exo-**7-Acetoxy-1,6-dimethylbicyclo[4.1.0]heptane.**[18]—To a solution of 5.0 g (29.8 mmoles) of *exo* acid, mp 137–139°, in 100 ml of anhydrous ether, was added with stirring 160 ml of a solution of methyllithium in ether containing 59.6 mmoles of total base as determined by titration. After 5 min the reaction mixture was worked up, yielding 1.75 g of recovered starting material, mp 136–139°, and 3.34 g of neutral product. The small amount of less volatile tertiary alcohol (2.87 μ) contaminating the product was removed by distillation through a spinning-band column at oil pump pressure which gave 2.08 g of ketone (65% based on unrecovered acid): bp 29–30° (0.2 mm); λ_{max}^{film} 5.92 μ; $\lambda_{max}^{95\%\ EtOH}$ 210 mμ (ϵ 6800); τ (CCl_4) 7.89 (3 H) and 8.80 (6 H).

To a slurry of 2.00 g (12.0 mmoles) of ketone and 26 g of dibasic sodium phosphate in 80 ml of methylene chloride was added, with stirring, a solution of peroxytrifluoroacetic acid prepared by adding, with stirring, 1.0 ml (37 mmoles) of 90% hydrogen peroxide and 6.2 ml (44 mmoles) of trifluoroacetic anhydride to 15 ml of ice-cooled methylene chloride. Work-up gave 1.50 g of crude product which was first subjected to short-path distillation (oil bath 105–140°) and then preparative gc. Material corresponding to the major peak (85%) at 6.7 min was collected: λ_{max}^{film} 5.73 μ; τ (CCl_4) 6.42 (1 H) 8.00 (3 H), 9.03 (6 H).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.53; H, 9.89. Found: C, 72.76; H, 10.07.

Conversion of the cyclopropyl acetate to cyclopropanol was effected by using freshly distilled solvents for each run (including work up). Typically, a solution of 37 mg of acetate in a mixture of 2.5 ml of methanol and 1.5 ml of 0.3 *N* sodium hydroxide solution was allowed to stand at room temperature for 50 min under nitrogen. Water (10 ml) was then added and the mixture was extracted with three 3-ml portions of pentane. The combined extracts were washed with 2 ml of water and then dried over sodium sulfate. Evaporation of solvent left a white solid showing hydroxylic (2.8 and 2.9 μ) but no carbonyl absorption; τ ($CDCl_3$) 6.93 (1 H), 8.07 (1 H), 8.98 (1 H, singlet superimposed on complex absorption).

The white solid from one run was treated with excess acetic anhydride in pyridine. Work-up, using carbon tetrachloride as solvent, gave a solution showing the same nmr absorption as starting acetate. Capillary gc of the concentrated solution showed, apart from solvent, only one peak with a retention time corresponding to that of starting acetate.

endo-**7-Acetoxy-1,6-dimethylbicyclo[4.1.0]heptane** was similarly prepared[18] from *endo* acid, mp 120–122°; 1.450 g of the acid yielding 0.800 g of crude ketone which showed only weak hydroxyl absorption in the infrared spectrum. A portion (589 mg) of this crude ketone was subjected to Baeyer–Villiger oxidation, giving 549 mg of crude product which showed on gc two major peaks in the ratio 6:1 at 5.7 and 9.3 min. Material corresponding to the peak at 5.7 min was collected and shown to be unresolved on capillary gc: $\lambda_{max}^{CHCl_3}$ 5.78 μ; τ (CCl_4) 6.71 (1 H), 7.99 (3 H) and 8.92 (1 H, singlet superimposed on complex absorption).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.53; H, 9.89. Found: C, 72.11; H, 10.03.

A portion of collected *endo* acetate was saponified and a white solid obtained as with the *exo* acetate. The solid was acetylated and the product shown by capillary gc to yield only one peak, apart from that due to solvent, with a retention time corresponding to that of starting acetate.

Cyclopropanol Openings.—In a typical run 37 mg of *exo* acetate was saponified and the resulting white solid was dissolved in 0.2 ml of a *t*-butyl alcohol solution prepared by dissolving 20 mg of potassium in 0.5 ml. This solution was transferred to an nmr tube containing 20 mg of *p*-dichlorobenzene and the tube was partially immersed in a Dry Ice bath. The tube was evacuated and filled with nitrogen several times before being sealed under vacuum. It was then placed in an oil bath at 57° and thereafter removed periodically; the nmr spectrum of the solution was recorded. After 60 hr the tube was opened, the contents were poured into 10 ml of water, and the mixture was extracted with two 3-ml portions of pentane which were combined, washed with 1 ml of water, and dried over sodium sulfate. Solvent was almost completely removed by evaporation; the product was subjected to capillary gc which showed, apart from residual solvent and *p*-dichlorobenzene (12.4 min), only two major peaks at 10.3 and 11.2 min. These retention times corresponded to those of *trans*- and *cis*-dimethyl aldehyde, respectively, as shown by peak enhancements after separate addition of authentic *trans* and *cis* aldehydes and resubjection to capillary gc. Although preparative gc could not separate the two aldehydes, material corresponding to the peak for both was collected and shown to be aldehydic, λ_{max}^{film} 3.72 and 5.81 μ.

(18) General procedures: G. Tegner, *Acta Chem. Scand.*, **6**, 782 (1952); W. D. Emmons and G. B. Lucas, *J. Am. Chem. Soc.*, **77**, 2287 (1955); C. H. DePuy and L. R. Mahoney, *ibid.*, **86**, 2653 (1964).

Synthesis and Characterization of the *cis*- and *trans*-Trimethylsilylcyclohexanols[1]

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The syntheses of the *cis*- and *trans*-3- and -4-trimethylsilylcyclohexanols are described. Catalytic hydrogenation of the *m*- and *p*-trimethylsilylphenols yielded predominantly the 3-*trans* and 4-*cis* isomers, respectively. Oxidation of these trimethylsilylcyclohexanols, followed by lithium aluminum hydride reduction, yielded predominantly the 3-*cis* and 4-*trans* isomers. The isomers were purified by elution chromatography. Structure assignments were made on the basis of the nmr spectra and were substantiated, in the case of the 4-trimethylsilylcyclohexanols, by the rates of ethanolysis of their tosylates. On the basis of the relative rates of the ethanolysis, it is concluded that the trimethylsilyl group, like the *t*-butyl group, controls the stereochemistry of the cyclohexane ring.

In the course of our investigations in the area of the synthesis and the study of the biological activity of organosilicon compounds,[3] it was desired to separate and characterize the *cis*- and *trans*-trimethylsilylcyclohexanols. The similarity of the trimethylsilyl group to the *t*-butyl group is suggestive that these silylcyclohexanols could be used to elucidate the steric influence of the trimethylsilyl group. This report deals with the synthesis and identification of these isomers.

The synthetic path leading to the isomeric 4-trimethylsilylcyclohexanols is outlined in Chart I. The synthetic steps up to the silylphenol **4** were straightforward; the methods described by Speier[4] were followed without major variation. Good yields (72–95%) were obtained in each of these steps. Speier obtained a mixture of the *cis*- and *trans*-4-trimethylsilylcyclohexanols (**5**) by hydrogenation of **3** followed by hydrol-

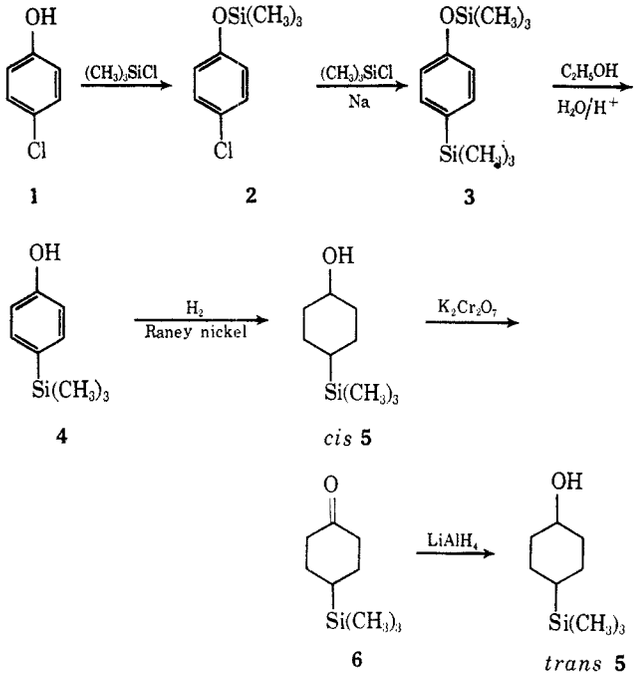
(1) (a) This work was supported in part by a grant from the National Science Foundation (GP315); (b) taken in part from the M. S. thesis of K. Seeler.

(2) Alfred P. Sloan Fellow, 1965–1967.

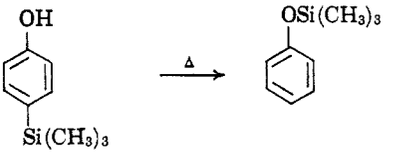
(3) R. Fessenden and M. D. Coon, *J. Med. Chem.*, **8**, 604 (1965).

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

CHART I



ysis of the resulting 4-trimethylsilyl(trimethylsiloxy)-cyclohexane. He noted that the reduction of **3** failed in certain runs for no apparent reason. In hopes of circumventing this problem in this study, the silylphenol **4** was hydrogenated. This route proved satisfactory provided that certain precautions were followed. If the Raney nickel contained trace amounts of ethanol, only cleavage products (cyclohexanols) could be detected. Successful hydrogenations of **4** were obtained only when the Raney nickel had been scrupulously washed with isooctane, the hydrogenation solvent. Temperature control was also important; at temperatures >120°, rearrangement of the silylphenol occurred.[4,5]



The hydrogenation led primarily to one of the two geometric isomers, which was later shown to be the *cis* isomer. In order to obtain a sufficient amount of the other isomer, **5** was oxidized with dichromate to the ketone **6**, which was then reduced using lithium aluminum hydride. The product contained predominantly the other isomer, later identified as the *trans* isomer. These general observations agree with the expected stereochemical courses of these reactions.[6]

The synthesis of the 3-trimethylsilylcyclohexanols (**7**) was carried out using the same synthetic path. In the one attempt to obtain the 2-trimethylsilylcyclohexanols (**8**), only cleavage products were observed in the hydrogenation step.[7]

(5) G. D. Cooper, *J. Org. Chem.*, **26**, 925 (1961).

(6) (a) W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Am. Chem. Soc.*, **78**, 2579 (1956); (b) R. D. Schuetz and L. R. Caswell, *J. Org. Chem.*, **27**, 486 (1962).

(7) It is not surprising that this hydrogenation failed to yield **8**, since the starting *o*-trimethylsilylphenol is far more susceptible to rearrangement than the other phenols used in this study (see ref 5).

The separation of the *cis* and *trans* isomers of the 3- and 4-trimethylsilylcyclohexanols (**5** and **7**) was effected by elution chromatography. With the 4-trimethylsilylcyclohexanols, the *cis* isomer was eluted first, followed by the *trans* isomer. The chromatography was followed using analytical gas phase chromatography. These two isomers were white crystalline solids. With the 3-trimethylsilyl compounds, the *trans* isomer was eluted first, followed by the *cis* isomer. These compounds were liquid and were characterized as the solid 3,5-dinitrobenzoates.

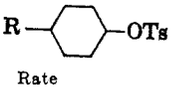
After this work was completed, preparative glpc became available. It was observed that the *cis* and *trans* isomers of both **5** and **7**, as well as *cis*- and *trans*-4-*t*-butylcyclohexanol, could be conveniently separated using either a 20-ft Carbowax or DEGS column and that the purity of the samples was conveniently assayed using thin layer chromatography.

Assignment of structure to the *cis* and *trans* isomers of **5** was based on both the rates of ethanolysis of their tosylates and the nmr spectra. Each isomer was converted to its corresponding tosylate, which was subjected to solvolysis using standard procedures. To provide standard values for reference, cyclohexyl tosylate and *cis*- and *trans*-4-*t*-butylcyclohexyl tosylates were synthesized and subjected to the same reaction conditions.

It has previously been shown that a tosylate group in an equatorial position undergoes ethanolysis at a slower rate than does a tosylate in an axial position.[8] The size of the trimethylsilyl group should be sufficiently large that it should exert some stereochemical control upon a cyclohexane ring. In particular, the relative rates of ethanolysis of the tosylates of the *cis*- and *trans*-4-trimethylsilylcyclohexanols should differ significantly and they should be similar to the ethanolysis rates of *cis*- and *trans*-4-*t*-butylcyclohexyl tosylates under the same reaction conditions. Indeed, this was observed to be the case (see Table I). The 4-trimethylsilyl isomer assigned *cis* and the *cis*-4-*t*-butylcyclohexyl tosylate underwent reaction at rates 3–5 times faster than the 4-trimethylsilyl isomer assigned *trans* and the *trans*-4-*t*-butylcyclohexyl tosylate.

TABLE I

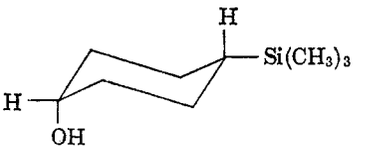
RELATIVE RATES OF ETHANOLYSIS AT 50.20 ± 0.01°



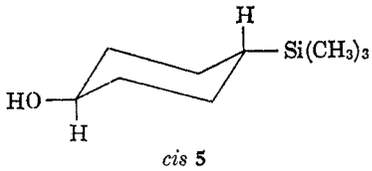
R	Rate constants, sec^{-1} × 10^6	Std dev × 10^6	Relative rate, 95% confidence levels
H	1.79	0.04	1.00 (1.00–1.00)
cis-*t*-C_4H_9	5.67	0.12	3.17 (2.90–3.45)
cis-$(CH_3)_3Si$	6.29	0.06	3.51 (3.30–3.75)
trans-*t*-C_4H_9	1.75	0.17	0.98 (0.75–1.22)
trans-$(CH_3)_3Si$	1.25	0.08	0.70 (0.55–0.82)

(8) S. Winstein and N. J. Holness, *J. Am. Chem. Soc.*, **77**, 5562 (1955).

The nmr spectra of the two 4-trimethylsilylcyclohexanols are in agreement with this structure assignment. In the 4-*t*-butyl series,[9] the 1 equatorial proton of the *cis* isomer can be seen downfield at 233 cps from TMS. The peak is relatively narrow in comparison to that of the 1 axial proton of the *trans* isomer, which is observed at 201 cps and is broad owing to axial–axial splitting.



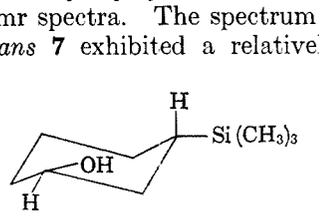
trans **5**



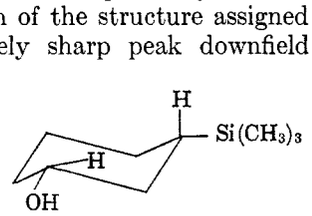
cis **5**

The same type of pattern was observed with the 4-trimethylsilylcyclohexanols. The broad peak of a 1 axial proton of *trans* **5** was observed at 203 cps, while that of the 1 equatorial proton of the *cis* isomer was relatively narrow and observed at 233 cps. The only other absorption at this frequency was due to the hydroxy proton, which could be easily distinguished by its shift after the sample had been shaken with deuterium oxide. The exact assignment of the absorption frequencies for the 1 axial or 1 equatorial protons is complicated by the partial masking of the TMS internal standard by the nine protons of the trimethylsilyl group. The values reported are based on the chloroform peak at δ 7.27 as the reference and may be in error owing to the intermolecular association of chloroform with the hydroxy group. With the exception of the singlet due to the trimethylsilyl protons, the rest of the spectrum was broad and complex.

The structure assignments for the *cis*- and *trans*-3-trimethylsilylcyclohexanols are based primarily on their nmr spectra. The spectrum of the structure assigned *trans* **7** exhibited a relatively sharp peak downfield



trans **7**



cis **7**

from TMS at 238 cps, which would correspond to absorption from the 1 equatorial proton. The nmr spectrum of the alcohol assigned the *cis* configuration showed a broad band at 204 cps, which would correspond to absorption from the 1 axial proton. As in the case with the 4-trimethylsilylcyclohexanols, absorption due to the hydroxy proton could be easily identified by its shift after the sample was shaken with deuterium oxide.

Experimental Section[10]

p-Trimethylsilylphenol.—Trimethyl (*p*-trimethylsilylphenoxy)-silane, bp 84° (1.8 mm), n^{23}D 1.4814 [lit.[4] bp 132° (25 mm), n^{25}D 1.4794], was prepared in 72% yield using the method of Speier.[4] The phenol, mp 74–75° (lit.[4] mp 74–74.2°), was obtained in 95% yield using the hydrolysis procedure of Speier.[4]

4-Trimethylsilylcyclohexanol. A. Preparation of Hydrogenation Catalyst.—The procedure described by Billica and Adkins[11] for the preparation of Raney nickel, activity W-6, was followed, up to the washing with absolute ethanol. The nickel was then transferred to a round-bottomed flask arranged with distillation take-off. Purified isooctane was added to the flask and the mixture of isooctane, water, and ethanol was codistilled. The isooctane was separated from the two-layered distillate, purified, and recycled into the distillation flask. The process was continued until the distillate contained only isooctane, as judged by boiling point (100°) and refractive index (n^{23}D 1.3888).

B. Hydrogenation.—In a hydrogenation bomb were placed 400 ml of purified isooctane, 7.5 g of ethanol-free Raney nickel, and 100.0 g (0.60 mole) of *p*-trimethylsilylphenol. A plug of glass wool was inserted into the hydrogenation vessel to disperse the catalyst. The hydrogenation was carried out with 2000 psi of hydrogen at 90–100° for 24 hr. After filtering, distillation yielded 67.8 g (65.5%) of 4-trimethylsilylcyclohexanol, bp 98–111° (8–7 mm), mp 53–57°. Gas phase chromatographic analysis of this fraction showed two peaks with an area ratio of 9:1, later shown to be due to the *cis* and *trans* isomers, respectively.

4-Trimethylsilylcyclohexanone.—In a 125-ml flask were placed 20.0 g (0.12 mole) of the isomeric mixture of 4-trimethylsilylcyclohexanols and 30 ml of glacial acetic acid. In a separate flask, 11.9 g (0.04 mole) of sodium dichromate was dissolved in 20 ml of glacial acetic acid. Both flasks were cooled to 15° and the dichromate solution was added quickly to the trimethylsilylcyclohexanol solution. The mixture was kept at 15° for 10 min, then was allowed to warm slowly. The temperature was held at 45–55° with intermittant cooling until the exothermic reaction had subsided. When the temperature had returned to room temperature, the mixture was subjected to steam distillation. The distillate was extracted with three 50-ml portions of ether, dried with magnesium sulfate, then distilled, yielding 11.7 g (60%) of 4-trimethylsilylcyclohexanone, bp 82–83° (2.8 mm), n^{23}D 1.4629. After standing overnight, the ketone solidified, mp 28–28.5°; the 2,4-dinitrophenylhydrazone derivative melted at 154–155°.

Anal. Calcd for $C_9H_{18}OSi$: C, 63.47; H, 10.65; Si, 16.47. Found: C, 63.46; H, 10.78; Si, 16.41.

Reduction of 4-Trimethylsilylcyclohexanone.—In a 500-ml round-bottomed flask were placed 0.90 g (0.023 mole) of lithium aluminum hydride and 150 ml of anhydrous ether. To this mixture was added dropwise a solution of 11.3 g (0.066 mole) of 4-trimethylsilylcyclohexanone in 75 ml of ether. After the addition, the mixture was stirred at room temperature for 0.5 hr, then carefully decomposed with 2 *N* hydrochloric acid. The aqueous layer was extracted with ether, the combined ethereal solutions were dried with magnesium sulfate, and the ether was removed by distillation. The residue (11.3 g) solidified, mp 48–58°. Gas phase chromatography showed that the mixture consisted of the *cis* and *trans* isomers in a ratio of about 1:9.

Separation of the *cis*- and *trans*-4-Trimethylsilylcyclohexanols.—Elution chromatography using 2.0-g samples of the isomeric mixtures of the 4-trimethylsilylcyclohexanols and 61 g of neutral alumina (activity 2) was employed. The *cis* isomer was obtained from the chromatography of the high-pressure hydrogenation product, while the *trans* isomer was obtained from the lithium aluminum hydride reduction product. As elution solvents, were used petroleum ether (bp 30–60°), carbon tetrachloride, ethyl ether, and chloroform. The relative concentrations of the solvents were varied 25% by volume for each 10-ml addition, and 1–5-ml fractions were collected. The course of the chromatography and the purity of the fractions were followed by gas phase

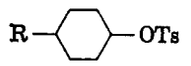
(9) A. H. Lewin and S. Winstein, *J. Am. Chem. Soc.*, **84**, 2464 (1962).

(10) All melting points and boiling points are uncorrected. Melting points were determined on a Fisher-Johns melting point apparatus. Carbon, hydrogen, and nitrogen analyses were performed by the Berkeley Microanalytical Laboratory, and the silicon analyses were performed in this laboratory using the wet ash method. Distillations were carried out using the apparatus that was described by J. Cason and H. Rapoport, "Laboratory Text in Organic Chemistry," 2nd ed, Prentice-Hall, Co., Inc., Englewood Cliffs, N. J., 1962, p 289. Gas chromatographic analyses were carried out with a Wilkens A-90c instrument with a 10 ft × 0.25 in. Carbowax column at 180° and a flow rate of approximately 120 cc/min. The areas reported are qualitative. Nmr spectra were recorded using a Varian A-60 instrument in $CHCl_3$-*d* with $CHCl_3$ impurity and TMS as the internal standards.

(11) H. R. Billica and H. Adkins, *Org. Syn.*, **29**, 24 (1949).

TABLE II

ETHANOLYSIS OF CYCLOHEXYLTOSYLATES



R	Concn × 10²	Temp, °C	Rate constants, sec^{-1} × 10⁵	Std dev × 10⁵	ΔH^{*},[a] kcal/mole	ΔS^{*},[a] eu
H	1.02	50.20	0.179	0.004	27	−1.5
	1.19	59.86	0.639	0.014		
	1.02	70.19	1.95	0.045		
	1.03	70.19	2.11	0.054		
	1.10	70.16	2.03	0.092		
cis-t-C_4H_9	1.01	50.20	0.567	0.012	25	−5
	0.986	59.86	1.98	0.14		
	1.21	70.21	5.23	0.079		
trans-t-C_4H_9	1.03	50.20	0.175	0.017	25	−7
	1.01	59.86	0.588	0.014		
	1.04	70.21	1.83	0.14		
cis-$(CH_3)_3Si$	1.02	50.20	0.629	0.006	26	−2
	1.03	59.86	2.28	0.075		
	1.01	70.21	6.52	0.15		
trans-$(CH_3)_3Si$	1.02	50.20	0.125	0.008	27	−2
	0.986	59.86	0.516	0.011		
	0.980	70.21	1.51	0.054		

[a] Reported:[8] cyclohexyl, ΔH^{*} = 25.5 kcal/mole, ΔS^{*} = −6 eu; 4-*trans-t*-butylcyclohexyl, ΔH^{*} = 26.6 kcal/mole, ΔS^{*} = −4 eu; 4-*cis-t*-butylcyclohexyl, ΔH^{*} = 24.4 kcal/mole, ΔS^{*} = −8 eu.

chromatography. The *cis* isomer was eluted first from the column and the *trans* isomer, last. The intermediate fractions contained both isomers and showed depressed melting points (52–59°): *cis* isomer, mp 66–67°, 3,5-dinitrobenzoate mp 128–129° (*Anal.* Calcd for $C_9H_{20}OSi$: C, 62.73; H, 11.69; Si, 16.28. Found: C, 62.77; H, 11.54; Si, 16.33.); *trans* isomer, mp 81–82°, 3,5-dinitrobenzoate mp 131–132° (*Anal.* Calcd for $C_9H_{20}OSi$: C, 62.73; H, 11.69; Si, 16.28. Found: C, 62.77; H, 11.69; Si, 16.30.).

Since this work was completed, it has been observed that a more convenient method for the separation of these compounds is preparative glpc using a 20-ft Carbowax or DEGS column at 200°. The purity can be determined by tlc using silica gel with chloroform as the developing solvent.

m-Trimethylsilylphenol.—Trimethyl(*m*-trimethylsilylphenoxy)-silane, bp 70–72° (2.0 mm), $n^{23}D$ 1.4798 [lit. bp 60° (2.0 mm), $n^{20}D$ 1.4770], was obtained in 72% yield using the method of Benkeser and Krysiak.[12] The silylphenol, bp 100° (3.2 mm), $n^{23}D$ 1.5170 [lit.[12] bp 70° (1 mm), $n^{20}D$ 1.5190], was obtained in 98% yield by hydrolysis. After standing at room temperature, the phenol solidified, mp 31–32°.

Hydrogenation of *m*-Trimethylsilylphenol.—Hydrogenation of 45.3 g of *m*-trimethylsilylphenol in 400 ml of purified isooctane, using 13 g of Raney nickel (free from ethanol), was carried out as previously described. After the isooctane was removed by distillation, the crude residue was treated with 3 *N* sodium hydroxide until cloudiness ceased to form. The basic mixture was then extracted with three 25-ml portions of ether. The ether extracts were combined, dried, and distilled, yielding 6.4 g (14%) of the 3-trimethylsilylcyclohexanol, bp 111–118° (15 mm), $n^{23}D$ 1.4649–1.4700.

Gas phase chromatography analysis indicated that the mixture consisted of the *cis* and *trans* isomers in a ratio of 1:4.

The basic aqueous residue was acidified with 3 *N* hydrochloric acid, the organic layer was separated, and the water layer was extracted with three 15-ml portions of ether. Upon distillation of the combined ethereal solutions, there was recovered 21.6 g (48%) of the starting silylphenol.

3-Trimethylsilylcyclohexanone.—Using the procedure that was described for the preparation of 4-trimethylsilylcyclohexanone, there was obtained 11.0 g (42%) of the ketone. The product was purified by means of the bisulfite addition compound[13] and distilled, bp 71° (1.0 mm, $n^{24}D$ 1.4620. The 2,4-dinitrophenylhydrazone derivative melted at 109–110°.

Anal. Calcd for $C_9H_{18}OSi$: C, 63.47; H, 10.65; Si, 16.47. Found: C, 63.42; H, 10.79; Si, 16.51.

Reduction of 3-Trimethylsilylcyclohexanone.—Reduction of 12.3 g (0.072 mole) of the ketone with 0.7 g (0.018 mole) of lithium aluminum hydride yielded 10.0 g (80%) of 3-trimethylsilylcyclohexanol, bp 103–104° (5.5 mm), $n^{24}D$ 1.4692. Gas chromatographic analysis of this material indicated that the *cis–trans* ratio was 9:1.

Separation of the *cis*- and *trans*-3-Trimethylsilylcyclohexanols.—The isolation of the *cis* isomer was carried out using the lithium aluminum hydride reduction product, and the isolation of the *trans* isomer, using the hydrogenation product. Adsorption chromatography, using the elution scheme described for the 4-trimethylsilylcyclohexanol was employed. In each case, the product was an oil, which was converted to the 3,5-dinitrobenzoate for analysis: *cis* isomer, $n^{24}D$ 1.4685, 3.5-dinitrobenzoate derivative mp 142–143° (*Anal.* Calcd for $C_{16}H_{22}N_2O_6Si$: C, 52.45; H, 6.01; N, 7.65. Found: C, 52.15; H, 5.93; H, 7.35.); *trans* isomer, $n^{24}D$ 1.4702, 3,5-dinitrobenzoate mp 100–101° (*Anal.* Calcd for $C_{16}H_{22}N_2O_6Si$: C, 52.45; H, 16.01; N, 7.65. Found: C, 52.52; H, 15.97; N, 7.46.).

o-Trimethylsilylphenol.—Trimethyl(*o*-trimethylphenoxy)silane, bp 74–76° (2.7 mm), $n^{23}D$ 1.4850 [lit.[4] bp 128° (25 mm), $n^{25}D$ 1.4830], was obtained in 86% yield using the procedure of Speier.[4] The silylphenol, $n^{20}D$ 1.5065 (lit.[4] $n^{20}D$ 1.5155), was obtained by hydrolysis in 96% yield.

Attempted Hydrogenation of *o*-Trimethylsilylphenol.—Using the procedure as described previously, 25 g of isooctane, 5 g of Raney nickel (free from ethanol), and 23 g of the phenol were heated at 90° in a hydrogenation bomb at 6000 psi. After the pressure had dropped to 5000 psi, the bomb was disassembled and the solvent was removed by distillation. In the gas chromatogram of the residue, $n^{23}D$ 1.4665, only one peak, corresponding to cyclohexanol, was detected. No further attempt was made at hydrogenation. The fate of the silyl moiety (presumably lost as gaseous trimethylsilane) was not determined.

Ethanolysis of the *p*-Toluenesulfonates. *cis*- and *trans*-4-Trimethylsilyl *p*-Toluenesulfonates.—4-Trimethylsilylcyclohexanol (1 g, 5.8 mmoles) (purified *cis* or *trans*), 1.84 g (9.6 mmoles) of *p*-toluenesulfonyl chloride, and 10 ml of pyridine were allowed to stand overnight at room temperature. The reaction mixture was then poured into 100 ml of ice-cold 10% hydrochloric acid. The solid material was collected and recrystallized from pentane: *trans* isomer, 76% yield, mp 97–98° (*Anal.* Calcd for $C_{16}H_{26}O_3SiS$: C, 58.90; H, 8.03; S, 9.51. Found: C, 59.21; H, 7.89; S, 9.59.); *cis* isomer, 50% yield, mp 83–84° (*Anal.* Calcd for $C_{16}H_{26}O_3SSi$: C, 58.90; H, 8.03; S, 9.51. Found: C, 58.83; H, 7.74; S, 9.68.).

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Weighed samples of the *p*-toluenesulfonates were dissolved in 50.0 ml of magnesium-dried ethanol, which was then divided into 6-ml aliquots and sealed into ampoules. The ampoules were placed in a constant-temperature bath (±0.01°). The rates were followed by withdrawing the sealed ampoules at the specified time interval, quenching the reaction by cooling in a Dry Ice–acetone bath, and titration of a 5.0-ml aliquot with standard sodium hydroxide.

The rate constants were obtained for each titration point using the formula ln $[a(a - x)] = kt$, where a = concentration of tosylate at time t_0 and x = concentration of sulfonic acid at time t. The infinite titer method was used to obtain a and $a - x$. The ΔH^* was obtained from a plot of ln K_r *vs.* $1/T$°K. The ΔS^*, at 50.20°, was calculated from the formula ln K_r = ln $RT/Nh - \Delta H^*/RT + \Delta S^*/R$.

The results are summarized in Table II.

1,4,5,6-Tetrahydropyridines from Catalytic Reduction of Nicotinoyl Derivatives and Their Ring Opening with Hydrazine

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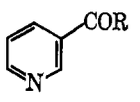
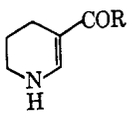
Pyridines with a carbonyl function (exemplified by ketones, an ester, and an amide) in the 3 position can be hydrogenated to the corresponding 1,4,5,6-tetrahydropyridine derivatives in good yield. The alkaloid myosmine (IV), possibly through a preliminary ring opening to a ketone (V), also gives such a derivative. 1,4,5,6-Tetrahydronicotinamide, as well as the corresponding ethyl ester, reacts with hydrazine to give a product of ring opening, 4-(3-aminopropyl)-2-pyrazolin-5-one. The net conversion of a nicotinic acid derivative to a pyrazolone represents a potentially useful means for the degradation of the pyridine ring in biosynthetic studies.

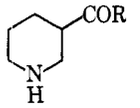
Ethyl γ-hydroxy-γ-(3-pyridyl)butyrate was needed in some synthetic studies, and an attempt was made to prepare it by catalytically reducing the ketone function of ethyl β-nicotinoylpropionate (Ia). However, with a palladium–carbon catalyst, 2 moles of hydrogen were absorbed, giving a product still containing a keto group. The infrared and ultraviolet spectra failed to show the characteristic pyridine bands and suggested that the keto grouping was conjugated. The tetrahydropyridine structure IIa was suspected and this was confirmed by the nmr spectrum. A similar result was obtained on attempted reductive amination, with benzylamine, of ethyl nicotinoylacetate (Ib); the ketone group was unattacked and the amide IIb was isolated. At about the same time, Freifelder[2,2a] reported the reduc-



Ia, R = CH_2CH_2COOEt
b, R = CH_2COOEt
c, R = OEt
d, R = NH_2



IIa, R = CH_2CH_2COOEt
b, R = $CH_2CONHCH_2C_6H_5$
c, R = OEt
d, R = NH_2



IIIc, R = OEt
d, R = NH_2

tion of 3-acetylpyridine to a similar tetrahydropyridine and it appeared that the pyridine ring is particularly susceptible to this mode of reduction if a 3-keto function is present. The products are examples of "vinylogous amides;" they show carbonyl stretching absorption in the infrared at much lower frequencies than would be expected for simple unsaturated ketones, and have the intense ultraviolet absorption near 300 mμ now well established for compounds of this type.[2,3]

Δ^2-Tetrahydropyridines unsubstituted on nitrogen have rarely been prepared,[4] and several alkaloids thought to contain this moiety have recently been reassigned to the corresponding Δ^1 structure.[5] Since the double bond in the Δ^1 compounds is readily reduced, considerable stabilization must be present in the Δ^2 compounds through interaction between keto and amino groups to account for the preservation of the double bond under reductive conditions. This suggested that such stabilization might be provided by other functions involving carbonyl groups. Thus, the infrared spectra of β-amino-α,β-unsaturated esters suggest this effect, since the carbonyl group absorbs at unusually low frequencies.[6] We therefore examined the catalytic reduction of ethyl nicotinate (Ic) and nicotinamide (Id) and found that in each case yields greater than 70% of the apparently unreported tetrahydro derivative (IIc and IId) could be isolated. The reactions were allowed to proceed until no hydrogen absorption was observable. The small quantities of the piperidines (IIIc and IIId) which were isolated apparently did not, therefore, arise from further reduction of the tetrahydro products, a phenomenon noted previously,[2] unless this reduction occurred on particularly active sites of the catalyst which became poisoned by the piperidines when produced. Both ethyl nicotinate[7]

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(2a) NOTE ADDED IN PROOF.—E. Wenkert, K. G. Dave, and F. Haglid [*J. Am. Chem. Soc.*, **87**, 5461 (1965)] have now demonstrated the similar partial reduction of *t*-butyl nicotonate.

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