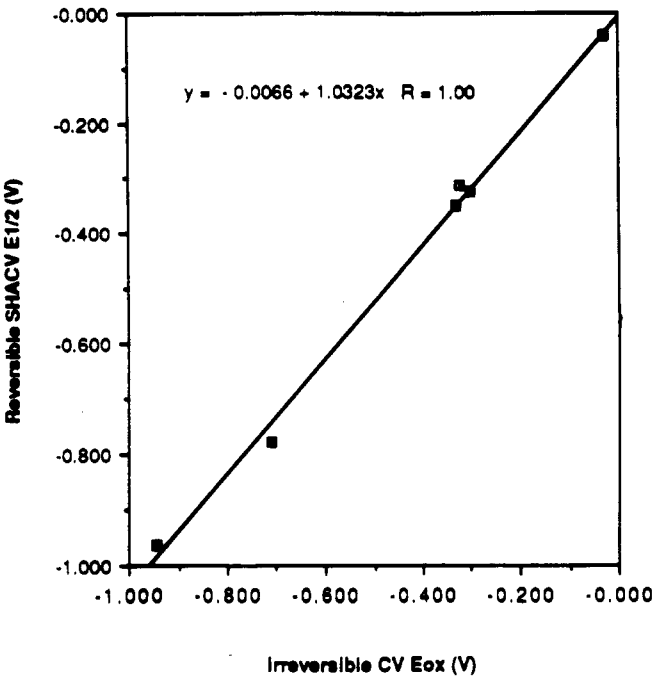

Figure 1. Plot of reversible oxidation potentials ($E_{1/2}$) obtained from second harmonic alternating current cyclic voltammograms vs irreversible cyclic voltammograms for six amides (Table III). (Courtesy of N. G. Harvey, Duke University.)

in the analogous carbon-centered radicals studied previously.[2]

Experimental Section

Materials and Acidities. The sources and properties, including pK_{HA} values in DMSO, for these compounds have been described in earlier publications.[1,4]

Electrochemistry. Research in the laboratory of Professor E. M. Arnett at Duke University has shown that there is a very good correlation (R^2 = 0.998; slope = 1.0) between the irreversible cycliic voltammetric (CV) potentials that we have reported in DMSO for substituted fluorenide ions and the reversible second harmonic alternating current (SHACV) oxidation potentials measured in his laboratory.[24] Since the nitranions obtained from parent carboxamides and sulfonamides listed in Table I were among the worst anions that we have seen with regard to fouling the electrode during oxidation potential measurements, and giving broad CV waves, it was important to check our $E_{ox}(A^-)$ values for these with those obtained by the SHACV technique. On the other hand, the anions derived from hydroxamic acids, carbohydrazides, and their derivatives are all better behaved electrochemically than are the anions derived from the parent carboxamides. The waves are narrow and sharp, and the $E_{ox}(A^-)$ values, although irreversible, are readily reproducible to within ±30 mV by independent investigators. The much greater stability of the radicals being formed on oxidation explains the improved electrochemical behavior. The results of SHACV measurements for acetamide, thioacetamide, acetohydroxamic acid, *N*- and *O*-methylhydroxamic acids, and acetohydrazide are summarized in Table III.

A comparison of the CV values given in Table III shows that our CV values are all slightly less negative than those measured in Arnett's laboratory, and that these, in turn, are usually less negative than the $E_{1/2}$ values by about 30 mV, as expected. A plot of the reversible SHACV data vs the CV data, both measured by N. G. Harvey, reveals a remarkably good correlation (Figure 1). Note that the correlation covers a range of 0.84 V (19 kcal/mol) and includes representatives from several types of amides.

Acknowledgment. This research was supported by a grant from the National Science Foundation. We express our appreciation to E. M. Arnett and N. G. Harvey for providing the electrochemical data using the second harmonic alternating current technique. We are indebted to A. V. Satish for the preparation of *N*-benzylbenzohydroxamic acid and the pK_{HA} and electrochemical measurements with this compound. Discussions with X.-M. Zhang were helpful in formulating some of the interpretations.

(24) Private communication from E. M. Arnett and J.-P. Cheng.

Hydroxylated Metabolites of Loratadine: An Example of Conformational Diastereomers Due to Atropisomerism

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The structures of two metabolites of the nonsedating antihistamine loratadine (1) were confirmed by synthesis. The metabolites **3a** and **3b**, which are hydroxylated in the bridgehead, were each prepared from tricyclic ketone **8** in seven steps. Each of these compounds was found to exist as a pair of conformational diastereomers which interconvert slowly at room temperature. These conformers arise due to the restricted conformational mobility inherent to the diaryl[*a*,*d*]cycloheptane ring system.

Introduction

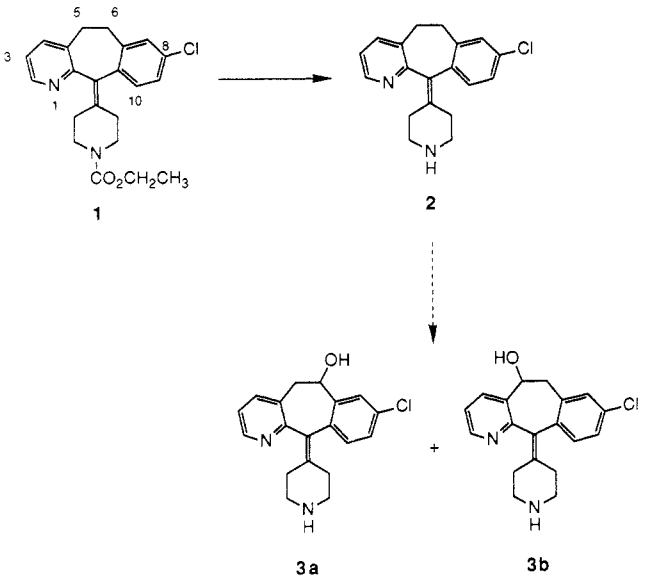
Loratadine (1) is a potent nonsedating H_1-antihistamine[1] presently in clinical use.[2] A study aimed at identifying the metabolites of loratadine revealed that the compound is first hydrolyzed to the piperidinylidene amine **2** and then hydroxylated at several positions. These hydroxylated derivatives may be conjugated and are ultimately excreted in the urine in their free or conjugated form.[3] Two of the major hydroxylated derivatives were isolated and tentatively identified as hydroxy metabolites **3a** and **3b**. In order to confirm the structural assignments of these hydroxylated metabolites and also evaluate their pharmacological profile, alcohols **3a** and **3b** were prepared.

(1) Villani, F. J.; Magatti, C. V.; Vashi, D. B.; Wong, J.; Popper, T. L. *Arzneim.-Forsch/Drug Res.* **1986**, *36*(II), 1311.

(2) (a) Barnett, A.; Iorio, L. C.; Kreutner, W.; Tozzi, S.; Ahn, H. S.; Gulbenkian, A. *Agents Actions* **1984**, *14*, 590. (b) *Drugs Future* **1987**, *12*, 544.

(3) Katchen, B.; Cramer, J.; Pramanik, B.; Chan, T., unpublished results.

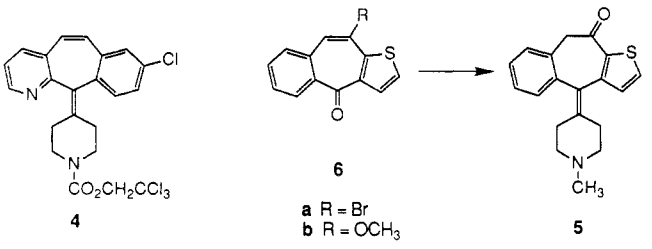
0022-3263/90/1955-3341$02.50/0



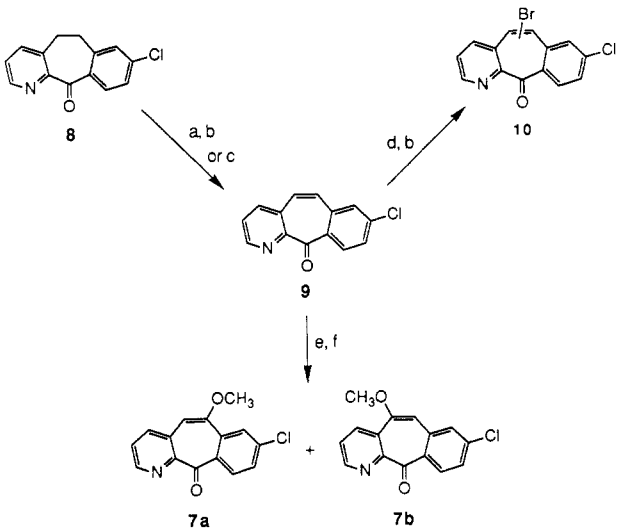
We herein report on the synthesis of these hydroxylated metabolites **3a** and **3b**. Unexpectedly, it was found that these alcohols each exist as a pair of two compounds which equilibrate at room temperature. We attribute this effect to the existence of conformational diastereomers, due to the inherent atropisomerism[4] that results from the reduced conformational mobility of the diaryl[*a*,*d*]cycloheptane ring system.[5,6]

Chemistry

The preparation of the hydroxylated metabolites **3a** and **3b** initially centered on the selective functionalization of the disubstituted double bond of the bis-olefin **4**. All attempts to selectively react the bridgehead double bond (e.g., hydroboration, epoxidation, oxymercuration, etc.) failed. Consequently, an approach similar to that reported for the synthesis of ketotifen (**5**)[7] was employed, wherein, the bridgehead carbonyl was masked at an equivalent oxidation level as either a vinyl bromide (i.e. **6a**) or a vinyl ether (i.e. **6b**).



Scheme I[a]



[a] (a) NBS/AIBN/CCl_4/Δ; (b) DBU/CH_2Cl_2/Δ; (c) DDQ/dioxane/Δ; (d) Br_2/CH_2Cl_2/room temperature; (e) Br_2/$AgNO_3$/CH_3OH/room temperature; (f) DBU/$CHCl_3$/Δ.

The preparation of the two isomeric vinyl ethers **7a** and **7b** is shown in Scheme I. The tricyclic ketone **8**[8] was converted to keto olefin **9** via a modification of the bromination–debromination sequence reported by Villani.[8] Bromination of tricyclic ketone **8** with *N*-bromosuccinimide and catalytic AIBN in carbon tetrachloride followed by elimination of the generated bromides with DBU in methylene chloride produced keto olefin **9** in yields ranging from 35 to 50%. Alternatively, **9** could be obtained in one step via dehydrogenation of tricyclic ketone **8** with DDQ in refluxing dioxane, albeit in lower yield (24%).

Bromine smoothly added to keto olefin **9** in methylene chloride at room temperature to produce the dibromide which, following treatment with DBU, afforded a 3/1 mixture of the two isomeric vinyl bromides **10** in 86% yield. Likewise, treatment of **9** with bromine in methanol, containing powered silver nitrate, produced the corresponding bromo ethers. Subsequent base-induced elimination of the bromides using DBU in refluxing chloroform afforded a 3/1 mixture of the isomeric vinyl ethers **7a** and **7b** in 57% yield. The vinyl ethers [R_f = 0.39 (major), R_f = 0.15 (minor); 50% EtOAc in hexanes] were separated and identified as the 6-methoxy vinyl ether **7a** (major) and the corresponding 5-methoxy derivative **7b** (minor). These assignments were made on the basis of their NMR spectra. The C-7 aromatic proton resonance of the major isomer **7a** was at 8.09 ppm (d, J = 2.0 Hz) as opposed to 7.46 ppm (d, J = 1.9 Hz) for the same proton of isomer **7b**. The downfield shift of this proton in **7a** is due to its proximity to the methoxy substituent at C-6. Likewise, the C-4 proton resonance of the minor isomer **7b** is further downfield (8.45 ppm, dd, J = 8.2, 1.5 Hz) than it is in isomer **7a** (7.82 ppm, dd, J = 8.0, 1.4 Hz).

The Grignard reagent of 4-chloro-1-methylpiperidine was added to the mixture of vinyl bromides **10** to render the two isomeric carbinols **11** in 46% yield (Scheme II). Similarly, each of the two vinyl ether carbinols **12a** and **12b** was obtained in 61% and 53% yields, respectively.

(4) Although this is not an example of atropisomerism in the strictest sense of the work, since it involves rotation about two bonds instead of one, we feel that the term best describes the phenomenon observed here.

(5) (a) Ebnother, A.; Jucker, E.; Stoll, A. *Helv. Chim. Acta* **1965**, *48*, 1237. (b) Tochtermann, W. *Fortschr. Chem. Forsch.* **1970**, *15*, 378. (c) Öki, M. *Topics in Stereochemistry*; John Wiley and Sons: New York, 1983; Vol. 14, pp 1–81.

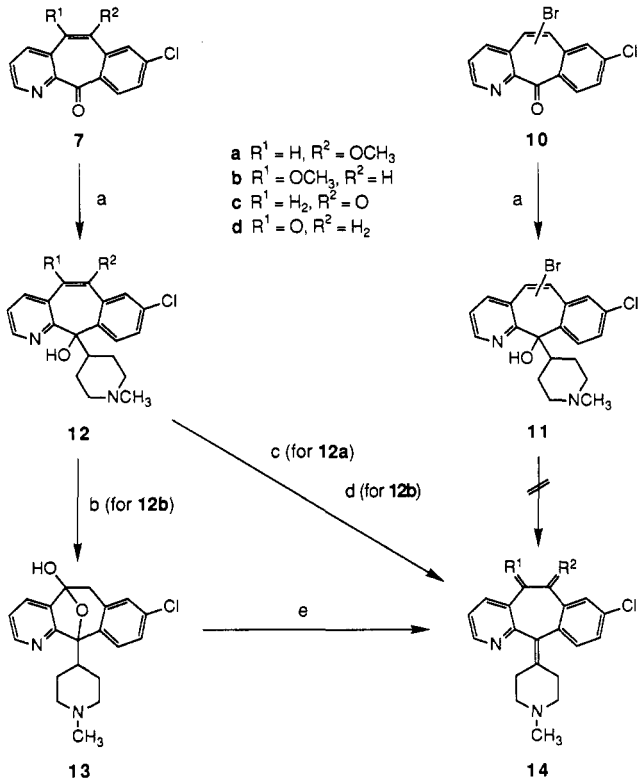
(6) Atropisomerism has been extensively investigated in the diaryl[*a*,*d*]cyclohept*ene* ring system: (a) Tochtermann, W.; Walter, U.; Mannschreck, A. *Tetrahedron Lett.* **1964**, 2981. (b) Murahashi, S.-I.; Moritani, I.; Nishino, M. *J. Am. Chem. Soc.* **1967**, *89*, 1257. (c) Tochtermann, W. *Chimia* **1972**, *26*, 565. (d) Rokach, J.; Girard, Y.; Atkinson, J. G. *J. Chem. Soc., Chem. Commun.* **1975**, 602. (e) Remy, D. C.; Rittle, K. E.; Hunt, C. A.; Anderson, P. S.; Arison, B. H.; Engelhardt, E. L.; Hirschmann, R.; Clineschmidt, B. V.; Lotti, V. J.; Bunting, P. R.; Ballentine, R. J.; Papp, N. L.; Flataker, L.; Witoslawski, J. J.; Stone, C. A. *J. Med. Chem.* **1977**, *20*, 1013. (f) Young, S. D.; Baldwin, J. J.; Cochran, D. W.; King, S. W.; Remy, D. C.; Springer, J. P. *J. Org. Chem.* **1985**, *50*, 339. (g) Rupard, J. H.; Paulis, T.; Janowsky, A.; Smith, H. E. *J. Med. Chem.* **1989**, *32*, 2261.

(7) Waldvogel, E.; Schwarb, G.; Bastian, J.-M.; Bourquin, J.-P. *Helv. Chim. Acta* **1976**, *59*, 866.

(8) Villani, F. J.; Daniels, P. J. L.; Ellis, C. A.; Mann, T. A.; Wang, K.-C. *J. Heterocycl. Chem.* **1971**, *8*, 73.

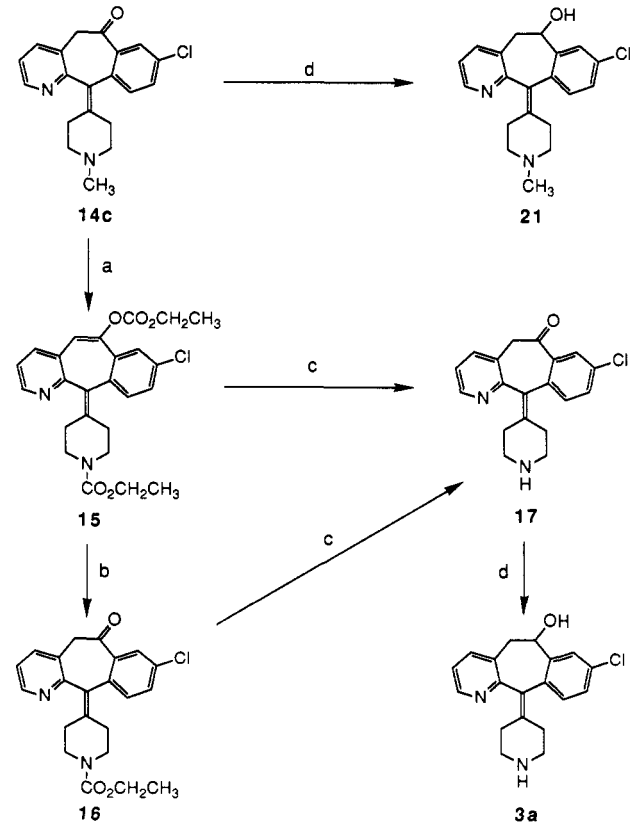
(9) Engelhardt, E. L.; Zell, H. C.; Saari, W. S.; Christy, M. E.; Colton, C. D.; Stone, C. A.; Stavorski, J. M.; Wenger, H. C.; Ludden, C. T. *J. Med. Chem.* **1965**, *8*, 829.

Scheme II[a]



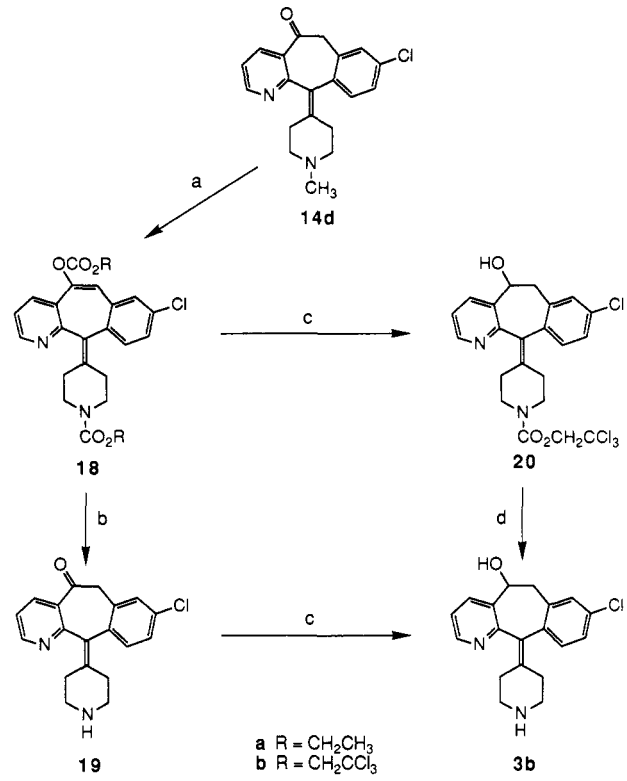
[a] (a) $ClMgC_5H_9NCH_3$, THF, room temperature; (b) 85–95% H_2SO_4, room temperature; (c) 87% H_2SO_4, room temperature, then CF_3SO_3H, 115 °C; (d) 95% H_2SO_4, room temperature, then CF_3SO_3H, room temperature → 70 °C; (e) CF_3SO_3H, 45 °C.

Scheme III[a]



[a] (a) $ClCO_2CH_2CH_3$, Et_3N, $C_6H_5CH_3$, 80 °C; (b) KOH, H_2O, CH_3OH, Δ, 25 min; (c) KOH, H_2O, CH_3OH, Δ, 1–2 days; (d) $NaBH_4$, CH_3OH.

Scheme IV[a]



[a] (a) $ClCO_2CH_2CH_3$ or $ClCO_2CH_2CCl_3$, Et_3N, $C_6H_5CH_3$, 80 °C; (b) KOH, H_2O, CH_3OH, Δ, 25 h; (c) $NaBH_4$, CH_3OH; (d) Zn, AcOH, Δ.

Although the vinylic bromide moiety of **11** resisted hydrolysis under a variety of conditions, the vinyl ether moieties in **12a** and **12b** were readily hydrolyzed with aqueous sulfuric acid at room temperature. Consequently, the synthesis of metabolites **3a** and **3b** was completed using vinyl ethers **12a** and **12b**.

The conversion of the 6-methoxy carbinol **12a** directly to olefinic ketone **14c** was accomplished in one step. Treatment of the vinyl ether with 87% aqueous sulfuric acid at room temperature, followed by the addition of an equal amount of trifluoromethanesulfonic acid with heating at 115 °C to eliminate the tertiary hydroxyl group, produced the olefinic ketone **14c** in 77% yield. The NMR spectrum of **14c** exhibited an AX quartet centered at 4.11 ppm for the bridgehead methylene protons. The resonance at 8.10 ppm (1 H, d, J = 2.4 Hz) corresponded to the C-7 aromatic proton, which was deshielded by the carbonyl at C-6. The aromatic proton at C-10 resonated further upfield at 7.35 ppm (1 H, d, J = 8.2 Hz) than it did in carbinol **12a** (8.14 ppm, 1 H, d, J = 8.5 Hz) since it was no longer deshielded by the hydroxyl group.

When the 5-methoxy carbinol **12b** was subjected to similar reaction conditions (87% aqueous sulfuric acid then triflic acid, 130 °C) total decomposition resulted. If the reaction was conducted at a lower temperature (T = 50–70 °C) **14d** was obtained in only 16% yield. It was found that olefinic ketone **14d** was best obtained in two steps from carbinol **12b**. Hydrolysis of the vinyl ether with 88% aqueous sulfuric acid provided the desired ketone in 92% yield, which existed predominately as its hemiketal **13** (~95% in $CDCl_3$). Subsequent treatment of **13** with neat trifluoromethanesulfonic acid at 45 °C for 3 h afforded olefinic ketone **14d** in 53% yield for the two steps. Its NMR spectrum displayed a similar pattern to that of **14c** with the exception that the C-4 instead of the C-7 proton resonance was shifted downfield by the carbonyl at C-5

to 8.41 ppm (1 H, dd, J = 8.0, 1.6 Hz).

Demethylation of olefinic ketones **14c** and **14d** was accomplished as illustrated in Schemes III (for **14c**) and IV (for **14d**). Treatment of **14c** in toluene at 80 °C with 5 equiv of ethyl chloroformate gave ethyl carbamate **15** in 84% yield. The vinyligous carbonate moiety was selectively hydrolyzed by short exposure (t = 25 min) of **15** to refluxing aqueous potassium hydroxide to produce keto carbamate **16** in 63% yield. However, longer exposure of either **15** or **16** under identical reaction conditions resulted in the hydrolysis of the carbamate as well, to provide the desired amino ketone **17** in 67% and 84% yields, respectively.

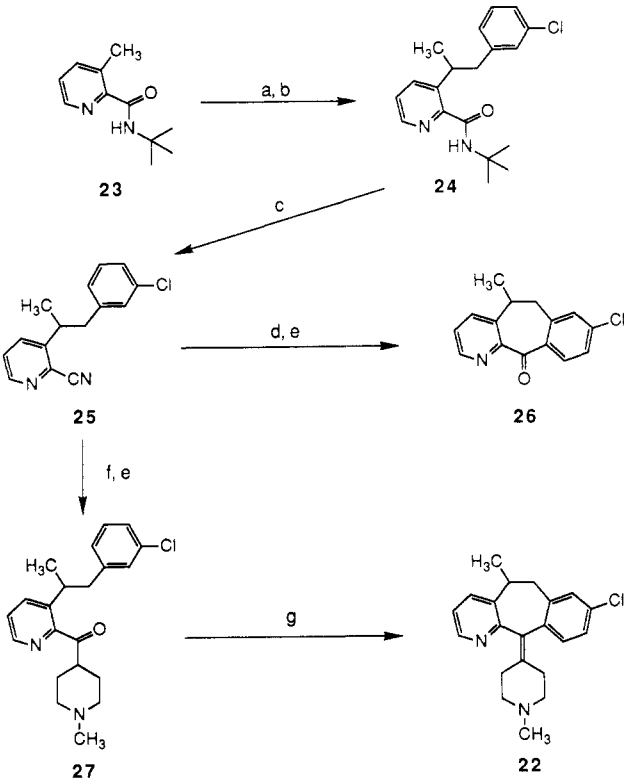
The reduction of **17** with sodium borohydride in methanol provided the 6-hydroxy metabolite **3a** in 85% yield. Unexpectedly, the alcohol existed as a 2/1 (CD_3OD) mixture of two components. The same ratio of components was also obtained from the reduction of **17** with L-Selectride (Aldrich), indicating either no difference in selectivity between the reducing agents or equilibration of the resultant components to an equilibrium mixture. The resonances for the C-6 methine protons appeared as doublets of doublets at 5.31 ppm (J = 8.9, 4.3 Hz) for the major component and much further upfield at 4.72 ppm (J = 11.8, 5.5 Hz) for the minor one. In the case of each component, the C-6 hydroxyl group caused a downfield shift of the C-7 aromatic proton resonance to 7.55 ppm (major) and 7.47 ppm (minor) from where it usually appears at 7.22 ppm. The hydroxyl group had little effect on the position of the C-4 aromatic proton signal.

The olefinic ketone **14d** was also converted to ethyl carbamate **18a** and subsequently hydrolyzed to amino ketone **19** in 66% overall yield for the two steps (Scheme IV). Reduction of this isomeric ketone with sodium borohydride afforded the 5-hydroxy metabolite **3b** in 89% yield, again as a 2/1 mixture of two components. Its proton NMR spectrum (CD_3OD) displayed the C-5 methine proton resonances at 5.33 ppm (dd, J = 9.2, 4.3 Hz) and 4.76 ppm (dd, J = 11.7, 5.3 Hz) for the major and minor components, respectively. As expected, the resonances of the C-4 aromatic protons were shifted approximately 0.3 ppm further downfield to 7.99 ppm (major) and 7.91 ppm (minor) from where the C-4 proton absorption usually appears. The relative positions of the C-7 proton signals remained the same. Alternatively, treatment of troc-carbamate **18b**, formed in 80% yield from **14d**, with sodium borohydride in methanol provided hydroxy carbamate **20** as a 7/3 mixture of two components in 83% yield. Subsequent removal of the N-troc protecting group with zinc in acetic acid at 65 °C gave the same 2/1 mixture of 5-hydroxy metabolites **3b** in 69% yield.

Just as the reduction of amino ketones **17** and **19** provided their corresponding alcohols as a mixture of two components, the reduction of **14c** (i.e. the N-methylated derivative of **17**) also produced a mixture (7/3 in CD_3OD) of the corresponding N-methyl alcohols **21** in 97% yield (Scheme III). Apparently, the alcohols always existed as a mixture of two components independent of the nature of the starting ketone or the mode of its reduction. This is best rationalized by considering that the two components in each of the alcohol mixtures are just different conformations of the same compound, which should be interconvertible at some temperature.

Heating alcohol **3a** to 70 °C (DMSO-d_6) resulted in no broadening of any of the NMR proton resonances corresponding to the two components. Consequently, the rate of interconversion at this temperature is much slower than 1 s^{-1}. Furthermore, no additional distinct components were observed at lower temperatures (−70 °C in CD_2Cl_2) in the NMR spectrum of **3b**. Since the energy barrier for the interconversion of the conformers appeared to be quite high, an attempt at their separation was made. This was accomplished for the 5-hydroxy alcohol **3b** at −25 °C using preparative TLC [10% CH_3OH saturated with NH_3 in $CHCl_3$; R_f = 0.15 (major); R_f = 0.10 (minor)]. Although the conformers were separated, they reequilibrated to the same 3/2 mixture in less than 30 min at room temperature as evidenced by HPLC.

Scheme V[a]



[a] (a) 2 equiv of n-BuLi, THF, −40 °C, then CH_3I; (b) 1 equiv of n-BuLi, then NaBr, m-$ClC_6H_4CH_2Cl$; (c) $POCl_3$, Δ; (d) PPA, 190–200 °C, 2 h; (e) HCl, H_2O; (f) $ClMgC_5H_9NCH_3$, THF, 55 °C; (g) CF_3SO_3H, 65–70 °C, 23 h.

In an effort to further characterize the nature of these conformational diastereomers by NMR spectroscopy, the 5-methyl derivative **22** was prepared (Scheme V). Its synthesis was achieved using a sequence similar to that described for the more recent synthesis of loratadine (**1**).[10,11] The dianion of *tert*-butyl amide **23**,[10] formed by treating **23** with 2 equiv of n-butyllithium at −40 °C, was selectively alkylated on carbon when quenched with 1 equiv of methyl iodide. Subsequent regeneration of the dianion by adding an additional equivalent of n-butyllithium followed by an equivalent of m-chlorobenzyl chloride provided *tert*-butyl amide **24**. Without purification, the crude product was readily dehydrated to the corresponding nitrile **25** with refluxing phosphorous oxychloride in 75% overall yield from *tert*-butyl amide **23**. The nitrile **25** could then be cyclized to the seven-membered ring imine by heating it in polyphosphoric acid at 195 °C. Although the imine could be isolated [IR ($CHCl_3$) 1587 cm^{-1}], it was best hydrolyzed in situ with aqueous hydrochloric acid to provide the 5-methyl ketone **26** [IR

(10) Schumacher, D. P.; Murphy, B. L.; Clark, J. E.; Tahbaz, P.; Mann, T. A. *J. Org. Chem.* **1989**, *54*, 2242.

(11) For the earlier synthesis of loratadine (1) see ref 1 and references cited therein.

Table I. Chemical Shifts[a] and Coupling Constants[b] of the C-5 and C-6 Protons of 3a, 3b, 21, and 22

compd	Proton	major conformer δ (J)	minor conformer δ (J)
3a[d]	H-5	3.55 (15.9, 4.3)	3.10 (12.8, 5.5)
	H-5′	2.91 (15.9, 8.9)	3.52 (12.8, 11.8)
	H-6	5.31 (8.9, 4.3)	4.72 (11.8, 5.5)
3b[d]	H-5	5.33 (9.2, 4.3)	4.76 (11.7, 5.3)
	H-6	3.57 (16.2, 4.3)	3.04 (12.6, 5.3)
	H-6′	2.88 (16.2, 9.2)	3.54 (12.6, 11.7)
21[d]	H-5	3.55 (16.0, 4.2)	3.10 (13.2, 5.5)
	H-5′	2.91 (16.0, 9.0)	3.50 (13.2, 11.6)
	H-6	5.30 (9.0, 4.2)	4.72 (11.6, 5.5)
22[e]	H-5[c]	3.59 (10.1, 4.0)	3.09 (12.5, 5.2)
	H-6	3.43 (16.3, 4.0)	2.75 (13.1, 5.2)
	H-6′	2.58 (16.3, 10.1)	3.20 (13.1, 12.5)

[a] In ppm downfield from TMS. [b] In hertz. [c] After decoupling the C-5 methyl group. [d] In CD_3OD. [e] In $CDCl_3$.

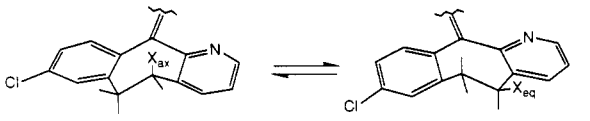
($CHCl_3$) 1667 cm^{-1}] in 34% yield from nitrile **25**. The NMR spectrum of ketone **26** ($CDCl_3$, CD_3OD or C_6D_6) revealed the presence of only one conformer with a single methyl resonance at 1.35 ppm (3 H, d, J = 7.0 Hz) in $CDCl_3$.

Alternatively, nitrile **25** can be treated with the Grignard reagent of 4-chloro-1-methylpiperidine,[9] which, following acid hydrolysis, yielded piperidyl ketone **27** in 63% yield. Intramolecular cyclization of **27**, using trifluoromethanesulfonic acid provided the targeted 5-methylpiperidinylidene **22** in 89% yield. As expected, **22** existed as a mixture of two conformers (11/9 in CD_3OD or $CDCl_3$) as evidenced by its NMR spectrum. The methyl doublets for the conformers appeared at 1.33 ppm (major) and 1.40 ppm (minor) and were coupled to the C-5 methine protons whose signals were at 3.59 ppm (major) and 3.09 ppm (minor), respectively. However, unlike the 5- and 6-hydroxy counterparts, the C-4 and C-7 proton resonances were not deshielded and appeared at their expected positions.

Discussion

The synthetic 5- and 6-hydroxy derivatives **3a** and **3b** were identical (NMR, MS, HPLC) to the hydroxylated metabolites isolated from urine samples of metabolized loratadine (**1**). Each of these alcohols exists as a mixture of two spectroscopically similar components,[12] which can be readily separated at −25 °C and interconverted at room temperature. As a consequence, it appears that these two components are conformational diastereomers which arise due to some restricted conformational mobility inherent to the ring system. While this restricted mobility may be due to either a slow axial to equatorial exchange of the C-5 or C-6 substituent due to rotation about the central bridgehead bond or a slow piperidinylidene ring flip from one face of the tricyclic ring system to the other, we believe that the latter process is operative here.

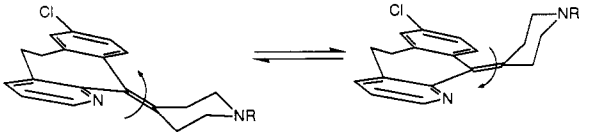
The axial to equatorial exchange of a substituent in a seven-membered ring is usually very rapid.[5b] However, the tricyclic ring system may impart a certain degree of rigidity to the seven-membered ring which would render interconversion sluggish. While the substituent (X) may occupy either the equatorial or axial positions (note: the axial position contains no 1,3-diaxial interactions), the process



(1)

of flipping from one to the other may be slow (eq 1).

Alternatively, the generation of an asymmetric center by either hydroxylation (e.g. **3a**, **3b**, and **21**) or methylation (e.g. **22**) of the bridgehead may just serve to allow the atropisomerism of this ring system to be more readily observed; namely, by generating conformational diastereomers from conformational enantiomers. The flip of the piperidinylidene ring past the C-10 proton and pyridine nitrogen from one face of the tricyclic ring to the other may be slow enough so that it imparts overall asymmetry to these molecules (eq 2). The restricted mobility of this piperidinylidene ring flip has been observed in similar systems.[5,6,12]



(2)

Although the 5-methylpiperidinylidene **22** exists in two conformations at room temperature, the corresponding keto derivative **26** appears to be present as only one. Consequently, at this temperature the methyl group of **26** may occupy either an axial or equatorial position, or alternatively, it may be in rapid equilibrium between both. The NMR spectrum of **26** (C_6D_6) reveals that the C-6 methylene protons at 2.43 ppm (1 H, dd, J = 17.0, 2.1 Hz) and 2.19 ppm (1 H, dd, J = 17.0, 9.2 Hz) are coupled geminally (J = 17.0 Hz) and vicinally with the C-5 methine proton at 2.59 ppm. While the absolute magnitude of a particular coupling constant is influenced by many factors, the relative values for adjacent pairs is dependent to a first approximation on the dihedral angle.[13] Application of the Karplus equation to the magnitude of the vicinal coupling constants (J = 9.2 and 2.1 Hz) indicates that the dihedral angle between each pair of C-5 and C-6 protons is about 120° greater for one than the other. Such an arrangement would require the C-5 proton to be predominately axial with its methyl group equatorial. An equatorial C-5 proton should display similar coupling constants with each of the protons at C-6.

Each of the conformers of the 5-hydroxy (**3b**), 6-hydroxy (**3a**), 6-hydroxy-*N*-methyl (**21**), and 5-methyl (**22**) derivatives displays a similar coupling pattern upon examination of their C-5 and C-6 proton resonances (Table I). Although the magnitude of the coupling constants between these protons differs slightly in each conformer, each pair of vicinal J values for each conformer has a large and a small value as was observed for ketone **26**. The coupling constants for each of the conformers listed are in close agreement with those reported for similar systems containing an equatorial substituent.[14] Consequently, the C-5 or C-6 substituent (X = CH_3 or OH) probably occupies predominately an equatorial position. However, even though no additional conformers were observed at −70 °C, we cannot preclude the fact that both populations of axial and equatorial isomers exist and are in rapid equilibrium

(12) A similar observation was made with the structurally similar bridgehead hydroxylated derivatives of amitriptylene. Although the authors speculated that the two components arise due to a slow ring inversion, a detailed analysis of this phenomenon was not reported. See: Lassen, N.; Perregaard, J. *Acta Chem. Scand.* **1983**, *B37*, 335.

(13) Williams, D. H.; Fleming, I. *Spectroscopic Methods in Organic Chemistry*, 2nd ed.; McGraw Hill: New York, 1973; pp 101–117.

(14) (a) Ellefson, C. R.; Swenton, L.; Bible, R. H., Jr.; Green, P. M. *Tetrahedron* **1976**, *32*, 1081. (b) Bellucci, G.; Berti, G.; Chiappe, C.; Lippi, A.; Marioni, F. *J. Med. Chem.* **1987**, *30*, 768.

Table II. Difference NOE Measurements of the C-5 Methine and the Methyl Group Hydrogens of 5-Methyl Piperidinylidene 22

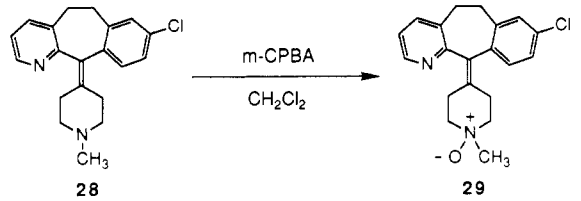
saturation of C-4 proton (in ppm)	conformer	% NOE	
		C-5 methine	C-5 methyl hydrogens
7.55	major	2.5	4.5
7.43	minor	7.5	3.1

with each other. This may explain the slight differences in the magnitude of the coupling constants[15] between the major and minor conformers; wherein, the major conformer may have a higher percentage of the axial isomer in rapid equilibrium with the equatorial isomer. In either case, this axial to equatorial substituent exchange due to twisting about the C-5–C-6 bond cannot be responsible for the existance of the two conformers at room temperature.

Therefore, the sluggish piperidinylidene ring flip from one face of the tricyclic ring to the other must be responsible for the atropisomerism observed in these compounds. The substituent (X) at either C-5 or C-6 serves only to render this restricted mobility more easily observable by introducing another site of asymmetry in the molecule (i.e. conformational diastereomers from conformational enantiomers).

Examination of one of the conformers of 5-methylpiperidinylidene **22** using molecular models revealed that the C-4 proton is close to the methyl group at C-5 than it is to the hydrogen at C-5. When the piperidinylidene ring is flipped to the other face of the tricyclic ring to produce the other conformer, the C-4 proton moves closer to the C-5 hydrogen and further from the C-5 methyl group. NOE experiments, wherein the C-4 proton is saturated and the enhancements of the C-5 hydrogen and methyl group hydrogens are measured, agree with this observation (Table II). In going from one conformation to the other the increased enhancement measured for one set of hydrogens was paralleled by a decrease in the enhancement of the other set.

Introduction of an asymmetric center in any position of the parent ring system (i.e. **2**) should produce conformational diastereomers that are observable at room temperature, as long as the change does not disturb the rate of the sluggish piperidinylidene flip. As expected, oxidation of *N*-methyl amine **28**[16] with 1 equiv of *m*-CPBA produced amine oxide **29** in 98% yield as a 2/1 mixture ($CDCl_3$) of two conformers.



28 29

A more detailed analysis of the exact nature of this restricted conformational mobility is in progress. These results as well as the energetics of the interconversion will be reported shortly.

(15) Although electronegative substituents can also influence the magnitude of coupling constants, especially if they are trans coplanar to a hydrogen,[13] they appear to exert a relatively minor effect here. Comparison of the coupling constants of the bridgehead protons of **3b** where hydroxyl is the substituent with **22** where methyl is the substituent reveals that they parallel each other quite closely despite the difference in the electronegativity of the substituents.

(16) Villani, F. J.; Daniels, P. J. L.; Ellis, C. A.; Mann, T. A.; Wang, K.-C.; Wefer, E. A. *J. Med. Chem.* **1972**, *15*, 750.

Experimental Section

General. Solvents and reagents were used as received unless otherwise noted. Anhydrous solvents were obtained via distillation from either sodium benzophenone ketyl (tetrahydrofuran) or phosphorous pentoxide (methylene chloride). All anhydrous reactions were conducted with the careful exclusion of moisture. The apparatus was flame-dried and cooled under an atmosphere of argon or nitrogen. All reaction mixtures were magnetically stirred unless otherwise noted. High-pressure liquid chromatography (HPLC) was carried out on the Water's Associates Model 590 pump system using a Whatman partisil 5 ODS-3 column (250 mm, 4.6 mm i.d.). The mobile phase was usually methanol/water (60/40) with 0.05 M phosphate buffer adjusted to pH = 3. Flash chromatography was carried out using the apparatus described by Still and co-workers[17] and was carried out using Baker flash silica gel (~40 μm average particle size). Gravity column chromatography was carried out using silica gel from Davison Chemical, Grace (60–200 mesh). Analytical thin-layer chromatography (TLC) was performed using Analtech silica gel GF plates and visualized using ultraviolet light. Preparative thick-layer chromatography was carried out on silica gel GF 1000 plates of 20 × 20 (Analtech). Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra (IR) were recorded on the Perkin-Elmer 1320 spectrophotometer. Proton magnetic resonance spectra (^1H NMR) were recorded on the Varian XL-400 (400 MHz), the Varian XL-300 (300 MHz), the Varian Gemini 300 (300 MHz), or the Varian XL-200 (200 MHz) spectrometers and are reported in ppm (δ) from tetramethylsilane as the standard. Coupling constants are reported in hertz and are accurate to within 0.3 Hz; the abbreviations b, s, d, t, q, AB, and m refer to broad, singlet, doublet, triplet, quartet, AB quartet, and multiplet, respectively. Long-range coupling constants of less than 1.0 Hz are not reported. Mass spectra were taken on the Varian MAT CH5 (EI), the Varian MAT 312 (FAB), or the VG Analytical ZAB-SE (FAB) instruments. Some of the major fragments are reported as *m/e* (relative intensity).

8-Chloro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-one (9). A mixture of 25.99 g (107 mmol) of tricyclic ketone **8**, 21.35 g (120 mmol) of recrystallized *N*-bromosuccinimide, and 167 mg (1.02 mmol) of AIBN in 400 mL of carbon tetrachloride was refluxed under an argon atmosphere for 1.25 h. The solution was slowly cooled to 50 °C, and the resultant precipitate was filtered off. The crude precipitate and 20 mL (134 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene in 400 mL of methylene chloride was refluxed for 1 h. It was then washed with water (3×), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was recrystallized from methylene chloride/toluene to give 8.93 g (35%) of keto olefin **9** as colorless needles: mp 158–160 °C; IR ($CHCl_3$) 1658, 1588 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.91 (1 H, dd, *J* = 4.4, 1.6 Hz, H-2), 8.19 (1 H, d, *J* = 9.2 Hz, H-10), 7.94 (1 H, dd, *J* = 8.0, 1.6 Hz, H-4), 7.62–7.52 (3 H, m), 7.05 (2 H, AB, *J* = 12.1 Hz, Δν = 24.6 Hz, H-5, H-6); MS (EI) *m/e* (%) 243 (M^+, 33), 241 (M^+, 95), 213 (100), 178 (67). Anal. Calcd for $C_{14}H_8NClO$: C, 69.58; H, 3.34; N, 5.80; Cl, 14.67. Found: C, 69.32; H, 3.26; N, 5.83; Cl, 14.55.

8-Chloro-6-methoxy-11*H*-benzo[5,6]cyclohepta[1,2-*b*]-pyridin-11-one (7a) and 8-Chloro-5-methoxy-11*H*-benzo-[5,6]cyclohepta[1,2-*b*]pyridin-11-one (7b). To a mixture of 8.15 g (33.7 mmol) of keto olefin **9** and 23.19 (137 mmol) of powdered silver nitrate in 300 mL of dry methanol at room temperature and under an argon atmosphere was added dropwise 5.10 mL (99.0 mmol) of bromine. After 8 h another 5.90 g (34.7 mmol) of powdered silver nitrate followed by 1.70 mL (33.0 mmol) of bromine was added. After 30 min the mixture was poured into water and extracted with methylene chloride (4×). The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo to give a mixture of the crude bromo ethers.

The product was dissolved in 200 mL of methylene chloride at room temperature and placed under an argon atmosphere. To the solution was then added 20.0 mL (134 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene after which it was refluxed for 1.33 h. Another 10.0 mL (67 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene

(17) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

was added, and the mixture was refluxed for another hour. The mixture was poured into water and extracted with methylene chloride (3×). The combined organic phases were washed with water, dried over $MgSO_4$, filtered, and concentrated in vacuo. The two isomeric vinyl ethers were separated and purified via flash chromatography (40–75% ethyl acetate in hexanes) and then recrystallized from ethyl acetate/hexanes to give 1.51 g (16.5%) of the 5-methoxy vinyl ether **7b** and 3.68 g (40%) of the more polar 6-methoxy vinyl ether **7a**.

7a: mp 160–161 °C; IR ($CHCl_3$) 1665, 1630, 1589 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.74 (1 H, dd, J = 4.5, 1.4 Hz, H-2), 8.09 (1 H, d, J = 2.0 Hz, H-7), 8.00 (1 H, d, J = 8.4 Hz, H-10), 7.82 (1 H, dd, J = 8.0, 1.4 Hz, H-4), 7.58 (1 H, dd, J = 8.4, 2.0 Hz, H-9), 7.48 (1 H, dd, J = 8.0, 4.5 Hz, H-3), 6.24 (1 H, s, H-5), 3.99 (3 H, s, OCH_3); MS (EI) m/e (%) 273 (M^+, 46), 271 (M^+, 100), 243 (42), 200 (79). Anal. Calcd for $C_{15}H_{10}NClO_2 \cdot 0.33H_2O$: C, 63.50; H, 4.03; N, 4.94; Cl, 12.50. Found: C, 63.28; H, 3.85; N, 4.90; Cl, 12.47.

7b: mp 162–163 °C; IR ($CHCl_3$) 1663, 1627, 1587 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.91 (1 H, dd, J = 4.5, 1.5 Hz, H-2), 8.45 (1 H, dd, J = 8.2, 1.5 Hz, H-4), 7.97 (1 H, d, J = 8.5 Hz, H-10), 7.60 (1 H, dd, J = 8.2, 4.5 Hz, H-3), 7.46 (1 H, d, J = 1.9 Hz, H-7), 7.38 (1 H, dd, J = 8.5, 1.9 Hz, H-9), 6.35 (1 H, s, H-6), 3.98 (3 H, s, OCH_3); MS (EI) m/e (%) 273 (M^+, 34), 271 (M^+, 100), 243 (36), 200 (64). Anal. Calcd for $C_{15}H_{10}NClO_2$: C, 66.31; H, 3.71; N, 5.16; Cl, 13.05. Found: C, 66.48; H, 3.59; N, 5.11; Cl, 12.94.

8-Chloro-6-methoxy-11-(1-methyl-4-piperidinyl)-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ol (12a). To a mixture of 6.00 g (22.1 mmol) of the 6-methoxy vinyl ether **7a** in 80 mL of dry tetrahydrofuran at 0 °C and under an argon atmosphere was added dropwise over a 10-min period 17.7 mL (26.6 mmol) of a 1.5 M Grignard solution of 4-chloro-1-methylpiperidine[9] in tetrahydrofuran. After 1 h the mixture was quenched with water and extracted with ethyl acetate (3×). The organic portions were combined, washed with brine, dried over Na_2SO_4, filtered, concentrated in vacuo, and chromatographed on silica gel (0–5% methanol in methylene chloride) to give 5.01 g (61%) of the 6-methoxy carbinol **12a** as a solid. An analytical sample was prepared by recrystallization of the solid from isopropyl ether to give white needles: mp 159–160 °C; IR ($CHCl_3$) 3285, 1631 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.42 (1 H, dd, J = 4.5, 1.5 Hz, H-2), 8.14 (1 H, d, J = 8.5 Hz, H-10), 7.80 (1 H, d, J = 2.2 Hz, H-7), 7.65 (1 H, dd, J = 7.5, 1.5 Hz, H-4), 7.44 (1 H, dd, J = 8.5, 2.2 Hz, H-9), 7.25 (1 H, dd, J = 7.5, 4.5 Hz, H-3), 6.99 (1 H, s, OH), 6.14 (1 H, s, H-5), 3.99 (3 H, s, OCH_3), 2.82–2.64 (2 H, m), 2.32–2.12 (1 H, m), 2.15 (3 H, s, NCH_3), 1.82–1.40 (4 H, m) 0.96–0.82 (1 H, m), 0.53–0.38 (1 H, m); MS (EI) m/e (%) 372 (M^+, 1.5), 370 (M^+, 4.2), 274 (37), 272 (100). Anal. Calcd for $C_{21}H_{23}N_2ClO_2$: C, 68.01; H, 6.25; N, 7.55; Cl, 9.56. Found: C, 68.17; H, 6.28; N, 7.44; Cl, 9.53.

8-Chloro-5,11-dihydro-11-(1-methyl-4-piperidinylidene)-6*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-6-one (14c). A mixture of 2.00 g (5.39 mmol) of the 6-methoxy carbinol **12a** in 87% aqueous sulfuric acid was stirred at room temperature and under an argon atmosphere. After 30 min 30 mL of trifluoromethanesulfonic acid was added, and the mixture was heated to 115 °C. One hour later the mixture was cooled to room temperature, poured onto ice, basified with 5% aqueous sodium hydroxide, and extracted with methylene chloride (2×). The combined organic portions were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to give 1.41 g (77%) of the olefinic ketone **14c**. The material was recrystallized from ethyl acetate/isopropyl ether to give 1.12 g (61%) of the ketone as a granular solid: mp 181–183 °C; IR ($CHCl_3$) 1676, 1587 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.48 (1 H, dd, J = 4.9, 1.5 Hz, H-2), 8.10 (1 H, d, J = 2.4 Hz, H-7), 7.62 (1 H, dd, J = 7.6, 1.5 Hz, H-4), 7.48 (1 H, dd, J = 8.2, 2.4 Hz, H-9), 7.35 (1 H, d, J = 8.2 Hz, H-10), 7.16 (1 H, dd, J = 7.6, 4.9 Hz, H-3), 4.37 (1 H, d, J = 14.5 Hz, H-5), 3.85 (1 H, d, J = 14.5 Hz, H-5′), 2.84–2.70 (2 H, m), 2.66–2.47 (3 H, m), 2.29 (3 H, s, NCH_3), 2.33–2.02 (3 H, m); MS (EI) m/e (%) 340 (M^+, 12), 338 (M^+, 37), 295 (42), 294 (38), 96 (48). Anal. Calcd for $C_{20}H_{19}N_2ClO$: C,70.90; H, 5.65; N, 8.27; Cl, 10.46. Found: C, 70.85; H, 5.66; N, 8.25; Cl, 10.34.

Ethyl 4-[8-Chloro-6-[(ethoxycarbonyl)oxy]-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene]-1-piperidinecarboxylate (15). To a solution of 952 mg (2.81 mmol) of olefinic ketone **14c** and 0.59 mL (4.22 mmol) of triethylamine in 12 mL of toluene at 80 °C and under an argon atmosphere was added dropwise 1.34 mL (14.0 mmol) of ethyl chloroformate. After 30 min the mixture was cooled to room temperature, filtered, and concentrated in vacuo. The crude product was purified via flash chromatography (5% methanol in methylene chloride) to afford 1.11 g (84%) of ethyl carbamate **15** as a glass: IR ($CHCl_3$) 1765, 1680 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.62 (1 H, dd, J = 5.0, 1.5 Hz, H-2), 7.67 (1 H, dd, J = 8.0, 1.5 Hz, H-4), 7.55 (1 H, d, J = 2.0 Hz, H-7), 7.44 (1 H, dd, J = 8.5, 2.0 Hz, H-9), 7.30 (1 H, d, J = 8.5 Hz, H-10), 7.23 (1 H, dd, J = 8.0, 5.0 Hz, H-3), 6.83 (1 H, s, H-5), 4.27 (2 H, q, J = 7.0 Hz, OCH_2), 4.12 (2 H, q, J = 7.0 Hz, OCH_2), 3.92–3.70 (2 H, m), 3.14–2.81 (2 H, m), 2.44–2.00 (4 H, m), 1.37 (3 H, t, J = 7.0 Hz, CH_3), 1.23 (3 H, t, J = 7.0 Hz, CH_3); MS (FAB, thioglycerol matrix) m/z (%) 471 (M^+ + H, 35), 469 (M^+ + H, 100), 423 (33), 266 (36). Anal. Calcd for $C_{25}H_{25}N_2ClO_5$: C, 64.03; H, 5.37; N, 5.97; Cl, 7.56. Found: C, 63.72; H, 5.38; N, 5.86; Cl, 7.38.

Ethyl 4-(8-Chloro-5,6-dihydro-6-oxo-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-piperidinecarboxylate (16). A mixture of 2.85 g (6.08 mmol) of ethyl carbamate **15** and 40 mL of 11% aqueous potassium hydroxide (w/v) in 32.5 mL of ethanol was heated at 110 °C for 25 min. The mixture was poured into water and extracted with methylene chloride (2×). The combined organic portions were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified via flash chromatography (5% methanol in methylene chloride) and recrystallized from ethyl acetate/pentane to give 1.51 g (63%) of keto carbamate **16** as a yellowish solid: mp 122–124 °C; IR ($CHCl_3$) 1680 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.48 (1 H, dd, J = 5.0, 1.5 Hz, H-2), 8.12 (1 H, d, J = 2.4 Hz, H-7), 7.63 (1 H, dd, J = 7.8, 1.5 Hz, H-4), 7.49 (1 H, dd, J = 8.3, 2.4 Hz, H-9), 7.33 (1 H, d, J = 8.3 Hz, H-10), 7.18 (1 H, dd, J = 7.8, 5.0 Hz, H-3), 4.32 (1 H, d, J = 14.6 Hz, H-5), 4.16 (2 H, q, J = 7.0 Hz, OCH_2), 3.86 (1 H, d, J = 14.6 Hz, H-5′), 3.94–3.76 (2 H, m) 3.30–3.09 (2 H, m), 2.60–2.38 (3 H, m), 2.28–2.16 (1 H, m), 1.26 (3 H, t, J = 7.0 Hz, CH_3); MS (EI) m/e (%) 398 (M^+, 36), 396 (M^+, 100), 294 (41), 280 (39). Anal. Calcd for $C_{22}H_{21}N_2ClO_3$: C, 66.58; H, 5.33; N, 7.06; Cl, 8.93. Found: C, 66.21; H, 5.55; N, 6.80; Cl, 8.62.

8-Chloro-5,11-dihydro-11-(4-piperidinylidene)-6*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-6-one (17). Method A. A mixture of 758 mg (1.91 mmol) of keto carbamate **16** and 20 mL of 13% aqueous potassium hydroxide (w/v) in 15 mL of ethanol was refluxed under an argon atmosphere for 24 h. The mixture was poured into water and extracted with chloroform (3×). The combined organic portions were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford a product which was purified via flash chromatography (2% methanol saturated with ammonia in methylene chloride) to yield 520 mg (84%) of amino ketone **17**. An analytical sample was prepared by recrystallization of the product from ethyl acetate to give **17** as yellowish crystals: mp 207–209 °C dec; IR ($CHCl_3$) 3320, 1678, 1587 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.47 (1 H, dd, J = 5.0, 1.5 Hz, H-2), 8.10 (1 H, d, J = 2.4 Hz, H-7), 7.62 (1 H, dd, J = 7.6, 1.5 Hz, H-4), 7.48 (1 H, dd, J = 8.3, 2.4 Hz, H-9), 7.35 (1 H, d, J = 8.3 Hz, H-10), 7.16 (1 H, dd, J = 7.6, 5.0 Hz, H-3), 4.38 (1 H, d, J = 14.5 Hz, H-5), 3.85 (1 H, d, J = 14.5 Hz, H-5′), 3.18–3.04 (2 H, m), 2.82–2.61 (2 H, m), 2.54–2.34 (3 H, m) 2.27–2.17 (1 H, m); MS (EI) m/e (%) 326 (M^+, 27), 324 (M^+, 85), 296 (51), 295 (84), 294 (100), 280 (40), 204 (26). Anal. Calcd for $C_{19}H_{17}N_2ClO$: C, 70.26; H, 5.28; N, 8.63; Cl, 10.92. Found: C, 70.24; H, 5.11; N, 8.54; Cl, 10.68.

Method B. A mixture of 1.40 g (2.99 mmol) of ethyl carbamate **15** and 20 mL of 13% aqueous potassium hydroxide (w/v) in 15 mL of ethanol was refluxed under an argon atmosphere for 42 h. The mixture was poured into water and extracted with methylene chloride (4×). The combined organic portions were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified via flash chromatography (10–20% methanol in methylene chloride) and recrystallized from methylene chloride/pentane to give 655 mg (67%) of amino ketone **17**, identical with the material prepared via method A above.

8-Chloro-6,11-dihydro-6-hydroxy-11-(4-piperidinylidene)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (3a). To a mixture of 290 mg (0.893 mmol) of amino ketone **17** in 14 mL of methanol at 0 °C and under an argon atmosphere was added in

three portions 165 mg (4.36 mmol) of sodium borohydide. After 30 min the mixture was poured into water and extracted with methylene chloride (3×). The combined organic portions were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to give a product which was purified via flash chromatography (5–10% methanol saturated with ammonia in methylene chloride) to give 249 mg (85%) of the 6-hydroxy compound **3a** as a glass. The product is unstable in chlorinated solvents for extended periods of time possibly due to formation of its hydrochloride salt. It could be further purified via a subsequent flash chromatography (10% methanol saturated with ammonia in toluene) and lyophilization of the product from 10% ethanol in water to give the 6-hydroxy compound **3a** as a white solid: IR ($CHCl_3$) 3120, 1590 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 8.32 (0.67 H, dd, J = 5.0, 1.6 Hz, H-2), 8.31 (0.33 H, dd, J = 5.0, 1.5 Hz, H-2), 7.79 (0.33 H, dd, J = 7.6, 1.5 Hz, H-4), 7.63 (0.67 H, dd, J = 7.6, 1.6 Hz, H-4), 7.55 (0.67 H, d, J = 2.0 Hz, H-7), 7.47 (0.33 H, d, J = 2.4 Hz, H-7), 7.29–7.19 (2 H, m), 7.14 (0.33 H, d, J = 8.3 Hz, H-10), 7.11 (0.67 H, d, J = 8.2 Hz, H-10), 5.31 (0.67 H, dd, J = 8.9, 4.3 Hz, H-6), 4.72 (0.33 H, dd, J = 11.8, 5.5 Hz, H-6), 3.55 (0.67 H, dd, J = 15.9, 4.3 Hz, H-5), 3.52 (0.33 H, dd, J =12.8, 11.8 Hz, H-5′), 3.10 (0.33 H, dd, J = 12.8, 5.5 Hz, H-5), 2.91 (0.67 H, dd, J = 15.9, 8.9 Hz, H-5′), 3.05–2.03 (8 H, m); MS (EI) m/e (%) 328 (M^+, 35), 326 (M^+, 100), 298 (43), 297 (81), 296 (85), 284 (32), 282 (59), 280 (31); HRMS (FAB, thioglycerol matrix) m/z calcd for $C_{19}H_{19}N_2ClO$ (M^+ + H) 327.1264, found 327.1273.

8-Chloro-5-methoxy-11-(1-methyl-4-piperidinyl)-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ol (12b). To a mixture of 5.00 g (18.4 mmol) of the 5-methoxy vinyl ether **7b** in 70 mL of dry tetrahydrofuran at 0 °C and under an argon atmosphere was added dropwise over a 7-min period 15.0 mL (22.5 mmol) of a 1.5 M Grignard solution of 4-chloro-1-methylpiperidine[9] in tetrahydrofuran. After 30 min the mixture was quenched with a saturated solution of ammonium chloride (pH ~ 8) and extracted with chloroform (3×). The combined organic portions were washed with brine, dried over Na_2SO_4, filtered, concentrated in vacuo, and flash chromatographed (5% methanol in methylene chloride) to give 3.60 g (53%) of the 5-methoxy carbinol **12b**. An analytical sample was prepared by recrystallization of the resultant solid from isopropyl ether to give **12b** as a white powder: mp 168–170 °C; IR ($CHCl_3$) 3290, 1632, 1586 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.55 (1 H, dd, J = 5.0, 1.5 Hz, H-2), 8.16 (1 H, dd, J = 8.0, 1.5 Hz, H-4), 8.04 (1 H, d, J = 8.3 Hz, H-10), 7.33 (1 H, dd, J = 8.0, 5.0 Hz, H-3), 7.30–7.23 (2 H, m), 6.95 (1 H, s, OH), 6.24 (1 H, s, H-6), 3.96 (3 H, s, OCH_3), 2.78–2.62 (2 H, m), 2.29–2.16 (1 H, m), 2.14 (3 H, s, NCH_3), 1.77–1.42 (4 H, m), 0.90–0.81 (1 H, m), 0.50–0.41 (1 H, m); MS (EI) m/e (%) 372 (M^+, 1.6), 370 (M^+, 4.2), 274 (39), 272 (100). Anal. Calcd for $C_{21}H_{23}N_2ClO_2$: C, 68.01; H, 6.25; N, 7.55; Cl, 9.56. Found: C, 67.99; H, 6.19; N, 7.49; Cl, 9.48.

8-Chloro-6,11-dihydro-11-(1-methyl-4-piperidinyl)-5,11-epoxy-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-5-ol (13). To a mixture of 4.26 g (11.5 mmol) of the 5-methoxy carbinol **12b** in 6 mL of methanol at 0 °C and under an argon atmosphere was added slowly a cooled solution of 54 mL of 88% aqueous sulfuric acid. The mixture was then allowed to warm to room temperature. After 35 min the solution was poured onto ice, basified with 25% aqueous sodium hydroxide, and extracted with methylene chloride (3×). The combined organic portions were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was dissolved in a small amount of methylene chloride and precipitated by the addition of isopropyl ether. The resultant solid was triturated with isopropyl ether to give 3.78 g (92%) of the deprotected ketone which existed predominantly as its hemiketal **13** (~95% in $CDCl_3$): IR ($CHCl_3$) 3000 cm^{-1}, no carbonyl; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.60–8.90 (1 H, m, OH), 8.32 (1 H, dd, J = 5.0, 1.5 Hz, H-2), 7.66 (1 H, dd, J = 7.5, 1.5 Hz, H-4), 7.21 (1 H, d, J = 8.3 Hz, H-10), 7.12–7.03 (2 H, m), 6.99 (1 H, d, J = 2.0 Hz, H-7), 3.41 (1 H, d, J = 16.5 Hz, H-6), 3.05–2.94 (1 H, m), 2.85 (1 H, d, J = 16.5 Hz, H-6′), 2.90–2.73 (1 H, m), 2.48–2.36 (1 H, m), 2.29 (3 H, s, NCH_3), 2.21–1.23 (6 H, m); MS (EI) m/e (%) 358 (M^+, 8.4), 356 (M^+, 24), 260 (13), 258 (30), 98 (100), 96 (78). Anal. Calcd for $C_{20}H_{21}N_2ClO_2 \cdot 0.125(C_3H_7)_2O$: C, 67.42; H, 6.20; N, 7.58; Cl, 9.59. Found: C, 67.75; H, 6.43; N, 7.24; Cl, 9.37.

8-Chloro-6,11-dihydro-11-(1-methyl-4-piperidinylidene)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-5-one (14d). Method A. A mixture of 3.58 g (10.0 mmol) of hemiketal **13** in 50 mL of trifluoromethanesulfonic acid was heated at 45 °C under an argon atmosphere. After 3 h the mixture was poured onto ice, basified with 25% aqueous sodium hydroxide (w/v), and extracted with methylene chloride (3×). The combined organic portions were washed with brine, dried over Na_2SO_4, filtered, concentrated in vacuo, and chromatographed on silica gel (5% methanol in methylene chloride) to give 1.703 g (50% or 58% based on recovered **13**) of olefinic ketone **14d**. An analytical sample was prepared by recrystallization of the product with ethyl acetate/isopropyl ether to give **14d** as an off-white solid: mp 162–163 °C dec; IR ($CHCl_3$) 1680, 1580 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.73 (1 H, dd, J = 4.7, 1.6 Hz, H-2), 8.41 (1 H, dd, J = 8.0, 1.6 Hz, H-4), 7.36–7.21 (4 H, m), 4.40 (1 H, d, J = 14.0 Hz, H-6), 3.84 (1 H, d, J = 14.0 Hz, H-6′), 2.85–2.66 (3 H, m), 2.62–2.24 (3 H, m), 2.29 (3 H, s, NCH_3), 2.19–2.00 (2 H, m); MS (EI) m/e (%) 340 (M^+, 23), 338 (M^+, 67), 296 (40), 295 (75), 294 (71), 96 (58). Anal. Calcd for $C_{20}H_{19}N_2ClO$: C, 70.90; H, 5.65; N, 8.27; Cl, 10.46. Found: C, 70.57; H, 5.52; N, 8.18; Cl, 10.23.

Method B. A mixture of 576 mg (2.12 mmol) of the 5-methoxy carbinol **12b** in 95% aqueous sulfuric acid was stirred at room temperature and under an argon atmosphere. After 40 min 5 mL of trifluoromethanesulfonic acid was added, and the mixture was stirred at room temperature for 1 h, then at 45–55 °C for 2.5 h, and finally at 60–70 °C for 2.66 h. The mixture was cooled to room temperature, basified with 15% aqueous sodium hydroxide (w/v), and extracted with methylene chloride (7×). The combined organic portions were dried over $MgSO_4$, filtered, and concentrated in vacuo to give a residue, which was purified via flash chromatography (10% methanol in methylene chloride) to yield 128 mg (16%) of olefinic ketone **14d** which was identical with the material prepared in method A above.

Ethyl 4-[8-Chloro-5-[(ethoxycarbonyl)oxy]-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene]-1-piperidinecarboxylate (18a). To a solution of 617 mg (1.82 mmol) of olefinic ketone **14d** and 0.50 mL (3.58 mmol) of triethylamine in 12 mL of toluene at 80 °C and under an argon atmosphere was added dropwise over 2 min 0.87 mL (9.10 mmol) of ethyl chloroformate. After 25 min the mixture was cooled to room temperature, filtered, and concentrated in vacuo. The crude product was purified via flash chromatography (1% methanol in methylene chloride) to afford 834 mg (98%) of ethyl carbamate **18a** as a glass: IR ($CHCl_3$) 1766, 1682 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.67 (1 H, dd, J = 4.8, 1.7 Hz, H-2), 7.83 (1 H, dd, J = 8.0, 1.7 Hz, H-4), 7.41–7.23 (4 H, m), 6.88 (1 H, s, H-6), 4.25 (2 H, q, J = 7.1 Hz, OCH_2), 4.11 (2 H, q, J = 7.1 Hz, OCH_2), 3.90–3.71 (2 H, m), 3.10–2.83 (2 H, m), 2.40–2.00 (4 H, m), 1.35 (3 H, t, J = 7.1 Hz, CH_3), 1.23 (3 H, t, J = 7.1 Hz, CH_3); MS (FAB, thioglycerol matrix) m/z (%) 471 (M^+ + H, 38), 469 (M^+ + H, 100). Anal. Calcd for $C_{25}H_{25}N_2ClO_5$: C, 64.03; H, 5.37; N, 5.97; Cl, 7.56. Found: C, 64.33; H, 5.21; N, 5.91; Cl, 7.50.

8-Chloro-6,11-dihydro-11-(4-piperidinylidene)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-5-one (19). A mixture of 897 mg (1.91 mmol) of ethyl carbamate **18a** and 20 mL of 13% aqueous potassium hydroxide (w/v) in 15 mL of ethanol was refluxed under an argon atmosphere for 25 h. The mixture was poured into water and extracted with chloroform (3×). The combined organic portions were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified via flash chromatography (2% methanol saturated with ammonia in methylene chloride) and triturated with isopropyl ether to give 417 mg (67%) of amino ketone **19** as a white solid: mp 194–196 °C dec; IR ($CHCl_3$) 3020, 1680, 1582 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.72 (1 H, dd, J = 4.7, 1.9 Hz, H-2), 8.40 (1 H, dd, J = 8.0, 1.9 Hz, H-4), 7.35–7.20 (4 H, m), 4.40 (1 H, d, J = 14.1 Hz, H-6), 3.84 (1 H, d, J = 14.1 Hz, H-6′), 3.22–3.01 (2 H, m), 2.82–2.39 (4 H, m), 2.37–2.25 (2 H, m); MS (EI) m/e (%) 326 (M^+, 27), 324 (M^+, 80), 297 (35), 296 (59), 295 (94), 294 (100), 280 (42). Anal. Calcd for $C_{19}H_{17}N_2ClO$: C, 70.26; H, 5.28; N, 8.63; Cl, 10.92. Found: C, 70.07; H, 5.23; N, 8.44; Cl, 10.93.

2,2,2-Trichloroethyl 4-[8-Chloro-5-[[[(2,2,2-trichloroethyl)oxy]carbonyl]oxy]-11*H*-benzo[5,6]cyclohepta[1,2-*b*]-pyridin-11-ylidene]-1-piperidinecarboxylate (18b). To a mixture of 121 mg (0.357 mmol) of olefinic ketone **14d** and 75 μL (0.537 mmol) of triethylamine in 3 mL of dry toluene at 80 °C and under an argon atmosphere was added dropwise over 20

min 250 μL (1.82 mmol) of [(2,2,2-trichloroethyl)oxy]carbonyl chloride. After 30 min the mixture was poured into 30% aqueous sodium hydroxide (w/v) and extracted with methylene chloride (3×). The combined organic portions were dried over $MgSO_4$, filtered, concentrated in vacuo, and purified via flash chromatography (0.5–1% methanol in methylene chloride) to give 192 mg (80%) of troc-carbamate **18b** as a glass: IR ($CHCl_3$) 1778, 1710 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.71 (1 H, dd, J = 4.4, 1.5 Hz, H-2), 7.88 (1 H, dd, J = 8.1, 1.5 Hz, H-4), 7.46–7.18 (4 H, m), 6.97 (1 H, s, H-6), 4.90–4.64 (4 H, m, OCH_2), 4.01–3.80 (2 H, m), 3.20–2.88 (2 H, m), 2.44–2.22 (3 H, m), 2.21–2.08 (1 H, m); MS (FAB, thioglycerol matrix) m/z (%) 679 (M^+ + H, 47), 677 (M^+ + H, 47), 675 (M^+ + H, 100), 673 (M^+ + H, 48), 641 (17), 527 (18), 501 (26), 499 (23). HRMS (FAB, thioglycerol matrix) m/z calcd for $C_{25}H_{20}N_2Cl_7O_5$ (M^+ + H) 672.9192, found 672.9172.

2,2,2-Trichloroethyl 4-(8-Chloro-5,6-dihydro-5-hydroxy-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-piperidinecarboxylate (20). To a mixture of 25 mg (0.037 mmol) of troc-carbamate **18b** in 2 mL of dry methanol at 0 °C and under an argon atmosphere was added in one portion 11 mg (0.29 mmol) of sodium borohydride. After 1 h the mixture was quenched with water and extracted with methylene chloride (4×). The combined organic portions were dried over $MgSO_4$, filtered, and concentrated in vacuo to yield 15.5 mg (83%) of hydroxy carbamate **20** as a glass: IR ($CHCl_3$) 3575, 1710 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.53–8.45 (1 H, m, H-2), 7.91 (0.7 H, dd, J = 8.0, 1.5 Hz, H-4), 7.82 (0.3 H, dd, J = 8.2, 1.5 Hz, H-4), 7.34–7.11 (4 H, m), 5.22 (0.7 H, dd, J = 6.8, 3.3 Hz, H-5), 4.87 (0.3 H, dd, J = 11.8, 5.2 Hz, H-5), 4.77 (2 H, s, OCH_2), 4.03–3.73 (2 H, m), 3.60 (0.7 H, dd, J = 15.0, 3.3 Hz, H-6), 3.51 (0.3 H, dd, J = 13.0, 11.8 Hz, H-5′), 3.43–3.14 (2 H, m), 3.08 (0.3 H, dd, J = 13.0, 5.2 Hz, H-5), 3.01 (0.7 H, dd, J = 15.0, 6.8 Hz, H-6′), 2.76–2.22 (4 H, m); MS (FAB, thioglycerol matrix) m/z (%) 507 (M^+ + H, 11), 505 (M^+ + H, 44), 503 (M^+ + H, 100), 501 (M^+ + H, 88), 587 (18), 585 (30), 583 (22); HRMS (FAB, thioglycerol matrix) m/z calcd for $C_{25}H_{20}N_2Cl_4O_3$ (M^+ + H) 501.0306, found 501.0302.

8-Chloro-6,11-dihydro-5-hydroxy-11-(4-piperidinylidene)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (3b). Method A. To a mixture of 457 mg (1.41 mmol) of amino ketone **19** in 30 mL of methanol at 0 °C and under an argon atmosphere was added in three portions each 5 min apart 263 mg (6.95 mmol) of sodium borohydride. After 1.8 h the mixture was poured into water and extracted with methylene chloride (3×) followed by ethyl acetate (3×). The combined organic portions were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford a product which was precipitated out of 10% methanol saturated with ammonia in methylene chloride to give 410 mg (89%) of the 5-hydroxy compound **3b** as a white solid. The product is unstable in chlorinated solvents for extended periods of time possibly due to formation of its hydrochloride salt. It could be further purified by crystallization of the product from ethanol to yield the 5-hydroxy compound **3b** as a white solid: mp 245–248 °C dec; ^1H NMR (CD_3OD, 400 MHz) δ 8.39 (0.33 H, dd, J = 4.8, 1.6 Hz, H-2), 8.37 (0.67 H, dd, J = 5.0, 1.7 Hz, H-2), 7.99 (0.67 H, dd, J = 7.9, 1.7 Hz, H-4), 7.91 (0.33 H, dd, J = 7.9, 1.6 Hz, H-4), 7.39 (0.33 H, d, J = 1.7 Hz, H-7), 7.37 (0.67 H, dd, J = 7.9, 5.0 Hz, H-3), 7.32 (0.33 H, dd, J = 7.9, 4.8 Hz, H-3), 7.22–7.16 (1.67 H, m, H-9, H-7), 7.14 (0.67 H, d, J = 8.2 Hz, H-10), 7.11 (0.33 H, d, J = 8.0 Hz, H-10), 5.33 (0.67 H, dd, J = 9.2, 4.3 Hz, H-5), 4.76 (0.33 H, dd, J = 11.7, 5.3 Hz, H-5), 3.57 (0.67 H, dd, J = 16.2, 4.3 Hz, H-6), 3.54 (0.33 H, dd, J = 12.6, 11.7 Hz, H-6′), 3.04 (0.33 H, dd, J = 12.6, 5.3 Hz, H-6), 2.88 (0.67 H, dd, J = 16.2, 9.2 Hz, H-6′), 3.09–2.08 (8 H, m); MS (EI) m/e (%) 328 (M^+, 34), 326 (M^+, 100), 298 (39), 297 (71), 296 (65), 282 (44), 266 (35); HRMS (FAB, thioglycerol matrix) m/z calcd for $C_{19}H_{19}N_2ClO$ (M^+ + H) 327.1264, found 327.1286.

Method B. A mixture of 116 mg (0.231 mmol) of the 5-hydroxy carbamate **20** and 137 mg (2.10 mmol) of zinc dust in 5 mL of glacial acetic acid was heated at 60–70 °C under an argon atmosphere for 6 h. Additional amounts of zinc dust were added after 2, 3.5, and 5 h [122 mg (1.87 mmol), 137 mg (2.10 mmol) and 145 mg (2.22 mmol), respectively]. The reaction mixture was basified with ice-cold 15% aqueous sodium hydroxide (w/v) and extracted with methylene chloride containing 10% methanol (5×). The combined organic portions were dried over $MgSO_4$, filtered, concentrated in vacuo, and purified via flash chromatography (10% methanol–10% methanol saturated with ammonia in chloroform) to give 52 mg (69%) of the 5-hydroxy compound **3b** which was identical with the material prepared via method A above.

8-Chloro-6,11-dihydro-6-hydroxy-11-(1-methyl-4-piperidinylidene)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (21). To a mixture of 277 mg (0.818 mmol) of olefinic ketone **14c** in 14 mL of methanol at 0 °C and under a nitrogen atmosphere was added in two portions 10 min apart 156 mg (4.14 mmol) of sodium borohydride. After 1 h, during which the mixture was slowly allowed to warm to room temperature, it was poured into water and extracted with methylene chloride (2×). The combined organic portions were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford a product which was crystallized from ethyl acetate/diethyl ether to provide 270 mg (97%) of the *N*-methyl alcohol **21** as a yellowish solid: mp 222–225 °C dec; IR ($CHCl_3$) 3585, 3000, 1590, 1567 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 8.33 (0.7 H, dd, J = 4.8, 1.6 Hz, H-2), 8.31 (0.3 H, dd, J = 5.0, 1.5 Hz, H-2), 7.80 (0.3 H, dd, J = 7.6, 1.5 Hz, H-4), 7.63 (0.7 H, dd, J = 7.8, 1.6 Hz, H-4), 7.56 (0.7 H, d, J = 2.1 Hz, H-7), 7.47 (0.3 H, d, J = 2.1 Hz, H-7), 7.29–7.21 (2 H, m), 7.15 (0.3 H, d, J = 8.3 Hz, H-10), 7.12 (0.7 H, d, J = 8.2 Hz, H-10), 5.30 (0.7 H, dd, J = 9.0, 4.2 Hz, H-6), 4.72 (0.3 H, dd, J = 11.6, 5.5 Hz, H-6), 3.55 (0.7 H, dd, J = 16.0, 4.2 Hz, H-5), 3.50 (0.3 H, dd, J = 13.2, 11.6 Hz, H-5′), 3.10 (0.3 H, dd, J = 13.2, 5.5 Hz, H-5), 2.91 (0.7 H, dd, J = 16.0, 9.0 Hz, H-5′), 2.79–2.66 (2 H, m), 2.60–2.07 (6 H, m), 2.28 (0.9 H, s, NCH_3), 2.27 (2.1 H, s, NCH_3); MS (EI) m/e (%) 342 (M^+, 8.1), 340 (M^+, 23), 297 (27), 296 (24), 282 (16). Anal. Calcd for $C_{20}H_{21}N_2ClO$: C, 70.48; H, 6.21; N, 8.22; Cl, 10.40. Found: C, 70.35; H, 6.31; N, 7.90; Cl, 10.17.

***N*-(1,1-Dimethylethyl)-3-[1-methyl-2-(3-chlorophenyl)ethyl]-2-pyridinecarboxamide (24).** To a mixture of 19.26 g (100 mmol) of *tert*-butyl amide **23**[10] in 200 mL of dry tetrahydrofuran at −45 °C and under an argon atmosphere was added dropwise, so that the internal temperature did not exceed −40 °C, 82 mL of 2.5 M *n*-butyllithium (205 mmol) in hexane. The resultant deep purple solution was stirred at this temperature for 30 min after which 7.40 mL (119 mmol) of methyl iodide was added dropwise so that the internal temperature did not exceed −20 °C. After the mixture was cooled back down to −45 °C and stirred for 10 min, another 43 mL of 2.5 M *n*-butyllithium (108 mmol) in hexane was added dropwise so that the internal temperature again did not exceed −40 °C. After 15 min 7.06 g (69 mmol) of sodium bromide was added followed by 14.0 mL (110 mmol) of 3-chlorobenzyl chloride so that the internal temperature did not exceed −40 °C. The reaction mixture was stirred for 1 h while it warmed to −5 °C. It was then quenched with water and extracted with ethyl acetate (2×). The combined organic portions were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to give 33.0 g (100%) of *tert*-butyl amide **24** as an oil. The crude material was pure enough to be utilized directly in the next step. However, an analytical sample was prepare via flash chromatography (15% ethyl acetate in hexanes) to give *tert*-butyl amide **24** as a colorless oil: IR ($CHCl_3$) 3360, 1669 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.35 (1 H, dd, J = 4.6, 1.6 Hz, H-2), 7.72 (1 H, dd, J = 8.0, 1.6 Hz, H-4), 7.56 (1 H, b s, NH), 7.33 (1 H, dd, J = 8.0, 4.6 Hz, H-3), 7.18–6.98 (4 H, m), 4.63 (1 H, ddq, J = 8.0, 6.8, 7.0 Hz, C*H*CH_2), 2.95 (1 H, dd, J = 13.4, 6.8 Hz, CHC*H*H), 2.71 (1 H, dd, J = 13.4, 8.0 Hz, CHCH*H*), 1.47 (9 H, s, $NCMe_3$), 1.25 (3 H, d, J = 7.0 Hz, CH_3); MS (EI) m/e (%) 332 (M^+, 17), 330 (M^+, 50), 275 (38), 273 (100), 258 (28), 256 (43), 230 (27), 228 (34). Anal. Calcd for $C_{19}H_{23}N_2ClO$: C, 68.98; H, 7.01; N, 8.47; Cl, 10.72. Found: C, 68.73; H, 6.85; N, 8.23; Cl, 10.49.

3-[1-Methyl-2-(3-chlorophenyl)ethyl]-2-pyridinecarbonitrile (25). A mixture of 33.0 g (99.8 mmol) of *tert*-butyl amide **24** in 130 mL of phosphorous oxychloride was refluxed under an argon atmosphere for 1.75 h. The mixture was cooled, carefully poured onto ice [*Caution*: rapid evolution of HCl gas and heat], basified with cooling using 50% aqueous sodium hydroxide (w/v), and extracted with methylene chloride (3×). The combined organic portions were dried over Na_2SO_4, filtered, and concentrated in vacuo. The resultant black oil was dissolved in ethyl acetate, treated with activated charcoal, filtered, and concentrated in vacuo again to afford 19.3 g (75%) of pyridyl nitrile **25** as a white solid: mp 56–57 °C; IR ($CHCl_3$) 2225 cm^{-1}; ^1H NMR ($CDCl_3$,

300 MHz) δ 8.57 (1 H, dd, J = 4.7, 1.6 Hz, H-2), 7.72 (1 H, dd, J = 8.1, 1.6 Hz, H-4), 7.49 (1 H, dd, J = 8.1, 4.7 Hz, H-3), 7.25–7.15 (2 H, m), 7.12–6.98 (2 H, m), 3.57 (1 H, ddq, J = 8.1, 6.7, 6.6 Hz, CHCH$_2$), 2.96 (1 H, dd, J = 13.6, 6.7 Hz, CHCHH), 2.83 (1 H, dd, J = 13.6, 8.1 Hz, CHCHH), 1.33 (3 H, d, J = 6.6 Hz, CH$_3$); MS (FAB, thioglycerol matrix) m/z (%) 259 (M$^+$ + H, 36), 257 (M$^+$ + H, 100). Anal. Calcd for $C_{15}H_{13}N_2Cl$: C, 70.18; H, 5.10; N, 10.91; Cl, 13.81. Found: C, 70.19; H, 5.20; N, 10.93; Cl, 13.70.

8-Chloro-5,6-dihydro-5-methyl-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-one (26). A mixture of 13.5 g (55.8 mmol) of pyridyl nitrile **25** in 335 g of polyphosphoric acid was heated between 190 and 200 °C under an argon atmosphere for 2 h. The mixture was poured onto ice, acidified with concentrated hydrochloric acid, stirred for 1 h, and extracted with ether (1×). The aqueous phase was basified to pH ~ 12 with aqueous sodium hydroxide and extracted with methylene chloride, which was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was dissolved in ethyl acetate, treated with activated carbon, filtered, concentrated again, and triturated with pentane/isopropyl ether/ethyl acetate to give 4.91 g (34%) of the 5-methyl ketone **26** as a white solid: mp 78–80 °C; IR ($CHCl_3$) 1667 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.68 (1 H, dd, J = 4.6, 1.6 Hz, H-2), 7.99 (1 H, d, J = 8.4 Hz, H-10), 7.68 (1 H, dd, J = 7.8, 1.6 Hz, H-4), 7.40 (1 H, dd, J = 7.8, 4.6 Hz, H-3), 7.33 (1 H, dd, J = 8.4, 2.1 Hz, H-9), 7.23 (1 H, d, J = 2.1 Hz, H-7), 3.46–3.37 (2 H, m, H-5, H-6), 3.05 (1 H, dd, J = 16.6, 8.3 Hz, H-6′), 1.35 (3 H, d, J = 7.0 Hz, CH$_3$); ^{1}H NMR (C_6D_6, 400 MHz) δ 8.44 (1 H, dd, J = 4.6, 1.5 Hz, H-2), 7.88 (1 H, d, J = 8.6 Hz, H-10), 6.87 (1 H, dd, J = 8.6, 2.0 Hz, H-9), 6.84 (1 H, dd, J = 7.9, 1.5 Hz, H-4), 6.70 (1 H, d, J = 2.0 Hz, H-7), 6.65 (1 H, dd, J = 7.9, 4.6 Hz, H-3), 2.59 (1 H, ddq, J = 9.2, 2.1, 7.0 Hz, H-5), 2.43 (1 H, dd, J = 17.0, 2.1 Hz, H-6), 2.19 (1 H, dd, J = 17.0, 9.2 Hz, H-6′), 0.75 (3 H, d, J = 7.0 Hz, CH$_3$); MS (EI) m/e (%) 259 (M$^+$, 28), 257 (M$^+$, 82), 256 (59), 244 (27), 242 (81), 229 (30), 222 (100), 216 (22), 215 (33), 214 (56). Anal. Calcd for $C_{15}H_{12}NClO$: C, 69.91; H,4.69; N, 5.44; Cl, 13.76. Found: C, 69.70; H, 4.58; N, 5.36; Cl, 13.66.

(1-Methyl-4-piperidinyl)[3-[1-methyl-2-(3-chlorophenyl)ethyl]-2-pyridinyl]methanone (27). To a mixture of 429 mg (1.81 mmol) of pyridyl nitrile **25** in 10 mL of dry tetrahydrofuran at 50–60 °C and under a nitrogen atmosphere was added dropwise over 10 min 2.5 mL (3.75 mmol) of a 1.5 M Grignard solution of 4-chloro-1-methylpiperidine[9] in tetrahydrofuran. The mixture was then heated at this temperature for 30 min, after which it was cooled to room temperature and quenched with 10 mL of water. A solution (10 mL) of 10% aqueous hydrochloric acid was added, and the mixture was stirred for 1.5 h. It was then basified with 20% aqueous sodium hydroxide and extracted with ethyl acetate (3×). The combined organic portions were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give a product, which was purified via flash chromatography (8% methanol in methylene chloride) to give 406 mg (63%) of piperidyl ketone **27** as a colorless oil: IR ($CHCl_3$) 1696 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.47 (1 H, dd, J = 4.6, 1.5 Hz, H-2), 7.77 (1 H, dd, J = 8.0, 1.5 Hz, H-4), 7.39 (1 H, dd, J = 8.0, 4.6 Hz, H-3), 7.19–7.09 (2 H, m), 7.06–7.02 (1 H, m), 7.00–6.94 (1 H, m), 3.63 (1 H, ddq, J = 7.9, 7.0, 6.9 Hz, CHCH$_2$), 3.62–3.47 (1 H, m, COCH), 2.96 (1 H, dd, J = 13.5, 7.0 Hz, CHCHH), 2.96–2.79 (2 H, m), 2.69 (1 H, dd, J = 13.5, 7.9 Hz, CHCHH), 2.30 (3 H, s, NCH$_3$), 2.15–1.97 (2 H, m), 1.90–1.47 (4 H, m), 1.24 (3 H, d, J = 6.9 Hz, CH$_3$); MS (FAB, thioglycerol matrix) m/z (%) 359 (M$^+$ + H, 35), 357 (M$^+$ + H, 100), 356 (22), 355 (48). Anal. Calcd for $C_{21}H_{25}N_2ClO$: C, 70.67; H, 7.06; N, 7.85; Cl, 9.93. Found: C, 70.51; H, 7.13; N, 7.73; Cl, 9.95.

8-Chloro-6,11-dihydro-5-methyl-11-(4-piperidinylidene)-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (22). A mixture of 266 mg (0.745 mmol) of piperidyl ketone **27** in 5 mL of trifluoromethanesulfonic acid was heated between 60 and 70 °C under a nitrogen atmosphere for 21 h. The mixture was poured into an ice-cold solution of 10% aqueous sodium hydroxide (w/v) and extracted with methylene chloride (4×). The combined organic portions were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified via flash chromatography (5% methanol saturated with ammonia in methylene chloride) to give 225 mg (89%) of the 5-methyl piperidinylidene **22** as a glass: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.40 (0.55 H, dd, J = 5.1, 1.5 Hz, H-2), 8.38 (0.45 H, dd, J = 5.0, 1.8 Hz, H-2), 7.54 (1.65 H, dd, J = 7.8, 1.5 Hz, H-4), 7.41 (0.45 H, dd, J = 7.9, 1.8 Hz, H-4), 7.23 (0.45 H, d, J = 1.6 Hz, H-7), 7.18–7.04 (3.55 H, m), 3.59 (0.55 H, ddq, J = 10.1, 4.0, 6.9 Hz, H-5), 3.43 (0.55 H, dd, J = 16.3, 4.0 Hz, H-6), 3.20 (0.45 H, dd, J = 13.1, 12.5 Hz, H-6′), 3.09 (0.45 H, ddq, J = 12.5, 5.2, 6.7 Hz, H-5), 2.75 (0.45 H, dd, J = 13.1, 5.2 Hz, H-6), 2.58 (0.55 H, dd, J = 16.3, 10.1 Hz, H-6′), 2.28 (1.35 H, s, NCH$_3$), 2.27 (1.65 H, s, NCH$_3$), 2.84–1.98 (8 H, m), 1.40 (1.35 H, d, J = 6.7 Hz, CH$_3$), 1.33 (1.65 H, d, J = 6.9 Hz, CH$_3$); MS (EI) m/e (%) 340 (M$^+$, 17), 338 (M$^+$, 50), 298 (39), 296 (25), 295 (51), 294 (48), 282 (21), 281 (22), 280 (46), 268 (19), 266 (44). Anal. Calcd for $C_{21}H_{23}N_2Cl$: C, 74.43; H, 6.84; N, 8.27; Cl, 10.46. Found: C, 74.43; H, 7.03; N, 8.00; Cl, 10.11.

8-Chloro-11-(1-methyl-1-oxo-4-piperidinylidene)-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridine (29). To a mixture of 106 mg (0.326 mmol) of the *N*-methyl amine **28**[16] in 5 mL of dry methylene chloride at 0 °C and under an argon atmosphere was added dropwise a solution of 58 mg (0.336 mmol) of *m*-chloroperoxybenzoic acid in 1.5 mL of dry methylene chloride. The reaction mixture was slowly allowed to warm to room temperature. After 3 days it was poured into 10% aqueous sodium hydroxide (w/v) and extracted with methylene chloride (3×). The combined organic portions were dried over $MgSO_4$, filtered, concentrated in vacuo, and purified via flash chromatography to afford 109 mg (98%) of amine oxide **29** as a tan solid: mp 186–188 °C dec; IR ($CHCl_3$) 955 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.42 (0.33 H, dd, J = 4.9, 1.5 Hz, H-2), 8.38 (0.67 H, dd, J = 4.8, 1.6 Hz, H-2), 7.48–7.40 (1 H, m, H-4), 7.22–7.03 (4 H, m), 3.58 (0.67 H, td, J =11.4, 3.8 Hz), 3.51–3.15 (5.33 H, m), 3.30 (2 H, s, NCH$_3$), 3.26 (1 H, s, NCH$_3$), 3.08–2.38 (6 H, m); MS (EI) m/e (%) 342 (M$^+$, 1.8), 340 (M$^+$, 7.5), 324 (52), 282 (46), 281 (96), 280 (91), 266 (80). Anal. Calcd for $C_{20}H_{21}N_2ClO{\cdot}0.5H_2O$: C, 68.66; H, 6.05; N, 8.01; Cl, 10.13. Found: C, 68.64; H, 6.39; N, 7.65; Cl, 10.28.

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