Stereochemistry of the 4-Phenylquinolizidin-1-ol Diastereoisomers. Conformational Free Energy of the Quinolizidine Ring Fusion, and of Their Intramolecular OH···N Hydrogen Bonds

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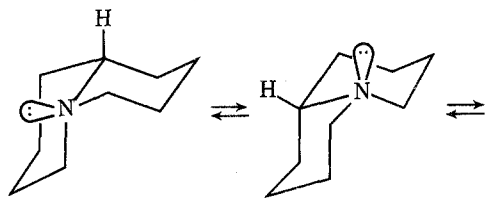
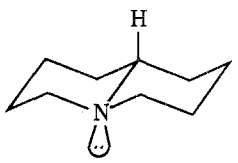
Received July 29, 1975

The four diastereoisomers of 4-phenylquinolizidin-1-ol have been synthesized and separated, and their relative configurations assigned. Three of the isomers contain an intramolecular OH···N hydrogen bond. From dilute solution ir spectra, the position of the conformational equilibrium in each of the isomers has been determined. By conformational analysis, the inherent free energy difference between the cis and trans quinolizidine ring fusion ($\Delta G°_Q$) and the conformational free energy of their intramolecular hydrogen bonds ($\Delta G°_{OH\cdots N}$) have been rigorously and independently derived. In this system, $\Delta G°_Q$ was found to be 2.0 kcal/mol, in favor of the trans conformation, and $\Delta G°_{OH\cdots N}$ to be 0.6 kcal/mol (attractive), for $\Delta\nu_{OH} \sim 83$ cm^{-1}, at 33°.

Quinolizidine, the bridgehead nitrogen analog of decalin, occurs as a substructure in many natural products.[1] Whereas decalin exists as separable cis and trans isomers, quinolizidine exists as an equilibrium mixture of cis (two) and trans conformers, which rapidly interconvert at ordinary temperature by simple ring flip (cis ⇄ cis), and pyramidal inversion[2] of the nitrogen (cis ⇄ trans). This equilibrium is



cis cis



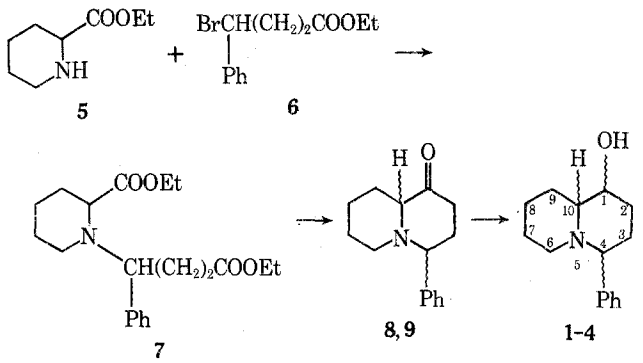
trans

known to favor, strongly, the trans-fused conformer, if to an uncertain degree, what with values of 2.6[3] and 4.4 kcal/mol[4] having been reported. Suitable substituents can shift this equilibrium to a point where appreciable quantities of both cis- and trans-fused species are present,[3,5] or further, to where a cis-fused form largely predominates.[6-9] In no case, however, have a pair of stable conformers been isolated.[10] Thus, earlier claims[11-13] for two forms of substituted quinolizidines, that differ only in the stereochemistry of the ring fusion, were subsequently shown[6,14,15] to have been erroneous structural assignments.[7,16,17]

Apart from the question of the equilibrium position in the unsubstituted parent, the conformational assignments of substituted quinolizidines have been almost invariably given as simply cis or trans, corresponding to the ring fusion of the major species (in solution). More quantitative assignments of such equilibria are necessary, however, if one is to assess the conformational factors that operate in the quinolizidine ring system. Accordingly, we now report a study of the 4-phenylquinolizidin-1-ol isomers, from which the free-energy difference between the cis and trans ring fusion in the interesting *trans*-4,10-*H*-4-phenylquinolizidine system[8] is rigorously derived.

Results

4-Phenylquinolizidin-1-ol was synthesized by the following route. In this synthesis, the product obtained from a



Dieckmann condensation of the diester **7** was hydrolyzed and decarboxylated to a mixture of epimeric ketones **8** and **9**, from which a pure sample of major isomer **8** was obtained. Reductions of small amounts of **8** gave mixtures of alcohol isomers **1** and **2**. However, since the ketones (especially minor isomer **9**) were found to deteriorate on standing, the ketone mixture was not separated in the large-scale run, but was directly reduced to alcohol isomers **1–4**. The composition of this carbinol mixture (**1** plus **2** and **3** plus **4**) corresponds to that of the ketone mixture from which it was obtained, based upon the configurational assignments given below. A pure sample of each alcohol was obtained by adsorption chromatography on alumina, the separation being monitored by GLC on Carbowax 20M. The isomers are numbered according to their order of elution, and the same order was obtained from both the alumina and Carbowax columns. The ir spectrum of each alcohol isomer was recorded in dilute CCl_4 solution (Figure 1), where intermolecular hydrogen bonding has been eliminated. The data are given in Table I. Only isomer **2** was found to contain 100% free OH. For intramolecular bonded isomers **1**, **3**, and

Table I
Ir Spectral Data for 4-Phenylquinolizidin-1-ol Isomers in Dilute CCl_4 at 33°

		Free OH			Bonded OH···N	
Isomer	Mp, °C	ν_{OH}, cm^{-1}	B, l. mol^{-1} cm^{-2}	Mol %	ν_{OH}, cm^{-1}	$\Delta\nu_{OH}$, cm^{-1}
1	109–111	3630	300	7.5	3552	78
2	117–118	3637[a]	3970	100		
3	Liquid	3635	600	15	3549	86
4	133–134	3630	3200	80.5	3550	80

[a] Shoulder at 3610 cm^{-1}, assigned to a free OH rotamer form.[18]

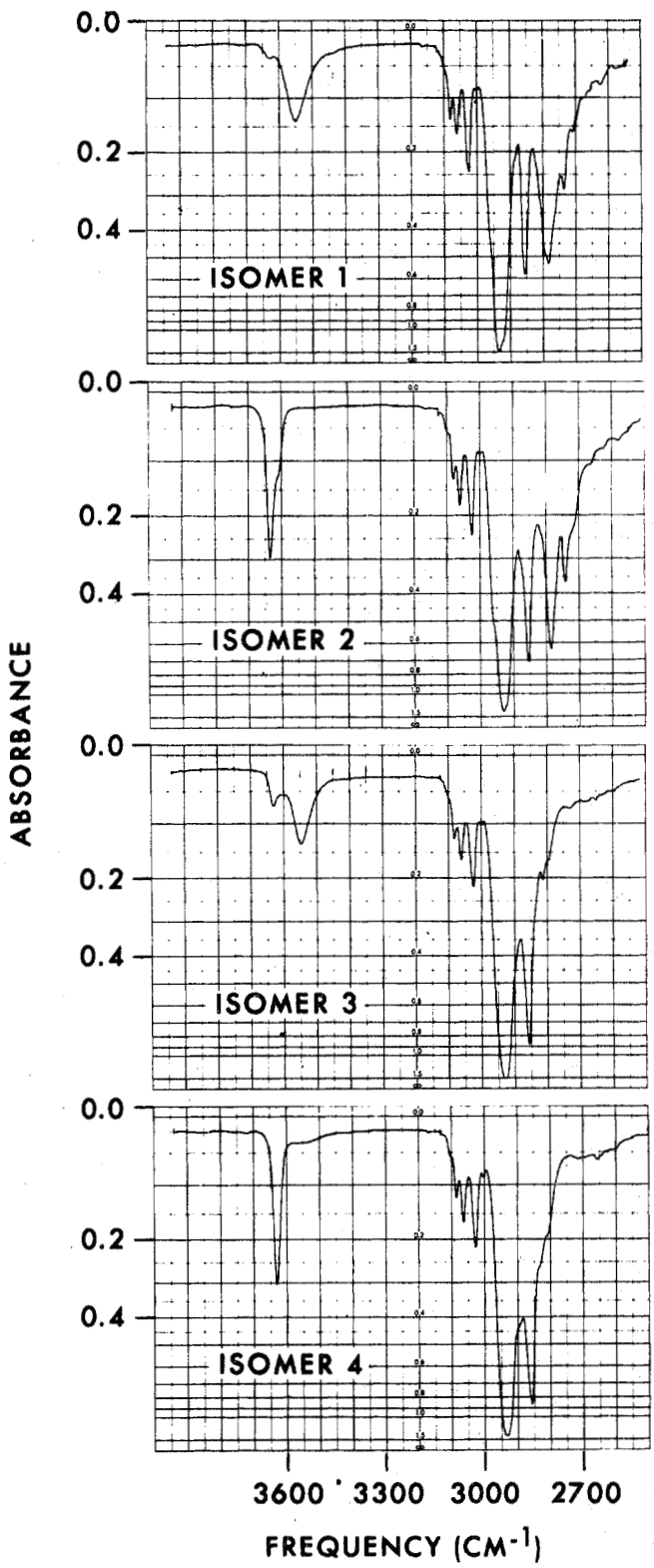
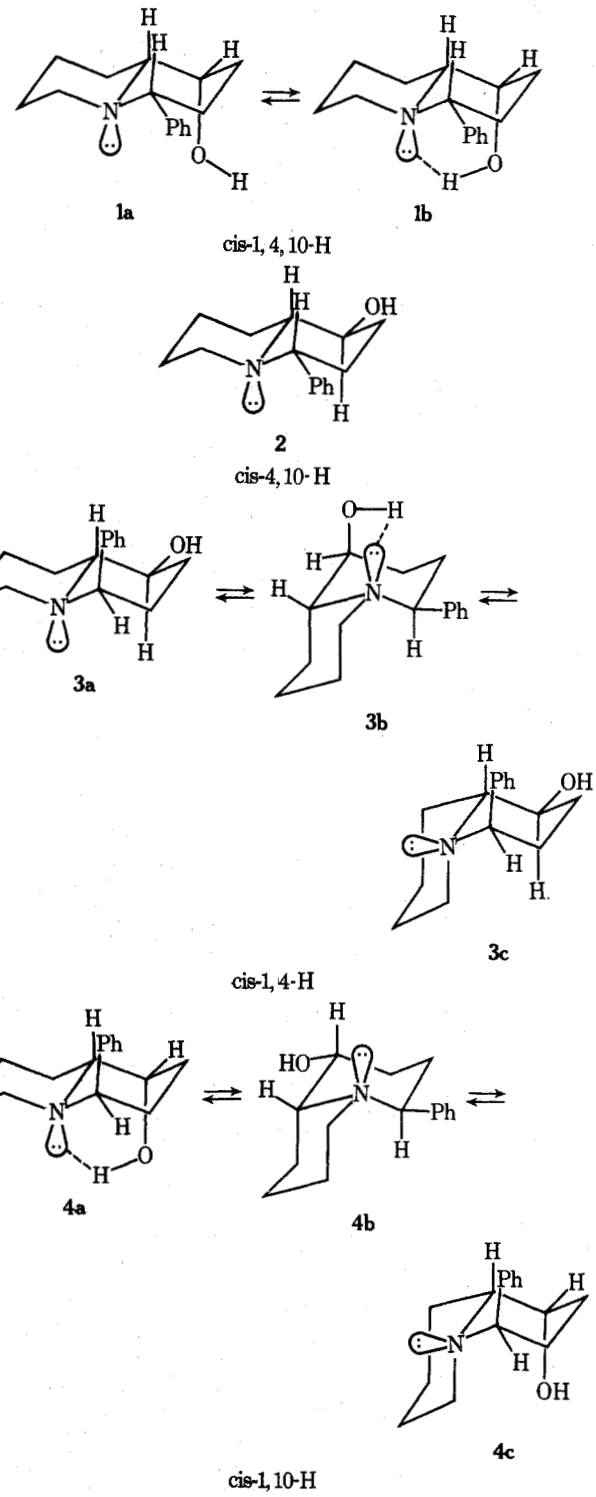


Figure 1. Dilute solution ir spectra of the 4-phenylquinolizidin-1-ol isomers in CCl_4, all at 2.6×10^{-3} *M*, 2-cm cell path.

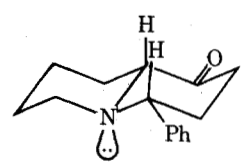
4, the percentage of free OH was calculated from the area (*B*) of the free OH band of each, relative to that of isomer 2, as the 100% free-OH reference model.[18] For these closely related structures, the values are assumed to be accurate to ±3 mol %.

The NMR spectral data are given in the Experimental Section. The proton signals have been assigned by analogy to literature data, and are consistent with the configurational and conformational assignments given below.

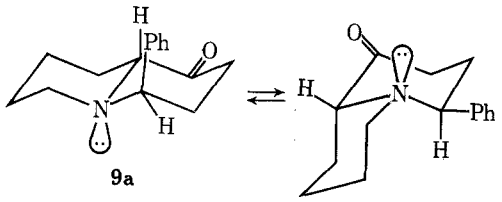


Discussion

Ketone Epimers 8 and 9. Ketone 8 is assigned a trans ring fusion with a preferred equatorial 4-phenyl substituent (hence, cis-4,10-H configuration, as shown), based on the strong Bohlmann bands[19] observed in the 2700–2800-cm^{-1} region of its ir spectrum. Conversely, an 8–9 mixture



had only weak absorption in this region, which suggests that **9** exists in solution in an equilibrium, which contains an appreciable amount (predominant if calculated by methods given below) of the cis quinolizidine form (**9b**).



9a ⇌ **9b**

trans-4,10-H

Regardless of the exact equilibrium position, however, the ir data are consistent with a **9** trans-4,10-H configuration, since even the trans-fused form **9a** should absorb relatively weakly in the Bohlmann region, because it has a 4-axial substituent, hence contains only one *secondary* hydrogen anti-trans to the N-electron pair.[20]

Alcohol Isomers 1–4. The structural formulas and conformational equilibria of these isomers have been assigned as discussed below. Although each isomer, of course, exists in equilibrium between one trans- and two cis-fused conformers, except for structure **4c**, only those forms which are present in any significant concentration are shown. Also, only one enantiomer of each isomer is depicted, although they all exist (also **8** and **9**) as a racemic pair. Thus, a trans ring fusion for amino alcohol isomers **1** and **2** and a predominantly cis ring fusion for isomers **3** and **4** are assigned from the presence and absence, respectively, of the Bohlmann ir bands, corresponding to a preferred equatorial 4-phenyl substituent for each, in agreement with the assignment of the 4-phenylquinolizidine isomers.[8] Previously, the 1- and 3-hydroxyquinolizidines were found to exist with a trans ring fusion, and this stereochemistry was not affected by an intramolecular OH···N hydrogen bond that would be formed in a cis-fused form.[21] Therefore, the configuration of each hydroxyl group in **1–4** may be assigned based on whether it is predominantly free or hydrogen bonded in its dilute solution ir spectrum. For **1**, the 7.5 mol % free OH absorption at 3630 cm^{-1} is assigned to an OH rotamer form (**1a**), in which the axial OH group is oriented away from the nitrogen electron pair. Such a rotamer form (i.e., band) has been observed in weakly bonded OH···N systems,[22] but was not detected in the bonded isomers of 1- and 3-hydroxyquinolizidine,[21] apparently because of their slightly stronger hydrogen bonds ($\Delta\nu \sim 100$ cm^{-1} in CCl_4),[18] compared to **1**. An alternate possibility, whereby this free OH band might be due to a cis ring-fused conformer of **1**, is excluded by the extremely unfavorable syn-axial steric interactions that exist in such a structure.

In the case of isomers **3** and **4**, the presence of both free OH and OH···N bonded species is undoubtedly due, based on conformational analysis, to the presence of a significant concentration of both cis- and trans-fused quinolizidine conformers in the equilibrium mixture. Therefore, for these isomers, all three ring-fused species must be considered. In **4**, however, the concentration of **4c** can be ignored, owing to the unfavorable syn-axial OH–CH_2 interactions that are present in this form. In **3**, a small percentage of **3c** can also be ignored, to a first approximation, in order to simplify the calculations. Then, as shown below, the results can be corrected to reflect the presence of this species. First, the total free OH observed for **3** and **4** (Table I) must be divided into that which is due to equatorial OH conformations **3a** and **4b**, and that which is due to a nonbonded OH rotamer form of axial OH conformations **3b** and **4a**, respectively. Therefore, taking the 7.5:92.5 ratio observed for the comparably strongly bonded (based on $\Delta\nu_{OH}$, Table I) **1a–1b** equilibrium, and applying it to **3** and **4**, one calculates 7 mol % free OH rotamer form associated with 85 mol % **3b**, and about 1.5 mol % free OH rotamer form with 19.5 mol % **4a**. On this basis, one calculates free OH species **3a** equal to 8 mol % (15 − 7%), and **4b** to 79 mol % (80.5 − 1.5%), respectively. Then, as calculated for conformational equilibria in other hydrogen-bonded systems,[23] the **3a–3b** equilibrium may be defined by the free-energy difference between the two conformations, as

$$-RT \ln (\mathbf{3b})/(\mathbf{3a}) = \Delta G^\circ_{\mathbf{3b}} - \Delta G^\circ_{\mathbf{3a}} \quad (1)$$

The ΔG°_{3a} and ΔG°_{3b} values in turn are calculated from the algebraic sum of the individual syn-axial and peri[24a] conformational interactions, taking repulsive interactions as positive, and attractive interactions as negative, in sign. Thus, **3b**, the dominant species, is favored by the conformational free energy of the hydrogen bond ($\Delta G^\circ_{OH\cdots N}$), but is opposed by the inherent conformational preference for the trans quinolizidine ring fusion (ΔG°_Q).[3,4] In addition, **3b** is opposed by both a syn-axial interaction of the OH group with the 3β hydrogen (ΔG°_{OH-H}) and a peri interaction of the phenyl group with the 6α hydrogen, that is essentially equivalent to a syn-axial Ph–H interaction. Conformation **3a**, in turn, is opposed by three syn-axial Ph–H interactions (involving the 2, 6, and 10β hydrogens), plus a peri interaction of the hydroxyl group with the 9β hydrogen that is essentially equivalent to a syn-axial OH–H interaction. Therefore, the **3** equilibrium may be defined, according to eq 1, by

$$-RT \ln (\mathbf{3b})/(\mathbf{3a}) = (\Delta G^\circ_Q + \Delta G^\circ_{OH-H} + \Delta G^\circ_{Ph-H} - \Delta G^\circ_{OH\cdots N})_{\mathbf{3b}} - (3\Delta G^\circ_{Ph-H} + \Delta G^\circ_{OH-H})_{\mathbf{3a}} \quad (2)$$

which reduces to

$$-RT \ln (\mathbf{3b})/(\mathbf{3a}) = \Delta G^\circ_Q - 2\Delta G^\circ_{Ph-H} - \Delta G^\circ_{OH\cdots N} \quad (3)$$

By a similar analysis of the **4a–4b** equilibrium, in which the intramolecular OH···N bond is now in conformational opposition to the dominant species (**4b**), the system may be defined by

$$-RT \ln (\mathbf{4b})/(\mathbf{4a}) = (\Delta G^\circ_Q + \Delta G^\circ_{Ph-H} + \Delta G^\circ_{OH-H})_{\mathbf{4b}} - (3\Delta G^\circ_{Ph-H} + 2\Delta G^\circ_{OH-H} - \Delta G^\circ_{OH\cdots N})_{\mathbf{4a}} \quad (4)$$

which reduces to

$$-RT \ln (\mathbf{4b})/(\mathbf{4a}) = \Delta G^\circ_Q - 2\Delta G^\circ_{Ph-H} - \Delta G^\circ_{OH-H} + \Delta G^\circ_{OH\cdots N} \quad (5)$$

Conformational Free Energy of the Intramolecular Hydrogen Bond ($\Delta G^\circ_{OH\cdots N}$). If one subtracts eq 5 from eq 3, and substitutes (from above) the values of **3a** (8%), **3b** (85%), **4a** (19.5%), and **4b** (79%), one obtains

$$-0.6 = -2\Delta G^\circ_{OH\cdots N} + \Delta G^\circ_{OH-H} \quad (6)$$

Substituting here for ΔG°_{OH-H} 0.35 kcal/mol (from one-half the conformational value of the hydroxyl group in aprotic media[24b]) gives $\Delta G^\circ_{OH\cdots N} = 0.5$ kcal/mol (attractive) in **3b** and **4a**, *independent of the actual values of* ΔG°_Q *and* ΔG°_{Ph-H}. If one now refines this calculation to reflect (see below) the presence of 3% of free OH species **3c**, a corrected concentration for **3a** of 5% should have been used in eq 3. On this basis, subtracting eq 5 from eq 3 gives

$$-0.85 = -2\Delta G^\circ_{OH\cdots N} + \Delta G^\circ_{OH-H} \quad (7)$$

from which $G^\circ_{OH\cdots N}$, corrected, is calculated to be 0.6 kcal/mol. The value of $\Delta G^\circ_{OH\cdots N}$ thus derived (for $\Delta\nu$ 83 ± 3 cm^{-1}) is in good agreement with that (0.5 kcal/mol, for $\Delta\nu$

100 cm^{-1}) recently calculated (but less rigorously) for other OH···N systems.[23]

Conformational Free Energy of the Quinolizidine Equilibrium ($\Delta G°_Q$). If one defines the **3b–3c** equilibrium, as above, one obtains

$$-RT \ln (\mathbf{3c})/(\mathbf{3b}) = (2\Delta G°_{Ph-H} + \Delta G°_{OH-H})_{3c} - (\Delta G°_{Ph-H} + \Delta G°_{OH-H} - \Delta G°_{OH\cdots N})_{3b} \quad (8)$$

which reduces to

$$-RT \ln (\mathbf{3c})/(\mathbf{3b}) = \Delta G°_{Ph-H} + \Delta G°_{OH\cdots N} \quad (9)$$

Substituting for $\Delta G°_{Ph-H}$ 1.55 kcal/mol (from one-half the conformational value of a phenyl group[24b]) and for $\Delta G°_{OH\cdots N}$ 0.5 or, corrected, 0.6 kcal/mol gives 3% **3c** in equilibrium with 85% **3b** at 33°. On this basis, one calculates **3a** equal to 5 mol % (8–3%), when corrected for free OH species **3c** that is also present. If one now adds eq 3 and 5, taking the corrected value of **3a** (5%), one obtains

$$-2.55 \text{ kcal/mol} = 2\Delta G°_Q - 4\Delta G°_{Ph-H} - \Delta G°_{OH-H} \quad (10)$$

Substituting for $\Delta G°_{OH-H}$ 0.35 kcal/mol and for $\Delta G°_{Ph-H}$ 1.55 kcal/mol gives $\Delta G°_Q$ 2.0 kcal/mol, in favor of the trans quinolizidine ring fusion. As here derived, this result is *essentially independent of the actual value of* $\Delta G°_{OH\cdots N}$, but reasonably assumes that $\Delta G°_{OH\cdots N}$ is essentially the same (if not identical, based on $\Delta\nu_{OH}$ 83 ± 3 cm^{-1}) in **3b** and **4a**. Any difference in $\Delta G°_{OH\cdots N}$ in these two species will reflect in the probable error of $\Delta G°_Q$. In these calculations, no specific conformational value was assigned to the nitrogen electron pair, hence its conformational factor (if any) will be contained within $\Delta G°_Q$.

Probable Error in $\Delta G°_{OH\cdots N}$ and $\Delta G°_Q$ Values, and Application of the Results to Other Systems. By directly comparing the 3 and 4 equilibria, values for the individual syn-axial interactions need not be assigned (except for $\Delta G°_{Ph-H}$ and $\Delta G°_{OH-H}$ in eq 10, and $\Delta G°_{OH-H}$ in eq 6 and 7), since they are presumably equivalent in either system. Therefore, the probable error in the calculated values of $\Delta G°_{OH\cdots N}$ and $\Delta G°_Q$ is mainly due to the uncertainty in the measured values (Table I) of the free OH band areas of **2**, **3**, and **4**. For these closely related systems, **2** should be the perfect 100% free OH reference model. We find that an absolute deviation of ±5 mol % in the assigned values for each of **3a**, **3b**, **4a**, and **4b** results in a probable error of ±0.35 kcal/mol in the calculated values of $\Delta G°_{OH\cdots N}$ and $\Delta G°_Q$, while a ±3 mol % error in the individual conformer assignments corresponds to a probable error of ±0.2 kcal/mol in each of the two calculated values. We believe that the probable error in the conformer assignments is less than ±5 mol %. In view of the various other assumptions and assignments that are required in these calculations, however, we estimate the reliability of the values calculated above for $\Delta G°_{OH\cdots N}$ and $\Delta G°_Q$ to be on the order of ±0.35 kcal/mol.

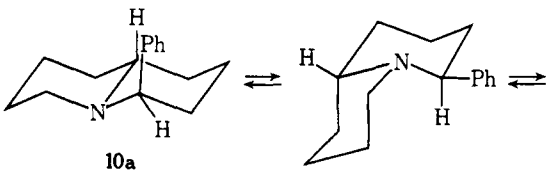
From the above results, the conformer population of *trans*-4,10-*H*-4-phenylquinolizidine[8] (**10**) can now be readily assigned. Thus, the **10** equilibrium may be defined, in part (for **10a**, **10b**), according to eq 1, by

$$-RT \ln (\mathbf{10b})/(\mathbf{10a}) = (\Delta G°_Q + \Delta G°_{Ph-H})_{10b} - (3\Delta G°_{Ph-H})_{10a} \quad (11)$$

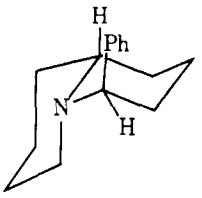
and in part (for **10b**, **10c**) by

$$-RT \ln (\mathbf{10c})/(\mathbf{10b}) = (2\Delta G°_{Ph-H})_{10c} - (\Delta G°_{Ph-H})_{10b} \quad (12)$$

Substituting for $\Delta G°_Q$ 2.0 ± 0.35 kcal/mol and $\Delta G°_{Ph-H}$ 1.55 kcal/mol as above, and solving these two equations (taking **10a** + **10b** + **10c** = 100%), one calculates 86 ± 6% cis-fused species (80% **10b** and 6% **10c**) in the equilibrium mixture at 25°.



10a ⇌ **10b** ⇌



10c

These results are particularly applicable to the conformational analysis of other 4-aryl substituted quinolizidine systems, including the Lythraceae alkaloids.[25] Vertaline, for example, which has been found to exist as a cis quinolizidine (as the hydrobromide) in the crystal,[26] as the *free base* should exist in solution as an equilibrium mixture which, according to our calculations, should actually favor the trans-fused conformation, by ~0.4 kcal/mol.

It should be noted that the value of $\Delta G°_Q$ derived above is specifically applicable only to derivatives of *trans*-4,10-*H*-4-phenylquinolizidine; it is only approximately applicable to other systems. Thus, for example, the value of $\Delta G°_Q$ for completely unsubstituted quinolizidine will actually differ from 2.0 kcal/mol by the difference in the conformational contribution of a gauche interaction of a phenyl–nitrogen electron pair (in **3b** and **4b**), compared to that of a gauche hydrogen–nitrogen electron pair interaction in the unsubstituted parent. This difference is probably small, however, and may even be within the experimental error of these methods, if one assumes that $\Delta G°_Q$ in the unsubstituted parent is approximately 2.6 kcal/mol,[27] as suggested by our earlier study,[3] and as calculated from the three gauche CH_2–H interactions that are present in the cis- but absent in the trans-fused form.[24c] However, a rigorous determination of $\Delta G°_Q$ for unsubstituted quinolizidine would better be obtained from the study of other quinolizidinol compounds.

Experimental Section

Dilute solution ir spectra (Figure 1) were recorded on a Perkin-Elmer 521 spectrophotometer and the mole percent values were calculated as described;[18] all other ir spectra were recorded on a Perkin-Elmer 237B spectrophotometer. NMR spectra were recorded on a Varian A-60D spectrometer, and mass spectral data were obtained on a Hitachi Perkin-Elmer RMU-6E spectrometer.

Ethyl Pipecolate (5). Ethyl picolinate (20 g, Aldrich Chemical Co.) was hydrogenated in an excess of aqueous HCl over platinum dioxide (0.75 g, J. Bishop & Co.) at 60 psig for 18 hr at room temperature in a Parr hydrogenator. After the catalyst was filtered off, the solution was brought to pH 10 and extracted with chloroform. The organic solution was then dried (Drierite), concentrated, and distilled at a pot temperature below 65°, recovery 17 g (85%) of **5**, bp 36–38° (0.3 mm). The product is best stored in the freezer, since it slowly dimerizes (with elimination of ethanol) on standing at room temperature.[28]

Ethyl 4-Bromo-4-phenylbutyrate (6). 5-Phenyldihydrofuranone (5-phenyl-γ-butyrolactone, Regis Chemical Co.) (20 g, 0.12 mol) was dissolved in 60 ml of absolute ethanol in a 200-ml round-bottom flask equipped with a thermometer, drying tube, and magnetic stirring bar. The stirred solution, maintained at 15°, was saturated during 3 hr with anhydrous HBr (Mathieson Gas Products), introduced through a Drierite tower. The mixture was allowed to warm overnight to room temperature, then was shaken with an equal volume of water, and the aqueous phase was extracted with ether. The combined ether–organic phase was washed

three times with sodium bicarbonate solution, then dried (Drierite) and concentrated on a rotary evaporator under reduced pressure at room temperature. An oil (28 g) was obtained, which contained 74% of **6** (62% yield), calculated from the weight of sodium bromide that precipitated, when an aliquot of the solution was warmed on the steam bath with an excess of sodium iodide in acetone. Except for residual solvent, the product appeared to be relatively pure, based on its ir spectrum (CCl_4): 1738 cm^{-1} (C=O), with only a trace of starting lactone (1795 cm^{-1}). For fear of possible dehydrohalogenation, no attempt was made to distil the product, or to remove the remaining solvent by heating under vacuum.

Diethyl Pipecolate-1-(4-phenyl-4-butyrate) (7).[29] Compound **6** (31 g, 0.072 mol based on 80% purity, by sodium iodide assay described above) was added in 5 min, dropwise with stirring, to 16 g (0.10 mol) of **5** in 75 ml of anhydrous acetone, which contained 28 g (0.20 mol) of a suspension of anhydrous potassium carbonate. After being stirred for 30 min at room temperature, the mixture was refluxed with stirring for 2 hr, then left to stand at ambient temperature over a 3-day weekend. The salts were filtered and washed with acetone, and the filtrate was concentrated under reduced pressure with gentle warming, at which time a precipitate began to form. After standing overnight, the residual oil was dissolved in ether, and the mixture was filtered to give ~1 g of (presumably) ethyl pipecolate hydrobromide, needles, mp 183–185°. Apparently, the original reaction had not been fully completed, and this salt was formed from the continued reaction of residual **5** and **6**, after the K_2CO_3 had been removed. The ethereal solution thus obtained was dried ($MgSO_4$), filtered, and concentrated on the steam bath, then under reduced pressure on a rotary evaporator to give 38 g of the crude product. This product (7 g) was subjected to a molecular distillation at 1 μ, and after a low-boiling forerun was removed (75–88° bath), the desired **7** was collected (5 g, 85%) at an oil bath temperature of 125–155°. This product appeared to be about 97% pure by GLC (retention time of 8 min, 10-ft column of 10% SE-30 at 255°, 30 ml/min): ir (CCl_4) 1735 (C=O, singlet), with (phenyl) bands at 3045, 3075, and 3100 cm^{-1}. It was not further characterized, but was used directly in the next step.

1-Oxo-4-phenylquinolizidine (8 and 9).[30] To a suspension of 1.5 g of sodium hydride (Ventron Corp., 57% in oil, 0.035 mol) in 40 ml of sodium-dried toluene in a 250-ml round-bottom flask equipped with a nitrogen inlet tube, dropping funnel, reflux condenser with drying tube, and magnetic stirrer was added 5.2 g (0.015 mol) of **7** in 60 ml of dry toluene. No evidence of any hydrogen evolution was observed until the mixture was heated. It was refluxed until hydrogen evolution had ceased (3 hr), then cooled in an ice bath, and 100 ml of 6 *N* hydrochloric acid was slowly added. A gummy precipitate formed. The mixture was refluxed, carbon dioxide evolution occurred, and the precipitate slowly dissolved. After 5 hr, carbon dioxide evolution could no longer be detected. The mixture was then cooled to room temperature, and the layers were separated. The aqueous phase was cooled in an ice bath and brought to pH 9 by slowly adding a concentrated sodium hydroxide solution. The product precipitated as a tan solid mixture of **8** and **9**, and was filtered off. The filtrate was brought to pH 10, and a little additional product was obtained. As described below, these ketones were found to be unstable; therefore, the two crops were combined and used directly (wet) in the next step. From the yield of alcohol isomers **1–4**, isolated in the next step, about a 90% yield of **8** and **9** had been obtained.

In an earlier experiment, the **8–9** product mixture (95% **8**, by GLC) obtained in this way was found to be completely soluble in ether. However, this product deteriorated on standing to produce an ether-insoluble residue, accompanied by a decrease (GLC) in the relative percentage of isomer **9** in the mixture. A 0.4-g sample of the mixture was chromatographed on 40 g of neutral alumina (Woelm, Grade I), and eluted with 1:1 ether–petroleum ether. The eluent was collected in 20-ml fractions, and the solvent was removed on a rotary evaporator. The composition of each fraction was determined by GLC on a 10-ft column of 10% SE-30 at 240°, at 85 ml/min helium flow. Under these conditions, the relative retention times were 5.0 (**8**) and 5.8 min (**9**), with irregular tailing of the peaks, possibly owing to some decomposition. Fractions 2 plus 3 gave 0.22 g of pure **8**, mp 89–92°, as white, crystalline stars, which darkened even when stored in the refrigerator: ir (CCl_4) 1725 (C=O), 3035, 3070, and 3090 (phenyl), 2720 (sh), 2740, 2750 (sh), and 2790 cm^{-1} (CH, Bohlmann bands). Fractions 4 plus 5 gave 41 mg of a yellowish oily product which contained (GLC) about 33% of **9**. Although the pure **9** was not isolated, the relative intensity of the Bohlmann bands in the ir spectrum of this mixture was much smaller than that of the pure **8**. Ketones **8** and **9** were not further characterized, but were reduced to the corresponding amino alcohols under a variety of chemical and catalytic conditions.[31] The best preparative route to the total carbinol isomer mixture (i.e., which gave the largest percentage of minor isomer **3**) is reported below.

4-Phenylquinolizidin-1-ol Isomers (1–4). The mixture of isomers **8** and **9** (from 5.2 g of **7**) was dissolved in 75 ml of methanol, and shaken in a Parr hydrogenator at 50 psig hydrogen with 0.2 g of platinum dioxide (J. Bishop Co.) for 40 min, at which time the hydrogen uptake had ceased. The catalyst was filtered off and the filtrate was concentrated on a rotary evaporator to give a mixture which consisted (GLC)[32] of 80% **1**, 16% **2**, 1% **3**, and 3% **4**. The remaining methanol was then removed, and the residue was taken up in ether, filtered to remove a small insoluble residue, concentrated to about 25 ml, cooled, and seeded with a crystal of **1** (obtained from earlier hydrogenation experiments) to give 1.3 g of mainly **1**, mp 103–107° (from GLC, 93% **1**, 6% **2**, a trace of **3**, and about 1% of **4**). The filtrate was concentrated to dryness, and the residue (1.3 g) was chromatographed on 170 g of Woelm neutral alumina (1 × 11 in. column) in ether, using ether as the eluent, and a slight positive pressure to speed the flow. After 100 ml of blank solvent was collected, the product began to elute. It was collected in 25-ml fractions, which were concentrated under reduced pressure, and examined by GLC. Fractions 1 and 2 contained a total of 0.55 g of pure **1**, mp 109–111°. Fractions 6–9 contained 82 mg of **2**, 97% pure by GLC (3% **1**), which was recrystallized from ether–petroleum ether to give 46 mg of pure **2**, mp 117–118°. Fractions 14–21 were combined to give pure **3**, obtained as 41 mg of pale yellow oil, after being pumped to constant weight over phosphorus pentoxide at 10 μ. This isomer could not be induced to crystallize. Fractions 25–38 gave 0.13 g of pure **4**, mp 133–134°. The melting points of **1** and **4**, above, did not change on recrystallization from ether–petroleum ether. Including the mixed isomer fractions, a quantitative recovery was obtained from the separation.

The mass spectra of the four isomers were very similar. All had major peaks (*m/e*) at 231 (mol wt) and 230 (loss of H), with the next major peaks (loss of H_2O) at 213 and 212, then 136 (loss of phenyl).

The NMR spectra of these isomers in $CDCl_3$ (internal Me_4Si) follow: **1**, δ 7.3 (s, 5, Ph), 3.8–3.4 (m, 1, CHOH), 3.1–2.4 (m, 3, OH, CHPh, and C_6 eq H), and 2.3–1.1 (m, 12); **2**, 7.25 (s, 5, Ph), 3.75–3.15 (m, 1, CHOH), 3.1–2.45 (m, 2, CHPh and C_6 eq H), and 2.4–1.0 (m, 13, including OH at 1.6); **3**, 7.3 (m, 5, Ph), 4.15–3.8 (m, 1, probably CHOH), 3.8–3.4 (m, 2, OH and probably CHPh), 3.35–2.1 (m, 3, C_6H_2 and $C_{10}H$), and 2.1–0.8 (m, 10); **4**, 7.3 (m, 5, Ph), 4.25–3.8 (m, 2, CHOH and CHPh), 3.5–3.1 (m, 1, $C_{10}H$), 2.95–2.4 (m, 2, C_6H_2), 2.25 (s, 1, OH), and 2.4–0.8 (m, 10). The position of the OH proton was assigned from the change in the spectrum obtained by either heating the solution or adding D_2O. The other proton assignments were made by analogy to those reported for the quinolizidin-1-ol[21] and 4-phenylquinolizidine[8a] systems.

Anal. Calcd for $C_{15}H_{21}NO$: C, 77.9; H, 9.2; N, 6.1. Found: **1**, C, 77.6; H, 9.5; N, 6.0; **2**, C, 77.7; H, 9.5; N, 6.2; **4**, C, 77.5; H, 9.6; N, 6.1.

Acknowledgments. We thank Thomas Barbish and Paul Reichert for some synthesis assistance, Lester Daasch for the mass spectra, Linda Szafraniec for the NMR spectra, and Marge Buckles for the elemental analyses.

Registry No.—**1**, 56454-11-6; **2**, 56454-12-7; **3**, 56454-13-8; **4**, 56454-14-9; **5**, 15862-72-3; **6**, 56454-15-0; **7**, 56454-16-1; **8**, 56454-17-2; **9**, 56454-18-3; ethyl picolinate, 2524-52-9; 5-phenyldihydrofuranone, 1008-76-0; ethyl pipecolate HBr, 56454-19-4.

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Some Reactions of DL-*trans*-4,5-Dicarbomethoxy-2-phenyl-2-oxazoline

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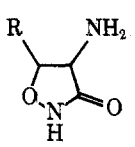
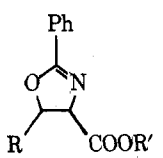
Received May 5, 1975

The synthesis and some anomalous reactions of the title compound (**4**) are discussed. Treatment of **4** with hydroxylamine caused oxazoline ring opening to form the amidoxime **5**. When the diester **4** was saponified, the *O*-benzoyl zwitterion **6** crystallized from solution in excellent yield. The structure of **6** was secured by its rearrangement into DL-*threo*-*N*-benzoyl-β-hydroxyaspartic acid (**10**) and its conversion into DL-*threo*-β-hydroxyaspartic acid dimethyl ester. In contrast, the oxazoline ring in monoester **2** (R = H; R′ = CH_3) is stable to both hydroxylamine and alkali.

We have been interested in the synthesis of derivatives and analogs of the antibiotic cycloserine (**1**, R = H) for many years. Recently, we have been working toward the synthesis of a 5-carbamido analog (**1**, R = $CONH_2$) of cycloserine, since this compound might reasonably be expected to inhibit asparagine synthetase. Since the original synthesis[1] of cycloserine proceeded through an oxazoline intermediate, **2** (R = H), we decided to investigate a synthetic scheme using the oxazoline dicarboxylic acid (**2**, R = COOH; R′ = H).

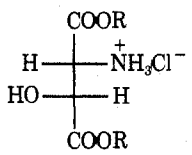


1

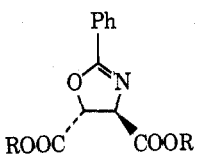


2

The starting material for this approach was β-hydroxyaspartic acid, the synthesis and stereochemistry of which we had investigated previously.[2] Esterification of the threo amino acid (**3**, R = H) followed by conversion of the ester into the oxazoline (**4**, R = CH_3) by reaction with ethyl benzimidate[3] was uneventful. The oxazoline ester was a crystalline compound, which was unstable at ambient temperatures but could be kept indefinitely in a refrigerator.



3



4

The difficulties with the oxazoline approach to **1** (R = $CONH_2$) began when attempts were made to convert the oxazoline ester into the corresponding dihydroxamic acid (**4**, RO = NHOH). The use of the standard methods of hydroxamic acid synthesis, i.e., treatment of the diester with at least 2 equiv of hydroxylamine in basic or neutral solution,[4] gave only highly colored products of a polymeric nature. All attempts to crystallize salts of the desired product from the mixture failed. Treatment of the crude product with ethanolic cupric acetate followed by isolation of the precipitated salts and liberation of the organic conjugate acids with hydrogen sulfide gave only tarry products. When, however, **4** was treated with 1 equiv of methanolic hydroxylamine, a white crystalline product, $C_{13}H_{16}N_2O_6$, was obtained in yields of 35–71%. The empirical formula indicated that 1 mol of oxazoline had combined with 1 mol of hydroxylamine. Significantly, the ester functions of the starting material were still present in this product as shown by infrared, NMR, and ^{13}C NMR spectroscopy. It gave a negative $FeCl_3$ test, but showed positive Tollens and Griess[5] tests indicating the presence of a reducing group, probably –NHOH or =NOH, in the molecule. Of all the possible structures considered, only the amidoxime structure **5** was consistent with all the spectral and chemical data. Importantly, when the proton decoupled ^{13}C NMR spectrum of the ester **4** (R = CH_3) was compared with that of the unknown compound, a signal at 152.2 ppm in the