Silicon-Substituted Medicinal Agents. Silacarbamates Related to Meprobamate[1]

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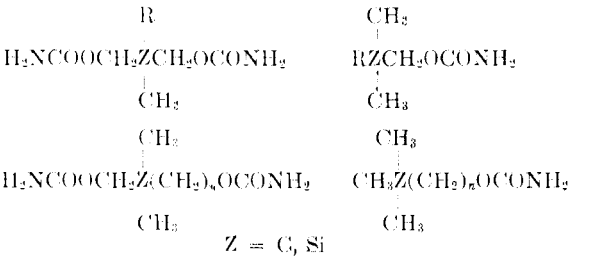
The study is concerned with the medicinal effect of a silicon atom substituted into the skeleton of a known drug molecule. Twelve pairs of carbamates, each pair differing by only one atom (a silicon in place of a carbon), have been prepared and assayed for comparative biological activity. The study indicates that a silicon compound can be used as a bioisostere of a carbon drug system.

It is of interest to note that silicon, in spite of its abundance on earth as silicates, plays no discernible role in mammalian biochemistry.[2] Although one may speculate on the reasons for this evolutionary discrimination,[3] the fact remains that organosilicon compounds are organic rather than inorganic in their properties.

The silicon–carbon bond is covalent, sp^3 in character, about 20% longer than the carbon–carbon bond, and the silicon is electropositive. Consequently, it would be expected that two organic compounds, which differ only in the substitution of a silicon atom for a carbon atom, would differ subtly in stereochemistry and in physical and chemical properties. The literature and our own preliminary work are suggestive that silicon compounds can be used as bioisosteres of carbon compounds.[4] In order to obtain a larger group of compounds to evaluate such a use of silicon compounds, we have prepared and studied, in a preliminary manner, 12 pairs of compounds, each pair differing only by one atom (silicon in place of carbon). The drug system chosen was the alkanediol dicarbamates and related monocarbamates. The most prominent of the series is the muscle relaxant and mild tranquilizer, meprobamate (**5**, Table I).



Chemistry.—The yields and the physical constants of the carbamates prepared in the study are listed in Table I. These compounds were prepared by the reaction of the appropriate purified alcohol with phenyl chloroformate in the presence of pyridine, followed by cleavage of the phenoxy group from the carbonate in liquid ammonia.[5]

$$ROH + C_6H_5OCOCl + C_5H_5N \rightarrow ROCO_2C_6H_5 \xrightarrow{NH_3} ROCONH_2 + C_6H_5OH$$

The carbon alcohols required for the preparation of the carbamates either were available commercially or were prepared using known methods (see Experimental). The chemistry used for the preparation of the organosilicon alcohols is outlined in Charts I and II. In general, the synthesis of these alcohols was carried out using known methods and does not require discussion.

Pharmacology.—The carbamates were tested using mice for acute toxicity, and for sublethal activity the rotating rod test and the extension of hexobarbital sleeping time were used. The intent of this biological work was to provide comparative data using "equivalent" conditions. The data obtained are summarized in Table II.

Each pair of compounds tested, with the exception of **19** and **20**, were essentially equivalent in their acute toxicities and exhibited muscle relaxant activity. The compounds that showed activity in the rotating rod test were all short acting with the exception of meprobamate.

In the dicarbamate series, the first pair of compounds, dimethyl dicarbamates **1** and **2**, showed no sublethal activity in either test. The second pair **3** and **4**, in which the side chains were increased from methyl to ethyl, exhibited a significant difference in sublethal activity; the carbon compound **3** showed no activity in the rotating rod test, while the silicon compound **4** exhibited a measurable activity. A further increase in the size of the alkyl group resulted in meprobamate **5**

(1) (a) This research was supported by Public Health Service Research Grant GM10122, from the National Institute of General Medical Sciences. (b) Presented to the Division of Medicinal Chemistry of the American Chemical Society, Chicago, Ill., Sept. 1964.

(2) Silicon, however, is found as a trace element in nearly all living matter. For example, the silicon content of brain tissue has been the subject of a number of investigations [A. O. Voinar and A. K. Rusanov, *Biokhimiya*, **14**, 102 (1949); *Chem. Abstr.*, **43**, 6719 (1949); S. I. Dorfman and S. A. Shipitsyn, *Biokhimiya*, **20**, 136 (1955); *Chem. Abstr.*, **49**, 12651 (1955); M. Kinitsuki, *Fukuoka Acta Med.*, **46**, 998 (1955); *Chem. Abstr.*, **50**, 12252 (1956); V. A. Del'va, *Byul. Eksperim. Biol. i Med.*, **52**, 59 (1961); *Chem. Abstr.*, **56**, 9257 (1962)].

(3) The incorporation of the silicon is important in the plant kingdom. For example, see S. Mitsui and H. Takato, *Nippon Dojo-Hiryogaku Zasshi*, **30**, 535 (1960); *Chem. Abstr.*, **56**, 725 (1962). With the diatom, silicon assimilation appears to be an enzymatic process [J. C. Lewin, *J. Gen. Physiol.*, **37**, 589 (1954); *Chem. Abstr.*, **48**, 8339 (1954)]. Silicate-consuming bacteria have also been reported [Z. P. Tesic and M. S. Todorovic, *Zemljiste Biljka*, **7**, 233 (1959); *Chem. Abstr.*, **54**, 8980 (1960)].

(4) (a) S. Fregert and H. Rorsman, *Nature*, **192**, 989 (1963); R. Fessenden and M. D. Coon, *J. Med. Chem.*, **7**, 561 (1964). (b) The majority of the biological evaluation of organosilicon compounds has been for toxicity. For example, the toxicology of the halosilanes has been studied by a number of investigators [see V. K. Rowe, H. C. Spencer, and S. L. Bass, *J. Ind. Hyg. Toxicol.*, **30**, 332 (1948); *Chem. Abstr.*, **43**, 1866 (1949); J. Vrba, *Pracovni Lekar.*, **8**, 210 (1956); *Chem. Abstr.*, **50**, 15961 (1956); S. F. Belova and E. A. Korlyakova, *Gigiena i Sanit.*, **23**, 72 (1958); *Chem. Abstr.*, **53**, 10560 (1959); N. K. Kulagina and T. A. Kochetkova, *Toksikol. Novykh Prom. Khim. Veshchestv*, **5**, 149, 165, 182 (1963); *Chem. Abstr.*, **61**, 6251 (1964)]. (c) Biologically active organosilicon compounds are not unknown [P. L. DeBenneville and M. J. Hurwitz, U. S. Patent, 2,876,209 (1959); *Chem. Abstr.*, **53**, 12321 (1959); Dow Corning Corp., British Patent 630,952 (1949); *Chem. Abstr.*, **44**, 4491 (1950); M. Ya. Marova, M. G. Voronkov, and B. N. Dolgov, *Zh. Prikl. Khim.*, **30**, 650 (1957); *Chem. Abstr.*, **51**, 13302 (1957); Midland Silicones, Ltd., British Patent 778,272 (1957); *Chem. Abstr.*, **52**, 429 (1958); T. M. Voronkina, I. T. Strukov, and M. F. Shostakovskii, *Zh. Obshch. Khim.*, **34**, 1464 (1964); *Chem. Abstr.*, **61**, 5683 (1964)].

(5) W. H. McLamore, S. Y. Pan, and A. Bayley, *J. Org. Chem.*, **20**, 1379 (1955).

TABLE I

PHYSICAL CONSTANTS OF SOME DICARBAMATES AND CARBAMATES AND THEIR CORRESPONDING SILICON ANALOGS

No.	Structure	Procedure	Mole run	% yield	M.p. or b.p. (mm.), °C.	Crystn. solvent	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Silicon, % Calcd.	Silicon, % Found
1	$(CH_3)_2C(CH_2OCONH_2)_2$[a]	A	0.11	79	149–150	Water	...	...	...	...	...	...	...	...	...
2	$(CH_3)_2Si(CH_2OCONH_2)_2$	A	0.12	51	104.5–106	Water	$C_6H_{14}N_2O_4Si$	34.93	35.21	6.85	6.89	13.58	13.91	13.59	13.59
3	$C_2H_5(CH_3)C(CH_2OCONH_2)_2$[a]	A	0.12	58	134–136	Water	...	...	...	...	...	...	...	...	...
4	$C_2H_5(CH_3)Si(CH_2OCONH_2)_2$	B	0.09	48	57.5–58	Water	$C_7H_{16}N_2O_4Si$	38.17	38.25	7.33	7.44	...	...	12.72	12.62
5	$C_3H_7(CH_3)C(CH_2OCONH_2)_2$[a]	A	0.12	60	102–102.5	Water	...	...	...	...	...	...	...	...	...
6	$C_3H_7(CH_3)Si(CH_2OCONH_2)_2$	A	0.15	38	70.5–71	Butanol–ethanol	$C_8H_{18}N_2O_4Si$	...	...	...	...	11.96	11.90	11.99	12.21
7	$C_4H_9(CH_3)C(CH_2OCONH_2)_2$[b]	A	0.21	74	110.5–111	Water–acetone	...	...	...	...	...	...	...	...	...
8	$C_4H_9(CH_3)Si(CH_2OCONH_2)_2$	A	0.09	64	75.5–76.5	Acetone	$C_9H_{20}N_2O_4Si$	43.51	43.75	8.13	8.01	11.28	11.41	11.31	11.32
9	$NH_2COOCH_2C(CH_3)_2CH_2CH_2CH_2OCONH_2$[c]	..	0.15	58	150–152	Water–acetone	...	...	...	...	...	...	...	...	...
10	$NH_2COOCH_2Si(CH_3)_2CH_2CH_2CH_2OCONH_2$	B	0.10	36	76–77	Acetone	$C_8H_{18}N_2O_4Si$	...	...	...	...	...	...	11.99	12.02
11	$(CH_3)_3CCH_2OCONH_2$	B	0.12	60	82–82.5	Ether	$C_6H_{13}NO_2$	54.92	55.04	10.01	9.72	10.68	10.44	...	...
12	$(CH_3)_3SiCH_2OCONH_2$	B	0.23	58	66.5–67	Ether	$C_5H_{13}NO_2Si$	40.79	40.86	8.91	8.77	9.51	9.39	19.04	19.12
13	$C_2H_5(CH_3)_2CCH_2OCONH_2$	B	0.08	40	71–71.8	Acetone	$C_7H_{15}NO_2$	57.89	57.67	10.43	10.25	9.65	9.48	...	...
14	$C_2H_5(CH_3)_2SiCH_2OCONH_2$	B	0.08	41	49–51, 119 (11)	Acetone	$C_6H_{15}NO_2Si$	44.67	44.54	9.39	9.51	...	...	17.38	17.25
15	$C_3H_7(CH_3)_2CCH_2OCONH_2$	B	0.22	53	69.5–70	Acetone	$C_8H_{17}NO_2$	60.33	60.04	10.78	10.38	8.80	8.66	...	...
16	$C_3H_7(CH_3)_2SiCH_2OCONH_2$	B	0.23	68	97[d] (2.0)	...	$C_7H_{17}NO_2Si$	47.94	48.25	9.79	9.53	...	...	16.02	16.21
17	$C_4H_9(CH_3)_2CCH_2OCONH_2$	B	0.07	64	43–44.5, 113 (3.0)	...	$C_9H_{19}NO_2$	62.38	62.47	11.07	10.94	8.08	8.19	...	...
18	$C_4H_9(CH_3)_2SiCH_2OCONH_2$	B	0.18	75	114[e] (3.2)	...	$C_8H_{19}NO_2Si$	50.74	50.69	10.13	9.86	...	...	14.83	14.85
19	$(CH_3)_3CCH_2CH_2OCONH_2$	B	0.29	67	58.5–59	Acetone	$C_7H_{15}NO_2$	57.89	57.80	10.43	10.21	9.65	9.47	...	...
20	$(CH_3)_3SiCH_2CH_2OCONH_2$	B	0.05	52	51–52	Acetone	$C_6H_{15}NO_2Si$	44.67	44.42	9.39	9.24	8.69	8.41	...	...
21	$(CH_3)_3C(CH_2)_3OCONH_2$	B	0.09	49	91.5–92	Acetone	$C_8H_{17}NO_2$	60.33	60.38	10.78	10.66	8.80	9.02	...	...
22	$(CH_3)_3Si(CH_2)_3OCONH_2$	B	0.14	70	53.3–54	Acetone	$C_7H_{17}NO_2Si$	47.94	48.13	9.79	9.65	...	...	16.02	16.15
23	$(CH_3)_3C(CH_2)_4OCONH_2$	B	0.06	51	70–77.5	Acetone	$C_9H_{19}NO_2$	62.38	62.19	11.07	10.89	8.08	8.55	...	...
24	$(CH_3)_3Si(CH_2)_4OCONH_2$	B	0.09	78	31–32, 112 (2.5)	Acetone	$C_8H_{19}NO_2Si$	50.74	50.89	10.13	9.93	...	...	14.83	14.79

[a] B. S. Ludwig and E. C. Plech, *J. Am. Chem. Soc.*, **73**, 5779 (1951). [b] British Patent 802,978 (1958); *Chem. Abstr.*, **53**, 9145*e* (1958). [c] H. Wiley and H. Kraus, *J. Org. Chem.*, **22**, 994 (1957). [d] $n^{25}D$ 1.4505. [e] $n^{25}D$ 1.4519.

CHART I

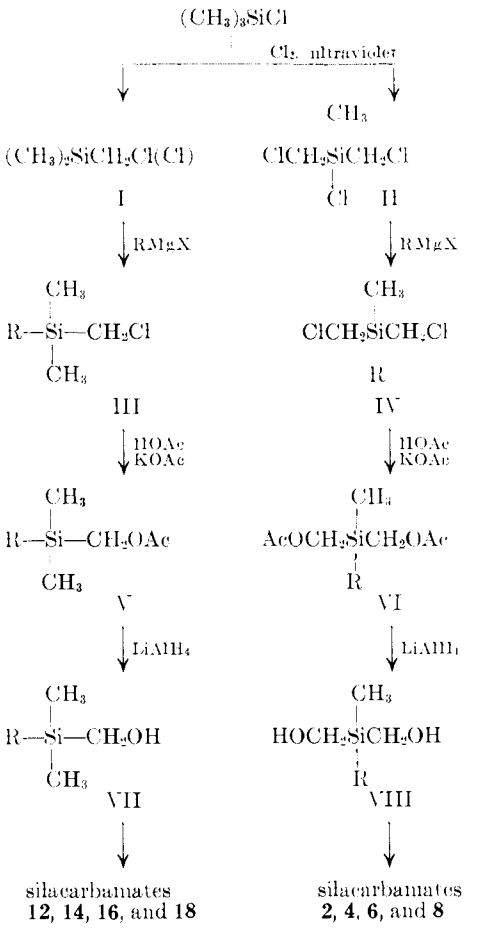
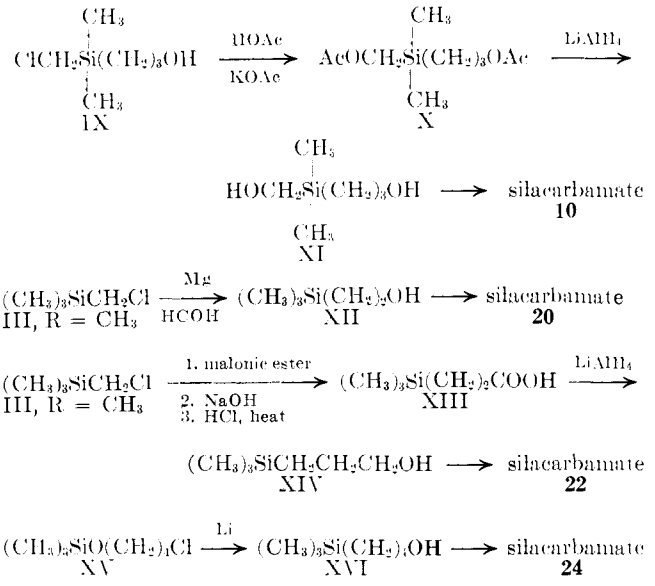


CHART II



and silameprobamate **6**. This pair had equivalent effective doses in both sublethal tests. The di-*n*-butyl dicarbamates **7** and **8** were also equivalent in their sublethal activities in the tests that were performed.

The abrupt appearance of activity with **4** in this series of dicarbamates, followed by the equivalent activities of **5** and **6**, and **7** and **8**, is suggestive of a minimal but nonspecific steric requirement in this drug series.

TABLE II

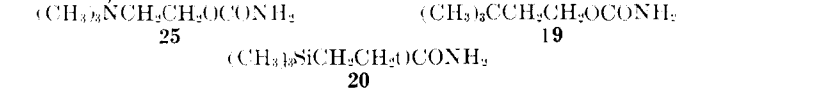
PHARMACOLOGICAL EVALUATION OF THE CARBAMATES PREPARED IN THIS STUDY[a]

Compd.	LD_{50},[b] mg./kg.	ED_{50} rotating[c] rod (95% confid. levels), mg./kg.	Duration of activity,[d] min.	Extension of sleep, min.[e]	Probability[f]
1	>1000	>500	..	23	0.9
2	>1000	>500	..	27	
3	>1000	~900	..	78	0.01
4	>1000	339 (300–383)	17	84	
5	700	176 (156–199)	56	83	0.4
6	>1000	158 (148–169)	13	66	
7	>1000	215 (187–247)	37	147	0.2
8	900	203 (182–227)	10	101	
9	>1000	>630	..	21	0.01
10	>1000	238 (214–264)	17	128	
11	560	92 (80–107)	11	26	0.1
12	400	92 (80–107)	15	50	
13	530	81 (68–99)	5	2	0.1
14	600	59 (48–72)	5	91	
15	580	81 (71–91)	7	43	0.1
16	400	70 (64–76)	7	27	
17	630	135 (113–161)	30	50	0.8
18	560	110 (103–118)	10	54	
19	32	*g*	*g*	*g*	
20	450	69 (61–77)	10	44	
21	670	120 (107–134)	20	33	0.8
22	470	61 (54–67)	12	39	
23	600	159 (134–189)	15	38	0.1
24	420	118 (92–149)	15	86	

[a] All compounds were introduced intraperitoneally as suspensions in a 2.5% tragacanth gel. Female, Swiss Webster white mice, 13–20 g., were used in all tests. The values reported were calculated using the method of J. T. Litchfield and F. Wilcoxon, *J. Pharmacol. Exptl. Therap.*, **96**, 99 (1949). [b] The LD_{50} was calculated after 48 hr. [c] A rotating rod apparatus was used [N. W. Dunham and T. S. Miya, *J. Am. Pharm. Assoc.*, **46**, 208 (1957)] and 24 to 36 animals were used per compound. [d] The duration of activity is defined as the mean time (from time of injection to the final pass in the rotating rod test) for the animals receiving a dose between the ED_0 and ED_{100}. [e] The extension of the hexobarbital sleeping time was measured by injection of the compound ED_{81} of the rotating rod value, followed within 30 sec. by 100 mg./kg. of hexobarbital (intraperitoneally). Twenty mice (10 test and 10 controls) were used per compound and both controls and compounds were run concurrently. The criterion for sleep was the righting reflex. The controls regained their righting reflex in 10 to 20 min. from the time of injection. The values reported are the mean time for the test group corrected for the mean time of the control group. [f] The probability that the pair do not differ significantly in the hexobarbital sleep test was evaluated using the Student's *t* method. [g] No activity was noted at sublethal levels.

The monocarbamates **11**–**18**, in general, showed greater activity, but were also short acting. The pairs did not exhibit significantly different activities.

An increase in the distance between the carbamate function and the alkyl branching (**19**–**24**) yielded pairs of compounds which, in general, were significantly different from each other. The most notable example in this group is the pair **19** and **20**. These compounds differed by a factor of 10 in toxicity. Also, approximately 45 min. after dosing with **19**, the animals became convulsive, while animals dosed with **20** showed only ataxia lasting for approximately 10 min. This



pair is of further interest because of the structural relationship to carbachol (**25**).

It should be emphasized that the data reported in Table II were obtained using intraperitoneal dosing. With this route of administration, meprobamate and silameprobamate do not differ in their effective doses, although they do differ in duration of activity, meprobamate acting approximately four times longer than silameprobamate. These two compounds also differ when administered orally, silameprobamate showing no appreciable activity (ED_{50} 470 mg./kg., rotating rod).[6]

The data obtained in this study indicate that a silicon atom can be used as a nonionic, tetravalent bioisostere of a carbon atom in a drug system. These observations are suggestive that studies which are designed to correlate the chemical and physical properties of pairs of compounds (such as those used in this study) with pharmacological and biochemical differences could provide a useful tool for the elucidation of the properties of a drug system.[7]

Experimental[8]

Synthesis of the Carbamates (Table I).—To 0.10 mole of the alcohol dissolved in 40 ml. of dry pyridine was added, over a period of 10–20 min., 15.7 g. (0.10 mole) (or 31.4 g., if a diol were used) of phenyl chloroformate. The mixture was stirred at room temperature for 2 hr., then decomposed by the addition of 100 ml. of water. The organic material was extracted with three 100-ml. portions of ether. The ether extracts were washed with two 100-ml. portions of 6 *N* HCl, 100 ml. of saturated $NaHCO_3$ solution, and finally with 100 ml. of saturated NaCl solution. After the solution was dried ($MgSO_4$), the ether was removed by distillation, and the residue was further concentrated under vacuum. The residue was then added to *ca.* 250 ml. of liquid ammonia, and the mixture was stirred at room temperature until the excess ammonia had evaporated. The remainder of the procedure (A or B) for each particular carbamate is noted in Table I.

Procedure A.—The residue from the ammonia reaction was cooled in an ice bath, and 200 ml. of 10% NaOH was added. The resulting solid was filtered, washed with cold water, and recrystallized, using the solvent noted in Table I.

Procedure B.—To the residue from the ammonia reaction was added 100 ml. of ether. The ethereal mixture was filtered to remove any solid material, then the solution was washed with two 100-ml. portions of 10% NaOH solution. The solution was dried ($MgSO_4$), and the ether was removed under reduced pressure. If the carbamate solidified at this stage, it was recrystallized from the solvent indicated in Table I. If solidification did not occur, the product was distilled under vacuum.

Synthesis of Alcohols. A. Carbon Alcohols.—The alcohols not mentioned below were purchased. The yields and physical properties of the alcohols prepared in this portion of the study are summarized in Table III.

1. 2-Butyl-2-methyl-1,3-propanediol, 2,2-dimethyl-1,5-pentanediol, and 5,5-dimethyl-1-hexanol were obtained by the $LiAlH_4$ reduction of diethyl butylmethylmalonate, dimethyl 2,2-dimethylglutarate, and 5,5-dimethylhexanoic acid, respectively.

2. 2,2-Dimethyl-1-butanol, 3,3-Dimethyl-1-butanol, and 4,4-Dimethyl-1-pentanol.—To a Grignard reagent prepared from the appropriate alkyl chloride (1.0 mole) was added 30.0 g. of solid paraformaldehyde, and the mixture was heated at reflux for 24 hr. The mixture was then decomposed with a saturated solution of NH_4Cl. The organic layer was extracted with two 100-ml. portions of ether and dried ($MgSO_4$), and the alcohol was isolated by fractional distillation. In the case of 2,2-dimethyl-1-butanol, gas chromatographic analysis of the distillation fractions indicated that the alcohol was only 95% pure. The sample used for the preparation of carbamates ($n^{25}D$ 1.4201) was obtained using a preparative gas chromatography column.

B. Organosilicon Alcohols. 1. (Chloromethyl)chlorosilanes.[9]—In a 1-l. round-bottomed flask, fitted with a Dry Ice–acetone condenser, mechanical stirrer, and gas inlet tube (o.d. 8 mm., without a fritted glass tip) reaching to the bottom of the flask, was placed 300 g. of trimethylchlorosilane. A gas exit tube was attached to the top of the condenser leading through back-up traps to a beaker containing a known weight of water. The chlorosilane was saturated with Cl_2. The gas flow was stopped, and reaction was initiated using ultraviolet light. After the initial gas evolution had subsided, Cl_2 was introduced into the reaction flask at a moderate rate (caution). The extent of the reaction was monitored by the weight of the HCl that dissolved in the water. The chlorination was carried to a 1:1 *M* reaction.

Fractional distillation of the liquid yielded 134 g. of the starting chlorosilane, b.p. 40–102°, 172 g. of (chloromethyl)dimethylchlorosilane, b.p. 112–115°, 84 g. of (dichloromethyl)dimethylchlorosilane, b.p. 144–147°, and 39 g. of bis(chloromethyl)methylchlorosilane, b.p. 160–167°. Redistillation of the desired chlorosilanes was required. Higher conversion to the (chloromethyl)dimethylchlorosilane was obtained when the chlorination was carried to only 20% completion and the unreacted trimethylchlorosilane was recycled.

2. Alkyl(chloromethyl)silanes.—To 0.65 mole of the appropriate Grignard reagent was added 115 g. (0.65 mole) of bis(chloromethyl)methylchlorosilane or 93 g. (0.65 mole) of (chloromethyl)dimethylchlorosilane, and the mixture was heated at reflux for 12 hr. Work-up was accomplished by decomposition of the salt complex with 2 *N* HCl, extraction with ether, and drying ($MgSO_4$). The final product was isolated by fractional distillation. The yields and physical properties are summarized in Table IV.

3. Acetoxyalkylsilanes.—A mixture of 0.2 mole of the chloromethylsilane, 1.0 mole of potassium acetate, and 160 ml. of acetic acid was heated at reflux for 16 hr. The reaction mixture was diluted with 400 ml. of water, and the organic material was extracted with two 100-ml. portions of ether. The ethereal solution was washed with two 100-ml. portions of water and 100 ml. of 10% NaOH solution, dried, and distilled. The yields and physical properties are summarized in Table V.

The available 3-hydroxypropyl(chloromethyl)dimethylsilane (IX)[10] was also converted to the diacetate X using this procedure. Its yield and physical properties are also summarized in Table V.

4. Hydroxyalkylsilanes.—The acetoxyalkylsilane (0.20 mole) was added dropwise, with cooling, to 0.43 mole of $LiAlH_4$ (0.21 mole of $LiAlH_4$ for the monoacetoxyalkylsilanes) using 500 ml. of ether as solvent. After the addition was complete, the mixture was stirred at room temperature for 0.5 hr., then decomposed by the addition of water. The aqueous mixture was then acidified; the bis(hydroxymethyl)silanes were not obtained unless this acidification was carried out. The organic material was extracted with three 100-ml. portions of ether, then dried ($MgSO_4$). The water-soluble bis(hydroxymethyl)silanes were obtained by a 24-hr. continuous extraction of the aqueous layer with ether. The product, in either case, was isolated by fractional distillation. The yields and physical properties are summarized in Table VI.

5.—The following three organosilicon alcohols were prepared by individual procedures. Their yields and physical properties are also summarized in Table VI.

β-(Trimethylsilyl)ethanol.—To a Grignard reagent prepared from 122.7 g. (1.0 mole) of (chloromethyl)trimethylsilane (III, R = CH_3) was added 30.0 g. of solid paraformaldehyde and the mixture was heated at reflux for 24 hr. The mixture was decomposed by the addition of saturated NH_4Cl solution, and the organic material was extracted with ether. The product was isolated by distillation.

γ-(Trimethylsilyl)propanol.—To a cooled solution of 12.2 g. (0.31 mole) of $LiAlH_4$ was added, over a period of 35 min., 35.0 g. (0.24 mole) of γ-(trimethylsilyl)propanoic acid.[11] After the

(6) After oral dosing rats with silameprobamate, 80% of the silicon can be accounted for in the urine within 48 hr. The identification of the detoxication products of silameprobamate will be the subject of another report.

(7) H. Gilman and G. E. Dunn, *Chem. Rev.*, **52**, 77 (1953).

(8) All melting points are corrected. The carbon, hydrogen, and nitrogen analyses were performed by the Berkeley Microanalytical Laboratory. Silicon analyses were performed in this laboratory by the wet ash method. Gas phase chromatography was carried out using a Wilkens Aerograph instrument.

(9) R. H. Krieble and J. R. Elliott, *J. Am. Chem. Soc.*, **67**, 1810 (1945).

(10) R. Fessenden and M. D. Coon, *J. Org. Chem.*, **29**, 1607 (1964).

(11) L. H. Sommer and N. S. Marans, *J. Am. Chem. Soc.*, **72**, 1935 (1950).

TABLE III
PHYSICAL PROPERTIES AND YIELDS OF CARBON ALCOHOLS USED IN THIS STUDY

Compd.	% yield	B.p., °C. (mm.)	n_D (°C.)
$C_4H_9(CH_3)C(CH_2OH)_2$[a]	81	131–133 (7)	1.4550 (26)
$HOCH_2C(CH_3)_2(CH_2)_3OH$[b]	69	122–125 (4)	1.4580 (24)
$C_2H_5C(CH_3)_2CH_2OH$[c]	(65)	71–72 (100)	1.4201 (25)
$(CH_3)_3CCH_2CH_2OH$[d]	65	140–142 (atm.)	1.4129 (27)
$(CH_3)_3CCH_2CH_2CH_2OH$[d]	60	158–162 (atm.)	1.4315 (17)
$(CH_3)_3CCH_2CH_2CH_2CH_2OH$[e]	70	179–181 (atm.)	1.4248 (25)

[a] H. Yale, E. J. Pribyl, W. Braker, F. H. Bergeim, and W. A. Lott, *J. Am. Chem. Soc.*, **72**, 3710 (1950). [b] R. F. Brown and G. H. Schmidt, *J. Org. Chem.*, **27**, 1288 (1962). [c] F. K. Beilstein, "Beilstein's Handbuch der Organischen Chemie," Vol. 1, 1918, p. 412. [d] M. S. Malinovskii, E. E. Volkova, and N. M. Morozova, *Zh. Obshch. Khim.*, **19**, 114 (1949); *Chem. Abstr.*, **43**, 6155 (1949). [e] This compound has not been reported previously in the literature and was not completely characterized in this study.

TABLE IV
PHYSICAL PROPERTIES AND YIELDS OF SOME CHLOROALKYLSILANES

Compd.	R	% yield	B.p., °C. (mm.)	n_D (°C.)
III	C_2H_5[a]	57	128 (atm.)	1.4283 (26)
III	C_3H_7[b]	82	149 (atm.)	1.4327 (25)
III	C_4H_9[c]	83	52 (1.2)	1.4355 (28)
IV	CH_3[d]	53	155–157	1.4480 (23)
IV	C_2H_5[e]	56	185 (atm.)	1.4639 (24)
IV	C_3H_7[f]	38	59–60 (4.0)	1.4647 (25)
IV	C_4H_9[e]	56	96–108 (13)	1.4620 (28)

[a] A. D. Petrov, V. F. Mironov, and N. A. Pogonkina, *Dokl. Akad. Nauk SSSR*, **100**, 81 (1955); *Chem. Abstr.*, **50**, 1573*g* (1956). [b] V. F. Mironov and N. A. Pogonkina, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 161 (1955); *Chem. Abstr.*, **50**, 1574 (1965). [c] S. Nozakura, *Nippon Kagaku Zasshi*, **75**, 958 (1954); *Chem. Abstr.*, **51**, 1453*f* (1957). [d] H. Freiser, M. V. Eagle, and J. L. Speier, *J. Am. Chem. Soc.*, **75**, 2821 (1953). [e] Purified, but not completely characterized. [f] *Anal.* Calcd. for $C_6H_{14}Cl_2Si$: C, 38.91; H, 7.63; Cl, 38.29. Found: C, 38.94; H, 7.71; Cl, 38.06.

TABLE V
PHYSICAL PROPERTIES AND YIELDS OF SOME ACETOXYALKYLSILANES

Compd.	R	% yield	B.p., °C. (mm.)	n_D (°C.)
V	CH_3[a]	32	122–124 (atm.)	1.4176 (25)
V	C_2H_5[b]	65	161–163 (atm.)	1.4175 (25)
V	C_3H_7[c]	66	86 (30)	1.4210 (26)
V	C_4H_9[d]	74	93 (20)	1.4259 (25)
VI	CH_3[a]	74	79–82 (1.5)	1.4349 (20)
VI	C_2H_5[c]	80	86–87 (2)	1.4378 (25)
VI	C_3H_7[e]	91	124–127 (7)	1.4398 (23)
VI	C_4H_9[f]	88	120–122 (5)	1.4407 (25)
X[c]		77	156–158 (8)	1.4393 (25)

[a] J. L. Speier, B. F. Daubert, and R. R. McGregor, *J. Am. Chem. Soc.*, **70**, 1117 (1948). [b] A. D. Petrov, V. F. Mironov, N. A. Pogonkina, *Dokl. Akad. Nauk SSSR*, **100**, 81 (1955); *Chem. Abstr.*, **50**, 1573*g* (1956). [c] No analysis was performed. [d] *Anal.* Calcd. for $C_9H_{20}O_2Si$: Si, 14.89. Found: Si, 14.78. [e] *Anal.* Calcd. for $C_{10}H_{20}O_4Si$: C, 51.55; H, 8.67. Found: C, 51.55; H, 8.62. [f] *Anal.* Calcd. for $C_{11}H_{22}O_4Si$: Si, 11.39. Found: Si, 11.51.

TABLE VI
PHYSICAL PROPERTIES AND YIELDS OF SOME HYDROXYALKYLSILANES

Compd.	R	% yield	B.p., °C. (mm.)	n_D (°C.)
VII	CH_3[a]	33	122–123 (atm.)	1.4169 (25)
VII	C_2H_5[b]	49	142–143 (atm.)	1.4300 (26)
VII	C_3H_7[c]	87	161–162 (atm.)	1.4320 (25)
VII	C_4H_9[d]	84	178–180 (atm.)	1.4372 (25)
VIII	CH_3[e]	76	130 (27)	1.4611 (22)
VIII	C_2H_5	(91)[f]		1.4670 (22)
VIII	C_3H_7[g]	69	119 (4.0)	1.4631 (30)
VIII	C_4H_9[h]	65	114–115 (2.2)	1.4637 (29)
XI[i]		65	121–122 (3.8)	1.4662 (23)
XII[i]		52	93–94 (100)	1.4216 (25)
XIV[k]		87	73–74 (13)	1.4298 (24)
XVI[k]		53	96–97 (25)	1.4326 (23)

[a] K. Shiina and M. Kumada, *Kagyo Kagaku Zasshi*, **60**, 1395 (1957); *Chem. Abstr.*, **53**, 17889 (1959). [b] A. D. Petrov, V. F. Mironov, and N. A. Pogonkina, *Dokl. Akad. Nauk SSSR*, **100**, 81 (1955); *Chem. Abstr.*, **50**, 1573 (1956). [c] D. Seyferth, *J. Am. Chem. Soc.*, **81**, 1844 (1959). [d] *Anal.* Calcd. for $C_7H_{18}OSi$: Si, 19.18. Found: Si, 19.00. [e] Dow Corning, British Patent 630,952 (1949); *Chem. Abstr.*, **44**, 4991 (1950). [f] Not purified. [g] *Anal.* Calcd. for $C_6H_{16}O_2Si$: C, 48.57; H, 10.90; Si, 18.94. Found: C, 48.38; H, 10.75; Si, 18.94. [h] *Anal.* Calcd. for $C_7H_{18}O_2Si$: Si, 17.30. Found: Si, 17.61. [i] *Anal.* Calcd. for $C_6H_{16}O_2Si$: Si, 18.94. Found: Si, 19.00. [j] J. L. Speier, B. F. Daubert, and R. R. McGregor, *J. Am. Chem. Soc.*, **70**, 1117 (1948). [k] Ref. 12.

addition had been completed, the mixture was stirred at room temperature for 1.5 hr., then decomposed by the addition of water. The material was acidified with 6 *N* HCl, and the organic material was extracted with 100 ml. of ether. The alcohol was isolated by fractional distillation.

δ-(Trimethylsilyl)butanol.—To 4.2 g. (0.61 g.-atom) of lithium wire and 50 ml. of ether was added dropwise, over a period of 30 min., 43.9 g. (0.24 mole) of 4-trimethylsilyl-1-chlorobutane.[12] The mixture was heated at reflux for 24 hr., then the excess metal was decomposed by the addition of 20 ml. of 95% ethanol. After work-up, the alcohol was isolated by distillation.

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(12) J. L. Speier, *J. Am. Chem. Soc.*, **74**, 1003 (1952).