NITROGEN-CONTAINING ORGANOSILICON COMPOUNDS

VI. SYNTHESIS AND ANTIMICROBIAL ACTION OF TRIALKYL(3-AMINOPROPYL)SILANES

E. Lukevits, A. Ya. Zile, L. V. Kruzmetra, Yu. I. Khudobin, and M. G. Voronkov

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Continuing our investigation of the antimicrobial activity of nitrogen-containing organosilicon compounds [1-12], we have synthesized a number of trialkyl(3-aminopropyl)silanes and studied the effect on their fungistatic and bacteriostatic activity of the nature of the alkyl groups bonded to the silicon atom. Three strains of pathogenic fungi – representatives of the Candida, Trichophyton, and Epidermophyton genera – and the Gram-positive bacteria Staphylococcus aureus haemolyticus 209 and Bac. mycoides 537 were used as the test microbes.

The trialkyl(3-aminopropyl)silanes were obtained by hydrosilylation of allylamine with trialkylsilanes in the presence of a 0.1 M solution of $H_2PtCl_6 \cdot 6H_2O$ in 2-propanol via the scheme

$$RR'_2SiH + CH_2=CHCH_2NH_2 \rightarrow RR'_2SiCH_2CH_2CH_2NH_2.$$

The antimicrobial activity of the synthesized compounds is presented in Table 1, while their yields and physical constants are given in Table 2.

The fungistatic activity of trialkyl(3-aminopropyl)silanes $R_3Si(CH_2)_3NH_2$ (I-VI) that contain three identical unbranched alkyl groups attached to the silicon atom with respect to Candida albicans 67/846 decreases in the following order

TABLE 1. Minimal Concentration (in μg/ml) of Trialkyl(3-aminopropyl)silanes $RR'_2Si(CH_2)_3NH_2$ that Suppresses the Growth of Microorganisms

Compound	R	R′	Test microbe				
			Candida albicans 67/846	*Epidermophyton Kaufmann-Wolf* 41	*Trichophyton gypseum* 4/3	*Staphylococcus aureus haemolyticus* 209	*Bac. mycoides* 537
I	CH_3	CH_3	>200	>83,3	>83,3	>300	>300
II	C_2H_5	C_2H_5	200	66,7	66,7	533	533
III	C_3H_7	C_3H_7	41,7	13,8	13,8	70	14
IV	C_4H_9	C_4H_9	15,6	10,4	5,2	333	333
V	C_5H_{11}	C_5H_{11}	66,7	50	50	16,6	16,6
VI	C_6H_{13}	C_6H_{13}	133	200	100	66,6	133,3
VII	CH_3	C_2H_5	>200	100	100	133,3	133,3
VIII	CH_3	C_3H_7	33,3	33,3	33,3	33,3	66,6
IX	CH_3	C_4H_9	16,7	4,2	8,3	16,6	33,3
X	CH_3	iso-C_4H_9	167	41,7	41,7	15,7	15,2
XI	CH_3	C_5H_{11}	50	66,7	33,3	>266	>266
XII	CH_3	C_6H_{13}	10,4	10,4	20,9	1,3	2,5
XIII	CH_3	C_7H_{15}	133	66,7	133	33,3	33,3
XIV	CH_3	C_9H_{19}	167	125	250	250	125
XV	C_2H_5	C_3H_7	16,7	8,3	8,3	8,3	8,3
XVI	C_2H_5	C_4H_9	33,3	16,7	16,7	8,3	8,3
XVII	C_2H_5	C_5H_{11}	20,9	10,4	10,4	500	20,9
XVIII	C_3H_7	C_3H_7	83,3	41,7	41,7	41,7	167
XIX	C_4H_9	C_2H_5	20,9	31,2	31,2	41,7	41,7
XX	C_5H_{11}	C_2H_5	7,8	15,6	7,8	15,6	15,6
XXI	$N(CH_2CH_2O)_3$		200	200	200	133	133

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TABLE 2. Physical Properties, Analytical Results, and Yields of Trialkyl(3-aminopropyl)silanes

Compound	Yield, %	bp, °C	n_D^{20}	d_4^{20}	MR_D found	MR_D calc.	N found, %	Empirical formula	N calc., %
V	51	158—161 (1,5 mm)	1,4585	0,8351	97,89	98,57	4,38; 4,46	$C_{18}H_{41}NSi$	4,67
VI	52	185—188 (3 mm)	1,4600	0,8405	111,35	112,46	3,96; 4,01	$C_{21}H_{47}NSi$	4,10
VIII	59	84—86 (4 mm)	1,4480	0,8218	61,05	61,53	7,18; 7,26	$C_{10}H_{25}NSi$	7,47
IX	65	107—109 (3 mm)	1,4525	0,8233	70,67	70,63	6,48; 6,50	$C_{12}H_{29}NSi$	6,50
X	57	68—69 (1 mm)	1,4510	0,8224	70,54	70,63	6,36; 6,40	$C_{12}H_{29}NSi$	6,50
XI	64	129—131 (4 mm)	1,4525	0,8265	79,56	80,05	5,56; 5,57	$C_{14}H_{33}NSi$	5,75
XII	69	146—148 (3 mm)	1,4562	0,8309	88,84	89,31	5,19; 5,27	$C_{16}H_{37}NSi$	5,15
XIII	65	152—155 (1 mm	1,4569	0,8295	98,36	98,57	4,38; 4,47	$C_{18}H_{41}NSi$	4,68
XIV	65	191—194 (2 mm	1,4598	0,8360	116,32	117,09	3,70; 3,78	$C_{22}H_{49}NSi$	3,94
XV	63	97—98 (2 mm)	1,4549	0,8291	65,92	66,04	6,72; 6,75	$C_{11}H_{27}NSi$	6,95
XVI	42	129—131 (5 mm)	1,4569	0,8336	74,95	75,14	5,79; 5,81	$C_{13}H_{31}NSi$	6,10
XVII	62	123—125 (2 mm)	1,4559	0,8311	84,33	84,56	5,14; 5,23	$C_{15}H_{35}NSi$	5,43
XVIII	63	84—86 (3 mm)	1,4530	0,8286	61,13	61,29	7,20; 7,28	$C_{10}H_{25}NSi$	7,47
XIX	63	92—94 (4 mm)	1,4554	0,8322	65,67	65,84	6,72; 6,84	$C_{11}H_{27}NSi$	6,95
XX	61	99—101 (1,5 mm)	1,4555	0,8338	70,11	70,55	6,38; 6,41	$C_{12}H_{29}NSi$	6,50

as a function of the nature of substituent R:

$$C_4H_9 > C_3H_7 > C_5H_{11} > C_6H_{13} > C_2H_5 > CH_3.$$

Almost the same dependence of the fungistatic action on the nature of the alkyl groups bonded to the silicon atom is also observed with respect to Epidermophyton Kaufmann—Wolf and Trichophyton gypseum 4/3. Methyldibutyl(3-aminopropyl)silane (IX) is the strongest fungistat in the series of $CH_3R_2Si(CH_2)_3NH_2$ (VII-XIV) compounds, the activities of which decrease in the following order as R changes:

$$C_4H_9 > C_6H_{13} > C_3H_7 > C_5H_{11} > C_7H_{15} > C_2H_5 > C_9H_{19} > CH_3.$$

Branching of the butyl group lowers the activity — the compound with R = iso-C_4H_9 (X) has a lower fungistatic effect than its isomer with R = C_4H_9(IX).

In the analogous $C_2H_5R_2Si(CH_2)_3NH_2$ series (II, XV-XVII), the fungistatic activity decreases in a different order:

$$C_3H_7 > C_5H_{11} > C_4H_9 > C_2H_5.$$

Of the compounds of the $R(C_2H_5)_2Si(CH_2)_3NH_2$ series (II, VII, and XVIII-XX), the most active is the derivative with R = C_5H_{11}(XIX):

$$C_5H_{11} > C_4H_9 > C_3H_7 > C_2H_5 > CH_3.$$

In the case of Staphylococcus aureus haemolyticus 209, the dependence of the bacteriostatic activity of the organosilicon amines on the nature of the alkyl groups bonded to the silicon atom is basically close to that observed in the investigation of their fungistatic action. An exception to this is the increased activity of methyldihexyl(3-aminopropyl)silane (XII) and the order of change in the bacteriostatic effect of compounds in the $R_3Si(CH_2)_3NH_2$ series, which, in contrast to the order of fungistatic activity, decreases in the order indicated below:

$$C_5H_{11} > C_6H_{13} > C_3H_7 > C_4H_9 > C_2H_5.$$

Analysis of the data obtained shows that Candida albicans 67/846 is the most resistant of all of the investigated fungi to the action of trialkyl(3-aminopropyl)silanes. Amyldiethyl(3-aminopropyl)silane depresses it most markedly (the minimum concentration that suppresses growth is 7.8 μg/ml), followed by methyldihexyl(3-aminopropyl)silane (10.4 μg/ml). However, their activity is lower than that of the antibiotic nystatin (3.5 μg/ml).

Some of the compounds suppress the growth of Epidermophyton Kaufmann—Wolf 41 extremely effectively. This class includes methyldibutyl(3-aminopropyl)-silane (4.2 μg/ml) and ethyldipropyl(3-aminopropyl)silane (8.3 μg/ml), the activity of which is comparable to that of nystatin (6.9 μg/ml).

Trialkyl(3-aminopropyl)silanes most effectively suppress the growth of Trichophyton 4/3. Tributyl(3-aminopropyl)silane (5.2 μg/ml) acts more strongly than nystatin (7.8 μg/ml), while the diethylamyl (7.8 μg/ml), methyldibutyl (8.3 μg/ml), and ethyldipropyl derivatives (8.3 μg/ml) approach it in activity.

These same compounds (except for the tributyl derivative) also display a definite bacteriostatic activity, which, nevertheless, is considerably lower than that of known antibiotics and nitrofuran preparations.

The antimicrobial activity of trialkyl(3-aminopropyl)silanes is not in agreement with their basicity and is apparently in great measure determined by their three-dimensional structure. Thus in the $RR_2'SiCH_2CH_2CH_2NH_2$ series an increase in the steric accessibility of the silicon atom (R, R' = CH_3, C_2H_5) leads to a decrease in activity. However. this is not often observed in the $R_nR'_{3-n}SiCH_2CH_2CH_2NH_2$ series (R = CH_3, C_2H_5)as n increases. Moreover, XII, XV, and XX, and also IV and XVI with different substituents attached to the silicon atom, including one or two of the lower alkyl groups (C_2H_5, CH_3), have the highest fungistatic and bacteriostatic activity of the investigated compounds. The antibacteriostatic activity increases when the n-butyl groups are replaced by the more sterically hindered isobutyl groups, while the fungistatic activity decreases. The fungistatic activity of organosilicon amines that contain the Si—C—C—C—N fragment decreases sharply when there are two hydrocarbon substituents attached to the nitrogen atom or when a triple bond is introduced into the three-carbon chain. Entry of a silicon atom into the silatrane grouping (XXI) also sharply decreases the antimicrobial activity of the 3-aminopropylsilyl grouping.

EXPERIMENTAL

Hydroxylation of Allylamine. Allylamine (0.1 mole) was added gradually to a heated (to 100°) mixture of trialkylsilane (0.1 mole) and 0.1 ml of catalyst (0.1 M solution of $H_2PtCl_6 \cdot 6H_2O$) in 2-propanol, and the mixture was refluxed for 24 h. The unchanged starting reagents were removed by vacuum distillation (water aspirator). Vacuum fractionation of the residue gave the trialkyl(3-aminopropyl)silanes (V, VI, and VII-XX).

The remaining compounds were obtained by known methods: I and VII by the method in [13], II-IV by the method in [14], and XXI by the method in [15].

Fungistatic Activity. The fungistatic activity was determined in experiments in vitro by the method of twofold serial culture. Inoculation of a 3-5 days growth of a culture of the pathogenic fungi of the Candida genus and of a 2-3 week culture of the Epidermophytons and Trichophytons were used to contaminate the media containing the investigated compounds. The experiments were carried out at 28 ± 1° for 3-30 days (depending on the genus of the investigated fungus). The results were evaluated visually and compared with the growth in a control test tube.

The antibacterial activity was determined in vitro by the method of serial cultures in Hottinger broth.

LITERATURE CITED

1. Z. Atare, M. G. Voronkov, S. Gutberga, et al., in: Proceedings of the Conference on Organosilicon Compounds [in Russian], Vol. 4, Moscow (1966), p. 25.
2. M. G. Voronkov, L. N. Alekseeva, B. Brizga, et al., Khim.-Farmats. Zh., No. 5, 26 (1967).
3. M. G. Voronkov and E. Lukevits, Usp. Khim., 38, 2173 (1969).
4. E. Ya. Lukevits, A. E. Pestunovich, A. Ya. Zile, et al., Otkrytiya, No. 34,72 (1971); USSR Author's Certificate No. 320,500 (1970).
5. E. Ya. Lukevits, A. E.Pestunovich, L. V. Kruzmetra, et al., Otkrytiya, No. 12, 92 (1972); USSR Author's Certificate No. 334,222 (1970).
6. M. G. Voronkov, G.I. Zelchan, and E. Ya. Lukevits, Silicon and Life [in Russian], Riga (1971), p. 236.
7. V. S. Ganin, L. E. Khundanov, L. Ya. Urbanovich, et al., Dokl. Irkutsk. Protivochumnogo Inst., 9, 109 (1971).

8. É. Ya. Lukevits, L. I. Libert, and M. G. Voronkov, Izv. Akad. Nauk Latv. SSR, Seriya Khim., 451 (1972).
9. É. Ya. Lukevits and A. E. Pestunovich, Usp. Khim., 41, 1994 (1972).
10. V. E. Udre and É. Ya. Lukevits, Khim. Geterotsikl. Soedin., 493 (1973).
11. É. Lukevits and L. I. Libert, Zh. Obshch. Khim., 43, 778 (1973).
12. É. Lukevits, "Investigatin of biologically active nitrogen-containing organosilicon compounds," Author's Abstract of Doctoral Dissertation, Riga, (1973).
13. É. Lukevits and M. G. Voronkov, Zh. Obshch. Khim., 38, 2322 (1968).
14. N. S. Nametkin, A. V. Topchiev, and T. I. Chernysheva, in: Research on Organosilicon Compounds [in Russian], Moscow (1962), p. 56.
15. C. M. Samour, US Patent No. 3,118,921 (1964); Chem. Abstr., 60, 10,715 (1964).