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HETERO-ORGANIC DERIVATIVES OF FURAN. XXIV.* SYNTHESIS AND PSYCHOTROPIC PROPERTIES OF FURYL- AND THIENYLSILATRANES

E. Lukevits, S. Germane, O. A. Pudova, and N. P. Erchak

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We previously established that 3-aminopropylsilanes with 2-furyl groups on the silicon atom have psychotropic activity of the depressant type [2]. A sedative effect is exhibited by 1-alkyl- and 1-alkenylsilatranes [3, 4]. On the other hand, 1-phenyl- [5] and 1-(2-thienyl)silatranes [6] induce motor excitation in animals. Taking the specific nature of the structure of furylsilatranes into account [7], it seemed worthwhile to study their psychotropic properties as compared to the thienylsilatranes as well as to establish the influence of the position of the silatrane group with respect to the furan ring.

Furylsilatranes and their thiophene analogs, in which the silatrane group is bound directly to the furan or thiophene ring at positions 2 or 3 or is separated from it by methylene groups, were synthesized by reesterification of heteryltriethoxysilanes with triethanolamine:

$$RSi(OEt)_3 + (HOCH_2CH_2)_3N \xrightarrow[-3EtOH]{} R\overline{Si(OCH_2CH_2)_3N}$$

R = 2-furyl (I), 3-furyl (II), 5-methyl-2-furyl (III), β-(2-furyl)-ethyl (IV), 2-thienyl (VIII), 3-thienyl (IX).

In a similar manner 1-(2-thienyl)germatrane (VII) was obtained from 2-thienyltriethoxygermane.

Furyl- and thienylsilatranes containing a second silicon atom between the silatrane group and the heterocycle were synthesized by hydroxylation of 1-vinylsilatrane by heterylsilanes in a benzene solution in the presence of a catalyst, a decimolar solution of chloroplatinic acid in tetrahydrofuran (THF):

$$Me_{3-n}RSiH + CH_2{=}CH\overline{Si(OCH_2CH_2)_3N} \longrightarrow Me_{3-n}RSiCH_2CH_2\overline{Si(OCH_2CH_2)_3N}$$

R = 2-furyl, n = 1 (V), n = 2 (VI); R = 2-thienyl, n = 1 (X), n = 2 (XI).

*Report XXIII see [1].

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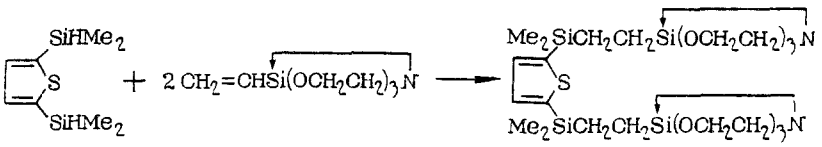
TABLE 1. Furyl- and Thienylsilatranes

Compound	Yield, %	Melting point, °C	Found, %			Molecular formula	Calculated, %		
			C	H	N		C	H	N
I	88	187	49,85	6,11	5,57	$C_{10}H_{15}NO_4Si$	49,77	6,22	5,50
II*	75	149	49,72	6,25	5,75	$C_{10}H_{15}NO_4Si$	49,77	6,22	5,50
III	62	212	51,28	6,70	5,71	$C_{11}H_{17}NO_4Si$	51,74	6,71	5,51
IV	71	165	53,38	7,17	5,20	$C_{12}H_{19}NO_4Si$	53,51	7,11	5,20
VII	60	227	39,92	5,10	4,47	$C_{10}H_{15}GeNO_3S$	39,79	4,97	4,64
IX	70	176	46,34	5,84	5,60	$C_{10}H_{15}NO_3SSi$	46,67	5,87	5,44
X	82	113	48,39	7,27	4,15	$C_{14}H_{25}NO_3SSi_2$	48,94	7,33	4,08
XI	88	149	49,53	6,31	3,48	$C_{17}H_{25}NO_3SSi_2$	49,60	6,12	3,40
XII	77	197	57,50	9,18	5,83	$C_{24}H_{46}N_2O_6SSi_4$	57,30	9,22	5,57
XIV	85	82 (1)†	51,72	4,55	—	$C_9H_{10}S_2Si$	51,43	4,76	—

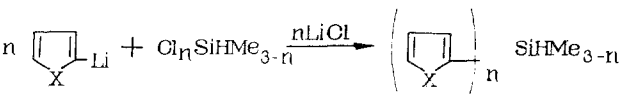
*Synthesized by A. Ashmane.
†Boiling point, °C (mm).

Compounds containing two silatrane groups were obtained by a similar attachment of 2,5-bis-(dimethylsilyl)thiophene to 1-vinylsilatrane:



XII

The initial 2-furyl- and 2-thienylhydrosilanes can be obtained by reacting heteryllithium with hydrochlorosilanes [8]:



X=O, S

However, simultaneously with the condensation reaction, substitution takes place at the Si-H bond, which in the case of methyl-di(2-furyl)silane becomes predominant. Hence, 2-furyl- and 2-thienylsilatranes are more easily prepared by organomagnesium synthesis. When this is done, the yields of methyldi(2-furyl)silane (XIII) and methyldi(2-thienyl)silane (XV) amounted to 88 and 85%, respectively.

The physicochemical properties and analytic data for the new compounds are presented in Table 1.

Experimental investigation of furylsilatranes and their thiophene analogs showed that all the compounds synthesized, except 1-(2-furyl)silatrane (I), 1-[β-(2-furyl)ethyl]silatrane (IV), 1-(2-thienyl)silatrane (VIII), and VII, possess neurotropic activity of primarily the depressant type. When this is present, there is a definite relationship between the extent of the depressant effect, toxicity, and the chemical structure of the compounds (Tables 2-4). Thus, maximum acute toxicity and neurotropic activity is possessed by compounds in which the heterocycle is directly attached to the silatrane fragment, but even for them the magnitude of the LD_{50} varies over a rather wide range depending on the nature of the heterocycle attached to the silicon atom. For example, VIII is usually toxic for warmblooded animals. The fatal dose for BALB/c strain mice is only 0.3 mg/kg, which is comparable to the toxicity of 1-phenylsilatrane (LD_{50} of 0.33 mg/kg [5]). Replacement of the thienyl ring by a furyl ring results in a decrease in toxicity to 1/417. The neurotropic activity of 1-(2-furyl)-silatrane is also reduced. Just as for the phenyl derivatives [9], the toxicity of VII is almost 2 orders of magnitude lower than the toxicity of the corresponding silatrane VIII. At the same time, I and VIII as well as 1-(2-thienyl)germatrane, like 1-phenylsilatrane [9], in doses considerably lower than the LD_{50}, exhibit stimulating properties. It is curious that the nature of pharmacologic action becomes just the opposite upon conversion from 1-(2 heteryl)- to 1-(3-heteryl)silatranes. Thus, 1-(3-furyl)- and 1-(3-thienyl)silatranes induce tranquilization in animals, decrease the orienting response and motor activity, and relax skeletal musculature. The toxicity of 1-(3-furyl)silatrane (44.5 mg/kg) is increased when compared to the 2-isomer of I (125 mg/kg), whereas 1-(3-thienyl)silatrane, on the contrary, is six times less toxic than 1-(2-thienyl)silatrane.

TABLE 2. Pharmacologic Activity of Furyl- and Thienyl-substituted Silatranes in Experiments on 17-23 g Female BALB/c Strain Mice Following Intraperitoneal Administration

Compound	LD_{50}, mg/kg	ED_{50}, mg/kg				
		rotating rod test	"tubes" test	hypothermia	analgesia	electroshock
I	125 (107—146)	14,5 (8—26)	14,5 (8—26)	14,5 (8—26)	9,3 (8—11)	>100
II	14,5 (11—19)	1,5 (1—2)	1,5 (1—2)	1,5 (1—2)	>3	>20
III	2100 (1273—3465)	10 (6—18)	10 (6—18)	16 (11—20)	16,5 (94—289)	>500
IV	235 (147—376)	14 (11—19)	16 (11—25)	14 (11—19)	75 (50—113)	>250
V	700 (569—861)	14 (10—22)	20 (13—32)	25 (16—39)	120 (73—198)	>500
VI	2450 (1600—3675)	92 (59—143)	92 (59—143)	>500	160 (80—320)	540 (474—616)
VII	16,5 (11—25)	1,0 (0,6—1,8)	1,0 (0,6—1,8)	2,7 (1,9—3,8)	17 (9—31)	>20
VIII	0,3 (0,2—0,6)	0,0016 (0,001—0,002)	0,0016 (0,001—0,002)	0,008 (0,005—0,01)	0,016 (0,01—0,02)	—
IX	1,8 (1,3—2,5)	0,0016 (0,0009—0,003)	0,0016 (0,0009—0,003)	0,005 (0,003—0,01)	0,9 (0,7—1,2)	—
X	1650 (1269—2145)	92 (59—143)	92 (59—143)	135 (84—216)	98 (67—142)	330 (297—366)
XI	3900 (3145—4836)	150 (113—198)	150 (113—198)	82 (50—135)	72 (55—95)	>500
XII	3300 (2420—4290)	135 (87—209)	135 (87—209)	92 (59—143)	80 (55—116)	>500
XIII	1600 (1194—2144)	56 (37—84)	56 (37—84)	56 (37—84)	115 (74—178)	>500
XIV	1650 (1213—2244)	100 (67—150)	100 (67—150)	140 (106—185)	90 (64—126)	>500

TABLE 3. Effect of Furyl- and Thienyl-Substituted Silatranes on the Duration of Narcosis (min) Induced by Administration of Sodium Thiopental (intravenously), Sodium Barbital, and Chloral Hydrate in Experiments on 18-22 g Male BALB/c Strain Mice Upon Intraperitoneal Administration (n = 10)

Compound	Sodium thiopental (30 mg/kg)		Sodium Barbital (150 mg/kg)		Chloral hydrate (300 mg/kg)	
	$M \pm m$	I_t	$M \pm m$	I_b	$M \pm m$	I_c
I	9,5±1,3*	2,16	36,0±3,6*	0,67	16,5±3,6*	0,58
II	6,9±0,6*	2,03	103,5±11,9*	1,92	39,5±3,3*	1,41
III	4,6±0,9*	1,35	80,5±7,2*	1,50	44,0±3,4*	1,57
IV	6,8±0,8*	2,00	38,5±3,7*	0,71	25,5±5,7*	0,91
V	5,0±0,8*	1,47	85,5±7,0*	1,58	40,0±4,0*	1,43
VI	17,0±2,1*	5,00	177,0±8,3*	3,28	82,7±8,0*	2,95
VII	2,0±0,5*	0,58	35,5±5,4*	0,66	25,0±7,7*	0,89
VIII	19,8±1,8*	5,82	69,5±13,4*	1,29	30,2±5,2*	1,08
IX	6,0±0,6*	1,76	98,5±12,3*	1,83	43,5±5,3*	1,55
X	16,9±1,6*	4,97	166,5±6,7*	3,09	37,0±3,5*	1,32
XI	15,9±2,6*	4,68	84,0±4,8*	1,56	41,5±3,1*	1,48
XII	19,6±3,4*	5,76	103,0±12,2*	1,91	80,0±3,3*	2,86
XIII	5,2±0,4*	1,52	112,0±13,3*	2,08	104,5±9,8*	3,73
XIV	6,5±0,8*	1,91	142,0±8,5*	2,64	139,0±13,7*	4,96
Control	3,4±0,4	1,00	53,2±2,9	1,00	28,0±3,4	1,00

*Differences with respect to the control were statistically reliable at $P \leq 0.05$.

When the 2-furyl radical is separated from the silatrane core by two methylene groups, the toxicity of compound IV is reduced (from 125 to 235 mg/kg), but not as sharply as in the benzene series where similar structural changes reduce the LD_{50} 1000-fold [9]. The remaining pharmacologic characteristics essentially do not change.

Methyl substituents in the furyl and phenyl ring exhibit an altogether opposite effect. The toxicity of 1-(n-tolyl)silatrane [9] is twice as great as the toxicity of 1-phenylsilatrane. Introduction of a methyl group at position 5 of the furan ring of 1-(2-furyl)silatrane, on the other hand, reduces the acute toxicity of the compound from 125 to 2100 mg/kg. At the same time the compound loses its excitatory properties.

Taking into account the results of x-ray structural analysis [7], which reveal the structural similarity of aryl- and heterylsilatranes, gas chromatography findings [1] on silatrane polarity (the increase in the polarity of the system in question corresponds to the increase in its LD_{50}), as well as the pharmacologic properties of furyl- and thienylsilanes XIII and XIV, which do not contain the silatrane group, it can be assumed that the specific pharmacologic behavior of thienyl- and furylsilatranes to a certain extent depends on the nature of the electron interaction between the heterocycles and the silatrane group.

Insertion of a second silicon atom between the silatrane group and the furan ring results in a decrease in the acute toxicity of not only I and IV, but XIII as well. An increase in the number of 2-furyl and 2-thienyl groups in the molecule, like an increase in the number of silatrane groups, reduces the toxicity of compounds V and VI, X and XI, and X and XII.

All of the compounds studied, except VII, inducing coordination disorders in animals on the rotating rod, in doses equal to 1/2 the ED_{50}, and have the ability to potentiate the narcotic action of sodium thiopental (see Table 3). In these same doses, the silatranes studied to a greater or lesser degree potentiate the narcotic action of sodium barbital and chloral hydrate. Excluded are I, IV, and VIII, besides VII (see Table 3). These compounds potentiate phenamine stereotypy, but 1-β-[dimethyl(2-thienyl)silyl]ethyl- (X), 1-β-[methyl-di(2-thienyl)-silyl]ethyl- (XI), and 1-(5-methyl-2-furyl)silatranes (III), XIII, and XIV considerably shorten the duration of stereotypical movements by the animals (see Table 4).

None of the compounds investigated was capable of preventing corazole convulsions. Only silatranes VI and X prevent electroshock colvulsions.

The studies conducted show that derivatives of furyl- and thienylsilatranes possess substantial psychotropic activity. Compounds in which the silatrane group is directly attached

to the thiophene or furan ring at position 2 or separated from it by two methylene groups as well as 1-(2-thienyl)germatrane have certain stimulating properties, and the rest of the compounds exhibit a depressant action.

EXPERIMENTAL CHEMISTRY

1-(2-Thienyl)germatrane (VII). To 1.46 g (0.005 mole) of 2-thienyltriethoxygermane is added 0.75 g (0.005 mole) of triethanolamine. The reaction starts immediately after the reagents are combined. The crystalline substance formed is dissolved in chloroform and purified on a column of aluminum oxide with second degree activity. After evaporation, the residue is recrystallized from a chloroform–hexane (1:1) mixture and 0.9 g of VII are obtained.

In contrast to germatrane, synthesis of silatranes I-IV and VIII-IX is achieved by heating the initial reagents in xylene. Product yield, melting point, and the results of elemental analysis are shown in Table 1.

Methyl-di(2-furyl)silane (XIII). At room temperature is added 2-furyllithium, obtained from 14 g of lithium wire and 92 g (1 mole) of butylchloride in 500 ml of THF at 25-30°C, to a suspension of 1 mole of mixed magnesium salt (ClMgi) in ether. The Grignard reagent obtained is titrated with a solution of 57.5 g (0.5 mole) of methyldichlorosilane in 50 ml of pentane until the medium is neutral, heated on a water bath for 1 h to 35°C, and allowed to stand at room temperature for 20 h. The precipitate is separated out by filtration on a Büchner funnel, the solvent is distilled off, the residue is fractionated, and 78.3 g (88%) of XIII are isolated. Mp: 67°C, (4 mm); n_D^{20}: 1.5046; d_4^{20}: 1.0388.

Methyl-di(2-thienyl)silane (XIV). To 12.1 g (0.05 mole) of magnesium, activated by a few iodine crystals, in 250 ml of ether with intense stirring is added dropwise 81.5 g (0.5 mole) of 2-bromothiophene at a rate which keeps the ether boiling uniformly. To the Grignard reagent obtained 29 g (0.25 mole) of methyldichlorosilane is added, and then 100 ml of THF. To complete the condensation of the reaction mixture, the mixture is heated again for 1 h until boiling on a water bath and allowed to stand at room temperature for 20 h. The precipitate is removed by filtration, the solvent is distilled off, and the residue fractionated; 44.2 g of XIV are isolated. n_D^{20}: 1.5952; d_4^{20}: 1.1508.

1-β-[Methyl-di(2-thienyl)silyl]ethylsilatrane (XI). To a solution of 2 g (0.01 mole) of vinylsilatrane in 30 ml of benzene is added 2.1 g (0.01 mole) of methyl-di(2-thienyl)silane, 1 drop of a 0.1 M solution of chloroplatinic acid in THF, and this is then heated for 30 min at 80°C. After distilling off the solvent, the precipitate is washed with hexane, recrystallized from a hexane–benzene (2:1) mixture, and 3.6 g of XI are isolated.

Compounds V, VI, X, and XII are obtained analogously.

TABLE 4. Effect of Furyl- and Thienyl-Substituted Silatranes on the Duration of Phenamine Stereotypy in Experiments on Female White Rats Following Intraperitoneal Administration (n = 10)

Compound	Dose, mg/kg	Duration of stereotypy, min (M ± m)		Changes in the duration of stereotypy	
		control	experiment	min	%
I	5	83,1±4,1	119,4±16,2	+36,3	143,7
II	1	171,8±8,1	153,1±15,1	—18,7	89,1
III	10	138,1±6,6	108,7±8,6*	—29,4	78,7
IV	10	85,0±4,2	115,6±8,3*	+30,6	136,0
V	10	180,6±16,5	176,8±11,7	—3,8	97,9
VI	50	124,0±7,1	139,5±15,6	+15,5	112,5
VII	1	138,5±8,9	182,0±9,8*	+43,5	131,4
VIII	0,005	106,9±6,7	137,5±5,3*	+30,6	128,6
IX	0,01	15,61±7,8	153,3±11,1	—2,6	98,2
X	50	183,1±9,6	123,1±17,8*	—60,0	67,2
XI	100	182,5±6,2	111,2±10,2	—71,3	60,9
XII	100	160,0±4,3	141,9±18,5	—18,1	88,6
XIII	50	161,3±10,2	119,4±11,9*	—41,9	74,0
XIV	100	161,1±6,0	110,5±10,7*	—50,6	68,59

*Deviations from the control are statistically reliable at $P \leq 0.05$.

EXPERIMENTAL PHARMACOLOGY

Experiments were conducted on 18-23 g BALB/c strain mice of both sexes and 180-250 g noninbred female white rats. The substances were administered intraperitoneally in the form of an aqueous suspension with Tween-80 30 min before testing. A corresponding amount of distilled water was administered to the control animals.

The effect of the compounds in question on the central nervous system was evaluated by a battery of tests currently being used to detect the psychotropic activity of chemicals [6, 10].

The experimental data were analyzed statistically and the median effective (ED_{50}) and lethan (LD_{50}) doses were calculated by the Litchfield and Wilcoxon method [11]. In order to statistically evaluate the data on the duration of the narcotic action of sodium thiopental, sodium barbital, and chloral hydrate, as well as to determine the duration of phenamine stereotypy, arithmetic means and their standard errors were computed ($M \pm m$). The differences were considered reliable at $P \leq 0.05$. In addition, in these experiments the I indices of changes in the narcotic effect were determined, i.e., the ratio between the average duration of narcosis among the experimental animals in the experimental group to the average duration of narcosis among the animals in the control group.

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PREDICTING THE SOLUBILITY OF BIOLOGICALLY ACTIVE COMPOUNDS UNDER SCREENING CONDITIONS.

III. SOLUBILITY IN WATER AND VAN DER WAALS VOLUME OF MOLECULES

N. A. Epshtein and S. V. Nizhnii

UDC 615.451.014.24:577.2

Under the term "van der Waals volume of an atom" i (V_{Wi}), we usually understand it to be the volume of a sphere with the radius numerically equal to the van der Waals radius of the atom (r_{Wi}) [1, 2], i.e., one half of the equilibrium distance between the centers of similar atoms with no chemical bond between them. The van der Waals volume of the molecule V_W is not equal to the sum of the V_{Wi} of its atoms, since the chemical bonds cause an approach of the centers of the neighboring atoms, which is considerably greater than the sum of r_{Wi} between them. For example, the length of the covalent C-C bond is 1.5 Å, while $2r_{W_S}$ = 3.4 Å [3]. This drawing together leads to an overlap of the spheres corresponding to the van der Waals volumes of the atoms, and during the calculation of V_W requires the corresponding corrections for the overlap β for different types of bonds [3]. Thus, the van der Waals volume of the molecule can be numerically represented as:

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