352-32-9; **4** (R = *m*-Me), 352-70-5; **4** (R = H), 462-06-6; **4** (R = *o*-Cl), 348-51-6; **4** (R = *p*-Cl), 352-33-0; **4** (R = *m*-Cl), 625-98-9; **5** (R = *o*-OMe), 613-70-7; **5** (R = *p*-OMe), 1200-06-2; **5** (R = *o*-Me), 533-18-6; **5** (R = *m*-Me), 122-46-3; **5** (R = *p*-Me), 140-39-6; **5** (R = *o*-Cl), 4525-75-1; **5** (R = *m*-Cl), 13031-39-5; **5** (R = *p*-Cl), 876-27-7; **5** (R = H), 122-79-2; F_2, 7782-41-4; CH_3COOF, 78948-09-1; *N,N*-dimethylaniline, 121-69-7.

The Stereochemistry of 2,6-Di-*tert*-butyl-1,2,5,6-tetrahydropyridine and *cis*- and *trans*-2,6-Di-*tert*-butylpiperidine

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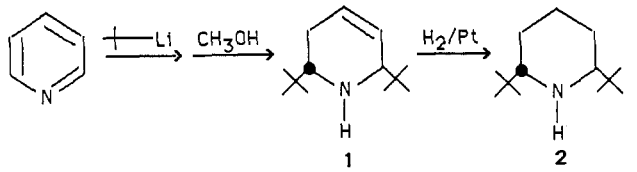
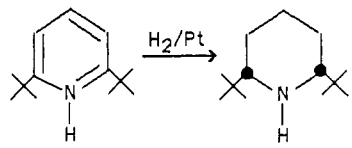
The isolation of 2,6-di-*tert*-butyl-1,2,5,6-tetrahydropyridine (**1**) from a reaction of pyridine with excess *tert*-butyllithium has been reported from this laboratory.[1] Catalytic hydrogenation of tetrahydropyridine **1** gave a product whose spectral and elemental analyses were in agreement with a 2,6-di-*tert*-butylpiperidine (**2**). Piperidine **2** was assumed to be the trans isomer based on the following observations.



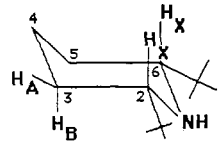
1 **2**



3 **4**

Catalytic hydrogenation of 2,6-di-*tert*-butylpyridine (**3**) produced a 2,6-di-*tert*-butylpiperidine (**4**) whose spectral properties were different from those of piperidine **2**. Because of the preference for syn addition of hydrogen in catalytic hydrogenation, piperidine **4** was assumed to be *cis*-2,6-di-*tert*-butylpiperidine. In addition, the ^1H and ^{13}C NMR data for piperidine **4** were in agreement with those reported by Day[2] for *cis*-2,6-di-*tert*-butylpiperidine obtained from the reduction of 2,6-di-*tert*-butylpyridine with lithium in 1,2-ethanediamine.

The assignment of a cis configuration to piperidine **4** is also supported by partial analysis of its NMR spectrum. In *cis*-2,6-di-*tert*-butylpiperidine (**4**), the trans coupling between protons H_B and H_X is expected to be much larger than the gauche coupling between protons H_A and H_X. Booth and Little[4] have shown these values to be 10.6 and 1.9 Hz, respectively, for *cis*-2,6-dimethylpiperidine. By first-order analysis of the doublet of doublets at 2.12 ppm, the trans and gauche coupling constants $J_{B,X}$ and $J_{A,X}$ in piperidine **4** were determined to be 10.2 and 1.8 Hz, respectively. These data support a conformationally rigid structure for *cis*-2,6-di-*tert*-butylpiperidine (**4**) in which the protons at C_2 and C_6 (H_X) occupy axial positions.



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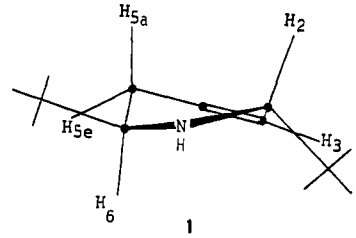
Allinger[3] has shown by thermodynamic studies that *trans*-1,3-di-*tert*-butylcyclohexane exists in a twist-boat conformation, and piperidine **2** was expected to exhibit the same stereochemistry. This paper deals with NMR studies which confirm these initial stereochemical assignments.

The ^1H NMR spectrum of the compound assumed to be *trans*-2,6-di-*tert*-butylpiperidine (**2**) shows a singlet at 0.90 ppm for the *tert*-butyl groups and a doublet of doublets at 2.40 ppm assigned to the protons at C_2 and C_6. The remainder of the spectrum is a complex of absorption lines between 1.09 and 1.51 ppm. Analysis of the stereochemistry of piperidine **2** by NMR shift reagent studies was unsuccessful. Generally, the shift reagents produced only small chemical shifts associated with signal broadening. However, 2,6-di-*tert*-butyl-1,2,5,6-tetrahydropyridine (**1**), the precursor of piperidine **2** did produce distinct lanthanide-induced chemical shifts with Yb(FOD)$_3$ and was chosen for study. Since the synthesis of piperidine **2** from tetrahydropyridine **1** only requires catalytic reduction of the carbon–carbon double bond, we assumed that the configuration of the *tert*-butyl groups would remain unchanged in the conversion of **1** to **2**.

The ^1H NMR studies of the stereochemistry of tetrahydropyridine **1** focused on a twist-boat conformation in which the *tert*-butyl groups occupy pseudoequatorial positions. A cis configuration was ruled out because of the previously mentioned comparison of the reduction products of tetrahydropyridine **1** and of 2,6-di-*tert*-butylpyridine. A chair conformation of the trans isomer seemed unlikely since, in this conformation, a *tert*-butyl group would be required to occupy an axial position. These conclusions are supported by the data obtained from chemical shift reagent studies which are incompatible with either the cis configuration of a chair conformation of the trans isomer.

The ^1H NMR spectrum of tetrahydropyridine **1** shows two singlets at 0.93 and 0.97 ppm (*tert*-butyl groups), a singlet at 1.33 ppm (NH), a complex multiplet centered at 1.90 ppm (H_5, H_6), a doublet of doublets at 2.64 ppm (H_7), a multiplet centered at 3.04 ppm (H_2), and a complex multiplet at 5.87 ppm (H_3, H_4). The chemical shift assignments in tetrahydropyridine **1** are in general agreement with those assigned by Shoolery[6] to the protons in 1,2,5,6-tetrahydropyridine.



1

The lanthanide-induced chemical shifts, summarized in Figure 1, show that H_2 and H_{5a} experience large chemical shifts and that each is shifted approximately the same. This result suggests that these protons are in close proximity to the lanthanide metal location. A trans relation-

(1) Francis, R. F.; Davis, W.; Wisener, J. T. *J. Org. Chem.* **1974**, *39*, 59.
(2) Day, J. C. *J. Org. Chem.* **1978**, *43*, 3646.
(3) Allinger, N. L.; Freiberg, L. A. *J. Am. Chem. Soc.* **1960**, *82*, 2393.
(4) Booth, H.; Little, J. H. *Tetrahedron* **1968**, *24*, 279.
(5) Hooper, D. L.; Kardos, A. *Can. J. Chem.* **1973**, *51*, 4080.
(6) Shoolery, J. N. *Discuss. Faraday Soc.* **1962**, *34*, 104.

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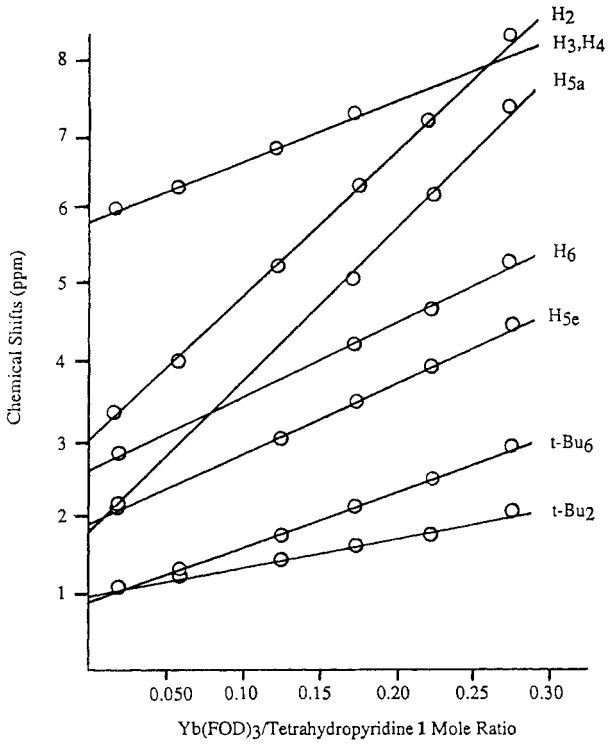

Figure 1. Plot of $Yb(FOD)_3$/tetrahydropyridine 1 mole ratio vs. chemical shift.

ship of H_6 to H_2 and H_{5a} is suggested by the fact that H_6 is shifted only about half as much as either H_2 or H_{5a}. A trans relationship for the *tert*-butyl groups is supported by the observation that one *tert*-butyl group is shifted twice as much as the other.

The ^1H NMR spectrum of tetrahydropyridine 1 also was analyzed by computer techniques.[7] The ^1H NMR parameters from these studies are summarized in the Experimental Section. Certain of these proton–proton coupling constants provide important information concerning the stereochemistry of tetrahydropyridine 1. In the twist-boat conformation, H_6 is trans to H_{5a} and gauche to H_{5e}. Thus, the approximate $J_{5a,6}$ and $J_{5e,6}$ values expected[10] are 10 and 3 Hz, respectively. The computer-generated NMR parameters for tetrahydropyridine 1 show coupling constants between H_6 and H_{5a} and H_{5e} to be 10.0 and 4.3 Hz. A computer-generated ^1H NMR spectrum derived from these parameters was in agreement with the experimentally obtained spectrum of tetrahydropyridine 1.

A three-dimensional model of tetrahydropyridine 1 was generated with the Stereochemical Iteration Program (SCIP). The coordinates obtained from this program and the assigned lanthanide-induced shifts for the protons were analyzed in terms of pseudocontact relationship by the Lanthanide Induced Shift Structure Agreement Program (LISSAP). These calculations showed an agreement factor of 0.052 (standard deviation = 0.717) between the observed and calculated chemical shifts.

The ^{13}C NMR spectrum of *trans*-2,6-di-*tert*-butylpiperidine (2) shows only three absorption peaks for ring carbons. This result is consistent with a rapidly inverting ring in which C_2 and C_6 are equivalent and C_3 and C_5 are equivalent. Because of the low solubility of piperidine 2 in appropriate solvents at low temperatures, a low-temperature study of the ring-inversion process was unsuccessful.

Experimental Section

General Methods. Elemental analyses were performed by Chemalytics, Inc. Infrared spectra were recorded on a Perkin-Elmer Model 257 spectrometer. The IR spectra of solids were taken as thin film Nujol mulls between sodium chloride disks. Nuclear magnetic resonance spectra were obtained on Varian HA-100 and Nicolet 200 instruments. Spin decoupling for ^1H spectra was accomplished by use of a Hewlett-Packard Model 200CD wide range oscillator. Chemical shift assignments for ^{13}C spectra were based on the spectra of related compounds[12] and on the use of off-resonance proton decoupling. Analyses of reaction product mixtures were obtained on a Varian Aerograph 90-P3 gas chromatograph equipped with a 20 ft × 318 in. column composed of 30% SE-30 on Chromosorb W (60/80 mesh). Samples for spectral analysis were collected by preparative GLC using the same column. Alkylithium compounds were obtained as solutions in varying concentrations from Alfa-Ventron Corp.

***trans*-2,6-Di-*tert*-butyl-1,2,5,6-tetrahydropyridine (1).** To a 1-L, three-necked flask equipped with a mechanical stirrer and a thermometer (+50 to −100 °C) were added 10.0 g (0.127 mol) of pyridine and 150 mL of anhydrous hexane. The system was flushed with dry nitrogen and cooled to −70 °C (dry ice–isopropyl alcohol mixture). In a drybox under a nitrogen atmosphere, one-half of 353 mL (0.635 mol) of 1.8 M *tert*-butyllithium in pentane was placed in each of two 250-mL pressure-equalizing addition funnels. The addition funnels were attached to the reaction flask, and the *tert*-butyllithium in pentane was added dropwise over 3.5 h. The temperature was maintained near −70 °C, and the mixture was stirred for 5 days.

The reaction was terminated by adding 250 mL of a 60% methanol–40% water solution while maintaining the temperature near −70 °C. The organic layer was separated, and the aqueous layer was extracted with four 100-mL portions of hexane. The combined organic portions were dried ($MgSO_4$). Removal of the solvents by rotary evaporation gave a light yellow oil. GLC analysis of the oil indicated a 45% conversion to tetrahydropyridine 1. Samples of the product to be used in the NMR studies were obtained by preparative GLC: 100-MHz ^1H NMR δ 0.93 (s, 3 CH_3), 0.97 (s, 3 CH_3), 1.33 (s, NH), 1.7–2.2 (m, H_5, H_6), 2.64 (dd, H_7), 3.0–3.2 (m, H_2), 5.8–6.0 (m, H_3, H_4); 200-MHz ^{13}C NMR 26.3 (3 CH_3), 27.7 (3 CH_3), 33.5 (quaternary C), 36.8 (quaternary C), 57.4 (C_6), 62.2 (C_2), 126.7 (C_4), 127.3 (C_3) ppm.

***trans*-2,6-Di-*tert*-butylpiperidine (2).** A 1.41 g (0.57×10^{-3} mol) sample of 2,6-di-*tert*-butyl-1,2,5,6-tetrahydropyridine was diluted with 50 mL of methanol and 0.5 mL of glacial acetic acid. The solution was placed in a Parr reaction flask with 0.57 g of platinum oxide, and the mixture was shaken overnight in a Parr apparatus at an initial pressure of 54 psi. The liquid was decanted from the catalyst, and the catalyst was washed with two 40-mL portions of methanol. The washings were combined with the reaction solution, and the methanol was removed by rotary evaporation. The solution was made basic to litmus by adding a small amount of 50% sodium hydroxide solution. The free organic base was taken up in 75 mL of hexane and dried ($MgSO_4$). Removal of hexane by rotary evaporation gave a colorless liquid which GLC analysis showed to contain a single product. Samples of piperidine 2 for analysis were obtained by preparative GLC: picrate, mp 165.5–166 °C; 100-MHz ^1H NMR δ 0.90 (s, 6 CH_3), 2.40 (dd, 2 CH), ca. 109–1.51 (m, $CH_2CH_2CH_2$); 200-MHz ^{13}C NMR 20.8 (C_4), 23.3 (C_3, C_5), 26.9 ($6CH_3$), 35.1 (2 quaternary C), 59.6 (C_2, C_6) ppm. Anal. Calcd for $C_{13}H_{27}N$: C, 79.11; H, 13.79; N, 7.10. Found: C, 79.06; H, 13.94; N, 7.60.

***cis*-2,6-Di-*tert*-butylpiperidine (5).** The procedure described for the catalytic hydrogenation of tetrahydropyridine 1 was used with a 3.0-g (0.015 mol) sample of 2,6-di-*tert*-butylpyridine dissolved in 50 mL of methanol and 0.5 mL of glacial acetic acid.

(7) Used were the NMR Iteration (NMRIT IV) and the NMR Energy Level (NMREN I) programs,[8] which were translated into Fortran IV and segmented for the IBM 7096.[9] They were adapted to the IBM 370/155 by E.L.C.

(8) Swalen, J. D.; Reilly, C. A. *J. Chem. Phys.* **1962**, *37*, 21.

(9) Fraenkel, G.; Cooper, J. C. *Tetrahedron Lett.* **1968**, *15*, 1825.

(10) Bovey, F. A. *Nuclear Magnetic Resonance Spectroscopy*; Academic Press: New York, 1969; p 366.

(11) Eisentraut, K. J.; Sievers, R. E. *J. Am. Chem. Soc.* **1965**, *87*, 5254.

(12) Shamma, M.; Hindenlang, D. *Carbon-13 NMR Shift Assignments of Amines and Alkaloids*"; Plenum: New York, 1979; p 37.

GLC analysis of the residue obtained on workup showed a single product. Samples of piperidine **5** for analysis were collected by preparative GLC: picrate, mp 224–225 °C; 100-MHz ^{1}H NMR δ 0.88 (s, 2 CH_3), 2.12 (dd, 2 CH), ca. 0.98–1.94 (m, $CH_2CH_2CH_2$); 200-MHz ^{13}C NMR 26.3 (C_4), 27.0 (6 CH_3), 27.2 (C_3), 34.1 (2 quaternary C), 67.0 (2 CH). Anal. Calcd for $C_{13}H_{27}N$: C, 79.11; H, 13.79; N, 7.10. Found: C, 78.94; H, 13.92; N, 6.98.

Chemical Shift Reagent Studies. Studies were attempted by using *trans*-2,6-di-*tert*-butylpiperidine (**2**) and the tris-(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionato) derivatives of ytterbium(III), praseodynium(III), and europium-(III):[Yb(FOD)$_3$, Pr(FOD)$_3$, and Eu(FOD)$_3$ respectively] obtained from Alfa-Ventron and tris(diisobutyrylmethanato)ytterbium(III) [Yb(DIMB)$_3$], which was prepared from a known[11] procedure.

In the shift reagent study of 2,6-di-*tert*-1,2,5,6-tetrahydropyridine (**1**) progressively larger amounts of Yb(FOD)$_3$ were added to 0.30 M solutions of tetrahydropiperidine **1** in $CDCl_3$. The data from these studies are summarized in Figure 1.

Computer Analysis of NMR Parameters. NMR parameters of 2,6-di-*tert*-butyl-1,2,5,6-tetrahydropyridine (**1**) were obtained by using NMRIT IV and NMREN I: chemical shifts ($\delta \pm 0.001$) 1.854 (H_{5a}), 1.950 (H_{5e}), 2.635 (H_6), 3.035 (H_2), 5.819 (H_3), 5.917 (H_4); coupling constants (Hz ● 0.2) $J_{2,3} = 3.4$, $J_{2,4} = -1.9$, $J_{2,5a} = 2.9$, $J_{2,5e} = 0$, $J_{2,6} = 0$, $J_{3,4} = 10.8$, $J_{3,5a} = -2.5$, $J_{3,5e} = 0$, $J_{3,6} = 0$, $J_{4,5a} = 4.3$, $J_{4,5e} = 0$, $J_{4,6} = 0$, $J_{5a,5e} = -10.0$, $J_{5a,6} = 10$, $J_{5e,6} = 4.3$.

Acknowledgment. We express appreciation for support of this research to the Robert A. Welch Foundation and the Organized Research Fund of The University of Texas at Arlington.

Registry No. **1**, 101166-51-2; **2**, 101166-52-3; **5**, 66922-18-7; 2,6-di-*tert*-butylpyridine, 585-48-8; pyridine, 110-86-1; *tert*-butyllithium, 594-19-4.

[2-(Trimethylsilyl)ethoxy]methyl (SEM) as a Novel and Effective Imidazole and Fused Aromatic Imidazole Protecting Group

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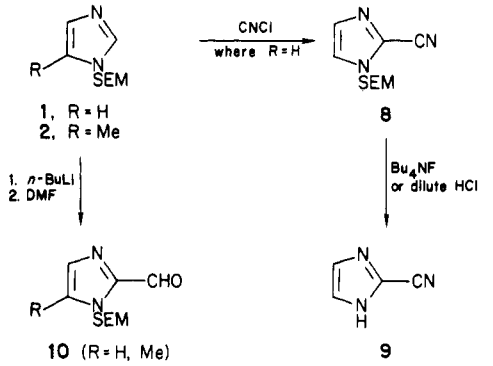
The abundance of imidazole-containing pharmaceutical, agricultural, and natural products has led to an extensive synthetic effort to obtain novel imidazoles. Synthesis often requires protection and subsequent deprotection of the imidazole 1H nitrogen. Many of the imidazole nitrogen protecting groups that have been commonly used often are not removable under reaction conditions compatible with other functional groups in the molecule.[1] There have been several recent advances in imidazole protection, notably the diethoxymethyl[1] and trityl groups.[2] However, the diethoxymethyl group is extremely moisture-sensitive, while trityl-protected imidazoles are often obtained in poor yields.[3] We required a novel imidazole protecting group which was easily introduced, stable, selectively removed, and which assisted purification.[4,5]

The [2-(trimethylsilyl)ethoxy]methyl group (SEM) fulfills the above criteria based on the following observations: *N*-Alkoxymethyl groups are easily introduced into imidazole and increase the selectivity of certain reactions, e.g., metalations.[6] The silyl-modified alkoxymethyl group, the SEM group, has recently been used as an alcohol protecting group which is easily introduced and stable to a wide range of conditions but is also easily removed.[7] Finally, the SEM group has recently been used as a pyrrole protecting group.[8]

Reaction of imidazole, 4-methylimidazole, and 4-(trifluoromethyl)imidazole and even the highly unstable 4-methoxyimidazole[9] with 50% sodium hydride in DMF followed by treatment with SEMCl gave the corresponding [[2-(trimethylsilyl)ethoxy]methyl]imidazole derivatives as mixtures of the 4(5) isomers (**1–4**) as distillable, stable



liquids in 64–85% yield (see Table I). Using similar procedures, the SEM group was also introduced as a N protecting group on the fused aromatic imidazole derivatives benzimidazole, 4-azabenzimidazole, and even on the highly insoluble 2,2′-bi-1*H*-imidazole[4,10] to give distillable, stable liquids (**5–7**) in good yields.

Removal of the SEM group from alcohols and pyrroles has been reported to proceed with concentrated anhydrous tetrabutylammonium fluoride solutions.[7,8] We have found that reaction of SEM-imidazoles with 1 M tetrabutylammonium fluoride solutions at reflux resulted in good yields of the deprotected imidazoles. More conveniently, the SEM-imidazole derivatives can be deprotected in excellent yield by warming with dilute acid.

SEM-protected imidazoles were shown to be amenable to a number of synthetic operations. SEM-imidazole (**1**) was converted to 2-cyano-SEM-imidazole (**8**) in 66% yield by treatment with cyanogen chloride and a suitable base.[5] Subsequent treatment with 1 M tetrabutylammonium fluoride in THF at reflux for 45 min provided 2-cyanoimidazole (**9**) in 70% yield. Alternatively, deprotection with 0.5 M aqueous ethanolic HCl gave **9** in quantitative yield.

1-SEM-imidazole (**1**) and 1-SEM-4(5)methylimidazole (**2**) were readily metalated with *n*-butyllithium in the 2-position, and subsequent treatment with DMF provided almost quantitative yields of imidazole-2-carboxaldehydes **10**. 1-SEM-7-azabenzimidazole (**6**) on similar treatment

(1) Curtis, N. J.; Brown, R. S. *J. Org. Chem.* **1980**, *45*, 4038.
(2) Kirk, K. L. *J. Org. Chem.* **1978**, *43*, 4381.
(3) Kelley, J. L.; Miller, C. A.; McLean E. W. *J. Med. Chem.* **1977**, *20*, 721.
(4) Matthews, D. P.; Whitten, J. P.; McCarthy, J. R. *Synthesis*, in press.
(5) McCarthy, J. R.; Matthews, D. P.; Whitten, J. P. *Tetrahedron Lett.* **1985**, *26*, 6273.
(6) Tang, C. G.; Davalian, D.; Huang, P.; Breslow, R. *J. Am. Chem. Soc.* **1978**, *100*, 3918.
(7) Lipshutz, B. H.; Pegram, J. J. *Tetrahedron Lett.* **1980**, *21*, 3343. Lipshutz's group has also informed us that they are currently investigating the use of the SEM group as an imidazolo protecting group.
(8) Muchowski, J. M.; Solas, D. R. *J. Org. Chem.* **1984**, *49*, 203. Edwards, M. P.; Ley, S. V.; Palmer, B. D. *J. Chem. Soc., Chem. Commun.* **1983**, 630.
(9) Hosmane, R. S. *Tetrahedron Lett.* **1984**, *25*, 363.
(10) 2,2′-Bi-1*H*-imidazole has a water solubility of 1.2 mg/L at 25 °C and approximately 1 g/L in boiling DMF.

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