Dramatic Reversal of Diastereoselectivity in an *N*-Acyliminium Ion Cyclization Leading to Hexahydropyrrolo[2,1-*a*]isoquinolines. A Case of Competing Steric Interactions

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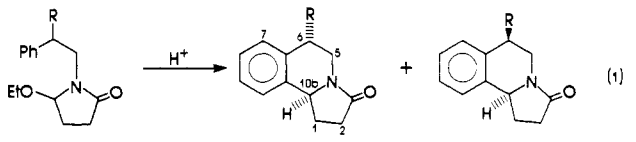
The *N*-acyliminium ion cyclization 1 → **2** + **3** (eq 1) with various aliphatic substituents (R = ethyl, cyclohexyl, and *tert*-butyl) was carried out, as an extension of our work in ref 2. The following **2**:**3** ratios were obtained: 39:61, 12:88, and 15:85, respectively. The results indicate a dramatic reversal of diastereoselectivity in going from the phenyl case in ref 2 (**2a**:**3a** = 93:7) to the cyclohexyl and *tert*-butyl cases, which is attributed to competition between syn-axial and A(1,3) steric interactions and the spatial properties of the substituent. Unusual boat isoquinoline conformations were found to contribute substantially to the solution disposition of the 6α,10bα (cis) lactams **2d** and **2e**; in chloroform **2d** has about 50% boat form and **2e** has at least 85–90%. A single-crystal X-ray analysis is reported for trans cyclohexyl lactam **3d**, which shows a flattened half-chair ("bent-planar") isoquinoline conformation with a pseudoaxial substituent. Some empirical force-field calculations (MM2) on lactams (**2a**, **3a**, **2d**, and **3d**) are discussed relative to steric interactions in the product lactams. Steric factors involved in the observed cyclization stereoselectivities are also discussed.

Heterocyclization reactions involving *N*-acyliminium ions have become popular for alkaloid synthesis because of the high stereocontrol often realized.[1,2] In our study of cyclizations leading to substituted isoquinoline derivatives, we found various examples of high stereoselectivity with respect to aromatic substituents at certain ring positions.[2] For example, approximately 93% selectivity in favor of the alpha, or pseudoequatorial, phenyl group was observed in the reaction illustrated in eq 1 with R = phenyl (**1a** → **2a** + **3a**). However, when one of the phenyl groups in **1a** was replaced by a methyl group, cyclization (**1b** → **2b** + **3b**) afforded substantially diminished stereoselectivity, 72:28 in favor of the α (cis) diastereomer, **2b**. The



1 2 (6α,10bα) 3 (6β,10bα)

a: R = phenyl d: R = cyclohexyl (cHx)
b: R = methyl e: R = tert-butyl
c: R = ethyl

stereochemical outcome of this type of reaction was rationalized in terms of a transition state resembling a chair-like arenium ion, **4**, in which a single 1,3 syn-axial steric interaction between the substituent and the 10a proton is an important stereodeterminant.

To develop our initial impression about this diastereoselection process, we decided to examine this reaction with substituents from a wider steric spectrum. We have now studied the series ethyl, cyclohexyl, and *tert*-butyl to expand the earlier phenyl and methyl data. Although this standard sort of stereochemical protocol might have been rather routine, considering the syn-axial steric explanation, such was not the case. Indeed, the cyclohexyl and *tert*-butyl cyclizations demonstrated an unexpected, dramatic reversal in diastereoselectivity, with an ca. 15:85 bias for the β (trans) stereochemistry (viz. **3**) in the lactam product mixture. This reversal was that much more remarkable given the results reported by Macco and co-workers for a related polyene cyclization involving stereoselectivity with a methyl vs. *tert*-butyl substituent.[3] In this paper we present our recent results along with a discussion of the stereochemical features that may control diastereoselection in this type of acyliminium cyclization (eq 1).

Results and Discussion

Synthesis. Acyliminium ion precursors **1c–1e** were prepared from the corresponding imides via reduction with sodium borohydride and acid in ethanol.[4] The requisite succinimides were obtained as follows. 2-Phenylbutyronitrile was reduced with borane–THF to 2-phenylbutylamine (95%), which was condensed with succinic anhydride by using acetyl chloride as a dehydrating agent, as described earlier (80%).[2] Similarly, cyclohexylphenylacetonitrile was converted to amine (78%) and then imide **6** (92%). The *tert*-butyl compound (**7**) was synthesized by the protracted scheme outlined in eq 2. Pivalophenone

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(2) Maryanoff, B. E.; McComsey, D. F.; Duhl-Emswiler, B. A. *J. Org. Chem.* **1983**, *48*, 5062.

(3) (a) Macco, A. A.; deBrouwer, R. J.; Buck, H. M. *J. Org. Chem.* **1977**, *42*, 3196. (b) Macco, A. A.; deBrouwer, R. J.; Nossin, P. M. M.; Godefroi, E. E.; Buck, H. M. *Ibid.* **1978**, *43*, 1591.

(4) Hubert, J. C.; Winjberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1975**, *31*, 1437. A modification of this procedure involving methanesulfonic acid was employed (see ref 2).

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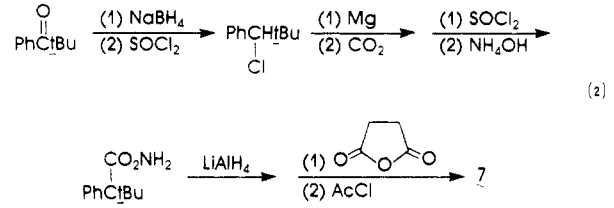


was reduced with sodium borohydride (100%) and converted to phenylneopentyl chloride with thionyl chloride (72%).[5] The chloride was reacted with magnesium in THF, and the Grignard reagent was quenched with dry carbon dioxide at atmospheric pressure to give *tert*-butylphenylacetic acid (84%).[6] The acid chloride was reacted with concentrated ammonium hydroxide (82%), and the amide was reduced with lithium aluminum hydride to 3,3-dimethyl-2-phenyl-1-aminobutane[7] (95%), which was transformed to the succinimide, **7** (72%).

Ethoxypyrrolidin-2-ones **1c–1e** were cyclized with polyphosphoric acid (PPA) at 100 °C to pyrroloisoquinolin-3-one products, as described before.[2] The reaction yields (of **2** + **3**) and diastereomer ratios are given in Table I, along with results for cyclization of **1a** and **1b**. The high α stereoselectivity observed for the case with R = phenyl is typical for such cyclizations.[2] Understandably, α stereoselectivity is diminished for the smaller substituent, R = methyl, as related in our earlier article.[2] On increasing the size of the alkyl substituent, from methyl → ethyl → cyclohexyl → *tert*-butyl, we expected to find enhancement of stereoselectivity for the α diastereomer, that possessing a quasi-equatorial substituent. However, just the opposite result was obtained! In fact, the cyclohexyl and *tert*-butyl cyclizations greatly favored the β isomer: **2:3** = 12:88 and 15:85, respectively (Table I). Even the reaction with R = ethyl showed some unexpected bias toward the β isomer (**2c:3c** = 39:61), compared to the methyl case as a reference (**2b:3b** = 72:28) (Table I).

Stereochemistry and Conformational Analysis of the Lactams. The relative configuration of the 6 and 10b stereocenters in the lactam diastereomers can be established by ^{1}H NMR.[2] In our previous article,[2] we pointed out that vicinal coupling constants between protons on the 5 and 6 positions were effective determinants, given a half-chair conformation for the nitrogen-containing six-membered ring. This was verified by a single-crystal X-ray analysis on **2a**.[2] The vicinal coupling values for **2a** are 6.0 and 11.0 Hz; those for **3a** are 5 and 2–3 Hz.[2] Spectra for compounds with alkyl, instead of aryl, substituents at C-6 are more difficult to analyze because two of the key protons (H_{5a} and H_6) are shifted upfield, where they are more readily concealed under other aliphatic protons. Nevertheless, in the case of the methyl derivatives, **2b** and **3b**,[2] proton H_{5e} is isolated enough to furnish the necessary coupling parameters. The α isomer, **2b**, had ^3J = 5 Hz (δ 4.28); the β isomer, **3b**, had ^3J = ca. 2 Hz (δ 4.02).[2]

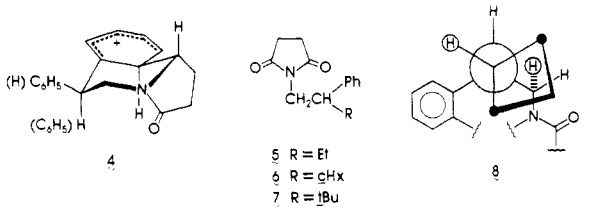
The cyclohexyl compounds were examined by 360-MHz ^{1}H NMR. The crystalline major isomer, **3d**, exhibited the following spectral parameters for the non-cyclohexyl aliphatic protons: δ 1.80 (ddd, J = 9, 9, 9 Hz, H_1), 2.4–2.7 (m of 4 protons, H_1, 2 H_2, and H_6), 2.97 (ddd, J = 0.9, 4.3, 13.4 Hz, H_{5a}), 4.39 (dd, J = 1.2, 13.4 Hz, H_{5e}), 4.73 (dd, J = 6.2, 9.9 Hz, H_{10b}). The proton designations and coupling constants were determined by double irradiation of the resonances at δ 2.97, 4.39, and 4.73. The small vicinal coupling constant of 1.2 Hz for H_{5e} suggested the β isomer assignment; the H_{5a} vicinal coupling of 4.3 Hz, although smaller than usual, still supported this. The H_{5a}-proton also showed an extra small coupling (0.9 Hz), not observed with **3a** or **3b** (possibly because spectra of these had been obtained at 90 MHz). We first thought this minor coupling to be a long-range interaction with the cyclohexyl methine proton[8] because of a possible "W" pathway[9] in a predominant solution conformation. (With an equatorially disposed cyclohexane ring and a staggered arrangement for the cyclohexyl–isoquinoline linkage, such a "W" pathway exists in the conformer represented by **8**, which is close to that depicted in the X-ray analysis discussed below.) However, since the *tert*-butyl congener (**3e**) also exhibited this extra minor coupling (vide infra), a long-range coupling between H_{5a} and the cyclohexyl methine had to be rejected. To resolve the question about this extra coupling, we performed a two-dimensional J-correlated (COSY) study on **3d**.[10] The one-dimensional spectrum for the aliphatic region and the corresponding contour plot are contained in the microfilm supplement.[12] In the four-proton multiplet between δ 2.4 and 2.7, we discerned the positions (proceeding in an upfield direction) of H_{1e} (correlated to H_{10b}), H_6 (correlated to H_{5e}), and one of the protons on the 2 position (α to the carbonyl group), which has the small, long-range coupling to H_{5a}. This type of 5-bond (homoallylic) coupling through an amide linkage, which has precedent in the literature,[11] is presumably maximized when the protons are oriented 180° to one another; thus, based on a Dreiding model, the 2-proton is assigned as H_{2e}.

The oily minor isomer, **2d**, gave the following spectral parameters: δ 1.93 (m, H_1), 2.4–2.7 (m, H_1 and 2 H_2), 2.82 (ddd, J = 6, 6, 6 Hz, H_6), 3.32 (dd, J = 6.7, 12.7 Hz, H_{5a}), 3.84 (dd, J = 5.9, 12.5 Hz, H_{5e}), 4.73 (dd, J = 6.5, 13 Hz,

Table I. Results of *N*-Acyliminium Cyclizations (1 → 2 + 3)

R	2:3 ratio[a]	yield, %
Ph[b]	93:7	84[c]
Me[b]	72:28	50[d]
Et	39:61	88[c]
c-Hx	12:88	91[c]
t-Bu	15:85	74[c]

[a] Determined by GLC. [b] From ref 2. [c] Isolated yield based on the succinimide. [d] Isolated yield based on the primary amine.



(5) Winstein, S.; Morse, B. K. *J. Am. Chem. Soc.* **1952**, *74*, 1138.
(6) Aaron, C.; Dull, D.; Schmiegel, J. L.; Jaeger, D.; Ohashi, Y.; Mosher, H. S. *J. Org. Chem.* **1967**, *32*, 2797.
(7) This amine was prepared before by a different procedure, see: Pine, S. H.; Munemo, E. M.; Phillips, T. R.; Bartolini, G.; Cotton, W. D.; Andrews, G. C. *J. Org. Chem.* **1971**, *36*, 984.
(8) This extra coupling could not be confirmed by irradiation of the cyclohexyl methine around δ 1.7–1.8 because this broad signal was largely obscured.
(9) (a) Bhacca, N. S.; Williams, D. H. "Applications of NMR Spectroscopy in Organic Chemistry"; Holden-Day: San Francisco, 1964, pp 115–121. (b) Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed.; Pergamon Press: Oxford, 1969; pp 334–338.
(10) Jelinski, L. W. *Chem. Eng. News* **1984**, Nov 5, 26, and literature cited therein. Aue, W. P.; Bartholdi, E; Ernst, R. R. *J. Chem. Phys.* **1976**, *64*, 2229. Bax, A. "Two-Dimensional NMR in Liquids"; Delft University Press: Delft, Holland, 1982. Bax, A; Freeman, R. *J. Magn. Reson.* **1981**, *44*, 542.
(11) Reference 9b, pp 316–328 (especially pp 326–327).
(12) See paragraph at the end of this paper regarding supplementary material.

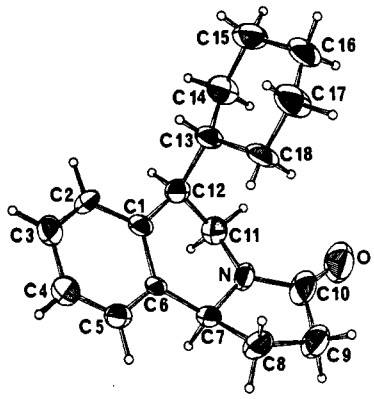


Figure 1. ORTEP representation of independent molecule B of lactam **3d** giving the crystallographic numbering system used. Thermal ellipsoids for non-hydrogen atoms represent 35% probability. Only minor conformational variations differentiate molecule A from molecule B.

H_{10b}). The proton assignments and coupling constants were established by double irradiation of the resonances at δ 1.93, 2.45, 2.6, 2.82, 3.32, 3.84, and 4.73. The multiplet for the cyclohexyl methine, centered at δ 1.81, was identified on irradiation of H_6. Interestingly, the H_5–H_6 vicinal coupling values do not conform with the 6-Hz/11-Hz ($\beta\beta/\alpha\beta$ 5,6-protons) paradigm for an α isomer (as defined by **2a** and **3a**, vide supra); rather, the values are 5.9 and 6.7 Hz, respectively. Also, it is noteworthy that one of the vicinal coupling constants between H_1 and H_{10b} (13 Hz) is unusually large (it commonly ranges from 8–10 Hz). Since the minor isomer is the α isomer, it must be adopting a solution conformation that is not a half-chair isoquinoline with a pseudoequatorial cyclohexyl group, the isoquinoline conformation generally realized previously.[2] This suggests a significant population in **2d** of a *boat-like isoquinoline nucleus with a pseudoaxial cyclohexyl substituent*, which is extraordinary, indeed. According to a Dreiding molecular model, this structure would have dihedral angles between the protons on positions 5 and 6 of 40–45° ($\beta\beta$) and 75–80° ($\alpha\beta$), producing J_{56} values of about 7 Hz and 1 Hz, respectively. An approximately 50:50 mixture of the boat and chair forms would thus nearly account for the observed coupling values [0.5(6) + 0.5(7) = 6.5 and 0.5(11) + 0.5(1) = 6 Hz]. Also, MM2 calculations (vide infra) provided a relatively low energy boat conformation in which the dihedral angles are 52° ($\beta\beta$) and −63° ($\alpha\beta$), corresponding to vicinal couplings of 2.2 and 3.5 Hz. A 50:50 mixture of boat and chair forms in this instance would give J values of 4.8 [0.5(6) + 0.5(3.5)] and 6.6 [0.5(11) + 0.5(2.2)] Hz.

Because of the unusual NMR data for **2d**, and to corroborate the stereochemical assignment, we performed a single-crystal X-ray analysis on crystalline isomer **3d**. Crystals of **3d** contain eight molecules per unit cell ($P2_1/c$) that represent two crystallographically independent sets, denoted A and B. An ORTEP representation of molecule B, with the crystallographic numbering system (used exclusively in this paragraph), is depicted in Figure 1 and a stereoview of molecules A and B is presented in the microfilm supplement.[12] The two independent molecules (A and B) differ by only minor conformational features. Details of the X-ray work are supplied in the Experimental Section and microfilm supplement.[12] The X-ray analysis demonstrates that **3d** does possess the β (trans) stereochemistry. In the solid state, a half-chair conformation is adopted by the piperidine ring of the tetrahydroisoquinoline subunit, with flattening in the vicinity about the amide nitrogen and benzene carbon atoms. In molecule B, atoms N, C_7, C_6, C_1, and C_{12} are nearly coplanar, while C_{11} is ca. 0.5 Å below the plane, giving rise to a bent-planar or envelope conformation (related to the envelope conformation of cyclopentane).[12] Even though **3d** has an envelope-type conformation and a pseudoaxial substituent instead of a pseudoequatorial one, the overall geometry of the tricyclic nucleus of **3d** is very similar to that of **2a**.[2] The pseudoaxial chair cyclohexyl group in **3d** assumes a staggered conformation in its connection to the isoquinoline moiety, with dihedral angles of 54.7° for the array C18–C13–C12–C11 and −73.2° for the array C14–C13–C12–C11 (molecule B). The dihedral angle between the protons on this C13–C12 linkage is ca. 75°. Unfortunately, the vicinal coupling between these two protons was not available from the 360-MHz spectrum, preventing an assessment of the solution conformation about this linkage.

The *tert*-butyl compounds were also examined by high-field ^1H NMR. The spectral parameters for the major isomer, **3e**, closely parallel those observed for **3d**: H_6 (δ 2.57, part of 4-proton m, J = 4.6 Hz), H_{5a} (δ 2.94, J = 1.4, 4.6, 13.8 Hz), H_{5e} (δ 4.57, J = 0.9, 13.8 Hz), and H_{10b} (δ 4.73, J = 5, 8 Hz). Given our first consideration for the extra H_{5a} coupling in **3d**, we had been surprised to find a similar extra coupling for H_{5a} in this case, since now there is a quaternary carbon attached to position 6 of the tricycle. As indicated above, the long-range coupling in **3d** and **3e** is ascribed to interaction between H_{5a} and H_{2e}. The minor *tert*-butyl diastereomer, **2e**, revealed ^1H NMR parameters related to those of **2d**, but even stranger than the original protocol (that for **2a** and **2b**): H_6 (δ 2.88, J = 1.7, 8.1 Hz), H_{5a} (δ 3.59, J = 8, 14 Hz), H_{5e} (δ 3.87, J = 0.5, 14.0 Hz), and H_{10b} (δ 4.75, J = 5, 8 Hz). Comparing the data for **2e** and **2d**, it is evident that the conformational equilibrium has shifted to some degree, especially with respect to the end of the tricycle bearing the substituent. Indeed, for **2e** *a boat conformer with a pseudoaxial tert-butyl group appears to predominate greatly*, at least to the extent of 85–90% (note that the J_{56} values of 0.5 and 8 Hz are very close to those predicted from a Dreiding model of the boat conformer—vide supra).[13]

The stereochemical assignment for **2e** and **3e** was corroborated by X-ray analysis of a derivative. Thus, **3e** was reduced with borane–THF to the corresponding amine and its hydriodide salt was subjected to X-ray diffraction (see Experimental Section).[14] The molecule possesses the β (trans) stereochemistry with a cis-fused 5–6 ring junction and a pseudoequatorial *tert*-butyl group.

The 360-MHz ^1H NMR spectrum for ethyl analogue **3c** displayed $J_{5e,6}$ and $J_{5a,6}$ values of 1.3 and 3.6 Hz, respectively (δ_{5e} 4.26; δ_{5a} 3.05), in analogy with values for **3a**, **3b**, **3d**, and **3e**. The methyl triplet for **3c** was centered at δ 1.02. The NMR spectrum for **2c** was not first-order even at 360 MHz. A COSY study on **2c** allowed proton assignments to be made: δ 0.96 (t, CH_3, J = 7.4 Hz), 1.6 and 2.0 (pair of m, 2, CH_2 of Et), 1.9 (m, H_1), 2.4–2.7 (m, H_1 and 2 H_2), 2.88 (m, 2, H_{5a} and H_6), 4.22 (m, H_{5e}), 4.77 (dd, H_{10b}, J = 7, 8 Hz). The $ABCK_3TX$ spin system [A = one

(13) (a) For information on 1-substituted 1,4-dihydronaphthalenes, which have boat conformations usually with pseudoaxial substituents due to a peri interaction, see: Lamberts, J. J. M.; Hassnoot, C. A. G.; Laarhoven, W. H. *J. Org. Chem.* **1984**, *49*, 2490 and references cited therein. This reference also points out instances of the small steric demand of phenyl groups. (Also see: Rabideau, P. W.; Mooney, J. L.; Hardin, J. N. *Ibid.* **1985**, *50*, 5737 and references cited.) (b) The energy differences connected with the isomer ratios in Table I were correlated with Verloop's B_2 parameter (Verloop, A., Hoogenstraaten, W.; Tipker, J., In "Drug Design"; Ariens, E. J., Ed., Academic Press, New York, 1976; Vol VII). This parameter is a measure of each substituent's bulk and shape. The equation $\Delta E = -3.4 + 1.5\ B_2$ was derived for the five data sets (n = 5), the fit of which is reasonably good: R^2 = 0.77, F = 13.6.

(14) Details of this X-ray work will be published elsewhere (Maryanoff, B. E.; McComsey, D. F.; Parvez, M.; Olofson, R. A., to be submitted).

of the CH_2 protons, B = one of the CH_2 protons, C = H_6, K = CH_3, T = H_{5a}, X = H_{5e}] was analyzed by computer simulation of the 8-spin system with a LAOCN3-like program.[15] Thus, we obtained the coupling constants, $J_{5e,6}$ = 6.2 Hz, $J_{5a,6}$ = 9.7 Hz, and $J_{5a,5e}$ = −12.9 Hz (with $\Delta\nu_{5a,6}$ = 4 Hz), suggesting the predominance of a half-chair conformation with an equatorial ethyl group.

The prevalence of a boat conformation in **2d** and **2e**, relative to **2a** and **2b**, may be explained on the basis of competitive steric effects. There is potentially a severe steric interaction in the half-chair structure of **2d** and **2e** between the pseudoequatorial bulky substituent and the hydrogen at the 7 position—a peri interaction or A(1,3) strain—that effectively counteracts the undesirable 1,4 steric interaction in the boat structure between the pseudoaxial substituent and the proton at position 10b (see Figure 2). In the half-chair structure, there can also be an undesirable steric interaction between the substituent and H_{5e}/H_{5a}, which represents a gauche butane-type effect (see Figure 2). In MM2 calculations, the lowest energy half-chair conformation of **2d** shows these two steric problems, which are relieved in the boat form (vide infra). In the case of **2b**, A(1,3) strain is not a significant factor because of the small size of the methyl group; in the case of **2a**, it is apparently not important because the phenyl substituent can assume a nearly perpendicular (±30°) orientation relative to the plane of the half-chair tricycle, which would diminish A(1,3) interaction. This disposition of the phenyl group is substantiated by a 0.3–0.4 ppm upfield shift for the "peri" proton, H_7, in the ^1H NMR spectrum of **2a**, attributable to shielding by the pendant benzene ring;[16] this orientation also prevails in the solid-state structure and MM2 energy-minimized structure of **2a**.[2]

We were able to ascertain the difference in free energy between **2a** and **3a** by base-catalyzed equilibration.[2] The ratio of **2a**:**3a** at ca. 100 °C was 50:50 (reached from both directions), for a ΔG of zero.[2] MM2 calculations on **2a** and **3a** (representing an enthalpy difference, ΔH) gave minimized half-chair conformations with total energies of 8.3 and 7.8 kcal/mol, respectively, indicating a 30:70 ratio of **2a**:**3a**.[2,17] Since a similar equilibration of **2d** and **3d** was unsuccessful (due to extensive decomposition of the lactams probably because of the absence of a benzhydryl-type proton at C_6), we evaluated the relative energetics for **2d** and **3d** by force-field calculations with Allinger's MM2 method.[18] (Computational details are given in the Experimental Section.)

For the cyclohexyl derivatives, we performed a search of conformational space to arrive at all relevant energy minima. This exhaustive process was necessary because of the prevalence of the boat conformer, in addition to the half-chair, in the NMR analysis of **2d** (and **2e**). For **2d** and **3d** we obtained low energy minima for half-chair (HC), boat (B), and bent-planar (BP) or envelope isoquinoline conformations (Figure 2). Seven conformers of **2d** were found within a low-lying 5-kcal/mol range; however, three of these accounted for about 99% of the conformational mixture (assuming a Boltzmann distribution at 20 °C). The boat conformer (Figure 2b) is 1.8 kcal/mol less stable than the most stable half-chair conformer (Figure 2a), the global minimum for **2d**. The third-ranked conformer (not shown) was a half-chair related to the global minimum, but with a rotation (by 140°) of the cyclohexyl group. Although the calculations point to a measurable contribution of the boat form, the 24:1 ratio of half-chair to boat conformers is *not* in quantitative agreement with the ca. 1:1 ratio derived from NMR data on **2d**. Five conformers of **3d** were found within a low-lying 5-kcal/mol range, and three of these accounted for 99.9% of the conformer population (assuming a Boltzmann distribution at 20°C). All of these structures had bent-planar (or envelope) conformations with different torsion angles for the pendant cyclohexyl group, and these structures were distributed over a narrow energy range (only 0.8 kcal/mol). The most stable boat conformer (not shown) was 4.4 kcal/mol less stable than the global minimum (bent-planar conformer shown in Figure 2c), so that the boat occupied less than 0.1% of conformational space. The MM2 calculations on **3d** agree well with the NMR data. The X-ray structure

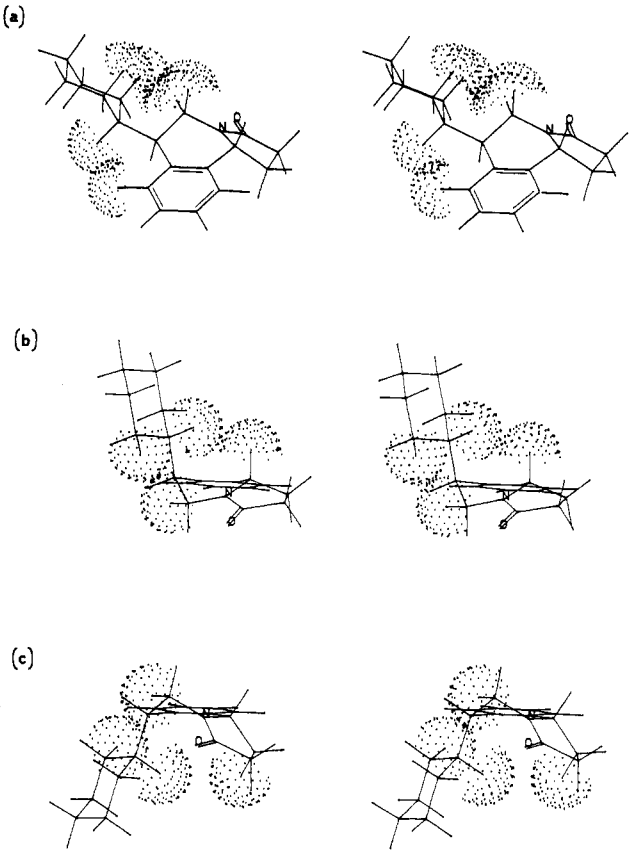


Figure 2. Stereoviews of a half-chair (HC), bent-planar (BP), and boat (B) conformation from MM2 calculations (for **2d** or **3d**). (a) Low energy half-chair conformer for **2d** (18.3 kcal/mol). (b) Boat conformer for **2d** (20.2 kcal/mol). (c) Bent-planar conformer for **3d** (17.1 kcal/mole), analogous to the X-ray structure (see Figure 1). van der Waals surfaces for nearest approaching atoms are shown, with sighting approximately orthogonal to the axis of closest approach. These dot surfaces depict gauche-butane, cross-ring, and/or A(1,3) interactions involving the pendant cyclohexyl group. The diagrams were generated by using the SYBYL molecular modeling program.

(15) (a) For LAOCN3, see: Bothner-by, A. A., Castellano, S. M., in "Computer Programs for Chemistry", Detar, D. F., Ed.; N. A. Benjamin: New York, 1968; Vol. 1, Chapter 3. We used the program available on the Bruker AM-360 called PANIC. (b) The interrelationship of the NMR resonances for H_{5e}, H_{5a}, and H_6 was proven by the 2-D *J*-correlated (COSY) study on **2c**. (c) We also calculated the spectrum for the other aliphatic protons on positions 1, 2, and 10b (5-spin system). A complete set of spectral parameters and a figure depicting the observed and calculated spectra are furnished in the supplementary material.[12]

(16) This type of shielding has been observed in related structural situations, see: Weber, H. P.; Petcher, T. J.; Loosli, H. R. *Helv. Chim. Acta* **1977**, *60*, 2886. Oppolzer, W.; Achini, R.; Pfenninger, E.; Wever, H. P. *Ibid.* **1976**, *59*, 1186. Charlton, J. L.; Durst, T. *Tetrahedron Lett.* **1984**, *46*, 5287.

(17) The relative energetics were mistakenly reversed in ref 2 (p 5068). The more stable isomer from computation was the β isomer (**18b**); the ratio for **18a**:**18b** was 30:70. This does not alter the point of discussion, especially since MM2 calculated energies are variable at least to ±0.5 kcal/mol.

(18) Allinger, N. L.; Yuh, Y. H. *QCPE* **1980**, *12*, 395.

of **3d** is similar to, but not identical with, the calculated bent-planar structures. The differences amount mainly to a noncorrespondence of cyclohexyl orientation due to torsional angle variability. From the calculations, β isomer **3d** is much more stable than α isomer **2d**; under equilibration the ratio of **3d**:**2d** would be ca. 90:10.

Stereochemistry in the Cyclization Process. We have rationalized[2] the stereochemistry of the *N*-acyliminium ion cyclization in terms of a 1,3 syn-axial interaction between the substituent stereocenter and the stereocenter that develops in an incipient arenium ion intermediate (see **4**, and Scheme I in ref 2). The results reported[2] for the formation of **2a**/**3a**, **2b**/**3b**, and phenyl-methyl lactams were consistent with a late, chair-like transition state en route to an arenium ion in which the bulkier substituent assumes an equatorial position because of syn-axial steric interaction involving H_{10a}. However, our data with **2c–e**/**3c–e** indicate that this earlier picture is incomplete. The high stereoselectivity for β isomer in the cyclizations leading to **2d**/**3d** and **2e**/**3e** requires an alternative steric influence. It is reasonable that bulky substituents, such as cyclohexyl and *tert*-butyl, as opposed to the planar phenyl, will experience A(1,3) interactions to a greater extent.[13] This is also true for substituent interaction with protons on the 5 position, which represents an A(1,3)-like effect (actually a gauche butane-type interaction). Thus, in a more complete analysis, the lactam stereochemistry will derive from a balance of A(1,3), gauche butane, and 1,3 syn-axial steric forces in the cyclization transition state. Also, in contrast to our previous discussion,[2] the boat-like transition state (and arenium ions), which would lead to a preference for the β isomeric product, may play a role in the stereoselection process.[20]

We should take a moment to amplify on the polyolefin cyclization of Macco et al. (see Introduction), involving a thiophene nucleophile and a suitably situated *tert*-butyl substituent, as we discussed this reaction in reference 2.[3] In this case extremely high (at least 100:1) stereoselectivity for the α (rather than β) isomer was observed. However, the chair-like transition state, resembling a cyclized thiophenium ion, contains two syn-axial interactions and A(1,3) strain is reduced by two structural features. Significantly, the thiophene sulfur atom in the peri position provides only an electron pair for interaction; also, there is a wider angle subtended between the five- and six-membered rings.

Experimental Section

General Information and Procedures. Proton NMR spectra were recorded on a Varian EM-390 (90 MHz), Varian EM-360 (60 MHz), or Bruker AM-360 (360 MHz) spectrometer with $CDCl_3$ as solvent and $(CH_3)_4Si$ as an internal standard, unless otherwise indicated. NMR abbreviations used are as follows: s = singlet, d = doublet, t = triplet, dd = doublet of doublets, ddd, = d of d of d, m = multiplet, q = quartet, br = broad. IR spectra were obtained on a Perkin-Elmer spectrophotometer in KBr (pellets). Mass spectra were obtained on a VG Micro Mass 7035, Finnigan GC-MS-DS Model 9500-3300-1600, or AEI MS-902 instrument. GLC analyses were performed on a Perkin-Elmer 3920B instrument (flame-ionization detector) equipped with a Hewlett-Packard Model 3352 data system and 18652A A/D converter, using a glass column (1/8 in. × 6 ft) with 3% SE-30 on Chromosorb Q packing. TLC separations were conducted on 250-μ silica gel plates with visualization by UV fluorescence and iodine. Melting points are corrected. Preparative high-performance LC separations were performed on a Waters Prep LC/System 500 instrument using silica gel columns. Chemical microanalyses were determined by Atlantic Microlab, Inc., Atlanta, GA.

2-Phenyl-3,3-dimethylbutanamine. Pivalophenone (10.0 g, 0.067 mol) in 95 mL of absolute ethanol and 5 mL of methanol was treated portionwise with 2.35 g of $NaBH_4$ powder (4 molar equiv). After 2 h, the reaction was concentrated to one-third volume and partitioned between water and ether. The aqueous layer was reextracted with ether, and the combined ethereal solution was rinsed with brine, dried ($MgSO_4$), and concentrated to a colorless oil (10.8 g). Thionyl chloride (20.3 g, 0.15 mol) was cooled in an ice-salt bath, and the oil was added in small portions with stirring. After the reaction stood at 23 °C overnight, the excess $SOCl_2$ was evaporated. The residue was diluted with dry ether, rinsed with 5% Na_2CO_3 solution, rinsed with water, dried (K_2CO_3), and concentrated to a brown liquid. This was distilled by kugelrohr at 0.2 torr to give 8.6 g of pale yellow material (a small sample of which solidified to light tan needles). The chloride (8.6 g, 0.047 mol) in 10 mL of dry THF was added to magnesium turnings (1.22 g, 0.05 mol) under 15 mL of THF. A small amount of chloride solution was added first to initiate reaction. The reaction was initiated with difficulty. The best procedure was activation of Mg turnings separately in dry ether with methyl iodide, and addition of some activated chips to the reaction mixture. The alkyl chloride solution was added slowly with heating at ca. 45 °C. The magnesium eventually dissolved. The reaction was refluxed for 1 h, then cooled to 0 °C. Dry CO_2 gas (from evaporation of dry ice and passage of the gas through concentrated H_2SO_4, then anhydrous $CaSO_4$) was passed into the Grignard mixture with rapid stirring for 1 h (gas inlet just above the liquid surface). The reaction was treated with 1 N HCl, then diluted with ether to a final volume of 150 mL. The organic layer was separated, rinsed with brine, and dried ($MgSO_4$). Evaporation of solvent gave 7.6 g of tan syrup (satisfactory ^1H NMR and IR data). This was dissolved in 15 mL of $SOCl_2$ and the solution heated at reflux for 1.5 h. After cooling, the black solution was concentrated in vacuo. A solution of the dark residue in 50 mL of dry ether was added slowly with stirring to cold, excess concentrated ammonium hydroxide with ice-bath cooling. The reaction was stirred vigorously and the layers were separated. The brown ether solution was shaken with brine and filtered, and the layers were separated. The organic phase was dried (Na_2SO_4) and concentrated to 6.2 g of crystalline residue. Recrystallization from hexane/ethyl acetate (25:1) afforded 3.4 g of tan solid, mp 119–122 °C. Part of the amide (1.91 g, 10 mmol) was reduced with $LiAlH_4$ (0.9 g, 23 mmol) in dry ether (50 mL) for 20 h. Typical workup furnished 1.7 g of yellow liquid, 95% pure by GLC (SE-30 column). This material was used to make imide **7**, which has been fully characterized (see below).

Preparation of Imides. Imides were prepared using acetyl chloride in refluxing ethyl acetate.[2] Thus, crude **5** was prepared and purified via short-path distillation (0.025 torr/100 °C) to give an oil. ^1H NMR (90 MHz) δ 0.78 (t, 3 H, J = 7.5 Hz), 1.64 (m, 2 H, 7.5 Hz), 2.47 (br s, 4 H), 3.0 (m, 1 H), 3.62 (m, 2 H), 7.16 (m, 5 H, aromatic). Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.62; H, 7.46; N, 5.99.

Imide **6** was prepared in a like manner and recrystallized from ethanol/water to give white crystals, mp 65–67 °C. ^1H NMR (60 MHz) δ 0.70–2.1 (m, 11 H), 2.30 (s, 4 H), 3.0 (m, 1 H), 3.80 (m, 2 H), 6.9–7.4 (m, 5 H, aromatic).

Imide **7** was recrystallized from methanol/water (10:3) to give white crystals, mp 97.5–99 °C. ^1H NMR (90 MHz) δ 0.98 (s, 9 H), 2.30 (s, 4 H), 3.16 (dd, ^1H, J = 4.5, 12 Hz), 3.61 (dd, 1 H, J = 4.5, 13 Hz), 4.18 (dd, 1 H, J = 12, 13 Hz), 7.13 (s, 5 H, aromatic). Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 73.97; H, 8.20; N, 5.34.

(19) The parameters used for MM2 for the amide functionality were: bond C(sp^2)–N, k_s = 8.3, l = 1.325; angles C(sp^3)–N–C(sp^2), k_b = 0.6, θ = 122°; O(sp^2)=C(sp^2)–N, k_b = 1.25, θ = 122.9°; C(sp^3)–C(sp^2)–N, k_b = 1.4, θ = 116.6°; torsion angles C(sp^3)–C(sp^2)–N–C(sp^3), V_1 = 0.0, V_2 = 5.0, V_3 = 0.0; O(sp^2)=C(sp^2)–N–C(sp^3), V_1 = −1.0, V_2 = 4.5, V_3 = 0.0; C(sp^3)–C(sp^3)–C(sp^2)–N, and C(sp^3)–C(sp^3)–N–C(sp^2), V_1 = 0.0, V_2 = 0.0, V_3 = −0.46.

(20) Out of curiosity, we performed some MM2 calculations on chair-like and boat-like arenium-ion species involved in cyclizations leading to **2a**/**3a** and **2d**/**3d** (atomic charges were calculated with CNDO/2[21]). However, these results were not especially decisive, and they have questionable validity because the parameterization is untested. Nevertheless, the geometries we obtained are reasonable and the calculations are at least as useful as Dreiding models coupled with stereochemical intuition. For the interested reader, our results are contained in the supplementary material.[12]

(21) Dobosh, P. A. *QCPE* **1969**, *11*, 141.

Preparation of Lactams. Lactams were prepared from the appropriate imide using the procedure described previously[2]—$CH_3SO_3H/NaBH_4$ reduction, followed by PPA cyclization. The crude mixture of lactams was analyzed by GLC (SE-30 column) to determine the isomeric ratio of diastereomers formed in the cyclization reaction and by GLC/MS to identify each isomer. Each isomer was isolated by preparative TLC (ethyl acetate), the appropriate spots were scraped, and the silica was extracted with methylene chloride/methanol (20:1). The extract was evaporated with a nitrogen stream to an oil, which was assayed by 360-MHz ^1H NMR.

Purification of 3d. The crude reaction mixture (39.0 g) was separated using preparative HPLC (ethyl acetate/hexane, 1:1). The major isomer **3d** (19.9 g) crystallized upon standing and was recrystallized from ethyl acetate/hexane to give white crystals, mp 105–106 °C. IR λ_{max} 1692 (C=O) cm^{-1}. Anal. Calcd for $C_{18}H_{23}NO$: C, 80.26; H, 8.61; N, 5.20. Found: C, 80.36; H, 8.64; N, 5.18.

Reduction of 3e. Lactam **3e** was fully characterized via the HBr salt of its corresponding amine, obtained from reduction. A mixture of **2e**/**3e** (180 mg, 0.75 mmol; ca. 90% **3e**) in 3 mL of dry THF was combined with 3 mL of 1 M BH_3·THF (Aldrich) at 5 °C and the solution was refluxed for 1 h. The reaction mixture was cooled, quenched with 1 mL of water and 1 mL of 12 N HCl, and refluxed for 30 min. The THF was distilled out and replaced with water; the aqueous solution was then refluxed for 20 min. The solution was cooled to 5 °C, made alkaline with 3N NaOH, and extracted with methylene chloride. The organic layer was washed once with saturated aqueous NaCl, dried (K_2CO_3), and evaporated in vacuo to an oil (110 mg). The hydrobromide salt was prepared in 2-propanol to give white crystals (50 mg). Slow recrystallization from 2-propanol gave analytically pure (C, H, N) white crystals, mp 184–185 °C, which were not suitable for X-ray analysis because of twinning. A portion was converted to the free base: ^1H NMR (360 MHz) δ 1.56–1.92 (m, 3 H), 2.18 (dd, H_{3a}, J = 8.5, 17.0 Hz), 2.27 (m, H_{1e}), 2.41 (dd, H_{5a}, J = 3.9, 11.6 Hz), 2.50 (ddd, H_6, J = 3.8, 1.0, 0.5 Hz), 2.96 (ddd, H_{10b}, J = 10.6, 6.1, 0.5 Hz), 3.04 (ddd, H_{3e}, J = 8.3, 8.3, 2.3), 3.38 (dd, H_{5e}, J = 11.6, 1.4 Hz), 7.06–7.24 (m, 4 H, aromatic). A single-crystal X-ray analysis was performed on the hydriodide salt, prepared from the free base and 47% hydriodic acid, and recrystallized from 2-propanol as colorless prisms, mp 196–198 °C.[14]

X-ray Crystallographic Analysis. Data were collected on an Enraf-Nonius CAD4 diffractometer (Mo Kα radiation, λ = 0.71073 Å) and programs were part of the Enraf–Nonius Structure Determination package as revised in 1982, implemented on a PDP 11/34 computer. Crystals of **3d** were grown from ethyl acetate/hexanes. The cut crystal used for analysis measured 0.22 × 0.27 × 0.32 mm^3.

1,5,6,10bα-Tetrahydro-6β-cyclohexylpyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one (**3d**): $C_{18}H_{23}NO$, mol wt 269.39; monoclinic, a = 21.586 (14) Å, b = 8.286 (4) Å, c = 18.465 (8) Å, β = 114.57 (4)°, V = 3003 (6) $Å^3$; d_{obsd} = 1.2 g/cm^3, d_{calcd} = 1.19 g/cm^3 for Z = 8 molecules/unit cell, space group $P2_1/c$ (the 2 unique molecules denoted A and B). Of the 4426 reflections collected up to 2θ = 45.3°, 1585 had $I > 2\sigma(I)$ and were used for the subsequent structure analysis (data corrected for Lorentz and polarization factors but not for absorption). Starting positions for all non-hydrogen atoms were determined from a MULTAN 78 calculation, and refinement was carried out by the full-matrix least-squares method. Final anisotropic refinement of non-hydrogen atoms (H's put in calculated positions assuming a C-H length of 0.97 Å with B = 5 $Å^2$) gave R = 0.080 and R_w = 0.083, where $R = (\sum||F_o| - |F_c||)/\sum|F_o|$, $R_w = [\sum(|F_o| - |F_c|)^2/\sum F_o^2]^{1/2}$, and the function minimized was $(\sum|F_o| - |F_c|)^2$. The final difference electron density map showed no residual electron density greater than 0.34 e/$Å^3$. A stereoview of the unit cell along with tables of atomic positional parameters, bond distances and angles, useful least-squares planes, and thermal parameters are available as supplementary material.[12]

Empirical Force-Field Calculations. Energy minimizations on **2d** and **3d** were performed using MM2.[18,19] Global minima were obtained in the conventional manner. To find important conformations of **2d** and **3d** within 10 kcal/mol of the global minima, potential ring conformers were generated by bending the minimized structures about two "hinges" defined by lines between C_5 and C_{10b} and between C_6 and C_{10b}. Atoms on one side of the hinge were held constant while those on the other side were rotated about the hinge. Thus, N_4 and C_5 were moved out of the plane of the benzo moiety in about 0.4-Å increments, affording various new conformations for ascertaining low-lying local minima. Each initial ring conformer was then processed with the SCAN function in CHEMLAB[22] to find the low energy rotations of the cyclohexyl group. Each of these starting geometries was then subjected to MM2 computation. Many of the starting structures converged to common local minimum configurations.

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Registry No. **1c**, 100366-78-7; **1d**, 100366-79-8; **1e**, 100366-80-1; **2a**, 73691-20-0; **2c**, 100366-81-2; **2d**, 100366-83-4; **2e**, 100366-85-6; **3a**, 87519-57-1; **3c**, 100366-82-3; **3d**, 100366-84-5; **3e**, 100366-86-7; **5**, 100366-89-0; **6**, 100430-67-9; **7**, 100366-88-9; pivalophenone, 938-16-9; α-(*tert*-butyl)benzyl chloride, 1688-17-1; α-(*tert*-butyl)phenylacetic acid, 83357-74-8; α-(*tert*-butyl)phenylacetamide, 100366-87-8; 2-(*tert*-butyl)phenethylamine, 27561-40-6.

Supplementary Material Available: Stereoview of the unit cell of **3d** and stereoview of the independent molecules, A and B; tables of atomic positional parameters, bond distances and bond angles, selected least-squares planes, and thermal parameters for **3d**; a figure showing calculated and experimental spectra for **2c**; a table of calculated ^1H NMR parameters for **2c**; force-field calculations on arenium ions involved in the acyliminium cyclization; and a figure of minimized structures and accompanying discussion (11 pages). Ordering information is given on any current masthead page.

(22) CHEMLAB's earlier version was CAMSEQ-II: Potenzone, R. D., Jr.; Cavicchi, E.; Weintraub, H. J. R; Hopfinger, A. J. *Comput. Chem.* **1977**, *1*, 187.