the calculated electrostatic properties of free CO. In Figure 1 we have also included $LiCO^+$ ($^1\Sigma^+$)[22] and Cl_2ScHCO.[23] In $LiCO^+$ the binding clearly is electrostatic, with no opportunity for back-donation. The possibility of σ donation is also very remote. In Cl_2ScHCO the Cl substituents remove electrons from Sc giving it considerable Sc^+ character. The calculated[23] ScCO bond length and bond energy (2.406 Å and 16.4 kcal/mol) are consistent with those calculated for the transition metal monocarbonyl cations.

(c) The Mulliken population analysis results indicate that very little charge transfer takes place. Notwithstanding the well-known pitfalls of the method,[20] the trends are rather clear.

The question naturally arises as to why the bonding is totally different between MCO and MCO^+? The σ-d_π view is a synergistic one: the σ ligand donation assists the d_π back-donation and vice versa. If the one cannot take place, the effect of the other is also greatly diminished. For the ionic systems the d_π metal back-donation does not occur mainly for energetic reasons. Electron transfer out of the M^+ ion is prohibitively costly in light of the values of the second IE of the metals. The second IE's for Sc^+, Ti^+, V^+, and Cr^+ are 12.9, 13.6, 14.2, and 16.5 eV, respectively, as opposed to ~6.7 eV on the average for the first IE of the metal atoms. The gain in energy due to covalent binding, if charge is transferred from M^+ to CO, cannot compensate for the cost of that transfer and therefore the electrostatic interaction dominates.

Acknowledgment. This work was partially supported under NSF Grants CHE8519752 (J.F.H.) and CHE 8722111 (J.A.).

Registry No. Sc^+, 14336-93-7; Ti^+, 14067-04-0; V^+, 14782-33-3; Cr^+, 14067-03-9.

Stereochemical Studies on Protonated Bridgehead Amines. ^{1}H NMR Determination of Cis and Trans B–C Ring-Fused Structures for Salts of Hexahydropyrrolo[2,1-*a*]isoquinolines and Related C Ring Homologues. Capture of Unstable Ring-Fused Structures in the Solid State†

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Abstract: Acid-addition salts of tricyclic isoquinolines **2a/b**, **3a/b**, **4a–4c**, **5**, **6a/b**, **7**, **8a/b**, **9a/b**, and **17a/b** were studied by high-field ^{1}H NMR in $CDCl_3$ solution. Cis (e.g., **14** and **15** in Figure 1) and trans (e.g., **13**) B–C ring-fused structures were identified by using the vicinal ^3J(CH–NH) coupling constants, which demonstrate a Karplus-like behavior. In some cases, we initially observed a trans form, which converted to a cis A form by NH proton exchange. For **4c**·HBr, the exchange process was slowed by addition of trifluoroacetic acid. In many cases, cis A and cis B structures were preferred in solution. The pendant phenyl group exerted a strong influence on the preferred solution structure. Observation of the initial, unstable trans-fused structures was related to their capture in the solid state and release intact on dissolution. X-ray diffraction was performed on the HBr salts of **2a** (B–C cis), **2b** (B–C cis), and **4c** (B–C trans). The result for **4c**·HBr confirmed the connection between the initial trans form in solution and the solid state. For **17b**·HCl two conformers, associated with hindered rotation about the bond connecting the 2,6-disubstituted phenyl group to the tricyclic array, were detected at ambient probe temperature; however, rotamers were not observed for either of the two forms (trans and cis A) of **17a**·HBr. Two conformers were also found for **16b**·HBr. Temperature-dependent behavior was recorded in the ^{1}H NMR spectra of **17b**·HBr and **16b**·HBr; the activation free energy for interconversion of conformers was estimated to be in the vicinity of 17 kcal/mol for the former and 14–15 kcal/mol for the latter. The ^{1}H NMR spectrum of butaclamol hydrochloride (**20**·HCl), a potent neuroleptic agent, in Me_2SO-d_6 revealed two species in a ratio of 81:19, which were assigned as trans and cis A forms, respectively. ^{1}H NMR data for various free bases are also presented and discussed. Empirical force field calculations on three model hydrocarbons are discussed from a perspective of finding an explanation for the configurational/conformational behavior of the bridgehead ammonium salts. Diverse literature examples of structures for protonated bridgehead amines are also discussed. A tentative rationale is suggested for the preference of cis A forms in some protonated tetrahydroisoquinoline derivatives.

Although substantial information has been acquired on the structural and conformational properties of alicyclic amines with nitrogen at the bridgehead position, such as bicyclic [*m.n.*0] compounds where *m* and *n* = 3 or 4, the corresponding protonated species (i.e., acid-addition salts) have been largely ignored.[1] Since this type of molecular framework is part and parcel of a wide variety of alkaloid structures,[2] as well as several biologically active compounds,[2-5] further study of acid-addition salts would be useful.

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† This paper was presented in part in the "Symposium on Heterocyclic Chemistry" at the 18th Middle Atlantic Regional Meeting of the American Chemical Society, Newark, NJ, May 1984; paper ORGN-246. It was also presented at the 194th National Meeting of the American Chemical Society, New Orleans, LA, Sept 1987; paper ORGN-122.

‡ McNeil Pharmaceutical.

§ The Pennsylvania State University.

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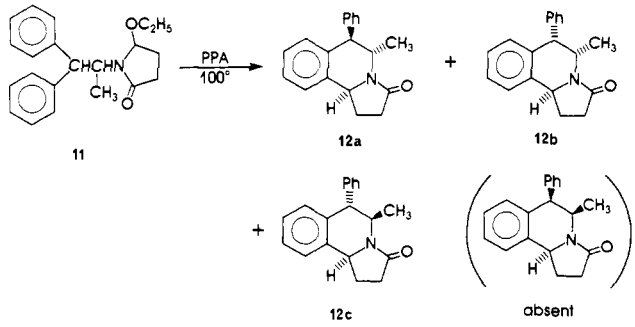
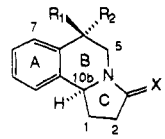
Scheme I



This paper deals in detail with the solution and solid-state structural properties of protonated tricyclic compounds containing a tetrahydroisoquinoline nucleus, which have been of special interest to us because they comprise our hexahydropyrrolo[2,1-*a*]isoquinoline series of inhibitors of the uptake of biogenic amine neurotransmitters (potential antidepressant agents).[4a]

Results and Discussion

In the course of our research on *N*-acyliminium cyclizations leading to polycyclic isoquinoline derivatives,[6] we encountered **1** as a 55:45 mixture of diastereomers **1a** and **1b**. After isomer



1a	R_1 = Me; R_2 = Ph; X = O	**5**	$R_1 = R_2$ = H; X = H_2
1b	R_1 = Ph; R_2 = Me; X = O	**16b**	R_1 = 2Cl-C_6H_4; R_2 = H; X = H_2
2a	R_1 = Me; R_2 = Ph; X = H_2	**17a**	R_1 = H; R_2 = 2Cl,6F-C_6H_3; X = H_2
2b	R_1 = Ph; R_2 = Me; X = H_2	**17b**	R_1 = 2Cl,6F-C_6H_3; R_2 = H; X = H_2
3a	R_1 = H; R_2 = Ph; X = H_2	**18a**	R_1 = H; R_2 = Ph; X = O
3b	R_1 = Ph; R_2 = H; X = H_2	**18b**	R_1 = Ph; R_2 = H; X = O

separation, attempted assignment of stereochemistry by ^1H and ^{13}C NMR was problematic. The quaternary center at C6 obviated a convenient ^1H NMR paradigm that we had employed for many similar compounds.[6] Although ^1H and ^{13}C NMR spectra for the corresponding amines **2a** and **2b**, or their HBr salts, were quite distinctive, no convincing stereochemical assignments could be made from these data. A tentative designation of structure **1a** to the major diastereomer was ultimately made from ^1H NMR LIS data for **1a** and **1b** [Eu(fod)$_3$]; however, we wanted unequivocal evidence.

A single-crystal X-ray analysis on the hydrobromide salt of the minor isomer (higher melting salt) verified structure **2b**. It was intriguing to us that **2b**·HBr possesses a cis fusion between rings B and C. Therefore, we also performed an X-ray study on the major isomer, **2a**·HBr (lower melting salt). Since it too was found

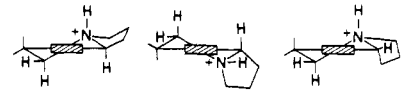
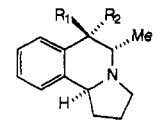
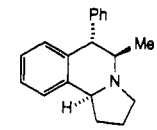


Figure 1. Trans, cis A, and cis B ring-fused structures illustrated for the pyrrolo[2,1-*a*]isoquinoline system.

to adopt a cis-fused structure in the crystal, we sought to establish the existence of such cis structures in solution by ^1H NMR. The NMR studies on **2a**·HBr and **2b**·HBr at 200 or 360 MHz, in $CDCl_3$ or CD_3OD between +25 and −60 °C or in Me_2SO-d_6, proved uninformative because of broadness of the resonance lines and some N–H exchange (the importance of having relatively slow N–H exchange is discussed later). Thus, we turned to the investigation of other molecules in the pyrrolo[2,1-*a*]isoquinoline series, such as **3a/b**, **4a–4c**, and **5**. By using high-field ^1H NMR,



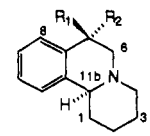


4a R_1 = Ph; R_2 = H

4b R_1 = H; R_2 = Ph

4c

we were able to characterize *cis*- and *trans*-indolizidine structures (the three species are shown in Figure 1) for various amine salts. In this work, some remarkable situations were discovered wherein an unstable trans structure was captured in the solid state, released intact on dissolution, and then transformed into a more stable cis form. Additionally, we have investigated several homologues having 6-, 7-, and 4-membered C rings: 7-phenylhexahydrobenzo[*a*]quinolizines **6a/b** and desphenyl analogue **7**, 8-phenyl-

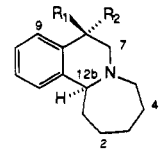


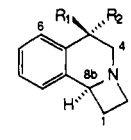
6a R_1 = H; R_2 = Ph

6b R_1 = Ph; R_2 = H

7 $R_1 = R_2$ = H

hexahydroazepino[2,1-*a*]isoquinolines **8a/b**, and 5-phenyltetrahydroazeto[2,1-*a*]isoquinolines **9a/b**, respectively.





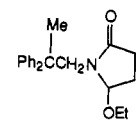
8a R_1 = H; R_2 = Ph

8b R_1 = Ph; R_2 = H

9a R_1 = H; R_2 = Ph

9b R_1 = Ph; R_2 = H

Chemical Synthesis. A 55:45 mixture of lactams **1a** and **1b** was produced via *N*-acyliminium ion cyclization of 5-ethoxypyrrolidin-2-one **10**, obtained from succinic anhydride and 2,2-diphenylpropylamine.[6a] Borane–THF reduction of the individual lactams furnished amines **2a** and **2b**.



10

The syntheses of compounds **3a/b**, **5**, **6a/b**, **8a/b**, **9a/b**, **16b**, and **17a/b** have already been reported by us.[4a,6a]

For the synthesis of **4a–4c**, the lactam (3-one) precursor was obtained by cyclization of **11** (from $Ph_2CHCH(Me)NH_2$ and

(3) (a) Csaky, T. Z. *Cutting's Handbook of Pharmacology*, 6th ed.; Appleton-Century-Crofts: New York, 1979. (b) Wolfe, M. E., Ed. *Burger's Medicinal Chemistry*; 4th ed.; Wiley: New York, 1979; Parts I–III.

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(5) Tertiary amines are generally protonated to the extent of 90–98% under physiological conditions (pH 7.3); thus, the protonated form is important in consideration of biological activity. E.g., see: Chrzanowski, F. A.; McGrogan, B. A.; Maryanoff, B. E. *J. Med. Chem.* **1985**, *28*, 399.

(6) (a) Maryanoff, B. E.; McComsey, D. F.; Duhl-Emswiler, B. A. *J. Org. Chem.* **1983**, *48*, 5062. (b) Maryanoff, B. E.; McComsey, D. F.; Almond, H. R., Jr.; Mutter, M. S.; Bemis, G. W.; Whittle, R. R.; Olofson, R. A. *Ibid.* **1986**, *51*, 1341. (c) Maryanoff, B. E.; McComsey, D. F. *Tetrahedron Lett.* **1979**, 3797.

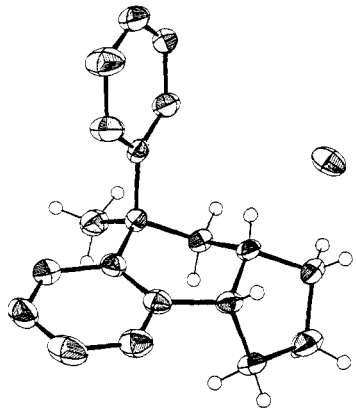


Figure 2. Molecular structure of **2a**·HBr from X-ray analysis (ORTEP drawing).

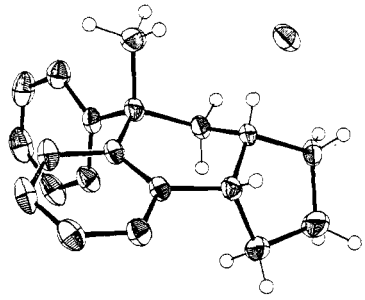


Figure 3. Molecular structure of **2b**·HBr from X-ray analysis (ORTEP drawing).

succinic anhydride) in polyphosphoric acid (PPA) at 100 °C (Scheme I).[4a,6] Three diastereomeric lactams, **12a–12c**, were produced in a 4:2:1 ratio; the fourth possible diastereomer was absent.[7] The compounds were separated by preparative HPLC and reduced with borane–THF to the corresponding amines, which were purified as acid-addition salts.[4a] X-ray analysis of major lactam **12a**[8] and amine salt **4c**·HBr (vide infra), which corresponds to minor lactam **12c**, established the respective stereochemistry.

Known[9] compound **7** was prepared by the *N*-acyliminium sequence on 1-(2-phenethyl)glutarimide, followed by borane reduction.

Stereochemical Background. There are three possible arrangements for the B–C ring fusion in the tricycles of interest here: one trans and two cis forms, the latter of which we designate cis A and cis B. These structures are depicted for the pyrroloisoquinoline class by structures **13–15**, respectively (Figure 1). The two cis-fused structures represent true conformations, which are in dynamic equilibrium in solution at normal temperatures because of rapid bond rotation that interconverts the two tetrahydroisoquinoline half-chair conformers; however, the trans and cis structures can interconvert only through fission of the N–H bond (i.e., via dissociation to free bases and recombination to salts). In the case of the free bases, all three species can interconvert by means of rapid pyramidal inversion at nitrogen and/or inversion of half-chair conformers; thus, the free amines truly represent three conformers. Since the breaking of the N–H bond is facile under ambient conditions, from time to time we may loosely refer to the three salt structures (e.g., **13–15**) as "conformers" or "conformations".

(7) The relative amount of these lactams is likely determined by a complex balance of various steric interactions.[6] The fourth possible lactam, which was not produced, would have developed adverse A(1,3) strain due to an equatorial 5-methyl group and adverse 1,3 syn-axial interactions in the intermediate arenium ion due to an axial 6-phenyl group. For the minor product **12c**, the cyclization would experience adverse A(1,3) strain due to the 5-methyl group. The preference for **12a** over **12b** is difficult to explain, but it may involve buttressing between the methyl and phenyl substituents and steric interaction between the phenyl group and H7.

(8) Details of this X-ray analysis are presented in the Experimental Section and the supplementary material.[34]

(9) Brown, D. W.; Dyke, J. F.; Sainsbury, M.; Lugton, W. G. D. *Tetrahedron* **1970**, *26*, 4985.

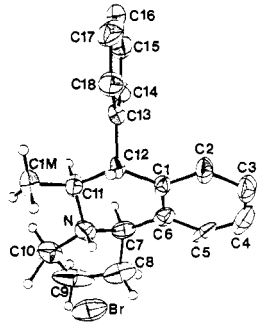


Figure 4. Molecular structure of **4c**·HBr from X-ray analysis (ORTEP drawing showing the atom numbering scheme).

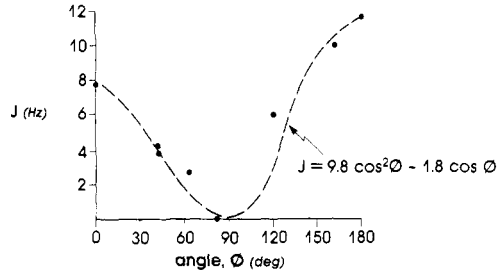


Figure 5. Angular dependence of ^3J(CH–NH) values from ref 10.

X-ray Diffraction Studies of Pyrroloisoquinolines. As mentioned above, X-ray analyses were performed on the HBr salts of **2a** and **2b**, molecular structures for which are presented in Figures 2 and 3, respectively. In both structures, the tetrahydroisoquinoline portion adopts a half-chair conformation with an axial NH group and the B–C ring fusion has the cis B arrangement (viz. **15**). The phenyl substituent in **2a**·HBr is oriented axially with its face directed toward the midpoint of the C10b–N bond, while the phenyl group in **2b**·HBr is equatorial and orthogonal to the plane of the tetrahydroisoquinoline. So, the cis B conformation in the solid state is independent of the positioning of the C6 substituents.

Compound **16b**·HBr, which lacks the 6-methyl group, also possesses the same gross structure in the solid state: a half-chair tetrahydroisoquinoline conformation, a cis B ring fusion, and an equatorial 2-chlorophenyl group (skewed ca. 30° from orthogonality).[4a]

The HBr salt of **4c** was found to have a half-chair tetrahydroisoquinoline system with equatorial methyl and phenyl groups and axial NH and H10b groups. The molecular structure is displayed in Figure 4. Although this salt adopts a trans B–C ring junction, that arrangement is probably imposed by crystal-packing forces. As discussed below, dissolution of **4c**·HBr involves transformation of this trans form to a more stable cis A form. In fact, the X-ray analysis of **4c**·HBr was originally carried out to support interpretation of its unusual NMR behavior (vide infra).

^{1}H NMR Studies. The HBr salts of **2a/b**, **3a/b**, **4c**, **5**, **6a/b**, **7**, **8a/b**, **9a/b**, and **17a**, HCl salts of **4a** and **17b**, and saccharin salt of **4b** were examined by 360-MHz ^{1}H NMR in deuteriochloroform at ambient probe temperature. Exchange of the NH was slow on the NMR time scale under the experimental conditions (slow-exchange limit), except for **2a/b**·HBr and **4b**·saccharin. Therefore, the NH resonances and the vicinal ^3J(CH–NH) coupling constants were generally recorded in their entirety. Selected ^{1}H NMR parameters for these salts, deduced with the aid of 2D homonuclear COSY and/or homonuclear decoupling, are collected in Table I. The COSY technique was particularly useful in analyzing mixtures of two isomeric species. Selected ^{1}H NMR data for some corresponding free bases and lactams (including **18a** and **18b** for reference purposes) appear in Table II; selected ^{13}C NMR data appear in Table III.

The key to understanding the stereochemical behavior of the amine salts in solution rests with the ^3J(CH–NH) values. Al-

Table I. Selected ^{1}H NMR Data for Amine Salts[a]

	chemical shifts (δ)									coupling constants (Hz)										
cmpd[b]	H3a	H3e	H5a	H5e	H6a	H6e	NH4	H10b	H7	5a,6e	5e,6e	5a,6a	5e,6a	4,3a	4,3e	4,5a	4,5e	4,10b	1,10b	1,10b	major forms[c]
2a·HBr[c]	2.91	4.28	3.08	4.15		(1.83)	*d*	4.75	7.32					*d*	*d*	*d*	*d*	*d*	~7	~7	cis A/B ?
2b·HBr	2.97	4.15	3.42	3.42	(2.01)		*d*	5.06	6.90					*d*	*d*	*d*	*d*	*d*	9	7	cis A ?
3a·HBr	2.87	4.08	3.09	4.04	5.20		11.97	4.41	6.93			11	6.9	~7	~3	10	0	~10	~12	~6	trans[f]
3a′·HBr	3.28	3.91	3.62	3.48	4.26		12.38	5.24	6.82			12.3	4.8	7.6	6.5	3.5	1.9	6.4	7.0	6.4	cis A[g]
3b·HBr	3.00	4.09	3.12	3.69	4.82		12.39	4.94	6.81			11.8	4.4	~4	5.8	11.7	3.8	6.5	10.4	7.1	cis B
4a·HCl	2.83	3.80	3.04	(1.19)	4.15		11.87	4.78	6.38			10.3		~5	~6	~8		~6	~10	~8	cis B
4b·saccharin	2.64	3.63	3.11	(1.17)	3.90		*d*	5.18	>7.0	2–3				*d*	*d*	*d*		*d*	~7	~7	cis A/B ?
4c·HBr	2.93	4.10	3.47	(1.56)	4.74		11.75	4.45	6.79			11.0		8.8	4.9	9.6		10.3	12	~7	trans[h]
4c′·HBr	3.21	3.66	3.94	(1.42)	3.96		12.07	5.34	6.71			~11		~8	6	~2		0	4	4	cis A[i]
5·HBr	~2.90	4.04	3.10	3.85	~2.95	~2.95	11.45	4.25	>7.0	*j*	*j*	*j*	*j*	~7	3.0	~11	<1	10.3	11.6	6.7	trans[k]
5′·HBr	3.05	3.97	3.12	3.61	3.30	2.95	12.06	4.92	>7.0	3.6	6.6	9.0	4.0	~9	5.9	~6	3.3	6.2	7.3	7.2	cis A[l]
17a·HBr	2.91	4.08	3.28	3.98	5.82		12.07	4.44	>7.0			10.6	8.7	8.2	4.0	~6	~1	9.7	10.8	6.6	trans[m]
17a′·HBr	3.28	3.88	3.42	3.88	5.04		12.52	5.21	6.87			12.7	4.8	7.5	*n*	1.5	*n*	5.8	7.0	4.9	cis A[o]
17b·HCl	3.05	4.06	3.40	3.60	5.50		13.52	4.87	6.68			11.8	4.6	3.1	5.5	10.2	3.2	~6	10.2	~8	cis B[p]
17b*·HCl	3.09	4.06	3.49	3.74	5.51		13.45	4.85	6.71			11.6	5.1	2.0	5.5	10.4	2.9	~5	~10	~8	cis B[p]
	H4a	H4e	H6a	H6e	H7a	H7e	NH5	H11b	H8	6a,7e	6e,7e	6a,7a	6e,7a	5,4a	5,4e	5,6a	5,6e	5,11b	1,11b	1,11b	
6a·HBr	2.89	3.67	3.12	3.61	5.39		11.54	4.31	6.85			12.0	5.7	10.2	<1	11.9	<1	10.0	11.2	<1	trans[q]
6a′·HBr	3.13	3.37	3.52	3.61	4.42		11.94	4.98	6.98			12.2	7.4	11.8	<1	2.6	2.4	<1	~5	~2	cis A[r]
6b·HBr	3.37	3.54	3.59	3.39	5.06		12.10	4.45	6.83			12.0	6.5	~2	2–3	10.6	<1	3	12	~2	cis B
7·HBr	2.92	3.67	3.10	3.62	4.09	2.86	11.17	4.14	>7.0	3.5	<1	11	6	10	2	10	1	10	12	1	trans[s]
7′·HBr	3.15	3.35	3.53	3.47	3.44	3.08	11.72	4.58	>7.0	*j*	*j*	*j*	*j*	5.5	2.6	5.4	~2	2.6	7.3	4.3	cis A[t]
	H5a	H5e	H7a	H7e	H8a	H8e	NH6	H12b	H9	7a,8e	7e,8e	7a,8a	7e,8a	6,5a	6,5e	6,7a	6,7e	6,12b	1,12b	1,12b	
8a·HBr	~2.98	3.75	3.03	3.65	5.32		11.18	4.58	6.77			12.0	3.8	*j*	~3	~10	2.8	9.0	9.0	<1	trans[u]
8a′·HBr	3.27	3.49	~3.6	~3.6	4.38		11.50	5.08	6.87			12.5	6.0	~8	~2	~2	*j*	~3	6.6	6.6	cis A[v]
8b·HBr	2.80	3.90	3.20	3.41	4.98		12.00	4.74	6.79			12.1	5.8	~9	4.6	10.1	0	3.7	9.0	0	cis B
	H2a	H2e	H4a	H4e	H5a	H5e	NH3	H9b	H6	4a,5e	4e,5e	4a,5a	4e,5a	3,2a	2,2e	3,4a	3,4e	3,9b	1,9b	1,9b	
9a·HBr	3.95	4.67	3.45	3.45	4.48		12.01	5.83	6.86			*w*	*w*	1–2	~4	0–4[x]	0–4[x]	~6	~8	~8	cis A
9b·HBr	3.55	4.75	3.41	3.85	4.41		11.86	5.92	6.82			10.6	3.3	~4	7.0	8.8	5.0	6.8	8.8	8.8	cis B

[a] ^{1}H NMR data were obtained in $CDCl_3$ at 360 MHz, usually at ambient probe temperature. Proton assignments were made and *J* values were confirmed by extensive homonuclear decoupling and/or homonuclear COSY 2D NMR experiments. Chemical shift values in parentheses are for methyl groups. [b] The prime denotes a second species that arises in the sample with time. The asterisk denotes a second conformer present originally because of hindered rotation of the appended aryl group about the sp^2–sp^3 linkage on the NMR time scale (see text). The diastereomers **17b**·HBr and **17b***·HBr were present in a ratio of 77:23. [c] Determined at −55 °C, where the spectral lines were sharper. [d] The NH resonance or *J* value was indeterminate due to rapid N–H exchange. [e] Structure suggested to comprise at least 85% of the material in solution for the particular measurement, unless noted otherwise. A "?" indicates some uncertainty in the assignment due to an incomplete set of spectral parameters. [f] Composition: **3a**:**3a′** = 75:25. [g] Composition: **3a**:**3a′** = ca. 10:90. [h] Composition: **4c**:**4c′** = ca. 95:5. [i] Composition: **4c**:**4c′** = ca. 10:90. [j] Could not be ascertained. [k] Composition: **5**:**5′** = 30:70. [l] Composition: **5**:**5′** = ca. 5:95. [m] Composition: **17a**:**17a′** = ca. 90:10. The tetrahydroisoquinoline ring adopts a boat conformation to a great extent (see text). [n] Because of overlap of resonances for H3e and H5e, *J* values could not be measured. The sum of *J*(4,3e) and *J*(4,5e) was estimated to be ca. 6 Hz. [o] Composition: **17a**:**17a′** = ca. 10:90. [p] **17b** and **17b*** are diastereomers that differ by aryl rotation (see footnote *b*). [q] Composition: **6**:**6′** = >95:5. [r] Composition **6**:**6′** = 80:20. [s] Composition: **7**:**7′** = 30:70. [t] Composition: **7**:**7′** < ca. 5:95. [u] Composition: **8a**:**8a′** = ca. 90:10. [v] Composition: **8a**:**8a′** = 45:55. [w] $[J(4,5) + J(4',5)]/2$ = 7.0 Hz; in DMSO-d_6, *J*(4a,5a) = 8.9 Hz and *J*(4e,5a) = 4.1 Hz. [x] $[J(2,3) + J(2',3)]/2$ = 2 Hz.

Table II. Selected ^{1}H NMR Data for Amines and Lactams[a]

	chemical shifts (δ)							coupling constants (Hz)					
compd	H5a	H5e	H6a	H6e	H10b	H7	Me	5a, 6e	5e, 6e	5a, 6a	5e, 6a	1, 10b	major forms[b]
2a[c]	2.69	3.03			3.30	>7.0	1.68					10, 6	trans
2b[c]	2.53	3.11			3.47	>7.0	1.71						trans
3a[c]	2.65	3.46	4.40		3.53	6.83				10.5	6.5	8, 8	trans
3b[c]	~3.0	~3.0		4.19	3.56	6.89		5	5			9, 7	trans
4a	3.05		3.77		3.95	6.72	1.03	.....	.....	5.5	.....	9, 7	B/T[d]
4b	3.30			4.33	4.28	>7.0	0.94	4.7				7, 7	cis B
4c	3.30			3.87	3.55	6.69	1.15			10.8		7, 7	trans
1a	3.32	4.05			4.88	~6.8	1.64					11, 6	
1b	3.06	4.41			4.82	~6.9	1.76					10, 6	
18a	3.06	4.44	4.15		4.92	~6.8				11	6	9, 7	
18b	3.43	4.29		4.22	4.88	~7.0		4	1			9, 7	
12a		4.54		4.00	4.84	6.87	1.29	.....	1	.....		9, 7	
12b		4.62		4.42	4.94	7.02	0.96	.....	6	.....		8, 8	
12c		4.72		4.11	4.39	>7.0	1.21	.....	1.5	.....		10, 5	*e*
	H6a	H6e	H7a	H7e	H11b	H8		6a, 7e	6e, 7e	6a, 7a	6e, 7a	1, 11b	
6a[c]	2.59	3.05	4.42		3.26	6.77				12	6	*f*	trans
6b[c]	~2.9[g]			4.01	3.24	6.94		*g*	*g*			12, 1	trans
	H7a	H7e	H8a	H8e	H12b	H9		7a, 8e	7e, 8e	7a, 8a	7e, 8a	1, 12b	
8a[c]	~2.9	3.19	4.20		3.99	6.75				9.0	4.6	9, 4	trans
8b[c]	~3.0	~3.0	4.00		4.19	6.82				8.8	3.7	8, 7	cis B
	H4a	H4e	H5a	H5e	H8b	H6		4a, 5e	4e, 4e	4a, 5a	4e, 5a	1, 8b	
9a	2.86	3.01	4.28		4.92	6.8				10.8	5.3	8, 4	cis A
9b	3.05	3.46	4.02		5.15	6.73				10.4	4.0	7, 6	cis B

[a] ^{1}H NMR spectra were generally obtained at 90 MHz (**1a**, **1b**, **18a**, and **18b**) or 360 MHz (other compounds) in $CDCl_3$ at ambient probe temperature. Homonuclear decoupling or homonuclear 2D COSY was employed when necessary to make an assignment. [b] Structure suggested to comprise at least 85% of the material in solution, unless noted otherwise. [c] IR spectra were recorded to evaluate Bohlmann bands (cm^{-1}): **2a**, 2791, 2735; **2b**, 2789, 2736; **3a**, 2796, 2745, 2730; **3b**, 2787, 2734; **6a**, 2801, 2755; **6b**, 2795, 2756; **8a**, weak; **8b**, weak (see ref 1b and 12). [d] B = cis B; T = trans. The trans form must possess a boat tetrahydroisoquinoline ring. [e] The isoquinoline ring is probably in a boat rather than a half-chair conformation (see ref 6b), due to A(1,3) strain between the 5-methyl and carbonyl groups. [f] Values could not be determined. [g] Protons H6a, H6e, and H7 defined a second-order ABX system; the AB pattern for H6a and H6e was centered at 2.89 ppm with a $\Delta\nu$ of ca. 2 Hz. The coupling constants for H6a, H6e, and H7 could not be read directly from the spectrum.

Table III. ^{13}C NMR Data for Selected Pyrroloisoquinolines[a]

cmpd	C1	C2	C3	C5	C6	C6a	C10a	C10b	C1′	Me
1a	31.6	27.9	173.3	51.0	44.4	143.5	137.1	57.1	146.0	27.7
1b	31.5	28.3	172.5	50.4	43.1	140.6	137.1	57.5	147.3	26.4
18a	31.6	28.8	172.9	44.6	45.4	137.8[b]	137.2[b]	57.0	141.8	
18b	31.7	28.7	173.1	44.1	44.4	135.5	137.6	56.8	143.5	
2a	29.7	21.7	53.9	65.8	45.3	143.4	138.4	64.9	148.8	29.4
2b	30.7	22.2	54.1	64.4	44.0	142.9	138.8	64.6	150.5	27.8
3a	30.4	22.0	53.0	58.3	45.4	139.3	137.6	64.0	144.3	
3b	30.4	22.3	54.3	56.2	46.2	139.0	137.3	63.6	146.0	
2a·HBr	30.9	22.7	57.5[b]	58.6[b]	42.4	139.3	131.5	60.4	142.1	27.5
2b·HBr	32.9	22.3	56.0[b]	59.0[b]	42.7	139.3	130.8	61.1	144.0	28.3
3a·HBr	34.2	23.0	51.7[b]	52.0[b]	38.5[c]	134.9	132.0	61.0[d]	138.3	
3b·HBr	32.1	22.5	53.4[b]	55.5[b]	42.8[e]	135.3	131.4	61.5[f]	138.5	

[a] ^{13}C NMR spectra were obtained in $CDCl_3$ at 15.1 MHz; carbon chemical shifts are reported in ppm downfield from Me_4Si. Signal multiplicities were determined by using off-resonance decoupling or INEPT. [b] Pair of signals may be interchanged. [c] ^1J(C–H) = 135.5 Hz. [d] ^1J(C–H) = 149.4 Hz. [e] ^1J(C–H) = 130.9 Hz. [f] ^1J(C–H) = 144.5 Hz.

though this parameter has received just scant attention in the literature, a sufficient foundation has been established to allow stereochemical assignments to be inferred.[10] The important work of Fraser[10a] and Crowley[10b] has provided the necessary information for describing the angular dependence of ^3J(CH–NH) in ammonium salts. As indicated in Figure 5, a Karplus-like relationship, analogous to that associated with ^3J(HC-CH), is manifested by ^3J(CH–NH). Fortuitously, each conformation possesses a unique set of ^3J(CH–NH) values, which exquisitely defines the structure. This can be illustrated for the pyrroloisoquinoline salts (Figure 1) by the following values for J(5a,NH) and J(10b,NH): (1) in the trans form both of these will be large (10–12 Hz); (2) in the cis A form J(5a,NH) will be small (ca. 3 Hz) and J-(10b,NH) will be moderate (ca. 6 Hz); (3) in the cis B form J(5a,NH) will be large (10–12 Hz) and J(10b,NH) will be moderate (ca. 6 Hz). This paradigm will carry over, more or less, to the other ring systems. Certain other parameters can also be of value. Since there is a chair piperidine in the benzoquinolizidines, the J(1,11b) values will differentiate the cis B form from the other two. In the cis forms, particularly the cis A form, the angular proton (H10b, H11b, H12b) tends to resonate at lower field relative to the trans form (Table I).[11] The J(1,10b) parameters are of value in distinguishing the cis A form in the pyrroloisoquinoline class.

We will start with a discussion of the pyrroloisoquinoline derivatives. After failing to acquire readily interpretable ^1H NMR for **2a**·HBr and **2b**·HBr at 360 MHz in deuteriochloroform at different temperatures and in Me_2SO-d_6 or CD_3OD, we examined analogous HBr salts lacking the 6-methyl group. Free bases **3a** and **3b** exploit ^1H NMR and IR (Bohlmann bands) properties indicative of a half-chair tetrahydroisoquinoline ring with a trans B–C ring junction (Table II).[12] The HBr salts are a different story. The ^1H NMR data for **3b**·HBr indicate that it assumes a cis B conformation (viz. **15**), with an equatorial phenyl group, to the extent of at least 90%. In particular, this was characterized by J(5a,6a) = 11.8 Hz, J(4,5a) = 11.7 Hz, and J(4,10b) = 6.5 Hz. On the other hand, **3a**·HBr assumed on initial dissolution a mixture of trans (viz. **13**) and cis A (viz. **14**) conformations in a 75:25 ratio. After it stood for 2–3 h, the mixture converted to an ca. 10:90 ratio of these forms. Presumably, the original composition in solution is imposed by the composition in the solid state. That is to say, the less stable trans form of **3a**·HBr is captured in the solid. One might suppose that **3b**·HBr adopts the cis B conformation to avoid an adverse 1,3 syn–axial interaction between the 6-phenyl and NH groups, although a potentially unfavorable syn–axial interaction between the C3 methylene and H5 is offered in trade. Consequently, the cis B form cannot be said to be intrinsically favored. However, in the case of **3a**·HBr the cis A conformation must be intrinsically preferred over the trans conformation. Many 6-aryl analogues (as HBr or HCl salts) that we have prepared demonstrate similar ^1H NMR behavior.[4a]

To assess the intrinsic predilection for cis structures, we needed to avoid the conformational bias introduced by the 6-phenyl group. Therefore, we studied **5**·HBr. The ^1H NMR spectrum of **5**·HBr just after dissolution showed a mixture of two species in a 30:70 ratio (**5**/**5′**). The transient initial species (**5**) was identified as a trans form by J(4,10b) = 10 Hz, δ(H10b) = 4.25. The second species, which increased over 2–6 h to a level of 95%, possesses a cis A conformation predominantly, as judged by the ^3J(CH–NH) values (Table I). Some cis B form may also contribute to the conformational profile since J(4,5a) is somewhat large and J-(5a,6a) is somewhat small, indicating that averaging is taking place. This indicates that the protonated hexahydropyrroloisoquinoline ring system has a high intrinsic propensity to adopt the cis A conformation and definitely disfavors the trans form. In the case of **3a**·HBr, the cis A form is presumably favored for two reasons: (1) in order to escape the disfavored trans form and (2) because the cis B form would dispose the 6-phenyl group axially.

Salts **4a**–**4c**, which have two biasing substituents, were also studied. Salt **4c**·HBr was particularly interesting. After dissolution of **4c**·HBr in $CDCl_3$, the ^1H NMR spectrum showed trans and cis A forms in a 90:10 ratio, both with a half-chair tetrahydroisoquinoline unit bearing equatorial phenyl and methyl groups. On standing, the ratio gradually changed over several hours until it became constant at a 10:90 ratio (the sample was monitored from time to time by NMR). The equilibration of this compound appeared to be the slowest, possibly due to greater steric hindrance around nitrogen. The rate of interconversion of **4c**·HBr was decreased by addition of a small amount of trifluoroacetic acid but not much affected by a small amount of water. X-ray analysis of **4c**·HBr (vide supra) served to verify the trans structure in the solid state, which apparently is captured by the crystal lattice. This result emphasizes the much greater stability of the cis A form relative to the trans form; however, it does not reflect on the cis B form, generation of which would require an unfavorable diaxial positioning of the phenyl and methyl groups. Salt **4a**·HCl was found to adopt a cis B structure with equatorial 6-phenyl and 5-methyl groups; **4b**·saccharin may be composed of a dynamic mixture of cis A (equatorial 6-phenyl and axial 5-methyl) and cis B conformations (axial 6-phenyl and equatorial 5-methyl). The inability to measure ^3J(CH–NH) values for **4b**·saccharin limited our analysis of the solution components. Nevertheless, support for the presence of cis B form came from the upfield resonance position for the methyl (as seen with **4a**·HCl) and the downfield resonance positions for H7 and H10b; support for the presence of cis A form came from the J(1,10b) values.

The NMR data for **2a**·HBr and **2b**·HBr suggest that each of these molecules adopts predominantly a cis B conformation in solution, with the 6-phenyl group axial in the former and equatorial

(10) (a) Fraser, R. R.; Renaud, R. N.; Saunders, J. K.; Wigfield, Y. Y. *Can. J. Chem.* **1973**, *51*, 2433. (b) Crowley, P. J.; Morris, G. A.; Robinson, M. J. T. *Tetrahedron Lett.* **1976**, 3375.

(11) The deshielding of this type of proton in cis conformers has been noted for related free bases: (a) Maryanoff, B. E.; McComsey, D. F.; Taylor, R. J., Jr.; Gardocki, J. F. *J. Med. Chem.* **1981**, *24*, 79. (b) Uskokovic, M.; Bruderer, H.; von Planta, C.; Williams, T.; Brossi, A. *J. Am. Chem. Soc.* **1964**, *86*, 3364. (c) Gribble, G. W.; Nelson, R. B. *J. Org. Chem.* **1973**, *38*, 2831. (In an equatorial orientation the proton is in the deshielding region of the fused benzene ring.)

(12) For background information on indolizidine conformations, see: (a) Reference 1b; (b) Catka, T. E.; Leete, E. *J. Org. Chem.* **1978**, *43*, 2125.

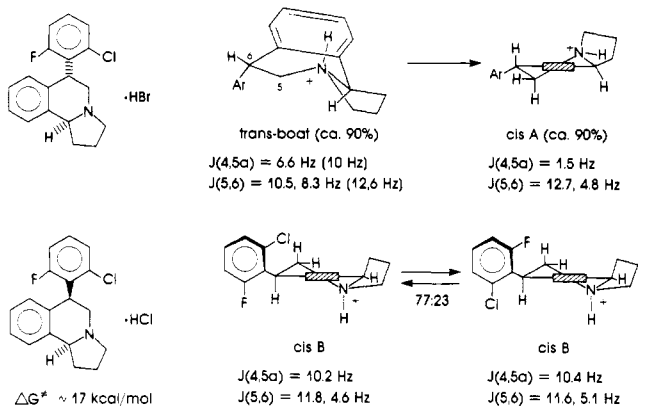


Figure 6. Structures adopted by the salts of **17a** and **17b** and representation of the conformers **17b** and **17b***.

in the latter. Without ^3J(CH–NH) values, we tentatively make this assignment on the basis of the chemical shifts for H7 and H10b. Although these assignments must be regarded as tentative at this time, it is interesting to note that the cis B structures are manifested in the solid state (vide supra).

We also studied salts of **17a** and **17b**, which possess a bulky 2,6-disubstituted C6 aryl group (Table I). The 360-MHz ^{1}H NMR spectrum of **17a**·HBr first showed a trans B–C ring-fused structure to the extent of ca. 90%, as would be expected. However, the tetrahydroisoquinoline moiety does not assume the usual half-chair conformation; rather it exists predominantly in a boat-type conformation (Figure 6). This boat form is characterized chiefly by three features: (1) the J(4,5a) value of 6.6 Hz, instead of ca. 10 Hz; (2) the J(5,6) values of 10.5 (quasi-5a,6a) and 8.3 (quasi-5e,6a) Hz, instead of ca. 11 and 6–7 Hz; and (3) failure of H7 to resonate upfield of 7.0 ppm. Presumably, the bulky 2,6-disubstituted phenyl group suffers severe steric interactions in the equatorial orientation, such as A(1,3) interaction with H7, causing this portion of the molecule to adopt a boat arrangement, wherein the phenyl group is removed from the plane of the tricyclic array (Figure 6). Over several hours, the trans form disappeared and the usual cis A form arose; the cis A form accounted for ca. 90% of the mixture at the end point of isomerization (presumably equilibrium). The 360-MHz ^{1}H NMR spectrum of **17b**·HCl displayed *two cis B structures* in a persistent ratio of 77:23 at ambient probe temperature (ca. 20 °C). The NMR parameters for these two species are closely parallel (Table I), consistent with an assignment of these as rotamers by virtue of hindered rotation about the bond connecting the 2,6-disubstituted phenyl group to the tricyclic network (Figure 6). Although it is not possible to assign which rotamer is which, given the data at hand, we tentatively suggest the structures depicted in Figure 6 for the major and minor forms. For **17b**·HCl, changing the probe temperature from 20 to 60 °C resulted in coalescence of H7 ($\Delta\nu$ = 10 Hz at −20 and +20 °C) with a coalescence temperature (T_c) of ca. 60 °C (other signals, such as those for H5e and H4, were also affected). This coalescence data can be used to *approximate* a rotational barrier of 17 kcal/mol, by employing $\Delta G^{\ddagger} = 4.57T_c[10.02 + \log (T_c/k_c)]$ with $k_c = 2.2\Delta\nu$.[13a,b]

The free bases **17a** and **17b** exist mainly as trans and cis B forms, respectively, in chloroform solution. Compound **17b** is anomalous not only for favoring a *cis B form* but also because it exists as two rotamers (ca. 3:1) in the 360-MHz ^{1}H NMR spectrum, in analogy with its HCl salt. Hallmark parameters in support of this assignment for **17b** are the following: the absence of Bohlmann bands, in contrast to **17a** (IR bands at 2816 and 2745 cm^{-1}; 4% wt/vol in $CHCl_3$), the presence of two H7 resonances upfield of δ 7.0 (ca. 6.73 ppm) and two H10b resonances at a position substantially downfield relative to **17a** (major at δ 4.02 and minor at δ 4.07; also, H6 occurred as a major dd at δ 5.02 (J = ca. 5, 10 Hz) and a minor dd at δ 5.06 (J = ca. 5, 11 Hz) indicative of an equatorial aryl group. For **17b** the bulky 2,6-disubstituted phenyl group is presumably disfavored when axially disposed in the trans form; thus, the cis B form with an equatorial aryl group is favored. In this case, a boat-type form is not prevalent, possibly because an unfavorable geometry would have to be adopted by the cis-fused pyrroloisoquinoline system. In connection with this view, one should note that the aforementioned boat structure for **17a**·HBr was observed only for the trans form of this compound, not for the cis A form. ^{1}H NMR data for **17a** indicate that it has a trans B–C ring junction and that it may adopt a boat form to some degree in combination with a half-chair form (H10b, dd at 3.52 ppm with J = 8, 8 Hz; H6, dd at 5.14 ppm with J = ca. 7, 9 Hz; H7, d at 6.75 ppm with J = 7.6 Hz).

After recording the rotamers for **17b**·HCl, we examined 2-chloro derivative **16b**·HBr (McN-5707-14). The 360-MHz ^{1}H NMR spectrum of this compound at ambient probe temperature showed broad envelopes for most of the signals instead of sharp resonances. We suspected that this was caused by slow interconversion of two rotamers, as discussed above, rather than by an N–H exchange process. Indeed, an NMR spectrum at −20 °C exhibited sharp signals for two species in a 55:45 ratio (integration of the NH resonances at δ 12.38 and 12.22, respectively), and a spectrum at 60 °C exhibited a single set of sharp signals, an NMR time-averaged situation. At the low temperature, the chemical shift difference between the signals for H7 in the two species of **16b**·HBr is 20 Hz ($\Delta\nu$). Given a coalescence temperature of ca. 0 °C for the two H7 signals, the activation free energy for this two-site exchange is in the range of 14–15 kcal/mol.[13]

Benzo[*a*]quinolizidines **6a** and **6b** (free base forms) have ^{1}H NMR (and IR) properties indicative of a tetrahydroisoquinoline half-chair conformation, a chair piperidine, and a trans ring fusion, with an equatorial or axial 7-phenyl group (Table II).[14] ^{1}H NMR data for the HBr salt of **6a** show that it adopts the trans conformation to the extent of >98% on initial examination in $CDCl_3$ but changes to an 80:20 trans–cis A mixture on standing for 22 h (end point). This behavior is related, but not quantitatively correspondent, to the observations with **3a**·HBr. By contrast, **6b**·HBr adopts a cis B form to the extent of at least 90%, in close analogy to the results for **3b**·HBr. Both salts appear to contain half-chair tetrahydroisoquinoline and chair piperidine rings, with an equatorial 7-phenyl substituent. The bias for the cis B form, as with **3b**·HBr, can again be attributed to alleviation of 1,3 steric interaction between an axial 7-phenyl substituent and an axial proton on nitrogen.

For the benzoquinolizidine series we also evaluated the parent compound, **7**·HBr, by 360-MHz ^{1}H NMR. One major species, present to the extent of ca. 95%,[15] was detected at first. The minor constituent gradually increased over 2–4 h, at the expense of the major species, to give ultimately an ca. 65:35 mixture enriched in the first species. The two forms were assigned trans and cis A structures, respectively, on the basis of ^3J(CH–NH) and J-(1,11b) values. Given this data, the protonated benzo[*a*]-quinolizidine system has, surprisingly, only a modest intrinsic preference for the trans form.

The azepino[2,1-*a*]isoquinolines, **8a**·HBr and **8b**·HBr, behaved somewhat more like the corresponding pyrroloisoquinolines, **3a**·HBr and **3b**·HBr. Salt **8a**·HBr initially gave a mixture of trans and cis A forms, with an equatorial 8-phenyl substituent, in a ratio

(13) (a) Kost, D.; Carlson, E. H.; Raban, M. *J. Chem. Soc. D* **1971**, 656. Sandstrom, J. *Endeavour* **1974**, *33*, 111. Sandstrom, J. *Dynamic NMR Spectroscopy*; Academic Press: London, 1982. Greenberg, A. *J. Chem. Educ.* **1972**, *49*, 575. (b) This equation for two-site exchange of nuclei applies to equal populations of species and to uncoupled nuclei. Thus, we are necessarily making an approximation here (±1 kcal/mol). (c) Given a T_c for the NH signals of **16b**·HBr of ca. 30 °C and a $\Delta\nu$ of ca. 60 Hz, we estimate a $\Delta G^{\ddagger}$ in the vicinity of 14–15 kcal/mol. However, this parameter may be limited because the NH chemical shift is fairly sensitive to temperature.

(14) For background information on benzo[*a*]quinolizidine cis and trans conformations, see: References 1d and 7a–7c.

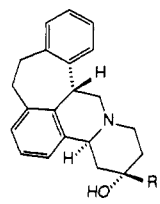
(15) Some variability was experienced with different samples of **7**·HBr. The NMR spectrum of a sample of **7**·HBr, recrystallized from 2-propanol and dried in air at 23 °C (mp 247–249 °C), exhibited the major trans-fused species to the extent of 95%. Enhancement of the minor component to 30% occurred on drying this sample for 24 h at 80 °C in vacuo (mp 248–249 °C).

of ca. 90:10. However, the original mixture slowly converted to a 45:55 final ratio on standing for several hours at 23 °C. Again, a special selection is achieved by sequestration of the trans form in the solid phase. Still, the 7-membered ring system does not exhibit as strong a bias for the cis A form compared to the 5-membered ring system. Salt **8b**·HBr was found to assume a cis B conformation with an equatorial 8-phenyl group, in solution. The free bases, **8a** and **8b**, largely adopted the trans and cis B conformations, respectively. It is intriguing that **8b** does not favor a trans form, in contrast to its congeners **3b** and **6b**. Whether the trans conformer with an axial 8-phenyl group and equatorial B–C ring at C12b is destabilized or the cis B conformer with an equatorial 8-phenyl and axial B–C ring at C12b is stabilized, relative to the other ring systems, is unclear at this time.

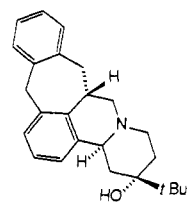
^{1}H NMR data for azeto[2,1-*a*]isoquinolines **9a**·HBr and **9b**·HBr revealed cis A and cis B structures with an equatorial 5-phenyl group, respectively. Analysis of the data for **9a**·HBr was complicated by isochrony of H4a and H4e in $CDCl_3$. The disposition of the free bases, **9a** and **9b**, paralleled the salts in this case, presumably due to the influence of ring strain associated with the fusion of 4- and 6-membered rings.

Related Protonated Bridgehead Amines in the Chemical Literature. Some configurational/conformational data on amine salts analogous to the salts discussed herein are scattered about the chemical literature.[4b,e,16] We have collected several relevant examples in this subsection for the purposes of background and comparison. Most of the available information pertains to structures in the solid state rather than in solution and comes from isolated cases rather than systematic studies.

Several salts encompassing the benzo[*a*]quinolizidine substructure have been examined by X-ray crystallography. Dexclamol (**19**),[16f] butaclamol (**20**),[16f] and isobutaclamol (**21**),[16g]

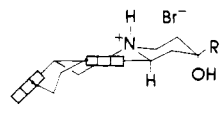


19 R = *i* Pr
20 R = *t* Bu



21

representatives of a series of potent neuroleptics, were studied as hydrobromide salts. The closely related compounds **19**·HBr and **20**·HBr show a trans ring junction (similar to that of the free base deoxybutaclamol in the solid state[17]); however, **21**·HBr adopts a cis B structure with axial benzylic and NH groups on the tetrahydroisoquinoline array (cf. representations **22** and **23**). The HBr



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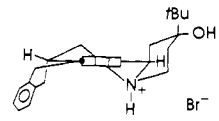
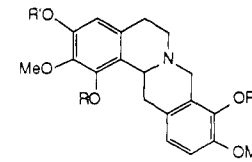
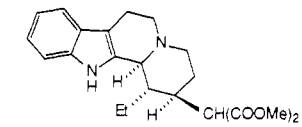


23

salts of the dibenzoquinolizidine (tetrahydroprotoberbine) alkaloids capaurine (**24a**) and **24b** exhibit a cis A structure,[16a] as does the HBr salt of indoloquinolizidine alkaloid **25**, in which there are diaxial malonyl and ethyl substituents (the form favored by the free base in solution).[16h]

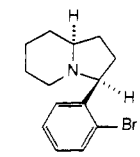


24a R = H; R' = Me
24b R = Me; R' = H



25

X-ray analyses for several salts of saturated systems have been reported.[4b,4e,16b–e] The salts (HCl, HCl, HBr, and HCl, respectively) of indolizidine derivatives **26** (McN-5195),[4b] **27**,[4e] **28** (gephyrotoxin),[16c] and **29**[16d] show a trans ring fusion. The hydrobromide salt of the ansa compound vertaline (**30**), which contains a quinolizidine nucleus, prefers a cis A structure,[16b] but quinolizidine salts of **31a** and **31b** (with binaphthyl phosphoric acid) possess a trans ring fusion.[16e]



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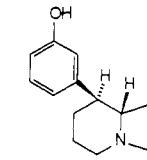
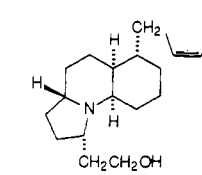
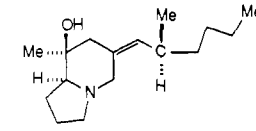


27



28



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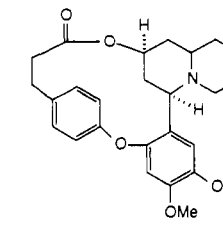

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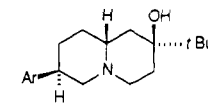
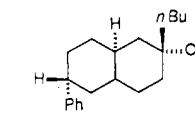
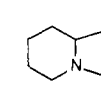


31a Ar = 2,4-Cl_2-C_6H_3



31b

A 360-MHz ^{1}H NMR study of the HBr salt of indolizidine (**32**) revealed a trans ring geometry in $CDCl_3$ solution; indolizidine free base also adopts the trans conformation nearly exclusively.[18] A high preference for a trans form was also observed for **26**·HBr by 360-MHz ^{1}H NMR in our laboratories.[4b,19]



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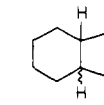


33

Source of the Preference for Cis-Fused Protonated Bridgehead Amines. The adoption of cis-fused structures by amine salts in the solid state is not particularly bothersome since that behavior could be attributed to crystal-packing forces. Such forces, which operate in the range of 1–2 kcal/mol, are sufficient to favor a cis form even when it is not intrinsically more stable. However, we may ask ourselves the reason for the preference of cis forms in solution in the absence of any driving force, such as the adverse placement of substituents.

It is possible that some understanding here might be achieved by reference to empirical force field (EFF) calculations. Such conformational energy calculations with MM2 have already been

(16) (a) Shimanouchi, H.; Sasada, Y.; Ihara, M.; Kametani, T. *Acta Crystallogr., Sect. B* **1969**, *25*, 1310. Shimanouchi, H.; Sasada, Y.; Wakisaka, K.; Kametani, T.; Ihara, M. *Ibid.* **1970**, *26*, 607. (b) Hamilton, J. A.; Steinrauf, L. K. *J. Am. Chem. Soc.* **1971**, *93*, 2939. (c) Daly, J. W.; Witkop, B.; Tokuyama, T.; Nishikawa, T.; Karle, I. L. *Helv. Chim. Acta* **1977**, *60*, 1128. (d) Daly, J. W.; Tokuyama, T.; Fujiwara, T.; Highet, R. J.; Karle, I. L. *J. Am. Chem. Soc.* **1980**, *102*, 830. (e) Imhof, R.; Kyburz, E.; Daly, J. J. *J. Med. Chem.* **1984**, *27*, 165. (f) Bird, P. H.; Bruderlein, F. T.; Humber, L. G. *Can. J. Chem.* **1976**, *54*, 2715. (g) Humber, L. G.; Philipp, A. H.; Voith, K.; Pugsley, T.; Ahmed, F. R.; Przybylska, M. *J. Med. Chem.* **1979**, *22*, 899. (h) Chiaroni, A.; Riche, C.; Grierson, D. S.; Husson, H.-P. *Can. J. Chem.* **1985**, *63*, 2979. (Steric features involved in the conformational behavior are discussed.)

(17) Fortier, S.; Przybylska, M.; Humber, L. G. *Can. J. Chem.* **1980**, *58*, 1444.

(18) Ringdahl, B.; Pinder, A. R.; Pereira, W. E., Jr.; Oppenheimer, N. J.; Craig, J. C. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1.

(19) Mutter, M. S.; Carson, J. R., unpublished results.

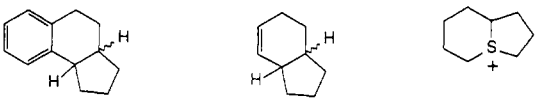
conducted on protonated forms of butaclamol and isobutaclamol (**20** and **21**) by Froimowitz and Matthysse.[20a] Cis B forms, in which the tetrahydroisoquinoline network bears axial phenyl and NH groups and an equatorial H11b, were found to be preferred by 1.4–1.9 kcal/mol; yet the trans arrangements were suggested to be important for neuroleptic activity.[20a] On the basis of our body of NMR results, we believe that the cis B form would not be favored under real conditions in solution. If any cis form were to be adopted, it would more likely be the cis A form.

To follow up on this point, we sought to study butaclamol hydrochloride (**20**·HCl) by ^{1}H NMR. Unfortunately, **20**·HCl is very insoluble in $CDCl_3$, so we could not collect adequate data in our preferred solvent. However, **20**·HCl did dissolve, albeit sparingly, in Me_2SO-d_6. The 360-MHz ^{1}H NMR spectrum (NH couplings italicized) of the dilute solution revealed two species in a ratio of 81:19, as determined by the NH resonances at 9.72 (minor) and 10.92 (major) ppm, as well as the "H11b" (actually H4a for this pentacyclic ring system) resonance of the minor form at 5.11 ppm (J = 5.3, 0, *0* Hz) vs the "H7" (actually H13b) resonance of the major form at 5.42 ppm (J = 5.7, 12.8 Hz). This is virtually the same end point (presumably equilibrium) that we registered for **6a**·HBr in $CDCl_3$. Other readily assigned resonances for the major species were as follows: δ 4.80 (ddd, "H11b", J = 10.7, *9.5*, ca. 1 Hz), 4.19 (ddd, "H6a", J = 12.4, 12.4, *12.1* Hz), 3.72 (ddd, "H6e", J = 12.1, 6.0, ca. *1* Hz). For the minor species they were as follows: δ 4.65 (dd, "H7", J = 11.9, 3.6 Hz). This evidence readily permits the assignment of the trans form to the major species. Moreover, given the close analogy that exists between these results and those for **6a**·HBr, we suggest that the minor species of **20**·HCl in Me_2SO-d_6 solution is the cis A form. Consequently, the cis B form of protonated butaclamol has little relevance under these conditions.

Since the MM2 calculations on protonated butaclamol and isobutaclamol indicate that the cis B form is preferred by a considerable margin,[20a] there seems to be a problem with the application of computational methods here.[20b] Perhaps, this difficulty is associated with correlating the MM2 gas-phase results (applicable to "isolated" molecules) with solution phenomena involving polar or charged species (i.e., ammonium salts). Also, there may be an intrinsic problem with performing MM2 calculations on such chemical entities (e.g., incomplete parametrization for ammonium ions or domination by coulombic terms with same). Therefore, for additional understanding of the origin of the configurational/conformational effects, we decided to explore MM2 calculations on hydrocarbon systems that parallel the ammonium systems in this paper.

The hydrocarbon hydrindan (**33**), which corresponds to protonated indolizidine (**32**·HX), not only has been treated already by MM2[21a] but has also been studied by experiment.[21b] The MM2 and experimental energies (heats of formation (ΔH), at 25 °C in the gas phase) for each of the two isomers are in excellent agreement and indicate a substantial preference (by 1.0–1.2 kcal/mol) for the trans conformation (calcd vs exptl (kcal/mol): trans, −31.63 vs −31.45; cis, −30.46 vs −30.41).[21] Since there is a significant difference in entropy between the cis and trans isomers of **33**, which is absent in the protonated indolizidines, the free energy for **33** will reflect an extra stabilization of the cis isomer relative to the trans isomer. That is why the trans isomer predominates only slightly in the liquid phase at 25 °C (cis:trans = 39:61). Consequently, the computational results for hydrindan (**33**) are quite consistent with the strong preference for the trans form of **32**·HCl in $CDCl_3$ solution.[18] Although it may be unorthodox, if not invalid, to correlate computational results on hydrocarbon systems with the corresponding ammonium salts,[20b] some useful insight may yet derive from such extrapolation. Certainly, the comparison of **33** and **32**·HCl offers an encouraging precedent.

Hydrocarbon **34**, which corresponds to protonated **5**, was modeled with SYBYL and searched for low-energy conformers.



34 **35** **36**

One trans and two distinct cis conformers were found, and each conformer was minimized by using MM2[21a,23] to give the following energies (kcal/mol) in descending order of stability: cis A (−78.4) > cis B (−78.0) > trans (−77.6). Significantly, *both cis forms are favored over the trans form*, in contrast to what was seen for hydrindan. Calculations with MNDO (in AMPAC)[24] gave the same rank order (kcal/mol) with an even wider spread: cis A (−2.4), cis B (−1.6), trans (2.1). Therefore, the fusion of a benzene ring onto that particular bond of hydrindan (α to the bridgehead in the 6-membered ring) causes a dramatic change in the relative stability of cis- and trans-fused structures. This outcome deviates from the computational results for protonated butaclamol and isobutaclamol,[20a] where the cis B form was found to be most stable by ca. 1.5 kcal/mol.

We wondered if A(1,3) steric strain might be responsible for the reversal of MM2 energies between **33** and **34**. As a test, we performed calculations on hydrindene **35** but recorded a similar preference for the cis A form, with the following energy values (kcal/mol): cis A (15.1) > cis B (15.8) > trans (16.3). Again, MNDO calculations gave the same rank order of energies: cis A (−15.0), cis B (−14.8), trans (−9.5). Thus, *the preference for a cis A form seems to be encouraged by unsaturation α to the bridgehead* in the hydrindan system, possibly because of the half-chair structure that is adopted by the unsaturated 6-membered ring and the loss of one crucial syn-axial interaction by the presence of a strategically located sp^2 center. Extrapolating this concept to the protonated indolizidine and pyrroloisoquinoline compounds, we have a tentative rationale for the observed preference of a trans geometry in the former case and a cis A geometry in the latter.

For the purpose of further comparison, it is interesting to note that the sulfonium congener of indolizidine, thioniabicyclo[4.3.0]nonane salt **36**, strongly prefers a cis B geometry.[25] In this case, a cis isomer was expected to be much more stable than the trans isomer from data on *cis*- and *trans*-1,2-dimethylthianium salts, and the cis A form was the one anticipated from data on the *cis*-thianium isomer. The results for thianium salts,[25] along with those that we presented in the above discussion, point to the subtleties in steric factors that can influence the ultimate distribution of structure types in such bicyclic and tricyclic molecules. It is difficult to assemble any clearer picture of the intimate structural features responsible for particular configurational/

(20) (a) Froimowitz, M.; Matthysse, S. *Mol. Pharmacol.* **1983**, *24*, 243. (b) Eliel, E. L., private communcation, 1988. Professor Eliel communicated data that underscore the need to exercise caution in computing structures for ammonium salts and in relating calculations on hydrocarbons to the corresponding ammonium salts. The configurational/conformational distribution of bridgehead ammonium salts can be influenced by solvent and counterion (Olefirowicz, E. M., Ph.D. Dissertation, The University of North Carolina at Chapel Hill, 1987). For example, two protonated hexahydrobenzo[*a*]quinolizine diastereomers were found to have a significant variation of their composition: in one, the $\Delta G°$ varied from 0.1 to 0.9 kcal/mol and, in the other, $\Delta G°$ varied from 0.6 to 1.0 kcal/mol. (Also, see ref 27g.)

(21) (a) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127. (b) Blanchard, K. R.; Schleyer, P. v. R. *J. Org. Chem.* **1963**, *28*, 247.

(22) (a) Eliel, E. L. *Sterochemistry of Carbon Compounds*; McGraw-Hill: New York, 1962; p 215. (b) The cis and trans isomers of **33** are chiral and racemic, contributing an entropy of mixing term (R ln 2) for each, and the trans isomer also has a C_2 axis, contributing a symmetry number term ($-R$ ln 2) to its free energy.[22a] (There is also an inconsequential, small positive entropy in the trans isomer due to the e,e/a,a equilibrium, wherein the axial–axial conformer is thinly populated.) Thus, the entropy, and thereby the free energy, of *cis*-hydrindan is significantly different from that of the *trans*-hydrindan. For the protonated indolizidine isomers, the trans form is desymmetrized so that there is no significant entropy difference between the cis and trans isomers.

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

(24) (a) Dewar, M. S.; Stewart, J. J. P. *QCPE* **1986**, program no. 506. (b) For information on MNDO calculations, see: Clark, T. *A Handbook for Computational Chemistry*; Wiley: New York, 1985; Chapter 4, pp 140–232.

(25) Cere, V.; Paolucci, C.; Pollicino, S.; Sandri, E.; Fava, A. *J. Org. Chem.* **1982**, *47*, 2861.

conformational profiles at this time.

Conclusion

It should be evident at this point that the configurational/conformational properties of amines and their acid-addition salts can be quite different. Indeed, Eliel and co-workers[26] have discussed, in considerable depth, the subject of free amine vs salt structure for piperidine molecules in solution; moreover, they emphasized[26b] that this issue is frequently overlooked. Other studies have appeared on derivatives containing a substituted *N*-methylpiperidine unit,[27,28] some of which have disclosed examples of configurational/conformational differences between amines and their salts.[27] Several reports pertain to the important opioid analgesic morphine and its congeners,[27a,c-e] where there has been a long-standing question about the orientation of the piperidine *N*-alkyl group in opiate molecules and the expression of agonist or antagonist activity.[27c-e] Although details on opiate molecules are beyond the scope of this paper, we note that there are solid-state examples of configurational reversal at nitrogen in such protonated piperidines.[27c,d] Results analogous to those reported herein were obtained by Rozenberg et al. in an NMR study of a fused piperidine system (not a bridgehead amine).[27f] Although Glaser et al. found a correlation between the solid- and solution-phase structures of atropine sulfate and scopolamine hydrobromide when water was the NMR solvent, they reported configurational reversal at nitrogen for the latter salt in CD_2Cl_2.[27g] From this broad perspective, we believe that further systematic investigation of this area would be warranted.

The question of whether a molecule has the same configuration or conformation in the crystal and in solution is a significant one, especially when considering biological activity. We have provided several clear-cut examples for which there is a disparity of structures in these two environments. Basically, the form in the solid state for several protonated bridgehead amines was not the same as the most stable form in $CDCl_3$ solution. Kessler et al.[29] published an interesting paper on this topic in which two fascinating examples are described. They raised a cautionary note that is worth restating here: Conclusions about conformations or labile configurations of polar or charged molecules in solution, based on X-ray analyses or computer calculations, should be drawn with circumspection.

Experimental Section

General Methods. Melting points are corrected. IR spectra were determined on ca. 4% wt/vol solutions in CCl_4 or $CHCl_3$. 90-MHz ^1H NMR spectra were obtained on a Perkin-Elmer R-32 spectrometer and 60-MHz spectra were obtained on a Varian EM-360 spectrometer, in $CDCl_3$ (s = singlet, d = doublet, dd = doublet of doublets). ^{13}C NMR spectra were recorded on a JEOL FX-60Q spectrometer at 15.1 MHz in $CDCl_3$. ^{13}C peak multiplicities were determined by using INEPT or off-resonance decoupling. Certain ^{13}C peak assignments were facilitated by reference to Shamma and Hindenlang.[30] Proton and carbon chemical shifts are reported in ppm downfield from Me_4Si.

Starting structures for the MM2 calculations[23] were generated by using the SYBYL molecular modeling program (Tripos Associates, Inc., St. Louis, MO, Version 3.3).

The X-ray diffraction analyses of **2a**·HBr, **2b**·HBr, and **4c**·HBr were conducted by Prof. Olofson's group at The Pennsylvania State University; the X-ray analysis of **12a** was conducted by Molecular Structure Corp., College Station, TX.

^1H NMR Methods. ^1H NMR spectra were recorded on a Bruker AM-360WB instrument in the specified solvent (generally $CDCl_3$). Chemical shifts are reported in ppm downfield (δ) from Me_4Si. Typical conditions used for 1D spectra were the following: spectral width of 6024 Hz; quadrature detection; 32K data points acquired, zero filled to 64K data points (0.184 Hz/point) before transform; recycle time of 4.72 s; pulse width of 2 μs (25°). For 2D COSY spectra, the data matrix consisted of 512w (f_1) × 1K (f_2) points. The time domain matrix was zero filled to 1K points in f_1 with a sine-bell window function applied in both dimensions.

Example of Interconversion of Trans- and Cis-Fused Forms. Monitoring of the NMR Spectrum of 4c·HBr with Time. A sample of **4c**·HBr was dissolved in $CDCl_3$ and immediately examined by 360-MHz ^1H NMR. One major substance was evident to the extent of 95%; this was assigned the trans structure. Over time, minor peaks in the original spectrum grew and, after 3.5 h, an ca. 50:50 ratio of two substances was apparent. The new species was assigned the cis A structure. At 7.5 h, an ca. 25:75 mixture was recorded. A final ratio of 10:90, which held constant with time, was recorded at 48 h.

Synthesis and Isolation of Three Isomers of 1,2,3,5,6,10b-Hexahydro-5-methyl-6-phenylpyrrolo[2,1-*a*]isoquinoline (4a, 4b, and 4c). 1-Methyl-2-phenylbenzeneethanamine[4a] (27.4 g, 0.13 mol) in 100 mL of ethyl acetate was gradually added to a suspension of succinic anhydride (14.0 g, 0.14 mol) in 75 mL of ethyl acetate, with rapid stirring. The mixture was heated to reflux and allowed to cool. Acetyl chloride (17 mL) was added, and the reaction was refluxed in a dry atmosphere for 16 h. The solution was concentrated to dryness and diluted with 300 mL of MeOH and then 30 mL of water. The white solid that crystallized was collected and dried in vacuo to give 31.3 g (82%) of imide, as bright white needles, mp 122–125 °C. The imide (25.0 g, 0.085 mol) in 400 mL of absolute ethanol was reduced at −5 °C by 13.0 g of sodium borohydride, with addition of 5 drops of 2 N ethanolic methanesulfonic acid every 15 min.[6] The reaction was worked up as described[6] before to give 27.0 g (98%) of ethoxypyrrolidinone **11**, as a light tan oil (which slowly crystallized on prolonged standing). Compound **11** was treated with 100 mL of polyphosphoric acid heated at 100 °C under a drying tube for 6 h. The solution was cooled to ca. 40 °C and quenched with 500 mL of water. The cooled mixture was extracted with methylene chloride (2 × 500 mL) and the combined extracts were rinsed with dilute aqueous NaOH, dried (Na_2SO_4), and concentrated to a light tan syrup (23.1 g, 100%). GLC analysis (SE-30 or OV-17 column)[4a] of this crude product showed three peaks in a 4:1:2 ratio (order of increasing retention), which were isomeric by GC–MS analysis (CI mode) with a parent ion (M + H) at *m/e* 278. A very minor, early eluting GLC peak (ca. 1%) may have been the fourth isomer; it was not confirmed. An 11.5-g sample was chromatographed on a Waters Prep 500 HPLC by using two silica gel columns with ethyl acetate/hexane (1:1) as an eluent. Thus, we obtained 3.8 g of front-running material (90% of **12a** and 7% of **12b** by GLC), 1.1 g of the next material (93% of **12c** and 1% of **12a** by GLC), and 1.0 g of the third material (81% of **12b**, 1% of **12a** and 1% of **12c** by GLC). (The unseparated fractions were combined and rechromatographed to get additional material.) A small sample (0.30 g) of the mixture enriched in **12a** was recrystallized from ethyl acetate/hexane (5:1) to give colorless hexagonal prisms (0.21 g), mp 126–128 °C. Slow recrystallization of the mixture enriched in **12b** (0.15 g) from the same solvent gave 0.04 g of off-white needles and of the mixture enriched in **12c** (0.15 g) from ethyl acetate gave 0.10 g of small colorless prisms. 360-MHz ^1H NMR data were collected on these three solid samples (Table II). A portion of **12a** was recrystallized again to furnish crystals for X-ray analysis.

The enriched mixtures were subjected to reduction with borane–THF to give the corresponding amines.[4a,6] The **12a** mixture (4.3 g) afforded

(26) (a) For details on protonated *N*-methylpiperidines, see: Eliel, E. L.; Kandasamy, D.; Yen, C.-Y.; Hargrave, K. D. *J. Am. Chem. Soc.* **1980**, *102*, 3698, and references cited therein. (b) Manoharan, M.; Eliel, E. L. *Tetrahedron Lett.* **1984**, *25*, 3267.

(27) (a) Glasel, J. *Biochem. Biophys. Res. Commun.* **1981**, *102*, 703. Also, see: Glasel, J. A.; Reiher, H. W. *Magn. Reson. Chem.* **1985**, *23*, 236. (b) Booth, H.; Little, J. H. *J. Chem. Soc., Perkin Trans 2* **1972**, 1846. (c) Maurer, P. J.; Rapoport, H. *J. Med. Chem.* **1987**, *30*, 2016, and references cited therein. (d) Belleau, B.; Conway, T.; Ahmed, F. R.; Hardy, A. D. *Ibid.* **1974**, *17*, 907. (e) Eliel, E. L.; Morris-Natschke, S.; Kolb, V. M. *Org. Magn. Reson.* **1984**, *22*, 258. (f) Rozenberg, S. G.; Zagorevskii, V. A.; Sharkova, L. M.; Kucherova, N. F. *Chem. Heterocycl. Cmpd.* **1978**, *14*, 869 (Russ. ed., p 1081). These researchers observed phenomena with acid-addition salts of substituted 1,2,3,4-tetrahydrobenzofuro[3,2-*c*]pyridines similar to those that we observed (i.e., a single diastereomer from the crystal was detected by NMR, and then an equilibrium mixture of two diastereomers, ca. 2:1, was eventually recorded). (g) Glaser, R.; Peng, Q.-J.; Perlin, A. S. *J. Org. Chem.* **1988**, *53*, 2172, and references cited therein. An interesting study of protonated *N*-methyltropane derivatives is reported. Besides a case of stereochemical reversal for scopolamine hydrobromide, this paper reports a dramatic solvent effect for said compound (water vs CH_2Cl_2).

(28) The interested reader may wish to consult additional structural studies on protonated piperidines: (a) Papers cited in ref 26a. (b) Duthaler, R. O.; Roberts, J. D. *J. Am. Chem. Soc.* **1978**, *100*, 3882. (c) Delpuech, J.-J.; Deschamps, M.-N. *Nouv. J. Chim.* **1978**, *2*, 563. (d) Beguin, C. G.; Deschamps, M.-N.; Boubel, V.; Delpuech, J.-J. *Org. Magn. Reson.* **1978**, *11*, 418. (e) Crowley, P. J.; Robinson, M. J. T.; Ward, M. G. *Tetrahedron* **1977**, *33*, 915, and references cited therein.

(29) (a) Kessler, H.; Zimmermann, G.; Foester, H.; Engel, J.; Oepen, G.; Sheldrick, W. S. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 1053. (b) For other examples of disparity between conformers in the liquid and the solid phase, see: MacNicol, D. D.; Murphy, A. *Tetrahedron Lett.* **1981**, *22*, 1131. Jensen, F. R.; Bushweller, C. H. *J. Am. Chem. Soc.* **1969**, *91*, 3223.

(30) Shamma, M.; Hindenlang, D. M. *Carbon-13 NMR Shift Assignments of Amines and Alkaloids*; Plenum: New York, 1979.

Table IV. X-ray Crystallographic Data

	2a·HBr	2b·HBr	4c·HBr	12a
formula	$C_{19}H_{22}NBr$	$C_{19}H_{22}NBr$	$C_{19}H_{22}NBr$	$C_{19}H_{19}NO$
MW	344.3	344.3	344.3	277.37
max 2θ, deg	60	56	60	150
space gp	$P\bar{1}$	$P\bar{1}$	Cc	$Pbca$
a, Å	8.603 (5)	9.416 (2)	10.975 (5)	15.087 (4)
b, Å	12.423 (4)	12.913 (7)	13.551 (5)	22.363 (5)
c, Å	7.825 (6)	6.980 (21)	11.936 (5)	9.108 (3)
α, deg	94.01 (5)	101.03 (10)	90.00	90.00
β, deg	90.92 (5)	91.02 (7)	107.14 (4)	90.00
γ, deg	102.16 (4)	81.57 (2)	90.00	90.00
V, Å^3	815 (2)	824 (3)	1686	3072.9
d_{obsd}, g/mL	1.4	1.4	1.4	
d_{calcd}, g/mL	1.403	1.388	1.357	1.20
Z	2	2	4	8
no. reflcns coll	5045	4297	2304	3157
no. reflcns obsd	2198	3120	958	1160
cutoff of obsd reflcns	$I > 3.0\sigma(I)$	$I > 3.0\sigma(I)$	$I > 2.5\sigma(I)$	$I > 3.0\sigma(I)$
R	0.063	0.037	0.036	0.092
R_w	0.071	0.041	0.033	0.125
residual electron density, e/Å^3	0.69	0.42	0.40	0.39

2.05 g of **4a**·HCl, as an off-white solid, which was recrystallized from ethyl acetate/methanol (5:1) to give 1.10 g of bright white crystals: mp 245–250 °C; homogeneous by TLC; 95% of **4a** and 5% of **4b** by GLC (OV-17). Anal. C, H, Cl.[4a] The **12b** mixture (1.8 g) afforded 2.07 g of white saccharinate salt, **4b**·saccharin, which was recrystallized from 95% methanol to give 1.62 g of white crystals: mp 222–228 °C; homogeneous by TLC; 97% of **4b** and 3% of **4a** and **4c** by GLC (OV-17). Anal. C, H, N.[4a] The **12c** mixture (1.9 g) afforded 1.68 g of **4c**·HBr, as an off-white powder (from 2-propanol/ethyl acetate): mp 272–278 °C (dec); homogeneous by TLC; >99% of **4c** by GLC (OV-17). Anal. C, H, Br.[4a] A small sample of **4c**·HBr was recrystallized from 2-propanol slowly to obtain small colorless prisms for X-ray analysis; mp 272–277 °C.

1,3,4,6,7,11b-Hexahydro-2*H*-benzo[*a*]quinolizine (7). This compound was prepared according to previously reported procedures.[4a,6] Glutaric acid (11.4 g, 0.10 mol) and phenethylamine (12.1 g, 0.10 mol) were heated in ethyl acetate with 25 mL of acetyl chloride to give the crude glutarimide, which was recrystallized from water/methanol to afford white crystals (16.5 g, 76%). This solid was reduced with sodium borohydride in acidic ethanol (11.4 g, 0.30 mol), and the resultant 6-ethoxypiperidin-2-one was cyclized with PPA (100 g) at 100 °C to give the crude lactam (11.5 g, 76%). The lactam was purified by preparative HPLC to give 5.8 g [60-MHz ^{1}H NMR δ 1.6–2.1/2.1–3.2 (m, 9) 4.5–5.0 (m, 2 H11b and H6e), 7.0–7.3 (m, 4)], which was reduced with 1 M borane–THF (85 mL, 0.085 mol) to give crude **7** (4.1 g, 76%). A small sample of HCl salt was prepared from ethanol, mp 245–247 °C (lit.[9] mp 241–243 °C). The HBr salt was prepared from 2-propanol with 48% HBr and recrystallized from ethanol to give white crystals (2.95 g, 51%), mp 247–249 °C: ^{1}H NMR (360 MHz, data not included in Table I) δ 1.74 (m, 1, H2), 1.87 (m, 1, H2), 2.15 (m, 2, H1/H3), 2.67 (m, 2, H1/H3), 7.1–7.3 (m, 4, aromatic).

X-ray Crystallographic Analysis on 2a·HBr, 2b·HBr, 4c·HBr, and 12a. Data for **2a**·HBr, **2b**·HBr, and **4c**·HBr were collected on an Enraf-Nonius CAD4 diffractometer (Mo Kα radiation, λ = 0.71073 Å). The programs employed were part of the Enraf-Nonius Structure Determination Package, as revised in 1977 (for **2a**·HBr and **2b**·HBr) or 1982 (for **4c**·HBr), implemented on a PDP 11/34 computer. Cell dimensions were determined from 25 reflections at moderate 2θ angles. General information on data collection and unit cell values are given in Table IV. The data were corrected for Lorentz and polarization factors but not for absorption. The starting position for the bromine atom in each case was determined by the Patterson method. Subsequent difference Fourier maps and full-matrix least-squares refinements gave starting positions for all atoms. The absolute configuration for **4c**·HBr was tested by creating the enantiomorphic pair ($1 - X$, $1 - Y$, $1 - Z$) before hydrogen atoms were added. Convergence at this point was achieved at R = 0.065 and R_w = 0.068, which were significantly larger than the convergence values of R = 0.059 and R_w = 0.061 for the structure chosen. In final anisotropic refinement of non-hydrogen atoms, B_{iso} was fixed at 4 Å^2 for hydrogen atoms in **2a**·HBr and **2b**·HBr and 5 Å^2 for hydrogen atoms in **4c**·HBr. Here $R = (\sum||F_o| - |F_c||)/\sum|F_o|$; for **2a**·HBr and **2b**·HBr, $R_w = [\sum(|F_o| - |F_c|)^2/\sum F_o^2]^{1/2}$; for **4c**·HBr, $R_w = [\sum w(|F_o| - |F_c|)^2/\sum wF_o^2]^{1/2}$, $w = 1/[\sigma(F_o)^2]$, and $\sigma(F_o)^2 = [\sigma(I^2) + (0.03F^2)^2]^{1/2}$ (where $F_o^2 = F^2/Lp$).

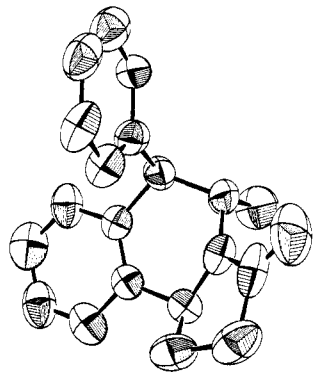


Figure 7. Molecular structure of lactam **12a** from X-ray analysis.

Data for **12a** were collected for a colorless prismatic crystal (ca. 0.2 × 0.2 × 0.2 mm) mounted on a glass fiber in a random orientation on an Enraf-Nonius CAD4 diffractometer (Cu Kα radiation, λ = 1.541 84 Å). Calculations were performed on a PDP-11/60 based TEXRAY system. Cell constants and an orientation matrix for data collection were obtained from a least-squares refinement, by using 14 reflections in the range $6° < \theta < 12°$. General information on data collection and unit cell values are given in Table IV. Lorentz and polarization corrections were applied to the data. No absorption correction was made. A secondary extinction correction was applied.[31] The structure was solved by direct methods. The non-hydrogen atoms were refined anisotropically; hydrogen atoms were not included in the calculations. The structure was refined in full-matrix least squares where the function minimized was $\sum w(|F_o| - |F_c|)^2$, with $w = 4F_o^2/\sigma^2(F_o^2)$. Anomalous dispersion effects were included in F_c;[32] the values of $\Delta F'$ and $\Delta F''$ were those of Cromer.[33] The final refinement cycle used $R = (\sum||F_o| - |F_c||)/\sum|F_o|$ and $R_w = [\sum w(|F_o| - |F_c|)^2/\sum wF_o^2]^{1/2}$. An ORTEP drawing of **12a** is presented in Figure 7.

Tables of bond distances, bond angles, torsional angles, and positional and thermal parameters for **2a**·HBr, **2b**·HBr, **4c**·HBr, and **12a** are presented in the supplementary material.[34]

Acknowledgment. We thank Dr. Harold R. Almond, Jr., for conducting the MM2 and MNDO calculations.

Registry No. (±)-**1a**, 118474-84-3; (±)-**1b**, 118474-85-4; (±)-**2a**, 118474-82-1; (±)-**2a**·HBr, 118474-70-7; (±)-**2b**, 118474-83-2; (±)-**2b**·HBr, 118474-71-8; (±)-**3a**, 90390-51-5; (±)-**3a**·HBr, 118474-72-9; (±)-**3b**, 90390-52-6; (±)-**3b**·HBr, 118474-73-0; (±)-**4a**, 118573-89-0; (±)-**4a**·HCl, 118626-07-6; (±)-**4b**, 118573-90-3; (±)-**4b**·saccharin, 118676-08-7; (±)-**4c**, 118573-91-4; (±)-**4c**·HBr, 118626-06-5; (±)-**5**·HBr, 118474-74-1; (±)-**6a**, 90390-65-1; (±)-**6a**·HBr, 118474-77-4; (±)-**6b**, 90390-84-4; (±)-**6b**·HBr, 118474-78-5; (±)-**7**·HBr, 118474-79-6; (±)-**8a**, 90390-66-2; (±)-**8a**·HBr, 90390-81-1; (±)-**8b**, 90390-85-5; (±)-**8b**·HBr, 90390-87-7; (±)-**9a**, 118474-88-7; (±)-**9a**·HBr, 118474-80-9; (±)-**9b**, 118474-89-8; (±)-**9b**·HBr, 118474-81-0; **11**, 118474-67-2; (±)-**11** (imide), 118474-69-4; (±)-**12a**, 118474-68-3; (±)-**12b**, 118573-87-8; (±)-**12c**, 118573-88-9; (±)-**17a**·HBr, 118474-75-2; (±)-**17b**·HCl, 118474-76-3; (±)-**18a**, 118474-86-5; (±)-**18b**, 118474-87-6; (±)-**20**·HCl, 36504-94-6; (±)-*cis*-**34**, 118474-91-2; (±)-*trans*-**34**, 118474-90-1; (±)-*cis*-**35**, 96308-38-2; (±)-*trans*-**35**, 118474-92-3; (±)-$Ph_2CHCH(CH_3)NH_2$, 118573-92-5; succinic anhydride, 108-30-5.

Supplementary Material Available: Tables of bond distances, bond angles, torsional angles, least-squares planes, general temperature factors, and positional and thermal parameters, ORTEP drawings featuring atom numbering schemes, and views of the unit cells for **2a**·HBr, **2b**·HBr, **4c**·HBr, and **12a** (27 pages). Ordering information is given on any current masthead page.

(31) Zachariasen, W. H. *Acta Crystallogr.* **1963**, *16*, 1139.
(32) Ibers, J. A.; Hamilton, W. C. *Acta Crystallogr.* **1964**, *17*, 781.
(33) Cromer, D. T. *International Tables for X-Ray Crystallography*; Kynoch Press: Birmingham, England, 1974; Vol. IV, Table 2.3.1.
(34) See paragraph regarding supplementary material at the end of this paper.