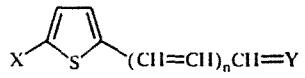
Chemistry of Heterocyclic Compounds, Vol. 31, No. 5, 1995

SYNTHESIS AND PSYCHOTROPIC PROPERTIES OF AZOMETHINE DERIVATIVES OF THIOPHENE

L. N. Khokhlova, S. Germane, N. P. Erchak, and É. Lukevits

A series of azomethine derivatives was obtained by condensation of 2-thiophenaldehyde and 5-substituted (alkyl, bromine, tert-butyl, trimethylsilyl)-2-thiophenaldehydes withsemicarbazide, thiosemicarbazide, aminohydantoin, and 2-semicarbazide acetic acid. Their psychotropic activity was investigated. It was found that incorporation of a tert-butyl group in position 5 of the thiophene ring potentiates the toxicity of the compound. 5-Trimethylsilyl- and 5-tert-butyl-2-thiophenaldehyde thiosemicarbazones exhibit elevated neurotropic activity. These compounds cause the stimulating effect of phenamine to appear, increasing the motor activity of animals by two times and prolonging the effect of hexenal-induced sleep. Substitution of thiosemicarbazone by semicarbazone decreases the activity except for hexenal sleep, where the 5-tert-butyl-2-thiophenaldehyde semicarbazone was 1.5 times more active than the thiosemicarbazone.

We previously showed that nitrogen-containing derivatives of thiophene exhibit psychotropic activity [1-3]. The psychotropic properties of azomethine derivatives of thiophene with alkyl, trimethylsilyl, and halogen substituents in position 5 of the thiophene ring were investigated here. A number of thiophene derivatives with the following general formula were synthesized for this purpose:



I–XI

I, III—VII n = 0, Y = NNHCSNH$_2$; I X = H; III X = Br; IV X = Me; V X = Et; VI X = CMe$_3$; VII X = SiMe$_3$; II X = H, n = 1; Y = NNHCSNH$_2$; VIII X = CMe$_3$, n = 0; Y = NNHCONH$_2$; IX—XI X = SiMe$_3$, n = 0; IX Y = NNHCONH$_2$; X Y = iminohydantoin, XI Y = NN(CH$_2$COOH)CONH$_2$

The compounds were prepared by condensation of the corresponding aldehyde with semicarbazide, thiosemicarbazide, aminohydantoin, and 2-semicarbazide acetic acid in boiling in 50% ethanol medium for 1 h.

5-tert-Butyl and 5-trimethylsilyl-2-thiophenaldehdyes are described in [4, 5]. The characteristics of the synthesized compounds are reported in Table 1, and the results of the pharmacological study are presented in Table 2.

In studying the acute toxicity, it was found that 2-thiophenaldehyde thiosemicarbazone (compound I) has moderate toxicity (LD_{50} = 325 mg/kg); its vinyl analog (compound II) is more than two times less toxic (LD_{50} = 708 mg/kg). Incorporation of a tert-butyl group in position 5 of the thiophene ring (compound VI) potentiates the toxicity of the compound by 6 times (LD_{50} = 56.4 mg/kg). Alkyl substituents and a trimethylsilyl group in this position have little effect on the acute toxicity index. Substitution of a thiosemicarbazone group by a semicarbazone group in 5-tert-butyl-2-thiophenaldehyde decreases the toxicity by more than two times. Incorporation of semicarbazone, aminohydantoin, and 2-semicarbazide acetic acid groups in 5-trimethylsilyl-2-thiophenaldehyde instead of a thiosemicarbazone group does not significantly affect the acute toxicity index.

Most of the compounds are moderately active (compounds II-V, VIII) based on neurotropic activity indexes ("rotating rod," "tube," "pulling on bar," hypothermia tests). The effective doses of the most active compound in this group, compound III, are within the limits of 11.2-25.8 mg/kg. Compounds I and IX-XI are not very active (ED_{50} of compound X = 44.7-70.8

Latvian Institute of Organic Synthesis, Riga, LV-1006. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 629-632, May, 1995. Original article submitted May 12, 1995.

0009-3122/95/3105-0553$12.50

TABLE 1. Characteristics of Synthesized Compounds I-XI

Compound	Empirical formula	Mp, °C	Yield, %	Compound	Empirical formula	Mp, °C	Yield, %
I	$C_6H_7N_3S_2$*	190...194	38	VII	$C_9H_{15}N_3S_2Si$	192	71
II	$C_9H_{10}N_3S_2$	120	90	VIII	$C_{10}H_{15}N_3OS$	230...235	68
III	$C_6H_6BrN_3S_2$ *2	180...182*2	38	IX	$C_9H_{15}N_3OSSi$	210	83
IV	$C_7H_9N_3S_2$ *2	160	85	X	$C_{11}H_{14}N_3O_2SSi$	235	98
V	$C_8H_{11}N_3S_2$	140	89	XI	$C_{11}H_{17}O_3N_3SSi$	224	52
VI	$C_{10}H_{15}N_3S_2$ *2	192...195*2	71				

*Mp of compound I = 185-186°C [7].

*2 Mp = 182-184°C for compound III, 160-161°C for IV, and 182-183°C for VI [8].

mg/kg). Compounds VI and VII — 5-trimethylsilyl-2-thiophenaldehyde thiosemicarbazone and its carbon analog — have elevated neurotropic activity (effective doses in the above tests within the limits of 2.1-5.15 mg/kg). They exhibit marked analgesic properties. Substitution of a thiosemicarbazone group by a semicarbazone group decreases the activity.

All of the substances investigated in the dose of 50 mg/kg prolonged the life of the animals in conditions of oxygen starvation. The best results were obtained with compounds II, III, and VII, whose administration prolonged the life of the animals by 235, 109, and 111%, respectively.

Incorporation of a trimethylsilyl group in position 5 of the thiophene ring caused the appearance of activity. Substitution of thiosemicarbazone by semicarbazone in 5-trimethylsilyl-2-thiophenaldehyde, as in its carbon analog, reduced the activity.

In the phenamine stereotype test, thiosemicarbazones of unsubstituted and 5-substituted 2-thiophenaldehyde with alkyl and halogen substituents (compounds I-V) antagonized the effects of phenamine. Compounds with tert-butyl and trimethylsilyl groups (compounds VI and VII) were exceptions. Administration of these compounds caused the stimulating effect of phenamine to appear, increasing the motor activity of the animals by 93 and 100%, respectively. Interesting results were obtained in substitution of the thiosemicarbazone of 5-trimethylsilyl-2-thiophenaldehyde by semicarbazone (compound IX) and aminohydantoin (compound X) — administration of these substances antagonized the effects of phenamine, decreasing motor activity by 43 and 76%, respectively.

Almost all compounds (except for II and X) potentiated the effect of hexenal-induced sleep. Compounds III and VI-VIII most effectively prolonged hexenal sleep (166, 117, 253, and 229%). Administration of 5-tert-butyl-2-thiophenaldehyde semicarbazone increased, while 5-trimethylsilyl-2-thiophenaldehyde semicarbazone decreased the duration of hexenal sleep.

EXPERIMENTAL

The composition and chemical structure of the synthesized compounds were confirmed by the data from elemental analysis, which were in agreement with the calculations.

General Method for Preparation of Compounds (I-XI). A mixture of 0.05 mole of the corresponding aldehyde and 0.05 mole of semicarbazide, thiosemicarbazide, aminohydantoin, or 2-semicarbazide acetic acid was boiled with a reflux condenser in 50% ethanol medium for 1 h. After cooling, the precipitated residue was filtered off and recrystallized from 50% ethanol.

Pharmacological Evaluation of the Synthesized Compounds. The neurotropic activity of the compounds was investigated on Icr:Icl, BALB/c, and CBA mice of both sexes weighing 18-23 g in the winter. The temperature in the premises was maintained within the limits of 21 ± 2°C. Aqueous suspensions of the substances prepared with addition of Tween-80 were administered intraperitoneally 30-45 min before the experiment began. The same volume of isotonic saline solution was injected into the peritoneal cavity of the control animals. The effect of the substances was comparatively evaluated on groups of 6-8 animals with administration of the compounds in the dose of 50 mg/kg. The experimental data were statistically processed. The mean values of the LD_{50} and ED_{50} for 12-25 observations was determined by the rapid method in [6]. The arithmetic mean values and standard error ($M \pm m$) were calculated to evaluate the mean duration of hexenal sleep, phenamine stereotypy,

TABLE 2. Psychotropic Activity of Azomethine Derivatives of Thiophene I-XI

Compound	LD_{50}, mg/kg	Test							
		ED_{50}, mg/kg					M±m, % of control		
		"rotating rod"	"tube"	"pulling on bar"	analgesia	hypothermia	hypoxia	phenamine stereotypy	hexenal sleep
I	325 (219...455)	70,8 (43...102)	51,5 (29,1...78,6)	51,5 (29,1...78,6)	> 250	56,4 (38,7...74,3)	136,5*	86,7	132,2*
II	708 (490...1019)	17,8 (13,6...23,0)	44,7 (26,5...64,3)	28,2 (18,3...37,2)	> 100	16,3 (10,9...22,7)	334,8*	113,4	75,1
III	205 (146...288)	11,2	12,9 (8,4...17,6)	11,8 (2,9...24,0)	29,6 (9,3...61,3)	6,9 (2,4...13,0)	209,6*	68,4*	266,3*
IV	477 (248...767)	25,8 (16,8...35,7)	41 (26,8...55,2)	41 (26,8...55,2)	> 100	37,9 (19,3...59,4)	104,4	57,2*	125,9
V	477 (313...569)	14,1 (9,2...20,9)	32,5 (21,9...45,6)	22,4 (14,4...28,5)	70,8 (43...102)	17,8 (13,8...23,0)	123,2	69,7*	115,5
VI	56,4 (34,2...81,4)	2,6 (1,7...3,6)	2,5 (1,7...3,6)	2,6 (1,6...4,2)	4,1 (1,7...3,6)	2,1 (1,5...2,9)	118,3	192,7*	217,6*
VII	224 (144...285)	2,82 (1,83...3,72)	5,15 (2,91...7,87)	4,47 (2,65...6,43)	> 200	4,47 (2,65...6,43)	211,4*	200,0*	352,7*
VIII	163 (109...227)	16,3 (10,9...22,7)	20,5 (14,6...28,8)	16,3 (10,9...22,7)	> 50	19,1 (16,8...20,4)	102,2	120,3	329,4*
IX	300	44,7 (31,3...59,6)	81,5 (56,7...111)	> 200	> 200	205 (146...288)	134,0	57,2	146,9*
X	400	70,8	44,7 (31,3...59,6)	> 200	> 100	51,5 (36,2...69,2)	132,2	24,0	71,5
XI	300 (158...489)	148 (35...294)	282 (183...372)	282 (59...419)	> 500	205 (146...288)	144,7	144,7	119,3

*Differences in comparison to the controls were statistically significant for $p > 0.05$.

hypoxia, and hypothermia. The significance of the differences between the mean values was estimated with Student's criterion, and the differences were considered reliable for a probability level of $p \leq 0.05$.

The acute toxicity was determined in intraperitoneal administration of the substances and establishment of the lethal dose, LD_{50}.

REFERENCES

1. L. N. Khokhlova, S. Germane, N. P. Erchak, and E. Lukevits, Khim. Geterotsikl. Soedin., No. 3, 316 (1994).
2. E. Lukevits, S. Germane, N. P. Erchak, and O. A. Pudova, Khim. Farm. Zh., No. 4, 42 (1981).
3. E. Lukevits, S. Germane, O. A. Pudova, and N. P. Erchak, Khim. Farm. Zh., No. 10, 52 (1979).
4. F. Shelly, J. Heterocycl. Chem., **3**, 493 (1966).
5. J. Belen'kii and A. P. Yakubov, Tetrahedron, **40**, 2471 (1984).
6. V. B. Prozorovskii, M. P. Prozorovskaya, and V. M. Demchenko, Farm. Toksikol., No. 4, 497 (1978).
7. F. E. Anderson, C. J. Duca, and J. V. Scudi, J. Am. Chem. Soc., **73**, 4967 (1951).
8. E. A. Campaigne, P. A. Monroe, and B. Arnwine, J. Am. Chem. Soc., **75**, 988 (1953).