Conformational Analysis. 38. 8-*tert*-Butyl-*trans*-decahydroquinolines: ^{13}C and ^{1}H Nuclear Magnetic Resonance and Infrared Spectra. The N–H Conformational Equilibrium†

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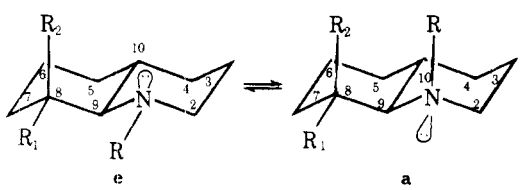
Synthesis and spectra (^{13}C and ^{1}H NMR, IR) of the two 8-*tert*-butyl-*trans*-decahydroquinolines (**4** and **5**) and of their *N*-methyl derivatives are reported. Comparison with the spectra of *trans*-decahydroquinoline (**1**) and of the two 8-methyl-*trans*-decahydroquinolines (**2** and **3**) suggests that the proton on N is preferentially equatorial in **1**, **2**, **3**, and **5**, but is forced into a predominantly axial position by the (equatorial) 8-*tert*-butyl group in **4**. The chemical shifts of the protons α to nitrogen (H_{2e}, H_{2a}) are not significantly influenced by the relative positions of the proton and electron pair on nitrogen.

Recently we have reported the ^{1}H- and ^{13}C-NMR spectra of a number of methyl-substituted *trans*- and *cis*-decahydroquinolines and of their *N*-methyl derivatives.[1-3] It was possible to calculate the equilibrium constant for the *N*-methyl inversion in *N*-methyl-*trans*-decahydroquinoline (**1m**—the notation **1m**, **2m**, etc., is used to denote the *N*-methyl derivatives of **1**, **2**, etc.; see Scheme I),[4] using as models various substituted *trans*-decahydroquinolines in which the NCH_3 group was forced to be either entirely equatorial (e.g., **3m**) or entirely axial (e.g., **2m**); a conformational free energy of ≥ 1.8 kcal/mol in favor of the NCH_3 equatorial position for **1m** was established. Lack of a model with totally axial NCH_3 and disregard of the nonnegligible shift effects of distant holding groups[5] led to the calculation of a ΔG^0 value for *N*-methylpiperidine[4] which has since been shown to be too low.[3,6]

No information as to the position of the axial–equatorial equilibrium of the proton on nitrogen for **1** and for the various ring-methyl substituted *trans*-decahydroquinolines could be extracted from the NMR spectra. The effect of an anti or gauche lone pair at nitrogen on the ^{13}C shifts of the β-carbon atoms was not known; the small shift differences at C(3) between **2** and **3** (0.5 ppm) might be due to substituent effects of the *C*-methyl groups rather than differences in the position of the N–H. The chemical shifts of the α protons (H_{2e}, H_{2a}) and the shift differences between them, easily measured from the spectra of multideuterated analogues[1] of **1**, **2**, and **3**, were nearly identical ($\Delta\delta$ (ppm): **1**, 0.39; **2**, 0.48; **3**, 0.43). The conclusion was reached that either a syn-axial CH_3 does not impose any noticeable bias on the axial–equatorial NH equilibrium[1] in **1**, and hence in piperidine, *or else* the shift difference between H_{2e} and H_{2a} is insensitive to the position (axial or equatorial) of the lone pair on the adjacent nitrogen. Since an important argument for the preference of axial N–H in piperidine is based in essence on the contrary view,[7] we decided to look for model compounds in which the proton/lone pair equilibrium might be shifted one way or the other by the use of biasing groups more bulky than methyl.[8] A tertiary butyl group at C(8) appeared suitable for this purpose and we succeeded in synthesizing the two *tert*-butyl analogues of **2** and **3**, 8α-*tert*-butyl-*trans*-decahydroquinoline (**4**) and 8β-*tert*-butyl-*trans*-decahydroquinoline (**5**) and their N–CH_3 derivatives (**4m**, **5m**). ^{1}H-NMR, ^{13}C-NMR, and IR spectra of these compounds were recorded and are described in the sequel, as are the conclusions based on the spectral observations.

Scheme I



e a

R_1		R_2	R = H	$R = CH_3$
H		H	1	1m
CH_3		H	2	2m
H	=	CH_3	= 3	= 3m
$C(CH_3)_3$		H	4	4m
H		$C(CH_3)_3$	5	5m

† Dedicated to Professor Egbert Havinga on the occasion of his 70th birthday.

Results

Synthesis of 8-*tert*-Butyl-*trans*-decahydroquinolines. An adaptation of a method described earlier[9,1] for the preparation of other octa- and *trans*-decahydroquinolines was used (Scheme II). The enamine of pyrrolidine and 2-*tert*-butylcyclohexanone was condensed with acrylonitrile in anhydrous ethanol. The cyanoethylated product (**7**) was reduced with lithium aluminum hydride, and the 8-*tert*-butyloctahydro-$\Delta^{1,9}$-quinolines were formed by distilling the 3-aminopropyl compound **8** at aspirator vacuum. The octahydroquinolines (**9**) were reduced with sodium in ethanol to give a mixture of **4** and **5** (plus traces of cis compounds[10]) which were separated by preparative gas chromatography. The method lent itself to the synthesis of the 2- and 9-deuterated analogues (see Experimental Section) used to aid in ^{13}C NMR spectral assignments.

^{13}C-NMR Spectra. The ^{13}C chemical shifts of **4**, **5**, **4m**, and **5m** and of their hydrochlorides in $CDCl_3$ are recorded in Table I. Assignment of the signals is based on comparison with the spectra[2] of **1**, **2**, and **3**, off-resonance decoupling, and observation of disappearance, shifting, splitting, or broadening of peaks of deuterated analogues.[2] It is of interest that in **1**-2-d_2, **4**-2-d_2, **5**-2-d_2, and their *N*-methyl analogues dideuteration at C(2) produced an upfield shift but no broadening at C(3) and a noticeable broadening (but no significant shift) at C(4). This observation suggests that $^{3}J(^{13}C/^{2}H) > {}^{2}J(^{13}C/^{2}H)$; the large ^{3}J is presumably that involving the equatorial (antiperiplanar) deuterium.

From the ^{13}C shifts it is evident that the configurational assignments for **4** and **5** are correct. Both compounds must have trans ring fusion: the steroid cis configuration (C(8) axial) is excluded because of the downfield position of C(2) in both

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Table I. ^{13}C Chemical Shifts of *trans*-Decahydroquinolines[a,b]

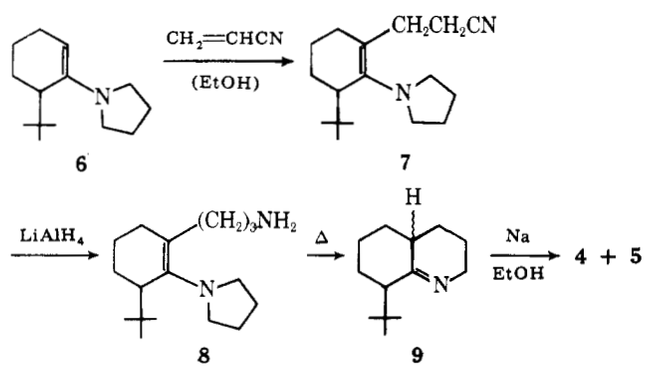
compd	registry no.	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-q	C-CH_3	N-CH_3
1[a]		47.3_3	27.2_9	32.4_6	32.6_4	26.2_9	25.6_4	34.0_0	62.0_9	43.3_4			
2[a]		47.5_5	26.9_3	32.6_2	33.0_2	25.8_4	34.9_0	37.5_1	67.9_7	42.2_2		18.5_9	
3[a]		47.6_7	27.4_6	(33.0_2)	(33.2_9)	20.2_3	(32.8_7)	33.1_6	64.5_8	35.6_1		12.6_3	
4	68366-99-4	47.3_2	27.6_1	33.4_9	33.6_1	26.4_1	28.3_7	50.9_9	65.4_7	43.7_8	33.0_5	29.8_9	
5	68367-00-0	48.7_3	27.3_1	34.6_2	33.8_4	22.0_2	29.9_4	46.5_7	68.2_3	36.1_2	34.4_0	32.7_1	
1m[a]		57.9_4	25.8_0	32.5_9	33.0_6	26.0_1	25.8_7	30.4_7	69.2_5	41.8_4			42.5_9
2m[a]		56.0_6	19.4_4	33.6_5	34.1_2	25.7_3	35.6_6	34.4_7	70.7_2	31.7_6		18.9_4	33.2_3
3m[a]		58.2_3	25.8_0	33.0_1	33.6_7	20.1_8	32.6_4	29.2_2	71.9_8	34.2_5		12.1_1	42.2_9
4m	68367-01-1	55.4_0	19.0_2	35.0_1	34.2_6	25.9_3	28.5_0	45.4_4	67.4_6	31.6_5	33.6_3	29.0_3	33.0_2
5m	68367-02-2	59.2_1	25.4_9	34.0_0	35.0_5	22.2_8	30.2_3	41.5_4	75.7_0	34.4_3	35.1_6	33.0_3	45.3_8
4·HCl	68367-03-3	47.9_9	21.7_4	31.1_5	33.1_1	24.8_9	27.6_1	49.2_5	65.0_6	39.1_2	32.7_7	29.9_0	
5·HCl	68367-04-4	47.7_3	22.1_0	32.3_6	33.6_5	20.7_1	29.6_3	43.9_8	66.4_1	33.3_1	33.9_1	32.7_3	
4m·HCl	68367-05-5	57.2_9	17.9_2	31.4_4	32.4_7	23.9_0	27.3_9	45.8_8	70.0_2	33.4_0	33.2_5	25.9_3	33.1_1
5m·HCl	68367-06-6	59.8_3	22.6_6	31.5_0	34.4_1	20.6_3	31.2_6	41.3_3	74.8_8	33.7_7	34.4_1	33.2_3	42.6_0

[a] From ref 2. [b] Solvent $CDCl_3$, ppm from internal Me_4Si. Values for which assignments are not unambiguous are parenthesized.

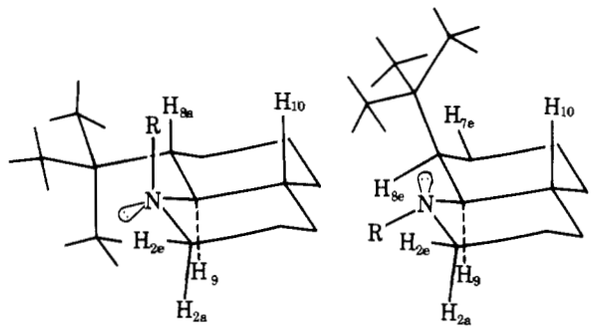
4 and 5 (47.3_2 and 48.7_3 instead of ~39–40 ppm[3]). The nonsteroid cis configuration (C(8) equatorial)[10] is similarly excluded since it displays at least two signals with chemical shifts less than 26 ppm (C(3) and C(5))[3] which are not present in 4 and 5. Comparison of the spectrum of 4 and 1 shows that 4 must have the *tert*-butyl group equatorial, since none of the carbon atoms of the *trans*-decahydroquinoline system are shifted upfield, and only C(8), C(7), and C(9) are shifted downfield by more than 1.5 ppm. Shifts of the more distant carbon atoms C(2) to C(6) and C(10) are only moderately affected, probably due to small deformations of the molecule by the bulky *tert*-butyl group; no serious deviations of the decahydroquinoline skeleton in 4 from the trans chair–chair conformation is evident.

In 5 the carbon atoms C(6) and C(10) are shifted upfield by 4.3 and 7.2 ppm, respectively, relative to 1, but shifted downfield by 1.8 and 0.5 ppm relative to 3. This indicates that the *tert*-butyl group is indeed in the axial position; the combination of γ and δ effects experienced by the above two carbon atoms leads to an upfield shift relative to 1. On the other hand replacement of the hydrogen atoms on the axial methyl substituent of 3 by methyl groups leads to additional δ effects on C(6) and C(10) which have been shown[3,11] to be downfield shifting. Carbon atoms C(7), C(8), and C(9) are obviously strongly influenced by the introduction of the *tert*-butyl group, C(2), C(4), and C(5) only moderately so. In any case the differences between 5 and 1 and 3 can be rationalized in terms of known shift effects; there is no indication that 5 exists in other than the double-chair conformation. The proton spectrum (see below) also supports the structural analogy of 5 to 1 and 3. Finally, the ^{13}C shifts engendered upon *N*-methylation of 5 are what one would expect for the introduction of an equatorial N-CH_3 in a *trans*-decahydroquinoline.[2] It thus appears that 5 exists in a double chair conformation with an

Scheme II



Scheme III



4a, R = H
4ma, R = CH_3

5e, R = H
5me, R = CH_3

axial *tert*-butyl substituent; the resulting strain is probably somewhat relieved by the substituent bending away from C(6) and C(10) (see Scheme III).[27]

The signals for N-CH_3 and for C(3) in **4m** are very close to the corresponding values in **2m**. Model considerations suggest that once the N-CH_3 group is axial (as in **4ma**) it is no longer subject to the severe interactions of **4me**. The similarity of the pertinent shifts in **4ma** and **2ma** indicates that the N-CH_3 group is already completely axial in **2m** as previously hypothesized,[4a] and that the geometry of **4m** is once again similar to the lower homologue lacking the bulky *tert*-butyl group. In **5m**, on the other hand, the N-CH_3 shift is 3.1 ppm more downfield than in **3m**. This is obviously not due to any N-CH_3-axial contribution in **3m** (since even without the biasing 8β-CH_3 group the equilibrium is >95% on the equatorial side) but to additional steric compression caused by the *tert*-butyl group.

^1H NMR Spectra. The 100-MHz ^1H-NMR spectrum of 4 (solvent $CDCl_3$) shows three signals resolved from the broad envelope of the remaining protons. A doublet (13 Hz) of multiplets at 3.09 ppm is assigned to the equatorial proton at C(2) (H_{2e}), an apparent triplet of doublets at 2.55 ppm to the axial proton at this carbon atom (H_{2a}). Both protons have chemical shifts similar to those in 1, 2, and 3. An apparent triplet (two anti couplings to H_{8a} and H_{10}; $J \simeq 8.5$ Hz) at 2.07 ppm is assigned to the proton at C(9) (H_9); this signal is shifted upfield by the CH_3 group at C(8) in 2[1] from its original position of 2.08 ppm in 1 but is now shifted back downfield by the *tert*-butyl group. The CH_3 signal of the *tert*-butyl group appears at 1.0 ppm.

In 5, H_{2e} is again a doublet of multiplets, at 3.15 ppm, and H_{2a} is an apparent triplet of doublets at 2.54 ppm coinciding with a doublet of doublets (H_9) at 2.55 ppm (J = 10, 5 Hz),

Table II. ^{1}H Chemical Shifts[a] and Shift Differences[b] for H_{2e} and H_{2a} in 1–5

compd	registry no.	solvent	δH_{2e}	δH_{2a}	$\Delta\delta$
1	767-92-0	$CDCl_3$	3.07	2.67	0.41
2	52730-00-4		3.11	2.61	0.50
3	52761-68-9		3.10	2.65	0.45
4			3.09	2.55	0.54
5[c]			3.15	2.54	0.61
1		$CFCl_3$	2.98	2.59	0.39
2			3.02	2.54	0.48
3			3.01	2.60	0.41
4			3.04	2.48	0.56
5[c]			3.10	2.53	0.57
1		CD_3OD	3.00	2.60	0.40
2			3.06	2.57	0.49
3			3.04	2.57	0.47
4			3.06	2.55	0.51
5[c]			3.11	2.49	0.62
1		C_6D_6	2.90	2.47	0.43
2			2.97	2.50	0.47
3			2.95	2.51	0.44
4			2.94	2.40	0.54
5[c]			2.97	2.37	0.60
1H$^+$[d]	57288-91-2	CF_3COOH	3.64	3.18[e]	0.46
2H$^+$[d]	57288-98-9		3.66	3.16	0.50
3H$^+$[d]	57289-01-7		3.65	3.20	0.45
4H$^+$[d]	68367-07-7		3.74	3.17[e,f]	0.57
5H$^+$[c,d]	68367-08-8		3.76	3.16	0.60
1H$^+$[g]	4678-90-4	$CDCl_3$	3.4_7	2.8_5	0.6_2
2H$^+$[g]	55905-31-2		3.6_0	2.8_7	0.7_3
3H$^+$[g]	55905-28-7		3.5_5	[h]	
4H$^+$[g]			3.7_9	2.9_8	0.8_1
5H$^+$[c,g]			3.7_0	2.8_4	0.8_6

[a] In ppm, from Me_4Si, at 100 MHz. Values are centers of signals in the spectra. Although coupled to adjacent protons the width of H_{2e} or H_{2a} in a certain solvent for **1–5** is practically identical, so the values are considered significant to ±0.02 ppm. Although of identical signal width, the coupling pattern (apparent triplet of doublets) of H_{2a} for **4** was less clear than in the compounds **1, 3,** and **5.** This was most pronounced in C_6D_6 and $CFCl_3$, less in $CDCl_3$, and least in CD_3OD. The apparent triplet of H_9 showed a similar behavior. A much less pronounced effect was seen for H_{2a} in **2** in C_6D_6 and $CFCl_3$. [b] $\Delta\delta = \delta H_{2e} - \delta H_{2a}$. [c] Signals of H_{2a} and H_9 were strongly overlapping, so **5-9-*d*** was used. [d] Gegenion CF_3COO^-. [e] Partly overlaid with H_9. [f] **4-9-*d*** was used for recording. [g] Gegenion Cl^-. Signals were extremely broad and ill resolved and are considered less reliable than the other series. [h] Not resolved since strongly overlaid.

shifted still more downfield from its position of 2.23 ppm in **3** by the replacement of the axial methyl by the *tert*-butyl group. The complex pattern is resolved in **5-2-*d*$_2$** and **5-9-*d*.** The coupling of H_9 provides an additional indication that the *tert*-butyl substituted cyclohexane ring is in the chair form. The pattern is closely similar to that in **3**;[1] if the cyclohexane ring were boat shaped, the coupling between H_{8e} and H_9 should change significantly. The similarity in shift and coupling of H_{2e} and H_{2a} in **1–5** provides strong evidence that all these compounds have the same (chair) geometry of the piperidine ring.

Another apparent doublet (12 Hz) of multiplets must belong to the equatorial proton at C(7) (H_{7e}) which is the only proton besides H_{2e} with only one large coupling (i.e., the geminal coupling with the axial proton on the same carbon atom); this signal is also strongly downfield shifted by the syn-axial CH_3 of the *tert*-butyl group. The CH_3 signal of the *tert*-butyl itself resonates at 1.12 ppm, considerably downfield from that in **4**, providing an indication of steric compression.

As mentioned above, shift differences between axial and equatorial geminal α protons have been used[7] as an indication of the position of lone pairs in *N*-alkylpiperidines and, by extension, in piperidines themselves. We therefore recorded (Table II) these differences for **1–5** in solvents $CDCl_3$, $CFCl_3$, C_6D_6, CD_3OD, and CF_3COOH (salts). Contrary to the earlier suggestion[7] there is no evidence that H_{2a} is at higher field when there is a supposedly greater proportion of the form with axial lone pair (see Scheme III; compare **3** with **2** and **5** with **4** in Table II). Moreover H_{2a} in **2** and **4** (where the pair is expected to be predominantly equatorial) is upfield rather than downfield from the parent **1.** Focussing on $\Delta\delta$[7] one sees that although $\Delta\delta$ increases as one goes from **1** to **3** to **5,** this increase seems to be due to the alkyl substituents and is due as much to variations in δH_{2e} as in δH_{2a}. It is certainly not due—again contrary to the earlier claim[7]—to a change in position of the lone pair, for the change in $\Delta\delta$ between **2** and **3,** or between **4** and **5,** is not only very small but also erratic as to its direction. Thus for **4** → **5** $\Delta\delta$ increases as expected in $CDCl_3$, CD_3CD, and C_6D_6 but remains constant in $CFCl_3$ and it increases also in CF_3COOH where there is no lone pair left. For **2** → **3,** on the other hand, $\Delta\delta$ decreases in all solvents. And, in almost all cases, $\Delta\delta < 0.1$ ppm for a pair of stereoisomers.

IR Spectra. Since neither ^{13}C- nor ^1H-NMR spectra yielded any information regarding the conformational equilibrium at N for the secondary amines, an attempt was made to get at least a qualitative indication from the Bohlmann bands.[12] IR spectra of **1–5, 1m–5m,** and the C(2) dideuterated analogues were recorded in 0.03 M solution in CCl_4; the pertinent regions of **2, 3, 4, 2m, 3m,** and **4m** (as well as 4-NCD_3) are shown in Figure 1.[13]

The spectra of the *N*-methylated compounds fall into two groups. Compounds **1m, 3m,** and **5m** display strong bands of nearly constant intensity in the region between 2815 and 2500 cm^{-1}. In **3m** and **5m** the *N*-methyl group is completely equatorial and in **1m** over 95% equatorial and the lone pair on nitrogen is anti to H_{2a},H_9 and to one of the protons of the N-CH_3 group; in addition one of the H_3C-N absorptions oc-

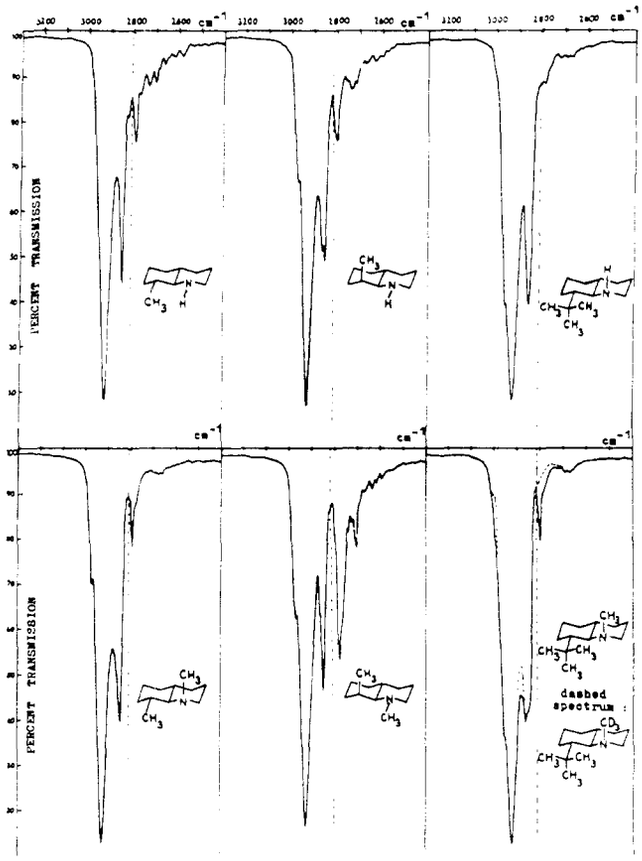


Figure 1. Infrared spectra in the 3400–2200-cm^{-1} region of compounds **2, 3, 4, 2m, 3m, 4m,** and **4m**-NCD_3

curs in that region. In **2m** and **4m** the NCH_3 group is completely axial; only a comparatively strong band at 2790 cm^{-1} (in **2m**) or 2800 cm^{-1} (in **4m**), again of practically constant intensity, remains, which is probably due to the NCH_3 absorption. In the spectrum of 4-NCD_3 this band disappears. Thus Bohlmann bands give a clear indication as to the position of the lone pair on nitrogen in *N*-methyl-*trans*-decahydroquinolines.[14]

The situation is different in the secondary amines. Compounds **1, 2, 3,** and **5** again show a pronounced absorption minimum at 2815 cm^{-1}, followed by a fairly strong band centered at 2790 cm^{-1}, and then by a number of weaker bands which gradually diminish toward 2500 cm^{-1}. Since there is no NCH_3, the bands must be expected to be weaker than in the corresponding tertiary amines, but it seems significant that there is no pronounced difference between **1, 2, 3,** and **5,** suggesting that H/pair equilibrium at N is quite similar in these four compounds. Compound **4** shows a very much reduced absorption in the region between 2800 and 2500 cm^{-1}; the minimum at 2800 (a near shoulder) is followed by only a small peak at 2780 cm^{-1}, and the absorption of 2760–2740 cm^{-1}, rather noticeable in **1–3** and **5,** has almost completely disappeared.

Attempts to make quantitative assessments from IR spectra are plagued by a number of difficulties. Only very simple semiquantitative treatments were therefore attempted. After converting from percent transmission to extinction, the areas of the two regions 3100 to 2815 cm^{-1} (presumably due to other C–H vibrations) and 2815 to 2500 cm^{-1} (due to Bohlmann bands and any overlap of the C–H region) were measured. The area from 2815 to 2500 cm^{-1} of 4-NCD_3, a compound in which no Bohlmann bands can occur, was used as background and consequently substracted from the 2815–2500-cm^{-1} region in **1–5** and **1m–5m.** The uncertainty in the intensities computed in this way is about 10%. The ratio of the corrected 2815–2500-cm^{-1} region to the total multiplied by 100 was taken as the percentage of Bohlmann bands and is indicated, together with the integrated intensities, in Table III.

The intensities of the Bohlmann band regions of **3m** and **5m** and of **2m** and **4m** should be identical; the agreement is reasonable. Since no lone pair is anti positioned to α protons in **4m,** an exchange of the protons at C(2) (to give **4m**-2-d_2) should not change the intensities in the 2815–2500-cm^{-1} region; again, the areas compare quite well.

Since additional C–H vibrations are introduced into the molecule going from **1** to **2** and **3** and to **4** and **5,** a direct comparison of percentages is not possible. If this is borne in mind, values for **1m** and **3m** compare reasonably well with **5m,** where the percentage is smaller due to the additional *tert*-butyl C–H stretches in the 3100–2815-cm^{-1} area; a similar argument applies to **2m** and **4m.** In the case of the secondary amines, the percentages are very similar for **1, 2,** and **3;** the value is again smaller for **5** because of the additional *tert*-butyl. However, in **4** the value has been reduced to 2.9%. Only a small part of this reduction is caused by the increase in the area from 3100 to 2815 cm^{-1} (about 2%; compare **2m** with **4m**), meaning that most, but not all, of the proton on nitrogen has been shifted to conformation **4a.**

In 1-NCD_3 and 4-NCD_3 the *N*-methyl group makes no contribution to the 2815–2500-cm^{-1} region, and the position of the conformational equilibrium of methyl vs. pair on nitrogen has been established[4] (≥95% R_{eq} in 1-NCD_3, 0% R_{eq} in 4-NCD_3). If the Bohlmann band regions of these compounds are used as probes for the secondary amines **1–5** (making the assumptions that the spectra can be compared, that the background in the 2815–2500-cm^{-1} region is identical, and that the Bohlmann band intensities of secondary and tertiary amines are comparable), the following values for N–H equatorial are obtained: **1,** ~70%; **2,** ~65%; **3,** ~75%; **4,** ~20%; and **5,** ~80%. Because of the various assumptions these values are regarded as only approximate; however, the value calculated for **1** is identical to the one reported[8] based on a different method.

The spectra of the C(2)-dideuterated compounds show reduced intensities between 3100 and 2815 and between 2815 and 2500 cm^{-1}, but three additional bands appear between 2300 and 2000 cm^{-1}. One band at 2300–2000 cm^{-1} is of approximately constant intensity in all six compounds, one at 2130–2070 cm^{-1} is strong when R on nitrogen is axial and the lone pair is equatorial, and one at 2070–2000 cm^{-1} is strong when R on nitrogen is equatorial and the lone pair is axial. The intensities of these bands are given in Table IV;[13] they confirm in a qualitative way the results from the protio analogues reported above.

Discussion

Much effort has been expended in establishing the conformational equilibrium of the N–H vs. the lone electron pair in piperidine; most of the results have been recently reviewed.[15,16] Very recently Anet and Yavari, in a DNMR investigation,[17] have succeeded in freezing the equilibrium at −170 °C; an 85%:15% ratio of the two conformers at this temperature was determined by ^{13}C NMR, corresponding to a ratio of 65%:35% at room temperature on the reasonable assumption that $\Delta S^0 = 0$. ^1H NMR at −172 °C suggested the major form to be the one with N–H equatorial.[17] This result, while agreeing with a number of earlier published ones,[15] is in contradiction to the findings of Lambert's group.[7] Indeed, in a recent review[16] Lambert has stated "Thus no flaw has yet been found in this method, but it suffers from being only qualitative", referring to his method of evaluating the degree of equatorial or axial character of a lone pair on nitrogen from the shift differences ($\Delta\delta_{ae}$) of the α protons.[7] The present work

Table III. Integrated Intensities[a] of the IR Bands in the Region of 3100 to 2500 cm^{-1}

compd	registry no.	3100–2500	3100–2815	2815–2500[b]	2815–2500[c]
1		34.52	28.92	5.60	4.26 (12.3)
2		35.10	29.91	5.19	3.85 (11.0)
3		37.56	33.01	5.89	4.55 (12.1)
4		41.90	39.33	2.57	1.23 (2.9)
5		46.95	40.77	6.15	4.84 (10.5)
1m	875-63-8	38.12	29.12	9.00	7.66 (20.1)
2m	55970-12-2	40.33	37.30	3.03	1.69 (4.2)
3m	52008-64-7	40.58	30.09	10.49	9.15 (22.5)
4m		47.88	45.40	2.48	1.14 (2.4)
5m		50.51	40.70	9.81	8.47 (16.8)
1-2-d_2	32204-77-6	25.35	22.59	2.67	1.42 (5.6)
4-2-d_2	68367-09-9	38.89	37.14	1.75	0.41 (1.1)
5-2-d_2	68367-10-2	38.38	34.60	3.78	2.44 (6.4)
1m-2-d_2	54193-92-9	32.96	26.47	6.49	5.15 (15.6)
1-NCD_3	54193-91-8	31.00	23.94	7.06	5.72 (18.5)
4m-2-d_2	68367-11-3	43.76	41.02	2.73	1.39 (3.2)
4-NCD_3	68367-12-4	41.06	39.72	1.34	0.0[c] (0.0[c])
5m-2-d_2	68388-79-4	44.46	38.08	6.38	5.04 (11.3)

[a] Unit: L cm^{-2} mol^{-1} × 10^{-3}; see Experimental Section. [b] Bohlmann band region. [c] Bohlmann band region corrected for background; the area of **4**-NCD_3, a compound in which no Bohlmann bands occur, was used. Parenthesized values are the ratio of corrected 2815–2500-cm^{-1} region to 3100–2500-cm^{-1} region multiplied by 100 = percent of Bohlmann bands.

Table IV. Integrated Intensities in the Region of 2300–2000 cm^{-1} of 2,2-Dideuterated Compounds[a]

compd	2300–2130	2130–2070	2070–2000
1-2-d_2	0.95	0.51	1.15
4-2-d_2	1.24	0.82	0.64
5-2-d_2	1.10	0.50	1.45
1m-2-d_2	0.86	0.31	1.67
4m-2-d_2	1.07	0.90	0.21
5m-2-d_2	0.86	0.30	1.30

[a] Unit: L cm^{-2} mol^{-1} × 10^{-3}; see Experimental Section.

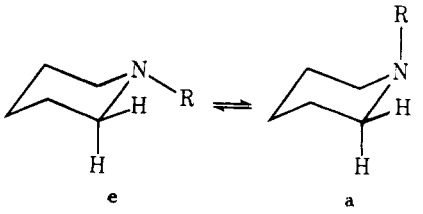
shows that, contrary to earlier (and at the time, entirely reasonable) expectations, the method is apparently not even qualitatively correct for piperidines with no *N*-alkyl substituent.

The argument to be presented depends on **4** and **5** (Schemes I and III) existing essentially in chair conformations, thus this point must be established at the onset. Neither the ^1H- nor the ^{13}C-NMR spectra give any indication that the geometry of **4** and **5** is substantially different from that of **1**. The conformational energy differences between the chair and the twist or boat forms in cyclohexane are 5–5.5 and about 6.5 kcal/mol, respectively;[18] in a recent calculation the conformational energy of an axial *tert*-butyl group has been determined to be 5.4 kcal/mol higher than that of an equatorial one.[19] Thus in *tert*-butylcyclohexane there is a near standoff between a twist form and a chair with axial *tert*-butyl. However, the situation in **5** is much less favorable to the twist or boat, for model considerations indicate that the constraints of the annelated piperidine ring are such that the twist or boat conformations with maximal relief of strain at the *tert*-butyl group are not accessible save at the expense of excessive flattening of the nitrogen-containing ring. And, in turn, those boat or twist conformations of the carbocyclic ring which preserve the piperidine ring as an unstrained chair provide little steric relief to the *tert*-butyl group. The only twist conformations we can envisage for **4** have more strain than the one shown in Scheme III. Thus both a priori conformational arguments and arguments based on ^{13}C- and ^1H-NMR spectra indicate that **4** and **5** are adequate models for an investigation of the conformational equilibrium of **1**.[27] The same goes for **4m** and **5m** as models for **1m**, and, indeed, all three spectroscopic methods applied to the *N*-methylated compounds confirm the earlier results[4] with **2m** and **3m**.

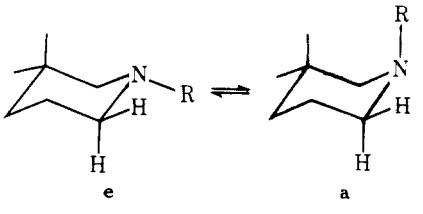
If it is granted that **4** and **5** are in chair conformations, a direct comparison of $\Delta\delta_{ae}$ between **4** and **5** as well as between **2** and **3** may be made, and as already pointed out (cf. Table II) there is no systematic indication that $\Delta\delta_{ae}$ is any larger for the **4/5** pair than for **2/3**, nor is there any indication for H_{2a} being at lower field in **2** and **4** than in **1**, **3**, and **5**. In other words, there is no evidence that an axial proton on carbon anti-periplanar to a lone pair on nitrogen in an NH compound is shifted upfield relative to one which is not so located.

This surprising finding may have one or another of two causes. *Either* there is indeed no upfield shift due to the anti-periplanar pair *or* the equatorial or axial substituents at C(8) methyl or *tert*-butyl do not affect the NH axial/equatorial equilibrium. NMR spectroscopy appears to be unable to distinguish between the two possibilities. We therefore turned to an investigation of Bohlmann bands in the infrared to arrive at a choice. This method has been used previously for the determination of the conformational equilibrium in piperidine;[12] in an investigation of both piperidine itself and a number of condensed piperidines[14] as well as with 2,6-di-

Scheme IV



10, R = H
10m, R = CH_3



11, R = H
11m, R = CH_3

deuteriopiperidine[20] a quantitative evaluation was attempted, with identical results for the proton and deuterio compounds. (70% NH equatorial). Of the several assumptions which were necessary in these investigations, at least one,[20] the adequacy of *N*-isopropylpiperidine as a model for a 100% axial lone pair, has since been confirmed.[4] The effect of two syn-axial methylene groups on the NH/N: equilibrium was calculated to be 0.52 kcal/mol, based on *trans-anti-cis*-perhydroacridine, the only conformationally homogeneous model compound with such an interaction available in this investigation.[14] It seems therefore that integration of the bands in the Bohlmann region is a reasonable method for establishing the NH conformational equilibrium especially in view of the fact that the results agree with the more recent DNMR determination.[17]

The results from the examination of the Bohlmann bands appear quite clear (see Results, IR spectra, and Table III); there are only small differences among compounds **1, 2, 3,** and **5** (from ~65 to ~80% N–H equatorial). Only compound **4** shows appreciably less intensity in the 2815–2500-cm^{-1} region, suggesting that the lone pair is substantially, but not exclusively, equatorial. For comparison, the *N*-methyl compounds, whose conformational behavior is well understood from previous work,[4] were investigated and showed the expected absorption intensities (see above).

It must be concluded that the absence of consistent differences between resonances of the α protons in **4** and **5** does not reflect a constant NH axial/equatorial equilibrium; Bohlmann bands clearly show that **4** has more axial H than **5.** The ^1H NMR signals are evidently not palpably affected by this difference. No conclusions can thus be drawn from the lack of consistent differences of the α-proton shifts in **2** and **3;** however, the evidence from the IR experiments suggests that with these compounds the NH equilibrium is not greatly affected by the configuration of the methyl group at C(8).[21]

The latter conclusion is contrary to that reached earlier[7] in a comparison of piperidine (**10**) and 3,3-dimethylpiperidine (**11**) (Scheme IV). It was argued[7] that the difference in $\Delta\delta_{ae}$ in **10** (0.44 ppm) and **11** (0.61 ppm) indicated a lesser proportion of the **11a** configuration in the latter. We have already pointed out that a δ substituent may have a direct effect (i.e., other than by affecting the NH configuration) on $\Delta\delta_{ae}$ (cf. Table II); since it has such an effect in *trans*-decahydroquinoline (substituent 8-Me or 8-*t*-Bu), it may also have a corresponding effect in piperidine (3-Me).[22] This point may be made more concrete by comparing **10m** and **11m.** It has been found[7] that $\Delta\delta_{ae}$ is increased from 0.94 ppm in **10m** to 1.11 ppm in **11m.** The difference of 0.17 ppm was ascribed to the greater proportion of **11me** compared to **10me.** However, it is now known[6] that the proportion of **10me** is 99%, thus that of **11me** cannot be significantly greater. Hence this 0.17-ppm difference is not due to a greater proportion of **11me** but must be due to a substituent effect of the *C*-methyl groups. If the same substituent effect (0.17 ppm) were operative in **11,** it would neatly explain the observed difference (0.17 ppm) in $\Delta\delta_{ae}$ in **10** and **11;** thus this difference should not be interpreted in terms of differing NH equilibria as between **10** and **11.** In other words, the earlier observations[7] are totally compatible with ours, even if their interpretation is not.[23]

Conclusions

1. The areas of the Bohlmann bands in the IR can be used to quantitatively estimate the N–R conformational equilibrium, both for R = H and alkyl, if the background of the 2815–2500-cm^{-1} region can be determined (for instance from deuterated analogues, or from *N*-benzoyl derivatives[14]). However, since the background area is small, qualitative conclusions can be drawn without this correction.

2. Syn-axial CH_3 groups change the NH conformational equilibrium in *trans*-decahydroquinolines only slightly, syn-axial *tert*-butyl groups considerably in favor of the isomer with the free electron pair syn-axial to the biasing group. The predominant conformation in *trans*-decahydroquinoline is the NH equatorial one.

3. The ^1H chemical shift difference method gives correct results only for the *N*-alkyl axial/*N*-alkyl equatorial equilibrium in *N*-alkyl-*trans*-decahydroquinolines (and piperidines); for the N–H analogues the chemical shifts of the α protons are insensitive to the N–H equilibrium. ^{13}C shifts of carbon atoms β to nitrogen are suitable probes only for *N*-alkyl but not N–H axial–equatorial equilibria.[24,25]

Experimental Section

Melting points were determined on a Kofler hot stage and are uncorrected.

Microanalyses were carried out at the Institute of Physical Chemistry, University of Vienna, by Dr. J. Zak.

The 60-MHz ^1H NMR spectra were recorded on a Varian EM 360 spectrometer with ^1H internal lock facility. The 100-MHz ^1H- and ^{13}C-NMR spectra were measured on a Varian XL-100 pulsed Fourier transform NMR spectrometer in FT mode at 29 ± 1 °C. The ^{13}C spectra were measured in $CDCl_3$ solution in 10 mm o.d. tubes at 25.16 MHz; the solvent provided the lock signal; 2% Me_4Si was added as an internal reference. Digital resolution was 0.6 Hz (0.025 ppm) at 8K data points and 2500 Hz sweep width. The 100 MHz ^1H spectra were recorded in 5-mm o.d. tubes in the solvents reported in Table II; the lock signal was deuterium or fluorine.

IR spectra were recorded on a Beckmann Model 4250 IR spectrometer in 0.5-mm NaCl cells on 0.03 M solution in CCl_4.[13] For determination of intensities the pertinent region was recorded with a chart expansion of 50 cm^{-1} = 1 in. Percent transmission was converted into extinction ($E = \log I_0/I = \epsilon cl$) for each wave number ν and the area was then determined by $\int \epsilon_\nu \, d\nu$. The estimated uncertainty of the intensities collected in Table III is ±10%.

Compounds **1, 2, 3, 1m, 2m, 3m,** and **1**-NCD_3 were prepared as previously reported.[1,4]

8-*tert*-Butyl-*trans*-decahydroquinolines (4, 5) (cf. Scheme II). *N*-(6-*tert*-Butylcyclohexenyl)pyrrolidine (6). A solution of 154 g (1 mol) of 2-*tert*-butylcyclohexanone,[26] 110 g of pyrrolidine, and 2 g of *p*-toluenesulfonic acid in 1.3 L of toluene was heated to reflux. No water separated in a Dean-Stark trap. The distillate was therefore passed over 400 g of 3 Å molecular sieves (previously activated at 300 °C/10^{-3} torr) in a Friedrich-type extractor and returned to the flask. After 30 days of this treatment the solvent was distilled at reduced pressure to give 90 g (58%) of unreacted *tert*-butylcyclohexanone (bp 80–85 °C/8 torr) and 78 g (38%) of **6** (bp 80–85 °C/0.5 torr): ^1H NMR (60 MHz) δ 4.85 (1 H, olefin; tr, J = 3.5 Hz), 3.25–2.40 (4 H, Hα pyrrolidine), 2.40–1.30 (11 H), 1.00 (9 H, *tert*-butyl, s).

1-*N*-Pyrrolidinyl-2-(2-cyanoethyl)-6-*tert*-butylcyclohexene (7). A solution of 30.75 g of **6** and 9 g of freshly distilled acrylonitrile in 50 mL of anhydrous ethanol was heated to reflux for 36 h. The solvent was distilled followed by distillation of the residue to give 28.7 g of **7** (74%), bp 131 °C/0.5 torr. The compound crystallized in the refrigerator: mp 40–42 °C; ^1H NMR (60 MHz) δ 3.5–2.6 (4 H, Hα pyrrolidine), 2.6–1.15 (15 H), 0.96 (9 H, *tert*-butyl; s).

1-*N*-Pyrrolidinyl-2-(3-aminopropyl)-6-*tert*-butylcyclohexene (8). A solution of 28.7 g of **7** in 100 mL of anhydrous ether was slowly added to a stirred suspension of 4.5 g of $LiAlH_4$ in 400 mL of anhydrous ether. The mixture was stirred overnight and was then carefully decomposed with the minimum amount of water. The ether solution was decanted from the suspended salts and the salts were washed repeatedly with ether. The ether phases were combined and concentrated. The residue was distilled without decomposition at 10^{-2} torr, by 120 °C, to give **8.** ^1H NMR (60 MHz) δ 3.50–2.45 (4 H, Hα pyrrolidine), 2.45–1.15 (19 H), 0.95 (*tert*-butyl; s).

8-*tert*-Butyl-$\Delta^{1,9}$-octahydroquinoline (9). Crude **8** (without previous distillation) was heated on a small Vigreux column at atmospheric pressure; the receiver was cooled with dry ice–acetone. The bath temperature was gradually raised to 180 °C. If no distillation took place, a few drops of water were added through the column to initiate reaction. After a few hours the pressure was slowly reduced to 30 torr and the bath temperature raised to 190–200 °C. The distillate consisted of pyrrolidine and **9.** The material was redistilled to give 15.6 g of **9** (from 24 g of **7**; 87% yield), bp 120 °C/16 torr. The product was a mixture of stereoisomers (major α-*tert*-butyl, ~75%; minor β-*tert*-butyl, ~25%): ^1H NMR (60 MHz) δ 3.51 (2 H, H-2's, s, half-width 11

Hz), 2.25–1.15 (12 H), 1.03 and 0.97 (ratio 75:25, together 9 H, *tert*-butyl).

α-**9:** ^{13}C NMR ($CDCl_3$) δ 172.78 (C(9)), 57.40 (C(8)), 49.19 (C(2)), 39.69 (C(10)), 36.44 (C(5)), 32.66 (**C**(CH_3)$_3$), 30.26 (C(7)), 28.10 (C(**C**H_3)$_3$), 27.79 (C(4)), 26.85 (C(6)), 20.02 (C(3)). β-**9:** ^{13}C NMR ($CDCl_3$) 175.26 (C(9)), 55.69 (C(8)), 49.54 (C(2)), 36.07 (C(5)), 34.11 (**C**(CH_3)$_3$), 33.76 (C(10)), 29.73 (C(**C**H_3)$_3$), (27.62) (C(4)), (26.58) (C(7)), 22.53 (C(6)), 20.52 (C(3)). Integration of ten pairs of signals gives an isomer ratio of 78:22.

Picrate (from stereoisomer mixture), mp 181–183 °C (ethanol). Anal. Calcd for $C_{19}H_{26}N_4O_7$: C, 54.02; H, 6.20. Found C, 54.24; H, 6.18.

8α-*tert*-Butyl-*trans*-decahydroquinoline (4), 8β-*tert*-Butyl-*trans*-decahydroquinoline (5). A solution of **5** g in 60 mL of anhydrous ethanol was reduced with 12 g of sodium in the manner previously reported.[1] The mixture of products was distilled in a Kugelrohr distillation unit: air bath temperature 150 °C at 25 torr, yield of distillation product 4.77 g (94%). The mixture of 8-*tert*-butyldecahydroquinolines (57% **4**, 6.6% 8α-*tert*-butyl-*cis*-decahydroquinoline,[10] and 37% **5** + traces of 8β-*tert*-butyl-*cis*-decahydroquinoline; composition determined by GC on a 20-m Pluronic 64 glass capillary column at 100 °C) was separated by preparative GC (on a 4-m aluminum column, o.d. 0.375 in.; 20% Carbowax 20 M + 10% KOH on Chromosorb A, 60/80 mesh, at 165 °C; carrier gas He). Two fractions were collected, the first one consisting of **4** and 8α-*tert*-butyl-*cis*-decahydroquinoline (not isolated),[10] the second mainly of **5**.

For ^{13}C and ^{1}H NMR and IR spectra of **4** and **5** see Tables I–III and text.

Picrate of **4:** mp 185–187 °C (ethanol). Anal. Calcd for $C_{19}H_{28}N_4O_7$: C, 53.77; H, 6.65. Found: C, 53.71, H, 6.52.

Picrate of **5:** mp 204–206 °C (ethanol). Anal. Calcd for $C_{19}H_{28}N_4O_7$: C, 53.77; H, 6.65. Found: C, 54.01, H. 6.54.

N-Methyl derivatives of **4** and **5** (**4m, 5m**) were prepared by the standard Clarke-Eschweiler procedure by heating with HCOOH and HCHO.

Picrate of **4m:** mp 153–155 °C (ethanol).

Picrate of **5m:** mp 142–144 °C (ethanol).

***N*-Trideuteriomethyl-8α-*tert*-butyl-*trans*-decahydroquinoline (4-NCD$_3$)** was prepared as reported for 1-NCD$_3$.[4] Reaction of the mixture of **4** and 8α-*tert*-butyl-*cis*-decahydroquinoline, obtained by preparative GC, with CH_3OCOCl did not take place quantitatively.[10] The unreacted amines were recovered from the basified aqueous solution. GC (see above) showed the cis compound enriched to a ratio of 31 to 69% **4**. The ^{13}C spectrum of the mixture allowed the assignment of the signals of 8α-*tert*-butyl-*cis*-decahydroquinoline ($CDCl_3$): 58.16 (C(9)), 51.70 (C(8)), 47.87 (C(2)), 37.73 (C(10)), 32.62 (**C**(CH_3)$_3$), 31.38 (C(4)), 29.08 (C(**C**H_3)$_3$), 27.16 (C(6)), 25.35 (C(5)), 21.77 (C(3), C(7)).

Compounds **4**-9-*d* and **5**-9-*d* were prepared by reduction of **9** with sodium in ethanol-*O*-*d* as described[1] for **1**-9-*d*.

Compounds **1**-2-d_2, **4**-2,d_2, and **5**-2-d_2 were prepared by reducing 1-*N*-pyrrolidinyl-2-(2-cyanoethyl)cyclohexene[9] or **7**, respectively, with $LiAlD_4$ instead of $LiAlH_4$ and otherwise proceeding as described above or elsewhere.[1,8]

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Registry No.—**4** picrate, 68367-13-5; **4m** picrate, 68367-14-6; **5** picrate, 68367-15-7; **5m** picrate, 68367-16-8; **6**, 68367-17-9; **7**, 68367-18-0; **8**, 68367-19-1; **9** isomer 1, 68367-20-4; **9** isomer 2, 68367-21-5; **9** isomer 1 picrate, 68367-22-6; **9** isomer 2 picrate, 68367-23-7; 2-*tert*-butylcyclohexanone, 1728-46-7; pyrrolidine, 123-75-1; acrylonitrile, 107-13-1; 8-*tert*-butyldecahydroquinoline, 68367-24-8.

Supplementary Material Available: The infrared spectra of **1–5**, **1m–5m**, 1-NCD$_3$, **4**-NCD$_3$, **1**-2-d_2, **4**-2-d_2, **5**-2-d_2, and the corresponding *N*-methyl-2-d_2 homologues (20 pages). Ordering information is given on any current masthead page.

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(21) If the (N):/CH_3 were comparable to (O):/CH_3, it would amount to 0.45 kcal/mol (cf. E. L. Eliel and M. C. Knoeber, *J. Am. Chem. Soc.*, **90**, 3444 (1968)). Again, if NH/CH_3 can be compared to CH/CH_3, it is assessed at 0.75 kcal/mol. With these values added to a difference of 0.5 kcal/mol as between equatorial and axial NH in *trans*-decahydroquinoline (i.e., ~70/~30; see text and ref 8), the percentages of NH equatorial would be 56% in **2** and 81% in **3**. The values found are different, indicating that ΔG^0(NH/CH_3) − ΔG^0((N):/CH_3) = 0.15 kcal/mol; it thus appears that the syn-axial (N):/CH_3 interaction is appreciably larger than (O):/CH_3.
(22) We see a similar effect in the shift of H_9 in *trans*-decahydroquinoline, 2.08 ppm, vs. the 3α-methyl homologue, 1.99 ppm.[1] Since the 3α-methyl group is equatorial, it can have no effect on the NH equilibrium.
(23) Part of the argument in ref 7 was based on the observation that $\Delta\delta_{ae}$ becomes the same for **10** and **11** in the corresponding hydrochloride salts. This seems to have been fortuitous; in the case of **1–5** the range of $\Delta\delta_{ae}$ is about the same in CF_3CO_2H (salts) as in any of the other solvents (free amines).
(24) In the NH axial conformer of **10** the ^{13}C signal of C-3,5 was found to be 1.8 ppm more downfield than in the NH equatorial conformer at −170 °C.[17] Based on the results of the IR spectra (~80% NH axial in **4**, ~20% NH axial in **5**) a shift difference for C-3 of 1.1 ppm might be expected for **4** and **5**, but only 0.3 ppm is found. There is a shift difference for C-3 of 0.42 ppm for **2m** and **4m** and of 0.31 ppm for **3m** and **5m**, which have identical conformation on N. The effects of the biasing substituents are obviously of the same order of magnitude as the probable shift differences engendered by the H/pair equilibrium on nitrogen.
(25) Similar conclusions are reached from the ^{15}N spectra: (a) R. O. Duthaler, K. L. Williamson, D. D. Giannini, W. H. Bearden, and J. D. Roberts, *J. Am. Chem. Soc.*, **99**, 8406 (1977); (b) R. L. Lichter et al., manuscript in preparation.
(26) L. Schmerling, *J. Am. Chem. Soc.*, **69**, 1121 (1947).
(27) **Note Added in Proof.** X-ray structure analysis of the picrate of **5** shows the *tert*-butyl group to be indeed axially positioned in a chair, with the main deformation being a 16° torsion of the *tert*-butyl group away from the staggered position: K. D. Hargrave and E. L. Eliel, unpublished observations.