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SYNTHESIS AND PSYCHOTROPIC PROPERTIES OF BIS(2-THENYLIDENE)DIAMINES AND THEIR SILYL DERIVATIVES

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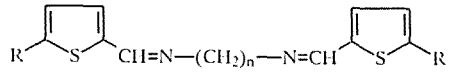
The condensation of diamines with the corresponding aldehydes gave bis(2-thenylidene)diamines and their silyl derivatives. The structure of the compounds has been confirmed by their PMR spectra. It has been shown that the introduction of the trimethylsilyl group increases the toxicity, prolongs the hexenal narcosis and the antihypoxy activity, has a positive effect on the memory processes, and has no influence on the coordination of movements, the muscle tone, and the body temperature. All compounds possess an antialcohol activity, whereby the silyl derivatives have the stronger one.

It has been established earlier that the silicon-functional derivatives of thiophene possess a psychotropic activity [1-3]. The present study is devoted to the influence of the trimethylsilyl group in position 5 of the thiophene ring on the psychotropic activity of carbon-functional derivatives of thiophene. With this objective in mind we have synthesize a series of bis(2-thenylidene)diamines and their silyl derivatives with the general formula:



Ia—e, IIa—e

Ia—e R = H; IIa—e R = Me_3Si; a n = 0, b n = 2, c n = 3, d n = 4, e n = 6

The compounds were obtained by the condensation of the corresponding aldehyde with the diamine by refluxing for 1 h in absolute ethanol. The synthesis of 5-trimethylsilyl-2-thiophene aldehyde has been described in [4]. The characteristics of the synthesized compounds are given in Table 1, the results of the pharmacological investigation of the synthesized compounds in Table 2.

When investigating the acute toxicity it was found that the toxicity of the non-silyl derivatives of the diamines Ia-e was low (LD_{50} = 1780-2000 mg/kg) (lethal dose); among the silyl analogs some compounds possess a medium toxicity (for IIb-d (n = 2-4) LD_{50} = 708-1030 mg/kg). The acute toxicity of compounds Ia and IIa, in which the methylene bridge between the nitrogen atoms is missing, is virtually the same (LD_{50} = 2000 and 2240 mg/kg respectively).

The influence of all investigated substances on the coordination of movements, the muscle tone, and the body temperature of the test animals is negligible (ED_{50} > 250 mg/kg).

When studying the influence of diamines I and II on the memory processes, the influence was assessed from the conditional reflex of passive avoidance (CRPA) and retrograde amnesia (RA). Better results were obtained for compounds Ia and IIa, after the introduction of which the latent period increased to 94.0 and 97.5 sec respectively (to 3.5 sec in the control test). These compounds prevented retrograde amnesia in 83.3 and 66.7% of the cases (in 10-15% of the cases in the control test). The latent period of CRPA was 10.8 and 12.5 sec respectively under the influence of silyl derivatives IIb, d (n = 2, 4) and under the influence of non-silyl derivatives Ib, d 48.3 and 51.6 sec. The retrograde amnesia coefficient for compounds Ib, d is higher by a factor of 2 than for compounds IIb, d. The opposite relationship was obtained for compounds Ic, e and IIc,

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TABLE 1. Characteristics of Synthesized Compounds

Compound	Empirical formula	mp, °C	PMR spectra, δ, ppm	Yield, %
Ia	$C_{10}H_8N_2S_2$	60	6,98...7,47 (H_{thioph}; 7,89 (—CH=)	68
Ib	$C_{12}H_{12}N_2S_2$	87	3,91 (N—CH_2); 7,04...7,38 (H_{thioph}; 8,36 (—CH=)	77
Ic	$C_{13}H_{14}N_2S_2$	68	2,11 (C—CH_2—C); 3,70 (N—CH_2); 7,00...7,42 (H_{thioph}; 8,38 (—CH=)	69
Id	$C_{14}H_{16}N_2S_2$	75	1,75 (—C—$(CH_2)_2$—C); 3,61 (N—CH_2); 7,00...7,42 (H_{thioph}; 8,37 (—CH=)	90
Ie	$C_{16}H_{20}N_2S_2$	45	1,39...1,69 (C—$(CH_2)_4$—C); 3,56 (N—CH_2); 6,99...7,39 (H_{thioph}; 8,34 (—CH=)	50
IIa	$C_{16}H_{24}N_2S_2Si_2$	132	0,35 (Si—CH_3); 7,23...7,48 (H_{thioph}; 8,81 (—CH=)	48
IIb	$C_{18}H_{28}N_2S_2Si_2$	82	0,31 (Si—CH_3); 3,91 (N—CH_2); 7,14...7,31 (H_{thioph}; 8,81 (—CH=)	51
IIc	$C_{19}H_{30}N_2S_2Si_2$	*	0,32 (Si—CH_3); 2,08 (—C—CH_2—C); 3,66 (N—CH_2); 7,05...7,37 (H_{thioph}; 8,38 (—CH=)	45
IId	$C_{20}H_{32}N_2S_2Si_2$	63	0,31 (Si—CH_3); 1,75 (—C—$(CH_2)_2$—C); 3,61 (N—CH_2); 7,17...7,29 (H_{thioph} 8,37 (—CH=)	36
IIe	$C_{22}H_{36}N_2S_2Si_2$	*	0,31 (Si—CH_3); 1,38, 1,69 (—C—$(CH_2)_4$—C); 3,56 (N—CH_2); 7,17...7,30 (H_{thioph}; 8,34 (—CH=)	53

*Oily liquid.

e (n = 3, 6). After the introduction of compounds Ic, e the latent period of CRPA corresponded to the control test and of the silyl analogs IIc, e it was equal to 58.3 and 50.8 sec. Retrograde amnesia was prevented by these compounds in 66.6% of the cases.

In a dose of 50 mg/kg all investigated substances prolonged the life of the animals at the conditions of hypoxic hypoxia, whereby the antihypoxic activity of the non-silylated derivatives Ia-e was pronounced more strongly. The best result was obtained with the compound Ie (n = 6), the introduction of which prolonged the life of the animals by 55%; the addition of compounds Ia and IIa prolonged the life by 41 and 43% respectively.

Under the influence of the silyl derivatives of the diamines the effect of the hexenal narcosis was intensified, while by the introduction of the non-silyl derivatives Ia and Id it was shortened by 25.3 and 28.8%.

In the test "phenamine locomotor activity" the introduction of compound Ia reduced it by 26% and the introduction of IIa increased by 86.3% the locomotor activity. The influence of the other compounds was negligible.

The results obtained in the ethanol narcosis were of the greatest interest for the further investigations. The addition of all synthesized compounds reduces the time of action of the ethanol narcosis; the non-silyl derivatives reduce it by 50-70%, the silyl derivatives by 71-83%. The best result was obtained with compound IIa (n = 0), the introduction of which reduced the duration of the ethanol narcosis by 83%. The antialcohol activity of the obtained compounds is probably related to the presence of an antihypoxic effect and to a favorable action on the memory processes.

EXPERIMENTAL

The PMR spectra were taken on a Bruker WH-90/DS spectrometer in $CDCl_3$, with TMS as the internal standard. The elemental analysis data for C, H, and N in the synthesized compounds correspond to the calculated values.

Bis(2-thenylidene)hydrazine (Ia). A mixture of 0.5 g (0.01 mole) hydrazine hydrate and 2.24 g (0.02 mole) thiophene aldehyde in 50 ml absolute ethanol is refluxed with a reflux condenser for 1 h in a stream of argon. The mixture is then cooled, treated with active carbon and refluxed for a further 10-15 min. The reaction mixture is filtered hot, the ethanol is stripped from the filtrate, leaving the product Ia. The compounds Ib-e and IIa-e are synthesized in the same way; the crystals remaining after removal of the ethanol are washed with ether.

TABLE 2. Psychotropic Activity of Bis(2-thenylidene)diamines Ia-e and of their Silyl Derivatives IIa-e

Compound	LD_{50}, mg/kg	Test										
		ED_{50}, mg/kg*				M ± m, % of control test						
		"rotating rod"	"tube"	"tightening on cross-beam"	hypothermia	CRPA	RA	hypoxia	hexenal narcosis	ethanol narcosis	corazol spasms	phenamine locomotor activity
Ia	>2000	258 (145...404)	205 (122...311)	125 (144...285)	258 (168...357)	94,0±18,6*2	83,3	141,8*2	75,8*2	41,8*2	86,7	74,1*2
Ib	1780 (1360...2300)	258 168...357)	204 (144...285)	258 (168...357)	282 (183...372)	48,3±25,0	33,3	113,0*2	87,3	30,4*2	70,0*2	132,8
Ic	1780 (1120...2530)	258 (168...357)	258 (168...357)	258 (168...357)	282 (183...372)	4,0±2,0	33,3	140,4*2	102,3	50,6*2	113,8	124,7
Id	1780 (1360...2300)	>500	>500	>500	>500	51,6±15,8*2	33,3	136,0*2	71,3*2	41,2*2	122,9	58,4*2
Ie	1780 (1380...2300)	443 (313...596)	325 (219...456)	447 (313...596)	410 (268...552)	5,0±2,2	16,6	155,0*2	150,2*2	41,1*2	69,4*2	145,0*2
IIa	2240 (1200...3320)	274 (99...529)	282 (159...419)	282 (159...419)	282 (159...419)	97,5±17,5*2	66,7	143,9*2	116,3	17,7*2	104,8	186,3*2
IIb	708 (501...925)	141 (68...209)	224 (144...285)	282 (159...419)	282	10,8±9,1	16,6	102,9*2	103,4	24,1*2	84,2	84,9
IIc	~500	>250	>250	>250	>250	58,3±20,4*2	66,7	120,8*2	96,6	25,9*2	86,7	87,4
IId	1030 (674...1384)	342 (78...734)	410 (218...552)	>500	355 (249...461)	12,5±10,2	16,7	126,2*2	104,5	28,5*2	88,3	74,5*2
IIe	>2000	325 (172...502)	410 (218...512)	410 (218...552)	325 (219...455)	50,8±15,7*2	66,6	123,8*2	100,0	21,5*2	104,5	76,8*2

*The limits of variations are shown in brackets.

*2The differences in comparison with the control test are statistically reliable at P = 0.05.

Pharmacological Assessment of the Synthesized Compounds. The neurotropic activity of the synthesized compounds was studied on mice of the lines Icr:Ic1, BALB/c, and CBA of both sexes with a mass of 18-23 g in the winter season. The room temperature was maintained within the limits 21 ± 2°C. Solutions of compounds IIc and IIe in olive oil or aqueous suspensions of the remaining substances, prepared with the addition of Tween-80, were introduced intraabdominally 30-45 min (the oily solutions 60 min) before the test. The same volume of a sodium chloride isotonic solution was injected into the abdominal cavity of the control animals. The effect of the substances was compared on groups of animals, consisting of 6-8 individuals when injecting the investigated compounds in doses of 50 mg/kg. The experimental data were treated statistically. The mean values of LD_{50} and ED_{50} for 12-25 observations were determined by a rapid method given in [5]. The arithmetical means and their standard deviations (M ± m) were calculated to assess the average duration of the narcotic effect of hexenal and the phenamine stereotypy, the protective properties in the corazol spasms and hypoxia, the degree of hypothermia, the influence on the memory processes, and retrograde amnesia. The significance of differences between mean values were assessed by Student's criterion: differences were considered as significant at a probability level $p \leq 0.05$.

The effect of the substances on the central nervous system was estimated from their influence on the coordination of movements and the muscle tone by the tests "rotating rod" (8 rpm for 2 min on an apparatus of the firm Ugo Basile), "tube" (glass tube with the dimensions 30 × 2 cm, for 30 sec), and "tightening on crossbeam" (metal wire, diameter 2 mm, for 5 sec); from the influence on the body temperature: by measuring the rectal temperature with an electric thermometer (the criterion for the test was a lowering of the temperature by 3°C and more); from the analgesic effect, determined by the "hot plate" method; from the antispasmodic activity, estimated by the maximum electric shock test (a.c. current with an intensity of 50 mA and a frequency of 50 pulses/sec, duration of stimulation 0.2 sec), from the corazol spasms test, caused by the intravenous titration with 1% corazol solution at a rate of 0.01 ml/sec; from the influence on the duration of the hexenal narcosis (70 mg/kg intravenously) and the ethanol narcosis (25% solution of ethanol intraabdominally, dose 5 g/kg); from the influence on the life time of the animals at the condition of hypoxic hypoxia, created by placing the mouse in a separate chamber with a volume of 220 cm^3 without absorption of CO_2; from the change in the locomotor activity, enforced by phenamine (10 mg/kg) subcutaneously); from the effect on reserpine hypothermia and the appearance of ptosis (0.01% reserpine in dose of 2.5 mg/kg intraabdominally, 2.5 h before the investigation), determined 1, 2, and 3 h after the injection of the investigated substances into the abdominal cavity; from the influence on the development of the conditional reflex of passive avoidance (latent period in seconds, spent by the animal in a light chamber), and the degree of retrograde amnesia, caused by an electric shock.

The acute toxicity was determine by the intraabdominal introduction of the investigated substances and by establishing the lethal dose (LD_{50}).

REFERENCES

1. É. Lukevits, S. Germane, N. P. Erchak, and O. A. Pudova, Khim.-farm. Zh., No. 4, 42 (1981).
2. É. Lukevits, S. Germane, O. A. Pudova, and N. P. Erchak, Khim.-farm. Zh., No. 10, 52 (1979).
3. É. Lukevits, S. Germane, N. P. Erchak, and E. P. Popova, Khim.-farm. Zh., No. 2, 67 (1978).
4. V. B. Prozorovskii, M. P. Prozorovskaya, and V. M. Demchenko, Farmakol. Toksikol., No. 4, 497 (1978).