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REVIEW ARTICLE

Organosilicon Entities as Prophylactic and Therapeutic Agents

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CONTENTS

Within the past 5 years, the synthesis and biological evaluations of organosilicon agents have rapidly developed into a potentially explosive area of medicinal chemistry. It has repeatedly been demonstrated that silicon analogs of recognized medicinal agents exhibit biological activity. Even more significant is the activity elicited by several types of organosilicon entities that are not isosteric to biologically active organic compounds. Ample evidence is also now available to establish that organosilicon compounds, *per se*, are not toxic. While certain classes of these compounds produce toxic responses, indeed, a few are highly poisonous, they too are not merely silicon congeners of toxic organic compounds. The diverse employment of these compounds—from therapeutic agents to agricultural chemicals—evidences the importance of, and exceptional potential for, these materials.

CHEMISTRY

The substitution of silicon for carbon in a specific molecule represents more than the replacement of one atom for a larger one. Even though the chemistry of carbon and silicon has a certain degree of similarity, the differences are significant and of paramount importance. The present discussion of silicon chemistry is of necessity brief; the reader is referred to the excellent books by Sommer (1) and Eaborn (2) and the reviews of Müller and Rochow (3) and Haiduc (4) for a comprehensive treatment of this topic.

The utilization of silicon in congeners of prophylactic and therapeutic agents is limited, to some extent, by the instability of certain silicon bonds. For example, nitrogenous compounds containing an Si—N bond do not form salts like organic amines but undergo cleavage: $R_3SiNH_2 + 2HX \rightarrow R_3SiX + NH_4X$.

Silylamines also undergo hydrolysis or alcoholysis, affording the corresponding silanol or alkyloxysilane

and amine. Those entities possessing silicon-to-sulfur and silicon-to-pseudohalide bonds are also susceptible to hydrolysis. Organosilicon compounds with Si—X bonding act more like acid halides than alkyl halides; they readily react with water, affording silanols and mineral acid. Silanols themselves do not behave like alcohols: $R_3SiX + H_2O \rightarrow R_3SiOH + HX$; they are much more acidic and readily lose water to form disiloxanes: $R_3SiOH \rightarrow R_3Si—O—SiR_3 + H_2O$. Indeed, the most characteristic chemical property of organosilicon compounds is their tendency to form Si—O bonds. Silyl ethers are chemically more similar to carboxylic acid esters than ethers in that the former readily react with alcohol under mild acidic catalysis: $R_3SiOR + R'OH \overset{H^+}{\rightleftarrows} R_3SiOR' + ROH$.

Organosilicon compounds with an Si—H bond are easily oxidized to silanols by Tollen's reagent. The silanes, which are hydrocarbon isosteres, readily react with water under basic conditions to give the corresponding silanol and hydrogen; however, they are reasonably stable under acidic or neutral conditions. Silicon-to-carbon bonding is generally stable, but the Si—C bond of aromatic moieties is broken in the presence of aqueous acid: $R_3SiAr + H_2O \xrightarrow{H^+} R_3SiOH + ArH$.

Compounds in which silicon forms a double bond (sp^2 bonding) are apparently unknown, thus precluding the incorporation of silicon in an aromatic ring or the preparation of silaketones, *etc.* Silicon-to-silicon bonding, while known, is weak and readily broken.

The differences in physical and chemical properties between carbon and silicon can be rationalized from the characteristics of their respective valence shells. Although both elements participate in sp^3 bonding, silicon also possesses vacant *d*-orbitals. In addition, both the difference in electronegativity (2.5 for carbon and 1.8 for silicon on the Pauling scale) and covalent radius (0.77 Å for carbon and 1.17 Å for silicon) contribute to their respective bonding characteristics.

In silicon, the vacant *d*-orbitals can participate in ($p \rightarrow d$) π-bonding with Si—N, Si—O, and Si—X (X = F, Cl) bonds. For example, π-bonding would account for: (*a*) the relatively high acidity of silanols as compared to that of alcohols, (*b*) an Si—O—Si bond angle of 145°, (*c*) the low basicity of siloxanes compared to that of ethers, and (*d*) the difference in the measured and calculated bond length of the Si—O bond (5). Interaction between π-aromatic electrons and silicon *d*-orbitals is reflected in the Hammett substituent constants for the trimethylsilyl group ($\rho = -0.07$) as compared to the *tert*-butyl moiety ($\rho = -0.20$) (5). On the basis of electronegativity alone, one would expect trisilylamine to be a stronger Lewis base than triethylamine. In fact, the silylamine is a poor donor; the lone electron pair on nitrogen is apparently engaged in π-bonding with the *d*-orbitals of silicon (2). The bonding and structural characteristics of silicon were recently reviewed (6), and the utilization of its *d*-orbitals was discussed in depth (7).

Although certain structural limitations are imposed in the employment of silicon in medicinal agents, the distinctive bonding characteristics of this element would appear to permit the preparation of agents with truly unique chemical, physical, and biological properties.

GENERAL BIOLOGICAL PROPERTIES

Disease and Siliceous Materials—Frequently, the element silicon is automatically associated with the chronic lung disease silicosis, one of several pneumoconioses caused by dust inhalation. The fibrogenic pneumoconioses (caused by free silica, asbestos, some talcs, and diatomaceous earth) are characterized by widespread fibrosis and are clinically manifested by shortness of breath and a greatly increased susceptibility to tuberculosis. In the case of asbestosis, the incidence of tuberculosis, although high, is lower than that observed with silicosis; however, exposure to asbestos has been implicated as a major factor in the causation of carcinoma of the lung (diffuse mesothelioma) (8).

Pulmonary response to accumulations of siliceous material involves four basic processes: (*a*) necrosis of microphages which had taken up and subsequently liberated silicon, (*b*) continued production of fresh phagocytes to reingest the silica, (*c*) formation of collagen, and (*d*) hyalinization (9). Numerous theories have been proposed to account for the mechanism of silicotic fibrogenesis. The earliest, the "mechanical theory," suggested that silicosis is caused by a sharp particle irritation; this theory has been discarded since other sharp particles (silicon carbide) do not lead to the pneumoconiosis. Current textbooks of medicine (*e.g.*, 10) state that silica is a chemical rather than a mechanical irritant and that the observed tissue changes are caused by soluble silicic acid produced by silica reacting with body fluids, or by some other physical–chemical reaction.

Recently, Heppleston (9) suggested that silica appears to exert its fibrogenic effect by virtue of its surface properties, which are not necessarily connected with solubility or surface area; he suggested that silica acts by a "surface effect" on the macrophages. Stalder (11) postulated that the effect of silica can be explained by damage to biological membranes, the injury being the result of a surface interaction—mainly an absorption process—between the mineral and membrane lipids or lipoproteins. There is considerable evidence that an immunological response is associated with silicosis. As pointed out in a recent review by Fessenden and Fessenden (12), there is a high content of γ-globulin (up to 50%) in the hyaline substance of the silicotic nodule and an increase in blood serum levels of globulins and histamine in silicotic individuals.

Clearly, the precise nature of the chemical and/or physical reaction of silica implicated with silicosis is yet unknown. It is most important to recognize that although the inorganic substance silica is a causative factor in this malady, *there is no evidence to suggest that organosilicon compounds evoke this condition.*

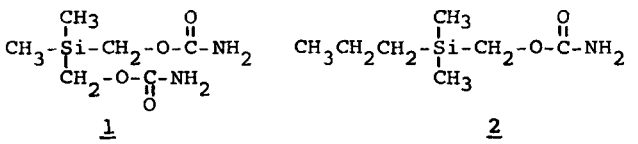
Current therapy for silicosis primarily consists of treatment of its concomitant conditions, namely, tuberculosis, emphysema, and other complications. At present, once fibrosis has developed in the lungs, there is no way to remove it. Within the past decade,

numerous therapeutic agents have been described; unfortunately, they do not exhibit a high degree of efficacy, nor are any widely accepted. These agents include: (*a*) inhalation of aluminum powder (10) and certain aluminum salts (13); (*b*) administration of trypsin as an inhaled aerosol (14); (*c*) steroid therapy with prednisolone (15, 16), cortisone (17), and other steroids (18); (*d*) subcutaneously administered $Na_2MgEDTA$ (19); and (*e*) inhalation (silicotic rats) of a poly(vinylpyridine *N*-oxide) aerosol (20–24). In the last instance, the antisilicotic action may be species and tissue specific (25). Ashbel *et al.* (26), in treating silicotic patients with an ascorbic acid aerosol[1], reported a normalization of capillary permeability and a distinct decrease in the intensity of infectious inflammation. Other investigators (28, 29), however, showed that the vitamin elicits a deleterious effect.

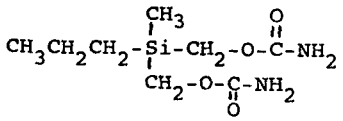
In addition to the pneumoconioses, it has been suggested that silicon compounds play a direct role in other pathological conditions (30, *cf.*, 31): "Numerous pathological processes, including cancer, atherosclerosis, tuberculosis, and diabetes, goiter, certain types of dermatitis, stone formations in the urethra, *etc.*, are associated with the breakdown of the metabolism of silicon compounds." These silicon-containing entities supposedly function by facilitating the urinary elimination of metabolites of foreign and toxic derivatives. Because of inadequate confirming evidence to the contrary, one cannot categorically dismiss the statement *in toto;* however, due to the absence of documentation and lack of independent verifying evidence, it is suggested that the generalizations are unwarranted.

Silicon is essential for reproduction in marine plankton and for nutrition in higher plants, although its precise function is little understood (32). The element is also present in mammals, including man, in different amounts in each organ (33). Silicic acid has been shown to stimulate *in vitro* collagen biosynthesis in chicken lung tissue (34), and Fregert (35) found relatively large amounts of silicon (presumably as organosilicon material) in keratinous tissue. Fregert suggested that these materials may be of biochemical significance to this specific tissue and that they may play a role in formation of the absorption barrier in skin and contribute to the solidity and chemical resistance of keratinous structures. Recently, in reporting the results of approximately 5000 quantitative, electron-probe microanalyses for calcium, phosphorus, and silicon in normal tibia of young mice and rats, Carlisle (36) showed silicon to be localized in active calcification sites; she implied that silicon may be linked to the initiation of mineralization of preosseus tissue.

Detoxification Patterns—When employing organosilicon compounds as medicinal agents, their fate in the treated subject is of major interest and importance. Not only is metabolism relevant to detoxification, but one might expect a difference in metabolic rates between silicon and carbon congeners (if not a completely different metabolic route) and thereby observe dramatic dissimilarities in physiological response. Fessenden and Ahlfors (37) recently published an account of the metabolic fate of three silicon-containing carbamates: bis(hydroxymethyl)dimethylsilane dicarbamate (*1*)[2], (hydroxymethyl)dimethyl-*n*-propylsilane carbamate (*2*), and bis(hydroxymethyl)methyl-*n*-propylsilane dicarbamate (silameprobamate, *3*). After



1 *2*



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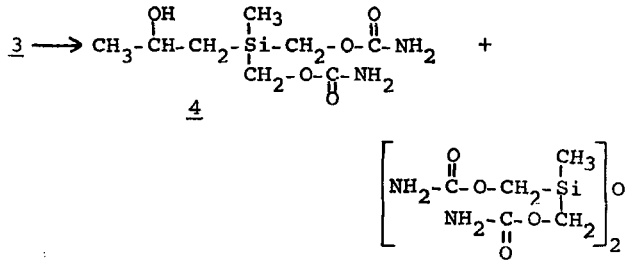
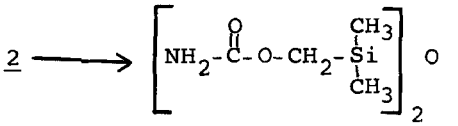
oral administration in rats, analysis of the urine showed that *1* was eliminated unaltered (53% recovery) whereas Compounds *2* and *3* afforded metabolic products. Oxidation of the propyl group in *3* produced its major metabolite, Compound *4;* a minor product, disiloxane *5*, was also isolated[3]. The formation of *4* parallels that for the metabolism of meprobamate itself. In



4 *5*

the case of *2*, no unchanged material could be detected in the urine; the disiloxane metabolite (*6*) was isolated and fully characterized. No other metabolic product of *2* was detected. The formation of disiloxanes *5* and *6* suggests that dealkylation may be a pathway in the



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detoxification of organosilicon compounds.

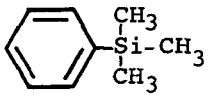
In another study, Fessenden and Hartman (38) described the urinary metabolic products of methyl-^{14}C-labeled phenyltrimethylsilane (*7*) and phenyldimethylsilane (*8*) upon oral (stomach tube) administration in rats. These compounds possess two key structural features common to many organosilicon entities,

[1] The specific medicament is galascorbin, a mixture of vitamin C and neutralized tannin in water (27).

[2] In the text, compound numbers appear in italic type. In the structures, these numbers are underscored.

[3] As pointed out by the investigators (37), Structures *4* and *5* must be considered tentative because they were unable to obtain the compounds analytically pure; the structure assignments were based on spectral evidence and qualitative tests.

the phenyl—silicon and the silicon—hydrogen bonds.



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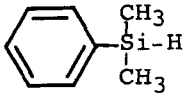

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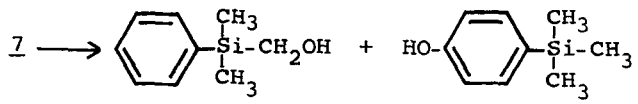
Compound *7* was oxidized to give three metabolites: (hydroxymethyl)dimethylphenylsilane (*9*), *p*-trimethylsilylphenol (*10*), and an unknown conjugate of *9;* the metabolites represent 31, 17, and 35% of the radioactive activity, respectively. No radioactive carbon dioxide from respiration was detected. In the metabolism of Compound *8*, approximately 90% of the



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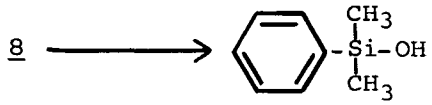
radioactivity was accounted for as phenyldimethylsilanol (*11*), which is unstable and readily loses water to give the corresponding disiloxane. From these data,



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it has been concluded that the Si—H bond is not stable *in vivo* and that this bond is the principal site for metabolic attack.

Naturally Occurring Organosilicon Compounds—The literature contains several reports on the existence of organosilicon compounds in animal tissue. Drechsel and Winogradow (39) described the isolation and partial characterization of a mixture of orthosilicate esters of cholesterol and cholesterol analogs, Isaacs (40) alluded to the presence of silicolipins in brain tissue, Holzapfel reported the existence of organosilicon compounds in silicotic lungs (41–43) and blood (44), Holt and Yates (45) quantitatively determined the silicon content of the ethanol-soluble portion of egg yolk, and Viehoever and Prusky (46) compiled an impressive amount of data from the older literature on the silicon content of various animal and plant tissues. However, in no instance has a pure organosilicon compound been isolated and fully characterized. An additional degree of uncertainty is introduced because most of the cited investigators employed ethanol for extraction, and ethyl silicate may presumably be formed during this procedure (45).

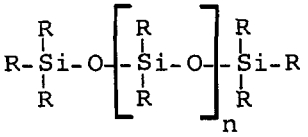
In a more recent investigation, Holt and Yates (47) determined the distribution of ^{31}Si injected in rats as soluble silica. They observed that the most radioactivity was present in the kidney and the least in muscle tissue. Part of the ^{31}Si could be extracted from the kidney with ethanol or dioxane; however, the greater portion could not be removed and, therefore, was probably present as inorganic silicate. These investigators suggested that the ethanol-soluble organosilicon materials may be micelles, consisting of hydrogen-bonded complexes between the hydroxyl functions of polymeric silicic acid and the hydroxyl groups of organic molecules such as cholesterol, or between other polar moieties in lecithin and choline.

TOXICOLOGY

Silicones—It is beyond the scope of the present communication to discuss in depth this important group of polymers. Nevertheless, their wide usage in medicine and pharmacy requires brief comment. The chemistry, technology, and medical use of these macromolecules have been exhaustively described elsewhere (48–50).

Although the term "silicone" is sometimes employed to encompass all organosilicon compounds with Si—C bonds, both monomeric and polymeric, the word is generally understood to refer only to organosilicon polymers containing Si—O—Si bonding. The preferred, more precise term for this class of polymers is polyorganosiloxane; however, because of the wide acceptance of the term silicone, it will be used interchangeably with polyorganosiloxane in the present discussion.

Being partially organic in constitution, the silicones exhibit structural and physical features of organic macromolecules; in addition, they also resemble the inorganic polymeric silicic acids and silicates. It is this dual nature, intermediate between inorganic and organic, that provides the silicones with their unique characteristics. A hypothetical silicone fluid is illustrated here. The representation illustrates only mono-



and difunctional structural units; branched subunits would be representative of a crosspolymerized silicone or silicone rubber.

The most striking biological feature of these substances is their general physiological inertness. Various studies in animals (*e.g.*, 51–56) and man (*e.g.*, 57–59) demonstrated a singular lack of pathogenic tissue response to systemically or orally administered silicones[4]. In one study, in which massive doses of dimethylpolysiloxane fluid were injected into rats (up to 540 ml. per animal), the only untoward effect reported was difficulty in locomotion (61).

The one exception to the biological inertness of silicones is eye irritation. In rabbits, a transitory conjunctival irritation develops within a few hours after contact with these polymers and usually completely disappears within 24 hr. (56). The human eye reacts to contact with a painful burning sensation (48), characterized by an erythema of the conjunctival membranes and frequently accompanied by edema

[4] This esoteric topic is not without its humorous facets. Helal (60), in rebuttal to a report citing an untoward effect allegedly caused by a silicone, quipped: "This statement, like the topless waitresses, is completely unsupported."

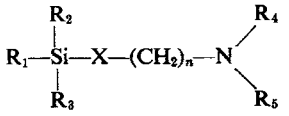


Table I—Mammalian Toxicity of Nitrogenous Organosilicon Compounds

Compound	R_1	R_2	R_3	X	n	R_4	R_5	LD_{50}[a], mg./kg.	Reference
12	C_2H_5O	C_2H_5O	CH_3	CH_2	3	H	H	0.045[b]	2
13	C_2H_5O	C_2H_5O	C_2H_5O	CH_2NH	6	H	H	1.5[c]	75
14	C_2H_5O	C_2H_5O	CH_3	CH_2NH	6	H	H	1.6[c]	75
15	C_2H_5O	C_2H_5O	CH_3	CH_2	0	H	C_2H_5	3.0[c]	75
16	C_2H_5O	C_2H_5O	C_2H_5O	CH_2	0	C_2H_5	C_2H_5	3.0[c,d]	75
17	C_2H_5O	C_2H_5O	C_2H_5O	CH_2	2	H	H	>4.0[c,e]	75
18	C_2H_5O	C_2H_5O	CH_3	CH_2	2	—$CH_2CH_2CH_2CH_2CH_2$—		6.6	30
19	C_2H_5O	C_2H_5O	CH_3	CH_2	2	H	H	40	30
20	C_2H_5	C_2H_5	CH_3	CH_2	2	H	H	47	30
21	C_2H_5	C_2H_5	C_2H_5	CH_2	2	—$CH_2CH_2CH_2CH_2CH_2$—		47	30
22	*n*-C_3H_7	*n*-C_3H_7	*n*-C_3H_7	CH_2	2	H	H	75	30
23	C_2H_5O	C_2H_5O	CH_3	CH_2	2	—CH_2CH_2—O—CH_2CH_2—		86	30
24	C_2H_5	C_2H_5	C_2H_5	CH_2	2	H	H	90	30
25[f]	C_2H_5	C_2H_5	C_2H_5	CH=CH	1	—$CH_2CH_2CH_2CH_2CH_2$—		110	30
26	C_6H_5	C_6H_5	C_2H_5	CH_2	2	H	H	120	30
27[f]	C_2H_5	C_2H_5	C_2H_5	CH_2	2	—$CH_2CH_2CH_2CH_2CH_2$—		120	30
28	C_6H_5	C_2H_5	C_2H_5	CH_2	2	H	H	140	30
29	CH_3	CH_3	CH_3	CH_2	2	H	H	155	30
30	C_2H_5	C_2H_5	C_2H_5	O	2	H	H	165	30
31	C_2H_5	C_2H_5	C_2H_5	CH_2	2	H	—[g]	185	30
32[f]	C_2H_5	C_2H_5	C_2H_5	C≡C	1	—$CH_2CH_2CH_2CH_2CH_2$—		195	30
33	C_2H_5O	C_2H_5O	C_2H_5	CH_2	2	H	H	215	30
34	C_2H_5O	C_2H_5O	C_2H_5O	CH_2	2	H	H	260	30
35	C_2H_5	C_2H_5	C_2H_5	O	2	—$CH_2CH_2CH_2CH_2CH_2$—		280	30
36	CH_3	CH_3	CH_3	O	2	H	H	320	30
37	C_2H_5	C_2H_5	C_2H_5	O	2	H	*n*-C_4H_9	360	30
38	CH_3	CH_3	CH_3	O	2	—$CH_2CH_2CH_2CH_2CH_2$—		400	30
39	C_2H_5	C_2H_5	C_2H_5	O	2	C_2H_5	C_2H_5	400	30
40	C_2H_5O	C_2H_5O	CH_3	CH_2	2	—$CH_2CH_2N(CH_3)CH_2CH_2$—		400	30
41	C_2H_5O	C_2H_5O	CH_3	CH_2	2	—$CH_2CH_2SCH_2CH_2$—		470	30
42	CH_3	CH_3	CH_3	O	2	C_2H_5	C_2H_5	500[h]	30
43	CH_3	CH_3	CH_3	O	2	CH_3	CH_3	620	30
44	CH_3	CH_3	CH_3	O	2	*n*-C_4H_9	*n*-C_4H_9	640	30
45	C_2H_5	C_2H_5	C_2H_5	O	2	CH_3	CH_3	670	30
46	C_2H_5	C_2H_5	C_2H_5	O	2	*n*-C_4H_9	*n*-C_4H_9	1650	30

[a] Tests by intraperitoneal injection of mice, rats, or rabbits. [b] Skin absorption (ml./kg.). [c] Atmospheric concentration (mg./l.). [d] LD_{100}, 10 mg./kg. (administered in a single dose *via* stomach tube). [e] Maximum allowable concentration 0.001 mg./l. (165). [f] Administered as the hydrochloride salt. [g] 2-Furanylmethyl. [h] A value of 630 is also reported (30).

of the lids. Interestingly, however, dimethylpolysiloxane fluids have been injected into the eye of animals and man as a replacement for aqueous and vitreous humor. The fluid is apparently well tolerated, with no tissue or inflammatory response. The varied use of liquid silicones in medicine and pharmacy is due largely to their low surface tension and antisurfactant activity. Selected silicones have been used with success as antiflatulents in the treatment of meteorism (62, 63) and for foam modulation in extracorporeal devices such as bubble oxygenators (64); others have been employed as antifoaming agents to control pulmonary edema (65–68). Because of their water-repellent characteristics, these polymers have been: (*a*) incorporated into ointments and pastes for skin protection; (*b*) proposed as additives for nail polishes, lipsticks, and antisunburn preparations; and (*c*) included in dentifrices (48). The silicone oils (69) and colloidal silicates (70) have also been employed in burn treatment. The use of silicone fluids in soft tissue augmentation (57) and the importance of resinous silicones to dentistry and surgery were recently discussed in depth (48).

Dimethylpolysiloxane and phenylmethylpolysiloxane were evaluated as potential agents for the treatment of atherosclerosis in rabbits (71–73). While the former may possibly exert a minor antihypercholesterolemic effect, the aromatic polymer definitely results in lowered blood cholesterol levels in animals fed high cholesterol diets.

Nitrogenous Organosilicon Compounds—This class of compounds, whose chemistry was recently reviewed (74), comprises the largest single group of entities for which toxicological data are available (Tables I–III).

Inspection of Table I reveals specific trends within the aminosilane series: (*a*) compounds containing alkoxy substituents on the silicon atom (R_1, R_2, and R_3) are more toxic than those with corresponding alkyl substitution (*cf.*, Compounds *18* with *21* and *19* with *20*); (*b*) compounds containing an oxygen atom between the silicon and amino moieties, where X equals O, are noticeably less toxic than the corresponding carbon analogs in which X equals C (*cf.*, Compounds *24* with *30*, *21* with *35*, and *29* with *36*); and (*c*) in comparing those entities where X is oxygen, the molecules containing a primary amino function are more toxic than those possessing a tertiary amino group. Voronkov and Lukevics (30) pointed out that the hydrochloride salts of the γ-aminopropylsilanes (*e.g.*, Compounds *17–29*) are less toxic than their corresponding free bases. Furthermore, in the instance of Compounds *85*, *86*, and *87*, it is interesting

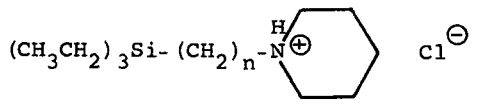
Table II—Mammalian Toxicity of Nitrogenous Organosilicon Compounds[a]

$(R_1)_{4-n}$—Si(O—CH_2CH_2—$NR_2R_2)_n$

Compound	R_1	R_2	n	LD_{50}, mg./kg.
47	C_2H_5	H	2	125
48	—	C_2H_5	4	230
49	CH_3	H	3	400
50	C_2H_5	C_2H_5	3	490
51	C_2H_5	H	3	500
52	C_6H_5	H	3	500
53	C_6H_5	C_2H_5	3	560
54	CH_3	H	2	570
55	CH_3	C_2H_5	3	600
56	C_2H_5	C_2H_5	2	600
57	CH_3	C_2H_5	2	720
58	C_2H_5	*n*-C_4H_9	2	2400
59	$O[Si(CH_3)_2CH_2CH_2CH_2NH_2]_2$			30
60	$C_6H_4[Si(CH_3)_2CH_2CH_2CH_2NH_2]_2$			74
61	$[(CH_3)_3SiOCH_2CH_2]_2NH$			1250
62	$[(C_2H_5)_3SiOCH_2CH_2]_2NH$			1850
63	$[(CH_3)_3SiOCH_2CH_2]_3N$			3500
64	$[(C_2H_5)_3SiOCH_2CH_2]_3N$			4000
65	$(CH_3)_3Si$—O—$Si(CH_3)_3$			4500

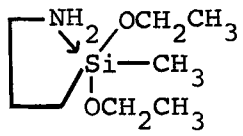
[a] Tests by intraperitoneal injection in mice, rats, and rabbits (30).

to note a decrease in toxicity (LD_{50} 60, 88, and 120 mg./kg., respectively) as the amino group is further removed from the silicon atom (30).



85, n=1
86, n=2
87, n=3

Compound *12* also elicits an extremely toxic response upon dermal application and was reported to cause serious injury in contact with the eye (2). Voronkov (76) suggested that the high physiological activity of *12* may be ascribed to intramolecular coordination of the γ-amino group with the silicon atom; this is

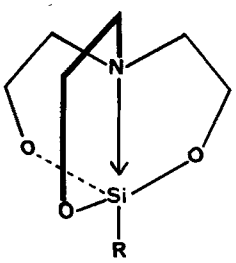


12

consistent with the observation that several compounds (*17–24*) containing an amino group gamma to the silicon atom are relatively toxic. Nevertheless, the exceedingly high toxicity of *12* remains anomalous and cannot be totally rationalized in terms of chemical structure.

Nitrogenous silanes containing more than one amino function appear to be relatively nontoxic (Table II). It is not immediately apparent why the introduction of a second amino group should have this effect.

Silatranes—This group of caged pentacovalent organosilicon compounds, with 1-alkyl- and 1-aryl-substituents, has been observed to elicit striking biological effects. In these compounds, which were studied by spectral and dipole moment techniques (76), silicon does not participate in sp^3 bonding but in sp^3d coordination with a tetrahedral nitrogen atom as shown here:



The 1-substituted silatranes can be readily prepared by several methods which were described in detail by Voronkov (76) and Zelchan (77). A number of 1-alkyloxy- and 1-acyloxysilatranes, which undoubtedly have similar bonding characteristics, have also been synthesized (77); while the former are gradually hydrolyzed in the atmosphere, the latter are extremely unstable and very difficult to purify. Neither has apparently been tested for physiological activity.

The most prominent physiological feature of the silatranes is the remarkable mammalian toxicity exhibited by some of the 1-aryl derivatives (Table III). 1-*p*-Tolyl- and 1-phenylsilatrane (Compounds *66* and *67*, respectively) are even more toxic than strychnine [LD_{100} (mice) 0.5–1.25 mg./kg.] or hydrocyanic acid [LD_{100} (mice) 3–10 mg./kg.] (78). When sublethal doses (0.20–0.25 mg./kg.) of *67* are intraperitoneally administered to white mice, the agent elicits a strong analeptic action as evidenced by motor excitation and accelerated breathing; at a slightly higher dose (0.35 mg./kg.), alternating clonic and tonic convulsions occur (79). The effect of *67* upon unanesthetized cats is similar to that with mice; however, when the compound is intravenously administered in a 10-fold lethal dose to cats anesthetized with ethyl carbamate or chloralose, the only effect is convulsive contraction of the skeletal muscles followed by intensive breathing. The same effect is observed upon anesthetized and unanesthetized rabbits.

Table III—Toxicity of Silatranes[a]

$RSi(OCH_2CH_2)_3N$

Compound	R	LD_{50}, mg./kg.
66	*p*-Tolyl	0.20
67	Phenyl	0.43
68	*m*-Chlorophenyl	4.4
69	Phenyl[b]	8.1
70	3,5-Dimethylphenyl	14.7
71	Hydro	100
72	Cyclohexyl	150
73	Phenoxy	200
74	*p*-Nitrophenoxy	700
75	*p*-Chlorophenoxy	1050
76	Benzyl	1115
77	*p*-Tolyloxy	1270
78	Methoxy	2100
79	5-Methyl-2-isopropylphenoxy	4000
80	Ethoxy	5000
81	Methyl	5000
82	Ethyl	5000
83	Isopropyl	5000
84	Allyl	5000

[a] Tests by peritoneal injection in white mice (30). [b] Compound *69* contains a 2-carbo substituent in the parent silatrane moiety.

Table IV—Mammalian Toxicity of Haloorganosilicon Compounds[a]

Compound	Structure	LD_{100}[b], g./kg.	LD_{100}[c], g./kg.	LD_{50}[d], mg./l.	Maximum Tolerance Dose, mg./l.	Maximum Allowable Concentration, mg./l.	Lethal[d] Concentration	Reference
88	$(CH_3)_3SiCl$	—	—	4	—	—	—	31
89	$(C_2H_5O)_2Si(H)Cl$	6.30[e]	—	—	—	—	—	85
90	$ClCH_2Si(CH_3)(H)Cl$	—	—	—	—	0.001	—	86
91	$ClCH_2Si(CH_3)_2Cl$	—	—	—	—	0.001	—	86
92	$(CH_3)_2SiCl_2$	1.0	0.10	—	—	—	—	56
—		—	—	—	—	0.02	0.44	87
—		—	—	10	—	—	—	31
93	$(C_2H_5)_2SiCl_2$	1.0	0.10	—	—	—	—	56
94	$C_6H_5Si(CH_3)Cl_2$	0.1–0.25 mg./l.[f]	—	—	—	—	—	88
—		—	0.25 mg./l.	0.15	—	0.08 (1.0)	0.01	89 (90)
95	$C_2H_5Si(C_6H_5)Cl_2$	—	—	—	—	0.005	—	91
96	*x*—$FC_6H_4Si(CH_3)Cl_2$	—	—	—	—	0.001	—	92
97	*x*—$ClC_6H_4Si(CH_3)Cl_2$	—	—	—	—	0.005	—	93
98	$(C_3H_4F_3)CH_3SiCl_2$	—	—	—	—	—	8.0	94
99	$SiHCl_3$	—	—	—	—	0.001	—	95
—		1.03[e]	—	—	—	—	—	85
100	CH_3SiCl_3	1.0	0.30	—	—	—	—	56
—		—	—	10	—	—	—	31
—		—	0.12–0.14[f]	—	0.08–0.1	0.02	—	87
101	$C_6H_5SiCl_3$	—	0.12–0.14[f]	—	0.08–0.1	0.05	0.60	87
—		2.39	—	—	—	—	—	96
102	$ClCH_2SiCl_3$	—	0.15–0.2 mg./l.	0.06	—	0.025 (1.0)	0.04	89 (90)
—		—	—	—	—	0.001	—	97
103	$C_2H_5SiCl_3$	1.0	0.03	—	—	—	—	56
—		—	0.08	—	0.05	—	0.44	87
104	*x,y*—$Cl_2C_6H_3SiCl_3$	—	—	—	—	0.001	0.08–0.1	98
—		—	0.1[f]	0.04	—	0.02	0.03	89
105	$C_2H_3SiCl_3$	1.28	—	—	—	—	—	96
106	$SiCl_4$	—	0.1[f]	5.0	—	—	—	31

[a] Tests performed on mice, rats, or rabbits. [b] Administered in a single dose *via* stomach tube. [c] Injected intraperitoneally. [d] Atmospheric concentration. [e] LD_{50}. [f] Administration route not specified.

Frogs are exceptionally resistant to 1-phenylsilatrane; doses of 30–40 mg./kg. (higher doses not being practical due to the compound's low water solubility) have no effect. Compound *67* does not markedly change the reaction of isolated m. rectus abdominis muscle (frog) to acetylcholine, nor does it cause contraction of perfused frog's hind legs. Thus, a direct influence on the peripheral neuromuscular mechanism is excluded (76). Accelerated breathing and convulsions are observed at low doses in decerebrated cats, and spasmodic twitching also is observed in spinally anesthetized cats; cats with "destroyed nervous systems" do not react to intravenous injections. Voronkov and Lukevics (30, 76) thus concluded that 1-phenylsilatrane acts upon the CNS and that its effect upon the spinal column is of great importance. They further suggest that the compound acts on an enzyme system, although it is not a cholinesterase inhibitor (76). The toxicity of 1-phenylsilatrane is highly species dependent, being extremely toxic to mammals and essentially nontoxic to frogs, bacteria, and fungi (75, 80).

Examination of the effect of 1-substitution upon silatrane toxicity (Table III) reveals that *only* the 1-arylsilatranes exhibit high toxicity; the 1-aryloxy-derivatives, 1-benzylsilatrane, and silatrane itself are only moderately toxic, and 1-alkyl- and 1-alkyloxysilanes are remarkably inert. It is known that silatranes undergo hydrolysis in aqueous solution and exhibit a first-order reaction (76, 77, 81); consequently, some physiological activity may be due to hydrolysis product(s). Because 1-phenylsilatrane is highly toxic and poorly soluble (82), it is suggested that distribution coefficients may be of major importance to toxicity with these compounds.

Haloorganosilicon Compounds—The chlorosilanes, important intermediates in the commercial production of silicones, must be considered a highly toxic class of compounds (Table IV). Materials such as tetrachlorosilane or tetrabromosilane and the hydrosilanes in general are reported to exhibit severe acute toxicity upon ingestion, inhalation, or application to the skin (83). Silicon tetrafluoride, a colorless toxic gas which evolves hydrogen fluoride in the presence of moisture, is known to cause acute fluoride poisoning by inhalation (84). Rowe *et al.* (56) cautioned that particular care must be exercised with these compounds, because even one small drop splashed into the eye could cause its loss.

Severe skin burns occur if halosilanes come into contact with dermal tissue; however, death is not likely unless a large portion of the body is involved. Voluntary inhalation of lethal concentrations of chlorosilanes is prevented by the marked irritation caused by these agents. Both alkyl- and arylchlorosilanes most often affect the upper respiratory tract; aryl compounds (such as the phenylchlorosilanes) cause infections of the mucous lining of the mouth. It was reported that people working with these agents can develop chronic occupational intoxication, characterized by chronic laryngotracheitis, and rhinitis accompanied by atrophic processes in the mucous lining of the nasopharynx (99). As an additional hazard, the volatile chlorosilanes are flammable; those entities containing a SiH moiety liberate hydrogen upon treatment with a protic solvent (100). The aryl-

Table V—Mammalian Toxicity of Alkyloxysilanes

Compound	Name	LD_{50}, g./kg.[a]	LD_{100}, g./kg.[b]		Maximum Allowable Concentration[c]
107	Ethoxytrimethylsilane	—	0.1	2.0	—
108	Diethoxydimethylsilane	—	0.4	10.0	—
109	Triethoxymethylsilane	—	0.4	10.0	—
110	Tetraethoxysilane	—	15	5.0	0.02
111	Triethoxysilane	—	—	—	0.001
112	Vinyltriethoxysilane	22.5	—	—	—
113	Amyltriethoxysilane	19.6	—	—	—
114	Tris(2-chloroethoxy)silane	0.19	—	—	—
115	Ethyltriethoxysilane	13.72[d]	—	—	—

[a] Oral administration in rats (96). [b] Oral administration in rats; the data in the left column are from Voronkov (31), and those on the right are from Rowe *et al.* (56). [c] Atmospheric concentration (milligrams per liter) according to Kulagina and Kochetkova (107). [d] Smythe *et al.* (85).

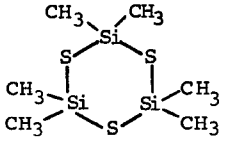
chlorosilanes are generally more toxic than the alkyl derivatives, although the former are less volatile (101). The presence of chloro or amino substituents on the alkyl or aryl group intensifies the toxicity, whereas the introduction of a cyano substituent decreases this effect (102).

It has generally been accepted that the toxicity of the chlorosilanes is due to the hydrochloric acid produced upon hydrolysis (12, 100, 102). Golubev (103), in investigating the inhalation toxicity of trifluoropropylmethyldichlorosilane, found that not only was the clinical symptomatology in mice the same for the halosilane and its hydrolysis product hydrochloric acid, but also that their lethal concentrations (LD_{50} 8.12 and 2.51 mg./l., respectively) were in good agreement for the calculated amount of acid released by hydrolysis. However, Voronkov (31) pointed out that dimethyldichlorosilane (*92*) and methyltrichlorosilane (*100*) are less toxic than trimethylchlorosilane (*88*). Not only do *92* and *100* produce more acid upon hydrolysis, but the two compounds hydrolyze more rapidly than *88*. This would suggest that the *in toto* chlorosilanes may be responsible for some of the toxic effects.

All of the values of maximum allowable atmospheric concentration (Table IV) were published in the Soviet literature; to the authors' knowledge, standards for these specific agents have not been established in the United States.

Alkoxysilanes—Very little data concerning the toxicological properties of the alkyloxysilanes are available. Tetraethoxysilane (*110*) was reported to be highly toxic, its vapor being irritating to the respiratory tract and affecting CNS function (104). Animals exposed to *110* expire with grave damage to lung, liver, and kidney tissue. It has been recognized for some time that the industrially important ethyl silicates, a mixture of *110* and various ethyl polysilicates, may cause serious damage to the lungs and kidneys (105). Indeed, the toxicological properties of ethyl silicates have long been recognized (85, 106). It can be seen from Table V that toxicity decreases with an increase in the number of alkoxy substituents.

Miscellaneous Compounds—Moody (108) described the synthesis and properties of hexamethylcyclotrisilthiane (*116*) and tetraphenylcyclodisilthiane (*117*). Both of these unique organosilicon heterocyclics readily produce hydrogen sulfide in contact with water and other protic substances.



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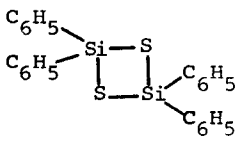
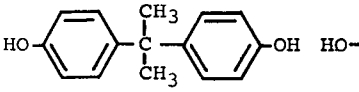


117

An interesting instance of allergy to an organosilicon compound was reported by Fregert and Rorsman (109). Four individuals, hypersensitive to 2,2-bis(4-hydroxyphenyl)propane (*118*), exhibited the identical response in a patch test with dimethyldi-(4-hydroxyphenyl)silane (*119*) as with *118*. None of the subjects had previously been exposed to Compound *119*.



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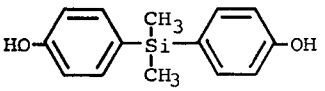
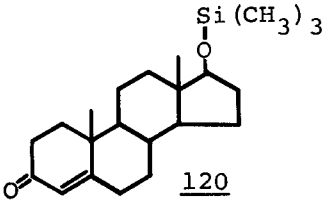


119

AGENTS ELICITING BIOLOGICAL ACTIVITY

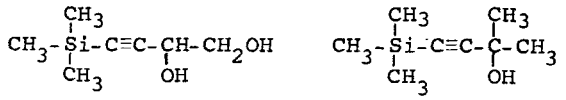
Compounds Affecting Metabolism—Chang and Jain (110) recently described six testosteroxysilanes and their respective androgenic and myotropic activities upon subcutaneous injection in rats. Within the series, only testosteroxytrimethylsilane (*120*) exhibited greater activity than testosterone itself. Observing that *120* was the most susceptible to hydrolysis (88% conversion to testosterone when incubated in water at 37° for 24 hr.) and least polar, as demonstrated by paper chromatography, it was postulated that its elevated activity was the result of rapid transport across the lipid membrane barrier and facile cleavage to the parent steroid. Brown and Laos (111), in de-



120

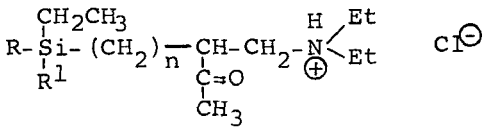
scribing another group of 17-trialkylsilyloxy steroids, also discussed the elevated androgenic activity of *120*. However, no comment was made regarding its mechanism of action, nor were any specific biological data reported. The fate of the trimethylsilyl residue from these compounds has apparently not been investigated; one may speculate on the formation of the corresponding innocuous disiloxane (*65*). The elaboration of other organosilicon entities and their potential toxicity must obviously not be discounted.

Cardiovascular Agents—Numerous silicon-containing compounds have been reported which lower blood pressure. For example, Ignat'eva and Kuznetsov (112) observed that 4-trimethylsilyl-3-butyne-1,2-diol (*121*) and 2-methyl-4-trimethylsilyl-3-butyne-2-ol (*122*)



121 122

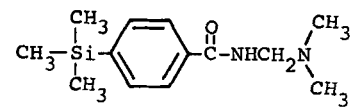
effected a decrease in the blood pressure of rats upon intravenous or intraabdominal injection; in greater doses, the compounds sporadically caused a rise in blood pressure. The magnitude of blood pressure change was unfortunately not reported. Toxic effects (spasms and miosis) were observed for *121* at doses up to 10 mg./kg.; at higher doses, general spasms and death occurred. In the case of *122*, subcutaneous administration caused a rise in respiration, and higher doses resulted in death (cessation of breathing). Shostakovskii *et al.* (113) reported that silyl ketoamines (*123–125*) reduce blood pressure, stimulate breathing, and elicit a spasmolytic effect; however, specific data were not given.



Compd.	R	R^1	n
123	C_2H_5	C_2H_5	1
124	C_2H_5	CH_3	2
125	CH_3	CH_3	2

Belsky *et al.* (114) reported that several amides of trimethylsilyl-substituted aromatic acids cause a lowering of blood pressure in anesthetized cats upon intravenous injection; a concomitant increase in respiration without a change in heart rate was also observed. The most efficacious of these agents (*126*) elicited the following effects [dose (mg./kg.), decrease in blood pressure (mm.), duration of decrease (min.), respiration rate increase (% of control)]: 1, 30, 4, 22; 2, 40, 4, 35; 4, 70, 20, 83; and 6, 100, 60, 81. In another study (115), these investigators showed that under the same conditions, at a dose of 10 mg./kg., *n*-(*p*-trimethylsilyl-*β*-phenethyl)morpholine hydrochloride (*127*) lowers arterial blood pressure 120 mm. for 40 min.

Frankel *et al.* (116) prepared and pharmacologically evaluated a group of *p*-trimethylsilyl- and *p*-trimethylsilylmethylphenethylamines. Those agents having the silyl substituents in the *para*-position elicit a blood pressure-lowering response, whereas the *ortho*- and *meta*-derivatives exhibit a hyperpressor effect. In comparing *o*-trimethylsilylphenethylamine hydrochloride and its *meta*-isomer, the pressor activity of the former was found to be greater. Testing these agents in anesthetized cats, the heart rate was not affected while respiration rate increased with the *para*-substituted compounds and decreased with the corresponding *ortho*- and *meta*-isomers. Among the compounds exhibiting depressor action, *p*-triethylsilylphenethylamine hydrochloride exhibited the greatest activity on both lowering blood pressure and duration (dose 5 mg./kg., −130 mm. for 150 min.). Neither introduction of a methyl group in the carbon atom of the aliphatic side chain nor addition of a methylene substituent between the silyl moiety and the benzene ring caused a significant change in blood pressure.



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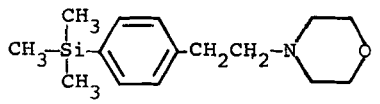

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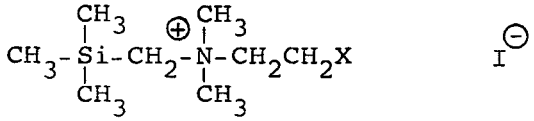
A series of trialkylsilyl derivatives of choline has been found to exhibit a hypotensive effect (*30*). Compounds *128* and *129* were particularly efficacious,



128, X=$OCOCH_3$
129, X=I

causing a decrease of 70–90 and 50–60 mm. Hg, respectively, at doses of 1 mg./kg. A number of the *O*-silyl derivatives caused an increase in blood pressure of short duration prior to the hypotensive action.

Loeper and his colleagues (*117–122*)[5] presented convincing evidence that silicon, or the lack of this element, probably plays an important role in atherosclerosis. In contrast to the earlier finding of Kvorning (123), these investigators showed that the silicon content of the aorta in normal man decreases with age. Expressing the aortic silicon content in mcg./100 mg. of tissue nitrogen, the following data were presented:

Age, Year	Silicon Content
Infants	205 ± 44
10–20	160 ± 43
20–30	125 ± 30
40	86 ± 16

[5] *References 117* and *118*, except for a slight modification in title and the introductory sentence, *are identical*, although published in two different journals; the reference with the most recent publication date (117) has the caption: "article original."

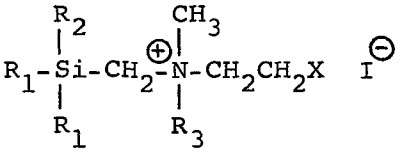


Table VI—Mammalian Toxicity of Organosilicon Derivatives of Choline[a]

Compound	R_1	R_2	R_3	X	ED_{50}[b], mg./kg.	EC_{50}[c], mg./kg.	LD_{50}[d], mg./kg.
142	C_2H_5	CH_3	CH_3	Cl	0.35	3.2×10^{-6}	71
143	CH_3	CH_3	CH_3	Cl	0.50	9.1×10^{-5}	124
144	CH_3	CH_3	CH_3	OH	0.56	8.0×10^{-4}	266
145	CH_3	CH_3	CH_3	CH_3COO	0.62	2.4×10^{-4}	328
146	CH_3	CH_3	CH_3	I	0.69	2.5×10^{-5}	40
147	C_2H_5	C_2H_5	CH_3	OH	0.85	4.9×10^{-6}	53
148	CH_3	CH_3	CH_3	C_6H_5COO	1.26	2.3×10^{-5}	465
149[e]	CH_3	CH_3	H	Cl	—	1.3×10^{-5}	137
150[f]	—	—	—	—	—	4.5×10^{-4}	238

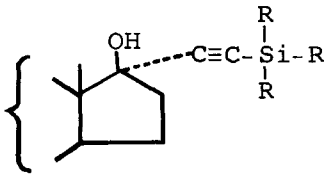
[a] Voronkov and Lukevics (30). [b] Ganglionic blocking in cats. [c] Cholinolytic action in frog muscle. [d] Intraperitoneal injection in white mice. [e] With chloride anion in place of iodide. [f] $[(CH_3)_3SiOCH_2CH_2N(CH_3)]I$.

Loeper and Polet (120) showed that normal human aorta and carotid arteries contain approximately 10 times more silicon than atherosclerotic arteries. In a more refined study (121), in which the sclerotic lesions were classified according to their severity, a much more striking correlation between silicon content of the aorta and disease condition was noted: (*a*) in those arteries free of atheromatous deposits, the value for silicon was found to be 180 ± 21 (mcg. silicon/100 mg. tissue nitrogen); (*b*) in arteries moderately altered with light subendothelial lipid deposits, discrete rarefaction of elastic fibers, and metachromasia of the ground substance, a silicon value of 105 ± 12 was obtained; and (*c*) in the instance of lesions where the arteries were greatly altered with lipid deposits uniting the media and intima, rarefaction and displacement of elastic fibers occurred, and calcium excess and augmentation of the ground substance were observed, the value for silicon was found to be 63 ± 8. The findings were experimentally verified in rabbits fed on high cholesterol diet. Here, again, the course of atheroma was marked by a significant decrease in aortic silicon level, the initial decrease being quite early in the disease process.

It has been suggested that silicon elicits its antisclerotic action by decreasing the permeability to lipid infiltration (121). More recently (118), evidence has been presented associating protection and development of elastic fibrils of the arterial wall with fibrillogenesis stimulation. Holt and Osborne (124) found the permeability of rat subcutaneous tissue membrane to be reduced after treatment with silicic acid, and Loeper *et al.* (121) showed that diffusion of a dye across rabbit skin is inhibited by small amounts of sodium silicate.

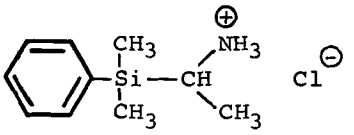
Rager (125, 126) was able to prevent the development of atherosclerosis in rabbits, fed an atherogenic diet, by intravenously administering "sodium monomethyltrisilanolorthoxybenzoate"—a complex of methylsilanetriol and sodium salicylate in an aqueous solution (127). The complex was also used with ionokinetic treatments (repeated daily for 16–20 days) in patients with coronary insufficiency and muscular ischemia. Although these individuals had previously been refractory to more conventional treatment, 75% of those with coronary insufficiency and 35% of those with ischemia were reported to have rapid improvement. Gendre recently described the effect of the complex upon the ultrastructure of rabbit arterial wall (128) and its action on lipid plaque deposits (129). Recently, Loeper and Loeper (118) investigated the prophylactic effects of sodium silicate, lysyl silicate, and the salicylate and citrate of methylsilanetriol upon experimental atheroma in rabbits. All of the compounds decreased the macroscopic atheromatous lesions, the incidence of plaques being 80% for the controls and 28% for the treated animals. The organosilicon entities were reported to be the most active.

Brown *et al.* (130) described a number of acetylenic silyl steroids with the D-ring substituted as shown here:



These compounds, in which R is methyl, ethyl, propyl, or phenyl, and ring A reflects the incorporation of several steroidal entities, are reported to elicit estrogenic, progestational, and hypocholesterolemic activity as well as counteracting the development of exogenously reduced hypercholesterolemia.

Agents Affecting Nervous System—The compound (α-aminoethyl)dimethylphenylsilane hydrochloride (*130*) and its carbon isostere have been compared in



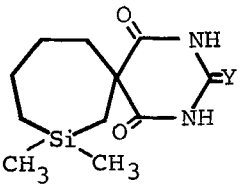
130

terms of their physiological activities (131). Their toxicities (LD_{50} 105–113 and 102–107 mg./kg., respectively) in white mice are nearly equivalent, and both compounds cause an increase in the rate and depth of respiration. ECG and EEG studies in rats anesthe-

tized with sodium pentobarbital revealed no analeptic activity at toxic doses; mice given sublethal doses exhibited intense excitement. No gross difference in pharmacological activity was observed between Compound *130* and its carbon analog. Several trimethylsilylphenethylamines were reported (132), but their biological activities were not described.

Compound *121* (4-trimethylsilyl-3-butyne-1,2-diol) was reported to induce spasms and miosis in white rats at doses up to 10 mg./kg.; higher doses caused general spasms and death (112). Animal tests of silyl ketoamines *123–125* demonstrated their spasmolytic effects (113).

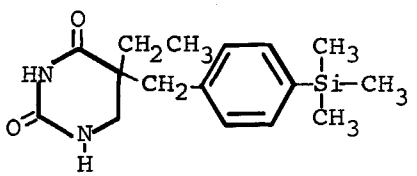
In the pharmacological evaluation of a group of silabarbiturates, Compound *131* gave the most rapid



Compd.	Y
131	O
132	S

onset of action and possessed the highest therapeutic ratio, whereas Compound *132* elicited a belated onset of action and the highest toxicity (133). Although these compounds did not give high therapeutic ratios, their level of biological activity is promising.

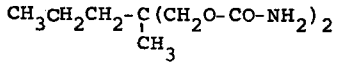
Belsky *et al.* (114, 115, 134) synthesized and evaluated numerous compounds which exhibit anticonvulsive activity. Upon oral administration of *p*-trimethylsilylphenylacetylurea to fasted male mice, the agent was more effective in protection against supramaximal electroshock than its carbon analog, phenylacetylurea (114); the compound was also the only member of a group of amides of silicon-containing aromatic carboxylic acids that exhibited an anticonvulsive effect against maximal pentylenetetrazole (115). The same investigators reported 5-(*p*-trimethylsilylbenzyl)-5-acetamidobarbituric acid (*133*) to show anticonvulsive



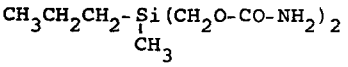
133

activity in male mice against pentylenetetrazole (134). The activity of Compound *133* was similar to, but lower than, that observed for phenobarbital. The preparation of several barbiturates, 2-thiobarbiturates and 2-aminobarbiturates substituted in the 5-position with one or two *p*-trimethylsilylbenzyl moieties, was reported (135); however, no data regarding their biological properties were presented.

An investigation of 24 alkanediol carbamates, monocarbamates, and their silicon isosteres revealed essentially equivalent muscle-relaxant activity, as measured in the rotating rod test (136). In intraperitoneal administration, meprobamate and silameprobamate (*134*) differed only in duration of activity (meprobamate acting four times longer than *134*) and not in their

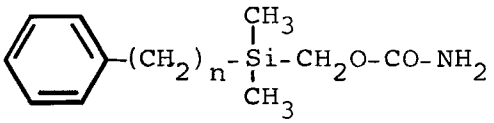


Meprobamate



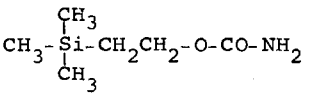
134

effective dose. However, upon oral administration, silameprobamate exhibited essentially no activity. Fessenden and Coon (137) reported that phenyl-substituted silacarbamates, Compounds *135–137*, exhibited muscle-relaxant properties with activity of short duration (10–20 min.). Evaluation of 2-trimethylsilyl-1-ethanol carbamate (*138*) and its carbon analog *139*



135, n=0
136, n=1
137, n=2

in the guinea pig ileum assay revealed that both compounds lack muscarinic activity; however, they were



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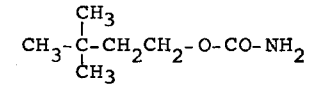
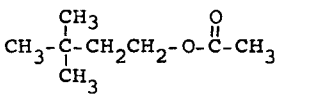


139

antagonistic to the muscarinic activity of both acetylcholine and carbachol (138). From these data, it has been inferred that although the compounds do not possess muscarinic activity, they do have an affinity for the muscarinic site.

Henderson *et al.* (139) studied the cholinergic effect of acetyl "carbocholine" (*140*) and its silicon isostere, acetyl "silicocholine" (*141*). These investigators concluded that both *140* and *141* should be considered as indirectly acting cholinergic (nonnicotinelike)



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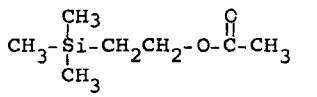


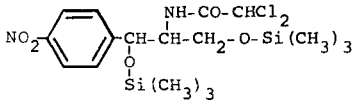
141

compounds, with their action being based on the stimulation of the release of acetylcholine from the presynaptic nerve terminals.

In studies employing frog stomach muscle, organosilicon derivatives of choline, acetylcholine, "chlorocholine," and "iodocholine" were shown to have a cholinolytic action (140). Voronkov and Lukevics (30) reported that other organosilicon derivatives of choline

(*142–150*, Table VI) exhibit cholinolytic activity. *N*-Trimethylsilylacetamide was claimed to exhibit hypnotic and anticonvulsant properties, but no specific pharmacological data were presented (141).

Compounds Effective against Bacterial and Fungal Infections—Improved properties over chloramphenicol have been claimed for its bis- and mono(trimethylsilyl) ethers (*151* and *152*, respectively) (142). The ethers are reported to possess a nonbitter taste and



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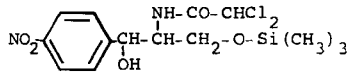
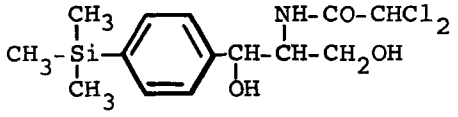


152

exert a prolonged activity in parenteral administration. Upon subcutaneous administration (as well as oral dosage for *151*), *152* demonstrated a substantial superiority over chloramphenicol. Other bis- and monotrialkyl ethers were described, but no pharmacological data were given. Frankel *et al.* (143) prepared an interesting analog of chloramphenicol, namely, *threo*-2-dichloroacetamide-1-(*p*-trimethylsilylphenyl)propan-1,-3-diol (*153*), but did not report it to possess antibacterial activity.



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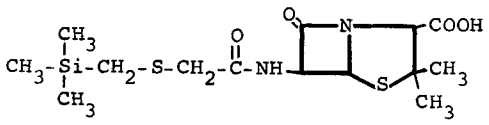
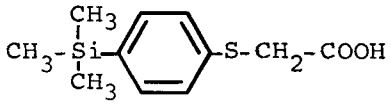
Voronkina *et al.* (144) synthesized trimethylsilylmethylmercaptomethylpenicillin (*154*) in an impure state and reported its antibiotic properties to be similar to those for benzylpenicillin. Gueyne and Duffaut



154

(145, 146) reported potassium "siliconate" complexes of penicillic acid and of benzyl penicillinate as therapeutic agents against infections. The mercaptoacetic acids (*e.g.*, Compound *155*) were found to be readily utilized by penicillin-producing molds in the biochemical formation of aliphatic-type penicillin (147).

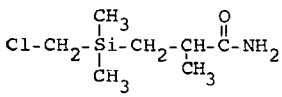


155

Both *p*-trimethylsilylphenethylamine hydrochloride and *p*-trimethylsilylmethylphenethylamine hydrochloride were evaluated against various types of bacteria and fungi (116). Inhibition of bacterial growth at concentrations of 500 and 100 mcg./ml. were observed for the compounds, respectively, whereas phenethylamine hydrochloride failed to inhibit growth even at 1000 mcg./ml. However, the presence of blood in the growth media significantly reduced the antibacterial activity of the latter organosilicon agent.

Cason and Rhone (148) described the synthesis of a large group of *ortho*- and *para*-trimethylsilylbenzoates of aminoalcohols. The compound β-diethylaminoethyl *p*-trimethylsilylbenzoate hydrochloride, for example, was found to exhibit antibacterial activity against *Streptococcus hemolyticus*. Other esters were reported to elicit analgesic and local anesthetic properties.

Twenty-eight agents, representative of different classes of nitrogen-containing organosilicon compounds, were tested against eight strains of bacteria and fungi (149). The most potent fungistatic activity was observed for *156* and *157*, both being less active than nystatin by a factor of 1.8 against *Trichophyton gypseum 4/3;* Compound *156* elicited activity against



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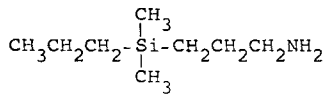
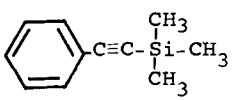


157

Epidermophyton Kaufmann-Wolf comparable to that of the standard. Activity against bacteria was, in all cases, markedly less than that for nystatin.

Growth inhibition of the fungi *Macrosporium* and *Cladosporium*, equivalent to that of mercuric chloride, was reported for several thiocyanato-substituted silanes (150). A concentration of 1–3% of these agents (*e.g.*, trimethylsilyl thiocyanate) in nutrient media infected with the fungi strongly suppressed or completely prevented fungal growth for a year or more. It does not appear possible to correlate toxic action with chemical structure; however, since some of the least active compounds are most readily hydrolyzed to thiocyanic acid, toxicity must not be only a result of hydrolysis. A group of isothiocyano-substituted silanes was also reported (151), but biological data were not included.

Some mercury-containing organopolysiloxane materials have been shown to provide bactericidal and fungicidal properties. For example, the growths of *Staphylococcus aureus* and *Salmonella dublin* were completely inhibited at 1:27,000 and 1:9000 dilutions, respectively, by a mercury-containing methyl(phenylethyl)-siloxane (152). The acetylenic organosilicon compounds *158* and *159* have been reported to inhibit the growth of *S. aureus*, *Trichophyton mentagrophytes*, and the mushroom fungus *Hormodendrum* sp. (153). Claims of bactericidal and fungicidal activity have been made



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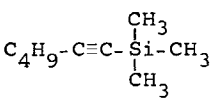


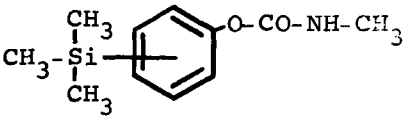
159

for numerous other organosilicon compounds (154–160).

Prophylactics against UV and Ionizing Radiation—Because of the water-repellent characteristics of polysiloxanes, several of these materials have been employed as skin-protective creams. For example, Black (161) and Morehouse (162) prepared polyphenylcarbamoylalkyl silicon compounds as sunscreen agents which absorb UV light in the 260–310-nm. range. Other polyethylsiloxanes were suggested by Bruevich as protective creams (163).

Silicon-substituted thiophene derivatives of mercaptoethylamine have been synthesized in anticipation of effecting protection against ionizing radiation (164). The silyl compounds were prepared in order to ascertain the effects of the trialkylsilyl moiety upon radioprotective activity; however, biological evaluation of these compounds has not been reported.

Insecticides and Insect Repellents—In an attempt to develop biodegradable insecticides, Metcalf and Fukuto (165) prepared the three (*ortho*, *meta*, and *para*) isomeric trimethylsilylphenyl *N*-methylcarbamates (*160*). The *meta*-isomer was the most potent inhibitor

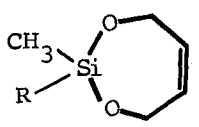


160

of fly-head cholinesterase, being nearly twice as potent as its carbon isostere and also the most active isomer against the larva and adult mosquito *Culex pipiens quinquefasciatus* Say.

Insecticidal properties have been reported for organosilicon polymers containing the sulfonamido moiety (156) and the dithiocarbamyl group (157) linked to the silicon atom through a polymethylene chain of at least three carbon atoms. The sulfonamido-containing polymers are also claimed to possess sunscreening properties and fungicidal activity. Silicon oils are also reported to exert a synergistic effect with other insecticidal agents (166–170).

Insecticidal, bactericidal, and antifungal properties have been claimed for some 2,2-dialkyl-1,3-dioxa-2-silacyclohept-5-ene derivatives (*161*), where R is methyl, ethyl, or vinyl (154). Similar biological properties have also been claimed for a group of alkylfluorosilanes (171). In the latter instance, toxicity is probably

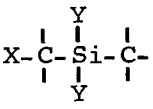


161

due, in part, to the hydrofluoric acid released by hydrolysis. Marova *et al.* (150) reported dimethyldiisothiocyanosilane to be a potent insecticide against insects of the Pentatomidae family. Several chlorinated arylsilanes with DDT-like structures have been synthesized (172) and tested against *Tribolium castaneum* (Hbn.) and *Oncopeltus fasciatus* (Dallas) but did not exhibit significant insecticidal activity (173).

Various cyclic silyl ethers, both polymeric and nonpolymeric, incorporating the well-known insect repellent 2-ethyl-1,3-hexanediol ("612"), have been found to be approximately equal in potency to the standard repellents "612" and *N,N*-diethyl-*m*-toluamide ("deet") (174). The high level of activity and known lability of silyl ethers to hydrolysis would suggest that the repellency may be due to hydrolytic release of the repellent diol.

Compounds Affecting Plant Growth—Leasure and his coworkers (175–177) reported that a group of haloalkylsilicon compounds possess strong herbicidal activity in both pre- and postemergent screening tests. For example, structures like *162*, where X is halide and Y is any of the groups commonly known



162

to be prone to hydrolysis from silicon (*e.g.*, alkoxy), are reported to exhibit strong herbicidal action (177). The greatest activity was observed when X was chlorine; changing the number of X groups on carbon to zero or two or the number of Y groups on silicon to zero, one, or three destroyed the activity. These investigators (178) also prepared several chloromethyl- and α-chloroethylsilanes which modify the growth characteristics of plants.

Bennett and Lee (179) described a group of acetylenic silanes, corresponding to formula $R_nSi(C{\equiv}CH)_{n-4}$ (where n = 0, 1, 2, or 3 and R is aryl or alkyl), which exhibit herbicidal activity; the highest potency is observed for those compounds in which n is three. Durquety and Magimel (180) claimed that an aqueous emulsion of methylpolysiloxane sprayed on leaves or buds delays the water and salt metabolism of the sprayed organs. They suggested that method for delay of flowering in plants, thus affording protection from spring frost.

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