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Synthesis and neurotropic activity of silyl-substituted furfural thiosemicarbazones*

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5-Silyl-substituted-2-furaldehyde thiosemicarbazones were prepared by the condensation of the corresponding furfurals or furfural diethylacetals with thiosemicarbazide. The neurotropic activity of the synthesized thiosemicarbazones has been studied. The majority of the compounds examined possess high or medium neurotropic activity of the depressant type. They also show antihypoxic activity and decrease the duration of phenamine stereotype behaviour. Structure–activity correlation has been found.

Keywords: silyl-substituted furfural thiosemicarbazones, toxicity, neurotropic activity.

INTRODUCTION

Several types of nitrogen-containing furan derivatives possess remarkable neurotropic activity.[1] For example, the antidepressant activity of 5-phenyl-2-furamidines *ortho*-substituted in the phenyl ring by NO_2 or NH_2 groups is comparable with that of tricyclic antidepressants.[2]

We have shown that nitrogen-containing organosilicon and organogermanium derivatives of furan also exhibit neurotropic activity. Furans, containing aminoalkylsilyl substituents in the 2-position, are characterized by medium depressant activity (ED_{50}, 10–100 mg kg^{-1}).[3,4] Furylgermatranes[5] possess the same type and degree of neurotropic activity, but they are low-toxicity substances with LD_{50} values within the 1630–2960 mg kg^{-1} range. The depressant activity of 5-germyl-substituted 2-furylamines is somewhat higher. Among them the quaternary ammonium compounds[6] show the highest activity in rotating-rod and tube tests (ED_{50}, 2.5–4.1 mg kg^{-1}).

The present communication deals with the synthesis and neurotropic activity of silyl-substituted furfural thiosemicarbazones. The structure–activity correlation has been studied and the biological action of silyl-substituted furans has been compared with the activity of carbon- and sulphur-containing analogues.

* Dedicated to Dr Frederick E. Brinckman on the occasion of his retirement.

EXPERIMENTAL

Syntheses

Organic thiosemicarbazones (**I–VI**) are shown in Tables 1–3 for comparison. The diethylacetals which were used to generate the corresponding thiosemicarbazones **VII–XI** were prepared according to known methods[7,8] (Scheme 1).

Hydrosilylation of mono-substituted acetylene and ethylene derivatives (in the presence of H_2PtCl_6) with 5-dimethylsilylfurfural diethylacetal gave the known starting materials for the preparation of compounds **XII–XVII** (Scheme 2).

5-tert-Butylfurfural and 5-formylfurfural diethylacetals, from which the compounds **III** and **VI**, respectively, were obtained, were synthesized by the formylation of 2-tert-butylfuran[9] and furfural diethylacetal.[10]

5-Butylthio- and 5-methylthiofurfural diethylacetals (starting products for compounds **IV** and **V**) were prepared according to a known method.[11]

Elementary analysis was performed using a Carlo Erba instrument (model 1106, 1108).

Synthetic details of this last step were as follows.

5-[Dimethyl(2-phenyleth-1′-enyl)silyl]furfural thiosemicarbazone (XVII)

To a solution of 1.48 g (4.5 mmol) 5-[dimethyl(2′ - phenyleth - 1′ - enyl)silyl]furfural diethylacetal in 70% ethanol (10 cm^3) was added 0.41 g (4.5 mmol) of thiosemicarbazide and a catalytic amount of *p*-toluenesulphonic acid. The reaction mixture was refluxed for 10 min, cooled and filtered. The white precipitate was washed with water, then pentane, and dried in vacuum to

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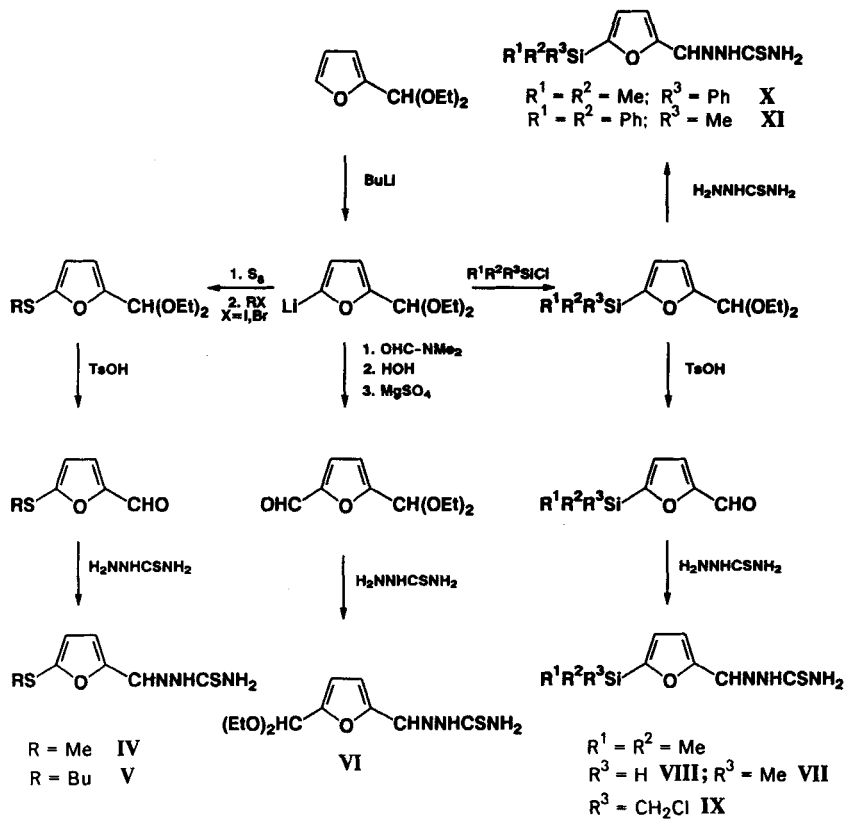


Scheme 1

yield 0.71 g of *trans*-5-[dimethyl(2′-phenyleth-1′-enyl)silyl]furfural thiosemicarbazone. When water was added to the filtrate the mixture of isomers (*cis*/*trans* ≈ 1:1) was obtained after filtration, washing and drying.

Compounds **X**, **XI** and **XIII–XVIII** were synthesized in the same way.

The reaction yields, elementary analysis data and melting points are summarized in Table 1.

5-[Dimethyl(3′,3′-dimethylbutyl)silyl]furfural thiosemicarbazone (XII)

To a solution of 1.3 g (5.5 mmol) 5-dimethyl(3′,3′-dimethylbutyl)silylfurfural in 70% ethanol (10 cm^3), 0.5 g (5.5 mmol) of thiosemicarbazide was added. The reaction mixture was refluxed for 10 min, cooled, filtered and washed with water, then pentane and dried in vacuum to yield 5-dimethyl(3′,3′-dimethylbutyl)silylfurfural thiosemicarbazone (1.32 g).

Compounds **I–IX** and **XII** were synthesized in the same way.

The reaction yields, elementary analysis data and melting points are summarized in Table 1. ^1H NMR spectra were recorded and were as expected for the proposed structures.

Pharmacological activity

The neurotropic activity of 5-substituted furfural thiosemicarbazones was studied on BALB/c, Icr:Icl, CBA mice and randomly bred rats. Solutions or aqueous suspensions of the compounds, prepared with Tween-80, were administered i.p. 30–45 min prior to the corresponding test. In all cases the control animals received an isotonic solution of sodium chloride with addition of the corresponding Tween concentrations administered i.p. The experimental study of the neurotropic properties was carried out in winter in accordance with previous work.[12]

The data obtained were processed statistically and the values of mean effective (ED_{50}) and mean lethal (LD_{50}) doses, in mg kg^{-1}, were determined according to a known method.[13] The neurotropic activity of the compounds **III**, **IX**, **XIII** and **XIX** was studied at a dose of 25 mg kg^{-1} and com-

pound **V** at a dose of 5 mg kg^{-1}. The others were studied at a dose of 50 mg kg^{-1}.

The mean duration of hexenal and ethanol anaesthesia, the interaction with phenamine and reserpine, the antihypoxic action and the anticorazole activity were established by determining average values and standard deviations ($M \pm m$). A student's t-test was applied to evaluate the statistical significance of differences between the mean values. Deviations were considered significant at $P \leq 0.05$.

RESULTS AND DISCUSSION

The study of the toxic properties demonstrated that the majority of the compounds examined possess medium toxicity (LD_{50}, 129–447 mg kg^{-1}; LD_{50} of compound **XIV**, 890 mg kg^{-1}; LD_{50} of compound **XV**, 708 mg kg^{-1}).

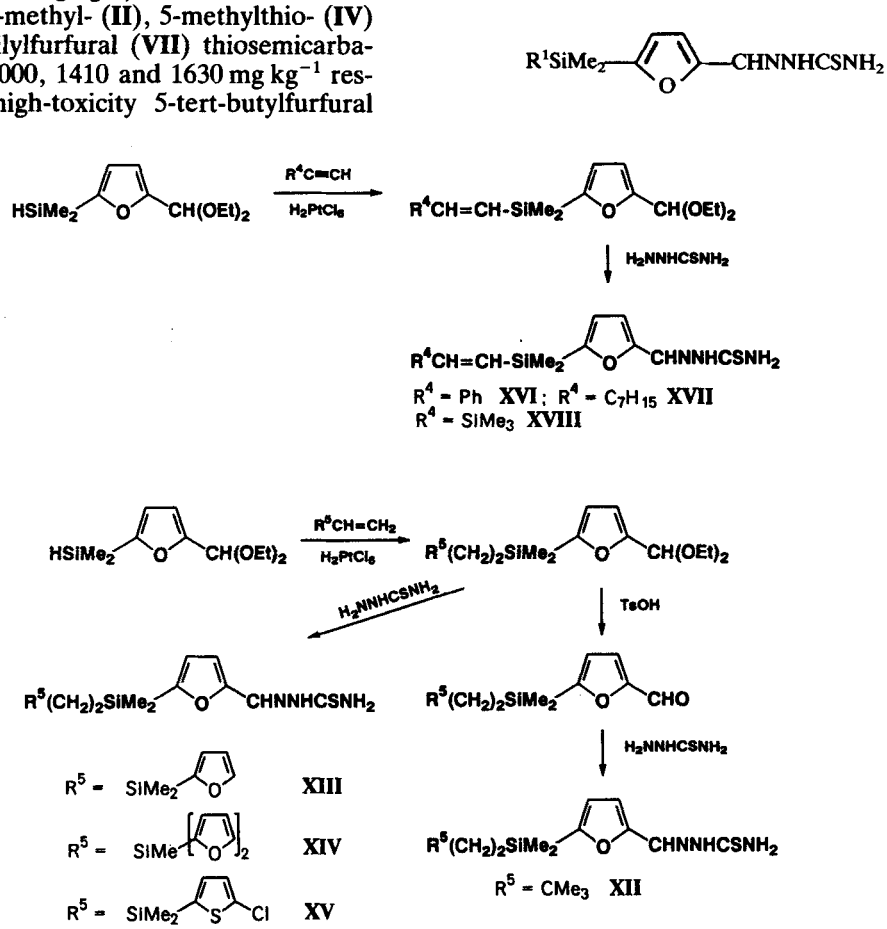
Low-toxicity 5-methyl- (**II**), 5-methylthio- (**IV**) and 5-trimethylsilylfurfural (**VII**) thiosemicarbazones (LD_{50}, >2000, 1410 and 1630 mg kg^{-1} respectively) and high-toxicity 5-tert-butylfurfural thiosemicarbazone **III** ($LD_{50} = 20.5$ mg kg^{-1}) are the exceptions.

The introduction of the methyl group in the 5-position of furan reduces the acute toxicity more than 15-fold. The insertion of a sulphur atom between the methyl group and the furan ring changes the LD_{50} value from >2000 mg kg^{-1} to 1410 mg kg^{-1}.

The substitution of two hydrogen atoms in the methyl group by ethoxy groups (compound **VI**) decreases the LD_{50} value 10-fold. The substitution of all hydrogen atoms in the methyl group of the compound **II** by methyl groups (compound **III**) evokes a sharp increase in the acute toxicity (100-fold).

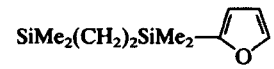
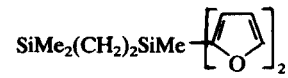
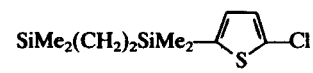
5-Trimethylsilylfurfural thioisemicarbazone (**VII**) the silyl analogue, is 80 times less toxic than 5-tertbutylfurfural thiosemicarbazone (III).

The lowest toxicity in the series of 5-silyl-substituted furfural thiosemicarbazones



Scheme 2

Table 1 5-Substituted furfural thiosemicarbazones

Compd	R	Yield (%)[a]	M.p. (°C)	Elemental analysis (%) Found C	H	N	Calc C	H	N
I	H	82.3	155	42.55	4.04	24.96	42.60	4.14	24.85
II	Me	85.1	170	46.11	4.91	22.95	45.90	4.92	22.95
III	CMe_3	88.7	175	53.13	6.43	18.74	53.31	6.71	18.65
IV	MeS	55.5	158	39.11	3.88	19.88	39.06	4.19	19.54
V	BuS	56.0	104	46.40	5.69	15.95	46.69	5.83	16.34
VI	$CH(OEt)_2$	85.0	147	48.12	6.25	15.00	48.71	6.27	15.5
VII	$SiMe_3$	90.1	176	45.08	6.28	17.39	44.81	6.22	17.42
VIII	$SiMe_2H$	72.3	177	42.03	5.69	18.21	42.26	5.76	18.48
IX	$SiMe_2CH_2Cl$	74.0	150	39.20	4.93	15.18	39.20	5.08	15.25
X	$SiMe_2Ph$	61.6	167	55.50	5.62	13.66	55.45	5.61	13.86
XI	$SiMePh_2$	80.2	150	62.58	5.20	11.24	62.47	5.21	11.51
XII	$SiMe_2(CH_2)_2CMe_3$	77.2	148	54.02	8.15	13.59	54.02	8.04	13.51
XIII		63.2	112	50.64	6.54	10.89	50.66	6.33	11.08
XIV		74.4	85	52.90	5.74	9.40	52.90	5.80	9.74
XV		63.7	132	44.76	5.52	9.74	44.70	5.59	9.78
XVI	$SiMe_2CH{=}CHPh$	66.9	157	58.61	5.86	13.03	58.36	5.78	12.77
XVII	$SiMe_2CH{=}CHC_7H_{15}$	68.8	120	57.89	8.55	11.85	58.12	8.26	11.97
XVIII	$SiMe_2CH{=}CHSiMe_3$	69.8	190	47.92	7.13	12.82	48.00	7.08	12.92

[a] Of the final step in the synthesis.

was displayed by compound **VII**. The substitution of the methyl group by H, CH_2Cl or Ph decreases the LD_{50} values four-to-six-fold. The introduction of the second phenyl group instead of the methyl one in compound **XI** produces no change in the LD_{50} value compared with compound **X**. The insertion of the alkenic —CH=CH— group between the silicon atom and R^1 leads to an increase of acute toxicity approximately two-fold. The substitution of the furan ring for thiophene in compound **XIII** as well as the replacement of the second methyl group at a silicon atom by the furyl group decreases the acute toxicity by a factor of two.

All the compounds examined exhibit, to different extents, action on locomotor activity, muscle tone and body temperature (Table 2).

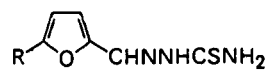
The starting thiosemicarbazide, the unsubstituted furfural thiosemicarbazone (except for the rotating-rod test, in which it has ED_{50} = 12.0 mg kg^{-1}) and also compounds **VII**, **X**, **XII**, **XIII**, **XVI** and **XVIII** demonstrated high depriming activity (ED_{50}, <1–10 mg kg^{-1}).

The therapeutic index of the initial thiosemicarbazide is small in all tests on locomotor activity, muscle tone and body temperature, owing to its high toxicity.

5-Trimethylsilylfurfural thiosemicarbazone (**VII**) exhibits the highest depriming activity and therapeutic index in these tests (ED_{50} in the rotating rod, tube, hypothermia tests is 0.69, 0.71 and 0.5 mg kg^{-1}, respectively; $I = LD_{50}/ED_{50} = 2362$, 2295 and 3260).

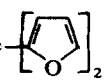
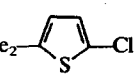
It has been found that 5-methylthiofurfural

Table 2 Acute toxicity of 5-substituted furfural thiosemicarbazones and their action on locomotor activity, muscle tone and body temperature in BALB/c and Icr:Icl mice (19–22 g)



Compd	R	LD_{50} (mg kg^{-1})	ED_{50} (mg kg^{-1}) Test				
			Rotating-rod	Tube	Traction	Hypothermia	Analgesia
I	H	129 (84–179)	12.0 (7.3–19.1)	6.0 (3.17–9.30)	4.47 (3.13–5.96)	7.55 (3.13–5.96)	25[a]
II	Me	>2000	44.7 (26.2–64.3)	44.7 (26.2–64.3)	>100	35.5 (24.9–46.1)	>100
III	CMe_3	20.5 (14.6–28.8)	16.3 (10.9–22.7)	17.8 (13.6–23.0)	21.6 (6.1–46.1)	20.5 (14.6–28.8)	20[a]
IV	MeS	1410 (920–2090)	258 (168–288)	239 (124–383)	>250	224 (144–285)	>250
V	BuS	190 (96–308)	17.8 (11.2–25.3)	14.1 (9.2–20.9)	16.3 (10.9–22.7)	17.8 (11.2–25.3)	50[a]
VI	$CH(OEt)_2$	205 (146–288)	112 (79–147.4)	56.4 (34.2–81.4)	44.7 (31.3–59.6)	95 (50.2–151.6)	103 (67.4–138.4)
VII	$SiMe_3$	1630 (1090–2270)	0.69 (0.24–1.3)	0.71 (0.5–0.93)	6.9 (2.4–13.0)	0.5 (0.31–0.6)	>50
VIII	$SiMe_2H$	447 (313–596)	21.8 (8.1–41.1)	44.7 (31.3–59.6)	41.0 (26.8–55.2)	27.4 (9.9–52.4)	500[a]
IX	$SiMe_2CH_2Cl$	410 (268–552)	16.3 (8.5–25.0)	89 (63.1–119.7)	17.8 (13.6–23.0)	16.3 (10.9–22.7)	100[a]

Table 2 *continued*

Compd	R	LD_{50} (mg kg^{-1})	ED_{50} (mg kg^{-1}) Test				
			Rotating-rod	Tube	Traction	Hypothermia	Analgesia
X	$SiMe_2Ph$	258 (168–357)	0.9 (0.63–1.2)	4.5 (3.1–5.9)	8.7 (3.0–1.64)	1.0 (0.67–1.38)	>50
XI	$SiMePh_2$	258 (168–357)	20.5 (14.6–28.8)	20.5 (14.6–28.8)	44.7 (26.5–64.3)	25.8 (16.8–35.7)	>100
XII	$SiMe_2(CH_2)_2CMe_3$	190 (96–308)	2.8 (1.6–4.2)	2.6 (1.7–3.6)	2.8 (1.6–4.2)	2.8 (1.6–4.2)	50[a]
XIII	$SiMe_2(CH_2)_2SiMe_2$– 	410 (268–552)	5.6 (3.4–7.4)	—	10.9 (4.1–20.6)	8.9 (5.6–12.9)	>50
XIV	$SiMe_2(CH_2)_2SiMe$– 	890 (631–1197)	22.4 (12–33.2)	22.4 (12–33.2)	17.8 (13.6–29)	20.5 (14.6–22.8)	>50
XV	$SiMe_2(CH_2)_2SiMe_2$– 	708 (430–1019)	89 (63.1–119.7)	—	205 (122–311)	258 (145–404)	>50
XVI	$SiMe_2CH{=}CHPh$	141 (68–209)	4.5 (3.1–5.9)	2.8 (1.6–4.2)	4.5 (3.1–5.9)	2.8 (1.8–3.7)	>250
XVII	$SiMe_2CH{=}CHC_7H_{15}$	355 (202–508)	41.0 (26.8–55.2)	22.4 (14.4–28.5)	51.5 (36.2–69.2)	2.8 (1.8–3.7)	100[a]
XVIII	$SiMe_2CH{=}CHSiMe_3$	205 (146–288)	0.5 (0.25–0.77)	0.35 (0.25–0.46)	8.9 (6.3–11.9)	0.32 (0.17–0.5)	>50
XIX	$H_2NNHCSNH_2.HCl$	12.9 (8.4–17.9)	2.24 (1.2–3.32)	2.24 (1.44–2.85)	1.9 (0.96–3.08)	2.9 (1.0–5.5)	10[a]

[a] No effect at these doses.

Table 3 Neurotropic activity of 5-substituted furfural thiosemicarbazones in BALB/c, Icr:Icl mice (body weight 19–22 g) and white male rats (body weight 180–210 g)

Compd	$M \pm m$ (% of control)					
	Hypoxia	Hexenal anaesthesia	Ethanol anaesthesia	Phenamine stereotype behaviour	Memory enhancement(s) (Retrogradal amnesia, %)	Corazole convulsions, clonic convulsions/ Lethal outcome
I	193.1*	117.2	—	—	—	146*/110
II	175.5*	128.0*	112.3	53.4*	0 (16.6)	96/182*
III	125.4	101.2	—	101.8	—	100/96
IV	156.2*	137.7*	143.4	40.0	0 (0)	79*/182*
V	163.7*	94.5	187.7*	105.2	—	112/127
VI	151.1*	159.3*	98.6	81.0*	—	142*/180*
VII	163.4*	152.2*	93.8	89.6	0 (0)	104/258*
VIII	125.1	135.5	—	59.2*	—	221*/109
IX	104.7	139.5*	98.8	50.5*	15.5 ± 12.3 (60)	111/120*
X	108.8	104.3	177.9*	35.8*	0 (0)	62*/156*
XI	115.4	228.2*	190.4*	26.5*	0 (0)	108/183*
XII	198.3*	225.8*	225.9*	96.8	117 ± 30.5* (60)	123/150*
XIII	139.2*	94.4	57.4*	141.6*	61 ± 7.2* (100)	109/111
XIV	188.9*	118.0	128.8	83.7	67 ± 27.7* (40)	119/194*
XV	133.3*	112.5*	132.2	39.4*	38.5 ± 11.3 (60)	127*/179*
XVI	215.5*	245.5*	331.0*	188.9*	65.0 ± 32.2 (30)	145*/190*
XVII	176.9*	326.1*	127.2*	65.5*	44.0 ± 26.0 (60)	123*/162*
XVIII	163.5*	169.2*	155.6	27.8*	55.0 ± 27.1 (33.3)	84/106
XIX	100.8	95.2	—	—	—	155*/95

* Differences are statistically significant vs control at $P \leq 0.05$.

thiosemicarbazone (IV) (ED_{50} in rotating rod and tube tests, 258 and 239 mg kg^{-1}, respectively) and 5-{dimethyl-β-[dimethyl(5′-chloro-2′-thienyl)silyl]- ethylsilyl}furfural thiosemicarbazone (XV) (ED_{50} in rotating rod and traction tests, 89 and 205 mg kg^{-1}, respectively) possess the lowest neurotropic activity of the depriming type.

The other derivatives show medium depressant activity; their ED_{50} values lie within the 10–100 mg kg^{-1} range in the tests mentioned above. It must be noted that 5-tert-butylfurfural thiosemicarbazone (III) possesses activity only in doses close to toxic.

The hypothermic action of the thiosemicarbazones studied is expressed approximately at the same doses as their action on locomotor activity.

The majority of 5-substituted furfural thiosemicarbazones studied at a dose of 50 mg kg^{-1} reliably increase the endurance of the animals under hypoxia. 5-[Dimethyl-(2-phenyl-eth-1′-enyl)silyl]furfural thiosemicarbazone (XVI) 5-[dimethyl(3′,3′-dimethylbutyl)silyl]furfural thiosemicarbazone (XII) and furfural thiosemicarbazone (I) are the most active among them, prolonging the life of animals by 115.5%, 98.3% and 93.1%, respectively. The antihypoxic activity of the compounds IX–XI is less expressed.

Almost all compounds studied at a dose of 50 mg kg^{-1}, and 5-chloromethyldimethylsilylfurfural thiosemicarbazone (IX) at a dose of 5 mg kg^{-1}, prolong hexenal anaesthesia. The greatest extension of the duration of hexenal anaesthesia (by 226.1%) was observed during administration of 5-dimethyl-(non-1′-enyl)silylfurfural thiosemicarbazone (XVII).

Ethanol anaesthesia is decreased by 42.6% under the influence of compound XIII at a dose of 5 mg kg^{-1}. The compounds VI, VII and IX do not change reliably the duration of ethanol anaesthe-

sia. The other derivatives prolong the anaesthetic action of ethanol by 27.2% (compound **XVII**) to 125.9% (compound **XII**).

The compounds examined (except compounds **XIII** and **XVI**) depress the pharmacological effects of phenamine. 5-Methyldiphenylsilylfurfural thiosemicarbazone (**XI**) and 5-[dimethyl(2′ - trimethylsilyl - eth - 1′ - enyl)silyl] - furfural thiosemicarbazone (**XVIII**) are the most active in this respect, decreasing the central stimulating action of phenamine by 73%. 5-Methylthiofurfural thiosemicarbazone (**IV**) and 5-dimethylphenylsilylfurfural thioisemicarbazone (**X**) decrease the duration of phenamine stereotype behaviour by 65%, and others follow them.

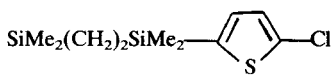
5 - [Dimethyl(2′ - phenyl - eth - 1′ - enyl)silyl] - furfural thiosemicarbazone (**XVI**) and 5-{dimethyl-β - [dimethyl(2′ - furyl)silyl]ethylsilyl}furfural thiosemicarbazone (**XIII**) on the contrary, strengthen stimulating action on phenamine locomotor activity and phenamine stereotype behaviour duration by 88.9% and 41.6%, respectively.

All the thiosemicarbazones studied, with the exception of compounds **III**, **V**, **XIII** and **XVIII**, display pronounced anticorazole activity, increasing the corazole dose necessary for tonic or clonic convulsions followed by a lethal outcome, by 49.7% to 178.7%.

Such compounds as 5-dimethyl(3′,3′-dimethylbutyl)silylfurfural thiosemicarbazone (**XII**), 5-{dimethyl-β-[dimethyl(2′-furyl)silyl]-ethylsilyl}furfural thiosemicarbazone **XIII**) and 5-dimethyl[2′(methyldifurylsilyl)ethyl]silylfurfural thiosemicarbazone (**XIV**) possess pronounced influence on memory processes, improving them. Compound **XIII** completely prevent retrogradal amnesia, caused by electric shock; compounds **IX**, **XII**, **XV** and **XVII** reduced it by 60%, **XVI** and **XVIII** by 30 to 40%.

In tracing the correlation to the structure of the thiosemicarbazones examined (their neurotropic activity) it is necesary to note that by varying the substituents in the 5-position of the furan ring, one can change the degree of the compound's activity, as well as the spectrum of its pharmacological action.

The presence of MeS (**IV**), $CH(OEt)_2$ (**VI**) and



(**XV**)

groups in the 5-position of furan causes strong reductions in depriming activity. The substitution of chloro-containing thiophene for furan (compounds **XV**) increases depriming activity in the rotating-rod test four-fold, and the traction test ten-fold; moreover it changes the neurotropic activity spectrum of the compound.

Thus, for example, 5-{dimethyl-β-[dimethyl(2′-furyl)silyl]ethylsilyl}furfural thiosemicarbazone (**XIII**) shows an activating effect on the central nervous system, i.e. it reduces the duration of ethanol anaesthesia, increases the duration of phenamine stereotype behaviour, possesses pronounced influence on memory processes, improving learning and completely prevents retrogradal amnesia, whereas 5-{dimethyl-β-[dimethyl(5′-chloro-2′-thienyl)silyl]ethylsilyl}furfural thiosemicarbazone (**XV**) on the contrary, shows a sedative effect in all these tests.

The appearance of the second phenyl group in the series: $R = SiMe_2Ph$ (**X**), $SiMePh_2$ (**XI**), $SiMe_2CH{=}CHPh$ (**XVI**) reduces depriming activity in different tests by 5- to 20-fold. The insertion of —CH=CH-group between the silicon atom and the phenyl group slightly changes the depriming activity.

The sedative activity of the compounds increases in the series: $R = SiMe_2CH{=}CHPh > SiMePh_2 > SiMe_2Ph$ according to their influence on the action of anaesthetic substances and corazole.

5-Dimethylphenylsilylfurfural thiosemicarbazone (**X**) and 5-methyldiphenylsilylfurfural thiosemicarbazone (**XI**) do not express antihypoxic activity and decrease the pharmacological effects of phenamine by 52.8% and 65.6%, respectively, whereas 5-[dimethyl(2′-phenyl-eth-1′-enyl)silyl]furfural thiosemicarbazone (**XVI**) prolongs animal life under hypoxia more than two-fold, increases the pharmacological action of phenamine by 89% and positively influences the memory processes.

The substitution of methyl groups in the $SiMe_3$ of 5-trimethylsilylfurfural thiosemicarbazone **VII** by H (**VIII**), CH_2Cl (**IX**) and Ph (**X**) causes decrease or complete loss of the antihypoxic activity.

To summarize the above results, we arrive at the conclusion that the majority of 5-substituted furfural thiosemicarbazones studied possess pronounced neurotropic activity. Silyl-substituted furfural thiosemicarbazones are more active than their unsubstituted carbon analogues and have a specific spectrum of pharmacological activity.

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