solution by addition of H_2O, the products were extracted following the usual procedure. Analysis of the crude product (mp 72 °C) by GLC and NMR showed that only *cis*-VI was present. No trace of I was detected.

2. In THF at 20 °C. *n*-Butyllithium in hexane (1 mL, 1.2 mmol) was added dropwise to a solution of *trans*-VIII (0.171 g, 0.6 mmol) in THF (10 mL). The dark red solution was stirred for 1 h and then D_2O was added. After extraction with ether following the usual procedure, an oily product was obtained. Analysis by GLC and NMR showed that the crude product consisted of *trans*-VIII (7%) and *cis*-VIII (93%). *cis*-VIII was isolated pure following chromatography on a silica column doped with picric acid (eluent petroleum ether). The amount of deuterium incorporation, determined by NMR, was 100% (8% on the 9 and 92% on the 10 positions).

Another experiment was carried out under the same conditions except that 1.1 equiv of n-butyllithium was used. In this run analysis of the crude reaction mixture by GLC and NMR showed that it was composed of *cis*-VIII and *trans*-VIII in a ratio of 65:35.

VI. Isopropylation of 9-(Trimethylsilyl)-9-deuterio-9,10-dihydroanthracene (V_D). To a stirred solution of V_D (0.806 g, 3.2 mmol, 80% deuterated) in THF (80 mL), under argon, at room temperature, was added a solution of *n*-butyllithium in hexane (2.62 mL, 3.2 mmol). Stirring was maintained for 1 h. Upon addition of isopropyl iodide (2 mL, excess) the solution turn pale yellow. Addition of acidified (HCl) ice water and ether, followed by conventional workup, afforded a pale yellow oil (0.846 g). GLC and NMR analysis showed IV, *trans*-IX, and V in a molar ratio of 33:16:51. Chromatography of the product mixture through a column of silica doped with picric acid (10% w/w), eluted with petroleum ether, gave successively IV (0.116 g), a mixture of IV and *trans*-IX (0.312 g), and V_D (0.350 g). Recristallization of the mixture from ethanol gave pure *trans*-IX (0.102 g). Mass spectrometry (MICROMASS VG 70-70) indicates that the compound is 97% monodeuterated. NMR analysis points to 42% D on the 9-position and 55% on the 10-position.

From NMR and mass spectrometry it is possible to evaluate the deuterium content for IV (25%) and recovered V_D (79%).

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Registry No. I, 68573-98-8; II, 68573-95-5; III, 68573-96-6; IV, 68573-97-7; V, 18002-83-0; V_D, 68574-01-6; *cis*-VI, 56272-38-9; *trans*-VI, 56272-37-8; *cis*-VII, 62257-79-8; *trans*-VII, 62257-80-1; *cis*-VIII, 62257-81-2; *trans*-VIII, 62257-82-3; *cis*-IX, 62257-83-4; *trans*-IX, 62257-84-5; XIa, 42332-94-5; XIb, 22702-34-7; Me_3SiCl, 75-77-4; anthracene, 120-12-7; 9,10-dihydroanthracene, 613-31-0; 9-lithio-9,10-dihydroanthracene, 17228-13-6; 9,9-dimethylanthrone, 5447-86-9; 9,9-diethylanthrone, 32363-34-1; isopropyl iodide, 75-30-9.

Stereochemistry of Intramolecular Amidoalkylation Reactions in the Synthesis of Polycyclic Isoquinoline Derivatives[1]

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N-Acyliminium cyclizations onto benzenoid rings to give tetrahydroisoquinoline ring systems were studied. Particular attention was paid to the stereochemical effect of substituents present on the isoquinoline ring. High stereoselectivity (≥90%) was observed with aryl substituents at (local) 4 and 3 positions of the isoquinoline ring (e.g., **2** → **3** and **30** → **31**). In addition to cyclizations onto benzenoid rings, some cyclizations onto heterocycles (pyrrole, thiophene, indole) were examined. Base-induced equilibration of isomer pairs was performed to obtain relative stabilities. The cyclizations were determined to be kinetic in nature. A discussion of our iminium cyclizations and relevant examples from the literature is presented.

Cationic π cyclization reactions have been used to fashion rings of complex multicyclic compounds with excellent stereochemical control.[3-6] A classical example is that of biomimetic polyene cyclizations, which have produced steroid-like polycycles with impressive stereoselectivity at ring junctions and substituent stereocenters on the carbocyclic framework.[4] For successful polyene cyclizations, a suitable cationic initiator functionality, such as an epoxide, acetal, or allyl alcohol, is important. Recent attention has been directed to *N*-acyliminium ions, which

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(6) Stereoselective acyliminium cyclizations: (a) For a review: Speckamp, W. N. *Recl. Trav. Chim., Pay-Bas* **1981**, *100*, 345. (b) Li, T.-T.; Lesko, P.; Ellison, R. H.; Subramanian, N.; Fried, J. H. *J. Org. Chem.* **1981**, *46*, 111. (c) Takano, S.; Takahashi, M.; Ogasawara, K. *J. Am. Chem. Soc.* **1980**, *102*, 4282. (d) Hart, D. J. *J. Org. Chem.* **1981**, *46*, 367. (e) Hart, D. J. *Ibid.* **1981**, *46*, 3576. (f) Hart, D. J.; Kanai, K. *Ibid.* **1982**, *47*, 1555. (g) Veenstra, S. J.; Speckamp, W. N. *J. Am. Chem. Soc.* **1981**, *103*, 4645. (h) Wijnberg, B. P.; Speckamp, W. N. *Tetrahedron Lett.* **1981**, *22*, 5079. (i) Winjberg, B. P.; Speckamp, W. N.; Oostveen, A. R. C. *Tetrahedron* **1982**, *38*, 209. (j) Hamersma, J. A. M.; Speckamp, W. N. *Tetrahedron Lett.* **1982**, *23*, 3811. (k) Nossin, P. M. M.; Hamersma, J. A. M.; Speckamp, W. N. *Ibid.* **1982**, *23*, 3207. (l) Evans, D. A.; Thomas, E. W.; Cherpeck, R. E. *J. Am. Chem. Soc.* **1982**, *104*, 3695. (m) Hart, D. J.; Yang, T.-K. *Tetrahedron Lett.* **1982**, *23*, 2761. (n) Hart, D. J.; Kanai, K. *J. Am. Chem. Soc.* **1983**, *105*, 1255. (o) Chamberlin, A. R.; Chung, J. Y. L. *Ibid.* **1983**, *105*, 3653.

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Table I. Isoquinoline Derivatives from the Keto Acid Route

compd	α/β ratio[a]	isolated yield, %
3	94:6	65
4	96:4	74
5	90:10[b]	~40
8	95:5	60
9	≥95:5[c]	80
11	≥95:5[c]	50
13	70:30	80
15	60:40	65

[a] Determined by GLC unless otherwise noted. α isomer = a and β isomer = b in the compd number. [b] From ^{1}H and ^{13}C NMR spectral data. [c] Estimated by using GLC, GLC/MS, and ^{1}H NMR.

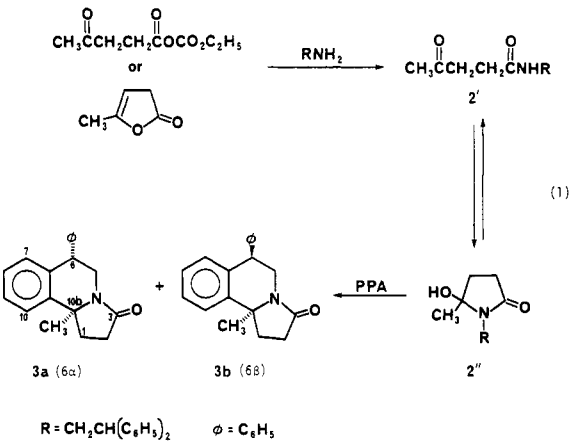
are readily generated, very reactive, and precursors to alkaloid products.[6-8]

Heterocyclizations involving *N*-acyliminium ions (intramolecular α-amidoalkylation reactions), although known for some time,[9] have only recently been examined for their usefulness in asymmetric organic synthesis. From the pioneering work of Speckamp,[6a,g-k,7] and the studies of others,[6b-f,l-o,8] such cyclizations have been found to achieve remarkable stereocontrol between proximate and remote chiral centers. In our preliminary communication,[8] we described some highly stereoselective acyliminium ion cyclizations onto aromatic rings, affording substituted isoquinoline derivatives. We now report further work on this useful isoquinoline synthesis, designed to expand the scope and define the origin of the diastereoselectivity.

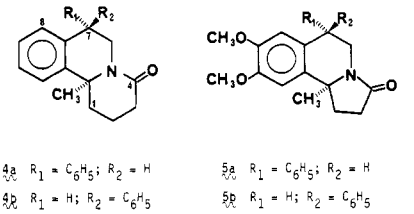
Acyliminium Ion Cyclizations

N-Acyliminium ion precursors were prepared by two routes. One started with a "keto acid", which, as either a mixed carbonic anhydride, ester, or ene lactone, was condensed with a 2-arylethylamine to give a *keto amide* or *enamide*. The other route involved condensation of succinic anhydride with a 2-arylethylamine to give an imide, which was converted, by the method of Speckamp,[7,10] to a 5-ethoxy-2-pyrrolidinone. Cyclization of precursors was effected by exposure to acid: either polyphosphoric acid (PPA), hydrogen chloride, or pyridinium polyhydrogen fluoride (PHF).

Keto Acid Route. Reaction of 2,2-diphenylethylamine (**1**) with the mixed carbonic anhydride of levulinic acid produced keto amide **2** as a mixture of ring and chain tautomers (eq 1).[11] Treatment of **2** with PPA at 100 °C for as little as 3 h effected cyclization to lactams **3**, a mixture of substituted 6α- and 6β-pyrrolo[2,1-*a*]isoquinoline diastereomers in a 94:6 ratio, in 35% yield from **1** (stereochemical assignments will be discussed later).[12] The overall yield was improved to 65% by the use of α-angelicalactone instead of the mixed anhydride (Table I).[13]



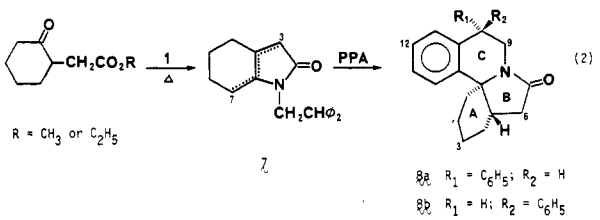
Similarly, reaction of the mixed carbonic anhydride of 4-acetylbutyric acid with amine **1**, followed by PPA cyclization, afforded a 96:4 mixture of 7α- and 7β-benzo[*a*]quinolizidines **4a** and **4b** in 74% yield (Table I). Thus,

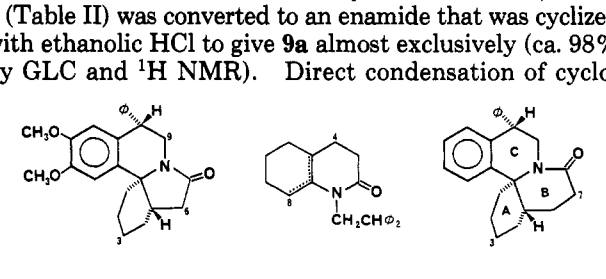


the high stereoselectivity was independent of the presence of a 5- or 6-membered lactam ring.

The adduct from amine **6** and α-angelicalactone was cyclized to lactams **5** with ethanolic HCl, again with high stereoselectivity (**5a**:**5b** = ca. 90:10).

A high degree of stereocontrol was also observed in the syntheses of erythrinane (**8**, **9**) and homoerythrinane (**11**) derivatives. Thermal condensation of cyclohexanone-2-acetic ester and **1** afforded a mixture of enamides **7**, consisting primarily of 3,3a- and 7,7a-olefin isomers (3:1) by ^{1}H NMR (eq 2). Cyclization of **7** in PPA at 100 °C produced one of four possible diastereomers almost exclusively, in good overall yield (**8a**:**8b** = 95:5). The major product was assigned structure **8a** on the basis of ^{1}H NMR studies (to be discussed later). By the same token, amine **6** (Table II) was converted to an enamide that was cyclized with ethanolic HCl to give **9a** almost exclusively (ca. 98% by GLC and ^{1}H NMR). Direct condensation of cyclo-





(7) (a) Schoemaker, H. E.; Dijkink, J.; Speckamp, W. N. *Tetrahedron* **1978**, *34*, 163. (b) Dijkink, J.; Speckamp, W. N. *Ibid.* **1978**, *34*, 173. (c) Schoemaker, H. E.; Speckamp, W. N. *Ibid.* **1980**, *36*, 951. (d) Nossin, P. M. M.; Speckamp, W. N. *Tetrahedron Lett.* **1980**, *21*, 1991.

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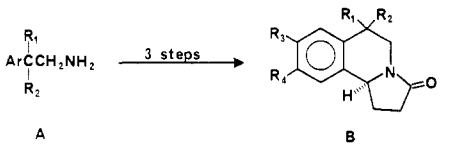
(10) Hubert, J. C.; Winjberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1975**, *31*, 1437.

(11) Houlihan, W. J.; Manning, R. E. U.S. Patent 3 502 675, 1970; U.S. Patent 3 383 388, 1968.

(12) (a) These and other isomer ratios were determined by GLC. (b) Throughout this paper, the letters **a** and **b** will be used after a compound number to differentiate "α" and "β" diastereomers.

(13) (a) Terzyan, A. G.; Khazhakyan, L. V.; Arntyunyan, N. A.; Tatevasyan, G. T. *Arm. Khim. Zh.* **1971**, *24*, 56; *Chem. Abstr.* **1971**, *75*, 20163g. (b) A 2:1 mixture of carbinol amide (**2''**) and keto amide (**2'**) tautomers, respectively, was observed in chloroform (^{1}H and ^{13}C NMR; IR analyses).

Table II. 6-Substituted Pyrrolo[2,1-*a*]isoquinolines from the Imide Route



A B

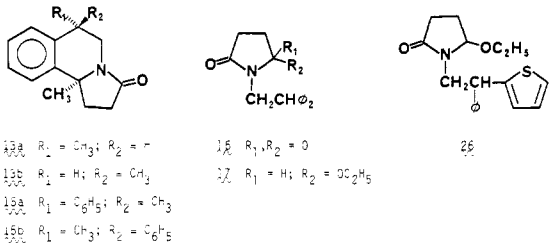
amine A	lactam B[a]	Ar[b]	R_1	R_2	R_3	R_4	α/β ratio[c]	isolated yield (A → B), %
1	18	Ph	Ph	H	H	H	93:7	60
19	20	ClPh	ClPh	H	H	Cl	93:7	50
6	21	DMPh	Ph	H	OCH_3	OCH_3	90:10	50
22	23	DMPh	DMPh	H	OCH_3	OCH_3	90:10	60
14	24	Ph	Ph	CH_3	H	H	55:45	55
12	25	Ph	CH_3	H	H	H	72:28	50

[a] α isomer (a): the larger group of R_1 and R_2 is cis to H_{10b}; β isomer (b): the smaller group is cis to H_{10b}. [b] Ph = phenyl; ClPh = 4-chlorophenyl; DMPh = 3,4-dimethoxyphenyl. [c] Determined by GLC.

hexanone-3-propionic ester[14] with **1** produced enamide **10**, predominantly the 4a,8a-olefin isomer by ^1H NMR, which was efficiently cyclized in PPA at 100 °C to β-homoerythrinane **11a**; again, excellent stereoselectivity was realized (Table I).[12a]

The type of α-amidoalkylation used here for erythrinane synthesis has been previously used by others,[15,16] and has been referred to as a Mondon-type synthesis.[15a] In some instances, the keto acid had been derivatized as a ketal,[16b,17] but this extra chemical manipulation is unnecessary. We have experienced good yields by direct thermal condensation of the keto ester with the phenethylamine, followed by acid-catalyzed cyclization. Cis stereochemistry for the A/B ring junction has been indicated for analogous acyliminium cyclizations;[15,18] nevertheless, we have independently corroborated the cis A/B stereochemistry by ^1H NMR studies (vide infra).

Much diminished stereoselectivity was obtained when a phenyl ring or the benzhydryl proton was replaced by a methyl group (Table I). Thus, reaction of amine **12** (Table II) with α-angelicalactone and cyclization with PPA at 100 °C gave a 70:30 mixture of **13a** and **13b**. The same sequence carried out on amine **14** (Table II) gave a 60:40 mixture of **15a** and **15b**.

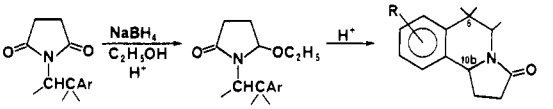


13a R_1 = CH_3; R_2 = H
13b R_1 = H; R_2 = CH_3
15a R_1 = C_6H_5; R_2 = CH_3
15b R_1 = CH_3; R_2 = C_6H_5

16 R_1,R_2 = O
17 R_1 = H; R_2 = OC_2H_5

26

Imide Route. The utility of ω-carbinol lactams as cyclic *N*-acyliminium precursors has been developed principally by Speckamp and co-workers.[6a,7] ω-Carbinol lactams are readily prepared by selective reduction of cyclic imides using $NaBH_4/H^+$, and may be isolated as such or as suitable ether derivatives. We applied this methodology to the preparation of tricyclic tetrahydroisoquinolines, and related compounds, lacking an angular substituent, as generally depicted in eq 3.



(3)

A representative synthesis is that of isomeric lactams **18** (see Table II). Succinimide **16**, from amine **1** and succinic anhydride, was transformed into **17** with $NaBH_4$ and CH_3SO_3H in absolute ethanol at −5 to 0 °C. Cyclization of **17** in PPA at 100 °C furnished a mixture of diastereomeric lactams **18a** and **18b** in a 93:7 ratio (Table II). The cyclization of **17** was also accomplished with PHF at 25 °C in less than 30 min.[19] The PPA procedure was employed for a variety of compounds wherein cyclization occurred on unactivated aromatic rings, such as phenyl or 4-chlorophenyl (Table II). High stereoselectivity, ≥90% of one diastereomer, was realized when the substituents at position 6 in the final products were aryl and H, whereas diminished stereocontrol was realized with CH_3/H (**25**) and phenyl/CH_3 (**24**) as 6-substituents (Table II).

Mild conditions were used to effect cyclization onto electron-rich aromatic groups. *N*-Acyliminium ion precursors containing a 3,4-dimethoxyphenyl group were readily converted to lactam products with ethanolic HCl at reflux (Table II). Heterocyclic derivatives (**27–29**) were also prepared under mild conditions, starting with 2-heteroaryl-2-phenylethylamines. Thienyl derivative **27**

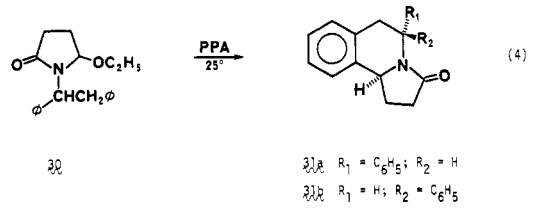
27 X = S
28 X = NCH_3

29

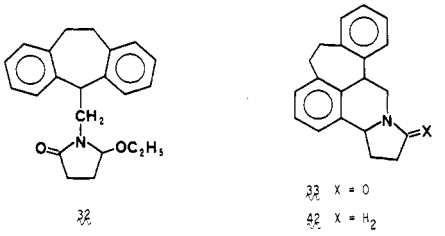
was obtained from acyliminium ion precursor **26** with ethanolic HCl (60% yield from starting primary amine); the α/β isomer ratio was 96:4. Pyrrole **28** and indole **29** lactams were generated in the midst of the imide reduction during acidification of the reaction mixture at 20 °C with CH_3SO_3H to ca. pH 1 (50% and 70% yields from starting primary amine). The α/β ratios for **28** and **29** were 74:26 and 92:8, respectively.

To examine the effect of a substituent α, instead of β, to nitrogen on the stereochemistry of the cyclization, we studied the conversion of **30** to **31** (eq 4). Treatment of

(14) Stork, G.; Brizzolana, A.; Lauderman, H.; Szmuszkovicz, J.; Tetrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207.
(15) For reviews: (a) Hill, R. K. In "The Alkaloids"; R. H. F. Manske, Ed.; Academic Press: New York, 1967; Vol. 9, p 483. (b) Dyke, S. F.; Quessy, S. N. In "The Alkaloids"; R. G. A. Rodrigo, Ed.; Academic Press: New York, 1981; p 1.
(16) (a) Wilkens, H. J.; Troxler, F. *Helv. Chim. Acta* **1975**, *58*, 1512. (b) Bergmann, E. D.; Migron, Y. *Tetrahedron* **1976**, *32*, 2847. (c) Oh-Ishi, T.; Iijima, I.; Itoli, N.; Sugasawa, S. *Chem. Pharm. Bull.* **1975**, *23*, 2573.
(17) Mondon, A. *Chem. Ber.* **1959**, *92*, 1461.
(18) Crabb, T. A. *Annu. Rep. NMR Spectrosc.* **1975**, *6A*, 249.
(19) Villani, F. J., McNeil Pharmaceutical, private communication.



30 with PPA at 100 °C afforded lactam **31** (57% yield from starting primary amine), which was virtually a single diastereomer (GLC, ^{1}H NMR). According to studies reported by Hart on olefin cyclizations induced by *N*-acyliminium ions, A$^{(1,3)}$ strain should have a strong influence on stereochemical outcome.[6d-f,20] Thus, one would suggest, a priori, that **31a** should be the product generated in eq 4. Indeed, this configuration, with an axial 5-phenyl group, was established by ^{1}H NMR spectral data (vide infra). Ethano-bridged derivative **33** was synthesized from **32** in



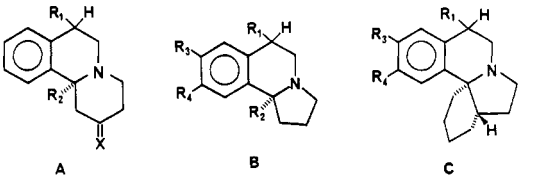
45% yield (from starting primary amine), with high stereoselectivity (α/β isomer ratio = 95:5). Bridging between the phenyl rings did not alter the usual stereochemistry of the iminium cyclization.

Equilibration Studies

Evidence for Kinetic Control of Cyclization. An opportunity to explore the question of kinetic vs. thermodynamic control in the cyclization reaction was afforded by the isolation of both epimeric lactams having activated aromatic rings, such as **21** and **23**. Exposure of **21a** to the cyclization conditions (refluxing ethanolic HCl) generated no discernible **21b**. In the case of **23**, both epimers, **23a** and **23b**, were subjected separately to ethanolic HCl, but no epimerization was observed in either case. In addition, the PPA cyclization reactions producing **3** and **18** were monitored over 24 h, and the product ratios (**3a**/**3b** = 94:6; **18a**/**18b** = 93:7) remained constant during and after the course of the cyclization. These results indicate that the high stereoselectivity observed in the cyclization reaction cannot be attributed to equilibration of diastereomeric lactams after their formation. Rather, the diastereomeric ratios are those of kinetic control, and the cyclization stereochemistry must be explained by steric effects manifested during the ring-closing process. This point will be addressed again in the mechanistic discussion (vide infra).

Equilibration of Diastereomeric Lactams and Amines. A method to equilibrate diasteromers was sought in order to evaluate their relative thermodynamic stability and to obtain ample quantities of β epimers. In this connection, we observed that Wolff–Kishner reduction of isomerically pure amino ketone **34a**[21] furnished a 1:1 mixture of epimeric amines **35a** and **35b** (Table III). Since reduction of the *p*-tosylhydrazone of **34a** with $NaBH_3CN$ under mild conditions[22] gave only amine **35a**, it appeared that equilibration was occurring under the hot, basic

Table III. Amine Structural Formulas[a]



amine							
A[a]	B[a]	C[a]	R_1[b]	R_2	R_3	R_4	X
34			Ph	H			O
35			Ph	H			H_2
36			Ph	CH_3			H_2
	37		Ph	H	H	H	
	42		Ph	CH_3	H	H	
	39		ClPh	H	H	Cl	
	40		Ph	H	OCH_3	OCH_3	
		41	Ph		H	H	
		46	Ph		OCH_3	OCH_3	

[a] See footnote *a* for Table I. [b] See footnote *b* for Table I.

Table IV. Equilibration of Lactams and Amines

		equilibrium α/β ratio[b]	
lactam[a]	amine[a]	lactam	amine
3	42	60:40	84:16[c]
4	36	52:48	70:30
8	41	63:37	90:10[c]
18	37	50:50[c]	64:36[c]
20	39	50:50	67:33
21	40	50:50	67:33
24	38	55:45	
25		38:62	
	34		60:40[c]
	35		47:53
27		68:32	
28		61:39	
33	47	14:86[c]	50:50[c]

[a] See footnote *a* for Table I. [b] Determined by GLC. [c] Equilibrium reached from both sides.

conditions of the Wolff-Kishner reaction.[23] To investigate this further, **35a** was treated with NaOD in Me_2SO-d_6/D_2O at 120 °C. After 1 h, **35a** and **35b** were present in a nearly 1:1 ratio (GLC, ^{1}H NMR, GLC/MS). The 7-position proton in each isomer exchanged with deuterium to the extent of 95%, and the 11b position showed 35% deuterium incorporation. Thus, two base-catalyzed mechanisms are available for equilibration, the one at the benzhydryl position (C_7) being more efficient than the one at the benzylic position (C_{11b}). Interestingly, the amino ketones (**34**) could be equilibrated by an acid-catalyzed procedure. Heating either pure **34a** or **34b** with a small amount of *p*-toluenesulfonic acid in refluxing toluene gave a 3:2 mixture of **34a**:**34b**,[21,24] very close to the ratio of 1:1 in the base-induced equilibration of **35**.

Base-catalyzed equilibration was performed on several amines (Table III) [prepared from reduction of the corresponding lactams with $LiAlH_4$ or borane–tetrahydrofuran (BH_3·THF)] by heating them with 10 N NaOH in dimethyl sulfoxide (Me_2SO) at 130 °C (Table IV). Equilibration of amines **37** and **42** was carried out from both sides of equilibrium. Thus, **37a** and **37b** gave the

(20) Hart, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 397.
(21) Maryanoff, B. E.; McComsey, D. F.; Taylor, R. J., Jr.; Gardocki, J. F. *J. Med. Chem.* **1981**, *24*, 79.
(22) Hutchins, R. O.; Milewski, C. A.; Maryanoff, B. E. *J. Am. Chem. Soc.* **1973**, *95*, 3662.
(23) Cason, J.; Rapoport, H. "Laboratory Text in Organic Chemistry", 2nd ed.; Prentice-Hall: Englewood Cliffs, NJ, 1962; pp 178–181.
(24) This isomerization process, observed for other β-amino ketones [Openshaw, H. T.; Whittaker, N. *J. Chem. Soc.* **1963**, 1461. Oppolzer, W.; Hauth, H.; Pfaffli, P.; Wenger, R. *Helv. Chim. Acta* **1977**, *60*, 1801], probably proceeds via a retroMannich reaction.

same end point of **37a**/**37b** = 64:36 and **42a** and **42b** each gave the ratio of **42a**/**42b** = 84:16. Erythrinanes **41a** and **41b** were also separately equilibrated, each giving an equilibrium ratio of **41a**:**41b** = 90:10. A comparison of the equilibrium α/β ratios for amines **35** and **36** (47:53 vs. 70:30) and **37** and **42** (64:36 vs, 84:16) indicates that the presence of an angular alkyl substituent affects the free energy difference between α and β diastereomers by favoring the α isomer. The 90:10 α/β ratio for erythrinane **41** is in accord with this principle.

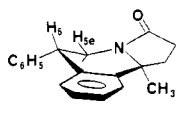
Equilibration of various lactams was conducted using K_2CO_3 in aqueous Me_2SO to avoid lactam hydrolysis (Table IV).[25] Treatment of **8a** with K_2CO_3 in Me_2SO-d_6/D_2O at 100 °C for several days produced a 63:37 equilibrium mixture of 6,6,10-trideuterated lactams **8a** (6,6,10-d_3) and **8b** (6,6,10-d_3), from which **8a**-d_3 was isolated and employed for assignment of cis stereochemistry to the A/B ring fusion (vide infra). Overall, the results of lactam equilibrations (Table IV) indicate that there is only a slight difference in thermodynamic stability between the α and β configurations. Thus, the high stereoselectivity in the cyclization reactions is not associated with a difference in free energy between diastereomeric lactam products, but rather with stereochemical factors that develop earlier in the reaction course.

It is interesting to note that equilibration of pentacyclic lactams **33a** and **33b**, which have a 2-carbon bridge connecting the aromatic rings, showed a much greater difference in $\Delta G°$ between α and β configurations, and, surprisingly, the β isomer is favored. Amine **47**, corresponding to **33**, gave a normal α/β ratio of 50:50.

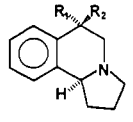
Stereochemical Assignments

Configurational assignments for the lactam diastereomers were established originally by ^1H NMR studies. Subsequently, a single-crystal X-ray analysis of **18a**, serving as a stereochemical anchor for the entire series, corroborated the NMR assignments. The structural work is presented in this section.

^1H NMR Studies. Lactam **3a**, the first to be synthesized, was studied most extensively. The structure of **3a** from Dreiding models, depicted as **43**, shows a half-chair



43



38a $R_1 = C_6H_5$; $R_2 = CH_3$

38b $R_1 = CH_3$; $R_2 = C_6H_5$

conformation, flattened around the amide nitrogen, for the tetrahydroisoquinoline subunit. The dihedral angles between the protons on C_5 and C_6 in **43**, $\phi_{5e,6}$ = 45° and $\phi_{5a,6}$ = 165°, determine coupling constants $^3J_{5e,6}$ and $^3J_{5a,6}$, which clearly characterize the α isomer. The β isomer (**43** with C_6H_5 and H_6 interchanged) has different dihedral angles, $\phi_{5e,6}$ = 75° and $\phi_{5a,6}$ = 45°, which define another set of characteristic vicinal coupling constants. (The angles in **43** are very close to those in the solid-state structure of **18a**, vide infra.) Assuming a reasonable value of 12 Hz for $J_{180°}$ and considering the Karplus relation,[26] the expected coupling constants for **3a** are $J_{165°}$ = ~11 Hz and $J_{45°}$ = ~6 Hz, while those for **3b** are $J_{75°}$ = ~2 Hz and $J_{45°}$ = ~6 Hz. With this preliminary analysis in hand, one can now examine the NMR data.

The 90-MHz ^1H NMR spectrum of **3a** ($CDCl_3$) displays a doublet of doublets at δ 3.07 (J = 11.5, 13.0 Hz), one at δ 4.15 (J = 11.5, 6.5 Hz), and another at δ 4.45 (J = 6.5, 13.0 Hz). Irradiation of the entire aromatic region (centered at δ 7.15) induced a specific sharpening ($W_{1/2}$ from 2.4 to 1.6 Hz) of the peaks at δ 4.15, presumably due to the loss of benzylic coupling;[27] thus, the H_6 assignment was suggested. An INDOR experiment[28] on **3a** indicated that the 13-Hz coupling value was opposite in sign from the other two, which designates it, rather than the 11-Hz value, as the geminal coupling $^2J_{5a,5e}$ (negative in sign as expected).[29] Since $^2J_{5a,5e}$ is absent from the pattern at δ 4.15, the H_6 assignment is confirmed. The resonances at δ 3.07 and δ 4.45 are assigned to H_{5a} and H_{5e}, respectively, based on (1) an expected strong downfield shift for H_{5e} because of its location within the deshielding region of the carbonyl group, and (2) the 3-fold greater shift sensitivity (Δ ppm/mol-equiv Eu) of H_{5e} (16.9) compared to H_{5a} (5.7) in lanthanide-induced shift (LIS) experiments with Eu(fod)$_3$ because of H_{5e}'s proximity to the Eu atom.[30] Thus, the vicinal coupling constants, $^3J_{5a,6}$ = 11.5 Hz and $^3J_{5e,6}$ = 6.5 Hz, are established independently of any a priori stereochemical assumptions, and they are in excellent accord with the values predicted for the α isomer in the preliminary analysis.[31]

For a comparison of α and β lactams, we consider the representative examples **18a** and **18b**. As expected, the 90-MHz ^1H NMR spectrum of α lactam **18a** shows a doublet of doublets at δ 3.06, 4.15, and 4.44 (J = 6.0, 11.0, and 13.0 Hz) for H_{5a}, H_6, and H_{5e}, respectively; there was an additional doublet of doublets at δ 4.92 (J = 8, 8 Hz) for the angular proton, H_{10b}.[32a] The spectrum of β lactam **18b** displays a doublet of doublets at δ 3.43 (J = 5, 13 Hz) for H_{5a}, δ 4.22 (J = 5, 3 Hz) for H_6, δ 4.29 (J = 13, ~2 Hz) for H_{5e}, and δ 4.83 (J = 6, 9 Hz) for H_{10b}. The H_5–H_6 vicinal coupling constants for **18b** are in excellent accord with those suggested in the preliminary analysis. A LIS study on **18a** with Eu(fod)$_3$ was very analogous to that for **3a** and a study on **18b** gave related results with diminished proton-shift sensitivities.[30c]

The characteristic vicinal coupling parameters observed for **18a** and **18b** were consistently seen throughout the series of lactams, and provided the best criterion for assignment of α and β isomers. Compounds with alkyl, instead of aromatic, substituents (i.e., **13** and **25**) posed some difficulties in ^1H NMR analysis because two of the key protons (H_{5a} and H_6) are shifted upfield such that they could be concealed beneath other aliphatic protons. However, one of the protons (H_{5e}), the one in the deshielding zone of the amide carbonyl, was isolated enough

(25) A K_2CO_3/D_2O procedure has been used successfully for deuterium exchange in lactams: Duffield, A. M.; Budzikiewicz, H.; Djerassi, C. *J. Am. Chem. Soc.* **1964**, *86*, 5536.

(26) Jackman, L. M.; Sternhell, S. "Applications of NMR Spectroscopy in Organic Chemistry", 2nd ed.; Pergamon Press: Oxford, 1969; Chapter 4-2, p 280.

(27) Reference 26, p 330.

(28) Perkin-Elmer NMR Quarterly, Sept 1972. Kowalewski, V. J. *Prog. NMR* **1969**, *5*, 1.

(29) Reference 26, Chapter 4-1, p 270.

(30) (a) Sievers, R. E., Ed., "NMR Shift Reagents"; Academic Press: New York, 1973. (b) The shift sensitivity for H_{5e} is even much greater than that of the protons on C_2 (9.4). (c) See paragraph at the end of this paper regarding supplementary material.

(31) An aromatic solvent-induced shift experiment on **3a** showed a large shift for the 10b-methyl group [$\delta(CDCl_3)$–$\delta(C_6D_6)$ = 1.62–1.22 = 0.40], which is consistent with the α isomer according to ASIS theory for amides (ref 26, p 111) since the pseudoaxial 6-phenyl substituent in the β isomer would severely hamper formation of the proper benzenamide solvation complex for shielding of the 10b-CH_3.

(32) (a) Irradiation of the multiplet centered at δ 1.9, for one of the protons on C_1, caused a collapse of H_{10b} to a doublet (J = 7 Hz), confirming the H_{10b} assignment. (b) Another distinguishing feature in the ^1H NMR spectra: **25a** δ 1.32 (d, CH_3, J = 7 Hz); **25b** δ 1.22 (d, CH_3, J = 7 Hz).

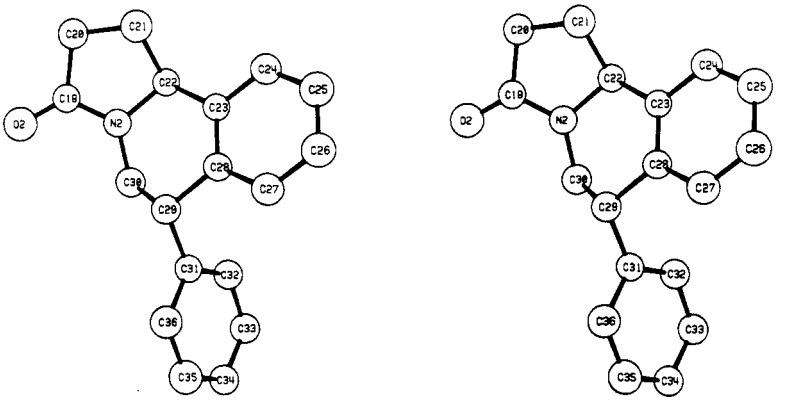


Figure 2. Stereoscopic view of one of the crystallographically independent molecules (B) in the unit cell of **18a**.

(δ 3.9–4.4), even at 60 or 90 MHz, to make isomer assignments possible (α isomer, ^3J = 5–6 Hz; β isomer, ^3J = 2–3 Hz). For example, **25a** displays a doublet of doublets for H_{5e} at δ 4.28 (J = 5, 12 Hz), while **25b** has one at δ 4.02 (J = ~2, 12 Hz).[32b]

In cases where the vicinal couplings are absent (**15** and **24**), because of replacement of the methine proton by a substituent, isomer assignment becomes a significant problem. Comparison of ^1H and ^{13}C NMR spectral data for the individual isomers of **24**, and correlation of this data with data for the isomers of **18** did not permit convincing stereochemical assignments because of conflicting trends for different chemical shift associations.[30c] ^1H NMR LIS data for the two isomers of **24**, in relation to data for **18**, hinted that the α isomer (**24a**) is the major one with a CH_3 resonance at δ 1.64 (rather than at δ 1.76), on the basis of the 2-fold greater shift sensitivity of the axial CH_3 group in **24a** compared to the equatorial CH_3 group in **24b**.[30c] The configurational assignment for **24** was firmly established by X-ray analysis of the hydrobromide salts of the corresponding amines **38a** and **38b**,[33] demonstrating that the major isomer of the iminium cyclization is α isomer **24a**. The isomer assignment for **15** was made by comparison of NMR spectral data for it with that for **24**.

The one isomer of **31** obtained from the cyclization reaction was examined by NMR to assign its stereochemistry.[34] The 60-MHz ^1H NMR spectrum shows a deceptively simple doublet for the two 6-position protons (nearly identical chemical shifts) at δ 3.30 with observed $^3J_{5,6}$ = 4 Hz, a doublet of doublets for H_{10b} at δ 4.48 with J = 7, 7 Hz, and a doublet of doublets for H_5 at δ 5.63 with observed $^3J_{5,6}$ = 4, 4 Hz. The assignment of **31a**, with an axial 5-phenyl group, is suggested by the far downfield resonance position for H_5 (i.e., H_{5e}), the shielding of H_{10b}, and the two small vicinal coupling constants, in comparison to ^1H NMR data for **18a** and **18b** (vide supra). A 360-MHz spectrum provided accurate NMR parameters and corroborated the **31a** assignment: δ 3.30 (H_{6e}, J = 16.6, 2.3 Hz), 3.3 (H_{6a}, J = 16.6, 6.4 Hz), 4.53 (H_{10b}, J = 7.7, 7.7 Hz), 5.6. (H_{5e}, J = 2.4, 6.4 Hz).

The presence of a new asymmetric center in the erythrinane derivatives **8**, **9**, and **11** necessitates an additional stereochemical assignment, that of the A/B ring junction. As mentioned earlier in this paper, cis A/B stereochemistry has been proposed for erythrinane products obtained via

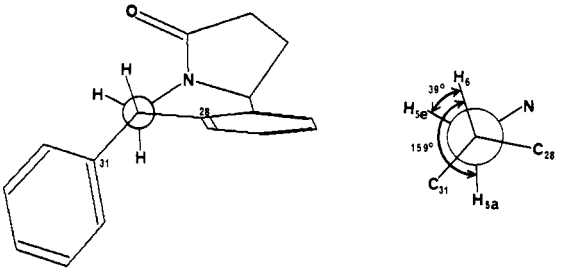


Figure 4. On the left: Computer graphics representation of molecule B viewed directly along the C_{29}–C_{30} ethano bond. The diagram was drawn using crystallographic coordinates except for the hydrogen atoms, which were placed into idealized positions. On the right: Expansion of the C_{29}–C_{30} region showing dihedral angles between protons used in making configurational assignments by ^1H NMR.

Mondon-type cyclizations.[15,17] We have verified the cis assignment by ^1H NMR, particularly by observation of the vicinal coupling constants between H_5 and H_6 in **8a** (J_{56} = 5, 5 Hz), a detailed discussion of which is presented in the supplementary material.[30c]

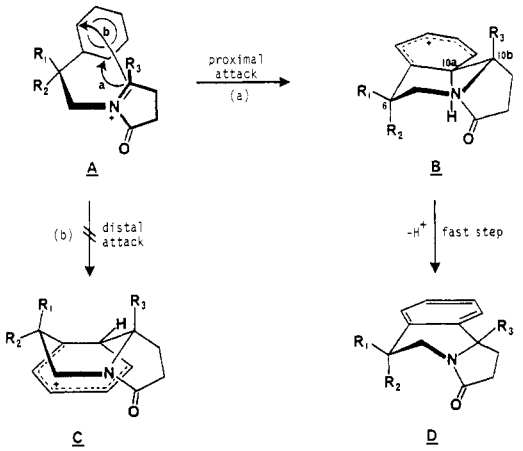
X-ray Analysis of 18a. A single-crystal X-ray structure analysis of lactam **18a** was performed to establish unequivocally the stereochemistry for most of the compounds, which had been assigned by using ^1H NMR vicinal coupling constants. Crystals of **18a** contain four molecules per monoclinic unit cell ($P2_1$) that represent two crystallographically independent sets. ORTEP drawings of the two molecules (A and B) are shown in Figure,[30c] a stereoview of molecule B is shown in Figure 2, and a stereoview of the unit cell is shown in Figure 3.[30c] (Figures 1 and 3 may be found in the supplementary material.) The two independent molecules are enantiomeric and possess small conformational differences and minor differences in bond angles and bond lengths. The greatest disparity between molecules A and B is the torsional angle adopted by the phenyl substituent. Details of the X-ray work are furnished in the Experimental Section and microfilm supplement;[30c] tables of bond distances, bond angles, selected torsional angles, least-squares planes, and positional and thermal parameters for the non-hydrogen atoms are available as supplementary material.[30c] The X-ray analysis demonstrates that **18a** (molecules A and B) possesses a half-chair conformation for the piperidine ring of the tetrahydroisoquinoline subunit, with flattening in the vicinity of the sp^2 amide nitrogen and sp^2 benzene carbon atoms.[30c]

The geometry of the tricyclic structure of **18a** from X-ray analysis is remarkably close to the geometry of a Dreiding molecular model. In Figure 4, molecule B is displayed so that it is viewed along the C_{29}–C_{30} bond. The dihedral angles between key protons H_{5a}, H_{5e}, and H_6 are

(33) These single-crystal X-ray analyses of **38a** and **38b** (both as hydrobromide salts), performed by Prof. R. A. Olofson at The Pennsylvania State University, will be reported in another paper at a later date. Information may be obtained on request.

(34) The other diastereomer was not available through epimerization with K_2CO_3 since decomposition occurred too readily. Anyway, it is a fair guess that the equatorial 5-phenyl isomer would be highly disfavored because of $A^{(1,3)}$ strain.[6d-f,20]

Scheme I



39° and 159°, which compare favorably with those from Dreiding models of 45° and 165°, respectively. Thus, the dihedral angles from Dreiding models, used to predict ^1H NMR vicinal coupling constants, are supported by experimental results.

Force Field Calculations.[35a] Empirical force field (EFF) calculations were carried out on lactams **18a** and **18b** with Allinger's MM2 force field method,[35b] using energy-minimized molecular coordinates derived from the MACCS computer graphics system as initial input. The calculated geometry of **18a** was close to the geometry of the X-ray structures, including the conformational angle of the diphenylmethyl two-bladed propeller. Both epimers, **18a** and **18b**, converged to the same tricyclic structure but differed by about 0.5 kcal/mol in calculated steric energy, with α isomer **18a** being more stable. If effects such as differential entropy and solvation are negligible, this energy difference suggests a 70:30 equilibrium ratio for isomers **18a** to **18b**. The ratio of **18a** to **18b** determined experimentally by base-catalyzed equilibration is 50:50 (Table IV), which is reasonably close to the calculated ratio.

Discussion

Stereochemistry and the Cyclization Mechanism. The stereoselectivities of the acyliminium-ion cyclizations that we studied can be rationalized, in principle, by either kinetic or thermodynamic arguments. However, equilibrations of diastereomeric pairs of lactams (Table IV) supplied thermodynamic stabilities for isomers that are inconsistent with isomer ratios obtained in the original cyclization reactions (q.v. **3**, **4**, **8**, **18**, **20**, **21**, **24**, **25**, **27**, **28**, **33**). Also, as mentioned earlier, lactam isomers do not appear to equilibrate under the cyclization conditions. Thus, to rationalize the stereochemical results one needs to consider the reaction mechanism.

A two-step process is depicted in Scheme I. The ring-closing step involves attack of the electrophilic site on the aromatic ring to generate an intermediate arenium ion; this step is probably the rate-determining one.[36a] The formation of two types of arenium ions, B and C, is possible. Cyclization pathway (b) proceeds via a boat-like transition state that leads to a highly strained boat-like arenium ion, C (Dreiding molecular models, with a planar nitrogen), whereas pathway (a) involves a chair-like transition state that affords ion B in a stable chair conformation (Dreiding models). Thus, pathway (a) should be much more favorable. Loss of the 10a-proton from B in the aromatization step is presumably very fast, so the stereochemistry of the cyclization product, D, must be determined by the conformational preferences of the substituents R_1 and R_2 in arenium ion B. This scenario is in agreement with the fact that stereoselectivity is independent of structural features (e.g., ring size, angular substituent) surrounding the lactam portion of the molecules (cf. **3**, **4**, **8**, **11**, **18**).

The preferred arrangement of arenium ion B, the one that produces the major diastereomer, would have the more sterically demanding substituent of the R_1/R_2 pair in a equatorial orientation to minimize 1,3 syn-axial interactions with the 10a-proton. If the transition state leading to B is product-like, the relative magnitudes of the 1,3 interactions will control the stereochemical outcome, whereas an early transition state would not result in substantial stereoselection for any R_1/R_2 pair. The stereochemical results (Tables I and II) are qualitatively consistent with a late, chair-like transition state in which the bulkier substituent of R_1/R_2 assumes an equatorial disposition. A sense of this mechanistic model derives from consideration of the conformational preferences of substituents R_1/R_2 in ion B relative to conformational free energies in the cyclohexyl system.[36b,c] There is a trend in stereoselectivity for three diverse steric situations that corresponds with cyclohexane A values, independent of whether R_3 = H or CH_3. The greatest A value (2.9 for phenyl/H) gives the highest stereoselectivity (93:7 for **18**) and the least A value (−0.3 for phenyl/methyl[36c]) gives the lowest (55:45 for **24**); the A value for methyl/H (1.7) relates to the 70:30 ratio for **25**. The two systems being compared, ion B and cyclohexane, are not strictly analogous since the former contains only one 1,3 syn-axial interaction and a distorted, fused half-chair ring. However, qualitative parallelism exists. The single 1,3 interaction may account for the stereoselectivities of the iminium cyclizations being lower than the cyclohexane A values would predict and for the reversal of substituent preference in the phenyl/methyl cyclization vs. the respective A value.

Stereocontrol in Cationic Cyclizations by Remote Substituents. In the aforementioned acyliminium cyclizations leading to tetrahydroisoquinoline derivatives, we mainly examined the influence of remote substituents on the stereochemistry of ring closure. The process superficially appears to exemplify stereocontrol by a substituent located 1,4 to the incipient stereocenter of ring closure; however, this is not so. As expressed in the mechanistic section above, stereodifferentiation is predicated on *1,3 interaction* between the substituent stereocenter and the stereocenter of ring closure within the modified benzene ring of an intermediate arenium ion (such as the 10a stereocenter in ion B). More precisely, the 1,3 interactions governing the diastereoselectivity develop in the product-like transition state en route to an intermediate arenium ion, such as B. The stereoselectivity was found to be high for phenyl substituents vs. hydrogen (ca. 13:1) but unfortunately low for a methyl substituent vs. hydrogen (ca. 2:1). Since remote substituent effects on cationic cyclizations have attracted considerable interest, and since profound stereocontrol has been observed in other systems, we discuss below some literature examples to formulate a comparison with our results.

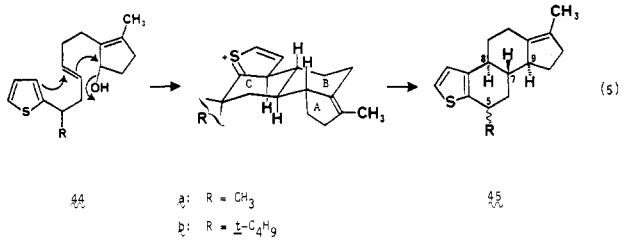
N-Acyliminium-ion cyclizations onto olefins show high stereoselectivity with respect to remote substituents.[6,7] Some particularly relevant examples were reported by

(35) (a) EFF Calculations were conducted by Dr. Harold R. Almond (McNeil Pharmaceutical). Details of these computations, available on request, will be published elsewhere in due course. (b) Allinger, N. L.; Yuh, Y. H. *QCPE* **1980**, *13*, 395.

(36) (a) March, J. "Advanced Organic Chemistry", 2nd ed.; McGraw-Hill: New York, 1977; Chapter 11. (b) Hirsch, J. A. *Top. Stereochem.* **1967**, *1*, 199. (c) Eliel, E. L., Manoharen, M. *J. Org. Chem.* **1981**, *46*, 1959.

Speckamp[7d] and Hart[6f,20] (details are given in the microfilm supplement[30c]). Greater stereocontrol with a methyl substituent (ca. 85–90%) is observed in Speckamp's example[7d] compared to **13** and **25**, which may be attributed to different geometric properties in the transition states leading to intermediate cyclic carbocations. The high stereoselectivity in the cyclization of **30** to **31** (eq 4) is in accord with Hart's results on related structures.[6f,20,37a]

Some biomimetic polyene cyclizations represent asymmetric induction by remote substituents in close analogy to the type of diastereoselection that we have studied.[4c,4e,4f] Macco and co-workers reported[4e,4f] that cyclizations of **44** with either a methyl or *tert*-butyl substituent gave tetracyclic product **45a** highly enriched in α isomer ($\alpha:\beta$ = 97:3) or **45b** with exclusively α isomer ($\alpha:\beta$ = 100:0).[37b] The high stereoselectivity in these cationic cyclizations (e.g., eq 5)[4c,4e,4f] has been ascribed to a product-like transition state



44 a: R = CH_3 b: R = t-C_4H_9 45

of a concerted cyclization in which the substituents strongly prefer an α (or equatorial) orientation in a chair-like ring because of nonbonded interactions of the 1,3-diaxial variety. The enhanced stereoselectivity for a methyl group (9:1 to 32:1) in the polyolefin cyclizations,[4c,e,f] relative to our acyliminium cyclizations (2.5:1), may be connected with the presence of two 1,3 syn-axial interactions in the former but only one in the latter. Substituent stereoselectivities in the polyene cyclizations of **44a** and **44b** seem to parallel more closely A values for substituents on cyclohexane, bolstering the argument for two syn-axial interactions in this case. The requisite consideration of two 1,3 syn-axial interactions with the substituent in the polyene cyclizations to explain the high stereoselectivity compels one to consider the arenium (or thiophenium) ion as a discrete intermediate along with interactions in the transition state that resembles this ion.

Experimental Section

General Information and Procedures. Proton NMR spectra were recorded on a Perkin-Elmer R-32 (90 MHz), Varian EM-360 (60 MHz), or Bruker WH-360 or WM-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. Lanthanide-induced shift (LIS) experiments were conducted with $Eu(fod)_3$ by addition of incremental amounts to the test compound (ca. 20 mg) in $CDCl_3$ (ca. 0.4 mL). Carbon-13 NMR spectra were recorded on a JEOL FX60Q spectrometer (15.00 MHz) in $CDCl_3$ with $(CH_3)_4Si$ as an internal reference. Both proton noise-decoupled and off-resonance-decoupled ^{13}C spectra were determined; only noise-decoupled data are presented. IR spectra were obtained on a Perkin-Elmer 521, 727B, or 283 spectrophotometer in KBr (pellets), unless otherwise noted. Mass spectra (electron impact) were obtained on a Hitachi Perkin-Elmer RMU-6E or a VG MicroMass 7035 instrument at an ionizing voltage of 70 eV. Diastereomeric ratios were determined by GLC on samples prior to recrystallization or chromatography assuming a response factor of 1.0 between each isomer of a mixture. All isomers were identified by GLC/MS and many were identified by isolation. 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 Chromasorb Q packing or with 1.35% OV-17 on Chromosorb W AW/DMS packing (SE-30 used unless otherwise specified). TLC separations were conducted on silica gel plates with visualization by UV fluorescence and I_2 staining. Melting points are corrected; melting ranges may be preceded by softening ranges, in parentheses. 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, or by Scandinavian Labs, Herlev, Denmark. The single-crystal X-ray analysis on **18a** was conducted by Molecular Structure Corp., College Station, TX. Some molecular modeling was conducted with the MACCS computer graphics system (Molecular Design Ltd., Hayward, CA) and the IMAGE computer graphics system developed at McNeil. Data characterizing the various lactams, and/or amines corresponding to synthesized lactams, are presented in Table V. Elemental analysis was obtained for either lactam or amine derivatives of a set, generally not both.

Preparation of Lactams via the Keto Acid Route. A. Mixed Anhydride Method. General Procedure. Keto acid (0.10 mol) and dry triethylamine (10.2 g, 0.10 mol) were combined in 50 mL of methylene chloride and cooled to 0 °C. Ethyl chloroformate (11.3 g, 0.10 mol) in 25 mL of methylene chloride was added slowly at 0–5 °C and stirred at 0 °C for 2 h and then at 10 °C for 1 h. 2,2-Diphenylethylamine (19.7 g, 0.10 mol) in 50 mL of methylene chloride was added to the mixture at 5 °C and the solution was stirred overnight at ambient temperature. Water (50 mL) was added and the reaction was stirred for 2 h. The organic phase was separated, washed once with 5% HCl and once with 5% Na_2CO_3, and dried (Na_2SO_4). The solution was filtered and evaporated in vacuo to give the crude keto amide. To this crude material was added PPA (104 g) and the mixture was stirred on a steam bath for 20 h. The mixture was poured into water and extracted with chloroform. The organic layer was washed once with H_2O and once with 5% Na_2CO_3 and dried ($CaCl_2$). Evaporation in vacuo gave crude lactam.

Example. 1,6,7,11b-Tetrahydro-11bα-methyl-7α-phenyl-2*H*-benzo[*a*]quinolizin-4(3*H*)-one (4a). The above procedure was followed with acetylbutyric acid (13.2 g, 0.10 mol), and a mixture (19/1, GLC) of crude lactams **4a** and **4b** (21.6 g, 74%) was obtained. The mixture was recrystallized twice from ethyl acetate to afford white crystalline **4a** (8.82 g, 30%): mp 177.5–179 °C; IR ν_{max} 1620 (C=O) cm^{-1}; ^1H NMR δ 1.74 (s, CH_3), 1.7–2.6 (m, 6 H, aliphatic), 2.97 (dd, H_{6a}, J = 12, 12 Hz), 4.15 (dd, H_7, J = 12, 5.5 Hz), 4.99 (dd, H_{6e}, J = 12, 5.5 Hz), 7.15 (m, 9 H, aromatic). Anal. Calcd for $C_{20}H_{21}NO$: C, 82.44; H, 7.26. Found: C, 82.31; H, 7.27.

B. Keto Ester Method. General Procedure. The keto ester (0.10 mol) and diarylethylamine (0.10 mol) were combined and heated at 130 °C for 24 h. The oil was placed under vacuum to remove any residual water or ethanol. This residue was combined with PPA (200 mL) and heated on a steam bath for 24 h. Water (750 mL) was added and solid lactam was filtered.

Example 1. 11α-Phenylerythrinan-8-one (8a). Cyclohexanone-2-acetic ester (18.1 g, 0.10 mol, ethyl and methyl esters 3:1) and 2,2-diphenylethylamine (20.0 g, 0.10 mol) were reacted according to the general procedure to give a quantitative yield of lactams **8a** and **8b** (19/1, GLC). The mixture was recrystallized once from ethyl acetate and once from methanol to give white prisms of **8a** (13.0 g, 41%): mp (175 °C) 177–178.5 °C; IR ν_{max} 1675 (C=O) cm^{-1}; ^1H NMR δ 1.4–2.8 (m, 11 H, aliphatic), 3.12 (m, H_{9a}), 4.35 (dd, H_{10}, J = 7, 15 Hz), 4.43 (dd, H_{9e}, J = 7, 16 Hz), 7.25 (m, 9 H, aromatic). Anal. Calcd for $C_{22}H_{23}NO$: C, 83.24; H, 7.30. Found: C, 83.08; H, 7.27.

Example 2. HCl Cyclization. Preparation of 9a. In a similar manner, amine **6** (5.2 g, 0.02 mol) was condensed with the

(37) (a) In a biomimetic polyene cyclization having a methyl substituent in an analogous position, but perforce no allylic or $A^{(1,3)}$ strain, the methyl group is strongly preferred in an equatorial (or β) orientation in the steroid-like products.[4b] Hart has drawn attention to this contrast between *N*-acyliminium-ion cyclizations and cyclizations of polyenes with iminium ions.[20] (b) A similar asymmetric polyene cyclization involving methoxybenzene as a nucleophile was reported by Groen and Zeelen.[4c]

(38) Sievers, R. E., Ed. "NMR Shift Reagents"; Academic Press: New York, 1973.

Table V. Data for Lactams and Amines[a]

compd	mp, °C (solv.)[b]	molecular formula[c]	^{1}H NMR data	elemental analysis
11a	186-187 (M)	$C_{23}H_{25}NO$	1.3-2.8 (m, 13 H, aliphatic), 3.28 (dd, H_{10a}, J = 13, 11), 4.51 (dd, H_{11}, J = 11, 7), 4.93 (dd, H_{10e}, J = 13, 7), 7.15 (m, 9 H, aromatic)	C, H
33a		$C_{20}H_{19}NO$	1.8-3.5 (m, 8 H, aliphatic), 3.78 (dd, H_{5a}, J = 9.3, 13), 4.37 (dd, H_6, J = 6.2, 13), 4.84 (dd, H_{10b}/H_{5e}, J = 7.2, 7.2), 6.9-7.3 (m, 7 H, aromatic)	d
33b		$C_{20}H_{19}NO$	1.7-3.0 (m, 6 H, aliphatic), 3.36 (dd, H_{5a}, J = 5, 14), 3.4-3.7 (m, 2 H), 4.77 (d, H_6, J = 5), 4.82 (dd, H_{10b}, J = 6.4, 10), 4.9 (d, H_{5e}, J = 14), 6.9-7.5 (m, 7 H, aromatic)	d
35a[e]	204-204.5 (M-EE)	$C_{19}H_{21}N \cdot C_4H_4O_4$	1.5-3.3 (m, 10 H, aliphatic), 3.57 (m, H_{11b}), 4.48 (dd, H_7, J = 6, 12), 6.7 (s, 2 H, olefin), 6.75 (d, H_8, J = 8), 7.2 (m, 8 H, aromatic), 9.0 (br s, exch. H)	C, H
35b[f]	195-203 (E)	$C_{19}H_{21}N \cdot C_4H_4O_4$	1.0-2.7 (m, 8 H, aliphatic), 2.87 (d, H_6, J = 4), 3.2 (m, H_{11b}), 4.06 (dd, H_7, J = 4, 4), 6.62 (s, 2 H, olefin), 7.2 (m, 9 H, aromatic)	C, H, N
36a	107-110 (M-W)	$C_{20}H_{23}N$	1.42 (s, CH_3), 1.5-2.1 (m, 9 H, aliphatic), 2.6-3.4 (m, 4 H, aliphatic), 4.37 (dd, H_7, J = 7.5, 10), 6.81 (d, H_8, J = 8), 7.2 (m, 8 H aromatic)	C, H
36b	194-197 (P)	$C_{20}H_{23}N \cdot C_7H_5NO_3S$	1.7-2.3 (m, 6 H, aliphatic), 2.02 (s, CH_3), 3.2-4.0 (m, 4 H, aliphatic), 5.05 (dd, H_7, J = 7, 10), 6.8-7.8 (m, 13 H, aromatic)	C, H, N
37a	236.5-241.5 (EA-M)	$C_{18}H_{19}N \cdot HCl$	1.9-4.1 (m, 8 H, aliphatic), 4.37 (dd, H_6, J = 7, 10), 5.2 (dd, H_{10b}, J = 6, 11.5), 6.82 (d, H_7, J = 7.5), 7.25 (m, 8 H, aromatic), 13.25 (br s, exch. H)	C, H
37b	170-172 (E)	$C_{18}H_{19}N \cdot C_4H_4O_4$	1.8-3.1 (m, 6 H, aliphatic), 3.14 (d, H_5, J = 6), 3.95 (m, H_{10b}), 4.3 (dd, H_6, J = 6, 6), 6.55 (s, 2 H, olefin), 6.73 (d, H_7, J = 7), 7.2 (m, 8 H, aromatic), 12.63 (br s, exch. H)	C, H, N
38a	219-226 (M-P-EE)	$C_{19}H_{21}N \cdot HBr$	1.78 (s, CH_3), 1.9-3.2 (m, 6 H, aliphatic), 4.15 (m, 2 H), 4.67 (m, H_{10b}), 7.3 (m, 9 H, aromatic)	C, H, N
38b	261.5-265.5 (M-P)	$C_{19}H_{21}N \cdot HBr$	2.0 (s, CH_3), 2.0-3.1 (m, 5 H, aliphatic), 3.43 (s, H_5), 4.15 (m, 1 H), 5.08 (m, H_{10b}), 6.9 (m, H_7), 7.25 (m, 8 H, aromatic)	C, H, N
39a[e]	182-184 (M-EE)	$C_{18}H_{17}Cl_2N \cdot C_7H_8SO_3$	2.31 (s, CH_3), 2.0-4.0 and 4.5 (m, 9 H, aliphatic), 5.1 (m, H_{10b}), 6.74 (d, H_7, J = 9), 7.0-7.6 (m, 10 H, aromatic)	C, H, N
40a[g]	212-213.5 (P)	$C_{20}H_{23}NO_2 \cdot HBr$	1.8-2.8 and 3.45 (m, 8 H, aliphatic), 3.58 (s, OCH_3), 3.87 (s, OCH_3), 4.3 (m, 1 H), 5.15 (m, H_{10b}), 6.24 (s, H_7), 6.63 (s, H_{10}), 7.25 (m, 5 H, aromatic)	C, H, N
40b	129-132 (M-P)	$C_{20}H_{23}NO_2 \cdot C_4H_4O_4 \cdot 0.5H_2O$	1.8-2.6 and 3.05 (m, 8 H, aliphatic), 3.45 (s, OCH_3), 3.72 (s, OCH_3), 3.9 (m, H_{10b}). 4.23 (dd, H_6, J = 5.5, 5.5), 6.22 (s, H_7), 6.52 (s, 2 H, olefinic), 6.78 (s, H_{10}), 7.24 (s, 5 H, aromatic), 9.75 (br s, exch. H)	C, H, N[h]
41a	290-305, dec (EA-M)	$C_{22}H_{25}N \cdot HCl$	1.3-2.8 and 3.2-4.3 (m, 15 H, aliphatic), 4.53 (dd, H_{10}, J = 6.5, 13), 6.9 (d, H_{11}, J = 7), 7.2 (m, 8 H, aromatic), 12.34 (br s, exch. H)	C, H, Cl
41b[f,g]	178.5-179.5, dec (P)	$C_{22}H_{25}N \cdot C_6H_{13}NO_3S$	0.9-2.5 and 2.6-4.3 (m, 28 H, aliphatic), 4.53 (dd, H_{10}, J = 5, 6), 6.91 (d, H_{11}, J = 6.5), 7.25 (m, 8 H, aromatic)	C, H, N
42a	121-124 (EA-M)	$C_{19}H_{21}N \cdot HCl \cdot H_2O$	1.5-1.9 (m, 1 H), 2.0-2.4 (m, 4 H, s for CH_3 at δ 2.07), 2.5-2.7 (m, 2 H), 3.1-4.1 (m, 4 H), 4.45 (dd, H_6, J = 12, 8) 6.8-7.5 (m, 9 H, aromatic)	C, H[h]

Table V (*Continued*)

compd	mp, °C (solv.)[b]	molecular formula[c]	^{1}H NMR data	elemental analysis
42b	136.5-138 (P-EE)	$C_{19}H_{21}N \cdot C_6H_{13}NO_3S \cdot 0.5H_2O$	0.9-2.6 (m, 18 H, s for CH_3 at δ 1.82), 3.0-3.4 (m, 3 H), 3.85 (dd, H_{5e}, J = 5, 12), 4.1-4.5 (m, 1 H), 4.78 (dd, H_6, J = 5, 11), 6.7-7.5 (m, 9 H, aromatic)	C, H, N[h]
46a	268-273, dec (95% E-Cl)	$C_{24}H_{29}NO \cdot HClO_4$	1.4-3.0 (m, 11 H, aliphatic), 3.2-4.1, (m, 2 H_7 and 2 H_9), 3.57 (s, OCH_3), 3.92 (s, OCH_3), 4.58 (dd, H_{10}, J = 7, 12), 6.26 (s, H_{11}), 6.72 (s, H_{14}), 7.1-7.5 (m, 5 H, aromatic), 8.8 (br s, exch. H)	C, H, Cl

[a] For **3a**, **4a**, **5a/5b**, **8a**, **9a**, **18a**, **18b**, **21a**, **23a/23b**, **27a**, **28a**, **31a** and **39b**, see text for data. [b] Recrystallization solvent is given in parentheses: M = methanol, EE = ethyl ether, E = ethanol, W = water, P = 2-propanol, EA = ethyl acetate, Cl = chloroform. [c] $C_4H_4O_4$ = fumaric acid, $C_7H_5NO_3S$ = saccharin, $C_7H_8SO_3$ = *p*-toluenesulfonic acid, $C_6H_{13}NO_3S$ = hexamic acid. [d] Known amines **47a** and **47b** [F. T. Bruderlein and L. G. Humber, U.S. Patent 3 657 250, 1972] were prepared by reduction of **33a** and **33b** and characterized. Satisfactory ^{1}H NMR and mass spectral data were obtained for **47a** and **47b**. [e] NMR solvent was $CDCl_3/Me_2SO$-d_6, 4:1. [f] NMR solvent was Me_2SO-d_6. [g] Trace amounts of 2-propanol was present in the compound. [h] H_2O analysis.

cyclohexanone acetic esters (3.4 g, 0.02 mol) at 150 °C. The oily product was dissolved in absolute ethanol, treated with 2 mL of saturated ethereal HCl, and heated for 10 min at reflux. Evaporation of the solvent gave 8.4 g of light brown glass. GLC analysis showed only one peak, a very major one, corresponding to the desired product (GLC/MS: M^+· 377, base peak 334). The material was chromatographed on a dry column of silica gel to remove polar impurities (ethyl acetate/hexane, 1:1); no fractionation was performed. The 6 g of off-white resin showed no minor isomer by GLC or NMR; **9a**: ^{1}H NMR δ 1.5–3.2 (m), 3.53 (s, OCH_3), 3.82 (s, OCH_3), 4.0–4.6 (m, 2), 6.18 (s, 1, H_{11}), 6.80 (s, 1, H_{14}), 7.0–7.5 (m, 5); ^{13}C NMR δ 20.2 (t), 21.3 (t), 27.6 (t), 36.2 (t), 37.0 (t), 37.5 (d, C_5), 42.4 (t, C_9), 43.5 (d, C_{10}), 55.7 (q, OCH_3), 56.0 (q, OCH_3), 62.6 (s, C_{14b}), 107.2 (d, C_{11} or C_{14}), 112.7 (d, C_{11} or C_{14}), 126.9 (d), 128.6 (d), 128.9 (d), 129.4 (s), 135.6 (s), 143.1 (C_1 of phenyl), 147.5 (C_{12} or C_{13}), 147.7 (C_{12} or C_{13}), 174.8 (C_7).

C. Ene Lactone Method. General Procedure. Ene lactone (0.11 mol) in 30 mL of methylene chloride was combined with diarylethylamine (0.10 mol) in 30 mL of methylene chloride and allowed to stand for 30 min. The solution was evaporated in vacuo to an oil, which was combined with PPA (200 g) and heated on a steam bath for 4 h. The reaction mixture was poured into water and extracted with methylene chloride. The organic phase was washed once with water and once with saturated NaCl and dried ($MgSO_4$). Evaporation in vacuo gave the lactam.

Example 1. 1,5,6,10b-Tetrahydro-10bα-methyl-6α-phenylpyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one (3a). 2,2-Diphenylethylamine (6.0 g, 0.03 mol) and α-angelicalactone (3.24 g, 0.033 mol) were combined according to the general procedure and upon workup gave a mixture (94/6, GLC) of lactams **3a** and **3b** (7.0 g, 84%). Recrystallization from ethyl acetate/petroleum ether gave white crystalline solid, **3a** (4.1 g, 49%): mp 135–136 °C; IR ν_{max} 1670 (C=O) cm^{-1}; ^{1}H NMR δ 1.66 (s, CH_3), 2.40 (m, 4 H, aliphatic), 3.07 (dd, H_{5a}, J = 11.5, 13 Hz), 4.15 (dd, H_6, J = 11.5, 6.5 Hz), 4.45 (dd, H_{5e}, J = 6.5, 13 Hz), 7.15 (m, 9 H, aromatic). Anal. Calcd for $C_{19}H_{19}NO$: C, 82.28; H, 6.90. Found: C, 82.13; H, 6.94.

Example 2. HCl Cyclization. Preparation of 5. Ethanolic HCl was used in place of PPA to induce cyclization onto the electron-rich aromatic groups to prepare **5a/5b**. For example, amine **6** (260 mg, 1.0 mmol) and α-angelicalactone (100 mg, 1.1 mmol) were combined in CH_2Cl_2 (2 mL) and heated on a steam bath to remove the solvent. Ethanol (2 mL) was added, followed by 50 μL of ethereal HCl. The reaction was heated at reflux for 10 min and worked up, affording 200 mg of brown oil. GLC analysis (SE-30; OV-17) showed one major peak (ca. 75% of mixture, for a yield of ca. 40%). The material was chromatographed on a 1000-μ silica gel prep TLC plate with ethyl acetate/hexane (2:1). The major band gave a colorless oil (100 mg), that was homogeneous by TLC and GLC (MS M^+· 331). The 60-MHz ^{1}H NMR spectrum showed mainly **5a**: δ 1.63 (s, 3, CH_3), 2.0–3.0 (m, 4), 3.04 (dd, 1, H_{5a}, J = 10, 12 Hz), 3.5–4.6 (m, 8; s for OCH_3 at δ 3.55 and 3.87), 6.26 (s, 1, H_7), 6.55 (s, 1, H_{10}), 7.0–7.5 (m, 5). A small singlet at δ 1.56 was assumed to belong to the CH_3 group of the β isomer, **5b**, in which case the ratio of **5a**:**5b** was estimated to be 90:10. This ratio was supported by ^{13}C NMR data, which showed two species, **5a** and (allegedly) **5b**, in an approximately 9:1 ratio. **5a**: ^{13}C NMR δ 27.7 (10b-CH_3), 30.6 (C_2), 34.9 (C_1), 42.0 (C_5), 44.7 (C_6), 55.8 (OCH_3), 56.1 (OCH_3), 61.2 (C_{10b}), 107.3 (C_7 or C_{10}), 112.1 (C_7 or C_{10}), 127.2 (s), 127.9 (d), 128.4 (d), 128.8 (d), 129.1 (d), 135.6 (s), 142.4 (C_1 of phenyl), 147.8 (C_8 or C_9), 148.6 (C_8 or C_9), 172.2 (C_3). **5b**: ^{13}C NMR δ (peaks that were independently observable) 26.8 (10b-CH_3), 41.5 (C_5), 44.2 (C_6), 61.0 (C_{10b}), 111.3 (C_7 or C_{10}), 112.4 (C_7 or C_{10}), 126.3 (d), 126.6 (d), 135.1 (s), 144.2 (s), 148.6 (s).

Preparation of Lactams via the Imide Route. General Procedure. The diarylethylamine (0.10 mol) in 100 mL of dry THF was added slowly to succinic anhydride (0.105 mol) in 100 mL of dry THF (or CH_2Cl_2) at 0 °C. The reaction was stirred at ambient temperature for 1 h and then evaporated in vacuo to the amide acid. Cyclization of the amide acid to the imide was accomplished by either (a) heating it without solvent at 175 °C for 4 h or (b) combining it with 25 mL of acetyl chloride (AcCl) in 100 mL of ethyl acetate and heating the solution at reflux for 10 h.[39] The resulting imide, which may be recrystallized before use, was mixed with 400 mL of absolute ethanol and cooled to −10 °C in an ice/methanol bath. $NaBH_4$ (0.40 mol) was added followed by CH_3SO_3H (15 drops). The temperature was maintained at −10 to 0 °C with efficient stirring, and five drops of 2 N ethanolic CH_3SO_3H were added every 15 min. After 5 h, the 2 N CH_3SO_3H was added more rapidly and the temperature was maintained at 0 °C until the pH was less than 3. During this addition, 200 mL of ethanol was added to decrease the viscosity of the foamy reaction solution. The reaction was stirred for 16 h at ambient temperature and then treated with water and methylene chloride. The organic solution was separated, washed once with water and once with saturated NaCl, and dried ($MgSO_4$). Evaporation in vacuo gave the ethoxypyrrolidinone. This ether was combined with PPA (100 mL) and heated on a steam bath for 6 h[40] (refluxing ethanolic HCl may be used instead of PPA when cyclizing onto electron-rich aromatic groups[41]). The reaction was poured into water and extracted with methylene chloride. The organic layer was separated, washed once with water and once

(39) The AcCl method of imide formation was useful for two reasons. (1) Thermal formation of imides generally produced succinic acid diamides as byproducts (10–30% of product), but this was avoided using AcCl as a dehydrating agent. (2) Thermal formation of imides was very sluggish when the amine had a substituent α to nitrogen, but the AcCl method circumvented the problem.

(40) Pyridine–polyhydrogen fluoride may also be used to induce cyclization. Thus, **17** (0.29 mmol) was dissolved in ca. 0.5 mL of pyridine·hydrogen fluoride (Aldrich) at 25 °C. After 30 min, basic (Na_2CO_3) workup gave an 80% yield of **18a**. (See footnote 19.)

(41) *N*-Methylpyrrole and indole were so electron rich that cyclization to **28** and **29**, respectively, occurred during the acid-catalyzed formation of the ethoxypyrrolidinone.

with saturated NaCl, dried ($MgSO_4$), and evaporated in vacuo to give the crude lactam.

Example 1. 1,5,6,10bα-Tetrahydro-6α-phenylpyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one (18a). When the general procedure was followed, 2,2-diphenylethylamine (19.7 g, 0.10 mol) and succinic anhydride (10.6 g, 0.105 mol, 99% assay) were combined and heated at 175 °C to give the imide (27.9 g). After reduction (ethoxypyrrolidinone: mp 67–68 °C) and cyclization with PPA, workup gave white solid lactams **18a** and **18b** (93/7, GLC; 22 g; 84%). Recrystallization from ethyl acetate/methanol gave white crystalline **18a** (14.3 g, 54%): mp 204.5–205.5 °C; IR ν_{max} 1665 (C=O) cm^{-1}; ^1H NMR δ 1.7–2.9 (m, 4 H, aliphatic), 3.06 (dd, H_{5a}, J = 11, 13 Hz), 4.15 (dd, H_6, J = 6, 11 Hz), 4.44 (dd, H_{5e}, J = 6, 13 Hz), 4.92 (dd, H_{10b}, J = 8, 8 Hz), 7.2 (m, 9 H, aromatic). Anal. Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51. Found: C, 81.93; H, 6.49.

Example 2. 1,5,6,10bα-Tetrahydro-8,9-dimethoxy-6α-phenylpyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one (21a). According to the general procedure, 2-(3,4-dimethoxyphenyl)-2-phenethylamine (35 g, 0.136 mol) and succinic anhydride (14.3 g, 0.143 mol) were combined and heated at 175 °C. The crude imide was recrystallized from methanol to give purified imide (34.1 g). The material (15.0 g, 0.044 mol) was reduced in the usual way to give the ethoxypyrrolidinone (15.8 g). This ether was dissolved in 100 mL of ethanol and 20 drops of ethereal HCl was added. The reaction was heated at reflux. Over the next 30 min, 1 mL of ethereal HCl was added at 10-min intervals to the reaction solution. The solution was concentrated in vacuo to give an oily mixture (9/1, GLC) of lactams **21a** and **21b** (13.5 g, 95%). The mixture was crystallized from ethyl acetate to afford white crystalline lactam **21a** (7.8 g, 55%): mp 140–141 °C; IR ν_{max} 1675 (C=O), 1252 (C–O) cm^{-1}; ^1H NMR δ 1.7–2.9 (m, 4 H, aliphatic), 3.0 (dd, H_{5a}, J = 11, 12.5 Hz), 3.58 (s, CH_3), 3.89 (s, CH_3), 4.12 (dd, H_6, J = 11, 6 Hz), 4.47 (dd, H_{5e}, J = 12.5, 6 Hz), 4.9 (m, H_{10b}), 6.28 (s, H_7), 6.66 (s, H_{10}), 7.25 (m, 5 H, aromatic). Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.19; H, 6.56; N, 4.34.

Example 3. 5,6,11,11bα-Tetrahydro-6α-phenyl-1*H*-indolizino[8,7-*b*]indol-3(2*H*)-one (29a). 3-(1-Phenyl-2-aminoethyl)indole[42] (24.98 g, 0.105 mol) and succinic anhydride (10.7 g, 0.106 mol) were combined in the usual fashion and heated at 140 °C for 5 h. The crude imide was recrystallized from xylene/methylene chloride (25.0 g). The imide (20.2 g, 0.063 mol) was mixed with 200 mL of dry THF[43] and 200 mL of ethanol and subjected to the usual reduction conditions with $NaBH_4$ (12.0 g, 0.32 mol). After quenching with 2 N ethanolic CH_3SO_3H (pH ~2), the mixture was stirred for 16 h, whereupon the ethoxypyrrolidinone cyclized to the mixture of lactams, **29a** and **29b** (92:8 by GLC). The usual workup afforded white solid **29a** + **29b** (18.6 g, 97%): EI MS 302 ($M^{+\cdot}$); IR (Nujol) ν_{max} 1655 (C=O) cm^{-1}.

Example 4. 1,5,6,10bα-Tetrahydro-5α-phenylpyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one (31a). 1,2-Diphenylethylamine (50.77 g, 0.25 mol) dissolved in 100 mL of ethyl acetate was added slowly to succinic anhydride (25.0 g, 0.25 mol) in 250 mL of warm ethyl acetate and the solution was heated at reflux for 30 min. The mixture was cooled in an ice bath as 50 mL of acetyl chloride was added and then heated at reflux for 10 h. The solution was evaporated in vacuo to an oil which was partially dissolved in a hot mixture of water (125 mL) and methanol (125 mL). After cooling in ice for several hours, white solid imide was filtered (69.23 g, 99%). The imide (10.0 g, 0.036 mol) was reduced in the usual manner to give the ethoxypyrrolidinone (10.3 g, 93%), which was cyclized using PPA (80 g) at room temperature for 1 h. The usual workup gave the product lactam **31a** (7.2 g, 83%): EI MS 263 ($M^{+\cdot}$); ^1H NMR (360 MHz) δ 1.9–2.7 (m, 4 H, aliphatic), 3.3 (dd, H_6, J = 16.6, 2.3 Hz), 3.37 (dd, H_6, J = 16.6, 6.4 Hz), 4.53 (dd, H_{10b}, J = 7.7, 7.8 Hz), 5.69 (dd, H_5, J = 6.4, 2.4 Hz), 7.0–7.4 (m, 9 H, aromatic).

Example 5. 4,5,9,9aα-Tetrahydro-4α-phenylthieno[2,3-*g*]indolizin-7(8*H*)-one (27a). 2-Amino-1-phenylethanol (100 g, 0.73 mol) and thiophene (157 g, 1.87 mol) were combined and the solution was cooled in an ice bath as 175 mL of trifluoroacetic acid was added. The solution was heated at reflux for 70 h, cooled, and evaporated in vacuo to a syrup. This material was dissolved in methylene chloride, washed once with 5% NaOH, once with water, and once with saturated NaCl, and dried (K_2CO_3). The solution was evaporated in vacuo to an oil, which was distilled (Kugelrohr, 140 °C at 0.8 torr) to give a colorless oil. This oil (a trifluoroacetamide) was dissolved in 250 mL of *tert*-butyl alcohol and 80 mL of 30% KOH was added. The mixture was heated at reflux for 18 h, then cooled. The solution was extracted with ether and the ether solution was washed once with water and once with saturated NaCl, and dried (Na_2SO_4). The solution was evaporated in vacuo to an oil (62.7 g, 42%), which was redissolved in ether and treated with HCl gas (bubbled into the solution until it was acidic). The HCl salt was filtered and recrystallized from ethanol/ether once and converted back to the free base by extraction between ether and dilute NaOH. The ether solution was dried (K_2CO_3) and evaporated in vacuo to give a mixture (85/15, ^1H NMR) of 2-(thien-2-yl)- and 2-(thien-3-yl)phenylethylamine (41.9 g, 28%). When this mixture of amines was used, the imide was prepared from succinic anhydride (20.0 g, 0.20 mol) in the usual way at 150 °C for 15 h. The imide was recrystallized from 50 mL of 2-propanol to give a white solid (48.8 g, 86%), mp 113–114 °C. Reduction of the imide (43.2 g, 0.15 mol) with $NaBH_4$ (23 g, 0.60 mol), in the usual way, and cyclization with HCl (see Example 2) gave the crude lactams. The mixture was separated using preparative HPLC (ethyl acetate/hexane, 1:1) and upon evaporation in vacuo gave lactam **27a** (19.1 g): EI MS 269 ($M^{+\cdot}$); ^1H NMR δ 1.7–2.7 (m, 4, aliphatic), 2.93 (dd, H_{5a}, J = 11.5, 11.5 Hz), 4.17 (dd, H_4, J = 11.5, 6 Hz), 4.53 (dd, H_{5e}, J = 11.5, 6 Hz), 4.82 (dd, H_{9a}, J = 7, 7 Hz), 6.75 (d, H_2, J = 5 Hz), 7.0–7.4 (m, 6, aromatic).

Example 6. 4,5,9,9aα-Tetrahydro-3-methyl-4α-phenyl-3*H*-pyrrolo[2,3-*g*]indolizin-7(8*H*)-one (28a). *N*-Methylpyrrole (54.3 g, 0.67 mol) and ω-nitrostyrene (50.0 g, 0.34 mol) were combined in 115 mL of glyme and 270 mL of dilute H_2SO_3 (pH = ~3).[44] The solution was maintained at 80 °C for 8 h, cooled, diluted with 200 mL of water, and extracted with methylene chloride. The organic layer was washed once with water, once with saturated $NaHCO_3$ solution, and once with saturated NaCl. The solution was dried (K_2CO_3) and evaporated in vacuo to a brown solid (77.7 g). The solid was recrystallized from methanol (140 mL) to give the tan crystalline nitroethane product (40.5 g; 52%; mp of a sample recrystallized from methanol, 83–85 °C). This material (36.3 g, 0.158 mol) in 500 mL of ether was reduced with LAH (17.39 g, 0.474 mol) in 300 mL of ether at room temperature. After 18 h, 18 mL of water was added dropwise, followed by 18 mL of 15% NaOH, and 54 mL of water. The precipitate was filtered and the ether layer was separated and dried (K_2CO_3). The solution was evaporated in vacuo to give orange solid amine (22.9 g, 73%). This amine (21.7 g, 0.108 mol) was combined with succinic anhydride (10.9 g, 0.107 mol) in the usual way at 175 °C for 5 h. The crude imide was dissolved in 300 mL of methylene chloride and this solution was washed once with 1 N HCl, once with 1 N NaOH, once with water, and once with saturated NaCl, dried ($MgSO_4$), and evaporated in vacuo to give imide (31.0 g). The imide (25.0 g, 0.089 mol) was reduced with $NaBH_4$ (13.5 g, 0.40 mol) according to the general procedure and during the acid workup the ethoxypyrrolidinone cyclized to give a mixture (3/1, GLC) of lactams **28a** (α) and **28b** (β) (22.8 g, 96%). This mixture was equilibrated with K_2CO_3 (60 g, 0.44 mol) in 180 mL of Me_2SO and 18 mL of water following the general procedure (see below). Workup gave a mixture (3:2) of lactams **28a** and **28b** (17.9 g), which were separated using preparative HPLC to give lactam **28a** (7.9 g): EI MS 266 ($M^{+\cdot}$); ^1H NMR δ 1.7–2.9 (m, 5, aliphatic), 2.92 (s, CH_3), 4.13 (dd, H_4, J = 6, 6 Hz), 4.43 (dd, H_{5e}, J = 6, 12 Hz), 4.78 (dd, H_{9a}, J = 6, 6 Hz), 5.9 (d, H_1, J = 2.5 Hz), 6.41 (d, H_2, J = 2.5 Hz), 7.0–7.4 (m, 5, aromatic).

Preparation, Separation, Isolation, and Attempted Acid-Induced Equilibration of 23. Imide (10.0 g), prepared from primary amine **22** (Table II) and succinic anhydride, was reduced with $NaBH_4$ (3.9 g) in 150 mL of absolute ethanol at 0 °C, adding

(42) Nolan, W. E.; Christensen, G. M.; Sauer, G. L.; Dutton, G. G. S. *J. Am. Chem. Soc.* **1955**, *77*, 456.

(43) Use of a cosolvent with ethanol allowed the imide to dissolve partially and the reduction to proceed. No reaction occurred under the standard conditions.

(44) This pyrrole substitution reaction is an application of a published procedure: Webb, I. D.; Borcherdt, G. T. *J. Am. Chem. Soc.* **1951**, *73*, 752.

two drops of 2 N ethanolic CH_3SO_3H every 15 min. After 3 h, the reaction was acidified (pH 3) slowly, let warm to 23 °C, and worked up. The light tan resin (10.1 g; ^1H NMR supported the 5-ethoxypyrrolidin-2-one) was chromatographed on a dry column of silica gel (40 g) with ethyl acetate to furnish 7.5 g of TLC-homogeneous material. This syrup in 100 mL of absolute ethanol was treated with 1 mL of ethereal HCl and heated for 10 min at reflux. Since TLC showed no starting material, the reaction was evaporated to dryness, affording 5.5 g of tan foam. A 350-mg sample was chromatographed on a 1000-μm silica gel prep TLC plate with ethyl acetate. The plate was dried in air and redeveloped with ethyl acetate; this process was repeated again. The major band provided 230 mg of pale blue resin, R_f 0.17, and the minor band provided 30 mg of greenish oil, R_f 0.28 (8:1 ratio of **23a**:**23b**). Mass spectral data for **23a** and **23b** were nearly identical (M^+· 383), confirming their isomeric relationship. **23a**: ^1H NMR (90 MHz) δ 1.7–2.1 (m, 1, H_1), 2.3–3.1 (m, 4, dd for H_{5a} at δ 2.98, J = 12, 12 Hz), 3.6–4.6 (m, 14; s for OCH_3 at δ 3.61, 3.82, 3.88 [2 OCH_3], dd for H_6 [slightly concealed] at δ 4.10, J = 6, 12 Hz, dd for H_{5e} at δ 4.42, J = 5, 12.5 Hz), 4.88 (dd, 1, H_{10b}, J = 7, 7.5 Hz), 6.36 (s, 1, H_7), 6.6–7.0 (m, 4). **23b**: ^1H NMR (90 MHz) δ 1.7–2.1 (m, 1, H_1), 2.2–2.8 (m, 3), 3.35 (dd, 1, H_{5a}, J = 4, 12.5 Hz), 3.6–4.4 (m, 14; s for OCH_3 at δ 3.77 [2 OCH_3], 3.81, 3.90, dd for H_6 [partly concealed] at δ 4.08, J = ~4, ~1 Hz, dd for H_{5e} at δ 4.28, J = 12.5, 2 Hz), 4.77 (dd, 1, H_{10b}, J = 9, 6.5 Hz), 6.45–6.9 (m, 5). A sample (1–2 mg) each of **23a** and **23b** was dissolved in 0.1 mL of absolute ethanol and treated with ca. 50 μL of ethereal HCl. The solutions were heated at reflux for 30 min, then examined by TLC. There was no evidence for the presence of the alternate isomer in either sample, showing the absence of acid-induced equilibration under the cyclization conditions which produced **23a** and **23b**.

Equilibration of Lactams. General Procedure. The lactam (0.10 mol) was dissolved in 200 mL of Me_2SO. Water (20 mL) and K_2CO_3 (100 g) were added. The reaction was heated at reflux (generally using an oil bath at 130 °C), which was maintained until equilibrium was reached. This usually required 1–3 h of heating. Reaction progress was monitored by removing aliquots, which were quenched in ice water, extracted with methylene chloride, and analyzed by GLC. The reaction was rapidly cooled with an ice bath and treated with water (500 mL) and methylene chloride (500 mL). The organic layer was separated, washed three times with water and once with saturated NaCl, and dried ($MgSO_4$). The solution was concentrated in vacuo to give a mixture of lactams, which was generally separated using preparative HPLC.

Example. 1,5,6,10bβ-Tetrahydro-6α-phenylpyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one (18b). The crude mixture (93/7, GLC) of lactams **18a** and **18b** (19.5 g, 0.075 mol) was combined with 150 mL of Me_2SO, 15 mL of water, and K_2CO_3 (75 g) according to the general procedure. At equilibrium the reaction was worked up to give a mixture (1/1, GLC) of lactams **18a** and **18b** (16.0 g, 82%). The lactams were separated using HPLC. Lactam **18b** was recrystallized from ethyl acetate to give white crystals (4.54 g, 47% based on the final 50:50 mixture): mp 126.5–132.5 °C; IR ν_{max} 1693 (C=O) cm^{-1}; ^1H NMR δ 1.7–2.9 (m, 4 H, aliphatic), 3.43 (dd, H_{5a}, J = 5, 13 Hz), 4.22 (dd, H_6, J = 5, 3 Hz), 4.29 (dd, H_{5e}, J = 13, 2 Hz), 4.83 (dd, H_{10b}, J = 6, 9 Hz), 7.1 (m, 9 H, aromatic). Anal. Calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 81.81; H, 6.40; N, 5.16.

Equilibration of Amines. General Procedure. The amine (0.01 mol) was dissolved in 30 mL of Me_2SO and 30 mL of 10 N NaOH (aqueous) and heated at reflux under N_2. When equilibrium was attained, the reaction was quickly cooled in an ice bath and treated with water (200 mL) and methylene chloride (200 mL). The organic phase was separated, washed three times with water and once with saturated NaCl, and dried (K_2CO_3). The solution was concentrated in vacuo to give a mixture of the amines.

Example. 9-Chloro-6α-(4-chlorophenyl)-1,2,3,5,6,10bα-hexahydropyrrolo[2,1-*a*]isoquinoline (39). Compound **39a** (0.50 g, 1.57 mmol) was dissolved in 5.0 mL of Me_2SO and 5.0 mL of 10 N NaOH and heated at reflux under N_2. After 1 h the reaction was worked up to give a mixture (2/1, GLC) of amines **39a** and **39b** (0.35 g, 70%).

Deuterium Exchange Reaction on Amine 35a. Compound **35a** (60.0 mg, 0.23 mmol) was dissolved in Me_2SO-d_6 (0.4 mL) and 10 N NaOD in D_2O (0.4 mL) and heated at reflux under N_2. After 2 h, the reaction was cooled in ice and extracted between water and chloroform. The chloroform was washed once with water and once with saturated NaCl and dried (K_2CO_3). The solution was evaporated in vacuo to give a mixture (1/1, GLC) of deuterated amines **35a** and **35b** (60.0 mg): MS 265 (M^+· dideuterio, 40%)/264 (monodeuterio, 100%), 236/235, 188/187; ^1H NMR showed no absorptions at δ 4.48 (**35a**, H_7) and 4.06 (**35b**, H_7) and a reduced (30–50%) absorption at δ 3.3 (H_{11b}).

Deuteration of 8. Analytically pure lactam **8a** (125 mg) was combined with D_2O (1 mL, 99.8% D) and Me_2SO-d_6 (1 mL). Anhydrous K_2CO_3 (100 mg) was added. The mixture was heated at reflux under nitrogen for 6 days, cooled, diluted with brine, and filtered. About 100 mg of dry, brownish solid was obtained. GLC analysis (OV-17) showed a peak corresponding to **8a** (coinjection) and a second peak corresponding to **8b** [GLC/MS verified that the two peaks were isomeric with M^+· 320 (for trideuterio species)] in a ratio of 1.5:1. Standard equilibration of **8a** gave an equilibrium ratio of **8a**/**8b** of 1.6:1 after four days of heating. A sample of trideuterio mixture (60 mg) was chromatographed on a 1500-μm silica gel prep TLC plate with ethyl acetate/hexane (1:1) to give 32 mg of the major material, **8a**-d_3, which had the same GLC retention time as **8a**. A 90-MHz ^1H NMR spectrum of **8a**-d_3 (31 mg in 0.4 mL of $CDCl_3$) showed a triplet for H_6 at δ 2.65 with J = 5, 5 Hz, a doublet at δ 3.10 (J = 13 Hz) for H_{10a}, and a doublet at δ 4.42 (J = 13 Hz) for H_{10e}. Protons H_7, $H_{7'}$, and H_{11} were absent.

Reduction of Lactams. General Procedure. The lactam (0.018 mol) was dissolved in THF (40.0 mL) and added slowly to borane·THF (Aldrich, 1.0 M, 0.05 mol) at 0 °C. The solution was heated at reflux for 1 h and cooled to 0 °C. Water (10.0 mL) followed by hydrochloric acid (12.0 M, 15.0 mL) were added (slowly). The reaction was stirred for 2 h at ambient temperature. Most of the THF was distilled off, 50 mL of water was added, and the solution was heated at reflux for 15 min. The solution was cooled in an ice bath, made alkaline with 1 N NaOH, and extracted with methylene chloride. The organic phase was washed once with water and once with saturated NaCl and dried (K_2CO_3). The solution was evaporated in vacuo to give the amine.

Example. 9-Chloro-6α-(4-chlorophenyl)-1,2,3,5,6,10bβ-hexahydropyrrolo[2,1-*a*]isoquinoline (39b). Lactam **20b** (6.0 g, 0.018 mol) and borane·THF (50.0 mL, 0.05 mol) were combined according to the general procedure. Workup gave crude amine **39b** (5.5 g, 96%). The perchlorate salt was prepared from methylene chloride/2-propanol. Recrystallization from methanol gave pure $HClO_4$ amine salt of **39b** (2.29 g, 30%): mp 242–245 °C; IR ν_{max} 1485 (aromatic), 1100 (ClO_4^-) cm^{-1}; ^1H NMR δ 2.0–3.9 (m, 8, aliphatic), 4.39 (dd, H_6, J = 5, 11 Hz), 4.82 (dd, H_{10b}, J = 8, 8 Hz), 6.65 (d, H_7, J = 8 Hz), 7.35 (m, 6, aromatic). Anal. Calcd for $C_{18}H_{17}Cl_2N·HClO_4$: C, 51.64; H, 4.33; N, 3.34. Found: C, 51.64; H, 4.58; N, 3.16.

Crystallographic Methods and Data. Lactam **18a** was further purified by an extra recrystallization from ethyl acetate–methanol (20:1). A small amount of this material was dissolved in acetone and let cool to afford colorless prismatic needles. Then, 0.22 g of material was dissolved in 15 mL of warm acetone, seeded with one prism, and let cool slowly. Air-dried crystals (80 mg), mp 205–207 °C (turned dark blue), had ^1H NMR and IR spectra that were identical with prior samples. Details of crystallographic methods are given in the microfilm supplement.[30c]

Computational Work. Lactams **18a** and **18b** were entered into a DEC-1091 computer using the MACCS computer graphic system with an Imlac System II terminal. The initial 2-D structures were assigned 3-D coordinates using the PRXBLD program (coarse energy minimization). In order to get a calculated structure that was reasonably close to the X-ray structure of **18a** with PRXBLD, it was necessary to use a zwitterionic amide group (i.e., $>N^+=C-O^-$) and to include hydrogen atoms on positions 5, 6, 7, 10, 10b, and on the two ortho phenyl positions. (All hydrogens could not be included because PRXBLD allows a maximum of 30 atoms.) These 3-D coordinates from PRXBLD were then used as a starting point for MM2 force field computations.[35b] Parameters for the bond, angle, and torsional angles of the *N*-methyl amide moiety[45] were added to the MM2 data

set to furnish a better fit of the calculated and X-ray data. Molecular superpositioning and distance comparisons were done with the IMAGE (Interactive Modeling And Geometric Exploration) programs developed at McNeil for performing computer graphics comparisons, measurements, and manipulations.

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Registry No. **1**, 3963-62-0; **3a**, 73691-11-9; **3b**, 73691-12-0; **4a**, 73691-22-2; **4b**, 87519-47-9; **5a**, 87519-48-0; **5b**, 87519-49-1; **6**, 36756-35-1; **8a**, 73691-21-1; **8a**-d_3, 87532-01-2; **8b**, 87583-46-8; **9a**, 87519-50-4; **11a**, 87519-51-5; **12**, 582-22-9; **13a**, 87519-52-6; **13b**, 87519-53-7; **14**, 34611-07-9; **15a**, 87519-54-8; **15b**, 87519-55-9; **16**, 87519-56-0; **17**, 73691-13-1; **18a**, 73691-20-0; **18b**, 87519-57-1; **19**, 85336-82-9; **20a**, 87519-58-2; **20b**, 87519-59-3; **21a**, 73691-18-6; **21b**, 87519-60-6; **22**, 87519-61-7; **23a**, 73691-19-7; **23b**, 87532-02-3; **24a**, 87519-62-8; **24b**, 87519-63-9; **25a**, 87519-64-0; **25b**, 87519-65-1; **27a**, 87519-66-2; **27b**, 87519-67-3; **28a**, 87519-68-4; **28b**, 87519-69-5; **29a**, 87519-70-8; **30**, 87519-71-9; **31a**, 87519-72-0; **33a**, 87519-73-1; **33b**, 87519-74-2; **34a**, 86457-11-6; **34b**, 75688-91-4; **35a**, 87519-75-3; **35a** fumarate, 87519-76-4; **35b**, 87519-77-5; **35b** fumarate, 87519-78-6; **36a**, 87519-79-7; **36b**, 87519-80-0; **36b**–saccharin, 87519-81-1; **37a**, 87519-82-2; **37a**·HCl, 87519-83-3; **37b**, 87519-84-4; **37b** fumarate, 87519-85-5; **38a**, 87519-86-6; **38b**, 87519-87-7; **39a**, 87519-88-8; **39a** *p*-toluenesulfoante, 87519-89-9; **39b**, 87519-90-2; **39b**·$HClO_4$, 87519-91-3; **40a**, 87519-92-4; **40a**·HBr, 87519-93-5; **40b**, 87519-94-6; **40b** fumarate, 87519-95-7; **41a**, 87519-96-8; **41b**, 87583-47-9; **41b**–hexamic acid, 87637-35-2; **42a**, 58371-38-3; **42b**, 58371-36-1; **46a**, 87519-98-0; ethyl 1,4-dioxopentyl carbonate, 73691-09-5; 5-methyl-2(3*H*)-furanone, 591-12-8; etyl 2-oxocyclohexanacetate, 24731-17-7; methyl 2-oxocyclohexaneacetate, 13672-64-5; succinic anhydride, 108-30-5; 3-(1-phenyl-2-aminoethyl)indole, 5027-78-1; 1,2-diphenylethylamine, 25611-78-3; thiophene, 110-02-1; 2-amino-1-phenylethanol, 7568-93-6; 2-(thien-2-yl)phenylethylamine, 87519-99-1; 2-(thien-3-yl)phenylethylamine, 87520-00-1; 2-[2-(2,5-dioxopyrrolidin-1-yl)-1-phenylethyl]thiophene, 87520-01-2; 1-[2-(3,4-dimethoxyphenyl)-2-phenylethyl]-2,5-pyrrolidinedione, 87520-02-3; 3-[2-(2,5-dioxopyrrolidin-1-yl)-1-phenylethyl]-1*H*-indole, 87520-03-4; 1-(1,2-diphenylethyl)-2,5-pyrrolidinedione, 87520-04-5; 1-[2-(3,4-dimethoxy)-2-phenylethyl]-5-ethoxy-4,5-dihydro-2(3*H*)-pyrrolone, 73691-14-2; *N*-methylpyrrole, 96-54-8; ω-nitrostyrene, 102-96-5; 1-methyl-2-(2-nitro-1-phenylethyl)-pyrrole, 87520-05-6; 1-methyl-2-(2-amino-1-phenylethyl)pyrrole, 87520-06-7; 1-[2-(1-methylpyrrol-2-yl)-2-phenylethyl]-2,5-pyrrolidinedione, 87520-07-8; 1-[2,2-bis(3,4-dimethoxyphenyl)-ethyl]pyrrolidine-2,5-dione, 87520-08-9; 1-[2,2-bis(3,4-dimethoxyphenyl)ethyl]-5-ethoxy-3,4-dihydro-2(3*H*)-pyrrolone, 73691-15-3.

Supplementary Material Available: ^1H NMR LIS data for **3a** (Table I), **18a** and **18b** (Table II), **24a** and **24b** (Table III), and **8a** (Table V), ^1H and ^{13}C NMR chemical shift data for **18a**, **18b**, **24a** and **24b** (Table IV), ^1H NMR discussion for **8a**, discussion of relevant acyliminium cyclizations from the literature, Figures 1 and 3, tables of bond distances, bond angles, selected torsional angles, least-squares planes, positional and thermal parameters, and intermolecular contacts, X-ray crystallographic methods and results, discussion of least-squares planes and geometry of **18a** (27 pages). Ordering information is given on any current masthead page.

(45) Parameters used for MM2: N–CO bond, K_s = 8.3, l = 1.325 Å; C(sp^3)–N–CO angle, K_b = 0.6, angle = 122°; torsion angles H–C(sp^3)–CO–N, V_1 = 0.167, V_2 = 0.0, V_3 = –0.1; H–C(sp^3)–N–CO, $V_1 = V_2 = V_3$ = 0.0.

Dealkylation of a Tertiary Amine Group by an Intramolecular Carbamyl Chloride Functionality[1]

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Compounds containing a 4-anilinopiperidine moiety react with phosgene to afford carbamyl chloride hydrochloride derivatives, which rearrange in the presence of nonnucleophilic amine bases. The rearrangement entails intramolecular acylation by the carbamyl chloride group of the free basic nitrogen, followed by cleavage of a carbon–nitrogen bond. Anilines **4a–4c** produce ureas **7a–7c**; so, the bicyclic ammonium ion intermediates fragment regiospecifically (one of three possible paths), presumably to maximize amide resonance in the transition state for C–N bond cleavage. In the rearrangement of **9** the piperidine ring is broken to give **11**, in preference to dealkylation of the 2-phenethyl group. Rates for the rearrangements of **6a–6c** to **7a–7c** were measured (**6c** rearranged fastest). X-ray crystallographic analyses for **7a** and **7b** are reported.

In a extension of our work[2] on benzo[*a*]quinolizidine analogues (**1a–1d**; see Table I) of the potent analgesic fentanyl (**2**), we prepared urea derivatives having general structure **3**. Secondary ureas were readily obtained by condensation of anilines **4** with isocyanates, but tertiary ureas were not produced effectively from **4** and carbamyl chlorides. For instance, aniline **4a** did not even react with $(CH_3)_2NC(O)Cl$ to afford **5a**. As an alternative to tertiary ureas, we treated anilines **4** with phosgene, then added dialkylamines; this route was so successful that it was adopted for making secondary ureas, as well. Interestingly, use of $CF_3CH_2NH_2$ in this phosgene procedure yielded a

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(2) Maryanoff, B. E.; McComsey, D. F.; Taylor, R. J., Jr.; Gardocki, J. F. *J. Med. Chem.* **1981**, *24*, 79.

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