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SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF DERIVATIVES OF 3-AMINOMETHYLENINDOLIN-2-ONE

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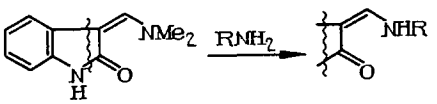
It is known that derivatives of oxindole include substances possessing marked biological activity [1, 2]. In the continuation of our investigations into the synthesis and study of properties and conversions of enamines of the oxindole series [3], the present work accomplished the transamination of 3-dimethylaminomethylenindolin-2-one (I) [3, 4] and its 5-substituted compounds, studied the ^{1}H NMR spectra of the enamines obtained, and investigated their pharmacological activity. The reaction of the compound (I) with β-phenylisopropyl- and β-phenylethylamine, N-acetylethylenediamine, β-hydroxyethylamine, and 1-amino-2,3-dihydroxypropane was studied in the first stage of the work. The process of transamination proceeded smoothly in all cases, and the β-enaminoindolin-2-ones (IIa-e) were synthesized with good yields. The decrease in the basicity of the amino group in the amine component utilized for the transamination reaction leads to complications. The reaction of (I) with glycine could not be performed either by the heating in alcohol or in acetic acid; the Na salt of glycine had to be introduced into the transamination for the isolation of the requisite product — N-carboxymethylaminomethylenindole (IIf). In the case of aminodicarboxylic acids — glutamic or aspartic acid, the corresponding enaminoacids could not be obtained.



I IIa-g

R=PhCH(Me)CH$_2$ (a), PhCH$_2$CH$_2$ (b), CH$_2$CH$_2$NHAc (c), CH$_2$CH$_2$OH (d), CH$_2$(OH)CH(OH)CH$_2$ (e), CH$_2$COOH (f), PhCH$_2$ (g) [3].

The following stage of the work comprises the synthesis of the 5-hydroxyoxindole [5], 5-nitrooxindole [6], and 5-aminooxindole [7], (III)-(V) correspondingly, as well as the condensation of these compounds with dimethylformamide diethylacetal (VI) and the transamination of some of the enamines synthesized on the basis of (III)-(V). The reaction of (III) with (VI) leads smoothly to the 3-dimethylaminomethylen-5-hydroxyindolin-2-one (VII), the reaction of which with aniline and benzylamine affords enaminoamides [(VIIIa) and (VIIIb) correspondingly]. The acetal (VI) is readily condensed at the 3-CH$_2$ group of the 5-nitrooxindole (IV) with the formation of the 3-dimethylaminomethylene derivative (IX), which provided the basis for the synthesis of primary (Xa) and secondary (Xb, c) enamines. The reduction of the 5-nitrooxindole (IV) with hydrazine hydrate in the presence of Raney nickel gave the 5-amino derivative (V), which reacts with the acetal (VI) at two centers — the methylene unit at the position 3, and the aromatic amino group — with the formation of the enaminoamidine (XI). This compound is not a convenient one for the reaction with amines since the amidine fragment is capable both of transamination [8] and cleavage [9] under these conditions, and the possibility of the isolation of 3-aminomethylen-5-aminoindolin-2-ones was shown by means of the reduction of the corresponding nitro-substituted amine (Xa). It is interesting that the hydrogenation of compound (Xa) in aqueous alcohol in the presence of 9% Pd/C leads to the formation of the 3-methyl-5-aminooxindole (XII); this is

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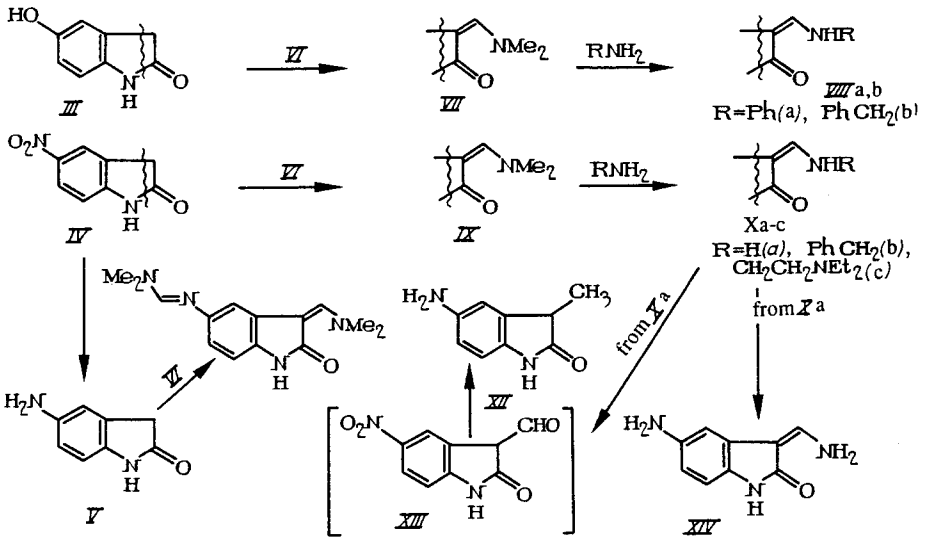
TABLE 1. Isolation of Secondary Enaminoamides

Compound	Initial enamino-amide	Amine	Molar ratio of re-agents	Solvent, ml on 1 g of the enaminoamide	Time of reaction, h
IIa	I	β-Phenylisopropylamine	1:1,2	Abs. alcohol (15)	2,5
IIb	I	β-Phenylethylamine	1:1,2	Abs. alcohol	3
IIc	I	N-Acetylethylenediamine	1:1,2	» »	7
IId	I	2-Aminoethanol	1:1,2	Abs. alcohol (16)	8
IIe	I	1-Amino-2,3-dihydroxypropane	1:1,1	Abs. alcohol (8)	9
VIIIa	VII	Aniline	1:7,7	Abs. alcohol (50), catalytic amount of DMF	8
VIIIb	VII	Benzylamine	1:5,1	Abs. alcohol(50)	2
Xb	IX	»	1:5	Alcohol (30) — DMF (30)	2
Xc	IX	β-Diethylaminoethylamine	1:5	Alcohol (30) — DMF (30)	3

probably due to the hydrolysis of the enamino fragment and the hydrogenation of the formyl substituent which was produced in the intermediate (XIII). The structure of the compound (XII) follows from the data of the elemental analysis, the mass spectrum ($M^{+\cdot}$ 162), and the ^1H NMR spectrum in d-DMSO (δ, ppm), which is as follows: 1.26 (d, 3H, I = 7.6 Hz, 3-CH_3), 3.25 (q, 1H, I = 7.6 Hz, 3-CH), 4.65 (s, 2H, 5-NH_2), 6.53 (d, 1H, 4-CH, $I_{4,6}$ = 2.2 Hz), 6.37 (qd, 1H, $I_{4,6}$ = 2.2 Hz, $I_{6,7}$ = 8.2 Hz, 6-CH), and 6.51 (d, 1H, $I_{6,7}$ = 8.2 Hz, 7-CH). For the suppression of the hydrogenation of the side chain, the process is conducted in the presence of a methanolic solution of ammonia, which delays the hydrolysis of (Xa) to (XIII); this results in the successful isolation of the 3-aminomethylen-5-aminooxindole (XIV) with the yield of ~30%.



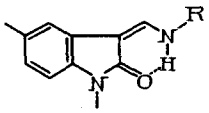
The conditions of synthesis and the properties of the substances synthesized are presented in the Tables 1-4. The ^1H NMR spectra of the compounds (IIa, b, f), (VII), (VIIIa, b), and (IX) (cf. Table 4) at room temperature contain a double set of all signals; this is caused by the occurrence of the mixture of geometrical isomers in relation to the enamine carbon–carbon double bond for the investigated substances in solutions. The data of Table 4 indicate the significant predominance of one of the isomers (73-90%) which, following from our investigations of other secondary enaminocarbonyl compounds [10], is determined by the stabilization of its NH...O=C intramolecular hydrogen bond (IntraMHB). This isomer is called the cis isomer in connection with the cisoid disposition of the amine fragment and the oxindole carbonyl group.

TABLE 2. IR Spectra of Some Enaminoamides

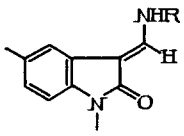
Compound	IR spectrum, ν_{max}, cm^{-1}	
	NH_2 NH, OH	CO
IIa	3300, broad 3140	1675
IIb	broad 3140	1680
IIc	3420, broad 3230	broad 1650
IId	3380, 3340, broad 3210, 3140	1680
IIf	3330	1710, 1660
VIIIb	3400, 3240	1655
Xa	3550, 3360, 3140	1685
XIV	3460, 3320, 3140	1675
VII	3610,broad 3140	1650
IX	broad 3100	1670

TABLE 3. Properties of the Compounds Synthesized

Compound	mp, °C	Solvent	Empirical formula	Yield, %
IIa	159—60	Isopropanol	$C_{18}H_{18}N_2O$	93
IIb	157—8	Acetonitrile	$C_{17}H_{16}N_2O$	90
IIc	212—4	Isopropanol	$C_{13}H_{15}N_3O_2$	78
IId	156—8	Acetone–ethyl acetate	$C_{11}H_{12}N_2O_2$	91
IIe	174—6	Isopropanol	$C_{12}H_{14}N_2O_3$	85
IIf	251—2	DMF–water (1:1)	$C_{11}H_{10}N_2O_3$	69
VII	237—9	Ethanol	$C_{11}H_{12}N_2O_2$	83
VIIIa	272—4	Acetone	$C_{15}H_{12}N_2O_2$	80
VIIIb	209—11	Ethanol	$C_{16}H_{14}N_2O_2$	90
IX	272—4	Methanol–DMF	$C_{11}H_{11}N_3O_3$	68
Xa	>300	Methanol–DMF	$C_9H_9N_3O_4$	82
Xb	>300	Methanol–DMF	$C_{16}H_{13}N_3O_3$	98
Xc	215—6	Acetone	$C_{15}H_{20}N_4O_3$	87
XI	205—7	Acetone–isopropanol	$C_{14}H_{18}N_4O$	70
XII	168—70	Ethanol	$C_9H_{10}N_2O$	41
XIV	238—40	Ethanol	$C_9H_9N_3O$	34



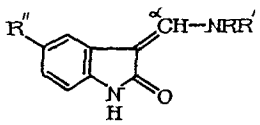
cis-isomer



trans-isomer

The indisputable proof for the correctness of the assignment of the signals, presented in Table 4, to the cis or trans isomers was obtained using the homonuclear Overhauser effect (NOE) taking the example of the compounds (VIIIa, b) and (IX). With the saturation of the signal of the proton at the position 4 pertaining to the predominating and minor isomers, it was established that the effect is only observed in the first case (the cis isomer) and the value of the NOE comprises 10-11% based on the signal pertaining to the vinyl proton of the substituted aminomethylene grouping. The assignment of the configuration

TABLE 4. ^{1}H NMR Spectra of the Enamines Synthesized



Compound and type of isomer	Isomer content, %	^{1}H NMR spectrum								Solvent
		$C_\alpha H$	NH (enamine)	NH (indole)	C(4)-H	R*	R′	R″	Ar	
IIa:										
cis	85	7,92 (d J=13 Hz)	8,91 (q)	10,10	~7,30	($CH_2CH(CH_3)$-Ph) 3,86 (m, CH), 2,92 (m, CH_2), 1,31 (d, CH_3, J_{CH}= =6,6 Hz)	H	H	6,80—7,48	d_7 = DMF
trans	15	~7,50	~7,50	9,82	7,76	3,04 (m, CH_2), 1,83 (d, CH_3)***	H	H		
IIb:										
cis	75	7,92 (d, J=13,2Hz)	9,05	10,07	~7,40	(CH_2CH_2Ph) 3,75 q, $NHCH_2$), 3,00 (t, CH_2Ph)	H	H	6,85—7,45	The same
trans	25	7,47	7,65	9,95	7,66	—***	H	H		
IIf:										
cis	77	7,94 (d, J=12,5Hz)	8,96	10,12	7,30	(CH_2COOH) 4,32 (d, CH_2)	H	H	6,80—7,00	» »
trans	23	7,60	7,62	9,92	7,67	4,28 (d)	H	H		
VII:										
cis	66	7,46 (s)	—	9,20	6,97	(CH_3) 3,34 (s, NMe_2)	CH_3	OH (8,32, s)	6,49 (qd), 6,67 (d)	$(CD_3)_2SO$
trans	34	7,17 (s)	—	8,97	6,65	3,46		8,22	6,44 (qd), 6,61 (d)	
VIIIa:										
cis	90	8,46 (d, J=13 Hz)	10,70 (d, J=13 Hz)	10,14	7,00	(Ph) 7,00—7,32	H	OH (8,70)	6,43 (qd), 6,60 (d)	The same
trans	10	7,66 (d, J=13 Hz)	9,30 (d, J=13 Hz)	9,82	7,44	—***	H	8,73	6,50 (qd), 6,57 (d)	
VIIIb										
cis	76	7,91 (d, J=13 Hz)	9,02 (quint. J_1=13 Hz, J_2=6,3 (Hz)	9,87	6,71	($PhCH_2$) ~7,36, 4,54 (d)	H	OH 8,62	6,33 (qd), 6,56 (d)	» »
trans	24	7,40 (d, J=13 Hz)	—**	9,60	7,15	—***		8,60	6,40 (qd), 6,53 (d)	
IX:										
cis	78	7,96 (s)	—	10,7	8,27	(CH_3)*4	CH_3	NO_2	7,83 (qd), 6,84 (d)	» »
trans	22	7,61 (s)	—	—***	8,18	—*4		NO_2	7,93 (qd), 6,93 (d)	
XIV individual isomer	100	7,56 (d, J=9 Hz)	NH_2 8,08 (d, J=9 Hz)	9,67	6,56 (d)	H	H	HN_2 4,38	6,20 (qd), 6,48 (d)	» »

*The signals of the protons of the aryl substituent for the compounds (IIa, b) are presented in the column Ar in the form of a general multiplet with the signals of the aromatic protons of the indole ring.

**For the compounds (IIa, b, f) with the R^1 = H cf. the column NH (enamine); for the R^{11} = H cf. the column Ar.

***The signals are superimposed by the more intense signals of the predominant isomer.

****The $N(CH_3)_2$ signals are superimposed by the signals of water in the $(CD_3)_2SO$.

of the remaining compounds was made on the basis of the comparison of the chemical shifts by analogy to what we did in the work [3]. It should thereby be noted that, for all the investigated enamines, the cis isomer is characterized by the position of the $C_\alpha H$ signal at lower field. At the same time, the chemical shift of the proton at the position 4 cannot be a criterion for the establishment of the configuration of the investigated enamines: differences in the chemical shifts of the cis and trans isomers were insignificant for the previously investigated tertiary enamines [3]. At the same time, the position of the signal of the C(4) proton is significantly dependent on the solvent employed and, for example, for the compound (IX) in d-DMSO and d-DMSO–CD_3OD, the chemical shifts of the C(4)–H differ by ~0.24 ppm (8.18 and 7.94 ppm correspondingly). The fact that the predominance of the cis isomers is mainly associated with the intramolecular H-bond is confirmed by the addition of small amounts of methanol to the solutions of the investigated substances: the marked increase in the content of the trans isomer is thereby observed. The last is probably associated with the competing capacity of alcohols to form intermolecular hydrogen bonds with molecules of the dissolved substance (with the breakdown of the intramolecular bonds).

EXPERIMENTAL (CHEMICAL)

The ^1H NMR spectra were recorded on the XL-200 spectrometer (of the firm "Varian"). The internal standard was TMS. The melting temperatures were determined on a "Boetius" heating stage (Germany). The IR spectra were taken on a "Perkin–Elmer 457" instrument in mineral oil. The values for the elemental analyses found correspond with the calculated values.

General Method for the Isolation of the (3-(N,N-Dimethylamino)methylenoxindoles (VII) and (IX). The mixture of the oxindole (III) or (IV) and the acetal (VI) (in the 1:1.2 molar ratio) is boiled in abs. alcohol (1:50) for 1 h. The acetal (VI) is added [taking 0.8 mole of (VI) for 1 mole of the oxindole] and the mixture is boiled for 1 h more. The reaction mass is cooled, and the precipitated residue of the 3-(N,N-dimethylamino)methylenoxindole (VII) or (IX) is filtered off.

General Method for the Isolation of the Enaminoamides (IIa-e), (VIIIa, b), and (Xb, c) by the Transamination of the 3-(N,N-Dimethyl)aminomethylenoxindoles (I), (VII), and (IX) (cf. Table 1). The mixture of the initial 3-(N,N-dimethyl)aminomethylenoxindole and the transaminating amine is boiled in an organic solvent. At the completion of the reaction, the mixture is cooled, and the precipitated residue of the secondary enaminoamide is filtered off [for the compounds (IIa, b, e), (VIIIa, b), and Xb], or the reaction mass is concentrated *in vacuo*. The residue is triturated with isopropanol [for (IIc)] or water [for (IId)], or the reaction mass is diluted with water, and the resulting residue [for (Xc)] is filtered off. The IR spectra are presented in Table 2.

3-[N-(Carboxymethyl)aminomethylen]oxindole (IIf). The mixture of 0.37 g (0.005 mole) of aminoacetic acid, 0.2 g (0.005 mole) of NaOH, and 30 ml of abs. alcohol is boiled for 10 min. To the reaction mass is added 0.94 g (0.005 mole) of the enaminoamide (I). The mixture is boiled for 1.5 h. The reaction mass is cooled, and the residue is filtered off and dissolved in 15 ml of water. The solution is filtered and acidified with 2 N HCl until the complete precipitation of the residue is achieved (the pH ~ 4.5). The yield of 0.75 g of (IIf) is filtered off.

3-(N,N-Dimethyl)aminomethylene-5-(N,N-dimethyl)aminomethylenaminooxindole (XI). The mixture of 3 g (0.002 mole) of compound (V), 7.25 g (0.05 mole) of the acetal (VI), and 125 ml of methanol is stirred at room temperature for 4 h. After the addition of 3.5 g of the acetal (VI), the mixture is stirred for 16 h. The reaction mass is filtered, and the mother liquor is concentrated; the residue is triturated with acetone. The yield of 3.6 g of (XI) is obtained. The IR spectrum (ν_{max}, cm^{-1}) was as follows: 3100 (NH), 1675 (CO), and 1635 (C=N).

3-Aminomethylene-5-nitrooxindole (Xa). Compound (IX) (5.1 g, 0.022 mole) is stirred at room temperature in 750 ml of a saturated methanolic solution of ammonia with the addition of 100 ml of methanol in the course of 2.5 h. Compound (Xa) (4.4 g) is filtered off in the form of the monohydrate.

3-Aminomethylen-5-aminooxindole (XIV). Compound (Xa) (4.5 g, 0.02 mole) in 150 ml of methanol, with a small added amount of a methanolic solution of NH_3, is hydrogenated in the presence of 0.45 g of 10% Pd/C at room temperature with the stirring of the mixture until the cessation of the absorption of hydrogen. The residue is filtered off, and the mother solution is concentrated by 2/3 prior to the cooling and isolation of 0.8 g of (XIV). The filtered residue is recrystallized from methanol, and 0.4 g more of (XIV) is obtained.

3-Methyl-5-aminooxindole (XII). Compound (Xa) (2 g, 0.009 mole) in 75 ml of rectified spirit alcohol is hydrogenated in the presence of 0.2 g of 9% Pd/C with boiling until the cessation of the absorption of hydrogen. The reaction mass is filtered,

concentrated to the volume of ~15 ml, and cooled. The yield of 0.6 g of (XII) is filtered off. The IR spectrum (ν_{max}, cm^{-1}) was as follows: 3350, 3280, broad, 3160 (NH, NH_2), and 1680 (CO).

EXPERIMENTAL (BIOLOGICAL)

Experiments were performed on male mice of mass 18-25 g using 10-12 animals for each dose. The compounds synthesized were investigated according to indicators of general action, influence on the CNS of the animals, and antihypoxic activity. The investigated compounds were applied po in doses of 1/2 to 1/10 LD_{50}. The general action of the compounds was studied by visual observation of the animals. Alternation of periods of rest (grouping) and activity (movement in the cell) and the interaction of animals in the group (absence, grooming, and aggressivity) were noted.

The central inhibiting action was evaluated from the presence of the hypnosedative effect and the potentiation of thiopental sleep in the mice. The hypnosedative effect was registered on the basis of the decrease in locomotion and the presence of the lateral position of the mice. Thiopental-sodium was injected iv into the mice at the dose of 30 mg/kg at 30-40 min after the investigated compounds.

The anticonvulsant action was studied from the influence on convulsions induced in the mice by Corazol (175 mg/kg, ip) and by maximal electroshock (MES: 50 mA, 60 imp/sec, 0.5 msec). The influence on the latent period (in min) of the convulsions and death, induced by Corazol, and the capacity for the prevention of the electroconvulsive attack were evaluated.

The antihypoxic action was evaluated using models of hypoxic and histotoxic hypoxia. Hypoxic hypoxia with hypercapnia was produced in a closed volume of the capacity 250 ml; histotoxic hypoxia was induced by sodium nitroprusside (25 mg/kg, sc). The antihypoxic effect was evaluated from the continuance of life in conditions of hypoxia.

The acute toxicity was investigated in the mice using po application and, in the case of soluble compounds, iv injection. The LD_{50} (in mg/kg) according to Kerber was calculated.

It was shown as a result of the investigations that the 5-substituted compounds not having a substituent at the nitrogen atom of the side chain [(Xa) and (XIV)] do not exert significant influence on the general state and behavior of the animals. At doses of 100-300 mg/kg, the compound (XIV) gives a 50% increase in the duration of sleep, induced by thiopental-sodium, in mice and the compound (Xa) increases the duration of life by 19% under conditions of hypoxic hypoxia.

The increase in the volume of the substituent at the nitrogen atom of the aminomethylene chain for both the 5-unsubstituted compound (I) and compounds having a substituent at the position 5 [(VII), (IX), and (XI)] leads to the isolation of substances exerting a marked influence on the general state and behavior of the animals. When the compound (I) is applied po starting from the dose of 100 mg/kg, it does not change the duration of the thiopental sleep. However, when the dose is increased to 300-600 mg/kg, it protects 50-100% of the animals from convulsions induced by the MES, and exerts antihypoxic effect on the two forms of hypoxia. Compound (VII) at the dose of 300 mg/kg protects 33% of the animals from convulsions induced by the MES, and does not exert a protective effect on the models of hypoxia. Compound (XI) shows antagonism to Corazole convulsions, increasing the latent period of onset of the convulsions and death. Compound (IX) is practically inactive in the tests indicated.

The increase in the length of the side chain [compounds (IIf), (IIg) [3], (VIIIb), and (Xb)] does not significantly alter the spectrum of activity of the investigated substances. The carboxymethylaminomethylene derivative (IIf) at the dose of 200 mg/kg increases the duration of the thiopental sleep by 100%. Among the benzylaminomethylene derivatives, only the compound (Xb) at the dose of 200 mg/kg increases the duration of the thiopental sleep by 50%, and increases the life duration of the mice by 23% under conditions of hypoxic hypoxia. The different benzylaminomethylene derivative (IIg) at the dose of 400 mg/kg exerts an insignificant effect with convulsions of the MES, and increases the life duration of mice with histotoxic hypoxia by 20%.

The further increase in the length of the aminomethylene chain leads to the isolation of compounds for which the inhibiting action on the CNS is more marked. Thus, the hydroxyethylaminomethylene derivative (IId), given at doses of 60-500 mg/kg po, induces sedation and increases the duration of the thiopental sleep by threefold, and the duration of life under conditions of histotoxic hypoxia by 20%. The acetylaminoethylaminomethylene derivative (IIc), given in doses of 60-250 mg/kg, gives practically no change in the general state and behavior of the animals, but increases the duration of life under conditions of hypoxic and histotoxic hypoxia by 15-18%. The diethylaminoethylaminomethylene derivative of 6-nitrooxindole (Xc), given in doses of 100-300 mg/kg, prevents the production of the convulsions of the MES in 100% of the animals, and increases the life duration of the animals with histotoxic hypoxia by 20%.

Compounds with the N-(β-phenyl)isopropyl substituent (IIa) and the 2,3-dihydroxypropyl substituent (IIe) do not show activity according to indicators of central action, but give 24 and 6% increases correspondingly in the life duration of the animals under conditions of hypoxic hypoxia.

The compounds investigated are of low toxicity; their LD_{50} values comprise >1000 mg/kg with po application.

Therefore, the investigation of a series of oxindole derivatives was conducted using indicators characterizing the influence on the CNS and the tolerability of hypoxia by the animals.

The investigations showed that the compounds have a varying degree of the expression of inhibitory action on the CNS of the animals, which is characterized by a weak sedative and anticonvulsant effect, as well as the capacity to potentiate the action of soporifics. A proportion of the compounds shows weak antihypoxic properties.

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