Some Analogues of 1,4-Disubstituted Piperazines as Hypnotic and Sedative Agents

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Preparation, analytical data, and biological properties such as acute toxicity, influence on spontaneous and amphetamine induced locomotor activity, hypnotic activity, influence on hexobarbital narcosis and anticonvulsant activity of new analogues of pyrimidyl piperazines - ethyl 3-[4-(2-pyrimidyl)-1-piperazinyl]-3-oxopropanoate (**4**), 1-[4-(2-pyrimidyl)-1-piperazinyl]-1,3-butandione (**5**), ethyl 3-[4-(2-pyrimidyl)-1-piperazinyl]butanoate (**6**) and 1-[4-(2-pyrimidyl)-1-piperazinyl]-2-acetyl-1-hexanone (**7**) - are reported.

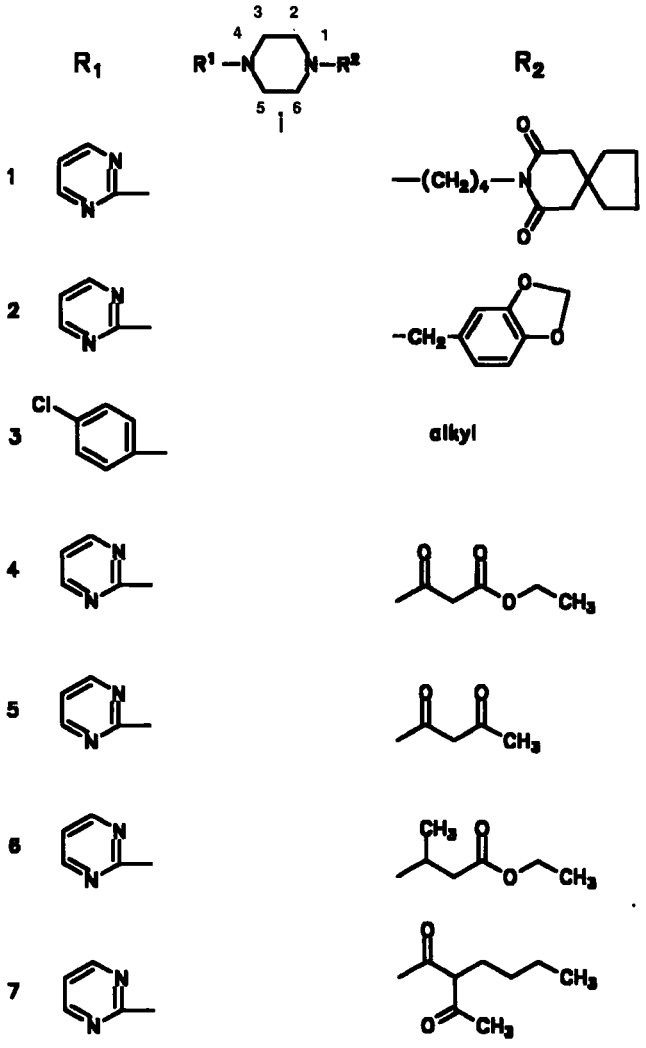
Einige Analoge von 1,4-disubstituierten Piperazinen als hypnotische und sedative Wirkstoffe

Herstellung, analytische und biologische Daten (akute Toxizität, Beeinflussung der spontanen bzw. durch Amphetamin induzierten lokomotorischen Aktivität, Wirkung als Hypnotikum, Beeinflussung der durch Hexobarbital hervorgerufenen Narkose und Wirkung als Antikonvulsivum) der vier neuen Pyrimidylpiperazin-Analogen - 3-[4-(2-Pyrimidyl)-1-piperazinyl]-3-oxopropionsäure Ethylester (**4**), 1-[4-(2-Pyrimidyl)-1-piperazinyl]-1,3-butandion (**5**), 3-[4-(2-Pyrimidyl)-1-piperazinyl]buttersäure Ethylester (**6**) und 1-[4-(2-Pyrimidyl)-1-piperazinyl]-2-acetyl-1-hexanon (**7**) - werden beschrieben.

Among piperazine derivatives there are potent agonists of dopaminergic and serontoninergic receptors. The compounds possessing aromatic substituents at one or both N-atoms of a piperazine fragment exhibit special pharmacological activity. To such compounds belong buspirone, *e.g.* (**1**) (Scheme 1), an anxiolytic drug which is an agonist of the serotonin receptor sub-type 5HT-1A[1,2] or piribedil (**2**) which directly activates a dopaminergic receptor[3-7] and acts as a blocker on postsynaptic cholinergic receptors in the cockroach CNS[8].

Topographic models of serotonin and dopamine receptors suggest that their ligands should possess an aromatic ring and an N-atom situated at a specified distance from the ring center[9-12]. In order to accomodate the 5HT-1A binding site the ligand should contain a basic N-atom. In the piperazine family of 5HT-1A ligands the basicity of N-4 plays a crucial role (Scheme 1). *Mokrosz et al.*[13] examined the influence of an aliphatic substituent at N-4 on the affinity to the 5HT-1A receptor for the series of compounds of general structure **3** (Scheme 1). They found that an aliphatic chain containing four to eight carbon atoms connected to the basic N-4 improves the affinity to the receptor. Presence of a carbonyl function at the C-atom α to N-4 reduces the affinity.

Here we report upon the preparation of four new 1,4-piperazine derivatives **4**, **5**, **6**, and **7** possessing an aliphatic chain with and without a carbonyl function at the α position to N-4. Instead of present in the compounds described earlier - chlorinated benzene rings - these compounds possess a pyrimidine moiety giving structures that may also exhibit affinity to an α-adrenergic receptor[14]. The compounds were originally synthesized for binding studies with the serotoninergic receptor. As could be expected ethyl 3-[4-(2-pyrimidyl)-1-piperazinyl]-3-oxopropanoate (**4**), 1-[4-(2-pyrimidyl)-1-piperazinyl]-1,3-butandione (**5**, ethyl 3-[4-(2-pyrimidyl)-1-piperazinyl]butanoate (**6**), and 1-[4-(2-pyrimidyl)-1-piperazinyl]-2-acetyl-1-hexanone (**7**) did not show any significant affinity to the serotonin (5HT) receptor of the 1A sub population[15]. Random behavioral screening revealed, however, that in the series studied three of the compounds possess pronounced hypnotic and sedative activity.



Scheme 1

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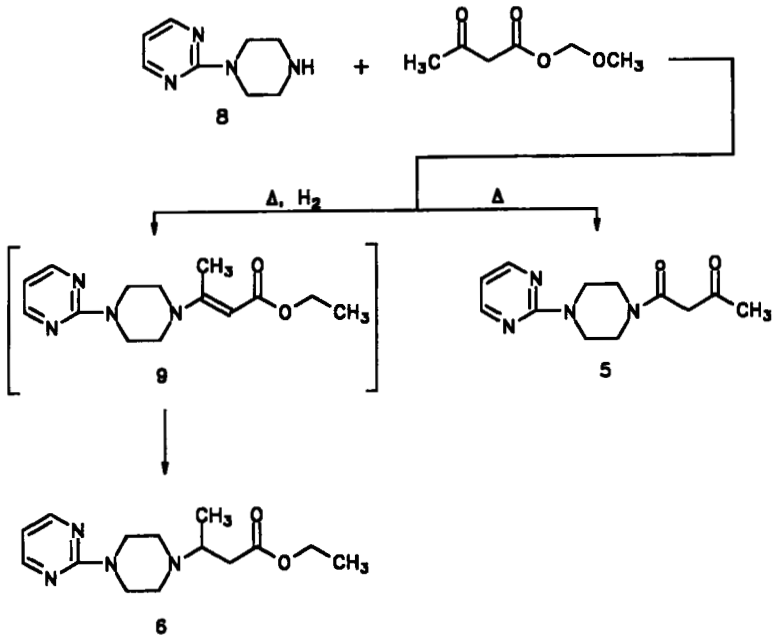

Scheme 2

Ethyl 3-[4-(2-pyrimidyl)-1-piperazinyl]-3-oxopropanoate (**4**) was the product of a reaction of diethyl malonate with 1-(2-pyrimidyl)piperazine (**8**). 1-[4-(2-Pyrimidyl)-1-piperazinyl]-1,3-butandione (**5**) and ethyl 3-[4-(2-pyrimidyl)-1-piperazinyl]-butanoate (**6**) were the products of a reaction of the compound **8** with ethyl acetoacetate. Compound **5** was prepared by heating of **8** with ethyl acetoacetate. When the reaction was carried out under H_2-pressure in the presence of a catalyst two compounds **5** and **6** - were formed. The formation of **6** may proceed through the enamine **9** followed by catalytic reduction of the resulting unsaturated compound (Scheme 2). 1-[4-(2-Pyrimidyl)-1-piperazinyl]-2-acetyl-1-hexanone (**7**) was prepared from 1-(2-pyrimidyl)piperazine[16] (**8**) and ethyl 2-butylacetoacetate.

Mass spectra of compounds **4-7** are characterized by a common ion (m/z 163) corresponding to the pyrimidylpiperazine group, formed by fission of N(1)-R bond. Ions originating from the further fragmentation of the pyrimidylpiperazine moiety as well as ions corresponding to the aliphatic side chains (R^+) of low relative intensity (3-7%) were also observed.

Acute toxicity and influence on behavior of mice

Compounds **4-7** possess relatively low acute toxicity as compared to phenobarbital. It fell in the 800 - > 2000 mg/kg and 600-800 mg/kg of body weight range for *per os* and intraperitoneal administration, respectively. Similarly to phenobarbital **4**, **5**, and **7** (but not **6**) in large doses cause ataxia and loss of the righting reflex. In the applied range of doses **6** did not promote any changes in the behavior of mice except of a small loss of locomotor activity for a short time in the 2000 mg/kg dose (Tab. 1).

Influence on spontaneous and amphetamine induced locomotor activity

In the 1/5 dose of LD_{50} **4**, **5**, and **6** did not significantly affect the spontaneous locomotor activity of mice. **7** decreased the activity by 41%. None of the compounds affected the amphetamine induced psychomotor stimulation.

Hypnotic activity was determined by assigning a dose causing loss of the righting reflex in 50% of mice (ED_{50}) and the time of the righting reflex loss for a given dose (phenobarbital as reference - Tab. 2). **7** possesses the highest activity. For **7** the therapeutic index (TI = LD_{50}/ED_{50}) was established on the level of 3.3 and 7.0 for intragastric and ip. administration, respectively. The corresponding values for phenobarbital were 2.3 and 2.5. The time of the righting reflex loss in a dose close to 1/2 of LD_{50} for intragastric administration was much longer for **7** (> 260 min) than for phenobarbital (71 min). The corresponding doses for ip. administration were comparable (43 and 32 min). The hypnotic action of **4** was coming relatively fast after the administration and was short lasting (4-5 min). It is worth noting that ataxia (as a preliminary phase for loss of the righting reflex) was much smaller for the tested comp-ounds than for phenobarbital. The latter caused strong ataxia connected with excitement.

Influence on hexobarbital narcosis

5 and **7** at 1/10th of the LD_{50} dose strongly increased the narcotic action of hexobarbital (Tab. 2). **4** alike phenobarbital in a similar dose did not exhibit any significant activity.

Tab. 1. Toxicity and Observation of Mice Behavior

Entry	Compound	LD_{50}[1] [mg/kg]	Route of. adm.	Minimal dose producing charges [mg/kg]
1.	4	⟩2,000	p.o.[2]	Decrease of locomotor activity [1,000]. Ataxia, loss of the righting reflex [2,000].
2.	4	1,000	i.p.[3]	Decrease of locomotor activity [300]. Ataxia, loss of the righting reflex [1,000].
3.	5	1,500	p.o.	Decrease of locomotor activity [300]. Ataxia, loss of the righting reflex [1,000].
4.	6	⟩2,000	p.o.	Slight decrease of locomotor activity [2,000].
5.	7	800	p.o.	Decrease of locomotor activity [100]. Ataxia, loss of the righting reflex [300].
6.	7	600	i.p.	Decrease of locomotor activity [30]. Loss of the righting reflex [100].
7.	Ref.[4]	250	p.o.	Strong ataxia, loss of the righting reflex [100].
8.	Ref.	250	i.p.	Strong ataxia, loss of the righting reflex [100].

[1] Acute toxicity.- [2] Per os.- [3] Intra peritoneal.- [4] Phenobarbital as reference compound.

Tab. 2 Hypnotic Action of **4**, **5**, **6**, **7**

Entry	Compound	Route of adm.	LD_{50}[1] [mg/kg]	L.R.L.[2] ED_{50} [mg/kg]	TI =[3] LD_{50}/ED_{50}	L.R.L.[4] Dose [mg/kg]	L.R.L.[4] Time [min]	I.H.N.[5]
1.	4	p.o.[6]	⟩2,000	⟨2,000	⟩1	2,000	5	-26/200
2.	4	i.p.[7]	1,000	651.5	1.5	1,000	4	not. test.
3.	5	p.o.	1,500	675.0	2.2	1,000	60	+263/150
4.	6	p.o.	⟩2,000	—[8]	—	—	—	not. test.
6.	7	p.o	800	242.1	3.3	400	⟩260	+133/80
7.	7	i.p.	600	85.4	7.0	200	43	not. test.
8.	Ref.[9]	p.o.	250	109.6	2.3	100	71	-17/25
9.	Ref.	i.p.	250	100	2.5	125	32	not. test.

[1] Acute toxicity.- [2] Effective dose for loss of the righting reflex.- [3] Therapeutic indice.- [4] Time of the loss of the righting reflex for a given dose.- [5] Influence on the hexobarbital (in dose = 1/10 of LD_{50}) narcosis in % of control; dose in mg/kg of weight is given after a slash.- [6] Per os.- [7] Intra peritoneal.- [8] Not detected.- [9] Phenobarbital as reference compound.

Anticonvulsant activity

None of the compounds in a dose up to 1/5th of LD_{50} exhibited any anticonvulsant activity in the maximal electroshock seizure test in mice.

Conclusions

Compounds **4**, **5**, and **7** (but not **6**) exert a depressive action on CNS. In large doses (alike phenobarbital) they produce loss of the righting reflex. Locomotor ataxia was,

however, much smaller for the tested compounds than for phenobarbital. Compounds **5** and **7** strongly increase the narcotic action of hexobarbital (263% and 133%). However, none of the compounds affects the amphetamine induced psychomotor stimulation. Compound **7** exhibits the most pronounced hypnotic and sedative properties. It decreases the spontaneous locomotor activity of mice by 41%. **7** induces long lasting loss of the righting reflex. Because of its low toxicity **7** appears to be much more effective than phenobarbital (especially when ip. routes of administration were compared). The corresponding therapeutic indices are 7.0 and 2.5, respectively. However, the action of **7** is not associated with anticonvulsant activity.

Rough examination of the structures of **4**, **5**, **6**, and **7** suggests that the presence of an exocyclic carbonyl group in the α position to the piperazine-N is a necessary condition for the observed biological activity. The piperazinyl-aliphatic moiety resembles the γ-aminobutyric acid. Structural similarities and the profile of pharmacological properties suggest that the action of the compounds could be mediated by the GABA receptor complex[17].

We thank Dr. *Kamil Eksanow* for running GC/MS spectra.

Experimental Part

M.p.'s: Boetius apparatus (Carl Zeiss, Jena), uncorrected.- IR-spectra: UR-20 spectrophotometer.- ^{1}H-NMR and ^{13}H-NMR spectra: Bruker WP-100SY spectrometer, δ values (ppm) relative to the internal standard $(CH_3)_4Si$.- GC/MS spectra: Hewlett-Packard GC model 5890 with 5970 mass detector by EI method.- Reagents and solvents were purchased from common commercial suppliers and were used as received; ethanol was dried prior to use.- Elementary analyses are within ± 0.4% of the theoretical value.

General procedure for the preparation of hydrochlorides

A compound was dissolved in anhydrous ethanol followed by an addition of the equimolar amount of 2.6 M HCl in ethanol. After 2 h at room temp. the mixture was concentrated to 1/2 of the initial volume, hydrochlorides were precipitated with ether, filterd off and air dried.

Ethyl 3-[4-(2-pyrimidyl)-1-piperazinyl]-3-oxopropanoate (**4**)

The mixture of 1-(2-pyrimidyl)piperazine (**8**) (2.00 g, 0.012 mole) and diethyl malonate (40.04 g) was stirred and heated at 80°C for 24 h. The excess of malonate was evaporated *in vacuo* to give 5.90 g of an oily residue which crystallized after treatment with diethyl ether. Yield 2.36 g (71%) of **4**, m.p. 86-90°C.- $C_{13}H_{18}N_4O_3$.- IR (KBr): 2861; 1727; 1641; 1587; 1549; 1488; 1361; 1333; 1254; 1176; 1033; 983 cm^{-1}.- ^{1}H-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 1.29 (t; J = 7.1 Hz, 3H, CH_2-C<u>H</u>$_3$), 3.53 (s; 2H, C(O)-CH_2-C(O)), 3.48-3.94 (m; 8H, 8 pip.-H), 4.22 (q; J = 7.1 Hz, 2H, C<u>H</u>$_2$-CH_3), 6.55 (t; J = 4.7 Hz, 1H, pyr.-CH-C<u>H</u>=CH), 8.33 (d; J = 4.7 Hz, 2H, pyr.-N=CH).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 167.27 (s), 164.46 (s), 161.15 (s), 157.58 (d), 110.34 (d), 61.33 (t), 45.99 (t), 43.48 (t), 43.22 (t), 41.57 (t), 41.14 (t), 13.96 (q).- MS m/z (%): 278 (M^+, 40), 233 (45), 210 (15), 163 (18), 135 (11), 134 (83), 122 (61), 121 (55), 115 (3), 108 (100), 80 (22), 79 (15).- Hydrochloride of **4**: m.p. 135-139°C.- $C_{13}H_{19}N_4O_3Cl$.

1-[4-(2-Pyrimidyl)-1-piperazinyl]-1,3-butandione (**5**)

The mixture of **8** (4.00 g, 0.024 mole) and ethyl acetoacetate (40 ml) was stirred and heated at 90°C for 15 h. The excess of ethyl acetoacetate was evaporated *in vacuo* to give an oily residue which crystallized from diethyl ether to give 4.00 g (67%) of **5**, m.p. 103-106°C.- $C_{12}H_{16}N_4O_2$.- IR (KBr): 2856; 1719; 1646; 1588; 1552; 1479; 1446; 1365; 1308; 1272; 1256; 1161 cm^{-1}.- ^{1}H-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 2.30 (s; 3H, CH_3), 3.43-3.92 (m; 10 H, 8 pip.-H, C<u>H</u>$_2$-C(O)), 6.54 (t; J = 4.8 Hz, 1H, pyr.-CH-C<u>H</u>=CH), 8.32 (d; J = 4.8 Hz, 2H, pyr.-N=CH).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 202.10 (s), 165.20 (s), 161.52 (s), 157.80 (d), 110.57 (d), 50.07 (t), 45.22 (t), 43.73 (t), 43.44 (t), 41.73 (t), 30.30 (q).- MS m/z (%): 248 (M, 55), 205 (4), 163 (16), 135 (10), 134 (69), 122 (68), 121 (60), 108 (100), 85 (7), 80 (30), 79 (21), 43 (56).- Hydrochloride of **5**: m.p. 126-128°C.- $C_{12}H_{17}N_4O_2Cl$.

1-[4-(2-Pyrimidyl)-1-piperazinyl]-1,3-butandione (**5**) and ethyl 3-[4-(2-pyrimidyl)-1-piperazinyl]butanoate (**6**)

The mixture of **8** (5.00 g, 0.030 mole) and ethyl acetoacetate (30 ml) was hydrogenated at atmospheric pressure of H_2 over 5% Pd/C (0.12 g) at 80°C for 15 h. The mixture was cooled, the catalyst was filtered off, and the filtrate evaporated *in vacuo* to give 9.00 g of a crystallizing oily residue which was chromatographed on silica gel. Eluting with $CHCl_3$ yielded 1.83 g (22%) of oily ethyl 3-[4-(2-pyrimidyl)-1-piperazinyl]butanoate (**6**).- $C_{14}H_{22}N_4O_2$.- IR ($CHCl_3$): 3450; 3168; 2973; 1733; 1587; 1548; 1504; 1447; 1393; 1360; 1307; 1261; 1207; 1179; 1159; 1079; 1039 cm^{-1}.- ^{1}H-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 1.07 (d; J = 6.6 Hz, 3H, > CH-C<u>H</u>$_3$), 1.26 (t; J = 7.1 Hz, 3H, CH_2-C<u>H</u>$_3$), 2.22-2.70 (m; 6H, 2 pip.-2H, 2 pip.-6H, > CH-C<u>H</u>$_2$), 3.08-3.38 (m; 1H, C<u>H</u>(CH$_3$)-CH_2), 3.71-3.92 (m; 4H, 2 pip.-3H, 2 pip.-5H), 4.14 (q; J = 7.1 Hz, 2H, C<u>H</u>$_2$-CH_3), 6.46 (t; J = 4.7 Hz, 1H, pyr.-CH-C<u>H</u>=CH), 8.29 (d; J = 4.7 Hz, 2H, pyr.-N=CH).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 172.19 (s), 161.79 (s), 157.68 (d), 109.83 (d), 60.35 (t), 56.68 (d), 48.04 (t), 43.72 (t), 38.32 (t), 14.74 (q), 14.21 (q).- MS m/z (%): 278 (M^+, 43), 233 (5), 217 (7), 191 (100), 170 (5), 163 (7), 158 (86), 134 (12), 122 (59), 121 (17), 115 (5), 108 (26), 56 (30).- Hydrochloride of **6**: m.p. 192°C (decomp.).- $C_{14}H_{23}N_4O_2Cl$.- Eluting with $CHCl_3$-MeOH 1:1 (v/v) gave 1.43 g (23%) **1**-[4-(2-pyrimidyl)-1-piperazinyl]-1,3-butandione (**5**), m.p. 99-100°C.

1-[4-(2-Pyrimidyl)-1-piperazinyl]-2-acetyl-1-hexanone (**7**)

The mixture of **8** (4.00 g, 0.024 mole) and ethyl 2-butylacetoacetate (12.00 g) was stirred and heated at 150°C for 24 h. The excess of acetoacetate was evaporated *in vacuo*, the residue was dissolved in CCl_4 and chromatographed on silica gel. Eluting with $CHCl_3$ yielded an oily product which after crystallization from hexane - ethyl acetate 1:1 (v/v) gave 3.09 g (42%) of **7**, m.p. 68-70°C.- $C_{16}H_{24}N_4O_2$.- IR (KBr): 2957; 1703; 1641; 1595; 1546; 1525; 1436; 1392; 1360; 1308; 1239; 1163; 1081; 1012 cm^{-1}.- ^{1}H-NMR ($CDCl_3$, 100 MHz): δ (ppm) = 0.91 (t; J = 6.1 Hz, 3H, CH_2-C<u>H</u>$_3$), 1.12-2.14 (m; 6H, CH_2-CH_2-CH_2), 2.18 (s; 3H, C(O)-CH_3), 3.62-4.01 (m; 9H, 8 pip.-H, > CH-), 6.56 (t; J = 4.8 Hz, 1H, pyr.-CH-C<u>H</u>=CH), 8.34 (d; J = 4.8 Hz, 2H, pyr.-N=CH).- ^{13}C-NMR ($CDCl_3$): δ (ppm) = 205.04 (s), 167.81 (s), 161.56 (s), 157.78 (d), 110.61 (d), 58.49 (d), 45.67 (t), 43.84 (t), 43.67 (t), 42.44 (t), 29.80 (t), 28.80 (t), 26.80 (q), 22.60 (t), 13.84 (q).- MS m/z (%): 304 ($M^{+\cdot}$, 98), 261 (47), 229 (10), 206 (10), 191 (11), 163 (45), 141 (5), 135 (10), 134 (75), 122 (83), 121 (57), 108 (100), 107 (7), 96 (21), 80 (19), 79 (13).- Hydrochloride of **7**: m.p. 96°C (dec.).- $C_{16}H_{25}N_4O_2Cl$.

Biological Tests

All tests were carried out on mice of the outbred stock Ipf:MIZ weighing 20-24 g. Hydrochlorides of the test compounds were dissolved in distilled water or suspended in 0.5% carboxymethyl cellulose and were administered in constant volumes ip. or per os in the amount of 0.1 ml/10 g and 0.2 ml/10 g of body weight, respectively. The control group of animals was obtaining the same amounts of the solvent.

Behavior of animals was monitored according to *Irwin*[18] during 4 h and *approximate acute toxicity* (LD_{50}) was evaluated according to *Morpurgo*[19] during 24 h by assigning a dose causing mortality in 50% of mice (LD_{50}) (if general condition of animals was bad monitoring was extended for the next 24 h). The tested compounds were administered in increasing doses from 3-2000 mg/kg of body weight.

Spontaneous locomotor activity of mice was observed in a test chamber equipped with a photocell during 30 min 1 h after administration of a compound.

Amphetamine induced locomotor activity

(+)-Amphetamine was administered to mice (5 mg/kg subcutaneously) 30 min after the treatment with a test compound (intragastic 1/5 of LD_{50}). After the next 30 min animals were placed in a test chamber and observed during 30 min. The control group obtained solvent and (+)-amphetamine.

Loss of the righting reflex

Compounds were administered in several increasing doses. After a few min animals were laid down in their spines. 30 sec of immobility was considered as a loss of the righting reflex.

Influence of hexobarbital narcosis

Hexobarbital (75 mg/kg intravenously) was administered to mice 1 h after treatment with test compounds. Time of narcosis was measured from the moment of loss of the righting reflex to its regaining.

Convulsions caused by electric shock (according to *Swinyard*[20])

Convulsions (the full tonic extension of all limbs) were provoked by means of maximal electroshock: 7 mA, 0.3 sec, corneal electrodes.

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