indole-1-acetate was hydrogenated at an initial pressure of 50 psi in 200 ml of ethanol in the presence of 1 g of platinum oxide. After 4 hr the catalyst was filtered, the filtrate was concentrated, and the residual oil was chromatographed on neutral alumina. Fractions eluted with ether were combined and concentrated, and the residual solid was recrystallized from ethyl acetate–hexane to give 3.0 g (30%) of ethyl 3-carbethoxy-1,2,3,4-tetrahydro-7,8-dimethoxy-2-oxopyrimido[1,2-*a*]indole-1-acetate: mp 96–98°; $\nu_{max}^{CHCl_3}$ 1736 (C=O ester) and 1682 cm^{-1} (C=O amide); $\lambda_{max}^{CH_3OH}$ sh 281 mμ (ε 8000), sh 289 (9700), and 314 (15,500).

Anal. Calcd for $C_{20}H_{24}N_2O_7$: C, 59.40; H, 5.98; N, 6.93. Found: C, 59.51; H, 5.98; N, 6.84.

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Synthesis of Some 5-Trimethylsilylindoles

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5-Trimethylsilylindole has been synthesized starting from indole which was N-benzylated and brominated in the 5 position, metalated to 5-lithio-N-benzylindoline, and treated with trimethylchlorosilane to yield 5-trimethylsilyl-N-benzylindoline. Catalytic hydrogenolysis in the presence of acetic anhydride gave 5-trimethylsilyl-N-acetylindoline, which was hydrolyzed by KOH in diethylene glycol to 5-trimethylsilylindoline, which in turn was converted into 5-trimethylsilylindole by catalytic dehydrogenation in boiling xylene in the presence of palladium–charcoal. 5-Trimethylsilylgramines were synthesized. 5-Trimethylsilylgramine methiodide was converted into the nitrile by reaction with sodium cyanide and the latter was hydrolyzed to 5-trimethylsilylindole-3-acetic acid, or reduced to 5-trimethylsilyltryptamine.

Various indole derivatives substituted in the 5 position have been synthesized, such as 5-acetyl-,[1] 5-amino-,[2] 5-chloro-,[3] and 5-fluorotryptamines[4] and 5-nitro- and 5-aminogramines.[5] These are interesting in that they are related to the physiologically active 5-hydroxytryptamine.

We report here the synthesis of 5-trimethylsilylindole and some of its derivatives.

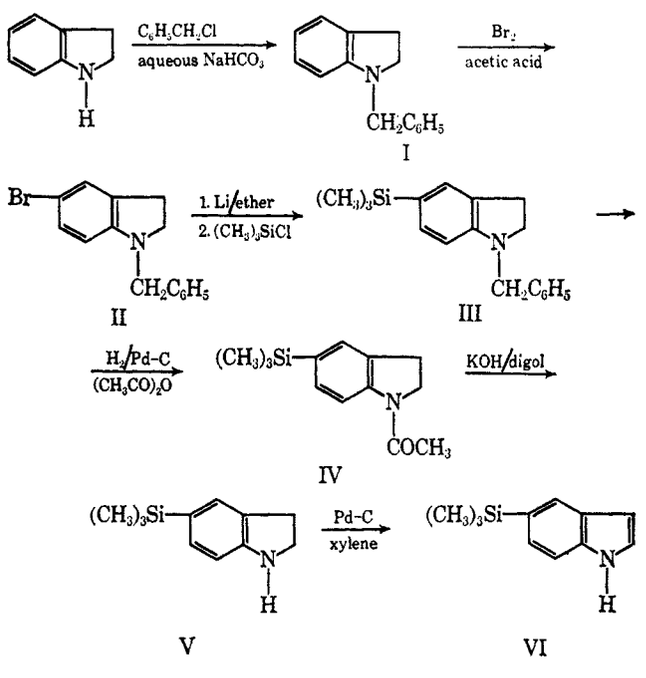
The preparation of compounds having a silicon–aryl bond involves difficulties because of the sensitivity of the silicon–aryl bond, to cleavage by acids and halogens. For this reason, although there are many methods for the preparation of indole derivatives, most of them are unsuitable for the preparation of silicon-containing indole derivatives since they require acid conditions in some step of the synthesis.

5-Trimethylsilylindole was synthesized starting from indoline[6,7] according to Scheme I.

N-Benzylindoline (I) was brominated with 1 equiv of bromine in acetic acid solution giving 5-bromo-N-benzylindoline (II), which was identical (melting point, mixture melting point, and ir spectrum) with the compound resulting from the N-benzylation of 5-bromoindoline.[8]

Catalytic hydrogenolysis of the N-benzyl group from 5-trimethylsilyl-N-benzylindoline (III) was easy, but in methanol, 2-propanol, or acetic acid solution it was accompanied by cleavage of the trimethylsilyl group. This was attributed to activation by the electron-releasing amino group in the *para* position. Consequently,

SCHEME I



hydrogenolysis was done in acetic anhydride, so that after the N-benzyl was split off the amino group was acetylated. The silicon–aryl bond was then stable and the resultant 5-trimethylsilyl-N-acetylindoline (IV) partially precipitated out of solution. The reaction was stopped immediately after the required amount of hydrogen was absorbed.

5-Trimethylsilylindole (VI) was obtained from V by catalytic dehydrogenation in boiling xylene in the presence of palladium–charcoal. The reaction at lower temperature (boiling toluene) was not satisfactory.

5-Trimethylsilylgramine (VII) was obtained from VI by the Mannich reaction using formaldehyde and dimethylamine. It was converted into 5-trimethylsilyl-3-piperidinomethylindole (VIII) by reaction with piperidine (Scheme II).

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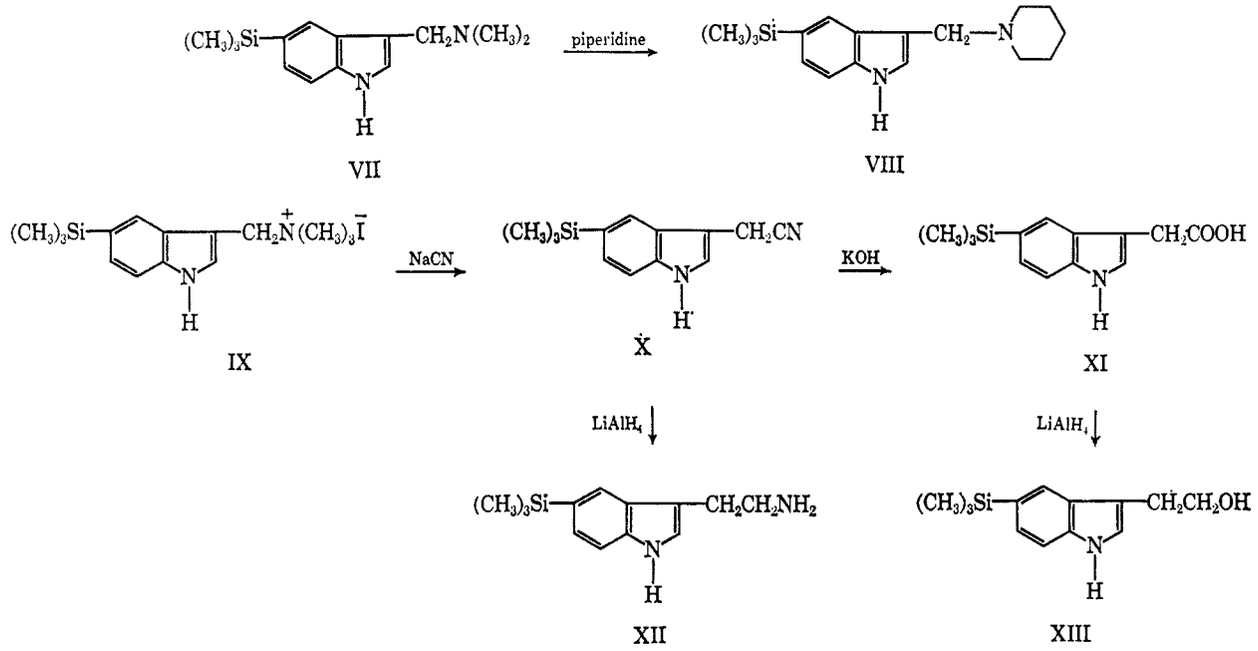
SCHEME II



Reaction of VII with methyl iodide gave the methiodide IX, which on reaction with sodium cyanide gave 5-trimethylsilylindole-3-acetonitrile (X). Compound X was hydrolyzed to the acid XI and was reduced to 5-trimethylsilyltryptamine (XII) (Scheme II).

5-Trimethylsilylindole-3-acetic acid (XI) was reduced to 5-trimethylsilylindolylethanol (XIII).

Experimental Section

Melting points were determined using a Fisher-Johns apparatus. The uv spectra were carried out in ethanol (J. T. Baker Alcohol Reagent) using a Beckman DU spectrophotometer.

N-Benzylindoline (I).—Indoline (119 g, 1 mol) was added to sodium bicarbonate (105 g, 1.25 mol) in 200 ml of water and the mixture was stirred with heating to 90–95°. Benzyl chloride (127 g, 1 mol) was added dropwise during 1.5 hr, and stirring and heating was continued for an additional 3.5 hr. After cooling the layers were separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with water and dried over magnesium sulfate. N-Benzylindoline was obtained in 90% yield (190 g): bp 146–149° (1 mm); $\lambda_{max}^{ethanol}$ 254 mμ (ε 10,000) and 302 (2500).

Anal. Calcd for $C_{15}H_{15}N$: C, 86.08; H, 7.22; N, 6.69; mol wt, 209.3. Found: C, 86.35; H, 7.47; N, 6.86; mol wt, 210.1 (on titration with perchloric acid in acetic acid using crystal violet as indicator).

5-Bromo-N-benzylindoline (II).—To a solution of N-benzylindoline (104.5 g, 0.5 mol) in glacial acetic acid (500 ml) under nitrogen atmosphere, a solution of bromine (80 mg, 0.5 mol) in acetic acid (250 ml) was added with stirring and external cooling during 2 hr. A heavy bluish white precipitate of 5-bromo-N-benzylindoline hydrobromide separated; it was stirred for another 15 min, filtered off, and washed thoroughly with petroleum ether (60–80°). The precipitate was added into 10% sodium hydroxide solution. The filtrate and washings were concentrated *in vacuo* and made alkaline with sodium hydroxide solution. The alkaline mixtures were combined and the amine was extracted with ether. The ethereal extracts were washed with water, dried over sodium sulfate, and distilled *in vacuo*. The 5-bromo-N-benzylindoline (124 g, 86%) distilled at 174–176° (1 mm) and solidified on cooling: mp 33° on recrystallyzation from ethanol or 2 propanol; λ_{max} 264 mμ (ε 15,000) and 313 (2600).

Anal. Calcd for $C_{15}H_{14}BrN$: C, 62.51; H, 4.90; N, 4.86. Found: C, 62.76; H, 5.03; N, 5.04.

The compound is unstable and decomposes on heating or on standing at room temperature for long periods of time. The crude material can be used in the following step.

N-Benzyl-5-trimethylsilylindoline (III).—A solution of 5-bromo-N-benzylindoline (144 g, 0.5 mol) in dry ether (200 ml) was added dropwise with stirring and cooling to lithium metal wire (7.4 g, 1.06 g-atom) in dry ether (150 ml) in an argon atmosphere. Stirring in the cold was continued for an additional 2 hr, until almost all the lithium reacted. The reaction mixture was then cooled in an ice–salt bath, and a solution of trimethylchlorosilane (60 g, 0.54 mol) in dry ether (200 ml) was dropped in with stirring. The reaction mixture was stirred in the cold for 1 hr, followed by 16 hr at room temperature, and was filtered through glass wool. The filtrate was added cautiously to cold 30% sodium hydroxide solution, so that the reaction mixture was always alkaline, and was extracted with ether. The ethereal extract was washed with water, dried, and distilled. The N-benzyl-5-trimethylsilylindoline (113 g, 80%) was collected at 179–181° (1 mm) which solidified on cooling: mp 55° (from methanol); λ_{max} 267 mμ (ε 15,800) and 299 sh (3300).

Anal. Calcd for $C_{18}H_{23}NSi$: C, 76.81; H, 8.24; N, 4.98; Si, 9.97. Found: C, 76.91; H, 8.21; N, 5.08; Si, 10.34.

N-Acetyl-5-trimethylsilylindoline (IV).—N-Benzyl-5-trimethylsilylindoline (10 g, 0.035 mol) in acetic anhydride (35 ml) was hydrogenated in a Parr apparatus (30 psi) at room temperature in the presence of 10% Pd–C (1 g). The theoretical amount of hydrogen was taken up in about 1–1.5 hr. The catalyst and precipitated material were filtered off and washed with petroleum ether. The filtrate was poured into a solution of sodium hydroxide (50 g) in crushed ice (500 g) and stirred until all the acetic anhydride was hydrolyzed. The precipitated N-acetyl-5-trimethylsilylindoline was filtered off, combined with the first precipitate, extracted with boiling ethanol, and filtered. The solution of the N-acetyl-5-trimethylsilylindoline was concentrated to a small volume and left to crystallize for 24 hr in the refrigerator. The yield was 5.1 g (61%): mp 191°; λ_{max} 262 mμ (ε 20,000), 285 (1100), and 295 (6400).

Anal. Calcd for $C_{13}H_{19}NOSi$: C, 66.91; H, 8.21; N, 6.00; Si, 12.02. Found: C, 66.85; H, 8.42; N, 6.37; Si, 12.21.

5-Trimethylsilylindoline (V).—N-acetyl-5-trimethylsilylindoline (14 g, 0.06 mol) was added to a solution of potassium hydroxide (20 g) in water (20 ml) and diethylene glycol (180 ml) and heated under reflux for 5 hr. The reaction mixture was cooled, diluted with water (600 ml), and extracted with ether. The ethereal extract was washed with water, dried over magnesium sulfate, and distilled. The 5-trimethylsilylindoline was obtained in 78% yield (9 g): bp 98–100° (1 mm); $n^{20}D$ 1.555; λ_{max} 252 mμ (ε 11,000) and 295 (2500).

Anal. Calcd for $C_{11}H_{17}NSi$: C, 69.05; H, 8.95; N, 7.32; Si, 14.67. Found: C, 68.72; H, 8.79; N, 7.23; Si, 14.38.

5-Trimethylsilylindole (VI).—A solution of 5-trimethylsilylindoline (8 g, 0.042 mol) in xylene (110 ml) was heated under reflux for 4 hr, in the presence of 10% Pd-C (0.9 g). The reaction mixture was filtered and fractionally distilled. The 5-trimethylsilylindole (6 g, 75%) distilled at 103–105° (1 mm) or at 110–114° (2 mm) and solidified to crystals: mp 42°; λ_{max} 223 mμ (ε 56,000), 274 (5600), and 293 (3500).

Anal. Calcd for $C_{11}H_{15}NSi$: C, 69.78; H, 7.98; N, 7.40; Si, 14.82. Found: C, 69.39; H, 7.89; N, 7.34; Si, 14.35.

5-Trimethylsilylgramine (VII).—A mixture of acetic acid (20 ml), dioxane (20 ml), 37% aqueous formalin solution (1.6 g), and 28% aqueous dimethylamine solution (3.2 g) was cooled to 0° in an ice bath, and 5-trimethylsilylindole (3.8 g, 0.02 mol) was dropped in slowly with stirring during 1 hr and left overnight. The reaction mixture was diluted with water to a volume of 300 ml and filtered. The filtrate was made strongly alkaline with sodium hydroxide solution, and the trimethylsilylgramine separated out as an oil which solidified on standing to yield 4.3 g (87%): mp 113° on recrystallization from petroleum ether; λ_{max} 226 mμ (ε 51,500), 282 (5300), and 292 (4200).

Anal. Calcd for $C_{14}H_{22}N_2Si$: C, 68.24; H, 9.00; N, 11.37; Si, 11.39. Found: C, 68.14; H, 9.13; N, 11.29; Si, 11.51.

5-Trimethylsilyl-3-piperidinomethylindole (VIII).—5-Trimethylsilylgramine (1 g, 0.004 mol) in piperidine (20 ml) was heated under reflux for 3 hr. Excess piperidine was removed *in vacuo*, and petroleum ether was added to the residual oil. The 5-trimethylsilyl-3-piperidinomethylindole (1 g, 86%) crystallized out: mp 126° on recrystallization from petroleum ether; λ_{max} 226 mμ (ε 50,000), 284 (5400), and 294 (4100).

Anal. Calcd for $C_{17}H_{26}N_2Si$: C, 71.27; H, 9.15; N, 9.77; Si, 9.80. Found: C, 71.11; H, 9.20; N, 9.60; Si, 9.62.

5-Trimethylsilylindole-3-acetonitrile (X).—Methyl iodide (4 ml) in petroluem ether (10 ml) was added with stirring into a solution of 5-trimethylsilylgramine (1.23 g, 0.005 mol), stirred for 30 min, and left overnight in the cold. The precipitated methiodide was filtered off, dried, and dissolved in 50% aqueous ethanol (100 ml). Sodium cyanide (3 g, 0.06 mol) was added and the solution was stirred and heated to 70–80° for 2 hr. Water (100 ml) was added and the 5-trimethylsilyl-3-indole acetonitrile was taken up in chloroform, washed with water, dried, and concentrated *in vacuo*. Petroleum ether was then added to the concentrated solution to precipitate the nitrile. A yield of 0.82 g (72%) was obtained: mp 105° on recrystallization from chloroform–petroleum ether; λ_{max} 225 mμ (ε 52,000), 283 (5500), and 283 (4100).

Anal. Calcd for $C_{13}H_{16}N_2Si$: C, 68.37; H, 7.06; N, 12.27; Si, 12.29. Found: C, 68.23; H, 6.85; N, 12.53; Si, 12.44.

5-Trimethylsilylindole-3-acetic Acid (XI).—5-Trimethylsilylindole-3-acetonitrile (1.2 g, 0.0052 mol) in ethanol (25 ml) was hydrolyzed by heating with a solution of potassium hydroxide (4.5 g) in water (15 ml) for 10 hr in a nitrogen atmosphere. The reaction mixture was cooled, diluted with water (200 ml), and filtered. The filtrate was brought to pH 7 with hydrochloric acid and left to crystallize out in the cold for several hours, yielding 1 g (77%) of 5-trimethylsilylindole-3-acetic acid: mp 110° on recrystallization from chloroform–petroleum ether; λ_{max} 229 mμ (ε 49,500), 284 (5200), and 294 (4000).

Anal. Calcd for $C_{13}H_{17}NO_2Si$: C, 63.12; H, 6.93; N, 5.66; Si, 11.34. Found: C, 62.27; H, 7.05; N, 5.39; Si, 11.62.

5-Trimethylsilyltryptamine (XII).—A solution of 5-trimethylsilylindole-3-acetonitrile (0.8 g, 3.5 mmol) in dry ether (50 ml) was added slowly with stirring into lithium aluminium hydride (2 g, 0.053 mol) in ether (80 ml), and the mixture stirred for 10 hr. Excess lithium aluminium hydride was destroyed by addition of ethyl acetate, followed by water and then by 20% sodium hydroxide solution (4 ml). The reaction mixture was filtered, the precipitate was washed thoroughly with ether, and the combined ethereal solutions were washed with water and dried over magnesium sulfate. Upon removal of the ether 5-trimethylsilyltryptamine remained as an oil which solidified on addition of petroleum ether to yield 0.59 g (78%): mp 103° on recrystallization from chloroform–petroleum ether; λ_{max} 227 mμ (ε 48,500), 285 (5000), and 295 (4000).

Anal. Calcd for $C_{13}H_{20}N_2Si$: C, 67.19; H, 8.68; N, 12.06; Si, 12.08. Found: C, 66.98; H, 8.64; N, 12.32; Si, 12.36.

β-(5-Trimethylsilylindolyl)ethanol (XIII).—A solution of 5-trimethylsilylindole-3-acetic acid (1 g, 4×10^{-3} mol) in dry ether (50 ml) was added slowly with stirring into lithium aluminium hydride (1.5 g, 0.04 mol) in ether (50 ml), and the reaction mixture was stirred for 15 hr. Excess lithium aluminium hydride was destroyed by addition of a minimal quantity of water and the reaction mixture was filtered. The precipitate was washed thoroughly with ether and the combined ethereal solutions were washed with bicarbonate solution, followed by water, and dried over magnesium sulfate. The ether was driven off *in vacuo* and the β-(5-trimethylsilylindolyl)ethanol (0.76 g, 82%) distilled at 138–142° (1 mm): λ_{max} 229 mμ (ε 42,500), 285 (4800), and 295 (3700).

Anal. Calcd for $C_{13}H_{19}NOSi$: C, 66.91; H, 8.21; N, 6.00; Si, 12.02. Found: C, 66.81; H, 8.23; N, 6.25; Si, 11.82.

A New Synthesis of 6-Phenyl-2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazole

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A four-step synthesis of the anthelmintic *dl*-6-phenyl-2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazole hydrochloride (tetramisole) from styrene oxide and ethylenimine is described. The key step is the reaction of α-phenyl-2-aziridineethanol with thiocyanic acid to give 2-imino-α-phenyl-3-thiazolidineethanol hydrochloride which proceeds in excellent yield.

The reported[1] broad spectrum anthelmintic activity of 6-phenyl-2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazole hydrochloride (VI) prompted the search for a new and more general synthetic route. The previous major synthesis[2] of VI involved the condensation of a phenacyl halide with 2-aminothiazoline, sodium borohydride reduction of the resultant 3-aroylmethyl-2-iminothiazolidine, and subsequent ring closure. This paper describes a new synthesis of VI starting with styrene oxide and ethylenimine.

Condensation of ethylenimine and styrene oxide gave α-phenyl-1-aziridineethanol (I), which reacted with thiocyanic acid to provide 2-imino-α-phenyl-3-thiazolidineethanol hydrochloride (III). Reaction of III with thionyl chloride, followed by ring closure gave VI.

Funke and Benoit[3] obtained crystalline I in a 48% yield from the reaction of styrene oxide with ethylenimine and a trace of water in a sealed tube at 100°. Initial results in this laboratory showed that the reac-

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