Dihydropyridines from Silylation of Pyridines

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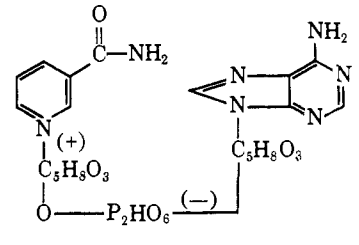
Abstract: Trimethylsilane adds to pyridine and the picolines in the presence of palladium and other catalysts to yield a variety of 1,2- and 1,4-dihydropyridines. A labile equilibrium in the presence of palladium causes the product distribution to vary considerably with time, temperature, and other conditions. The unsubstituted N-hydrodihydropyridines[1] are available for the first time from these N-silyldihydropyridines.

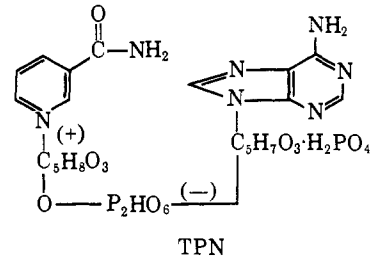
Two principal methods have been employed to form di- and tetrahydropyridines: (1) Hantzsch ring closure of aliphatic reagents and (2) reduction of pyridines. The ring closure has been most productive, and carbonyl compounds condensed in the presence of ammonia, primary amines, hydrazine, and ketimines have yielded hundreds of substituted hydropyridines.[2] Relatively few simple hydropyridines have been prepared, however, for the synthesis works best on highly substituted reagents.

Chemical reagents have been most useful in the reduction of pyridines. Sodium hydrosulfite, sodium borohydride, aluminum amalgam, sodium amalgam, and hydrogen over platinum—in approximately this order of importance—have been the principal reagents employed in reducing pyridinium salts.[2] Almost no success has been encountered with reduction of the free bases. The principal difficulties lie in the ease with which the partially reduced pyridines are reduced to piperidines, and the readiness with which the hydropyridines isomerize, oxidize, and polymerize. Compounds substituted with groups which will stabilize them against these side reactions have therefore received the most attention.

Dihydropyridines are of considerable interest because they play a key role in metabolic oxidation. Two such materials with very simple structures, except for the phospho nucleotide groups attached to the nitrogen, are very important hydrogen-transfer reagents



DPN



TPN

in biological systems.[3] The pyridinium nucleotides (DPN- and TPN-oxidized forms) accept hydrogen directly from a variety of oxidizable substrates to become dihydropyridines and then transfer the hydrogen to other acceptors. Progress in understanding these processes and in applying the method to laboratory reactions has been slow because methods for making model compounds have been difficult and often nonexistent.

There is need for better methods for making simple hydropyridines. The catalyzed addition of trimethylsilane to pyridines is simple, gives good yields, and is versatile for making dihydropyridines, tetrahydropyridines, and other related compounds. An unsubstituted dihydropyridine has been made by this process and isolated for the first time.[4]

Results and Discussion

When trimethylsilane is bubbled into an excess of pyridine containing palladium, an exothermic reaction ensues and the silane is consumed. The temperature, rate of stirring, and reaction time have a pronounced effect on the product distribution (Table I).

A trace of N-trimethylsilylpiperidine also appears in each of the reactions. Vpc analyses made during the course of the reaction at 30° showed that the 1,2-addition product isomerized to the 1,4 product as the reaction proceeded (Table II).[5]

That an equilibrium could be established among these products was shown by the reaction of pure III with palladium catalyst in pyridine for 40 hr at room temperature. The following products resulted: I, trace; II, 25%; III, 1–2%; IV, 18%; VII, 50%. Vpc data indicated the formation of approximately 5% V and 1% VI.

A study of other catalysts showed that palladium gave the fastest rate: Pd–C > Rh–C > $PdCl_2$ >>> Ni_{Raney}, Pt–C, Ru–C. Although rhodium was not so fast as palladium, it was more selective, producing no I or II, no dimer, and no disilylated products.

The silylation of methylpyridines was similar to the silylation of pyridine. At room temperature 2-picoline in the presence of palladium showed no reactivity toward trimethylsilane, 3-methylpyridine showed slightly greater reactivity than pyridine, and 4-methylpyridine about one-fourth the reactivity of pyridine.

When trimethylsilane was bubbled into 3-picoline at room temperature, an exothermic reaction occurred

(1) E. Klingsberg, "Pyridine and Derivatives," Part I, Interscience Publishers, Inc., New York, N. Y., 1960, p 77.
(2) W. Traber, Doctoral Dissertation, University of Zurich, 1963.
(3) See ref 1, Part II, 1961, p 52.
(4) N. C. Cook and J. E. Lyons, *J. Am. Chem. Soc.*, 87, 3283 (1965).
(5) See ref 1, p 78.

Table I

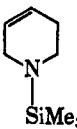
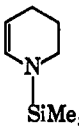
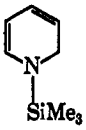
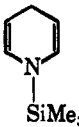
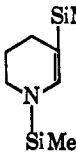
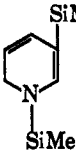
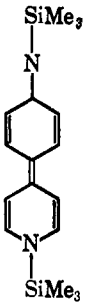
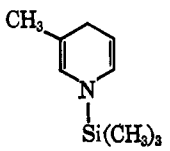
Conditions	Me_3SiH consumed, %	Yield of Products, % I	II	III	IV	V	VI	VII
								
30°, 25 hr, vigorous stirring	95	1.5	12	<25	35	0.8	0.2	25
42°, 3 days, slow stirring	95	1	7	1	43	9	1	30
60–80°, 4 hr, slow stirring	60	<1	3.4	2.2	60	17.5	4.5	12.5
0°, 11 days, slow stirring	37	0.6	5.8	4.7	51	8.5	1.2	28

Table II

Reaction time, hr	Me_3SiH consumed, %	Ratio of III/IV
2	10	2.5/1
17	65	1/1
25	95	3/4
29[a]		2/3

[a] 4 hr for filtering catalyst.

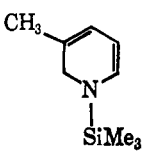
and the mixture rose to 40° where it was held for 20 hr. A single product was obtained in over 90% yield (VIII). No dimerization or hydrogenation was ob-



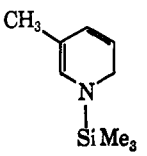
VIII

served. A trace of what might be a disilylated product was observed on vpc analysis, in quantities too small to isolate and identify.

When the same reaction was carried out at 24° for 18 hr, 70% of the 1,4 isomer (VIII) and 30% of a mixture of the two 1,2-isomers were formed.



IX

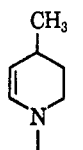
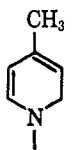
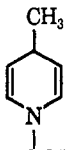
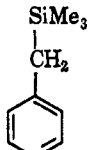


X

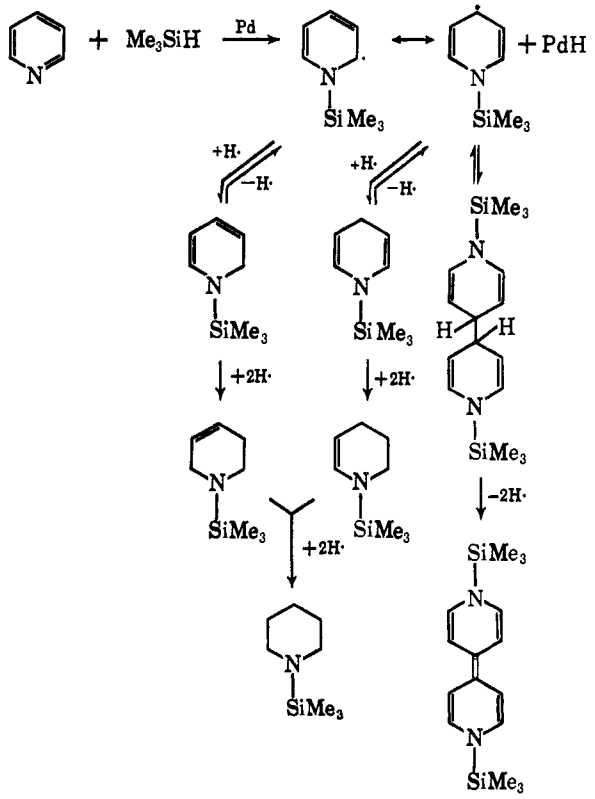
In contrast to 3-picoline, 4-picoline reacted considerably slower and gave as the major product a material (XIV) that was unexpected, No dimerized or disilylated products were observed (Table III).

A simple mechanism appears to be operating in all of these silylation reactions. The addition of the trimethylsilyl group to pyridine must occur on the surface of the palladium where intermediate resonance hybrids (probably radicals) are formed that (1) add hydrogen to give III and IV and (2) couple to make the reduced form of VII, which immediately loses hydrogen and

Table III

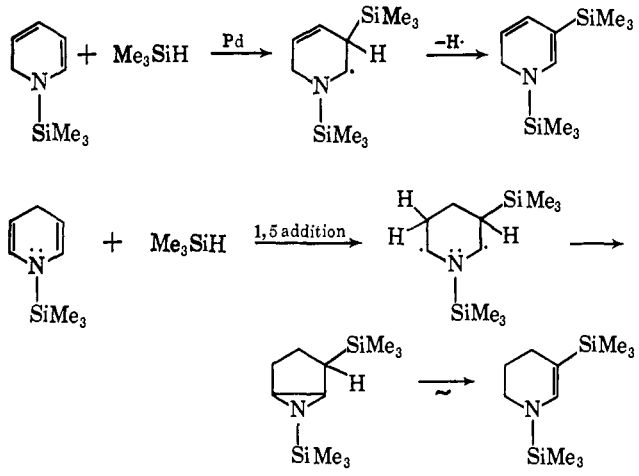
Reaction conditions	Me_3SiH consumed, %	Yield of products, % XI	XII	XIII	XIV
					
35–40°, 40 hr	95	35	5	20	40
50°, 5 hr					
24°, 5 days	90	30	18	17	35

forms VII. The hydrogen reacts with III and IV to give I and II and a trace of N-trimethylsilylpiperidine.



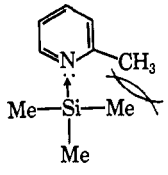
A marked similarity exists between these reactions and other metal addition reactions to pyridine.[6]

Further silylation of III and IV is probably the source of V and VI. The mechanism is not clear but it may be as follows.



It seems improbable that reduction of VI would yield the large amount of V produced, since VI was always isolated in relatively small amounts, and should not be more susceptible to reduction than III and IV.

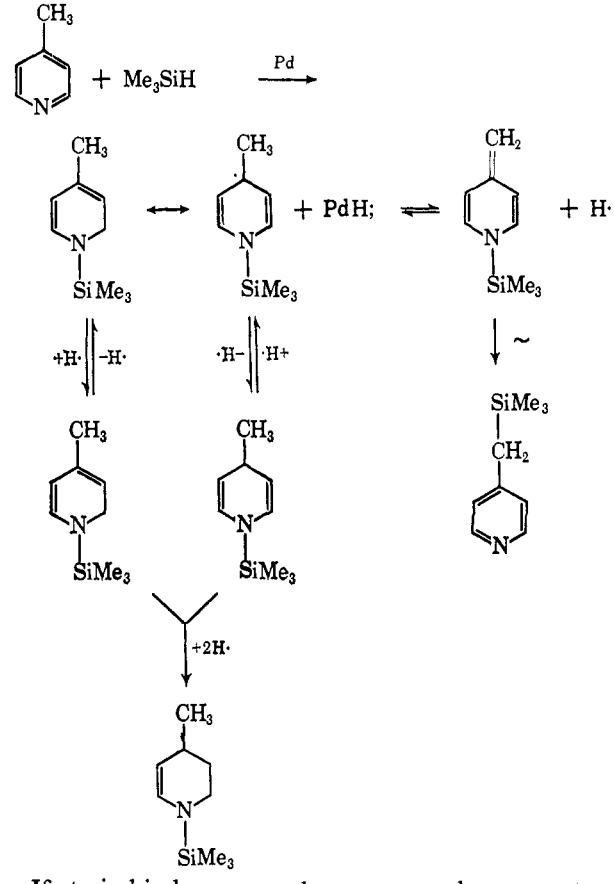
The silylation of the picolines must occur in a manner analogous to that of pyridine but steric hindrance of the methyl groups exerts a considerable effect on the products formed. The 2-picoline did not silylate at room temperature but did show a small trace of reaction after 24 hr at 50°. Inspection of the silylated model shows a great deal of crowding between the 2-methyl and 1-trimethylsilyl groups, thus hindering attack at the nitrogen.



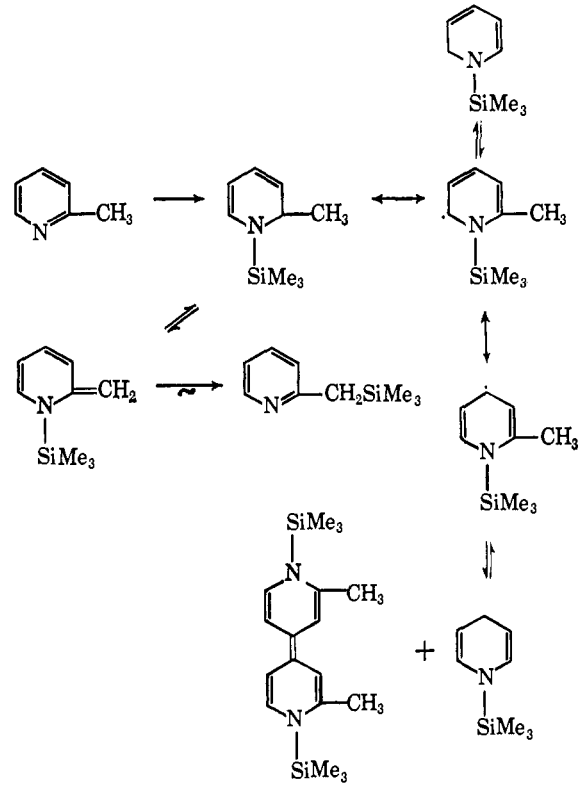
Also the steric effect of the methyl group in the silylation of 3-picoline prevents the dimerization of the 4 radical and subsequent hydrogenation of the silylated derivatives. This, coupled with the fact that disilylation did not occur, led to essentially a quantitative yield of only one product in the 40° silylation of 3-picoline.

Under slightly milder conditions, however, where equilibrium was not obtained, the 3-picoline gave the 1,2-dihydro derivatives, but the more sterically hindered material (IX) was formed in higher amounts than the other 1,2 isomer (X).

Compounds XI, XII, and XIII from the silylation of 4-picoline are analogous to products of silylation of pyridine and 3-picoline. The presence of XI, however, should be accompanied by the formation of a dimer or some other material that had furnished hydrogen for the reduction. Compound XIV is such a material. The radical intermediate probably lost hydrogen instead of coupling and formed 1-trimethylsilyl-4-methylene-1,4-dihydropyridine. This intermediate was probably present but rearranged in the injection port of the vpc to compound XIV. If compound XIV had been produced in the reaction mixture, it would probably have silylated further. There was no trace of disilylated products or any other materials boiling higher than compound XIV. (Efforts are presently being made to isolate the methylene isomer.) In the boat form of the compound the silicon approaches very closely to the carbon of the methylene group, making a rearrangement likely.



If steric hindrance can be overcome by more strenuous conditions, 2-methylpyridine will probably re-



(6) See ref 1, pp 53–56.

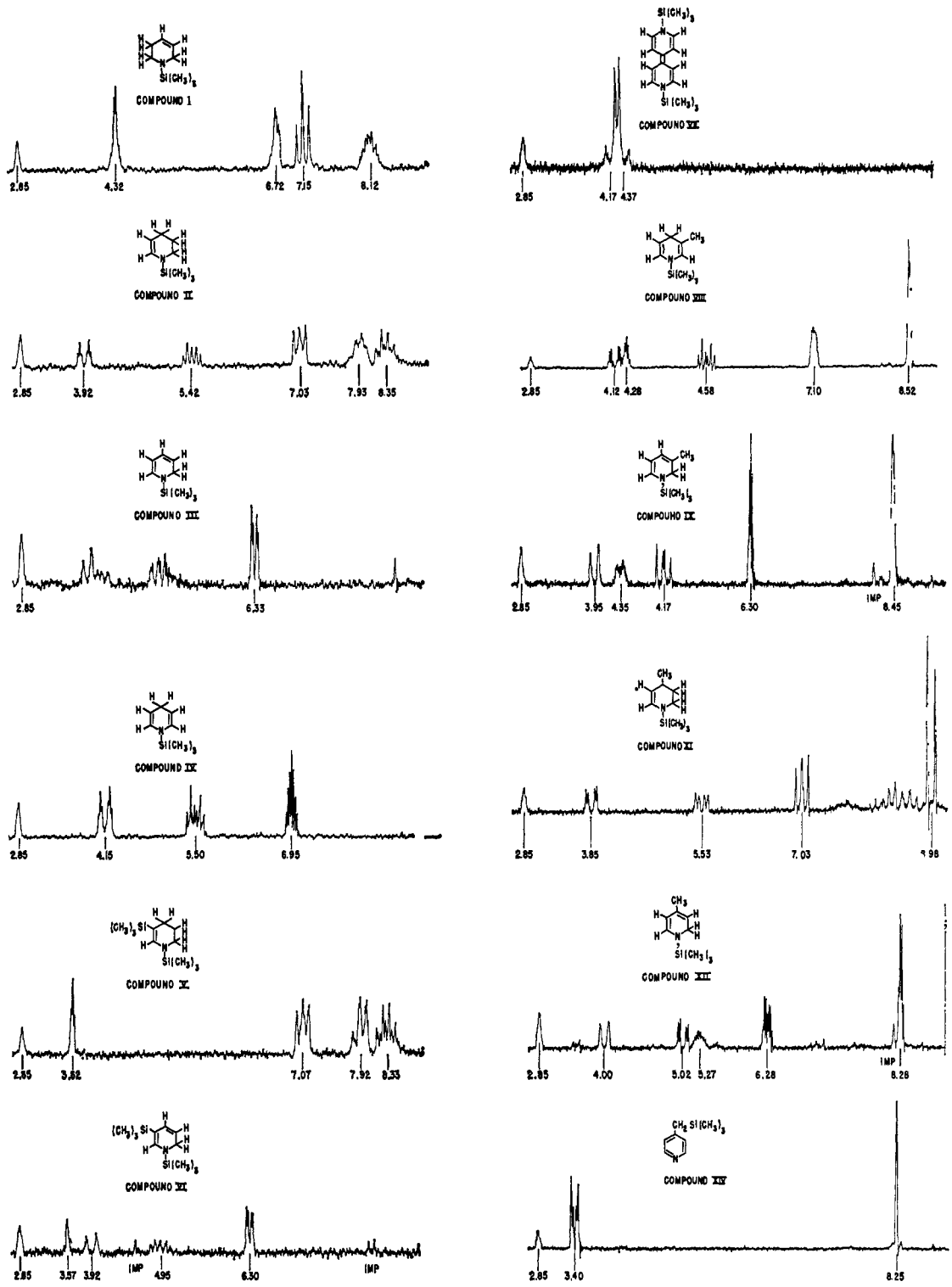


Figure 1. Nmr spectra of silylated pyridine derivatives.

semble both pyridine and 4-methylpyridine in its silylation. Since 3-methylpyridine cannot yield a radical mesomer with the electron in the 3 position, it does not produce any silylation on the methyl group.

The chemical reactions of these compounds will be reported in a subsequent paper. Briefly, however, it can be said that hydrogenation occurs readily over palladium to yield piperidines; oxidation is very rapid and vigorous to yield among other products pyridines and silanols; reaction with water and alcohols is slow unless catalyzed by base or acids to yield N-hydrodihydropyridines;[4] and halides react sluggishly in most cases to yield N-substituted dihydropyridines.

Properties and Proof of Structure

The properties and proof of structure of the new compounds prepared in this work are summarized in Table IV and Figure 1. Proton magnetic resonance, measured in deuteriobenzene with residual hydrogens generating a reference signal at τ 2.85, was the principal method used in establishing structure. Ultraviolet absorption spectra were in excellent agreement with those of anal-

Table IV. Properties of Silylated Pyridines

Compd no	Bp, °C (mm)	$n^{25}D$	Appearance	Infrared spectrum: Absorption freq, cm^{-1}	Infrared spectrum: Assignment	Ultraviolet spectrum[a]: Absorption freq, mμ	Ultraviolet spectrum[a]: Assignment
I	43 (70)	1.4527	Colorless liquid	3040 (m)	=C—H stretching	None	C—C=C—C
				1246 (s)	Me_3Si, sym def		
II	49 (6.5)	1.4568	Colorless liquid	3060 (m)	=C—H stretching	0.227	—C=C—N̈—
				1633 (s)	C=C stretching		
				1250 (s)	Me_3Si, sym def		
III	181 (atm)	1.4852	Pale yellow liquid	3050 (m)	=C—H stretching		
				1625 (m) and 1552 (s)	C=C stretching	0.320, 0.220	—C=C—C=C—N̈—
				1250 (s)	Me_3Si, sym def		
IV	57 (6.7)	1.4839	Colorless liquid	3060 (m)	=C—H stretching		
				1675 (s) and 1633 (m)	C=C stretching	0.288, 0.208	—C=C—N̈—C=C—
				1253 (s)	Me_3Si, sym def		
V	72 (2.6)	1.4714	Colorless liquid	3042 (w)	=C—H stretching		$SiMe_3$ | —C=C—N̈—
				1590 (s)	C=C stretching	0.237	
				1245 (s)	Me_3Si, sym def		
VI	70 (0.7)	1.4772	Pale yellow liquid	3040 (m)	=C—H stretching		$SiMe_3$ | —C=C—C=C—N̈—
				1615 (m) and 1540 (s)	C=C stretching	0.325, 0.255	
				1250 (s)	Me_3Si, sym def		
VII	Mp 167		Dark red crystals	3060 (m)	=C—H stretching		C=C, C=C, —N, C=C, N—, C=C, C=C
				1650 (s) and 1562 (w)	C=C stretching	0.380, 0.360, 0.220	
				1250 (m)	Me_3Si, sym def		
VIII	68 (6.1)	1.4872	Colorless liquid	3052 (m)	=C—H stretching		
				1692 (s) and 1628 (s)	C=C stretching	0.285, 0.216	—C=C—N̈—C=C—
				1252 (s)	Me_3Si, sym def		
IX	70 (6.1)	1.4884	Pale yellow liquid	3030 (m)	=C—H stretching		C | —C—C=C—C=C—N̈—
				1659 (m) and 1578 (s)	C=C stretching	0.321	
				1250 (s)	Me_3Si, sym def		
X	70 (6.1)		Pale yellow liquid			0.314	C | —C—C=C—C=C—N̈—
XI	195 (atm)	1.4639	Colorless liquid	3040 (m)	=C—H stretching		
				1626 (s)	C=C stretching	0.228	—C=C—N̈—
				1250 (s)	Me_3Si		
XII	200 (atm)	1.4883	Yellow liquid	3050 (m)	=C—H stretching		
				1654 (m) and 1568 (s)	C=C stretching	0.318	—C=C—C=C—N̈—
				1250 (s)	Me_3Si sym def		
XIII	202 (atm)	1.4825	Colorless liquid	3040 (s)	=C—H stretching		
				1670 (s) and 1608 (m)	C=C stretching	0.262, 0.215	—C=C—N̈—C=C—
				1251 (s)	Me_3Si, sym def		
XIV	210–212 (atm)	1.4975	Colorless liquid	1250 (s)	Me_3Si, sym def	0.257	

[a] Ultraviolet spectral data on analogous compounds are to be found in ref 7–9.

ogous compounds.[7–9] Chemical reactions, especially hydrogenation and oxidation, gave confirmatory support, but most of these data will be presented in a paper now in preparation.

Proton Magnetic Resonance Spectra

Compound I. Comparison of the proton magnetic resonance spectrum of compound I (Figure 1) with that of 1,2,5,6-tetrahydropyridine[10] leaves no doubt as to the identity of compound I. The splitting patterns are identical and the chemical shifts are very nearly so.

Compound II. The spectrum of compound II (Figure 1) is consistent only with the α,β-unsaturated silylamine. In particular, a pair of triplets at τ 3.92 is in direct support of this structure.

Compound III. A comparison of the spectrum of compound III (Figure 1) with that reported for 1-phenyl-1,2-dihydropyridine[8] shows a general similarity in splitting patterns and chemical shifts. Of particular importance is a set of doublets at τ 6.33 due to the methylene hydrogens adjacent to the ring nitrogen. It is concluded, therefore, that compound III has the

(7) N. Leonard and D. Locke, *J. Am. Chem. Soc.*, 77, 437 (1955).
(8) M. Saunders and E. H. Gold, *J. Org. Chem.*, 27, 1439 (1962).
(9) E. M. Kosower and T. S. Sorenson, *ibid.*, 27, 3764 (1962).
(10) "NMR Spectra Catalogue," Vol. I, Varian Associates, Palo Alto, Calif., 1962.

1,2-dihydro structure while compound IV is the 1,4-dihydropyridine.

Compound IV. Comparison of the spectrum of compound IV (Figure 1) with that reported for 1-phenyl-1,4-dihydropyridine[8] shows the splitting patterns to be identical while the chemical shifts are comparable. In particular, a seven-line pattern at τ 6.95 arising from the methylene protons appears to be characteristic of N-substituted 1,4-dihydropyridines.

Compound V. The spectrum of compound V (Figure 1) shows a single vinyl proton at τ 3.62 allylically coupled to one methylene. The low τ value for the vinyl proton shows it to be next to the nitrogen. Thus, the positions of both the vinyl proton and the second trimethylsilyl group are fixed. The spectrum further shows three groups of two protons, each assignable to three different kinds of methylene protons. Each of these groups is a complex multiplet. The only structure compatible with this spectrum is V.

Compound VI. The spectrum of compound VI closely resembles that of 1-trimethylsilyl-1,2-dihydropyridine. In particular, the pair of doublets at τ 6.30 has the identical pattern and chemical shift of the methylene in 1-trimethylsilyl-1,2-dihydropyridine (τ 6.33). This fixes the position of the methylene and supports the infrared and ultraviolet evidence of a 1,2-dihydropyridine. The splitting patterns of the three vinyl protons establish the position of the second trimethylsilyl group in the molecule.

Compound VII. The spectrum of compound VII (Figure 1) showed only trimethylsilyl protons at τ 10.0 and vinyl protons at 4.17 to 4.37 in the ratio of 9:4. The vinyl protons appear as an A_2B_2 pattern indicating that there are only two types of spin-coupled protons in the compound. The only reasonable structure consistent with this spectrum is that of VII.

Compound VIII. The presence of only two vinyl protons adjacent to the ring nitrogen at τ 4.12 indicates that this compound has the 1,4-dihydropyridine structure. The rest of the patterns are completely consistent with this structure, as is apparent on inspection of the spectrum.

Compound IX. That compound IX (Figure 1) must be a 1,2-dihydropyridine is shown by the presence of three protons adjacent to the ring nitrogen, a vinyl proton at τ 3.95 and a pair of methylene protons at 6.30. The vinyl proton α to nitrogen is a doublet further split by allylic coupling with proton D. Such a pattern rules out the 1,6-dihydropyridine structure.

Compound X. This material was never isolated in sufficient quantity and purity to determine its proton magnetic resonance spectrum.

Compound XI. The spectrum of compound XI (Figure 1) is consistent only with the α,β-unsaturated tetrahydropyridine. The α proton is a pair of doublets at τ 3.85 arising from splitting by the adjacent vinyl proton and further splitting due to allylic coupling with the single proton in the 4 position. This pattern also shows that the methyl group, which appears as a doublet due to coupling with the 4 proton, must occupy the 4 position on the ring. That the patterns of the other protons are consistent with this structure can be seen by inspection of the spectrum.

Compound XII. The spectrum confirms the assignment of compound XII. The chemical shifts of the protons of this compound are similar to those of 1-trimethylsilyl-1,2-dihydropyridine. That the patterns conform to a 1,2-dihydropyridine structure and not a 1,4-dihydropyridine structure is apparent on inspection of the spectrum, and comparing it with the others shown in Figure 1.

Compound XIII. This compound was not isolated in sufficient quantity to determine its proton magnetic resonance spectrum.

Compound XIV. 4-Trimethylsilylmethylpyridine. The proton magnetic resonance spectrum provides excellent evidence for this structure. Three different types of protons are observed, two of which are aromatic at τ 1.55 and 3.40, the other of which is aliphatic at 8.25. The only reasonable structure consistent with this spectrum is XIV.

Experimental Section

Silylation of Pyridine (T_{max} = 42°). A 1-l., round-bottom flask equipped with a magnetic stirrer, thermometer, silane inlet tube, and Dry Ice condenser which was connected to a nitrogen bypass, was charged with 400 ml of dry pyridine (freshly distilled from CaH_2) and 8 g of dry catalyst (10% Pd on carbon; Matheson Coleman and Bell). Trimethylsilane (48 g) was added to the stirred suspension over a 2-hr period, the temperature rising to 42°. After stirring at room temperature under nitrogen for 3 days, the mixture was filtered free of catalyst in a dry nitrogen box. The material was then distilled at a pressure of 2 μ and 100° in a rotary film evaporator in the absence of air or moisture, and the distillate was collected in a Dry Ice cooled receiver. A deep red residue which solidified on cooling remained in the flask. It was purified by recrystallization from benzene or cyclohexane (brilliant red needles) or by fractional sublimation of the residue. The compound (60–80 g, 24–36%) was shown to be N,N′-bistrimethylsilyl-1,1′-dihydro-4,4′-bipyridine (VII), mp 165–167°.

Anal. Calcd for $C_{16}H_{26}N_2Si_2$: C, 63.6; H, 8.6; N, 9.2; Si, 18.5. Found: C, 63.8; H, 8.7; N, 9.0; Si, 18.5.

The distillate contained six compounds which were partially fractionated on a spinning-band column and then isolated in the pure state by vapor phase chromatography (F & M) through a 12-ft Carbowax column. The temperature was programmed from 50 to 200° at a rate of 7.9°/min. Effective separation and reproducible curves were obtained only after proper conditioning of the column. This involved heating at 220° for 24 hr while pure helium was passed through the column followed by treatment with five to ten 30-mg samples of the silylamines over a 24-hr period to purge the column of reactive materials. Pure materials of 1–20-mg size were then collected in Freon-cooled melting point tubes (12 in. long) for elemental analysis, refractive indices, and infrared, ultraviolet, and nmr spectra.

1-Trimethylsilyl-1,2,3,6-tetrahydropyridine (I) weighed 1.9 g (0.8%), bp 43° (7 mm).

Anal. Calcd for $C_8H_{17}NSi$: C, 62.0; H, 10.9; N, 9.1; Si, 18.1. Found: C, 61.7; H, 10.9; N, 9.1; Si, 18.3.

1-Trimethylsilyl-1,2,3,4-tetrahydropyridine (II) weighed 14.9 g (6.6%), bp 49° (7 mm).

Anal. Calcd for $C_8H_{17}NSi$: C, 62.0; H, 10.9; N, 9.1; Si, 18.1. Found: C, 61.8; H, 10.9; N, 9.2; Si, 18.3.

1-Trimethylsilyl-1,2-dihydropyridine (III) showed a trace, bp 53° (7 mm).

Anal. Calcd for $C_8H_{15}NSi$: C, 62.8; H, 9.8; N, 9.15. Found: C, 62.7; H, 10.0; N, 9.2.

1-Trimethylsilyl-1,4-dihydropyridine (IV) weighed 96 g (42.7%), bp 57° (7 mm).

Anal. Calcd for $C_8H_{15}NSi$: C, 62.8; H, 9.8; N, 9.15; Si, 18.3. Found: C, 62.8; H, 10.0; N, 9.1; Si, 18.2.

1,5-(Ditrimethylsilyl)-1,2,3,4-tetrahydropyridine (V) weighed 20 g (8.9%), bp 70° (2.5 mm).

Anal. Calcd for $C_{11}H_{25}NSi_2$: C, 58.2; H, 11.0; N, 6.2; Si, 24.7. Found: C, 58.5; H, 11.1; N, 6.4; Si, 25.5.

1,5-(Ditrimethylsilyl)-1,2-dihydropyridine (VI) weighed 1.9 g (0.8%), bp 72° (2.5 mm).

Anal. Calcd for $C_{11}H_{23}NSi_2$: C, 58.7; H, 10.2; N, 6.2; Si, 24.8. Found: C, 59.5; H, 10.2; N, 6.6; Si, 25.0.

The nmr (Figure 1), infrared, and ultraviolet spectra (Table IV), elemental analysis reported above, and hydrogenation and

oxidation reactions (see below) completely confirm the structure assignments of the above compounds.

Silylation of Pyridine (T_{max} = 30°). A 3-l., round-bottom flask was equipped with a vibromixer stirrer, thermometer, silane inlet tube, a joint containing a small silicone rubber septum for siphoning samples through a syringe, and a Dry Ice condenser connected to a nitrogen bypass. To the thoroughly dry flask was added 1 l. of dry pyridine and 12 g of catalyst (10% Pd on carbon). Trimethylsilane (303 g) was added to the violently agitated suspension over an 80-min period and the temperature was kept below 30° by immersion in a water bath. Vigorous stirring was continued for 24 hr during which time the progress of reaction was periodically checked by vpc analysis. After 95% of the silane was consumed by the pyridine, the mixture was transferred to a dry nitrogen box and filtered free of catalyst in 4 hr. The material was distilled at 100° under reduced pressure in a rotary film evaporator. The system was kept free of air and the distillate was collected in a Dry Ice cooled receiver. A deep red residue, N,N′-bistrimethylsilyl-1,1′-dihydro-4,4′-bipyridine (VII), 144 g (25% by weight of total product) which crystallized on cooling, remained in the flask. Fractionation of the distillate in a spinning-band column followed by vpc analysis showed six products listed in Table I. Comparisons of refractive indices, infrared spectra, and vpc retention times with authentic samples identified the compounds.

Silylation of Pyridine (T_{max} = 0°). One gram of catalyst (10% Pd on carbon) was refluxed for 15 hr in 25 ml of dry pyridine; the catalyst was allowed to settle and filtered free of pyridine. The catalyst was then mixed with 50 ml of dry pyridine in a thoroughly dry 100-ml, round-bottom flask equipped with a magnetic stirrer, thermometer, silane inlet tube, and Dry Ice condenser connected to a N_2 bypass. The pot was immersed in an ice bath and trimethylsilane (12 g) was added to the stirred suspension over a 50-min period, the temperature never exceeding 2°. The mixture was stirred under dry nitrogen at 0°, and the extent of reaction was periodically checked by vpc. After 11 days the silane had decreased by 37%. (The yield of products totaled 34% of the theoretical.) Distillation on a small spinning-band column yielded 6.1 g (72%) of distillate and 2.33 g (28%) of a red solid, N,N′-bistrimethylsilyl-1,1′-dihydro-4,4′-bipyridine. Vpc analysis on a 12-ft Carbowax column with authentic samples as comparisons showed the composition of the liquid as reported in Table I.

Silylation of Pyridine (T_{max} = 80°). Trimethylsilane (4.5 g) was bubbled into a magnetically stirred suspension of hot dry pyridine (20 ml) and Pd catalyst (10% on carbon) (0.5 g) over a period of 4 hr. The silane vapors were returned to the flask by a Dry Ice condenser and the system was kept under a blanket of nitrogen at all times. The temperature dropped from 80° at the start of addition to 60° after all of the silane had been added. Stirring was continued for an additional 4 hr at 60–65°. The mixture was cooled to room temperature and vpc showed that approximately 60% of the trimethylsilane had been consumed. The catalyst was allowed to settle over a 15-hr period and the mixture was filtered in a dry nitrogen box. Distillation of the filtrate on a small spinning-band column yielded 3.5 g of distillate and a 0.5-g residue of red solid N,N′-bistrimethylsilyl-1,1′-dihydro-4,4′-bipyridine (VII). The composition of the distillate is shown in Table I. Vpc was used as before to identify these compounds.

Silylation of Pyridine with Different Catalysts. Into each of six 100-ml, round-bottom flasks equipped with magnetic stirrer, gas inlet, N_2 bypass, Dry Ice condenser, and thermometer, 50 ml of dry pyridine and catalyst as shown below were added. Trimethylsilane (9 g) was then added to each in 11–13 min at room temperature and the course of the reaction was then followed by vpc to determine the extent of the reaction (see Table V).

Rhodium gave only IV with no trace of the other products given by palladium. Raney nickel between 70 and 115° gave 1% reaction after 21 hr, 2% after 48 hr, and 4.5% after 60 hr. All the products produced by palladium were found.

Table V

Catalyst	Reaction, %
0.5 g of 5% Pd–C	1 day, 45; 2 days, 87; 3 days, 95
0.5 g of 5% Rh–C	1 day, 23; 2 days, 48; 3 days, 72
0.5 g of Pd Cl_2	1 day, 3; 5 days, 39; 6 days, 54
0.1 g of Ni_{Raney}	1 day, trace; 2 days, 1; 3 days, 2
0.5 g of 5% Pt–C	1 day, 0; 3 days, trace ...
0.5 g of 5% Ru–C	1 day, 0 ...

Isomerization of 1-Trimethylsilyl-2-hydro-1,2-dihydropyridine (III) with Palladium Catalyst. A small test tube charged with 50 mg of 1-trimethylsilyl-1-2-dihydropyridine, 200 mg of dry pyridine (distilled over CaH_2 under N_2), and 50 mg of Pd on carbon, sealed under nitrogen, was shaken for 40 hr and centrifuged. The supernatant liquid was deep red in color, indicating the presence of a large amount of N,N′-bistrimethylsilyl-1,1′-dihydro-4,4′-bipyridine. Due to the small scale of the reaction, the yield of red solid was not determined, but by difference and by matching oxidized to reduced material (II), there was approximately 50% N,N′-(ditrimethylsilyl)-4,4′-bipyridyl. Found in the mixture were: I, trace; II, 25% (13 mg); III, 1–2%; IV, 18% (9 mg); V, 5%; VI, 1%. Compounds II and IV were collected from the vpc and identified by infrared spectra and refractive index. I, III, V, and VI were identified by retention times of vpc analysis. No other materials were observed.

Silylation of 3-Picoline. A 100-ml, round-bottom flask was equipped with a magnetic stirrer, thermometer, silane inlet tube, a joint containing a small silicone rubber septum for siphoning samples through a syringe, and a Dry Ice condenser connected to a nitrogen bypass. To the thoroughly dry flask was added 40 ml of dry 3-picoline and 0.5 g of dry Pd catalyst (10% on carbon). Trimethylsilane (10 g) was added to the stirred suspension over a 40-min period, the temperature rising to a maximum of 32° and then dropping to 24°. The reaction mixture was stirred at 24° for 18 hr under dry nitrogen. At this point over 95% of the trimethylsilane had been consumed and the mixture was transferred to a dry nitrogen box where it was filtered free of catalyst immediately. The 3-picoline was distilled off at reduced pressure in a system free of air and moisture. The residue contained three compounds which were isolated in the pure state by vpc.

1-Trimethylsilyl-3-methyl-1,4-dihydropyridine (VIII) was recovered (70%), bp 68° (4 mm).

Anal. Calcd for $C_9H_{17}NSi$: C, 64.7; H, 10.2; N, 8.4; Si, 16.8. Found: C, 65.5; H, 10.3; N, 8.4; Si, 16.8.

1-Trimethylsilyl-3-methyl-1,2-dihydropyridine was recovered, bp 70° (6.1 mm).

Anal. Calcd for $C_9H_{17}NSi$: C, 64.7; H, 10.2; N, 8.4. Found: C, 64.5; H, 10.2; N, 8.5.

1-Trimethylsilyl-3-methyl-1,6-dihydropyridine was recovered, bp 70° (6.1 mm).

The yield of 1,2 and 1,6 isomers combined was 30%. It was possible to isolate the 1,2 isomer in the pure state by vpc, but not the 1,6 isomer. The structure of the 1,6 compound was determined by measurements made on mixtures of the two isomers. For instance, a C, H, N analysis of the mixture was identical with that of the 1,2 compound alone; hence the compounds are isomeric. Spectroscopic evidence further elucidated the structure.

When the same reaction was run keeping the temperature of the stirred mixture at 40° for 1 day, the only product observed was 1-trimethylsilyl-3-methyl-1,4-dihydropyridine isolated in better than 90% yield.

Silylation of 4-Picoline. A 100-ml, round-bottom flask was equipped with a magnetic stirrer, thermometer, silane inlet tube, a joint containing a small silicone rubber septum for siphoning samples through a syringe, and a Dry Ice condenser connected to a nitrogen bypass. To the thoroughly dry flask was added 33 ml of dry 4-picoline and 0.5 g of dry Pd catalyst (10% on carbon). Trimethylsilane (9 g) was added to the stirred suspension over a 45-min period, the temperature rising to a maximum of 32% and then dropping to 24°. The reaction mixture was stirred at 24° for 5 days after which time the mixture was filtered and the 4-picoline distilled off under dry N_2 at reduced pressure. The residue contained four compounds which were isolated in the pure state by vpc.

1-Trimethylsilyl-4-methyl-1,4-dihydropyridine (XIII) was recovered (16%), bp ~202° (1 atm).

Anal. Calcd for $C_9H_{17}NSi$: C, 64.7; H, 10.2; N, 8.4. Found: C, 65.0; H, 10.2.

1-Trimethylsilyl-4-methyl-1,2-dihydropyridine (XII) was recovered (17%), bp ~200° (1 atm).

Anal. Calcd for $C_9H_{17}NSi$: C, 64.7; H, 10.2; N, 8.4. Found: C, 65.1; H, 10.1; N, 8.8.

1-Trimethylsilyl-4-methyl-1,2,3-4-tetrahydropyridine (XI) was recovered (31%), bp ~195° (1 atm).

Anal. Calcd for $C_9H_{19}NSi$: C, 63.9; H, 11.2; N, 8.3. Found: C, 64.0; H, 11.3; N, 8.3.

4-Trimethylsilylmethylpyridine (XIV) was recovered (32%), bp 211° (1 atm).

Anal. Calcd for $C_9H_{15}NSi$: C, 65.5; H, 9.1; N, 8.5. Found:

C, 65.7; H, 9.4; N, 8.7.

When the same reaction was run keeping the temperature of the stirred mixture at 35–40° for 40 hr and 50° for 5 hr, 95% of the silane was consumed and the yields were: 35% of XI, 40% of XIV, 20% of XIII, and 5% of XII, based on 4-picoline reacted.

Silylation of 2-Picoline. When trimethylsilane was passed into a stirred suspension of Pd catalyst (10% on carbon) in dry 2-picoline in the same manner used for the other picolines, no reaction was observed. A faint trace (<1%) of reaction was observed after heating the material to 50° for 2 days, but the reaction was not continued to a point where any products could be isolated.

Hydrogenation of Products. Compounds II (44 mg), IV (45 mg), V (15.3 mg), and VII (50 mg) were hydrogenated in a microhydrogenation apparatus. Palladium catalyst (10% on charcoal) equal in weight to that of the compound was added to 10 ml of dry, O_2-free isooctane containing the material to be reduced. Quantitative absorption of H_2 in 5–10 min was observed for one double bond in II, and two double bonds in each of IV and V. Compounds II and IV gave material which had the same retention time as trimethylsilylpiperidine.

Compound VII took 15 hr for reduction and absorbed 80% of the theoretical amount for the five double bonds, going from a dark red to a colorless compound. Failure to get theoretical absorption was probably due to small amounts of oxidation that were extremely difficult to avoid.

Oxidation of N,N′-Bistrimethylsilyl-1,1′-dihydro-4,4′-bipyridine. Compound VII (0.764 g) was dissolved in 15 ml of anhydrous diethyl ether and dry air was bubbled through the solution for 4 min. The solution became yellow and after pulling off the volatiles (at 1 μ for 3 days) a mixture of tan crystals and a brown gum was obtained. From this mixture a 50% yield of 4,4′-bipyridine (white crystals, mp 111–113°) was obtained by recrystallization from isooctane.

Spectra. All ultraviolet spectra were recorded using a Cary recording spectrophotometer, Model 14, and made in dry, oxygen-free spectrograde cyclohexane.

Infrared data were obtained using a Perkin-Elmer 521 grating infrared spectrophotometer. The spectra were run on neat solutions in a microcell (0.15mm).

The proton magnetic resonance spectra were recorded with a Varian A-60 spectrometer. Measurements were made on 10–20% solutions in deuteriobenzene. Shifts were measured relative to the residual protons of deuteriobenzene. These have been converted to shifts relative to TMS by noting that the residual protons of deuteriobenzene appear 429 cps downfield from tetramethylsilane. The signals of the methylsilyl groups are not shown in the spectra of Figure 1 since they do not contribute to the elucidation of the structures.

Synthesis of 1-Epicyclocolorenone and Stereochemistry of Cyclocolorenone[1]

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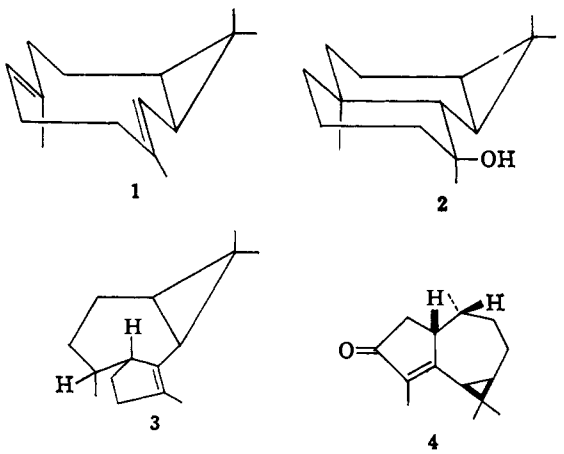
Contribution from the Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts. *Received April 9, 1966*

Abstract: 1-Epicyclocolorenone (**22**) has been synthesized from O-acetylisophotosantonic acid lactone (**6**). With the aid of optical rotatory dispersion and proton magnetic and ultraviolet spectroscopy, the stereochemistry of the synthetic product was elucidated. The naturally occurring cyclocolorenone is unstable in relation to its C_1 epimer (**22**) and the former isomer consequently has the relative and absolute configuration shown in **21**.

The sesquiterpene ketone cyclocolorenone was first isolated from *Pseudowintera colorata*,[3] a shrub endemic to New Zealand and, more recently, from *Compositae* species.[4] Its gross structure was established some time ago[3] but both relative and absolute stereochemistry remained unknown.

We assumed that the cyclodecane derivative **1**[5] derived from all-*trans*-farnesol is involved in the biosynthesis of cyclocolorenone. As previously pointed out[5] transannular, antiplanar Markovnikov-oriented addition of water gives maaliol (**2**). If proton addition to the first double bond follows an anti-Markovnikov course and if the cyclization process terminates by proton loss, a tricyclic hydrocarbon (**3**) results which subsequently could be oxidized to cyclocolorenone (**4**).



1 2 3 4

To provide experimental support for the stereochemical consequences of this suggestion, we attempted a synthesis of cyclocolorenone (**4**), and the readily available O-acetylisophotosantonic acid lactone (**6**)[6] was chosen as starting material. Treatment with concentrated sulfuric acid gave the previously described dienone lactone **7**[6] identical with a sample prepared

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