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REINVESTIGATION OF THE CONFORMATIONS OF A VARIETY OF HEXAHYDROBENZO[*C*]PHENANTHRIDINE ALKALOIDS BY 470 MHz PMR AND 50 MHz CMR SPECTROSCOPY

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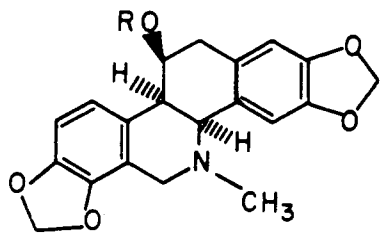
ABSTRACT.—The high resolution pmr and cmr spectra of a variety of benzo[*c*]phenanthridine alkaloids and their CF_3COOD salts were examined. The chemical shift of H-14 was found to be a reliable indicator of the orientation of the *N*-methyl group. The conformations of the C rings were assigned on the basis of the coupling constants between H-11 and the two H-12 protons. On the basis of the pmr spectra of (+)-14-epicorynoline (**9**) and (±)-14-epicorynoline-6,6,12α-d_3 (**13**), a revision of certain previous C ring conformations is indicated.

The conformations of certain hexahydrobenzo[*c*]phenanthridine alkaloids remain controversial despite considerable investigation by ir, pmr, and cmr spectroscopy. For example, the boat (1), half-chair (2-5),[1] and twist half-chair (6) conformations have all been proposed for the C ring of chelidonine (**1**), the principal alkaloid of *Chelidonium majus*. The last hypothesis was recently advanced in order to explain the fact that at 360 MHz the coupling of the C-11 proton to only one of the C-12 protons (J=4.3 Hz) is evident (6). This observation has raised some questions regarding the previous conformational assignments of a variety of related benzophenanthridines because they were made using a lower magnetic field strength that did not allow the resolution of the 12α and 12β protons (5).

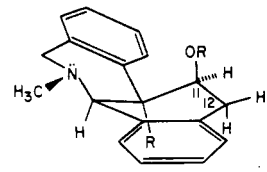


1, R=H
1-Ac, R=CH_3CO

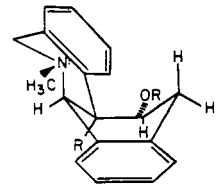
For the *cis*-fused alkaloids, two main conformational types may be discerned in which the aromatic A ring is either equatorial (type I) or axial (type II) with respect to the C ring. These two main conformational types may be subdivided further into forms in which the C ring is either in the half-chair or half-boat conformation (Figure 1). The twist forms of these half-chair and half-boat conformations must also be considered. The Newman projections of the various possibilities are presented in Figure 2.

It is of interest to know the conformations of the benzophenanthridines in solution because the solid-state conformations of certain members of this class have already been determined. The results of the conformation studies of these alkaloids in solution

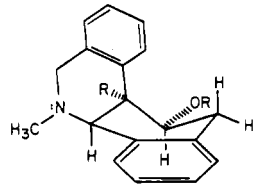
[1]The abbreviations ax and eq were used by Takao, *et al.* (5) to designate the relative configurations of the C-6 substituents. These correspond to α and β substituents, respectively. A reversal of the previous 12α, 12β proton designations in (+)-14-epicorynoline (**9**) is necessitated by the establishment of its absolute configuration [see Takao, *et al.* (7)], which is opposite of that previously portrayed (5).



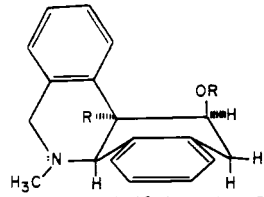
cis - Type-I half-chair ring C
equatorial *N*-methyl



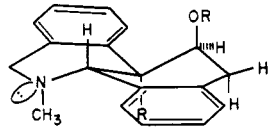
cis - Type-I half-boat ring C
equatorial *N*-methyl



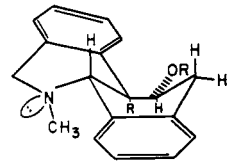
cis - Type-II half-boat ring C
equatorial *N*-methyl



cis - Type-II half-chair ring C
equatorial *N*-methyl

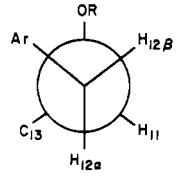


trans - half-chair ring C
axial *N*-methyl

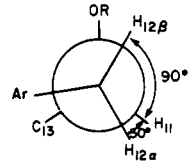


trans - half-boat ring C
axial *N*-methyl

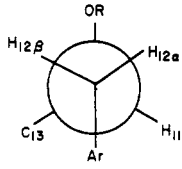
FIGURE 1. Conformational possibilities of the *cis*- and *trans*-hexahydrobenzo[c]phenanthridine alkaloids



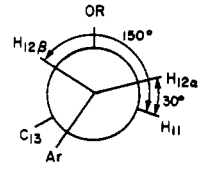
cis - Type-I half-chair ring C
cis - Type-II half-boat ring C
trans - half-chair ring C



cis - Type-I twist half-chair ring C
cis - Type-II twist half-boat ring C
trans - twist half-chair ring C



cis - Type-I half-boat ring C
cis - Type-II half-chair ring C
trans - half-boat ring C



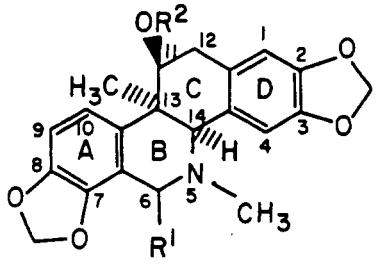
cis - Type-I twist half-boat ring C
cis - Type-II twist half-chair ring C
trans - twist half-boat ring C

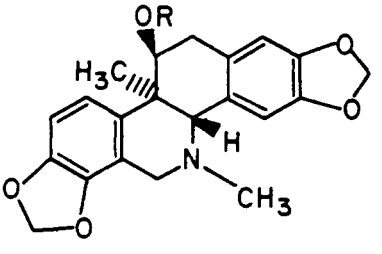
FIGURE 2. Newman projections of the various possible benzophenanthridine conformers along the C-11, C-12 bond.

should therefore be important in relation to the general question of how closely solid state conformations resemble solution conformations. X-Ray diffraction studies have established the *trans*-B/C-half-chair/twist half-chair conformation for (+)-14-epicorynoline (**9**) *p*-bromoacetate (7), the *cis*-type I-B/C half-chair/twist half-boat conformation for (±)-corynoline (**2**) *p*-bromobenzoate (8), the *cis*-type I-B/C-half-chair/half-chair for (±)-corynoline (**2**), and the *cis*-type II-B/C-twist half-chair/half-chair, and *cis*-type II-B/C-half-chair/twist half-chair for (+)-chelidonine (**1**) *p*-bromobenzoate (9). It has been suggested that (+)-14-epicorynoline (**9**) and its acetate (**9-Ac**) have nearly the same conformation as the bromoacetate of **9** (5,7), and (±)-corynoline acetate (**2-Ac**) adopts the same conformation as the bromobenzoate of **2** (10). The conformations of the B and C rings in solution have been shown in these cases to resemble those of the solid state.

A reinvestigation of the solution conformations of a variety of benzophenanthridines has now been completed using 470 MHz pmr spectroscopy. This study has provided new insights regarding the conformations of these substances as described in the present report. The compounds investigated were (+)-chelidonine (**1**) (11-13), (±)-corynoline (**2**) (14-15), (±)-6β-methylcorynoline (**3**) (16), (±)-6α-methylcorynoline (**4**) (16), (±)-corynolamine (**5**) (16), (±)-6α-acetonylcorynoline (**6**) (5), (±)-6α-vinylcorynoline (**7**) (5), (±)-6β-vinylcorynoline (**8**) (5), (+)-14-epicorynoline (**9**) (17-19), (+)-acetylchelidonine (**1-Ac**) (20), (±)-acetylcorynoline (**2-Ac**) (21), (±)-acetyl-6β-methylcorynoline (**3-Ac**) (5), (±)-acetyl-6α-methylcorynoline (**4-Ac**) (5), (±)-11-*O*-acetylcorynolamine (**5-Ac**) (16), (±)-diacetylcorynolamine (**5-diAc**) (16), (±)-acetyl-6α-acetonylcorynoline (**6-Ac**) (22), (±)-acetyl-6α-vinylcorynoline (**7-Ac**) (5), (±)-acetyl-6α-vinylcorynoline (**8-Ac**) (5), and (+)-acetyl-14-epicorynoline (**9-Ac**) (21). Compounds **1, 2, 5, 9, 2-Ac,** and **9-Ac** are natural products, while the remaining substances are synthetically derived.

It may be concluded after examination of Figure 2 that definite assignments of the conformations of the C ring can be made only when it is known whether the molecules exist predominantly in type I or type II conformations. Fortunately, it has already been



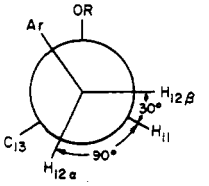


2, $R^1=R^2=H$
2-Ac, $R^1=H$, $R^2=CH_3CO$
3, $R^1=$ —CH_3, $R^2=H$
3-Ac, $R^1=$ —CH_3, $R^2=CH_3CO$
4, $R^1=$ ····CH_3, $R^2=H$
4-Ac, $R^1=$ ····CH_3, $R^2=CH_3CO$
5, $R^1=$ ····CH_2OH, $R^2=H$
5-Ac, $R^1=$ ····CH_2OH, $R^2=CH_3CO$
5-diAc, $R^1=$ ····CH_2OCOCH_3, $R^2=CH_3CO$
6, $R^1=$ ····CH_2COCH_3, $R^2=H$
6-Ac, $R^1=$ ····CH_2COCH_3, $R^2=CH_3CO$
7, $R^1=$ ····$CH=CH_2$, $R^2=H$
7-Ac, $R^1=$ ····$CH=CH_2$, $R^2=CH_3CO$
8, $R^1=$ —$CH=CH_2$, $R^2=H$
8-Ac, $R^1=$ —$CH=CH_2$, $R^2=CH_3CO$

9, R=H
9-Ac, $R=CH_3CO$

established that all of the B/C *cis*-fused compounds described in this report exist in the type I conformation, except (+)-chelidonine acetate (**1-Ac**), which adopts the type II conformation (5).

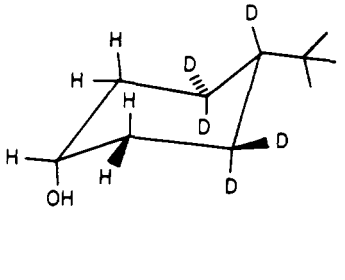
Examination of Table 1 reveals that in every case in compounds **1-9**, the C-11 proton is coupled to only one of the two C-12 protons. Three explanations are possible in order to account for this observation. The first is that the C rings exist in twist half-chair conformations in which the dihedral angles between the C-11 and C-12α protons are close to 90°, as shown in Figure 3. In this case, the C-11 protons would be coupled to



cis - Type-I twist half-chair ring C
trans - Type-I twist half-chair ring C

FIGURE 3. Newman projection of an unlikely benzophenanthridine conformer along the C-11, C-12 bond.

the C-12β protons. Examination of Dreiding models reveals that this is unlikely because of additional strain on the C ring in going from the half-chair to this twist half-chair. The second possible explanation is that the C rings exist in half-chairs. In this case, the difference in coupling between the C-11 proton and the two C-12 methylene protons cannot be attributed to a difference in dihedral angles because they are almost identical (Figure 2). However, it might be argued that this difference is due to a stereochemically dependent electronegativity effect of the pseudoaxial hydroxyl group in decreasing the coupling between the pseudoequatorial C-11 proton and the pseudoaxial C-12α proton (23,24). The difference observed here (0 *vs.* 4.3-5.0 Hz) seems to be too large to be explained by such an effect. For example, in compound **10** $J_{a,e}$=3.00 Hz and $J_{e,e}$=2.72 Hz (25). In 12α-acetoxy steroids **11** (24), $J_{a,e}$ is reported to be equal to $J_{e,e}$ (2.5 Hz). The half-chair conformation of the C ring of chelidonine does not appear



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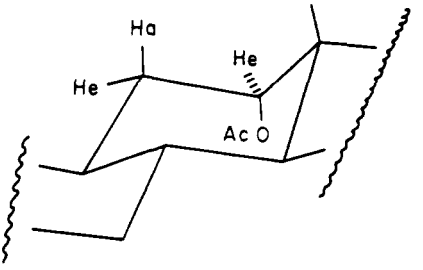

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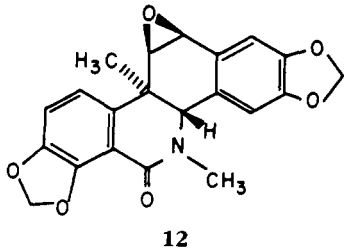

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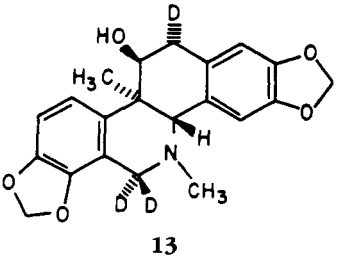


13

TABLE 1. Partial 470 MHz Pmr Spectra of 11-Hydroxybenzophenanthridines in $CDCl_3$

Assignment	Compound									
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**13**
4 and 1	6.65 (s) 6.63 (s)	6.64 (s) 6.62 (s)	6.64 (s) 6.59 (s)	6.64 (s) 6.60 (s)	6.75 (s) 6.63 (s)	6.63 (s) 6.58 (s)	6.63 (s) 6.57 (s)	6.64 (s) 6.61 (s)	7.17 (s) 6.61 (s)	7.17 (s) 6.61 (s)
11	4.22 (dd, 4.4, 2.2)	3.96 (m)	3.98 (m)	3.94 (m)	3.97 (m)	3.94 (m)	3.94 (m)	4.00 (brs)	4.32 (d, 5.0)	4.32 (s)
14	3.56 (d, 2.2)	3.32 (d, 1.7)	3.33 (d, 1.9)	3.84 (s)	4.30 (s)	3.69 (s)	3.88 (s)	3.37 (d, 1.9)	4.50 (s)	4.50 (s)
12β	3.20 (d, 17.6)	3.16 (d, 17.7)	3.18 (d, 17.8)	3.14 (d, 17.8)	3.11 (d, 17.8)	3.12 (d, 17.8)	3.14 (d, 17.7)	3.18 (d, 18.1)	2.82 (d, 18.3)	2.82 (bd s)
12α	3.07 (dd, 17.6, 4.4)	3.07 (dd, 17.7, 4.5)	3.11 (dd, 17.8, 4.9)	3.04 (dd, 17.8, 4.3)	3.04 (dd, 17.8, 4.4)	3.03 (dd, 17.8, 4.3)	3.03 (dd, 17.7, 4.3)	3.12 (dd, 18.1, 4.7)	3.20 (dd, 18.3, 5.0)	
N-CH_3	2.26 (s)	2.22 (s)	2.16 (s)	2.15 (s)	2.33 (s)	2.27 (s)	2.16 (s)	2.12 (s)	2.48 (s)	2.48 (s)

to be tenable (6). The third explanation is that the C rings of compounds **1-9** adopt the alternative *cis*-type I- or *trans*-twist half-chair conformations depicted in Figure 2. In this case, the C-11 protons of these compounds would be coupled to the C-12α protons.

In order to silence any persistent arguments about which of the three possible explanations above is correct, (±)-14-epicorynoline-6,6,12α-d_3 (**13**) was synthesized by reduction of the epoxide **12** (26) with lithium aluminum deuteride. Comparison of the spectra of **9** and **13** (Table 1) allows one to conclude that in compound **9** the C-11 proton is coupled only to the C-12α proton. This conclusion is only consistent with the third interpretation above, i.e., the C rings of **1-9** are in the *cis*-type-I-twist half-chair or *trans*-twist half-chair conformations.

The *cis*-compounds having an acetoxy group at C-11 are more problematic because the type I-half-chair or type I-twist-chair ring C conformers are no longer stabilized by intramolecular hydrogen bonds. Compound **1-Ac** was previously assigned the type-II conformation on the basis of upfield shifts for carbons C-12 and C-6 in its cmr spectrum (5). The coupling constants observed between H-11 and H-12α (5.0 Hz, Table 2), and H-11 and H-12β (11.3 Hz) therefore allow assignment of the half-chair conformation to the C ring of **1-Ac**. Compounds **2-Ac, 3-Ac,** and **8-Ac** are assigned the twist half-boat conformation of the C ring on the basis of the fact that the $J_{11,12\alpha}$ and $J_{11,12\beta}$ couplings are relatively large (6.0-8.6 Hz, Table 2) and are nearly the same in magnitude. In compounds **4-Ac, 5-Ac, 5-diAc, 6-Ac,** and **7-Ac**, these coupling constants are also nearly equal to each other, but they are smaller in magnitude (2.5-4.7 Hz), and these acetates may therefore be assigned the ring C half-chair conformation. Finally, the C ring of the *trans*-metabolite (+)-acetyl-14-epicorynoline (**9-Ac**) is assigned the twist half chair conformation. These conclusions are summarized in Table 3.

The second major problem to be addressed here concerns the orientations of the *N*-methyl groups in solution. The various possibilities for the *cis*-type I, *cis*-type II, and *trans*-compounds are depicted in Figure 4. X-Ray diffraction studies have confirmed the axial orientation of the *N*-methyl groups of (+)-14-epicorynoline (**9**) bromoacetate (7) and (+)-chelidonine (**1**) bromobenzoate (9), and the equatorial orientation for both (±)-corynoline (**2**) (10) and its bromobenzoate (8).

It was previously proposed that the *N*-methyl groups are equatorial in **1, 2, 3, 8, 2-Ac, 3-Ac,** and **8-Ac** because of the Bohlmann bands evident in the ir spectra of these compounds, while **9** and **9-Ac** have axial *N*-methyl groups because Bohlmann bands are absent (5, 27-29). In the latter compounds, the H-4 chemical shift appears at a lower field (δ 7.17-7.22) than in the former (δ 6.64-6.71). Evidently, the H-4 proton is deshielded by an equatorial lone pair of electrons on the nitrogen. Since the chemical shifts of this proton are intermediate between these two values in compounds **2-Ac** and **4-Ac** through **7-Ac**, this parameter suggests that these compounds exist with an equilibrium mixture of equatorial and axial *N*-methyl groups. In compounds **1-8, 3-Ac,** and **8-Ac**, the H-4 chemical shifts (δ 6.64-6.75) indicate an equatorial orientation of the *N*-methyl group.

Another indicator of whether or not an equilibrium mixture of equatorial and axial *N*-methyl groups exists proved to be the width at half-height (W_H) of the *N*-methyl signals. In all of the free bases studied (except **3-Ac** through **7-Ac**), W_H was 7 Hz or less. Significant broadening of the signals was observed in compounds **3-Ac** through **7-Ac: 3-Ac** (13 Hz), **4-Ac** (18 Hz), **5-Ac** (15 Hz), **5-diAc** (47 Hz), **6-Ac** (12 Hz), **7-Ac** (19 Hz). The effect was evident for most of the signals in these spectra but was most pronounced for the *N*-methyl signals. This broadening is attributed to the existence of equilibrium mixtures of the two possible *N*-methyl orientations in these compounds. In support of this interpretation, in every case in which this broadening of the *N*-methyl signal was evident, two sharp *N*-methyl signals appeared immediately after the

TABLE 2. Partial 470 MHz Pmr Spectra of *O*-Acetylated Benzophenanthridines in $CDCl_3$

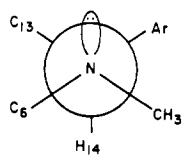
Assignment	Compound									
	1-Ac	**2-Ac**	**3-Ac**	**4-Ac**	**5-Ac**[b]	**5-diAc**[b]	**6-Ac**[b]	**7-Ac**	**8-Ac**	**9-Ac**
4 and 1	7.20 (s) 6.40 (s)	6.86 (s) 6.50 (s)	6.71 (s) 6.60 (s)	7.02 (s) 6.49 (s)	7.00 (s) 6.53 (s)	7.02 (s) 6.49 (s)	6.90 (s) 6.50 (s)	7.10 (s) 6.50 (s)	6.684 (s) 6.63 (s)	7.22 (s) 6.58 (s)
11	5.31 (ddd, 11.3, 5.0, 4.5)	5.20 (dd, 8.6, 6.0)	5.12 (t, 7.6)	5.37 (t, 4.8)	5.45 (dd, 4.5, 2.5)	5.43 (dd, 4.2, 2.8)	5.46 (dd, 4.0, 2.8)	5.46 (t, 3.9)	5.14 (t, 7.9)	5.49 (d, 3.8)
14	4.11 (d, 4.5)	3.49 (s)	3.31 (brs)	4.07 (s)	4.14 (m)	4.20 (s)	4.16 (s)	4.07 (s)	3.31 (brs)	4.50 (brs)
12β	2.88 (dd, 14.9, 11.3)	2.94 (dd, 15.2, 8.6)	2.93 (dd, 14.8, 7.6)	3.00 (dd, 16.7, 4.7)[a]	2.98 (dd, 18.0, 2.5)	2.85 (dd, 17.5, 3.8)[a]	2.85 (dd, 18.0, 2.8)	3.04 (dd, 17.3, 3.9)[a]	3.33 (dd, 14.8, 7.6)	2.80 (d, 18.7)
12α	2.74 (dd, 14.9, 5.0)	2.82 (dd, 15.0, 6.0)	3.31 (dd, 14.8, 7.6)	2.85 (dd, 16.8, 4.7)[a]	3.14 (dd, 18.0, 4.3)	3.09 (dd, 17.5, 4.2)[a]	3.08 (dd, 18.0, 4.0)	2.86 (dd, 17.3, 3.9)[a]	2.96 (dd, 14.8, 8.2)	3.24 (dd, 18.7, 4.8)
N-CH_3	2.54 (s)	2.46 (s)	2.16 (s)	2.25 (s)	2.25 (s)	2.23 (s)	2.13 (s)	2.20 (s)	2.12 (s)	2.47 (s)

[a]These assignments may be reversed.
[b]The spectrum was obtained at 200 MHz.

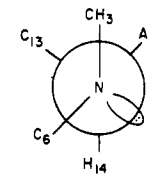
TABLE 3. Conformations of the C Rings and Orientations of the *N*-Methyl Groups of the Free Bases in $CDCl_3$ Solution and of the *N*-Methyl Groups in the Salts Formed Immediately after the Addition of CF_3COOD to $CDCl_3$ Solutions of the Free Bases.

Compound	C Ring Conformation[a]	Type[a]	*N*-Methyl[a]	% Equatorial[b]	% Axial[b]
1	twist half-chair	I	eq	100	0
2	twist half-chair	I	eq	100	0
3	twist half-chair	I	eq	100	0
4	twist half-chair	I	eq	100	0
5	twist half-chair	I	ax	0	100
6	twist half-chair	I	eq	100	0
7	twist half-chair	I	eq	100	0
8	twist half-chair	I	eq	100	0
9	twist half-chair	I	ax	0	100
1-Ac	half-chair	II	ax	95	5
2-Ac	twist half-boat	I	eq ⇌ ax	100	0
3-Ac	twist half-boat	I	eq ⇌ ax	80	20
4-Ac	half-chair	I	eq ⇌ ax	68	32
5-Ac	half-chair	I	eq ⇌ ax	25	75
5-diAc	twist half-chair	I	eq ⇌ ax	60	40
6-Ac	half-chair	I	eq ⇌ ax	13	87
7-Ac	half-chair	I	eq ⇌ ax	89	11
8-Ac	twist half-boat	I	eq	100	0
9-Ac	twist half-chair	I	ax	0	100

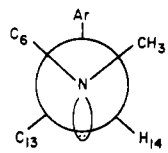
[a]Free bases
[b]Salts



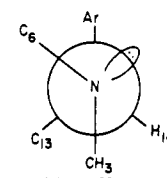
cis - Type I
equatorial *N*-methyl
axial lone pair



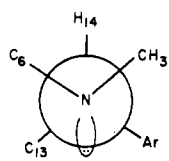
cis - Type I
axial *N*-methyl
equatorial lone pair



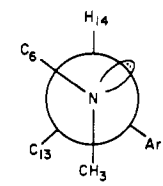
cis - Type II
equatorial *N*-methyl
axial lone pair



cis - Type II
axial *N*-methyl
equatorial lone pair



trans
equatorial *N*-methyl
axial lone pair



trans
axial *N*-methyl
equatorial lone pair

FIGURE 4. Newman projections of the various orientations of the nitrogen as viewed along the N-C_{14} bond.

addition of CF_3COOD to $CDCl_3$ solutions of the compounds (Table 4). The formation of diastereomeric mixtures of salts in these cases was also evident in the appearance of two sets of signals for the protons attached to the B and C rings as well as those of the C-methyls, the acetates, and the substituents located at C-6. The free bases displaying narrow *N*-methyl signals always produced only one narrow *N*-methyl signal after salt formation.

TABLE 4. Partial 470 MHz Pmr Spectra of *O*-Acylated Benzophenanthridines in $CDCl_3+CF_3COOD$ (4:1)

Assignment	Compound								
	1-Ac (Major, 95:5)	**1-Ac** (Minor)	**2-Ac**	**3-Ac** (Major, 80:20)	**3-Ac** (Minor)	**4-Ac** (Major, 58:32)	**4-Ac** (Minor)	**5-Ac** (Major, 75:25)	**5-Ac** (Minor)
4 and 1	6.85 (s) 6.67 (s)		6.81 (s) 6.70 (s)	6.76 (s) 6.69 (s)		6.74 (s) 6.70 (s)		6.85 (s) 6.67 (s)	
11	5.60 (m)	5.90 (m)	5.45 (brs)	5.46 (d, 6.3)	5.71 (d, 4.1)	5.44 (d, 5.5)	5.66 (d, 4.3)	5.66 (d, 4.5)	5.42 (d, 5.7)
14	4.62 (d, 4.2)	5.19 (d, 8)	4.23 (s)	4.14 (s)	4.86 (s)	4.34 (s)	4.91 (s)	4.96 (s)	4.13 (s)
12β	3.16 (dd, 18.6, 3.2)[a]		3.31 (d, 19.7)	3.16 (d, 19.7)	3.0 (overlap)	3.13 (d, 19.3)	3.00 (d, 19.0)	3.01 (d, 18.8)	3.11 (d 20.6)
12α	3.27 (dd, 18.6, 3.2)[a]		3.13 (dd, 19.7, 4.6)	3.38 (dd, 19.7, 6.3)	3.23 (dd, 19.0, 4.1)	3.29 (dd, 19.3, 5.5)	3.24 (dd, 19.0, 4.3)	3.26 (dd, 18.8, 4.5)	3.27 (20.6, 5.7)
N-CH_3	3.08 (s)	2.76 (s)	3.00	3.02 (s)	2.59 (s)	2.85 (s)	2.74 (s)	2.80 (s)	3.06 (s)
	5-diAc (Major)	**5-diAc** (Minor)	**6-Ac** (Major, 87:13)	**6-Ac** (Minor)	**7-Ac** (Major, 89:11)	**7-Ac** (Minor)	**8-Ac**	**9-Ac**	
4 and 1	6.79 (s) 6.70 (s)	7.03 (s) 6.67 (s)	6.79 (s) 6.69 (s)		6.69 (s) 6.65 (s)		6.79 (s) 6.69 (s)	6.70 (s) 6.87 (s)	
11	5.42 (d, 5.5)	5.66 (dd, 4.7, 1.3)	5.66 (d, 4.4)	5.56 (brs)	5.46 (d, 5.3)	5.67 (brs)	5.50 (d, 6.0)	5.69 (d, 5.0)	
14	4.70 (s)	5.02 (s)	4.70 (s)	4.41 (s)	4.37 (s)	4.86 (s)	4.25 (s)	5.30 (s)	
12β	3.14 (d, 19.2)	3.02 (dd, 17.9, 1.3)	3.02 (d, 18.2)		3.14 (d, 19.3)	3.00 (d, 18)	3.16 (d, 19.6)	2.93 (d, 19.4)	
12α	3.28 (dd, 19.2, 5.3)	3.26 (dd, 17.9, 4.7)	3.24 (dd, 18.2, 4.4)		3.28 (dd, 19.3, 5.2)	3.22 (m)	3.36 (dd, 19.6, 6.0)	3.37 (dd, 19.4, 5.0)	
N-CH_3	3.00 (s)	2.82 (s)	2.79 (s)	2.38 (s)	2.85 (s)	2.78 (s)	2.96 (s)	3.12 (s)	

[a]These assignments may be reversed.

In order to gain further insight into the cause of the broadening of the *N*-methyl signals observed in compounds **3-Ac** through **7-Ac**, a variable temperature pmr study of compound **5-diAc** was performed. As the temperature was decreased from 22° to −25°, W_H of the *N*-methyl signal decreased from 47 Hz to 8 Hz as it moved slightly upfield from δ 2.23 to δ 2.08. This change was accompanied by a general, but less dramatic narrowing of the other signals present in the spectrum. These results are consistent with the existence of an equilibrating mixture of axial and equatorial *N*-methyl groups in **5-diAc** at room temperature, which gradually approaches a single lower energy *N*-methyl orientation as the temperature is decreased. A variable temperature study of **5-diAc** was also performed at 200 MHz in toluene-d_8 in which the temperature was increased from 21° to 60°. The W_H of the *N*-methyl signal was also observed to gradually decrease under these conditions from 8.3 Hz at 21° to 2.4 Hz at 60°. This sharpening is indicative of the increase in the rate of nitrogen inversion.

A useful index of the *N*-methyl orientation is also provided by the chemical shift of H-14. This signal appears upfield in **2** (δ 3.31) relative to **9** (δ 4.50). It is well known that in piperidines having equatorial *N*-alkyl groups, the adjacent α-axial protons are shielded both by the lone pair situated antiperiplanar on the nitrogen atom and by the

equatorial *N*-alkyl groups (30). This parameter indicates equatorial *N*-methyl groups for compounds **1-4, 6-8, 3-Ac,** and **8-Ac**; axial *N*-methyls in **5, 9,** and **9-Ac**; and equilibrium mixtures in **4-Ac** through **7-Ac**. It does not disclose the orientation of the *N*-methyl in **1-Ac** because this compound adopts the type-II conformation. In **2-Ac**, the signal for H-14 appears at δ 3.49, and the intensity of the Bohlmann bands is less than in **2** (5). This suggests that there may be a small amount of the axial *N*-methyl in the equilibrium mixture. Our conclusions regarding the orientations of the *N*-methyls of the free bases in solution are summarized in Table 3.

The 470 pmr spectra of the salts formed immediately after the addition of CF_3COOD to $CDCl_3$ solutions of the compounds were also determined. These spectra are reported in Tables 4 and 5. Only one of the two possible diastereomeric salts could be detected for compounds **1-9, 2-Ac, 8-Ac**, and **9-Ac** (Table 3). In the salts of compounds **1-4, 6-8,** and **8-Ac** possessing equatorial *N*-methyl groups, the chemical shift of H-14 is in the δ 4.34-3.99 region, while in the salts of compounds **9** and **9-Ac** having axial *N*-methyls, the H-14 signal appears at δ 5.29 and δ 5.30, respectively. An axial *N*-methyl group is also suggested for the salt of compound **5**. In this compound, the free base having an equatorial lone pair on nitrogen may be stabilized by intramolecular hydrogen bonding to the hydroxymethyl group located at C-6. Equilibria were detected in **1-Ac, 3-Ac, 4-Ac, 5-Ac, 5-diAc, 6-Ac,** and **7-Ac** (Table 4). The pmr spectra recorded immediately after the addition of CF_3COOD to $CDCl_3$ solutions of these compounds showed the existence of two salts. The ratios are listed in Table 3. In each case, in dealing with these diastereomeric mixtures of salts, the salt producing the lower field H-14 signal was assigned an axial *N*-methyl group.

TABLE 5. Partial 470 MHz Pmr Spectra of 11-Hydroxybenzophenanthridines in $CDCl_3+CF_3COOD$ (4:1)[a]

Assignment	Compound								
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
4 and 1	6.75 (s) 6.72 (s)	6.75 (s) 6.72 (s)	6.75 (s) 6.70 (s)	6.76 (s) 6.67 (s)	6.84 (s) 6.75 (s)	6.75 (s) 6.68 (s)	6.74 (s) 6.59 (s)	6.76 (s) 6.72 (s)	6.80 (s) 6.72 (s)
11	4.61 (brs)	4.36 (s)	4.40 (brs)	4.37 (brs)	4.34	4.37 (brs)	4.36 (brs)	4.44 (m)	4.64 (d, 4.8)
14	4.34 (d, 3.1)	4.05 (s)	3.99 (s)	4.26 (s)	4.85 (s)	4.16	4.28 (s)	4.06 (s)	5.31 (s)
12β	3.25 (s)	3.20 (s)	3.20 (d, 18.8)	3.21 (s)	3.21 (m)	3.20 (s)	3.17 (s)	3.20 (d, 19.0)	2.98 (d, 19.1)
12α	3.24 (s)	3.20 (s)	3.27 (dd, 19.2, 3.6)	3.21 (s)	3.21 (m)	3.20 (s)	3.21 (s)	3.28 (dd, 19.0, 4.2)	3.37 (dd, 19.1, 4.8)
N-CH_3	2.89 (s)	2.83 (s)	2.84 (s)	2.68 (s)	2.87 (s)	2.59 (s)	2.67 (s)	2.77 (s)	3.11 (s)

The cmr spectra of several of the salts were also determined (Table 6). Significant upfield shifts are expected for carbons C-12 and C-6 in the type-II conformations because of gauche interactions between C-12 and C-10a, and C-6 and c-4a, which are absent in the type-I conformers (5). In the cmr spectra of the salts of chelidonine (**1**) and corynoline (**2**), the differences in the chemical shifts at C-11, 12, 14, and 10a are similar to those between both free bases having the type-I conformation. In comparison with the salt of chelidonine (**1**), upfield shifts were also not observed for carbons C-12 and C-6 in the salt of acetylchelidonine (**1-Ac**). The differences in the chemical shifts in the salts between chelidonine and its acetate and corynoline and its acetate are almost the same. From these observations, it may be concluded that both the salt of acetylchelidonine (**1-Ac**) and the salt of acetylcorynoline (**2-Ac**) adopt the *cis* type-I conformation. The differences in chemical shifts between the salts of **7** and **2** at C-6, C-6a, and C-14, and between **8** and **2** at C-6 and C-6a can be explained by the substituent ef-

fects of the pseudoaxial and pseudoequatorial vinyl groups at C-6, respectively. Therefore, both the salts of **7** and **8** exist in the *cis* type-I conformation.

The cmr spectra of the salts of **5-diAc** and **6-Ac** displayed two sets of signals indicating the formation of two salts (Table 6). The upfield shifts at C-6 and C-12 expected for the conversion from type-I to type-II conformations were not observed in the spectra of the salts of **5-diAc** or **6-Ac**. In **5-diAc,** C-14, C-11, C-6a, and C-1 in the minor salt showed upfield shifts relative to those of the major salt while the C-methyl group, the methylene carbon of the acetoxymethyl group, and the carbonyl carbon of the acetoxy group at C-11 appeared at lower fields in the minor salt when compared to the major salt. These shifts are explained by the major salt having an equatorial *N*-methyl group and the minor salt having an axial *N*-methyl group. The upfield shifts in the spectrum of the minor salt at C-11 and C-14 are due to the steric proximity of C-11 and the axial *N*-methyl group. The upfield shifts at C-6a and C-13 result from the γ-gauche interactions with the axial *N*-methyl group of the minor salt. The signal for the C-6 acetoxymethyl group of the minor salt appears at lower field because of the loss of the γ-gauche interaction with the equatorial *N*-methyl present in the major salt. The same considerations explain the difference in the chemical shifts between the two salts of **6-Ac**. The minor salt of **6-Ac** has the equatorial *N*-methyl while the major salt has the axial *N*-methyl when judged by the cmr data in Table 6.

Finally, the coupling constants between H-11 and H-12α or H-12β can be seen clearly in the salts of **3, 8,** and **9** (Table 5). These salts are assigned the twist half-chair conformation of the C-ring. No firm conclusions can be drawn regarding the conformations of the C rings in the salts of **1, 2,** and **4-7** at this time because of signal overlap. The salts of **2-Ac, 3-Ac** (major diastereomer), **4-Ac** (major and minor diastereomers), **5-Ac** (major and minor diastereomers), **5-diAc** (major and minor diastereomers), **6-Ac** (major diastereomer), **7-Ac** (major diastereomer), **8-Ac,** and **9-Ac** exist in the twist half-chair ring C as evidenced by the 470 MHz pmr data (Table 4). The situation is not clear in **3-Ac** (minor diastereomer) and **6-Ac** (minor diasteromer) because of signal overlap.

In conclusion, high field nmr studies of a variety of benzophenanthridines and their salts have provided new insights regarding the conformations of the C rings and the orientations of the *N*-methyl groups. These studies demonstrate an agreement of the solution and solid state conformations in this class of alkaloids. Specifically, the ring C twist half-chair solid state conformation for (+)-14-epicorynoline (**9**) *p*-bromoacetate (7) is identical to the ring C twist half-chair solution conformation of (+)-acetyl-14-epicorynoline (**9-Ac**). The *cis*-type I ring C twist half-boat solid state conformation of (±)-corynoline (**2**) *p*-bromobenzoate (8) is identical to the *cis*-type I ring twist half-boat solution conformation of (±)-acetylcorynoline (**2-Ac**), and the *cis*-type II ring C half-chair solid-state conformation of (+)-chelidonine (**1**) *p*-bromobenzoate (9) is identical to the *cis*-type II ring C half-chair solution conformation of (+)-acetylchelidonine (**1-Ac**). A study of the crystal structure of (+)-chelidonine (**1**) *p*-bromobenzoate has revealed that the two independent molecules *M*1 and *M*2 existing in the asymmetric unit have only minor differences in their conformations (9). The precise dihedral angles between H-11 and H-12α, and H-11 and H-12β in *M*1 and *M*2 may be calculated from the previously published (9) atomic coordinates using the X-ray 1972 program.[2] In molecule *M*1, the dihedral angle between H-11 and H-12α is 55°, while the dihedral angle between H-11 and H-12β is 165°. The corresponding values in *M*2 are 60° and 171°, respectively. These angles are in close agreement both with those estimated from

[2]The X-Ray System (version of June 1972, update of April 1974) Technical Report TR-192 of the Computer Science Center, University of Maryland, was used for these computations.

TABLE 6. Cmr Spectra of the Salts Formed Immediately after the Addition of CF_3COOD to $CDCl_3$ Solutions of the Free Bases

Assignment	Compound										
	1	**2**	**7**	**8**	**5-diAc** (Minor)	**5-diAc** (Major)	**1-Ac**	**2-Ac**	**9-Ac**	**6-Ac** (Major)	**6-Ac** (Minor)
$COCH_3$					20.81	20.57	20.86	20.64	20.86	20.86	20.68
C-13-CH_3		23.00	22.86	23.53	29.89	23.60		23.53	23.97	29.92	23.76
C-12	37.38	34.76	34.27	35.20	31.20	31.87	33.74	32.27	32.32	31.09	31.90
C-13	40.84	41.95	41.37	40.97	38.87	40.74	39.07	41.29	38.31	38.73	41.17
N-CH_3	41.06	42.31	39.29	39.42	39.27	40.83	42.48	43.73	40.53	38.39	39.41
C-6	53.14	53.94	63.48	68.05	60.62	61.09	52.25	53.80	52.07	58.17	55.99
C-14	65.62	72.49	65.12	70.50	61.81	66.84	65.57	71.92	63.39	59.85	66.65
C-11	72.36	77.02	76.44	75.82	73.12	78.33	74.58	78.58	75.82	73.11	78.61
OCH_2O	102.19	102.90	102.33	102.33	102.64	102.64	102.64	102.99	102.33	102.66	102.66
OCH_2O	102.55	103.35	102.77	102.33	103.31	103.31	102.99	103.44	102.90	103.29	103.29
C-1	109.74	110.76	110.18	110.45	107.49	109.85	109.96	110.32	110.32	106.69	109.84
C-9	110.09	110.76	110.76	110.45	109.85	111.24	110.32	110.85	110.32	110.07	110.96
C-4	111.96	113.34	112.54	112.67	111.43	112.75	110.98	113.29	103.57	111.26	112.47
C-10	121.41	120.49	119.95	120.08	119.56	120.14	121.95	120.39	118.97	119.82	120.59
C-6a	110.41	110.41	113.20	113.20	106.44	110.06	109.21	109.56	106.94	109.18	
C-12a	118.09	118.09	117.06	118.31	116.82	115.90	117.51	117.07	120.31	116.85	
C-4a	129.49	129.49	128.74	128.30	127.84	127.64	128.83	128.07	126.88	127.89	
C-10a	126.83	126.83	131.27	131.63	129.27	129.97	123.72	129.94	129.85	128.33	128.55
C-7	144.06	144.06	144.37	144.72	145.81	144.02	144.50	144.72	145.96	145.21	
C-2"	147.03	147.03	147.38	147.52	147.39	147.64	147.92	148.14	147.38	147.42	147.96
C-3"	147.38	147.38	147.38	147.83	149.16	147.80	147.92	148.36	148.41	149.39	
C-8"	150.94	150.94	151.03	151.26	150.68	151.56	151.38	152.14	149.07	150.70	
$COCH_3$					174.66	170.86	172.11	171.89	174.15	172.92	
Others			129.05, 125.94 (vinyl)	127.32, 130.07 (vinyl)	63.68, 172.57, 20.46 (CH_2OCOCH_3)	60.09, 172.57, 20.46 (CH_2OCOCH_3)				41.31, 215.37, 30.81 (CH_2COCH_3)	43.53, 29.64 (CH_2COCH_3)

a Dreiding model of the *cis*-type II ring C half-chair conformation and with those anticipated on the basis of the coupling constants of 5 Hz and 11.3 Hz observed in the pmr spectrum of (+)-acetylchelidonine (**1-Ac**).

EXPERIMENTAL

The high-resolution 470-MHz pmr spectra were obtained by using a Nicolet NTC-470 spectrometer and the data accumulated with 32K free-induction decays. The 200 MHz pmr spectra were run on a Varian XL-200 spectrometer. The cmr spectra were determined at 22.6 MHz on a Nippon Electric-Varian NV-21 spectrometer using an 8 mm tube or at 50.31 MHz on a Varian XL-200 spectrometer using a 10 mm tube. Chemical shifts are reported in parts per million downfield from TMS and the coupling constants are given in Hertz. The preparation of compound **13** from **12** was identical to the last step in our previous synthesis of (±)-14-epicorynoline (20) except $LiAlD_4$ was substituted for $LiAlH_4$.

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