FURYL- AND THIENYL-SILATRANES AND GERMATRANES

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We review our research on the synthesis and study of the physical and biological properties of furyl- and thienylgermatranes and -silatranes.

The major feature of the structure of tricyclic heteroorganic derivatives of triethanolamine (atranes) is the presence of the N → M intramolecular donor–acceptor interaction, which determines their unusual chemical and physicochemical properties. Broad biological testing has shown that this class of compounds possesses unique biological properties [1-3], and the use of these heterocyclic compounds is connected with the creation of whole directions in the therapy for various illnesses [4].

Therefore we have written a cycle of papers on the synthesis of hetarylsilatranes and germatranes, determined the characteristic features of their physicochemical behavior, and discovered the general rules correlating the structure and the pharmacological effect.

SYNTHESIS METHOD

At the present time, several ways have been developed to obtain hetarylgermatranes and -silatranes. The simplest and most general way is reaction of furyl- or thienyltrialkoxysilanes (germanes) with triethanolamine, which proceeds under mild conditions [5-8].

$$R\text{-}M(OEt)_3 + (HOCH_2CH_2)_3N \xrightarrow[-3EtOH]{} R\text{-}M(OCH_2CH_2)_3N$$

I - XVIII

M = Si I R = 2-furyl; II R = 3-furyl; III R = 2-furfuryl; IV R = β-(2-furyl)ethyl; V R = = 5-methyl-2-furyl ; VI R = 2-thienyl; VII R = 3-thienyl; VIII R = 5-methyl-2-thienyl; IX R = 5-bromo-2-thienyl

M = Ge X R = 2-furyl; XI R = 3-furyl; XII R = 2-furfuryl; XIII R = = 5-ethoxycarbonal-2-furyl; XIV R = 2-thienyl; XV R = 3-thienyl; XVI R = = 5-methyl-2-thienyl; XVII R = 5-ethyl-2-thienyl; XVIII R = 5-bromo-2-thienyl

A general method for obtaining the starting trialkoxyhetarylsilanes is the reaction of hetaryllithium or 2-thienylmagnesium bromide with the corresponding aloxy- or halosilatranes [9]:

$$R\text{-}M + XSiR^1_3 \longrightarrow RSiR^1_3$$

R = furyl, thienyl; X = Cl, OEt; R^1 = Cl, OEt; M = Li, MgBr

The trialkoxyhetarylgermanes are obtained by a simpler method, due to the ability of germanium dibromide to be inserted at the carbon-halogen bond in the corresponding halofurans and -thiophenes with subsequent alcoholysis of the trihalo derivatives obtained [7, 8]:

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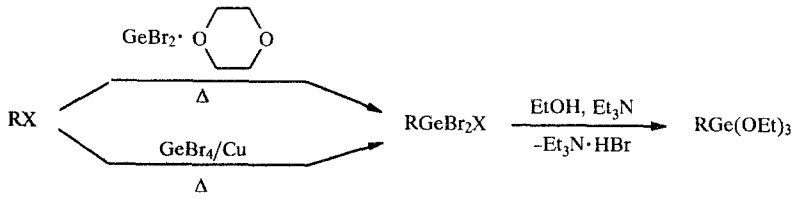
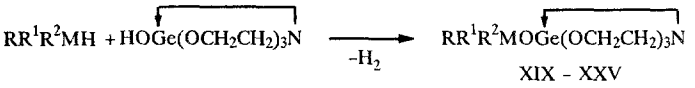
0009-3122/92/2806-0603$12.50



R = furyl, thienyl; X = Cl, Br

The second group of methods for synthesis of furyl- and thienylgermatranes includes O- or C-silylation (germylation) by hetarylsilanes (germanes) of compounds already containing the atrane skeleton. Thus hydroxygermatrane, obtained by reaction of germanium dioxide with triethanolamine, enters into a condensation reaction with hydrosilanes and -germanes, forming the corresponding siloxy- or germoxygermatranes [10]:



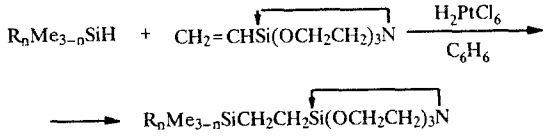
XIX - XXV

M = Si XIX R = R^1 = R^2 = 2-thienyl; XX R = R^1 = 2-thienyl, R^2 = Me; XXI R = 2-thienyl, R^1 = R^2 = Me; XXII R = R^1 = R^2 = Ph; XXIII R = R^1 = R^2 = Ph, R^2 = Me; XXIV R = Ph, R^1 = R^2 = Me

M = Ge XXV R = R^1 = R^2 = Ph

In this case, the thienylsilanes are considerably more reactive than the analogous phenylsilanes. Thus phenylhydrosilanes enter into the condensation reaction with germatranol only in the presence of chloroplatinic acid or Amberlyst 15, while thienylsilanes react with hydroxygermatrane even in the absence of a catalyst. The reaction rate increases with an increase in the number of thienyl groups in the hydrosilane molecule [10].

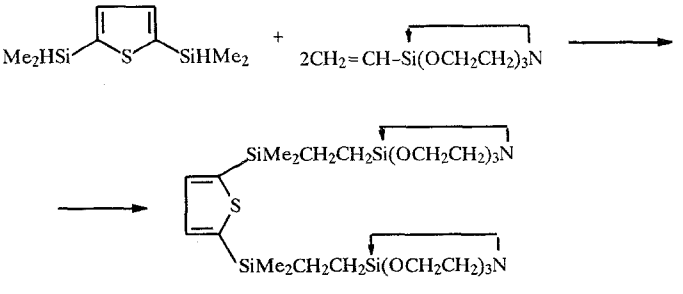
The high reactivity of the Si–H bond in thienyl- and furylsilanes allowed us to accomplish hydrosilylation of 1-vinylsilatrane in the presence of chloroplatinic acid and to obtain a number of furyl- and thienylsilatranes in which the atrane skeleton is separated from the heterocycle by several methylene groups [5]:



XXVI - XXX

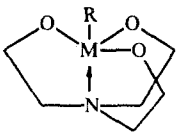
XXVI R = 2-furyl, n = 0; XXVII R = 2-furyl, n = 1; XXVIII R = 2-furyl, n = 2; XXIX R = 2-thienyl, n = 1; XXX R = 2-thienyl, , n = 2

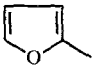
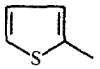
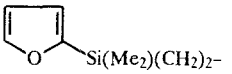
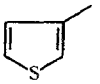
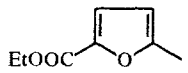
A compound containing two silatrane groups is obtained by analogous addition of two vinylsilatrane molecules to 2,5-bis(dimethylsilyl)thiophene [5]:



XXXI

TABLE 1. Interatomic Distances (N → M) and Deviations of the M Atom From the Equatorial Plane Δ(M) for Atranes



Compound	R	M	(N → M), Å	ΔM, Å
I		Si	2,11	0,14
IV		Si	2,17	0,20
VI		Si	2,13	0,16
XXVI		Si	2,23	0,23
VII		Ge	2,21	0,23
XIII		Ge	2,16	0,20

PHYSICOCHEMICAL INVESTIGATIONS

Study of the mass spectra of silatranes I-IX and germatranes X-XVIII showed that decomposition of these compounds under electron impact occurs in two competing directions: abstraction of the substituent R and decomposition of the atrane ring with retention of the M−R bond [11, 12]. The predominance of a specific fragmentation direction depends on the nature of the substituent R and on the strength of the M−R bond. Thus the mass spectra of silatranes I-IX are distinguished by the high molecular ion intensity. This is due to participation of the unshared electron pair of the oxygen or sulfur atoms of substituent R in charge delocalization, leading to redistribution of electron density and an increase in the strength of the Si−R bond. Delocalization of positive charge in the molecular ion as a result of a shift of electron density to the silicon atom is more energetically favorable than keeping it on the silatrane fragment.

Participation of the oxygen or sulfur atoms in charge delocalization is clearly apparent in the different electron-impact stabilities of 2-substituted silatranes and 3-substituted silatranes: the intensity of the peaks for 2-hetarylsilatranes (M^+, 100%) is higher than for 3-hetarylsilatranes (M^+, 56%), and due to breakdown of conjugation with the methyl fragment it is insignificant for furfurylsilatrane (M^+, 3%).

Fragmentation of hetarylgermatranes X-XVIII is characterized by α-rupture of the germatrane ring with respect to the nitrogen atom, with cleavage of one or two CH_2O molecules. Thus in hetarylgermatranes, the second decomposition direction predominates, due to preferred localization of the charge on the nitrogen atom, suggesting the absence of a N → Ge interaction in the gas phase and also a stable divalent state for germanium. The stronger transannular interaction of the N → Si bond compared with N → Ge in hetarylatranes is confirmed by chemical ionization and bombardment with fast atoms [13].

The specifics of decomposition noted for furfurylsilatrane II are also observed for furfurylgermatrane XII: the relatively low intensity of the molecular ion peak (M^+, 8%) and the dominant abstraction of the furfuryl group [11].

Introduction of an alkyl substituent in the 5 position of the thienyl ring does not exert a substantial effect on fragmentation of 2-thienylgermatranes under electron impact conditions.

TABLE 2. Acute Toxicity and Neurotrophic Activity of Silatranes $RSi(OCH_2CH_2)_3N$ (intraperitoneally in mice of the line BALB/c, Icr:Icl, CBA)

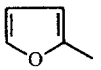
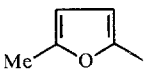
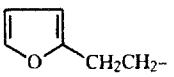
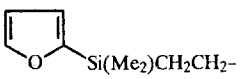
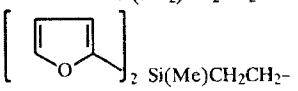
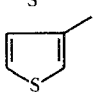
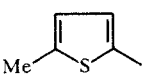
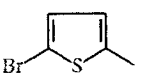
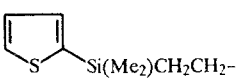
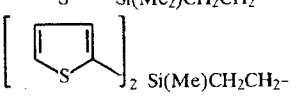
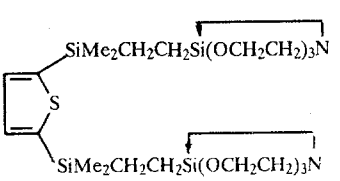
Compound	R	LD_{50}, mg/kg	ED_{50}, mg/kg	
			test	
			tubes	rotating rod
I		125	14,5	14,5
II		14,5	1,5	1,5
V		2100	10	10
IV		235	16	14
XXVII		700	20	14
XXXVIII		2450	92	92
VI		0,3	0,0016	0,0016
VII		1,8	0,0016	0,0016
VIII		0,42	—	—
IX		0,42	—	—
XXIX		1650	92	92
XXX		3900	150	150
XXXI		3300	135	135

TABLE 3. Acute Toxicity and Neurotrophic Activity of Germatranes $RGe(OCH_2CH_2)_3N$

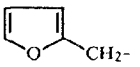
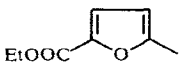
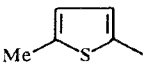
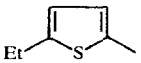
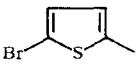
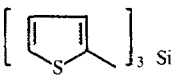
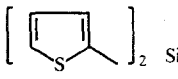
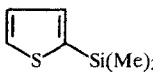
Compound	R	LD_{50}, mg/kg	ED_{50}, mg/kg test	
			tubes	rotating rod
X		2050	41	41
XI		1630	70,8	81,5
XII		2960	20,5	28,4
XIII		1030	708	590
XIV		16,5	1,0	1,0
XV		89	1,2	2,2
XVI		20,5	9,5	8,9
XVII		>1000	141	282
XVIII		21	20,5	16,3

TABLE 4. Neurotrophic Activity of Germatranes $ROGe(OCH_2CH_2)_3N$

Com-pound	R	ED_{50}, mg/kg test		Conditioned passive avoidance reflex (sec) and retrograde amnesia (%)
		tubes	rotating rod	
XIX		> 500	274	51,0±16,6 70,0
XX		282	355	30,5±13,8 50,0
XXI		~70,8	109	79,1±14,9 75
XXII	Ph_3Si	> 500	> 500	72,0±15,2 80
XXIII	$Ph_2Si(Me)$-	564	690	46,5±16,4 62,5
XXV	Ph_3Ge	> 500	> 500	92,7±12,4 77,7

It is interesting to note that the general form of decomposition of hetarylgermatranes and -silatranes displays more similarities to decomposition of acetylenes than phenyl derivatives of silatranes and germatranes, due to the increase in the interaction of the heteroaromatic system with the silicon or germanium atom. This leads to an increase in the strength of the R−M bond and accordingly to weakening of the donor−acceptor interaction N → M.

In silsatranes XXVI-XXX, there are two charge localization centers. Therefore we expected a complicated fragmentation pattern. However, in the mass spectra of silatranes XXVI-XXX, ~60% of the total ion current is found on the silatranyl cation peak. The peaks for the rest of the ionns have low intensity. In the case of silyl derivatives of germatrane

XXII, we observe an anomalously high intensity for the peaks from the $[M-Ph]^+$ and Ph_3Si^+ ions, connected with formation of the new transannular bond N → Si.

X-ray diffraction study of silatranes I, IV, VI, XXVI showed that in these systems, the silicon atom has a trigonal–bipyrimidal environment with the substituent R and the nitrogen in axial positions. The shift of the Si atom from the equatorial plane toward the substituent R(ΔSi) is 0.14-0.23 Å (Table 1). The nitrogen atom is pyramidal, and its deviation ΔN from the plane formed by the carbon atoms bonded to it, like ΔSi, correlates with the N → Si distance. For the three five-membered heterocycles comprising the silatrane skeleton, the characteristic conformation is the envelope; and the oxygen, nitrogen, silicon, and β-carbon atom lie in the same plane while the carbon atom in the α position relative to the nitrogen forms the flap of the envelope [14].

Among the hetarylgermatranes, the structure of germatrane XIII has been studied in detail [15]. The atrane skeleton of compound XIII is also formed by three five-membered rings with total donor-acceptor bond N → Ge of length 2.165 Å. The coordination polyhedron of the germanium atom is a distorted trigonal bipyramid with equatorial oxygen atoms. The Ge atom deviates from the equatorial plane by 0.196 Å (ΔGe). As in the case of silatranes, we observe a direct proportionality between the deviation of the Ge atom from the equatorial plane of the trigonal bipyramid and the length of the transannular bond N → Ge. The five-membered heterocycles in the atrane skeleton of germatrane XIII have the twist conformation: the α and β carbon atoms are located on different sides (relative to the nitrogen atom) of the plane passing through the Ge, N, O atoms, but the deivations of the α atoms is 2-2.5 times greater than the deviations of the β carbon atoms. The furyl ring is coplanar with the plane formed by the Ge, N, O atoms.

Study of the structure of siloxygermatrane XXII showed that the Si–O–Ge group is linear, while the length of the N → Ge coordinate bond is 2.126 Å [10]. Thus in the crystalline state the length of the N → M bond for the studied atranes is within the range 2.11-2.23 Å, which is significantly less than the sum of the van der Waals radii of the silicon (germanium) and nitrogen atoms.

BIOLOGICAL ACTIVITY

Comparison of physicochemical properties shows that hetarylsilatranes and hetarylgermatranes are similar, so we might assume that their biological properties are also similar. However, a toxicity study showed that silatranes are several times more toxic than their germanium analogs [3]. Thus 2-thienylgermatrane (the most toxic germatrane of all the studied germatranes) is 55 times less toxic than 2-thienylsilatrane [5, 16] (Tables 2 and 3). The most toxic among the hetarylsilatranes and -germatranes are compounds containing the 2-thienyl group bonded directly to the element. Removal of the atranyl group from the heterocycle substantially decreases the toxicity (see Table 2). Introduction of substituents (CH_3, Br) in the 5 position of the thiophene ring does not affect the toxicity much; at the same time, introduction of a methyl group in the 5 position of the furan ring of 2-furylsilatrane of an ethyl group in 2-thienylgermatrane sharply reduces the acute toxicity. It is interesting to note that in the thiophene series, the 2-derivatives are the most toxic, while in the furan series in contrast the 2-derivatives are less toxic than the 3-isomers [3, 16]. Introduction of a second silicon atom between the silatrane group and the furan ring leads to a decrease in the acute toxicity. An increase in the number of 2-furyl and 2-thienyl groups in the molecule, like an increase in the number of silatrane groups, also decrease the toxicity of silatranes (see Table 2).

Based on data on the acute toxicity of hetarylsilatranes and -germatranes, we might expect that in pharmacological studies the silatranes would display higher activity, since their toxicity is connected with action on the central nervous system. An indeed the 2- and 3-furyl- and thienylsilatranes proved to be more active in tube and rotating rod tests, and also in their analgesic and hypothermic action. In this case the compounds in which the silatrane group is bonded directed to the heterocycle in the 2 position or is separated from it by two methylene groups have activating properties, while the rest of the silatranes exert a depriming effect. Thus there is a certain correlation between the degree of expression of the depriming effect, the toxicity, and the chemical structure of the hetarylatranes.

The siloxygermatranes XIX-XXIV and the germoxygermatrane XXV are low-toxicity substances: their median lethal doses are greater than 1000 mg/kg. Both depriming and activating components are combined in their neurotrophic activity spectrum [10]. Thus triphenylsiloxygermatrane displays neurotrophic activity of the depriming type, while activating pharmacological effects predominate in its germanium analog (triphenylgermoxygermatrane).

All the investigated siloxygermatranes XIX-XXIV and germoxygermatrane XXV (in relatively low doses, 50 mg/kg) to some degree improve the memory processes and decrease or completely prevent amnesia induced by electric shock (Table 4) [10].

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