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Organosilicon Compounds III. Silicon-substituted Thiophene Derivatives of Mercaptoethylamine as Possible Radioprotective Agents (1).

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The preparation of the first organosilicon containing derivatives of mercaptoethylamine as possible radioprotective agents is described. The synthesis of these compounds via the thiazolidine intermediate was chosen due to the known radioprotective action of certain thiazolidines. We have prepared seventeen previously unreported organosilicon derivatives of which eleven contain the thiazolidine moiety and six are derivatives of mercaptoethylamine. The ability of these derivatives to protect against ionizing radiation will be determined.

The synthesis and evaluation of silicon-substituted medicinal agents is rapidly developing into an exciting and potentially explosive area of medicinal chemistry. The similarities, as well as the differences, between organo-carbon and organo-silicon compounds suggests that organosilicon containing medicinals would show unique physiological properties.

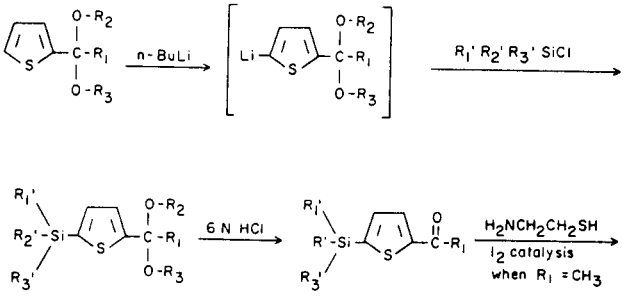
This concept appears particularly attractive when one considers that silicon, although larger than carbon, possesses covalent bonding characteristics (sp^3) and that the Si-C bond length is approximately 20% longer than the C-C bond. Furthermore, silicon has a lower electronegativity (en = 1.8) than carbon (en = 2.5), and it is able to utilize its 3*d*-orbitals for bond formation.

That organosilicons can function as medicinals was confirmed by Fessenden and Coon, who prepared organosilicons that exhibited muscle relaxant and tranquilizing properties (2,3).

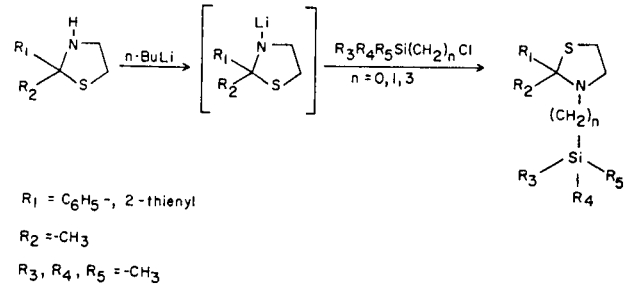
The marked lipid solubility of silicon ethers has been successfully established by Chang and Jain (4), who prepared several testosteroxysilanes and determined the effectiveness of these drugs. Similarly, Brown and Laos (5) have prepared a number of steroidal oxysilanes and have found these to have anabolic and androgenic activity. Ghoby and Neuworth (6) have prepared trimethylsilyl derivatives of salicylic acid while Gertner, Rosen and Zilkha (7) as well as Ruehlmann, Hils and Graubaum (8) have prepared organosilicon derivatives of aminoacids. Frankel and coworkers (9) have synthesized several silicon containing barbiturates, a silicon containing analogue of chloroamphenicol, and phenethylamine having a trimethylsilyl moiety attached to the aromatic grouping. Leasure and Speier synthesized a group of (haloalkyl) silicon compounds which were found to have strong herbicidal activity and in some cases to act as defolients (10).

The apparent potential of organosilicon medicinals coupled with the known radioprotective action of 2-aminoethanethiol has prompted us to synthesize silicon substi-

SCHEME A



SCHEME B



tuted thiophene derivatives of mercaptoethylamine. In doing so it was our objective to ascertain, to some extent, the effects of the organosilicon moiety upon radioprotective activity. Furthermore, since significant radioprotective activity has been demonstrated by thiazolidine derivatives (11,12), it appeared efficacious for us to synthesize the desired mercaptoethylamines via thiazolidine intermediates (Scheme A).

This investigation was of particular interest in that Takahashi (13) has reported that the physiological effects of Co^{60} radiation on rice plants were reduced by the presence of silicon.

The thienyl-aldehydes and -ketones employed in the synthesis of the desired thiazolidines were prepared according to the method described by Thames and McCleskey (14) (Scheme A).

Thiazolidine formation occurred readily and without catalysis when 5-silicon-substituted-2-thiophene carboxaldehydes were treated with mercaptoethylamine in refluxing benzene; however, condensation of mercaptoethylamine with 5-silicon-substituted-2-acetylthiophenes was somewhat sluggish and required extended reaction time with iodine catalysis.

Reduction of the thiazolidines to the corresponding mercaptans was affected with either sodium borohydride or lithium aluminum hydride. The reported critical stoichiometry requirements for lithium aluminum hydride reductions of thiazolidines (15) and our own experimental results prompted us to adopt the sodium borohydride reduction as the method of choice.

The preparation of 3-silylsubstituted thiazolidines was accomplished for the first time by the *N*-metalation of the respective thiazolidine with subsequent condensation with an appropriate silyl halide or silyl alkyl halide (Scheme B).

EXPERIMENTAL (16)

2-Mercaptoethylamine, used in the preparation of the following thiazolidines, was prepared according to the method of Mills and Bogert (17) in approximately 80% yields.

2[2-(5-Trimethylsilyl)thienyl] thiazolidine (I).

5-Trimethylsilyl-2-thiophenecarboxaldehyde (14.6 g., 0.079 mole) in 150 ml. of dry benzene and 2-mercaptoethylamine (6.1 g., 0.079 mole) were refluxed for 12 hours in a 500 ml. one necked flask equipped with a Barrett trap and reflux condenser. After the theoretical amount of water azeotroped, the mixture was cooled, washed twice with water and the benzene was removed by distillation. The residue was distilled under reduced pressure to yield 13.5 g. (70.5%) of product boiling at 114°/0.1 mm.

Anal. Calcd. for $C_{10}H_{17}NS_2Si$: C, 49.33; H, 7.04; S, 26.34. Found: C, 49.53; H, 6.28; S, 26.73.

The above method was employed as a standard procedure for the synthesis of the following thiazolidines.

2-Methyl-2-[2-(5-trimethylsilyl0thienyl] thiazolidine (II).

2-Acetyl-5-trimethylsilylthiophene (12.2 g., 0.062 mole), 2-aminoethanethiol (4.75 g., 0.065 mole) and a catalytic amount of iodine were reacted in the prescribed manner for 170 hours to afford 8 g. (51%) of the desired product boiling at 116°/0.2 mm.

Anal. Calcd. for $C_{11}H_{19}NS_2Si$: C, 51.31; H, 7.44; S, 24.90; Si, 10.91. Found: C, 51.19; H, 7.45; S, 25.05; Si, 11.03.

2-[2-(5-Dimethylethylsilyl)thienyl] thiazolidine (III).

2-(5-Dimethylethylsilyl)thiophenecarboxaldehyde (25.4 g., 0.118 mole) and 2-mercaptoethylamine (10 g., 0.13 mole) were reacted 30 hours in the usual manner to afford 21 g. (70%) of product boiling at 128°/0.07 mm; $n_D^{24} = 1.5670$.

Anal. Calcd. for $C_{11}H_{19}NS_2Si$: C, 51.31; H, 7.44; N, 5.44; S, 24.90; Si, 10.91. Found: C, 51.58; H, 7.58; N, 5.54; S, 24.71; Si, 10.86.

2-Methyl-2-[2-(5-dimethylethylsilyl)thienyl] thiazolidine (IV).

2-Acetyl-5-dimethylethylsilylthiophene (30 g., 0.141 mole), 2-mercaptoethylamine (10.8 g., 0.141 mole) and a catalytic amount of iodine were reacted (180 hours) to yield 22 g. (58%) of product boiling at 112°/0.025 mm; $n_D^{24} = 1.5561$.

Anal. Calcd. for $C_{12}H_{21}NS_2Si$: C, 53.08; H, 7.80; N, 5.16; S, 23.62; Si, 10.34. Found: C, 53.20; H, 7.89; N, 5.17; S, 23.80; Si, 10.57.

2[2-(5-Triethylsilyl)thienyl] thiazolidine (V).

2-(5-Triethylsilyl)thiophene carboxaldehyde (21 g., 0.093 mole) and 2-mercaptoethylamine (7.2 g., 0.092 mole) gave, after 15 hours, 20 g. (75.5%) of product boiling at 165°/0.48 mm; $n_D^{23} = 1.5681$.

Anal. Calcd. for $C_{13}H_{23}NS_2Si$: C, 54.68; H, 8.12; N, 4.91; S, 22.46; Si, 9.84. Found: C, 54.68; H, 7.99; N, 4.38; S, 22.63; Si, 9.74.

2-Methyl-2[2-(5-triethylsilyl)thienyl] thiazolidine (VI).

2-Acetyl-5-triethylsilylthiophene (20.9 g., 0.087 mole), 2-mercaptoethylamine (6.7 g., 0.093 mole) and a catalytic amount of iodine gave, after 100 hours, 18 g. (62%) of product boiling at 139°/0.1 mm; $n_D^{24} = 1.5536$.

Anal. Calcd. for $C_{14}H_{25}NS_2Si$: C, 56.13; H, 8.41; N, 4.68; S, 21.41; Si, 9.38. Found: C, 56.40; H, 8.60; N, 4.79; S, 21.65; Si, 9.62.

2-Methyl-2[2-(5-triphenylsilyl)thienyl] thiazolidine (VII).

5-Triphenylsilyl-2-acetylthiophene (7.2 g., 0.0187 mole) and 2-mercaptoethylamine (2 g., 0.026 mole) were reacted 180 hours in the usual manner. The solvent was removed *in vacuo*, the residue was taken up in ether and the free base was transformed to its hydrochloride salt by use of an ether solution of hydrogen chloride. Several recrystallizations from a methanol-ether solution afforded the product (19 g., 22%) with an m.p. of 169-171°.

Anal. Calcd. for $C_{26}H_{25}ClNS_2Si$: C, 65.04; H, 5.46; N, 2.92. S, 13.36; Si, 5.85; Cl, 7.38. Found: C, 64.80; H, 5.22; N, 2.70; S, 13.14; Si, 6.01; Cl, 7.55.

The preparation of mercaptans from their corresponding thiazolidines was carried out according to a modification of the procedure of Barrera and Lyle (18). In these procedures all glassware had been thoroughly dried and all reagents had been purged with dry nitrogen. All reactions were carried out under a nitrogen atmosphere.

The Preparation of 2-(5-Trimethylsilyl-2-α-methylthenylamino)-ethanethiol (VIII).

This will serve as an example procedure for the reduction of the thiazolidines to the corresponding percaptans. Compound II (11 g., 0.043 mole), in 25 ml. of 2-propanol was added dropwise to a 2-propanol (50 ml.) slurry of sodium borohydride (3 g., 0.08 mole). This mixture was stirred at room temperature for 1 hour, followed by heating to 58° for 2 hours, at which time the reaction

mixture was cooled in an ice bath, acidified to a *p*H of 3 with hydrochloric acid (3 *N*) and heated to 58° for an additional 0.5 hour. The mixture, when cooled to 0°, was treated with 50 ml. of dry ether and then with 20% potassium hydroxide, with stirring, until a *p*H of 9 was attained. The ether layer was separated and the aqueous layer was extracted with dry ether. The combined etheral extracts were dried over anhydrous sodium sulfate followed by solvent removal *in vacuo* and distillation of the residue to afford 7.5 g. (68%) of product boiling at 117°/0.17 mm; n_D^{23} = 1.5325.

Anal. Calcd. for $C_{11}H_{19}NS_2Si$: C, 51.31; H, 7.44; N, 5.44; S, 24.90; Si, 10.91. Found: C, 51.19; H, 7.45. N, 5.34; S, 25.05; Si, 11.03.

The following mercaptans were prepared in this manner:

2-[2-(5-Trimethylsilyl)thenylamino]ethanethiol (IX).

Compound I (12.3 g., 0.51 mole) and sodium borohydride (3.9 g., 0.1 mole) were reacted in the usual manner to yield 8.8 g. (71%) of product boiling at 123°/0.2 mm; n_D^{25} = 1.5512.

Anal. Calcd. for $C_{10}H_{19}NS_2Si$: C, 48.93; H, 7.80; N, 5.71; S, 26.12; Si, 11.44. Found: C, 49.13; H, 7.60; N, 5.87; S, 25.99; Si, 11.20.

2-(5-Triethyleilyl-2-α-methylthenylamino)ethanethiol (X).

Compound VI (9 g., 0.03 mole) and sodium borohydride (2 g., 0.052 mole) were allowed to react in the usual manner to produce 6.4 g. (71%) of product boiling at 136°/0.05 mm; n_D^{24} = 1.5305.

Anal. Calcd. for $C_{14}H_{27}NS_2Si$: C, 55.76; H, 9.02; N, 4.64; S, 21.26; Si, 9.31. Found: C, 56.03; H, 8.88; N, 4.45; S, 21.49. Si, 9.57.

2-(5-Triethylsilyl-2-thenylamino)ethanethiol (XI).

Compound V (10 g., 0.035 mole) and sodium borohydride (2.3 g., 0.061 mole) were reacted in the usual manner to yield 6.4 g. (64%) of product boiling at 134°/0.025 mm; n_D^{25} = 1.5623.

Anal. Calcd. for $C_{13}H_{25}NS_2Si$: C, 54.30; H, 8.76; N, 4.87; S, 22.30; Si, 9.77. Found: C, 54.55; H, 8.53; N, 4.75; S, 22.43; Si, 9.86.

2-(5-Dimethylethylsilyl-2-thenylamino)ethanethiol (XII).

Compound III (13.4 g., 0.052 mole) and sodium borohydride (3.4 g., 0.09 mole) were reacted to yield 9 g. (67%) of product boiling at 116°/0.03 mm; n_D^{24} = 1.5453.

Anal. Calcd. for $C_{11}H_{21}NS_2Si$: C, 50.91; H, 8.16; N, 5.40; S, 24.71; Si, 10.82. Found: C, 51.00; H, 7.98; N, 5.40; S, 24.68. Si, 10.62.

2-(5-Dimethylethylsilyl-2-α-methylthenylamino)ethanethiol (XIII).

Compound IV (14 g., 0.051 mole) and sodium borohydride (3.3 g., 0.088 mole) were reacted to produce 10 g. (72%) of product boiling at 105°/0.05 mm; n_D^{24} = 1.5311.

Anal. Calcd. for $C_{12}H_{23}NS_2Si$: C, 52.69; H, 8.48; N, 5.12; S, 23.44; Si, 10.27. Found: C, 52.75; H, 8.48; N, 5.24; S, 23.43; Si, 10.31.

Synthesis of all 3-substituted thiazolidines was carried out under a nitrogen atmosphere.

3-Trimethylsilyl-2-methyl-2-phenylthiazolidine (XIV).

To 2-methyl-2-phenylthiazolidine (19) (11.1 g., 0.062 mole), in 200 ml. of dry ether, in a 250 ml. three necked flask equipped with a dropping funnel, Truebore stirrer and a Fredrick condenser, was added *n*-butyllithium in hexane (42 ml., 1.46 *N*) in a dropwise fashion. The resulting mixture was stirred overnight at ambient temperature, after which time the lithium chloride was filtered, the ether removed by evaporation under reduced pressure and the residue distilled *in vacuo* to yield 9.6 g. (60%) of product boiling at 184°/23 mm.

Anal. Calcd. for $C_{13}H_{21}NSSi$: C, 62.15; H, 8.37. Found: C, 62.30; H, 8.47.

The above method will serve as a general procedure for the preparation of the following 3-substituted thiazolidines.

3-Trimethylsilyl-2-methyl-2-(2-thienyl)thiazolidine (XV).

2-Methyl-2-(2-thienyl)thiazolidine (6 g., 0.032 mole), *n*-butyllithium (22 ml., 1.6 *N*) and trimethylchlorosilane (3.5 g., 0.032 mole) were reacted to yield 5.4 g. (66%) of product boiling at 119°/0.05 mm.

Anal. Calcd. for $C_{11}H_{19}NS_2Si$: C, 51.31; H, 7.44. Found: C, 51.82; H, 7.70.

3-(γ-Trimethylsilylpropyl)-2-methyl-2-(2-thienyl)thiazolidine (XVII).

2-Methyl-2-(2-thienyl)thiazolidine (11.7 g., 0.063 mole), *n*-butyllithium (39 ml., 1.6 *N*) and γ-chloropropyltrimethylsilane (9.5 g., 0.063 mole) yielded 13 g. (70%) of product boiling at 140°/0.04 mm.

Anal. Calcd. for $C_{14}H_{25}NS_2Si$: C, 56.13; H, 8.41; Si, 9.38. Found: C, 56.27; H, 8.58; Si, 9.27.

3-Methyltrimethylsilyl-2-methyl-2-(2-thienyl)thiazolidine (XVII).

2-Methyl-2-(2-thienyl)thiazolidine (8 g., 0.043 mole), *n*-butyllithium (29 ml., 1.6 *N*) and chloromethyltrimethylsilane (5.3 g., 0.045 mole) were reacted as previously described; however, a reaction period of 24 hours was required, at which time the usual work-up procedure gave 6.7 g. (59%) of product boiling at 119°/0.05 mm.

Anal. Calcd. for $C_{12}H_{21}NS_2Si$: C, 53.08; H, 7.80; Si, 10.34. Found: C, 53.20; H, 7.95; Si, 10.22.

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