[CONTRIBUTION FROM THE RICHARDSON CHEMICAL LABORATORY OF TULANE UNIVERSITY]

SYNTHESIS OF SOME LONG CHAIN SILICON-CONTAINING FATTY ACIDS[1]

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In spite of the voluminous literature, particularly in recent years, in the field of organosilicon compounds, relatively little work has been done on the synthesis and examination of properties of silicon-containing fatty acids. Sommer and co-workers (1, 2) synthesized a variety of short chain carboxylic acids containing silicon using the Grignard, malonic ester, and acetoacetic ester syntheses on appropriate halogen compounds. Other workers (3, 4) have prepared some aromatic types in which the carboxylic acid group and the silicon atom are attached to aromatic and heterocyclic rings. The only previous report of a long chain silicon-containing fatty acid was by Gadsby (5) who carried out the addition of triphenylsilane to 9-hendecenoic acid[3] in the reported yield of 96%.

The synthesis of long chain silicon-modified fatty acids was of primary interest to us as a part of a program of evaluation of long chain types as antitubercular chemotherapeutic agents. The tubercle bacillus is well known for its ability to metabolize a variety of long carbon chain compounds, and it was considered possible that the presence of silicon in the carbon chain might be able to cause interference with the metabolic pattern of these bacilli. Largely because of convenience in synthesis, the compounds made had an —$Si(CH_3)_2$— group in place of a —CH_2— group in a long straight chain aliphatic carboxylic acid. However, the presence of the methyl groups branched from the chain gives these silicon-modified acids some resemblance to the branched methyl types which have been found in the lipid fraction of the tubercle bacillus (the literature on this subject is large, but for a leading reference see 6).

The method of synthesis used for the preparation of 13,13-dimethyl-13-silaheptadecanoic acid (VI) and two related types (13,13-dimethyl-13-silaoctadecanoic acid and 15-phenyl-13,13-dimethyl-13-silapentadecanoic acid) is shown below. All yields in the six-step synthesis were above 50%.

All steps in the synthesis would be expected to yield products of unequivocal structure with the possible exception of the addition of hydrogen bromide to the terminal unsaturated group (IV → V). While no rigorous structure proof was obtained to show that bromine added to the terminal carbon atom, there seems to be ample indication in the literature that in the presence of peroxides this would be the case (7–11). The formation of a primary bromide (V) is also

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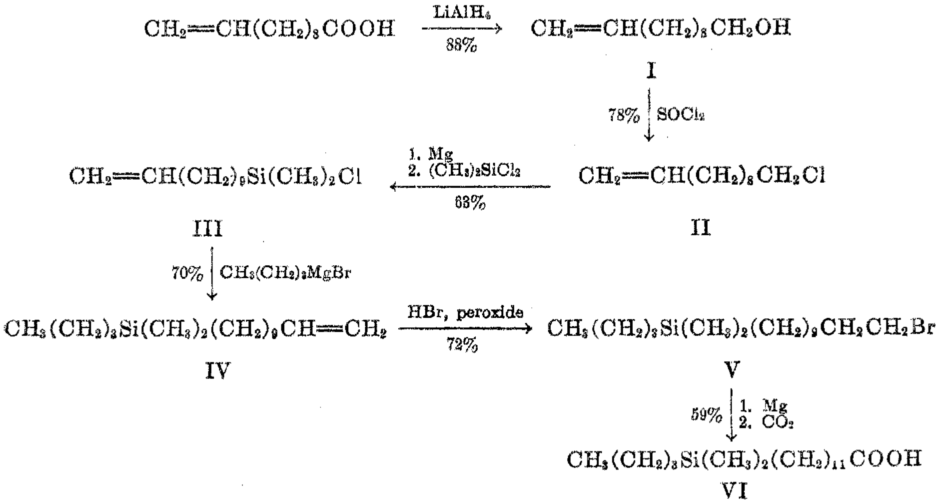
[3] The author of this paper mentions use of "9-undecylenic acid". It appears likely, however, that he means 10-hendecenoic or 10-undecenoic acid. The reaction was carried out in the presence of acetyl peroxide.

indicated in its stability under distillation and its ease of reaction with magnesium in forming the Grignard reagent.



$$CH_2{=}CH(CH_2)_8COOH \xrightarrow[88\%]{LiAlH_4} \underset{\text{I}}{CH_2{=}CH(CH_2)_8CH_2OH}$$

$$\text{I} \xrightarrow[78\%]{SOCl_2} \underset{\text{II}}{CH_2{=}CH(CH_2)_8CH_2Cl}$$

$$\underset{\text{III}}{CH_2{=}CH(CH_2)_9Si(CH_3)_2Cl} \xleftarrow[68\%]{1.\ Mg\quad 2.\ (CH_3)_2SiCl_2} \text{II}$$

$$\text{III} \xrightarrow[70\%]{CH_3(CH_2)_3MgBr} \underset{\text{IV}}{CH_3(CH_2)_3Si(CH_3)_2(CH_2)_9CH{=}CH_2}$$

$$\text{IV} \xrightarrow[72\%]{HBr,\ peroxide} \underset{\text{V}}{CH_3(CH_2)_3Si(CH_3)_2(CH_2)_9CH_2CH_2Br}$$

$$\text{V} \xrightarrow[59\%]{1.\ Mg\quad 2.\ CO_2} \underset{\text{VI}}{CH_3(CH_2)_3Si(CH_3)_2(CH_2)_{11}COOH}$$

Some other synthetic routes to silicon-modified acids were tried, and, while unsuccessful in producing the end product, these routes give some worthwhile information on organosilicon chemistry. For example, it was considered possible that the Si-Cl bond would be sufficiently reactive to couple with the Reformatsky reagent ($BrZnCH_2COOEt$) to give the $Si{-}CH_2COOEt$ grouping. While the Reformatsky reagent appeared to form in a satisfactory manner in the presence of *n*-octadecyltrichlorosilane or dimethyldichlorosilane, coupling could not be effected at temperatures up to the boiling point of xylene.

A second attempted synthetic method involved the reaction of an alkyldimethylchlorosilane with γ-phenoxypropylmagnesium bromide.

$$RSi(CH_3)_2Cl + C_6H_5O(CH_2)_3MgBr \rightarrow \underset{\text{VII}}{RSi(CH_3)_2(CH_2)_3OC_6H_5}$$

The product (VII) on cleavage with hydrogen bromide and conversion of the resulting bromo compound to the Grignard reagent would give the corresponding carboxylic acid. Instead of the expected product (VII), we obtained the dialkyltetramethylsiloxane, $R{-}Si(CH_3)_2{-}O{-}Si(CH_3)_2{-}R$. (VIII). This latter product could have been formed by either of two routes. If the alkyldimethylchlorosilane remained unreacted during treatment with the Grignard reagent, its subsequent hydrolysis by water would give the corresponding silanol which could then pass over to the siloxane. This route appeared unlikely because there was evidence of considerable reaction on addition of the Grignard reagent with the precipitation of a large quantity of inorganic salt.

A second possible route involved the decomposition of γ-phenoxypropylmagnesium bromide to propylene and phenoxymagnesium bromide. Interaction of the phenoxy salt and the chlorosilane would give the alkyldimethylphenoxysilane (IX). Hydrolytic cleavage of IX would then lead to the silanol and to the siloxane (VIII).

$$C_6H_5O(CH_2)_3MgBr \rightarrow CH_3CH = CH_2 + C_6H_5OMgBr$$

$$RSi(CH_3)_2Cl + C_6H_5OMgBr \rightarrow \underset{\text{IX}}{RSi(CH_3)_2OC_6H_5} + MgBrCl$$

$$RSi(CH_3)_2OC_6H_5 + H_2O \rightarrow RSi(CH_3)_2OH + C_6H_5OH$$

$$2\ RSi(CH_3)_2OH \rightarrow \underset{\text{VIII}}{RSi(CH_3)_2OSi(CH_3)_2R} + H_2O$$

There are several lines of evidence for this postulated route. Kipping (12) has shown that diphenoxydiphenylsilane is hydrolyzed by water and dilute base in the presence of acetone or alcohol with the cleavage of the phenoxy group. Some phenol was isolated from our reaction mixture. It has been shown (13a) that γ-phenoxypropyl bromide in ether is converted by sodium to sodium phenoxide, propylene, and cyclopropane. Amstutz (13b) has also shown that β-phenoxyethylmagnesium bromide readily decomposes to ethylene and phenoxymagnesium bromide.

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EXPERIMENTAL

10-Undecene-1-ol (I). The reduction of 10-undecenoic acid with lithium aluminum hydride in 95% yield has been reported by Gensler, Behrmann, and Thomas (14) but no details are given.

Lithium aluminum hydride (42 g. or 1.1 moles) was broken into small lumps and dissolved in 1000 ml. of absolute ether by a 1.5 hour reflux period. To the resulting solution was added dropwise with vigorous stirring a mixture of 185 g. (1.0 mole) of 10-undecenoic acid and 300 ml. of dry ether. The flask was cooled in an ice-bath during the addition. After completion of the addition the ice-bath was removed and stirring was continued for 30 minutes. The resulting mixture was hydrolyzed by the cautious, dropwise addition, with cooling, of dilute sulfuric acid. A total of 400 ml. of 10% and 400 ml. of 20% acid was required to complete hydrolysis and to effect solution of the salts. The ether layer was separated, washed with water, dried over sodium sulfate, and distilled. There was obtained 150 g. (88%) of 10-undecene-1-ol boiling at 114–115° at 6 mm. Three additional runs gave yields in the 80–90% range.

11-Chloro-1-undecene (II). Conversion of 10-undecene-1-ol to 11-chloro-1-undecene with thionyl chloride has also been reported by Gensler, *et al.* (14). We could not obtain high yields using pyridine as they suggest, and in our hands the procedure given below was found to be a more reliable one.

Thionyl chloride (1 kg. or 8.4 moles) was added dropwise to a solution of 414 g. (2.44 moles) of 10-undecene-1-ol and 600 ml. of chloroform. The mixture was refluxed for 8 hours after completion of the addition, and the chloroform and excess thionyl chloride were removed by distillation. The residue was mixed with ice water to destroy any remaining thionyl chloride and 300 ml. of ether was added. The ether layer was separated, and washed with water, dilute sodium hydroxide solution, and again with water. After drying over calcium chloride the solution was distilled to give 347 g. (78%) of 11-chloro-1-undecene boiling at 108–109° at 6 mm.

10-Undecenyldimethylchlorosilane (III). A few ml. of ethyl bromide was added to 20 g.

(0.82 g.-atom) of magnesium and a little dry ether. The mixture was stirred until reaction was complete and then 300 ml. of ether was added. 11-Chloro-1-undecene (120 g., 0.64 mole) was added dropwise with stirring and the mixture was refluxed for 1.5 hours after completion of the addition. The filtered Grignard solution was added dropwise to a solution of 150 g. (1.16 moles) of dimethyldichlorosilane (Dow-Corning) in 300 ml. of ether and the mixture was stirred and refluxed for 18 hours. Most of the ether was removed by distillation and the mixture was filtered to remove magnesium salts. The filtrate was distilled to give 100 g. (63%) of 10-undecenyldimethylchlorosilane boiling at 98° at 1.2 mm. or 113° at 2.8 mm.

Anal. Calc'd for $C_{13}H_{27}ClSi$: Cl, 14.4. Found: Cl, 14.1.

n-Butyl-10-undecenyldimethylsilane (IV). *n*-Butylmagnesium bromide was prepared in the usual manner from 106 g. (0.77 mole) of *n*-butyl bromide, 18.7 g. (0.77 g.-atom) of magnesium, and 250 ml. of ether. To the resulting Grignard reagent was added 95 g. (0.37 mole) of 10-undecenyldimethylchlorosilane. There was no evidence of evolution of heat or precipitation of magnesium salt during the addition or during a subsequent reflux period. *n*-Butyl ether (150 ml.) was added and solvent was distilled from the mixture until the liquid temperature reached 100°. The mixture was then stirred and refluxed for 18 hours. The resulting grey slurry was poured over crushed ice and sufficient dilute hydrochloric acid was added to dissolve the magnesium salts. The ether layer was separated, washed with water, dried over calcium chloride, and distilled to give 61 g. (68%) of *n*-butyl-10-undecenyldimethylsilane, b.p. 127–129° at 2.1 mm., n_D^{27} 1.4460.

Anal. Calc'd for $C_{17}H_{36}Si$: Si, 10.45. Found: Si, 10.41.

Two additional preparations carried out essentially as described above gave yields of 71 and 73%. A trial using *n*-butyllithium at the reflux temperature of ether gave no evidence of reaction.

11-Bromoundecyl-n-butyldimethylsilane (V). Hydrogen bromide prepared by the action of 38 g. of bromine on 50 g. of tetralin (15) was passed over copper turnings to remove bromine and then passed into a solution of 20 g. (0.075 mole) of *n*-butyl-10-undecenyldimethylsilane and 0.5 g. of benzoyl peroxide in 100 ml. of petroleum ether. The reaction mixture was cooled in an ice-bath and it was discovered that the addition of one or two drops of water to the reaction mixture was necessary for the rapid uptake of the hydrogen bromide. The addition of the hydrogen bromide required about 1 hour after which time the mixture appeared to be saturated. The resulting solution was washed with water, with aqueous ferrous sulfate solution to destroy peroxide, with 5% aqueous sodium hydroxide to remove benzoic acid, and finally with water. After drying the solution was distilled to give 19 g. (72%) of 11-bromoundecyl-*n*-butyldimethylsilane, b.p. 170–174° at 3.5 mm.

Anal. Calc'd for $C_{17}H_{37}BrSi$: Si, 8.02. Found: Si, 7.85.

13,13-Dimethyl-13-silaheptadecanoic acid (VI). A few ml. of *n*-butyl bromide were added to 4.5 g. (0.185 g.-atom) of magnesium and 100 ml. of ether. After the Grignard reaction was well started, 45.3 g. (0.13 mole) of 11-bromoundecyl-*n*-butyldimethylsilane was added dropwise with stirring and the mixture was stirred at reflux temperatures for 2 hours after completion of the addition. After cooling the reaction mixture was poured with stirring into a slurry of solid excess carbon dioxide and dry ether. After evaporation of the carbon dioxide, the mixture was hydrolyzed by the careful addition of excess dilute hydrochloric acid. The ether layer was separated, washed several times with water, dried over sodium sulfate, and distilled to give 18.5 g. (59%) of carboxylic acid, b.p. 194–195° at 2.4 mm.

Analysis of this material gave a silicon value of 8.39% (theory 8.92%) and a neutral equivalent of 350 (theory 314). A small sample of the acid was purified through its barium salt as follows. A solution of 1 g. of the acid in 30 ml. of ethanol was mixed with 0.5 g. of barium hydroxide in 30 ml. of ethanol. Alcohol was decanted from the precipitated barium salt and the residue was washed several times with fresh ethanol. The residual salt was dissolved in hot ether and filtered to remove excess barium hydroxide and the filtrate was added to excess acetone. The barium salt was removed by filtration and washed thoroughly with acetone. The barium salt was redissolved in ether and the solution shaken with several portions of dilute hydrochloric acid to convert the salt to the free acid. The resulting ether solution was dried over magnesium sulfate and the ether evaporated. The residual oil had a refractive index of n_D^{25} 1.4545.

Anal. Calc'd for $C_{18}H_{38}O_2Si$: C, 68.40; H, 12.15; Si, 8.92; Neut. equiv., 314.
Found: C, 68.48; H, 12.38;[4] Si, 8.76; Neut. equiv., 317.

The compounds listed below, unless otherwise noted, were prepared in essential accordance with the procedures given previously in detail.

n-Amyl-10-undecenyldimethylsilane. The reaction of *n*-amylmagnesium bromide, from 100 g. (0.66 mole) of *n*-amyl bromide with 86.3 g. (0.35 mole) of 10-undecenyldimethylchlorosilane (III) gave 68 g. (69%) of product, b.p. 142–144° at 2.0 mm., n_D^{27} 1.4467.

Anal. Calc'd for $C_{18}H_{38}Si$: Si, 9.90. Found: Si, 9.97.

β-Phenylethyl-10-undecenyldimethylsilane. The reaction of β-phenylethylmagnesium bromide, from 100 g. of β-phenylethyl bromide, with 69 g. (0.28 mole) of 10-undecenyldimethylchlorosilane gave 61 g. (69%) of β-phenylethyl-10-undecenyldimethylsilane, b.p. 177–179° at 2.4 mm., n_D^{27} 1.4870.

Anal. Calc'd for $C_{21}H_{36}Si$: Si, 8.86. Found: Si, 8.60.

11-Bromoundecyl-n-amyldimethylsilane. The addition of hydrogen bromide to 60 g. (0.21 mole) of *n*-amyl-10-undecenyldimethylsilane gave 53 g. (64%) of product boiling at 173–174° at 2.0 mm.

Anal. Calc'd for $C_{18}H_{39}BrSi$: Si, 7.72. Found: Si, 7.60.

11-Bromoundecyl-(β-phenylethyl)dimethylsilane. The reaction of 65 g. (0.21 mole) of β-phenylethyl-10-undecenyldimethylsilane with hydrogen bromide did not give a constant-boiling fraction upon distillation of the product. There appeared to be considerable unreacted olefin present and a mixed order of addition of hydrogen bromide appeared possible. Two fractions, b.p. 187–192° at 1.9 mm. (22.5 g.) and b.p. 193° at 2.1 mm. to 219° at 2.3 mm. (26.5 g.) were combined and used in the reaction with magnesium as described below.

13,13-Dimethyl-13-silaoctadecanoic acid. Conversion of 45 g. (0.124 mole) of 11-bromoundecyl-*n*-amyldimethylsilane to the Grignard reagent and carbonation as described previously gave 20 g. (49%) of carboxylic acid, b.p. 200–202° at 2.1 mm. This material showed a silicon content of 8.26% (theory 8.54%) and a neutral equivalent of 350 (theory 328). One gram of the acid was purified through its barium salt as described above to give the pure acid, n_D^{25} 1.4553.

Anal. Calc'd for $C_{19}H_{40}O_2Si$: C, 69.49; H, 12.27; Si, 8.54; Neut. equiv., 328.
Found: C, 69.48; H, 12.49; Si, 8.44; Neut. equiv., 332.

15-Phenyl-13,13-dimethyl-13-silapentadecanoic acid. The crude 11-bromoundecyl-(β-phenylethyl)dimethylsilane (39 g.) was converted to the Grignard reagent and carbonated in the usual manner. The product was distilled at reduced pressure (wide boiling range) until a residue of 4 g. remained in the distillation vessel. This residual acid was purified through its barium salt as described previously to give a product, n_D^{25} 1.4893, which analyzed correctly for 15-phenyl-13,13-dimethyl-13-silapentadecanoic acid.

Anal. Calc'd for $C_{22}H_{38}O_2Si$: Si, 7.73; Neut. equiv., 362.
Found: Si, 7.52; Neut. equiv., 364.

n-Octyldimethylchlorosilane. The Grignard reagent was prepared in the usual manner from 300 g. (1.5 moles) of *n*-octyl bromide. The *n*-octylmagnesium bromide was added with stirring to an ether solution of 258 g. (2.0 moles) of dimethyldichlorosilane (Dow-Corning Co.) and the resulting mixture was heated to reflux and stirred for 18 hours. The mixture was filtered and the filtrate distilled. After the forerun of unreacted dimethyldichlorosilane there was obtained 180 g. (59% based on *n*-octyl bromide) of *n*-octyldimethylchlorosilane, b.p. 222–225°.

Anal. Calc'd for $C_{10}H_{23}ClSi$: Cl, 17.2. Found: Cl, 17.0.

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[4] All carbon and hydrogen analyses are by the Galbraith Microanalytical Laboratories of Knoxville, Tenn.

Reaction of γ-phenoxypropylmagnesium bromide with n-octyldimethylchlorosilane. The Grignard reagent from 185 g. (0.85 mole) of γ-phenoxypropyl bromide (16) was prepared in the normal manner. A fine, grey solid precipitated during the addition of the bromide. To the resulting mixture was added 155 g. (0.75 mole) of *n*-octyldimethylchlorosilane and the reaction mixture was stirred and heated to reflux overnight and then poured into excess dilute hydrochloric acid. The ether layer was separated, washed with water, dried, and the ether removed by distillation, the last portion being removed under a vacuum. A brown colored liquid remained which possessed a strong phenolic odor. About 25 g. of this liquid was used in various tests to determine its possible composition and a suitable work-up procedure.

The balance of the brown liquid was washed twice with aqueous 3% sodium hydroxide solution to remove phenol and several times with water. It was then distilled to give the following fractions: (a) b.p. 45–70° at 1.1 mm., 10 g.; (b) 70–105° at 0.85 mm., 8 g.; (c) 105–115° at 0.75 mm., 106 g.; and (d) 115–125° at 0.75 mm., 17 g. Fraction (c) was redistilled to give 65 g. b.p. 98–99° at 0.57 mm., n_D^{25} 1.4740, d_4^{25} 0.8905. A molecular refraction of 113.0 was calculated from this data. The theoretical value for di-*n*-octyltetramethyldisiloxane from atomic refractions is 115.9. A value of 7.47 was used for silicon (17) and the Si—O—Si oxygen was considered an ether oxygen.

Anal. Calc'd for $C_{20}H_{46}OSi_2$: Si, 15.7. Found: Si, 15.7.

SUMMARY

1. A synthetic route to certain silicon-containing long chain fatty acids has been developed.

2. Using this route the following acids were prepared: 13,13-dimethyl-13-silaheptadecanoic acid, 13,13-dimethyl-13-silaoctadecanoic acid, and 15-phenyl-13,13-dimethyl-13-silapentadecanoic acid.

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