C)	109 (decomp., abs. ethanol)	
Ij·HCl	Et	Me	OH	O	76,0	239 (decomp., abs. ethanol - abs. ether)	$C_{10}H_{13}NO_3 \cdot HCl$
Ik·$C_2H_2O_4$	Et	Me	NEt_2	O	60,0 (D)	110 (Decomp. ethanol)	$C_{14}H_{22}N_2O_2 \cdot C_2H_2O_4 \cdot H_2O$
Il	Et	Me	$NH(CH_2)_2OH$	O	42,0 (D)	119—20 (*i*-PrOH)	$C_{12}H_{18}ClN_2O_3$
Im	Et	Me	$NH(CH_2)_2Cl$	O	23,4	70—1 (Decomp. eth.	$C_{12}H_{17}ClN_2O_2$
In·$2C_2H_2O_4$	Et	Me	2-piperidino-ethylamine	O	82,3	143—4 (petrol. ether)	$C_{17}H_{27}N_3O_2 \cdot 2C_2H_2O_4$
Io	Et	Me	NH_2	O	81,0	125—6 (benzene)	$C_{10}H_{14}N_2O_2$
Ip	Et	Me	NH_2	NOH	57,4 (E)	138—40 *i*-PrOH	$C_{10}H_{15}N_3O_2$
Iq	Me	Me	NH_2	NOH	56,4 (E)	151—2 *i*-PrOH	$C_9H_{13}N_3O_2$
Ir	Et	Me	NH_2	NOAc	79,3	111—2,5 (benzene—petrol.ether)	$C_{12}H_{17}N_3O_3$

By alkylating 2-R-6-R′-3-oxypyridines (IIa, b) with bromoacetate by the acetone-potash method we obtained the ethyl esters of 2-ethyl-6-methyl- and 2-tert-butyl-pyride-3-iloxyacetic acids (Ia, b) which were reesterified or amidated and converted to (Ic-i) respectively.

We know that alkylation of 3-oxypyridines, dependent upon the reaction conditions and presence of substituents in the pyridine ring, proceeds either in the hydroxyl group (O-alkylation) [3], or on the nitrogen atom (N-alkylation) which in the latter case results in the formation of betaines [8]. The reaction between 3-oxypyridines (IIa, b) and bromoacetate) results in the formation of the O-alkyl derivatives Ia, b. The structure of the latter compounds was primarily confirmed by UV-spectroscopic data. The UV-spectrum of compound Ia, recorded in ethanol, exhibits 2 absorption maxima: λ_{max} 220 nm and λ_{max} 283 nm (for 3-methoxypyridine λ_{max} 216 nm and λ_{max} 276 nm, and λ_{max} 249 nm and λ_{max} 320 nm for N-methyl-3-oxypyridine [10]). In a similar fashion the alkylation of oxypyridines IIa and IIc by chloroacetonitrile results in the formation of the corresponding nitriles which, when reacted with $H_2NOH \cdot HCl$ in the presence of EtONa, are converted into the ammidoximes Ip, q. The acetylation of Ia by acetic anhydride in dioxane yielded the acetate Ir. Saponification of Ia followed by treatment with HCl (acid) resulted in the formation of 2-ethyl-6-methyl-pyride-3-dioxyacetic chlorohydrate Ij from which the amides Ik, 1 were obtained through the chloroanhydride of the acid. The reaction between ethanolamide I1 and $SOCl_2$ in benzene results in β-chloroethylamide Im, which when reacted with piperidine, is converted to β-piperidinoethylamide In. The amide 2-ethyl-6-methylpyride-3-iloxyacetic acid Io was synthesized by reacting a methanol ammonia solution with the Ia ester.

The structure of the target products was confirmed by UV-, IR-, and PMR-spectra as well by element analysis.

EXPERIMENTAL (CHEMICAL)

The UV-spectra were recorded on a Perkin–Elmer-402 spectrometer (USA). IR-spectra were recorded on Specord 75 IR (GDR) and Perkin–Elmer-457 (USA) spectrometers. PMR-spectra were recorded on WP 80 SV (Bruker, FRG) and Varian T-60 (USA) instruments. Mass-spectra were recorded on a Varian MAT-112 (USA) chromatomassspectrometer and a direct sample input in an ion source at 100°C and an ionization voltage of 75 eV. TLC employed Al_2O_3 (alkaline form, IV degree of activity, and eluent was $CHCl_3$ – abs. alcohol, 10:1).

Ethyl 2-ethyl-6-methylpyride-3-iloxyacetate (Ia) (Method A). A 27.4 g (0.2 mole) portion of 2-ethyl-6-methyl-3-oxypyridine (IIa) was dissolved upon boiling in 300 ml of dry acetone to which 30.4 g (0.22 mole) of anhydrous K_2CO_3 was added. The mixture was then boiled for 2 h with stirring, cooled to room temperature after which 33 ml (0.3 mole) of bromoacetate was

TABLE 2. Pharmacological Activity of 2- and 6-Substituted Pyride-3-Iloxy Acetic Acid Derivatives

Compound	Dose, mg/kg	Antiamenestic effect (time in an illuminated compartment, sec)	Antihypoxic action (life longevity, sec)			Climbing up a screen (effect in %)
			container hypoxia	hemic hypoxia	hypobaric hypoxia	
	5	53,0±12,0	—	—	2,15±0,7	33,3
Ic		(54,6±15,0)			(6,1±5,12)	
	50	80,0±15,0				
	10	—	9,0±7,0			
Id			(23,0±5,2)	—	—	—
	50	104,0±15,5	25,0±12,4			
		(79,0±26,8)	(21,0±3,4)	—	—	16,6
	50	35,0±5,9	—	20,8±1,2	—	
Ie		(35,6±6,6)		(16,6±1,8)		
	200					66,6
If	50	89,2±40,7	25,6±3,8	21,9±4,1*	—	
		(89,2±38,4)	(23,2±3,1)	(16,7±2,7)		16,6
Ig	10	80,3±15,5*				
		(49,8±15,5)				
	50	108,1±24,8*	24,6±4,1	21,2±6,4	—	—
		(49,8±15,5)	(23,2±3,1)	(17,9±5,0)		
Ih	10	49,9±11,5				
		(61,0±9,5)	—	—	—	—
	50	59,1±18,8	22,3±4,5	17,6±3,6	—	—
		(16,0±7,2)	(23,2±3,1)	(17,9±4,9)		
Ii	50	61,1±16,7	—	23,3±1,4	—	—
		(35,6±6,0)		(19,8±2,5)		
	200	—	—	—	—	50
In	50	62,4±14,3	—	—	1,7±0,4	16,6
		(54,6±17,0)			(6,0±5,1)	
Ip	5	81,6±10*	—	—	12,3±4,0	16,6
		(57,2±8,4)			(12,0±4,7)	
	10	68,8±11,2				
		(57,2±8,4)	—	—	—	—
	50	39,6±5,7			11,3±5,1	
		(44,7±8,3)	—	—	(11,0±5,1)	
Ir	5	50±5,3				
		(57,2±8,4)	—	—	—	—
	50	53,6±17,0			1,5±0,3	
		(48,8±18,0)	—	—	(8,12±5,1)	—
Piracetam	300	81,8±20,8*	—	—	—	—
		(43,8±11,8)				
	500	—	29,2±3,5	—	—	0
			(29,5±1,6)			
	1000	—	26,1±4,7*	—	—	0
			(18,2±4,4)			
Meclofe-noxate	50	83,0±7,5*	—	—	—	—
		(41,4±5,5)				
	100	—	—	21,3±2,8	—	—
				(16,8±2,2)		
	200	—	—		11,1±3,4	—
					(6,0±2,7)	

Note. 1. Here and in Table 3: Asterisk denotes reliability of difference from the control at $P \leq 0.05$. 2. Parentheses contain indices for control animals. 3. The number of horizontal and vertical crossovers and number of peeks into apertures (total indices) in the open field condition for compound If 26.5 ± 12.3 (control −43.5 ± 14.8), for compound Ig 42.3 ± 26.8 (control 46.2 ± 24.0). 4. LD_{50} (dose in mg/kg that causes death in 50% of the animals) for compound Ic is 350-114, 350-150 for compound Ie, 370-46 for Ii; 120-57 for Ip.

added dropwise with stirring. The mixture was then boiled for 8 h. The acetone solution was vacuum-evaporated, and the excess bromoacetate was distilled off. The residue was vacuum-distilled to yield 39 g of substance Ia. IR-spectrum (CCl_4), ν_{max} cm^{-1}: 1766, 1741 (CO). UV-spectrum (alcohol), $\lambda_{max}(\log\varepsilon)$:220 nm (2.92), 283 nm (2.72). UV-spectrum (alcohol + 0.1N NaOH), $\lambda_{max}(\log\varepsilon)$:221 nm (3.026), 286 nm (2.80). UV-spectrum (alcohol + 0.1N HCl), $\lambda_{max}(\log\varepsilon)$:223 nm (2.85), 293 nm (2.82).

2-Dimethylaminoethyl 2-ethyl-6-methylpyride-3-iloxyacetic dioxalate (Ic) (Method B.). A 10 ml portion of 2-dimethylaminoethanol and 20 mg of Na were added to 4.47 g (0.02 mole) of ethyl 2-ethyl-6-methylpyride-3-iloxyacetate Ia in 200 ml of dry toluene and boiled for 2 h with a slow distillation of the toluene. Then another 10 ml of amino alcohol and 100 ml of dry toluene was added and the mixture was boiled again for 1.5-2 h with distillation of the toluene. The reaction mixture was vacuum-evaporated, the residue was dissolved in 150 ml of ether and washed with 10 ml of water. The ether solution was dried with K_2CO_3, the ether was evaporated and the residue was dissolved in 15 ml of abs. alcohol after which 2.9 g of oxalic acid was added. The mixture was then brought to a boil and left in a refrigerator for 16 h. The resultant precipitate was filtered off, washed

TABLE 3. Effect of Substances on Animal Behavior in the Conflict Situation Tests

Compound	Dose, mg/kg	Approaches to the drinking bowl	Drinks of water and electric shocks
Control	Physiological solution	2,6±1,2	2,0±0,5
Ic	100	2,6±0,8	5,0±0,8*
Id	100	4,4±4,5	5,2±0,8*
If	100	3,6±1,5	4,8±1,1
Ig	100	3,4±1,5	5,0±1,1
Ih	100	2,6±0,4	2,6±0,4
Diazepam	5	20,8±2,5*	20,5±6,4*

twice with abs. alcohol and abs. ether, and recrystallized from abs. alcohol to yield 5.0 g of dioxalate Ic, R_f 0.69. IR-spectrum (KBr), ν_{max}: 1766 cm^{-1} (CO). PMR spectrum (D_2O), δ, ppm: 1.5 t (3H, CH_3), 2.8 s [3H, CH_3 at C(6)], 3.05 s (6H, $N(CH_3)_2$), 3.1 q (2H, $-C-CH_2-C$), 3.65 t (2H, $N-CH_2-C$), 4.8 t (2H, $-COOCH_2-C$), 5.1 s (2H, OCH_2), 7.65 d (1H, C(5) Py, J = 8 Hz) and 8.05 d (1H, C(4) Py, J = 8 Hz). Mass spectrum (base): $M^{+\cdot}$ 266, 251, 236, 222, 195, 150.

3-Dimethylaminopropyl 2-ethyl-6-methylpyride-3-iloxyacetic dichlorohydrate (Id) A 0.1 g portion of Na followed by the dropwise addition of 22 g (0.2 mole) of 3-dimehtylaminopropanol-1 was added to a solution of 22.4 g (0.1 mole) of ethyl 2-ethyl-6-methylpyride-3-iloxyacetate Ia in 400 ml of toluene over a period of 5 min. The mixture was then boiled for 2 h. The solvent was distilled off after which 400 ml of toluene, 0.1 g of Na and 22 g (0.2 mole) of 3-dimethylpropanol-1 was added, and the mixture was boiled for 2 h. The reaction mass was then vacuum-evaporated and the residue was dissolved in 300 ml of toluene. The mixture was then washed with 100 ml of water, vacuum-evaporated and dissolved in 60 ml of acetone after which an HCl solution (gas) in i-PrOH was added upon cooling to bring the mixture to pH 3.5. The addition of 160 ml of acetone yielded 28.1 g of the dichlorohydrate Id. IR-spectrum (KBr), ν_{max}, cm^{-1}: 2630 and 2465 (R_3NH pyridinium), 2925 and 2865 (alkyl), 1740 (CO), 1625 and 1540 (C=C and C=N), 1280, 1200, 1050 (C–O).

2-Dimethylaminoethylamide-2-ethyl-6-methylpyride-3-iloxyacetic dioxalate (Ig) (Method C). A 4.46 g (0.02 mole) portion of ethyl 2-ethyl-6-methylpyride-3-iloxyacetate Ia and 3.5 g (0.04 mole) of N,N-dimethylethylenediamine in 25 ml of alcohol was boiled for 6 h. The reaction mass was thoroughly vacuum-evaporated with an addition of abs. benzene. The residual oil was dissolved in 10 ml of abs. alcohol to which was added a solution of 3.6 g of anhydrous oxalic acid in 10 ml of abs. alcohol. After 16 h the resultant precipitate was filtered off, washed with abs. alcohol, and recrystallized from alcohol to yield 5.7 g of dioxalate Ig, R_f 0.62. IR-spectrum (KBr), ν_{max}, cm^{-1}:3216 (NH), 1684 (CONH). PMR spectrum (D_2O + CF_3COOH), δ, ppm: 1.6 t (3H, CH_3), 3.0 s [3H, CH_3 at C(6)], 2.96 s (6H, $N(CH_3)_2$, 3.02 q (2H, $C-CH_2-C$), 3.4 t (2H, $N-CH_2-C$), 3.7 t (2H, $CONCH_2$), 4.8 s (2H, OCH_2), 7.5 d (1H, C(5) Py, J = 8 Hz) and 7.8 d (1H, C(4) Py, J = 8 Hz). Mass spectrum (base): $M^{+\cdot}$ 265.

2-Diethylaminoethylamide 2-ethyl-6-methylpyride-3-iloxyacetic dichlorohydrate (Ih). A mixture of 11.2 g (0.05 mole) of the ethyl ester Ia and 9.3 g (0.08 mole) of N,N-diethylethylenediamine in 60 ml of MeOH was boiled for 2 h after which 2.3 g (0.02 mole) of N,N-diethylethylenediamine in 10 ml of MeOH was added. The mixture was boiled for 1 h and the MeOH was vacuum-distilled. The residue was dissolved in 200 ml of toluene, washed with 250 ml of water, and the toluene solution was vacuum-evaporated, then dissolved in 40 ml of acetone after which an HCl solution in i-PrOH was added to bring the pH to 3.5 The mixture was then left overnight to yield 15.9 g of dichlorohydrate Ih. IR-spectrum (KBr), ν_{max}, cm^{-1}:3220 and 3190 (NH), 2960, 2930 and 2870 (alkyl), 2640 and 2480 (P_3NH, pyridinium), 1660 (CO-amide), 1630 and 1540 (C=C and C=N) and 1275 and 1050 (C–O).

2-Ethyl-6-methylpyride-3-iloxyacetic chlorohydrate (Ij). A mixture of 40 g (0.179 mole) of ethyl 2-ethyl-6-methylpyride-3-iloxyacetate, 8 g (0.2 mole) of NaOH, 70 ml of alcohol, and 70 ml of water was boiled for 4 h. The reaction mass was vacuum-concentrated to 0.5 volume and the acidified with HCl (acid) to pH 3.5-4. The resultant precipitate was filtered, washed with anhydrous acetone and ether to yield 31.3 g of chlorohydrate Ij. IR-spectrum (oil), ν_{max}, 1478 cm^{-1} (COOH).

Diethylamide 2-ethyl-6-methylpyride-3-iloxyacetate (Ik). (Method D). A mixture of 2.32 g (0.01 mole) of the chlorohydrate of acid Ij, 1 ml (0.013 mole) of $SOCl_2$ and 5 ml of anhydrous dichloroethane was heated for 3 h at 60-65°C and vacuum-evaporated after which 3.1 ml (0.03 mole) of Et_2NH in 5 ml of dichloroethane was added. After 16 h (20°C) the precipitate was filtered, washed with dichloroethane. The filtrates were evaporated and the residue was dissolved in $CHCl_3$. The solution was washed with a Na_3CO_3 solution and water, then dried over calcined K_2CO_3 and evaporated to yield 1.5 g of the diethylamide Ik which is converted to the oxalate. IR-spectrum (KBr), ν_{max}:1661 cm^{-1} (CONH).

β-Chloroethylamide 2-ethyl-6-methylpyride-3-iloxyacetate (Im). A mixture of 1.2 g (0.005 mole) of ethanolamide I1 and 0.5 ml (0.005 mole) of $SOCl_2$ in 5 ml of abs. benzene was boiled for 2 h and vacuum-evaporated. The residue was treated with petroleum ether and i-PrOH (10:1) to yield 0.3 g of substance Im.

2-Piperidinoethylamide 2-ethyl-6-methylpyride-3-iloxyacetic dioxalate (In). A solution of 1.2 g (0.005 mole) of ethanolamide I1 in 5 ml of abs. benzene and 0.5 ml (0.005 mole) of $SOCl_2$ was boiled for 2h and vacuum-evaporated after which 7 ml of piperidine was added to the residue and the mixture was heated for 4 h at 110-120°C. Abs. benzene was added to the reaction mass and the resultant precipitate was filtered, washed with water, and dried over K_2CO_3. After evaporation the residue was dissolved in abs. alcohol to yield the dioxalate In. IR-spectrum (KBr), ν_{max}, cm^{-1}:3304 (NH) and 1679 (CONH).

2-Ethyl-6-methylpyride-3-iloxyacetic amide (Im). A solution of 9 g (0.04 mole) of ethyl 2-ethyl-6-methylpyride-3-iloxyacetate in MeOH and 100 ml of 16% NH_3 was kept in an autoclave for 36 h at 20°C. The methanol was evaporated and the residue was recrystallized from a 10:1 mixture of benzene and petroleum ether to yield 6.5 g of the amine Io. IR-spectrum (KBr), ν_{max}, cm^{-1}:3340 and 3160 (NH), 1670 (CONH).

2-Ethyl-6-methylpyride-3-iloxyacetic amidoxime (Ip) (Method E). A solution of 2.74 g (0.02 mole) of 2-ethyl-6-methyl-3-oxypyridine IIa in 50 ml of methylethylketone and 3.1 g (0.022 mole) of anhydrous K_2CO_3 was boiled for 1 h with stirring after which 2.3 g (0.03 mole) of chloroacetonitrile in methylethylketone was added. The mixture was then boiled for 6 h. The reaction mass was filtered, the precipitate was washed with methylethylketone, the filtrates were vacuum-evaporated, and the residue was dissolved in ethylacetate, then washed upon cooling with 2N NaOH and water, then dried over $MgSO_4$. The solution was vacuum-evaporated to yield 3.0 g of the unpurified nitrile of acid Ij. A 1.1 g (0.016 mole) portion of $H_2NOH \cdot HCl$ was added to a solution of the nitrile in abs. alcohol, followed by the dropwise addition of a solution of EtONa (from 0.35 g of Na and 10 ml of abs. alcohol). The mixture was left overnight, then filtered. The precipitate was washed with methylethylketone, the filtrates were evaporated, and the residue was treated with water to yield the amidoxime Ip. IR-spectrum (KBr), ν_{max}, cm^{-1}:3520 (OH), 3300 and 3170 (NH_2), 1669 (C=N).

O-Acetylamidoxime(2-ethyl-6-methylpyride-3-iloxy)acetate (Ir). A 0.75 ml (0.0075 mole) portion of Ac_2O in 5 ml of dioxane was added upon cooling with ice to a suspension of 1.05 g (0.005 mole) of amidoxime Ip in 5 ml of abs. dioxane. The mixture was stirred at 20°C. After 16 h 50 ml of heptane was added after which the mixture was cooled to 0°C to yield the acetyl derivative Ir. The properties of Ia-r are given in Table 1.

EXPERIMENTAL (PHARMACOLOGICAL)

The Pharmacological testing of the substances was performed on non-pedigree white male mice weighing 16-20 g. The substances were administered i/p 30-60 min prior the beginning of the experiment. Antiamnestic action was examined by using a modified passive avoidance conditional reflex model (PACR) [2]. Electric shock at 50 mA lasting 0.2 sec transmitted through corneal electrodes immediately after a training session was employed as the amnesia-inducing factor in the mice. Reproduction of PACR was evaluated 24 h after training. Antihypoxic properties were evaluated in the mice on three hypoxia models: hypobaric, hemic, and hypercapnic in a hermetically sealed space [6]. Acute hypobaric hypoxia was created in a flow pressure chamber with a conditional elevation of the animals to an "altitude" of 11,000 m at a velocity of 50 m/sec. Hemic hypoxia was induced in the mice by the administration of sodium nitrite at a dose of 300 mg/kg subcutaneously. Hypoxia with hypercapnia in an air-tight space was simulated by placing the animals in 200 ml volume containers with hermetically sealed covers. The survival time of the animals was recorded. The anxiolytic properties of the substances was measured in experiments on rats in a conflict situation model and orientation – search behavior under open field conditions, and by climbing up a netting. Myorelaxant properties were evaluated by the rotating piston test [1]. Paracetam ("Polfa", Poland) and meclofenoxate ("Germed," GDR) were used as the reference preparations for comparison.

The results were statistically processed by calculating the arithmetical means and their confidence intervals by the Student method. The Wilcoxon–Mann–Whitney nonparametric criterion method [4] was also employed to evaluate the reliability of the results.

Our study of the pharmacological properties of the 2- and 6-substituted pyride-3-iloxyacetic acid derivatives allowed us to establish that compounds Ic, Ig, and Ii exhibited a pronounced antiamnestic effect at doses of 10 and 50 mg/kg. This was characterized by these substances' ability to eliminate the adverse effects that electric shock has on memory whereby the time the mice stayed in the illuminated cell was increased. The antiamnestic effect of compounds Id and Ih was significantly less. Upon exposure to these substances the animals exhibited a unreliable increase in reflex time in the PACR test. The rest of the compounds did not exhibit any antiamnestic properties (Table 2).

Our study of the antihypoxic activity of the 2- and 6-substituted pyride-3-iloxyacetic acids demonstrated that compounds If and Ie increased life longevity of the mice in sodium nitrite-induced hemic hypoxia. The other compounds of this series did not possess any antihypoxic properties.

The experiment employing the conflict situation model indicated that compounds Ic and Id exhibit tranquilizing activity characterized by a twofold increase of the basic behavioral index, i.e., the number of drinks of water taken, regardless of the current-carrying shocks. However, the effectiveness of the substances in this test was very slight and was significantly less than that of diazepam (Table 3).

None of the tested compounds at the applied doses exhibited anti-tremor activity in the subcutaneous corazole test, nor did they prevent convulsions induced by maximum electric shock. They did not have any significant effect on orientation-search behavior, motor activity, nor did they induce myorelaxation.

Thus, the examined derivatives of 2- and 6-substituted pyride-3-iloxyacetic acids exhibit pronounced antiamnestic activity, some manifestations of antihypoxic action and do not have any sedative or myorelaxant side effects. The test compounds exceed the nootropic activity of piracetam and are no less effective than meclofenoxate, but they do exhibit a relatively high degree of toxicity.

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