yielded III), 4-ethyl-2,3,4-trimethyl-2,3-hexanediol-*3*-$^{13}C$, and 4,4-diethyl-2,3-dimethyl-2,3-hexanediol-*3*-$^{13}C$ (which yielded X) were studied in a similar manner, since the interesting peaks from III or X are the same (*m/e* 43.045 for $-COCH_3$; 43.089 for $-CH(CH_3)_2$; 44.048 for $-^{13}COCH_3$; and 44.092 for $-^{13}CH(CH_3)_2$).

The isotopic study of 3,4-diethyl-5,5-dimethyl-3,4-hexanediol-*4*-$^{13}C$, 3,4-diethyl-5,5-dimethyl-3,4-heptanediol-*4*-$^{13}C$, and 3,4,5-triethyl-5-methyl-3,4-heptanediol-*4*-$^{13}C$ were carried out in the same conditions as for 3,4,5,5-tetraethyl-3,4-heptanediol-*4*-$^{13}C$ previously described.[4] These four glycols yielded the same fragmented ketone X, whose interesting peaks are *m/e* 57 for $-COC_2H_5$; 71 for $-CH(C_2H_5)_2$; 58 for $-^{13}COC_2H_5$; and 72 for $-^{13}CH(C_2H_5)_2$.[13]

**Kinetic Procedure for α,α'-Bis-*tert*-alkyl Ketones.** In a hemolysis tube, 0.6 ml of $H_2SO_4$ (96 wt %) and $6 \times 10^{-4}$ mol of ketone were mixed and placed in a thermostat at 25 °C. After a suitable delay, the mixture was poured onto ice. THF (10–12 drops) and two drops of heliantin were added. The solution was cooled in an ice bath and neutralized by 20% NaOH. This solution was salted out with sodium chloride at room temperature and extracted twice with THF. The combined extracts were dried over $Na_2SO_4$. Eight to ten samples were taken for each ketone. The percentages of different components were determined by GLC (10 ft × 0.125 in. column with 15% DEGS; programming temperature 4 °C/min; limit temperature according to boiling points of ketones composing the fraction[14]) using specific calibration factors for peak area measurement.[15] The percentage B of the different reaction pathways of the metathetical transposition is the average of the percentage obtained for each assay.

The GLC retention times and the ir and NMR spectra obtained for each of the fragmented ketones (separated by preparative GLC) were identical with those of authentic samples.

**Kinetic Procedure for Glycols.** In a hemolysis tube, 0.3 ml of $H_2SO_4$ (96 wt %) and $3 \times 10^{-4}$ mol of glycol were rapidly mixed (time <30 s) and immediately poured onto ice. The extractions by THF, the identification, and the determination of the percentages of different components were made in the same conditions as described above for the kinetic procedure of the ketones. Two to three assays were taken for each glycol.

**Acknowledgments.** We wish to thank Dr. J. A. MacPhee and Mrs. O. Bruno for their advice in preparing this manuscript, and to Mrs. S. Briand for her technical assistance.

## References and Notes

(1) The term migratory aptitude is used in a broad sense: the ability of a group to migrate.
(2) M. J. McCall, J. M. Townsend, and W. A. Bonner, *J. Am. Chem. Soc.*, **97**, 2743 (1975).
(3) The migratory aptitude of ethyl with respect to methyl varies in literature from 35 to 1: D. J. Cram and J. D. Knight, *J. Am. Chem. Soc.*, **74**, 5839 (1952); R. L. Heidke and W. A. Saunders, *J. Am. Chem. Soc.*, **88**, 5816 (1966).
(4) Cf. accompanying article: J. E. Dubois and P. Bauer, *J. Am. Chem. Soc.*, preceding paper in this issue.
(5) In a first approximation the interactions between these environments are considered negligible.
(6) The structure in which the migration takes place means the whole of the molecule or the ion excluding the migrating group.
(7) This network is termed theoretical when "*f*" in eq 5 is set equal to zero.
(8) J. E. Dubois, A. Panaye and J. MacPhee, *C. R. Acad. Sci. Ser. C*, **280**, 411 (1975).
(9) R. L. Heidke and W. H. Saunders, *J. Am. Chem. Soc.*, **88**, 5816 (1966).
(10) Cf. experimental section of the accompanying article.
(11) The ethyllithium was prepared according to the usual procedure in dried ether at −20 °C, then brought progressively to room temperature and decanted to another flask under argon pressure to eliminate excess lithium.
(12) According to the fragmentation rate of ketone III, either ketone III or fragmented ketone X is found in the medium.
(13) The use of high resolution was not required, since the fragments have distinctly different masses.
(14) Gas chromatographic analyses were run on a Varian Aerograph Model 1200 equipped with a flame ionization detector with an electronic integrator Varian Model 475. The precision of this method was verified from a standard solution containing the very same products as the reaction. For each product the average of the values found is ±0.5% of the theoretical value.
(15) R. Kaiser, "Gas Chromatography", Vol. 1, Butterworths, London, 1963, p 182.

# Conformational Preferences of Hexahydropyridazine Derivatives

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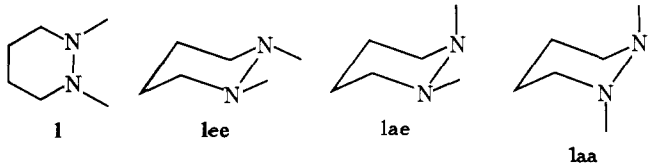
**Abstract:** The conformations of some hexahydropyridazine derivatives were determined by $^{13}C$ NMR. 1,2,3,3,6,6-Hexamethylhexahydropyridazine is an approximately 95:5 mixture of the axial–equatorial *N*-methyl (**ae**): **ee** conformations at −130 °C. 1-Ethyl-2-methylhexahydropyridazine is about a 91:9 mixture of **ae:ee** conformations at ca. −90 °C, although 1,2-dimethylhexahydropyridazine is about a 65:35 **ee:ae** mixture at −70 °C. Only **ee** conformations of 1,6-diazabicyclo[4.3.0]nonane and 1,6-diazabicyclo[4.4.0]decane were detected.

## Introduction

We have recently established by use of variable-temperature $^{13}C$ NMR[1] that for 1,2-dimethylhexahydropyridazine (**1**), the diequatorial **1ee** conformation is about 0.3 kcal/mol lower in enthalpy than **1ae**, but that **1aa** is not detectably populated at low temperature. In contrast, the 3,6-dimethylated analogues **2** and **3** exist so predominantly in **ae** conformations that peaks or even broadening caused by the presence of **ee** conformations were not observed. Activation parameters for conversion of **1ee** to the [**1ae** ⇄ **1ea**] mixture (involving the "nonpassing" ring reversal which does not force lone pairs to pass each other in



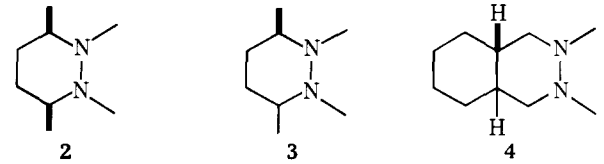



Table I. $^{13}C$ NMR Chemical Shifts for Some Hexahydropyridazines

| Compd | Temp, °C | Concn |  |  | Other carbons | | |
|---|---|---|---|---|---|---|---|
| 5 | +33 | 2.3[a] | 54.51 | 32.41 | 33.53 ($NCH_3$) | 26.43 ($CCH_3$) | |
| | −76 | 2.3[a] | 54.00 | 31.22 | 33.27 | 22.04<br>30.82 | |
| | −125 | 1.0[b] | 56.59 (A)<br>54.29 (B) | (A)[c]<br>30.87 (B) | (A)[c]<br>30.87 (B) | 15.66 (A)<br>(A)[c]<br>22.54 (B)<br>30.87 (B) | |
| 6 | +34 | a | 48.09 (C-6)<br>54.03 (C-3) | 22.53<br>27.20 | 30.93 ($N_2CH_3$)<br>39.60 ($N_1CH_3$) | 20.30 ($C_3CH_3$) | |
| 7 | +36 | 3.5[a] | 54.11[d] | 25.02 | 54.96[d] | 22.59 (C-8) | |
| | −123 | 1.5[b] | 53.96[d] | 24.62 | 54.63[d] | 22.31 (C-8) | |
| 8 | +33 | 0.5[a] | 58.05 | 25.44 | | | |
| | −49 | 0.5[a] | 57.61 | 25.04 | | | |
| 9 | +34 | 3.0[a] | 53.52 or 54.46 | 23.91 or 27.04 | 28.06 (C-4) | | |
| | −68 | 3.0[a] | 53.08 or 53.53 | 23.63 or 26.78 | 28.80 (C-4) | | |
| 10 | +34 | 4.8[a] | 45.33,[d] 51.17 (C-3) | 19.75, 22.71 | 35.80 ($N_2CH_3$) | 13.04 ($CCH_3$) | 46.28[d] ($N_1CH_2$) |
| | −93 | 1.75[b] | 52.47 (A),[d] 58.88 (A)<br>43.38 (B),[d] 50.76 (B) | 25.71 (A), 25.71 (A)<br>17.91 (B), 23.00 (B) | 44.57 (A)<br>31.50 (B) | 8.50 (A)<br>13.37 (B) | 48.47 (A)[d]<br>46.31 (B)[d] |
| 11 | +36 | 2.36[a] | 44.89[d] | 20.12 | 45.11 ($NCH_2$)[d] | 13.98 ($CCH_3$) | |
| | −118 | 1.54[b] | 44.32[d] | 19.83 | 44.96[d] | 14.04 | |

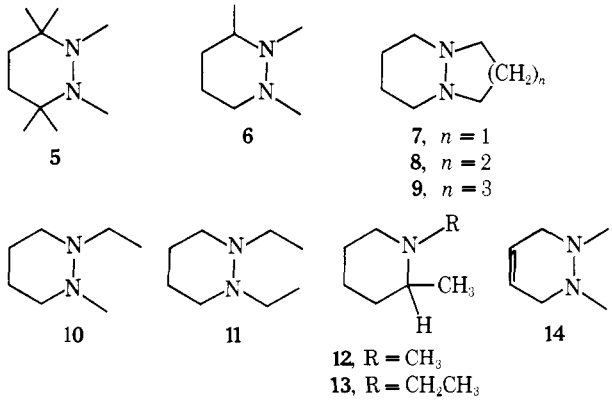
[a] Solvent $(CD_3)_2CO$. [b] Sample used at higher temperatures diluted to this concentration with $CF_2Cl_2$. [c] Peaks at 35.61 and 36.20 correspond to two of three peaks for this minor conformation. [d] These carbon assignments might be reversed.

the transition state), $\Delta G^{\ddagger}$ (−30 °C) = 10.3 ± 0.07 kcal/mol, and for conversion of **1ae** to **1ea** (the "nonpassing" nitrogen inversion, $\Delta G^{\ddagger}$ (−100 °C) = 7.56 ± 0.04 kcal/ mol) were determined directly, and those for the more difficult nitrogen inversion converting **1ee** to **1ae** (the "passing" nitrogen inversion) were established using **4** as a model (**4ee** → **4ea**, $\Delta G^{\ddagger}$ (+2 °C) = 12.60 ± 0.07 kcal/mol).

For interpretation of low-temperature electrolytic oxidations of six-ring hydrazines,[2] in which separate oxidation peaks are observed for different conformations, we needed to establish the conformational preferences for a variety of hexahydropyridazines, and we report conformational work on several such compounds and some model systems here.

## Results

The $^{13}C$ NMR spectra for seven hexahydropyridazines (**5–11**), two piperidines used as model systems (**12–13**), and the dimethyltetrahydropyridazine **14** are summarized in Tables I and II, respectively.




## Discussion

**Hexamethylhexahydropyridazine (5).** Compound **5** showed the expected four peaks at room temperature, and upon cooling, the $C(CH_3)_2$ resonance broadened and resharpened into a 1:1 doublet by −76 °C; the other lines were unaffected. The conformational cube showing interconversions for **5** is shown as Figure 1. When both of the processes crossed by the heavy line become slow on the NMR time scale, the geminal methyls will be frozen out (the situation is entirely analogous to the

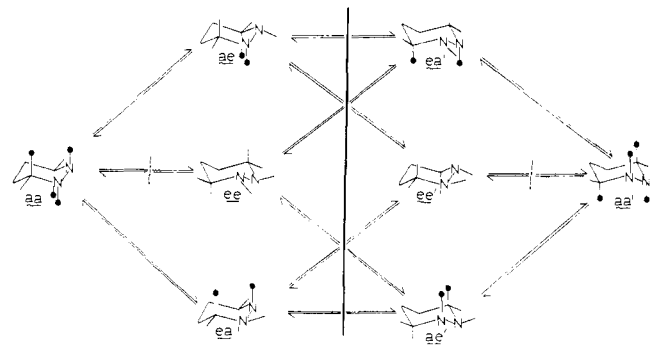



**Figure 1.** Conformational interconversions for **5.** The filled circles indicate methyls which have 1,3-diaxial methyl–methyl interactions.

$NCH_2$ signal of **1** in $^1H$ NMR[3]). Line shape analysis gave $\Delta G^{\ddagger}$ = 11.58 ± 0.02 kcal/mol (−23 °C), $\Delta H^{\ddagger}$ = 10.8 ± 0.2, $\Delta S^{\ddagger}$ = −3.0 ± 0.8 eu, $\Delta G^{\ddagger}$ (25 °C) = 11.72 ± 0.04.

Since conformation **5ae** has a 1,3-diaxial methyl–methyl interaction, we had thought that **5** would exist exclusively in the **5ee** conformation and were therefore very surprised when lowering the temperature caused all the lines to broaden and resharpen to a five-line set (set B) corresponding to a major conformation and a second, minor set of lines (set A). Only four lines of the set A were observed; the fifth presumably is obscured either by the set B lines or the acetone-$d_6$ signal. Electronic integration at −125 and −135 °C indicated that set A corresponds to only 5 ± 1% of the material. The free energy of activation for interconversion of sets A and B was calculated at −119 °C by line shape simulation, giving $\Delta G^{\ddagger}$ (−119 °C) value of 7.55 ± 0.13 (set A → B) and 8.45 ± 0.13 (B → A) kcal/mol. Further cooling led to such great viscosity broadening that it could not be determined whether conformational broadening was also present. We assign the 8 kcal/mol barrier to the "nonpassing" ring reversal crossed by the dotted line in Figure 1. Both the high and low barriers of 5 are lower than those of **1**, $\Delta(\Delta G^{\ddagger})$ = 0.4 kcal/mol (−30 °C) and 2.4–3.2 kcal/mol (−119 °C), respectively, presumably caused by steric destabilization of the ground states in **5.** Assigning sets A and B to **5ee** and **5ae** ⇌ **5ea** is a problem, since we were unable to freeze out the latter interconversion. Grant-type correlations are not available for 1,3-diaxial Me–Me interactions, but using the same type of calculations as used pre-

Table II. Chemical Shifts for Piperidines 12 and 13 and Tetrahydropyridazine 14

| Compd | Concn, M | Temp, °C | Shifts (ppm from internal $Me_4Si$ | | | |
|---|---|---|---|---|---|---|
| **12** | 2.7[a] | +33 | 59.82 (C-2) | 35.47 (C-3) | 25.36 (C-4) | 26.97 (C-5) |
| | 1.0[b] | −147 | 59.94 (C-2) | 34.71 (C-3) | 25.28 (C-4) | 26.26 (C-5) |
| | Neat[c] | amb | 59.8 (C-2) | 35.4 (C-3) | 25.3 (C-4) | 26.9 (C-5) |
| **13** | 3.0[a] | +28 | 55.90 (C-2) | 35.61 (C-3) | 24.86 (C-4) | 27.05 (C-5) |
| | 0.8[b] | −122 | 55.33 (C-2)[e] | 35.37 (C-3) | 25.66 (C-4) | 26.55 (C-5) |
| | 0.5[b] | −143 | 52.66 (C-2)[e]<br>(C-2)[f] | 35.17 (C-3) | 25.59 (C-4) | 26.45 (C-5) |
| **14** | 4.6[a] | +32 | 36.13 ($NCH_3$) | 49.96 (C-3,6) | 124.05 (C-4,5) | |
| | 0.7[b] | −116 | 28.07 ($N_1CH_3$-ax)<br>42.12 ($N_2CH_3$-eq) | 45.75 (C-3)<br>54.22 (C-6) | 123.13 (C-4,5)[d]<br>124.51 (C-5,4)[d] | |
| **12** | 2.7[a] | +33 | 57.66 (C-6) | 20.69 (Me-2) | 43.57 (Me−$N_1$) | |
| | 1.0[b] | −147 | 57.54 (C-6) | 21.16 (Me-2) | 43.62 (Me−$N_1$) | |
| | Neat[c] | amb | 57.5 (C-6) | 20.1 (Me-2) | 43.4 (Me−$N_1$) | |
| **13** | 3.0[a] | +28 | 51.9$_5$ (C-6)[d] | 19.33 (Me-2) | 47.86 ($CH_2$−$N_1$)[d] | 11.11 (N−$CH_2CH_3$) |
| | 0.8[b] | −122 | 52.14 (C-6)[d] | 20.88 (Me-2) | 47.49 ($CH_2$−$N_1$)[d] | 8.19 (N−$CH_2CH_3$)[e] |
| | 0.5[b] | −143 | 52.03 (C-6)[d] | 20.66 (Me-2) | 47.35 ($CH_2$−$N_1$)[d] | 5.33 ($NCH_2$−$CH_3$)[e]<br>13.07 ($NCH_2$−$CH_3$)[e] |

[a] Solvent $(CD_3)_2CO$. [b] Sample used at higher temperature diluted to this concentration with $CF_2Cl_2$. [c] Data from ref 13. [d] Assignments may be reversed. [e] Conformationally broadened. [f] The second C-2 peak could not be discerned; see text.

Table III. Calculated Chemical Shifts for **5ee**

| Position | $\delta_{calcd}$ | $\delta_{obsd}$ (set B) | $\delta_{obsd}$ (set A) |
|---|---|---|---|
| Me-1,2 | 38.4 | 33.2 | *a* |
| 3,6 | 55.1 | 54.3 | 56.6 |
| 4,5 | 35.3 | 30.9 | *a* |

[a] Unassigned peaks at 35.6 and 36.2 probably correspond to these carbons.

viously for **1**–**3**[1] gives the **5ee** shifts listed in Table III. Assignment of the major conformation (set B) to **5ee** gives large deviations at both the *N*-methyls and C-4, C-5, whereas the probable shifts for these carbons in the minor conformation (set A) are much closer to the expected numbers. We therefore assign set B as **5ae** ⇌ **5ea,** set A as **5ee,** an assignment which surely needs further verification. It is clear that **5ea** would have to be quite distorted to decrease its 1,3-diaxial interaction enough to be stabler than **5ee.** Both the high barriers and the low ring reversal barrier are lower for **5** than for **1,** as would be expected if flattening of the ring occurred, and our inability to "freeze out" **5ae** from **5ea** at temperatures where **1ae** is frozen out ($\Delta G^{\ddagger}$ = 7.56 ± 0.04 kcal/mol at −100 °C) indicates that nitrogen inversion is also more rapid for **5.**

One must certainly consider the possibility that the hexahydropyridazine ring is not a chair in **5.** Dalling and Grant[4] suggested that 1,1,2-trimethylcyclohexane was in a twist-boat conformation because of the inability of shift parameters to fit the observed spectrum for a chair form, but Kellie and Riddell[5] disputed this conclusion, pointing out that little of the gauche interactions are actually relieved in a twist boat form, and suggesting instead that either the chair is significantly distorted, or that the parameter set used in the calculation was inappropriate. Similarly, it appears to us that a twist-boat **5** would relieve little of the strain inherent in **5** and that distortions in chair **5** might well be more effective. We think that the 11.6 kcal/mol barrier observed for methyl equilibration in **5** would not be compatible with a twist-boat structure.

The photoelectron spectrum of **5**[6a] shows lone-pair absorptions separated by 0.99 eV, compared with 0.92 and 0.84 for the **ae** conformations of **2** and **3,** and 2.3 eV for **1ee.** This PES is incompatible with **5ee** as the major conformation of **5,** but is compatible with the set B = (distorted) **5ae** assignment made.

A tendency for six-membered ring heterocycles to avoid conformations with three adjacent equatorial substituents has been noted previously. The most studied case has been hexahydropyrimidines,[7] where general agreement has been reached that the 1,3-dimethyl compound shows only a very slight preference for the diequatorial form, but 1,2,3-trimethyl derivative shows a definite preference for the axial,equatorial form, $\Delta G°_{139}$ = 0.63 kcal/mol. Our previous results on **2** and **3**[1] indicated that the aversion to three adjacent equatorial substituents was of larger magnitude in the hexahydropyridazine system, and the effect seems to be large enough to raise the energy of **5ee** (which has four adjacent equatorial substitutents) substantially above that of **5ae** in spite of the 1,3-diaxial interaction.

**Trimethylhexahydropyridazine 6.** Most unfortunately, the low-temperature behavior of the spectrum of **6** was so complex that little could be concluded from these experiments. First, the lines broaden and resharpen, and a minor (<10%) conformation appears to be frozen out by −50 °C. Further cooling caused broading of all the lines, and by −95 °C a series of lumps were observed, which sharpened up to a series of at least eleven overlapping lines. Although it is apparent that at least three different conformations are present in detectable amount at −95 °C, no assignments could be made for the NMR spectrum. From the PES spectrum,[6b] the major conformations are **6ae** types, of which four different ones are possible. The PES spectrum also showed a minor **6ee** conformation, but this conformation might be a part of either the large or small set frozen out at −50 °C.

**Bridgehead Bicyclic Hexahydropyridazines (7–9).** Conformationally caused broadening of the $^{13}C$ NMR lines of **7** and **8** was not observed. Since the structures rule out diaxial conformations, the **ae** and **ee** conformations are interconverted by slow, lone-pair passing processes, leading to the conclusion that neither **7** nor **8** exists detectably in **ae** conformations. The assignment of the observed spectra to **7ee** and **8ee** is verified by chemical shift calculations in Table IV; small deviations between observed and values calculated for the related trans fused ("**ee**") hydrocarbons are found, but the deviations are large for the cis fused ("**ae**") hydrocarbons. Only peaks for **ee** conformations were found in the PES of **7** and **8.**[6b]

Thus, although **1ee** is only about 0.3 kcal/mol lower in enthalpy than **1ae, 7ee** is considerably lower in enthalpy than **7ae.** This trend is not reflected in the related hydrocarbons; *trans*-dimethylcyclohexane is about 1.7 kcal/mol lower in enthalpy than the cis form,[8a] and *trans*-hexahydroindane (*trans*-**7A**) is only 1.04 kcal/mol lower in enthalpy than *cis*-**7A.**[8b,c] Crabb and Newton[9] have suggested from NMR coupling constants of model compounds that the nitrogen of the monoaza analogue, *trans*-indolizidine (**7B**), is flattened, relieving the strain expected for trans-fused bicyclo[4.3.0]nonane

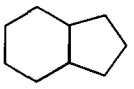
Table IV. Comparison of Chemical Shifts Calculated for **7** and **8 ee** and ae from the Shifts of the Related Hydrocarbons with Observed Values

| Position | $\delta_{ee}$ (X = CH) | Calcd ee[a] (X = N) | Calcd ee (X = N) − Obsd | $\delta_{ea}$ (X = CH) | Calcd ea[a] (X = N) | Calcd ea (X = N) − Obsd |
|---|---|---|---|---|---|---|
|  | 27.23 | 54.2 | −0.2 to +1.1 | 24.02 | 45.9 | +8.1 to 10.5 |
|  | 32.59[c] | 25.4 | −0.6 | 30.01[c] | 19.7 | +4.9 |
| Others | 47.40 (C-1,6)<br>31.90 (C-7,9)[c]<br>22.16 (C-8) | | | 40.00 (C-1,6)<br>28.17 (C-7,9)[c]<br>22.68 (C-8) | | |
|  | 28.0[b] | 57.1 | +0.5 | 25.2[b] | 46.2 | +11.4 |
|  | 35.5[b] | 26.0 | −1.0 | 30.3[b] | 20.9 | +4.1 |
| Others | 44.9[b] | | | 37.6[b] | | |

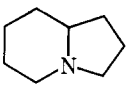
[a] Calculated by adding the shifts observed changing *trans*-1,2-dimethylcyclohexane to **1ee** and *cis*-1,2-dimethylcyclohexane to **1**ae; see ref 1. [b] Data from E. Lippmaa and T. Pehk, *Eesti NSV Tead. Akad. Toim., Keem., Geol.*, 17, 287 (1968); *Chem. Abstr.*, 15795g (1969). [c] These assignments could be reversed.

Table V. Integration of the Set A and B Lines of **10**

| Temp, °C | Mean % A |
|---|---|
| −74 | 8.4 |
| −82 | 8.7 |
| −93 | 9.2 |



**7A**



**7B**

system;[10] ir studies[11] had indicated that *trans*-**7B** is about 2.4 kcal/mol stabler than *cis*-**7B.** For decalins, the hydrocarbon models of **8,** the trans hydrocarbon is favored by 2.69 kcal/mol[12] over the cis one, a larger amount than in the dimethylcyclohexanes because of the extra gauche interaction in *cis*-decalin, so the trans-fused conformation **8ee** is certainly expected.

The seven-ring bridged compound **9** showed considerable broadening at −68 °C, and all of the lines broadened into shifting lumps at lower temperatures, which had not resharpened by −127 °C, the lowest temperature we were able to use for this compound. No matter how the carbons of the room-temperature spectrum are assigned, the shifts suggest probable predominance of **ee** conformations. The broadening at low temperatures may be associated with kinetic processes involving the seven-membered ring, but not affecting the six-ring fusion.

We had no better luck with two other seven-membered ring-containing compounds, 1.7-diazabicyclo[5.3.0]decane and 1,2-dimethylhexahydro-1*H*-1,2-diazapine, both of which just broadened into frustrating lumps at low temperature, and so no conformational information was obtained. The room-temperature chemical shifts for these compounds appear in the Experimental Section.

***N*-Ethyl Hexahydropyridazines.** We have been unable to unambiguously assign the ring methylene next to the *N*-ethyl group and the *N*-ethyl methylene carbons of **10** and **11,** as is indicated in Table I. These ambiguities do not affect the conformational arguments presented.

Broadening of all seven lines of **10** was apparent as the sample was cooled below −32 °C. Upon furthering cooling, the lines for a major component (set B) sharpened first, and below −74 °C, a minor set of lines (set A) appeared. All of the lines of set A except that of the terminal ethyl carbon at δ 8.5 continued to sharpen at lower temperatures until viscosity

Table VI. Correction Factors for Conversion of *N*-Methyl- to *N*-Ethylpiperidine

| Position | X = H[a] | X = $CH_3$[a] | Correction (X = $CH_3$) − (X = H) |
|---|---|---|---|
| $XCH_2$-1 | 47.1 | 53.5 | +6.4 (α) |
| 2 | 57.0 | 54.9 | −2.1 (γ) |
| 3 | 26.6 | 26.8 | +0.2 (δ) |
| 4 | 24.6 | 25.4 | +0.8 (ε) |

[a] Data from ref 17.

broadening became serious. This terminal ethyl carbon signal had broadened into the baseline by −110 °C. All of the set B lines became conformationally broadened at low temperatures and had also nearly disappeared into the baseline at −110 °C. The set B lines were starting to resharpen again at −127 °C, but viscosity broadening became so serious at still lower temperatures that we were unable to obtain "frozen" spectra for either set B or the terminal methyl carbon of set A.

Electronic integration of sets A and B was possible for six of the seven resonances at three different temperatures, and the results for the six lines showed good agreement. The results of these integrations, which we considered accurate to ±2%, appear in Table V.

Calculation of $\Delta G^{\ddagger}$ for the process interconverting sets A and B was possible for three line pairs at −74 °C (it is necessary that set B not be broadened by the lower temperature conformational process), and all gave the same free energy of activation, $\Delta G^{\ddagger}_{(A \rightarrow B)}$ (−74 °C) = 9.6 kcal/mol, $\Delta G^{\ddagger}_{(B \rightarrow A)}$ (−74 °C) = 10.4 kcal/mol.

From these observations, the ca. 9% minor component (set A) must be **10ee,** and the major component (set B) is the interconverting **10ae** ⇌ **10ea** mixture. These latter conformations should be unequal in population because of the different nitrogen substitutents.

Chemical shift correlations were made using the corrections necessary to convert the *N*-methyl piperidine chemical shifts to the *N*-ethyl ones (Table VI) and applying these corrections to **1ee.** We also applied the same corrections to **1ae** ⇌ **1ea,** but because the corrections are derived for equatorial substituents and because the **10ea** and **10ae** populations will be different, one expects far less successful agreement. The correlations appear in Table VII.

We assign the broadening of the terminal methyl signal of **10ee** (set A) to freezing out of *N*-ethyl rotation, as will be discussed in the section on piperidines.

Cooling **11** in the NMR probe had no effect on the line

Table VII. Chemical Shift Correlations for **10** Using the Corrections from Table VI

| Position | $\delta_c$ obsd (−93 °C)[a] Set A | Set B | $\delta_c$ calcd Set A (ee) | Set B (ea) | (Obsd) − (calcd) Set A | Set B |
|---|---|---|---|---|---|---|
| $CH_2$-1 | 48.5[a] | 46.3[a] | 51.1 | 42.2 | −2.6 | +4.1 |
| $CH_3$-2 | 44.6 | 31.5 | 44.9 | 36.0 | −0.3 | −4.5 |
| 3 | 58.9 | 50.8 | 58.4 | 48.6 | +0.5 | +2.2 |
| 4 | 25.7[b] | 23.0[b] | 26.4 | 21.2 | −0.7 | +1.8 |
| 5 | 25.7[b] | 17.9[b] | 25.6 | 20.6 | +0.1 | −2.7 |
| 6 | 52.5[a] | 43.4[a] | 56.1 | 46.3 | −3.6 | −2.9 |
| | | | | av deviation | 1.3 | 3.0 |

a, b Assignments with superscripts may be reversed.

Table VIII. Observed and Calculated Shifts for **11**

| Position | $\delta_c$ obsd (−118 °C) | $\delta_c$ calcd 11ae ⇌ **11**ea | 11ee | Error (obsd − calcd) **11**ae ⇌ 11ea | 11ee |
|---|---|---|---|---|---|
| $CH_2$-1,2 | 44.3[a] | 42.3 | 51.3 | +2.0 | −7.0 |
| 3,6 | 44.9[a] | 46.5 | 56.3 | −1.6 | −11.4 |
| 4,5 | 19.8 | 21.4 | 26.4 | −1.6 | −6.6 |

[a] These assignments might be reversed.

widths in the temperature range where sets A and B appeared for **10,** but conformationally caused broadening was apparent for all lines at −118 and −123 °C. Repeated efforts to obtain a "frozen" spectrum at still lower temperatures failed, due to sample freezing. We assign the conformation observed as **11** (**ae** ⇌ **ea**); even 2% of **11ee** would have produced detectable broadening in the intermediate temperature range, as was verified by simulations including this possibility. Chemical shift correlations are also consistent with the conformation being **11ae,** as shown in Table VIII.

These experiments show that $\Delta G°$ (**ee**-[**ea** ⇌ **ae**]) for **10** is 0.82–0.95 kcal/mol at −93 to −74 °C, while a lower limit of 1.8 kcal/ mol is estimated for **11.** The effect of replacing one *N*-methyl group of **1** with an *N*-ethyl group on the **ee** vs. [**ea** ⇌ **ae**] free-energy difference, $\Delta\Delta G°$ (**10** − **1**), is therefore 1.2 kcal/mol, and the second ethyl group introduced in **11** increments $\Delta G°$ by at least another 0.85 kcal/mol. These are large effects, indeed, for what seems like a trivial substitution!

***N*-Methyl- and Ethyl-2-methylpiperidine.** The remarkable size of the effect of ethyl for methyl substitution on the conformational preference of hexahydropyridazines caused us to wonder about how general such an effect might be. *trans*-1,2-Diethylcyclohexane is preferred over the cis isomer by the same amount as in the dimethyl compounds.[14] To see if having one nitrogen present is sufficient to cause the effect, piperidines **12** and **13** were examined.

As **12** was cooled in the NMR probe, the C-2, C-4, C-6, and Me-2 signals broadened from about −30 °C, but tantalizingly, they sharpened up again completely by −80 °C, without producing visible peaks for a minor conformation (S/N was over 50/1 in the −80 °C spectrum). We presume that interconversion with a minor conformation was being slowed in the −30 to −50 °C temperature range, but that the percentage of the minor conformation had become so low at temperatures where the lines for the minor conformation would have sharpened up, than no peaks could be discerned. Further cooling of **12** produced only viscosity broadening.

Cooling of **13** gave rather similar behavior to that of **12,** except that between −56 and −71 °, at least three tiny peaks belonging to the second conformation could be discerned. These constituted under 5% of the mixture, and at lower temperatures they had disappeared. Below −122 °C, the C-2 and ethyl $CH_3$ signals were preferentially broadened by another conformational change, and the −143 °C spectrum was well below the coalescence temperature for this process. Both

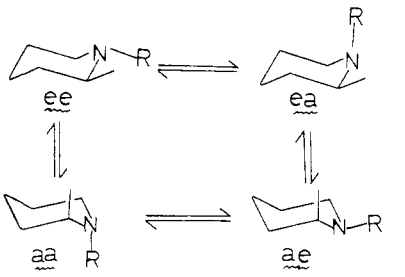



**Figure 2.** Conformational interconversions for **12** and **13.**

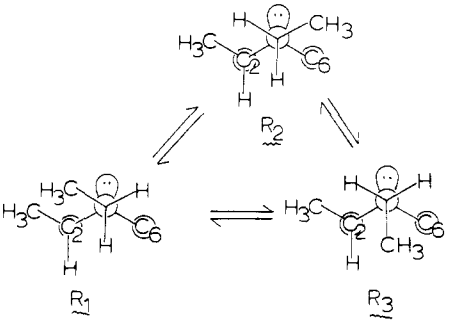



**Figure 3.** *N*-Ethyl rotamers for **13.**

ethyl $CH_3$ peaks were observed at −143 °C; the intensity ratio of the peak at 5.33 to that at δ 13.07 was 65 ± 10:35 ± 10, both by integration and chemical shift change. Unfortunately, only one C-2 peak was discernible. Useful spectra were not obtained at lower temperatures.

The conformational interconversions for **12** and **13** are shown in Figure 2, and at least two of the four processes must become slow for an observable effect on the $^{13}C$ NMR. We assign the line broadening observed for both **12** and **13** in the −30 to −50 °C range to slowing of both ring reversals, separating **ee** ⇌ **ea** from **aa** ⇌ **ae.** The major peaks are clearly expected to be those of the former set, and the minor peaks (under 5% in **13,** undetectably small for **12**) the latter. Failure to observe broadening in the major set corresponding to freezing out of nitrogen inversions is a powerful argument for domination of the **ee** conformations for both **12** and **13.**

Ellis and Jones[13] have pointed out that the chemical shifts observed for **12** are consistent with it existing as **12ee.** Application of the parameters of Booth and Griffiths[15] lead to the same conclusion. When the chemical shift increments observed comparing methylcyclohexane with *N*-methylpiperidine are applied to *trans*-1,2-dimethylcyclohexane shifts, these calculated **12ee** shifts show excellent agreement with experiment; an average deviation of 0.8 ppm was observed, with a maximum deviation of −1.4 ppm at C-3. The observed shifts for **13** are also entirely compatible with estimates for **13ee** (made by using the shifts of Table VI to convert the experimental **12ee** shifts to **13ee** ones), but show large deviations from calculated **13ae** shifts.

Thus **12** has the **ee** conformation at least 1.5 kcal/mol stabler than the **ae** conformation, and for **13, ee** is at least 1.0 kcal/mol stabler. Simple presence of an *N*-ethyl group clearly does not lead to greater stability for **ae** conformations, and the piperidine **13** resembles the cyclohexane system in its conformational preference; the hexahydropyridazine system is clearly a special case.

We assign the process frozen out at very low temperature, which affected only the ethyl terminal methyl group and C-2 of **13,** to *N*-ethyl rotation. Broadening was observed for a similar process in **10ee,** but a frozen spectrum could not be obtained in this case. Figure 3 shows the rotamers expected for the *N*-ethyl group of **13.** We expect $R_1$, which has a 1,3-diaxial methyl-methyl interaction, to be the highest in energy and

hence the least populated form. We presume, then, that the observed frozen spectrum is for $R_2$ and $R_3$ interconverting slowly on the NMR time scale. Since C-6 and the ethyl $CH_2$ resonance have the same number of gauche interactions in $R_1$ and $R_2$, it is not too surprising that large chemical shift differences do not occur at these carbons, whereas they are present in C-2 and the ethyl $CH_3$. Since conformation $R_3$ has the ethyl $CH_3$ in a position with one more gauche butane interaction than $R_2$, and this methyl is also trans to the nitrogen lone pair in $R_3$, we must assign the upfield resonance observed to $R_3$ and the downfield one to $R_2$. Both integration and chemical shift changes show that the signal for the upfield ethyl $CH_3$ resonance is of higher intensity than the downfield one; we estimate the ratio to be 65 ± 10:35 ± 10 for these signals. Preference for $R_3$ over $R_2$ is a surprising result, but distortion of the bond angles could relieve some of the 1,3-H,H interactions in $R_3$ relative to $R_2$. The coalescence temperature for freezing out the ethyl $CH_3$ resonance of **13** is about −133 °C, giving a $\Delta G^{\ddagger}$ (−133 °C) of 6.3 ± 0.3 kcal/mol by the coalescence temperature method. This value is compatible with an *N*-ethyl rotational barrier.[16]

**"Standard Geometry" of Hexahydropyridazines.** We suggest that an important reason for both the aversion for three equatorial substituents in a row and for **ee** methyl-ethyl and ethyl-ethyl interactions in the hexahydropyridazine system is a single geometrical one. With two nitrogens in a six-membered ring, substantial distortion from cyclohexane geometry might be present. We do not know the actual bond angles and bond lengths for any hexahydropyridazine, but if **1** is arbitrarily constructed with tetrahedral angles at all atoms and Pople's standard bond lengths ($d_{NN}$ = 1.45, $d_{CN}$ = 1.47, $d_{CC}$ = 1.54),[17] by use of MIRAGE,[18] the Me–Me distance for **1ee** is 2.73 Å, and that for **1ea** is 2.88 Å (the MeNNMe dihedral angles are 53.1° for **1ee** and 67.1° for **1ea**, whereas the $C_3NNC_6$ dihedral angle is 67.1°). Although the actual bond angles are undoubtably not exactly 109°28′, so the conformation discussed is considerably idealized, it is seen that the bond lengths of **1** tend to increase the alkyl–alkyl interaction for **1ee** compared with **1ae**. Since a **1ee** conformation also has a larger destabilizing lone-pair–lone-pair interaction than a **1ea** conformation, the balance between these conformations is quite fine and, as we have shown, is reversed even by substitution of one *N*-ethyl for *N*-methyl.

**1,2-Dimethyl-1,2,3,6-tetrahydropyridazine (14).** Although the barriers measured by Anderson[3] for **14** by $^1$H NMR of 12.0 kcal/mol and 8.5 kcal/mol several years ago are well known, and Anderson's assignment of **14ae** as the conformation of this molecule has now been accepted by the English group,[19] we reexamined this molecule by $^{13}$C NMR to see if any other conformation would be detectable. The conformational diagram for **14** is similar to that for **1**,[1] and the 12 kcal/mol barrier observed by $^1$H NMR does not affect the carbon spectrum. Our chemical shift data appears in Table II, and line shape analysis gives the following activation parameters for the "nonpassing" nitrogen inversion which converts **14ae** to **14aa** (and hence to **14ea**): $\Delta G^{\ddagger}$ (−86.5 °C) 8.11 ± 0.03, $\Delta H^{\ddagger}$ = 8.8 ± 0.35 kcal/mol, $\Delta S^{\ddagger}$ = +3.9 ± 1.9 eu, $\Delta G^{\ddagger}$ (25 °C) = 7.68 ± 0.21 kcal/mol (calculated with $\kappa$ = ½, 15 points, temperature range 48 °C).

The ring reversal separating **14ae** ⇌ **14ea** from **14ee** might be expected to have a significantly lower barrier than that for **1**, but no broadening in the lines for **1ae** was observed down to −127 °C. Line shape simulations with various relative populations convince us that **14ee** cannot constitute more than 10% of the total population at −116 °C; we were unable to detect any conformation other than **14ea** at any temperature. The great predominance of **14ea** compared with **1** is no doubt due to decreased 1,3-diaxial $CH_3$–H interaction as suggested by Anderson.[3]

## Experimental Section

The preparations of **5–9**, **11**, and **14** have been previously discussed.[6a]

**1-Methylhexahydropyridazine** was prepared by addition of 4.91 g (31 mmol) of 1-carboethoxyhexahydropyridazine[20] in 50 ml of ether to 2.85 g (75 mmol) of $LiAlH_4$ in 60 ml of ether over 30 min, followed by stirring at ambient temperature for 2 h, refluxing for 4 h, and quenching with 3 ml of $H_2O$, 3 ml of 15% NaOH, and 8 ml of $H_2O$. After drying and removal of solvent, the residue was filtered and distilled, bp (98 mm) 66–76 °C, 1.13 g (42%), >90% pure by VPC. Spectral data: NMR ($CDCl_3$) δ 1.42 (m, 2 H), 1.78 (m, 2 H), 2.44 (s, 3 H), 2.50 (br t, 2 H), 3.05 (br t, 2 H) (the NH signal was too broad to be observable); ir ($CCl_4$) 3315 cm$^{-1}$; empirical formula $C_5H_{12}N_2$ established by mass spectroscopy.

**1-Ethyl-2-methylhexahydropyridazine (10).** A mixture of 0.5 g (5 mmol) of 1-methylhexahydropyridazine, 1.65 g (15 mmol) of 40% aqueous acetaldehyde, and 0.53 g (8.44 mmol) of $NaBH_3CN$ in 25 ml of acetonitrile was treated with 5 drops of acetic acid every 15 min for 1.5 h and, after stirring 7 h, was made basic with NaOH pellets and extracted with 3 × 50 ml of pentane. Drying and concentration gave 0.35 g of a residue containing 87% **10** by VPC peak area ratios, 47%. Spectral data: NMR ($CCl_4$) δ 1.08 (t, 3 H), 1.60 (m, 4 H), 2.47 (s, 3 H), 2.72 (q, 2 H), 2.8 (m, 4 H); ir ($CCl_4$) no NH or C=O, empirical formula $C_7H_{16}N_2$ established by mass spectroscopy.

**1,2-Dimethylpiperidine (12)** was prepared in 28% yield (95% crude purity by VPC) by methylation of 2-methylpiperidine by the method used in preparing **10**, bp 125–128 °C (lit.[21] 126–127 °C).

**1-Ethyl-2-methylpiperidine (13)** was prepared in 14.5% yield by ethylation of 2-methylpiperidine by the method used in preparing **10**, bp 58–74 °C (50 mm) (lit.[21] 148–149 °C). Unfortunately, preparative VPC gave material containing an impurity, which was finally removed by distillation from tosyl chloride and repurification by preparative VPC. Alkylation with ethyl iodide gave a similarly low yield and impure material.

The methods used for the NMR experiments were identical with those of ref 1. All chemical shifts are reported in ppm downfield from internal $Me_4Si$.

**1,7-Diazabicyclo[5.3.0]decane.**[6a] $^{13}$C NMR (acetone-$d_6$) 25.04, 25.84, 30.13 (C(3,5)), 56.32, 58.50.

**1,2-Dimethylhexahydro-1*H*-1,2-diazapine.**[6a] $^{13}$C NMR (acetone-$d_6$) 26.60 (C(5)), 28.58 (C(4,6)), 38.26 ($NCH_3$), 55.13 (C(3,7)).

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# Conformational Analysis of Intramolecular Hydrogen-Bonded Amino Alcohols. Determination of the NH/N-Electron Pair Equilibrium and Assignment of Conformational Free Energies for Interactions in Decahydroquinoline and Piperidine Compounds in a Dilute Nonpolar Medium

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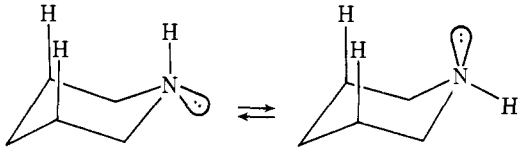
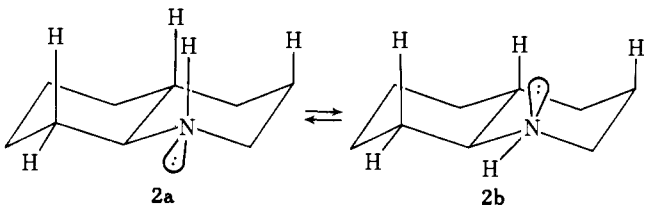
**Abstract:** The conformational equilibria between the free OH and OH···N bonded species in the *trans*-8α- (**3**) and -8β-decahydroquinolinol (**4**) epimers have been determined from their dilute solution ir spectral data. A comparative conformational analysis of these two systems proves that the controversial N–H/N-electron pair equilibrium in the unsubstituted parent *trans*-decahydroquinoline (**2**) favors the N–H equatorial form by 0.5 ± 0.1 kcal/mol in nonpolar solution at 33 °C. Relative values for all the conformation interactions in **2**, **3**, and **4** (including thatof the intramolecular OH···N and presumed NH···O hydrogen bonds in **3** and **4**) are assigned, based on their syn-axial and peri substituent relationships. Using these values, the conformational equilibrium of 3-piperidinol has now been fully defined.

Assignment of the preferred conformation of the N–H group in piperidine[1] (**1**) and related compounds (e.g., **2**) by a variety of experimental methods has led to opposite conclusions.[2,3] In our view, the most reliable of these is based upon the relative ir intensities of the N–H stretching band (a doublet, assigned as axial and equatorial N–H, respectively)[4] and indicates that the N–H equatorial form (**1b**) is preferred by



**1a** **1b**

0.4[4c]–0.6[4a] kcal/mol ($\Delta H$) in $CCl_4$ solution.[5] Taking all of the published data into account, Katritzky and co-workers suggest a $-\Delta G°$ value of 0.4 ± 0.2 kcal/mol for the gas phase and for solutions in nonpolar media. This conclusion, however, has not been fully accepted to date.[3] Accordingly, we now offer a simple, new, and (in our view) unequivocal proof of the equilibrium position of the N–H group in *trans*-decahydroquinoline (**2**) in $CCl_4$ solution, based upon a comparative conformational analysis of the *trans*-8-decahydroquinolinol epimers **3** and **4**. Furthermore, with this result, relative values for the individual conformational interactions in these compounds may be assigned and used to define similar equilibria in other systems, as shown below.



**2a** **2b**

## Results

The ir spectra (Figure 1) of the 8α- and 8β-decahydroquinolinols[6] (**3** and **4**), recorded in dilute solution where intermolecular hydrogen bonding has been eliminated, reveal a mixture of free OH and intramolecular bonded OH···N conformations. In each, the mole percent of free OH species may be determined from its band area ($B$) compared to that of 4-hydroxypiperidine (**5**) as the 100% free OH reference model,

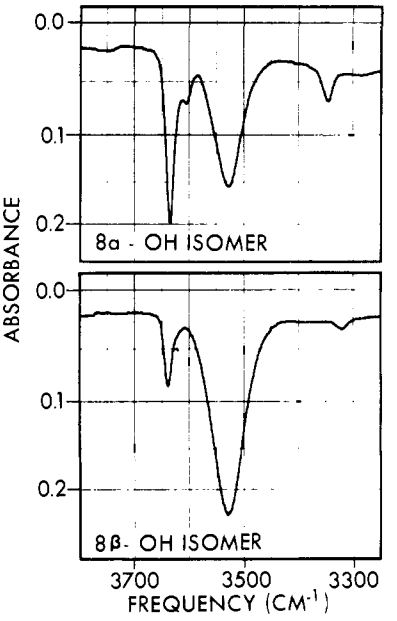



**Figure 1.** Dilute solution ir spectra of *trans*-8α (**3**) and 8β-decahydroquinolinol (**4**) isomers in $CCl_4$, both at $2.7 \times 10^{-3}$ M, 2-cm cell path.