McGraw-Hill, New York, N.Y., 1970, pp 110–113.
(18) J. C. Calabrese, "MIRAGE A General Vector Program for Obtaining Atomic Coordinates", Ph.D. Thesis (Appendix III), University of Wisconsin, Madison, 1971.
(19) R. A. Y. Jones, A. R. Katritzky, K. A. F. Record, and R. Scattergood, *J. Chem. Soc., Perkin Trans. 2*, 406 (1974).
(20) P. Barranger and J. Levisalles, *Bull. Soc. Chim. Fr.*, 704 (1957).
(21) W. Hohenemser and R. Wolffenstein, *Chem. Ber.*, **32**, 2520 (1899).

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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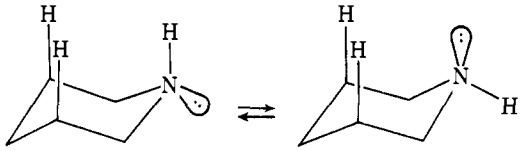
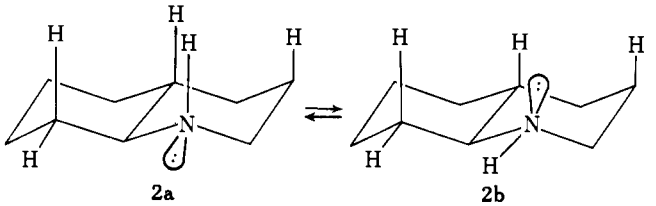
Abstract: The conformational equilibria between the free OH and OH···N bonded species in the *trans*-8α- (**3**) and -8β-decahydroquinolinol (**4**) epimers have been determined from their dilute solution ir spectral data. A comparative conformational analysis of these two systems proves that the controversial 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 (ΔH) 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,

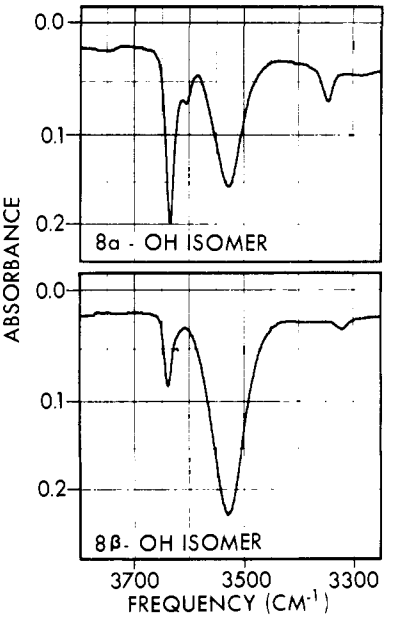


Figure 1. Dilute solution ir spectra of *trans*-8α (**3**) and 8β-decahydroquinolinol (**4**) isomers in CCl_4, both at 2.7×10^{-3} M, 2-cm cell path.

Table I. Ir Spectral Data for *trans*-Decahydroquinolin-8-ol Epimers in Dilute CCl_4 at 33 °C

	Free OH			Bonded OH···N	
Compd	ν_{OH}, cm^{-1}	B (l. mol^{-1} cm^{-2})	Mol %	ν_{OH}, cm^{-1}	$\Delta\nu_{OH}$, cm^{-1}
8α-ol (**3**)	3635[a]	1870	51	3527	108
8β-ol (**4**)	3638	575	16	3528	110
4-piperidinol (**5**)	3624	3660	100		

[a] Shoulder at 3607 cm^{-1}, assigned to a free OH rotamer form.[7a]

since it has been shown that free OH band areas are essentially equal for equatorial and axial secondary alcohols recorded on the same spectrometer.[7a,8] The percentage of each bonded form, therefore, is simply 100% minus the percentage of free OH. The pertinent spectral data are summarized in Table I.

Discussion

To analyze these spectral data, the following equilibria must be considered. However, the percentages of possible free OH conformers **3c** and **4c,** which are merely nonbonded OH rotamer forms of **3a** and **4b,** respectively, are judged to be negligible because no free OH species were observed for the comparably strongly ($\Delta\nu \sim 100$ cm^{-1} in CCl_4) hydrogen-bonded quinolizidinols **6** and **7**.[7] Compounds **3** and **4,** therefore, may be analyzed as strictly **3a,3b** and **4a,4b** equilibria. Since the hydrogen bonds in **3a** and **4b** have the same relative geometry and are of equal strength (identical $\Delta\nu_{OH}$ values, within experimental error), their conformational free-energy contribution to their respective equilibria must be equivalent. Thus, for example, if there were no inherent conformational preference of the N-H group in the unsubstituted parent (i.e., if percent **2a** were equal to percent **2b**), the percentage of bonded species in **3** should be equal to that in **4,** since all other steric factors appear to cancel. From even a qualitative comparison of their spectra, however, it is readily apparent that the 8β-OH compound (**4**) contains a greater percentage of its OH groups in the OH···N bonded form than does its 8α-OH epimer. One concludes, therefore, that the N-H position in the unsubstituted parent (**2**) must *inherently favor* the N-H equatorial form, i.e., corresponding to **4b.** Indeed, the position of the **2** equilibrium should be exactly the average of that of **3** and **4** when all are simply defined by the free-energy difference between their **a** and **b** conformations (cf., eq 12), as proven below.

An equilibrium system, defined by the free-energy difference between conformations as[8]

$$-RT \ln (\text{product})/(\text{educt}) = \Delta G^\circ_{\text{product}} - \Delta G^\circ_{\text{educt}} \quad (1)$$

corresponds, for *trans*-decahydroquinoline (**2**), to

$$\Delta G^\circ_2 = -RT \ln (\mathbf{2b})/(\mathbf{2a}) = \Delta G^\circ_{2b} - \Delta G^\circ_{2a} \quad (2)$$

Similarly, the conformational equilibrium of the 8α-OH isomer (**3**) is expressed by

$$\Delta G^\circ_3 = -RT \ln (\mathbf{3b})/(\mathbf{3a}) = \Delta G^\circ_{3b} - \Delta G^\circ_{3a} \quad (3)$$

and that of the 8β-OH isomer (**4**) by

$$\Delta G^\circ_4 = -RT \ln (\mathbf{4b})/(\mathbf{4a}) = \Delta G^\circ_{4b} - \Delta G^\circ_{4a} \quad (4)$$

If the free-energy difference between **3a** and **2a,** and, respectively, **3b** and **2b** are now defined by the difference between their syn-axial and equivalent (to a good approximation[9]) peri interactions (e.g., $\Delta G^\circ_{OH/(N):}$, etc.)[10] that result from introduction of the substituent OH group, one obtains

$$\Delta G^\circ_{3a} - \Delta G^\circ_{2a} = (\Delta G^\circ_{OH/(N):})_{3a} - (\Delta G^\circ_{H/(N):})_{2a} \quad (5)$$

and

$$\Delta G^\circ_{3b} - \Delta G^\circ_{2b} = (\Delta G^\circ_{OH/(N)H})_{3b} - (\Delta G^\circ_{H/(N)H})_{2b} \quad (6)$$

Similarly, the free-energy difference between **4a** and **2a,** and **4b** and **2b,** may be defined by

$$\Delta G^\circ_{4a} - \Delta G^\circ_{2a} = (\Delta G^\circ_{OH/(N)H} + 2\Delta G^\circ_{OH/H})_{4a} - (\Delta G^\circ_{H/(N)H} + 2\Delta G^\circ_{H/H})_{2a} \quad (7)$$

and

$$\Delta G^\circ_{4b} - \Delta G^\circ_{2b} = (\Delta G^\circ_{OH/(N):} + 2\Delta G^\circ_{OH/H})_{4b} - (\Delta G^\circ_{H/(N):} + 2\Delta G^\circ_{H/H})_{2b} \quad (8)$$

Subtracting eq 6 from eq 5 and, respectively, eq 8 from eq 7 gives, after canceling common terms and regrouping,

$$(\Delta G^\circ_{3a} - \Delta G^\circ_{3b}) - (\Delta G^\circ_{2a} - \Delta G^\circ_{2b}) = (\Delta G^\circ_{OH/(N):} - \Delta G^\circ_{H/(N):}) - (\Delta G^\circ_{OH/(N)H} - \Delta G^\circ_{H/(N)H}) \quad (9)$$

and

$$(\Delta G^\circ_{4a} - \Delta G^\circ_{4b}) - (\Delta G^\circ_{2a} - \Delta G^\circ_{2b}) = (\Delta G^\circ_{OH/(N)H} - \Delta G^\circ_{H/(N)H}) - (\Delta G^\circ_{OH/(N):} - \Delta G^\circ_{OH/(N):}) \quad (10)$$

If one now adds eq 9 and 10 to get

$$(\Delta G^\circ_{3a} - \Delta G^\circ_{3b}) + (\Delta G^\circ_{4a} - \Delta G^\circ_{4b}) = 2(\Delta G^\circ_{2a} - \Delta G^\circ_{2b}) \quad (11)$$

and substitutes from eq 2, 3, and 4, one obtains

$$RT \ln (\mathbf{3b})/(\mathbf{3a}) + RT \ln (\mathbf{4b})/(\mathbf{4a}) = -2\Delta G^\circ_2 \quad (12)$$

Substituting here the values of **3a** (49%), **3b** (51%), **4a** (16%), and **4b** (84%) from the data of Table I gives $\Delta G^\circ_2 = -0.52$ kcal/mol *independent of the actual values of the conformational interactions in* ***2, 3, and 4,*** assuming only that the same value is applicable in each case. The probable error in this result, therefore, is presumably due only to the uncertainty in the measured values of the free OH band areas of **3, 4,** and **5.** Also, any error that might result from the choice of **5** as the reference model is presumably less than the probable error of the experimental method. We find that a probable error of 3 mol % in each of the assigned values of **3a, 3b, 4a,** and **4b** results in a probable error of ±0.10 kcal/mol in ΔG°_2, while a 5 mol % error corresponds to ±0.15 kcal/mol. We believe the assigned values for the conformer percentages in these two closely related systems are good to ±3 mol % and that a value of $\Delta G^\circ_2 = -0.5 \pm 0.1$ kcal/mol should be assigned to the **2** equilibrium. This result corresponds (from eq 2) to an N-H equatorial (**2b**) to N-H axial (**2a**) ratio of ~70/30 for a carbon tetrachloride solution at ambient temperatures. Of course, this equilibrium position may differ somewhat for the neat liquid or for solutions in polar (especially alcoholic) media.[3]

Comparison of *trans*-Decahydroquinoline and Piperidine Equilibria. We do not know whether the inherent preference of the N-H for the equatorial position (**2b**), as deduced above, should be attributed mainly to syn-axial or vicinal gauche H/(N)H or H/(N): interactions, attractive or repulsive, as they may be. Nevertheless, for practical conformation analysis, this equilibrium may be *defined* with respect to the syn-axial and peri orientation of the N-H and N-electron pair, as for decahydroquinoline (**2**), by

$$\Delta G^\circ_2 = (3\Delta G^\circ_{\mathrm{H/(N):}} + \Delta G^\circ_{\mathrm{H/(N)H}})_{\mathbf{2b}} - (3\Delta G^\circ_{\mathrm{H/(N)H}} + \Delta G^\circ_{\mathrm{H/(N):}})_{\mathbf{2a}} \quad (13)$$

which reduces to

$$\Delta G^\circ_2 = 2(\Delta G^\circ_{\mathrm{H/(N):}} - \Delta G^\circ_{\mathrm{H/(N)H}}) \quad (14)$$

Since $\Delta G^\circ_2 = -0.5$ kcal/mol (from above), one obtains $(\Delta G^\circ_{\mathrm{H/(N):}} - \Delta G^\circ_{\mathrm{H/(N)H}}) = -0.25$ kcal/mol. That is, the conformational free-energy difference between an (N)-electron pair vs. an (N)-H group, both axial to a hydrogen substituent, is 0.25 kcal/mol in favor of the axial (N)-electron pair species. Since the piperidine equilibrium (**1**), similarly defined, is also represented by eq 14, we conclude that the **1** and **2** equilibria positions are probably very similar, if not identical, within the experimental error of the method.[11] Moreover, our result calculated for **2** above is in good agreement with results of four other independent spectral methods,[4,12] each based upon a different application of infrared spectroscopy, which fall within the limits of the value 0.5 ± 0.1 kcal/mol for the NH/N-electron pair equilibrium for piperidine and/or decahydroquinoline.[13]

Assignment of Conformational Values in Piperidine and Decahydroquinoline Systems. For the hydroxyl substituted derivatives **3** and **4,** the conformational factors that remain to be assigned are the intramolecular OH···N bond in **3a** and **4b** and the syn-axial (OH/(N)H relationship in **3b** and **4a.** One might presume that the latter interaction (relative to the H/(N)H interactions in **2a** and **2b**) should be essentially equivalent to that of the isosteric OH/H (relative to H/H) interaction, if intramolecular NH···OH bond formation does not occur. However, based on the results presented below, we conclude that a weak intramolecular association of this type does exist in these systems. Thus, the OH/(N)H interaction in **3b** and **4a** may be obtained from either the **3** equilibrium (eq 9) or the **4** equilibrium (eq 10), or better from the average of the two by subtracting eq 10 from eq 9, as

$$(\Delta G^\circ_{\mathbf{3a}} - \Delta G^\circ_{\mathbf{3b}}) - (\Delta G^\circ_{\mathbf{4a}} - \Delta G^\circ_{\mathbf{4b}}) = 2(\Delta G^\circ_{\mathrm{OH/(N):}} - \Delta G^\circ_{\mathrm{H/(N):}}) - 2(\Delta G^\circ_{\mathrm{OH/(N)H}} - \Delta G^\circ_{\mathrm{H/(N)H}}) \quad (15)$$

Substituting from eq 3 and 4 as in eq 12, above, one obtains

$$-0.5 \text{ kcal/mol} = (\Delta G^\circ_{\mathrm{OH/(N):}} - \Delta G^\circ_{\mathrm{H/(N):}}) - (\Delta G^\circ_{\mathrm{OH/(N)H}} - \Delta G^\circ_{\mathrm{H/(N)H}}) \quad (16)$$

Since the term $(\Delta G^\circ_{\mathrm{OH/(N):}} - \Delta G^\circ_{\mathrm{H/(N):}})$, which defines the conformational free energy ($\Delta G^\circ_{\mathrm{OH\cdots N}}$) of the intramolecular OH···N hydrogen bond, has been found for **8,** below, to be about −0.55 to −0.60 kcal/mol for $\Delta\nu \sim 100$ cm^{-1}, it follows that $(\Delta G^\circ_{\mathrm{OH/(N)H}} - \Delta G^\circ_{\mathrm{H/(N)H}}) \sim -0.05$ to −0.10 kcal/mol (attractive), assuming that $\Delta G^\circ_{\mathrm{OH\cdots N}}$ is essentially equivalent in these systems. Therefore, we conclude that the steric repulsion of an OH group syn-axial to the hydrogen (on the nitrogen) must be counterbalanced by a weak (N)H···OH attraction, such that the net conformational effect is slightly attractive, compared to a syn-axial H/(N)H interaction.

The conformational values that we have assigned to the syn-axial and peri substituents in decahydroquinoline and piperidine systems are summarized in Table II. These are, of course, relative values from which the free-energy difference between any two conformers in equilibrium in these systems may be defined.

To calculate conformer percentages from these assignments, it would be convenient to simply take an algebraic total of the individual syn-axial and peri interactions in each conformer, rather than to regroup related terms, as in Table II. Thus, if the isosteric $\Delta G^\circ_{\mathrm{H/H}}$ and $\Delta G^\circ_{\mathrm{H/(N)H}}$ terms are taken equal to zero, a relative value for each individual syn-axial relationship would be obtained. However, since it is not certain that these two terms are equivalent, we have used the more rigorous assignments given in the Table II. In any event, the conformation of the N-electron pair, if not its "size", is given explicit consideration in the conformational analysis of these systems.[14]

Table II. Relative Conformational Free-Energy Assignments for Syn-Axial (or Peri) Substituents in Piperidine and Decahydroquinoline Systems

Syn-axial substituents (product − educt)	ΔG°, kcal/mol[a]
$\Delta G^\circ_{\mathrm{OH/(N):}} - \Delta G^\circ_{\mathrm{H/(N):}}$	−0.55[b]
$\Delta G^\circ_{\mathrm{H/(N):}} - \Delta G^\circ_{\mathrm{H/(N)H}}$	−0.25
$\Delta G^\circ_{\mathrm{OH/(N)H}} - \Delta G^\circ_{\mathrm{H/(N)H}}$	−0.05[c]
$\Delta G^\circ_{\mathrm{OH/H}} - \Delta G^\circ_{\mathrm{H/H}}$	0.35[d]

[a] A (−) sign is attractive, a (+) sign repulsive, with respect to the equilibrium defined by eq 1. [b] Corresponds to the intramolecular OH···N hydrogen bonded form. [c] Corresponds to a (presumed) NH···O hydrogen bonded form. [d] Corresponds to one-half the conformational free energy of the OH group in nonpolar media.[19]

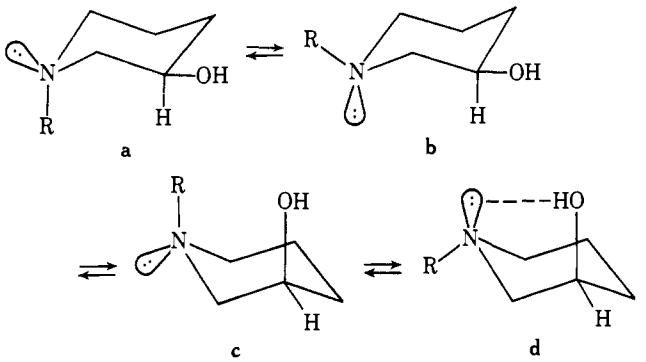
Conformational Analysis of the N-Methyl-3-Piperidinol (8) and 3-Piperidinol (9) Equilibria. Based on the results obtained from the analysis of **3** and **4** above and of **8** below, the 3-piperidinol equilibrium may now be fully described. Compounds **8** and **9** have been previously analyzed,[8] but due to disagreement in the literature regarding the ΔG° values of N-H[2] and N-CH$_3$,[9] the position of the N-CH$_3$/N-electron pair equilibrium in **8** and the N-H/N-electron pair equilibrium in **9** was purposely ignored. Accordingly, an apparent value of the conformational free energy of the hydrogen bond was derived, which was not explicitly related to the conformation of the N-electron pair. Now, however, the syn-axial OH/N-electron pair interaction is explicitly defined relative to that of an

H/N-electron pair, such that

$$\Delta G°_{OH\cdots N} = \Delta G°_{OH/(N):} - \Delta G°_{H/(N):} \quad (17)$$

If this treatment is reasonably presumed to be applicable to all systems (e.g., **3, 4, 8,** and **9**) with comparable $\Delta\nu_{OH}$ values and OH···N bond geometry, then the value of $\Delta G°_{OH\cdots N}$ (for $\Delta\nu_{OH} \sim 100$ cm^{-1}) may be assigned from a conformational analysis of the *N*-methyl-3-piperidinol equilibrium (**8**), in spite of the fact that the assignment of the $\Delta G°$ value of the N-Me group is still in dispute.[3b,9,15-18]

To rigorously analyze the piperidinol equilibrium, four conformers must be considered. A fifth conformer, corresponding to a free OH rotamer form of **d,** is presumably small enough to be ignored (cf. **6** and **7** above). In the **8** equilibrium,



8, R = CH_3; **9**, R = H

which was found[8] to contain 57% OH···N bonded species (**8d**), conformer **8c** is small enough to be ignored, due to the presence of the syn-axial CH_3/OH interaction. The total free OH species (43%), therefore, can be assigned (depending upon the value of $-\Delta G°_{NMe}$) as 0% **8a** and 43 mol % **8b,** if $\Delta G° = -2.7$ kcal/mol[15,16] is taken for the N-Me group, or 2.5 mol % **8a** and 40.5 mol % **8b** if $\Delta G° = -1.7$ kcal/mol is used,[9,12a] or 13 mol % **8a** and 30 mol % **8b** if $\Delta G°$ −0.7 kcal/mol is applied.[17,18] The **8d**/**8b** relationship, then, may be defined as above by

$$\begin{aligned} -RT \ln (\mathbf{8d})/(\mathbf{8b}) &= (\Delta G°_{OH/(N):} + \Delta G°_{OH/H} \\ &\quad + \Delta G°_{H/(N):})_{\mathbf{8d}} - (2\Delta G°_{H/(N):} + \Delta G°_{H/H})_{\mathbf{8b}} \\ &= (\Delta G°_{OH/(N):} - \Delta G°_{H/(N)}): \\ &\quad + (\Delta G°_{OH/H} - \Delta G°_{H/H}) \end{aligned} \quad (18)$$

Substituting for $(\Delta G°_{OH/H} - \Delta G°_{H/H})$ 0.35 kcal/mol (from half the conformational value of the OH group in nonpolar media)[19] and for **8d** (57%)[8] and **8b** from each of the possible values given above gives $\Delta G°_{OH\cdots N} = -0.52$ kcal/mol (attractive, i.e., in favor of **8d**) for 43 mol % **8b,** −0.56 kcal/mol for 40.5 mol % **8b,** or −0.74 kcal/mol for 30 mol % **8b,** respectively. Thus, a value of -0.63 ± 0.11 kcal/mol could be reasonably assigned to $\Delta G°_{OH\cdots N}$, regardless of the actual value of $\Delta G°_{NMe}$.[20] The value of $\Delta G°_{OH\cdots N} = -0.55$ kcal/mol given in Table II, however, corresponds to the apparently favored[3b] value of $-\Delta G°_{NMe} = 1.7$ kcal/mol in a nonpolar medium. In any event, either $\Delta G°_{OH\cdots N}$ assignment is in agreement with that recently found for two intramolecular bonded quinolizidinols, with comparable $\Delta\nu_{OH}$ values and OH···N bond geometry, which do not involve an NH or NMe equilibrium.[21]

Using the $\Delta G°$ values of Table II, the conformational free-energy difference between each of the conformers in the **9** equilibrium may now be defined and the percentage of each may be calculated (relative to 45 mol % **9d**),[8] as in eq 18, to give 14% **9a,** 32% **9b,** and 9% **9c,** respectively.[22] The value assigned above for $\Delta G°_{OH\cdots N} = -0.55$ kcal/mol gives the best results in these calculations, consistent with the sum of **9a, 9b,** and **9c** being equal to the experimentally observed value of 55 mol % free OH. These results are internally consistent within themselves and with those of **8, 3,** and **4,** as defined by the assignments in Table II, and calculated as in eq 18. The values given in Table II, therefore, are believed to be valid to within ±0.05 kcal/mol and applicable, as described above, to the conformational analysis of other heterocyclic compounds related to these general types.

Experimental Section

The *trans*-8-decahydroquinolinols were synthesized and separated as recently described[23] to give the 8α-ol epimer (**3**), mp 101-102 °C (lit.[23,24] 103°; 101-102 °C), and the 8β-ol epimer (**4**), mp 110-112 °C (lit.[23] 111-112 °C). 4-Piperidinol (Aldrich Chemical Co.), sublimed under vacuum before use, had mp 88-90 °C. Dilute solution ir spectral data were obtained with a Perkin-Elmer 521 spectrometer, as described.[7,8]

Acknowledgment. We thank Professor Ernest Eliel for his helpful comments and Mr. Morris Thompson for kindly translating part of ref 12c.

References and Notes

(1) Only the syn-axial and peri hydrogen atoms that are pertinent to this discussion are shown in the structural formulas.
(2) The literature through 1970 has been summarized by (a) R. A. Y. Jones, A. R. Katritzky, A. C. Richards, R. J. Wyatt, R. J. Bishop, and L. E. Sutton, *J. Chem. Soc. B*, 127 (1970), and (b) J. B. Lambert and W. L. Oliver, Jr., *Tetrahedron*, **27**, 4245 (1971), according to those that favor NH axial, NH equatorial, and equal proportions.
(3) Recently, the literature has been brought up to date and critically reviewed: (a) I. B. Blackburne, A. R. Katritzky, and Y. Takeuchi, *Acc. Chem. Res.*, **8**, 300 (1975); (b) J. B. Lambert and S. I. Featherman, *Chem. Rev.*, **75**, 611 (1975). A few pertinent references that were not cited in either of these or above[2] are included below.[4b,12b,12c]
(4) (a) R. W. Baldock and A. R. Katritzky, *J. Chem. Soc. B*, 1470 (1968); (b) F. Moll, *Tetrahedron Lett.*, 5201 (1968); (c) P. J. Krueger and J. Jan, *Can. J. Chem.*, **48**, 3236 (1970).
(5) It has been concluded[4a] that $\Delta H \simeq \Delta G$ for this equilibrium.
(6) A substituent is defined as β if it is cis to the substituent or H at C-10, α if it is trans.
(7) (a) H. S. Aaron, C. P. Ferguson, and C. P. Rader, *J. Am. Chem. Soc.*, **89**, 1431 (1967); (b) H. S. Aaron, G. E. Wicks, Jr., and C. P. Rader, *J. Org. Chem.*, **29**, 2248 (1964).
(8) H. S. Aaron and C. P. Ferguson, *Tetrahedron*, **30**, 803 (1974).
(9) (a) E. L. Eliel and F. W. Vierhapper, *J. Am. Chem. Soc.*, **96**, 2257 (1974); (b) *ibid.*, **97**, 2424 (1975).
(10) In this representation, the $\Delta G°$ subscript designates the two syn-axial or peri substituents, except that parentheses, e.g., as in (N):, designates the nitrogen as a member of the ring. Hydrogen, unless designated (N)H, is understood to be attached to a ring carbon atom.
(11) These equilibria might differ slightly if other factors, in addition to their syn-axial stereochemistry, are considered. Thus, **1** contains four hydrogens vicinal gauche to the N, while **2** contains three hydrogens and one methylene group. The actual difference in the equilibrium positions of **1** and **2,** however, is believed to be less than the probable error in the experimental method used to determine $\Delta G°_2$.
(12) (a) M. Tsuda and Y. Kawazoe, *Chem. Pharm. Bull.*, **16**, 702 (1968); (b) T. Masamune, M. Takasugi, and M. Matsuki, *Bull. Chem. Soc. Jpn.*, **41**, 2466 (1968); (c) O. S. Anisimova and Yu. A. Pentin, *Sovrem. Probl. Fiz. Khim.*, 7, 295 (1973); *Chem. Abstr.*, **80**, 70166j (1974).
(13) There is little difference in these results, which include both $\Delta H°$ and $\Delta G°$ values.[5] Also, one of these values[12a] has been corrected to 0.3 kcal/mol by others,[3a] based upon a reassignment of $-\Delta G°_{N\text{-}i\text{-}Pr}$. This correction may be unwarranted, however, because the original assumption that the isopropyl group is almost exclusively equatorial may still be correct.
(14) (a) N. L. Allinger, J. A. Hirsh, and M. A. Miller, *Tetrahedron Lett.*, 3729 (1967); (b) M. A. Robb, W. J. Haines, and I. G. Csizmadia, *J. Am. Chem. Soc.*, **95**, 42 (1973). See also footnote 8 in ref 9b for a pertinent comment on this matter.
(15) P. J. Crowley, M. J. T. Robinson, and M. G. Ward, *J. Chem. Soc., Chem. Commun.*, 825 (1974).
(16) D. C. Appleton, J. McKenna, J. M. McKenna, L. B. Sims, and A. R. Walley, *J. Am. Chem. Soc.*, **98**, 292 (1976).
(17) I. D. Blackburne, R. P. Duke, R. A. Y. Jones, A. R. Katritzky, and K. A. F. Record, *J. Chem. Soc., Perkin Trans. 2*, 332 (1973).
(18) V. M. Gittins, P. J. Heywood, and F. Wyn-Jones, *J. Chem.Soc., Perkin Trans. 2*, 1642 (1975).
(19) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis", Wiley-Interscience, New York, N.Y., 1965, p 44.
(20) In principle, the assignment of the percent **8b,** hence a value for $-\Delta G°_{NMe}$ (1.7 kcal/mol), can be made simply by comparing the *N*-methyl (**8**) and piperidinol (**9**) systems, taking **8b**/**8d** = **9b**/**9d,** assuming that $\Delta G°_{OH\cdots N}$ is essentially equal in both cases. Unfortunately, the probable error that exists in the individual conformer percentages does not permit a rigorous assignment of $\Delta G°_{NMe}$ in this way.
(21) H. S. Aaron and C. P. Ferguson, *J. Org. Chem.*, **40**, 3214 (1975). Here, a value of −0.6 kcal/mol, reported as $\Delta G°_{OH\cdots N}$, corresponds to $\Delta G°_{OH/N:} - \Delta G°_{H/N:}$.
(22) The 45:9 **9d**/**9c** ratio, which corresponds to 84:16 for the **4b**/**4a** model in

carbon tetrachloride, differs from that previously calculated for the model *trans*-decahydroisoquinolin-4α-ol equilibrium (74:26) in tetrachloroethylene.[8] (This compound reacted with carbon tetrachloride.) Since the solvent difference should presumably not be a factor, this discrepancy may be due to a maximum experimental error that reflects a 3–5 mol % probable error in the experimental values of the various conformer percentages. We favor the present assignments, however, due to the internal consistency of these results. For comparison, values of 53% **9d** and 10% **9c** have been reported by S. Vasickova, A. Vitek, and M. Tichy, *Collect. Czech. Chem. Commun.*, **38**, 1791 (1973), based upon other model systems.

(23) W. Barbieri, L. Bernardi, and P. Maggioni, *Chim. Ind.* (*Milan*), **52**, 240 (1970).
(24) S. Fujise, *Sci. Pap. Inst. Phys. Chem. Res.* (*Jpn.*), **8**, 161 (1928); *Chem. Abstr.*, **22**, 3890 (1928).

Application of a Modification of the Polonovski Reaction to the Synthesis of Vinblastine-Type Alkaloids

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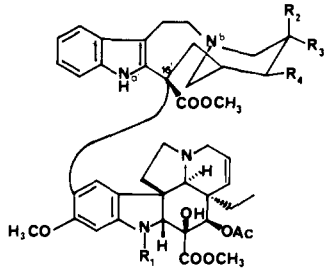
Abstract: A new C(16)–C(21) skeletal fragmentation of ibogane derivatives, induced by the modified Polonovski reaction, leads in the presence of aspidospermane derivatives to vinblastine-type compounds with the natural C(16′) configuration, which seems necessary for significant antitumor activity. This new method of coupling, which could be the same as the biogenetical pathway, has been and will be applied to partial synthesis of naturally occurring antitumor alkaloids of *Catharanthus roseus*. The circular dichroism technique is of high diagnostic value for this series of compounds to distinguish between the natural or unnatural C(16′) configurations. Another type of skeletal fragmentation at C(5)–C(6), also encountered during this study, was minimized under the experimental conditions.

Several antitumor alkaloids have been isolated from *Catharanthus roseus*,[1] including vinblastine[2] (**1a**), vincristine[2] (**1b**), leurosidine[3] (**1c**), and leurosine[3] (**1d**), and two of them, **1a** and **1b**, are widely used in cancer chemotherapy.



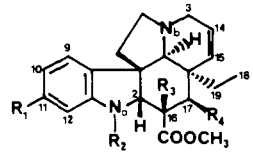
1a: $R_1 = CH_3$; $R_2 = OH$; $R_3 = Et$; $R_4 = H$
1b: $R_1 = CHO$; $R_2 = OH$; $R_3 = Et$; $R_4 = H$
1c: $R_1 = CH_3$; $R_2 = Et$; $R_3 = OH$; $R_4 = H$
1d: $R_1 = CH_3$; $R_2 = Et$; $R_3 + R_4 = \text{"O"}$

Unfortunately these compounds are present at very low concentrations in the plant material and their isolation is long, costly, and fraught with difficulty. For these reasons, their synthesis (partial or total) has been the subject of a considerable amount of work in the past ten years.[4-12]

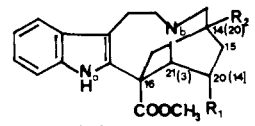
All these attempts were unsuccessful and led to compounds having "unnatural" configuration at C(16′) and consequently, biologically inactive. Therefore, we recently[13] introduced a new method based on a modification of the Polonovski reaction,[14] which was afterwards[15] adopted by other workers.[16]

The procedures used by our predecessors[7,9,10,12] consisted of condensing vindoline (**2a**) or one of its derivatives with compounds having the *tetracyclic* ibogane skeleton, **4** or **5**, obtained by cleavage[17] of the C(16)–C(21)[18] bond of catharanthine (**3a**) (Scheme I) or by total synthesis.[5b,5c]

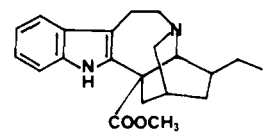
However, a plausible biogenetic hypothesis[10] proposes that the vinblastine-type alkaloids could well be formed in nature by direct coupling of vindoline (**2a**) with catharanthine (*pentacyclic* ibogane skeleton) (**3a**), major alkaloidal components of *C. roseus*. This hypothesis has been verified[19] in vivo; coupling of the two "monomeric" units could take place with concomitant breaking of the C(16)–C(21) bond of catharanthine (**3a**).



2a: $R_1 = OCH_3$; $R_2 = CH_3$; $R_3 = OH$; $R_4 = OAc$
2b: $R_1 = H$; $R_2 = CH_3$; $R_3 = OH$; $R_4 = OAc$
2c: $R_1 = H$; $R_2 = CH_3$; $R_3 = H$; $R_4 = H$
2d: $R_1 = OCH_3$; $R_2 = CH_3$; $R_3 = H$; $R_4 = H$
2e: $R_1 = OCH_3$; $R_2 = CHO$; $R_3 = H$; $R_4 = H$

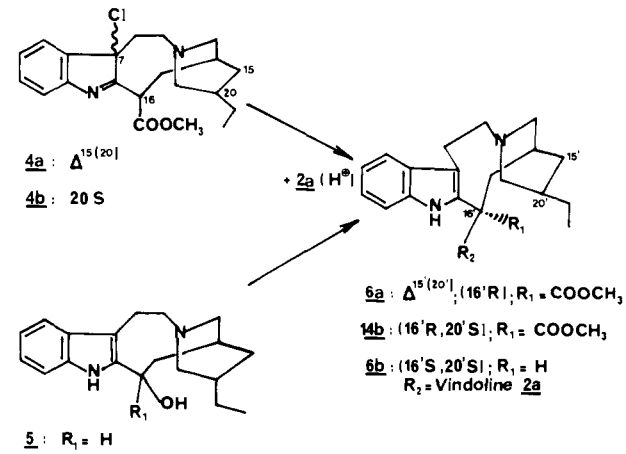


3a: $\Delta^{15(20)}$; $R_1 = Et$; $R_2 = H$
3b: $R_1 = 20S$ Et; $R_2 = H$
3c: Δ^{14}; $R_1 = H$; $R_2 = Et$
3d: $R_1 = H$; $R_2 = Et$



3e

Scheme I



4a: $\Delta^{15(20)}$
4b: 20 S
5: $R_1 = H$
6a: $\Delta^{15(20')}$; (16′R); $R_1 = COOCH_3$
6b: (16′S,20′S); $R_1 = H$; $R_2 =$ Vindoline **2a**

It is known that the Polonovski reaction[20]—action of an acid anhydride on an *N*-oxide—can give rise both to elimination