THE CONFORMATION OF CHELIDONINE

Mark Cushman* and T.-C. Choong
Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue Univeristy, West Lafayette, Indiana 47907

Abstract - The 360 MHz proton spectra of (+)-chelidonine and (±)-chelidonine-6,6,11-d_3 are not in agreement with the generally accepted B/C half chair-half chair conformation. An envelope (twist half chair) form of ring C is indicated.

(+)-Chelidonine (1) is the main alkaloid present in Chelidonium majus. Extensive chemical degradations provided a correct two-dimensional structure in 1930.[1] A B/C cis ring fusion together with an axial hydroxyl group were subsequently proposed in order to account for the presence of an intramolecular hydrogen bond, detected by IR spectroscopy.[2] The conformation of chelidonine and related benzophenanthridine alkaloids is known with less certainty. The B/C chair-boat[3] and B/C half chair-half chair[4,5] conformations have both been proposed. The evidence presented to date favors the latter possibility. Our recent execution of a new total synthesis of (±)-chelidonine also allowed the preparation of (±)-chelidonine-6,6,11-d_3 (2). Examination of the high-field proton NMR spectra of compounds 1 and 2 has provided new insights regarding the conformation of chelidonine.

The deuterated compound 2 was prepared by $LiAlD_4$ reduction of intermediate 3.[6] At 360 MHz all of the proton signals of the B and C rings of chelidonine were completely resolved and could be unambiguously assigned by comparison with the spectrum of compound 2 (Table I). The higher field C-6 methylene proton signal can be assigned to the axial C-6α hydrogen which is shielded by the anti-peri-planar non-bonded electrons on the nitrogen.[7] The equatorial C-6β proton is deshielded by the aromatic A ring. On replacement of the C-11 proton by deuterium the broad singlet for the C-4b proton of chelidonine changed to a doublet (J=3 Hz, figure 1). This establishes the expected long-range coupling between the C-4b and C-11 protons.

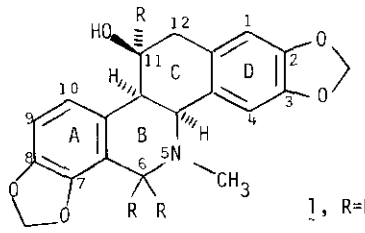
Particularly noteworthy is the fact that the C-11 proton is also coupled (J=4.3 Hz) to only one of the C-12 protons (Figure 1). If both the B and C rings exist in half chairs, the difference in coupling between the C-11 proton and the two C-12 methylene protons cannot be attributed to a difference in dihedral angles because they are almost identical (Figure 2). In this case the difference in coupling (0 vs. 4.3 Hz) might be explained by 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.[8] However, examination of the spectra of

model compounds reveals that this type of interaction is not expected to exert a significant effect in this case. For example in compound 4, $J_{a,e}$ = 3.00 Hz and $J_{e,e}$ = 2.72 Hz.[9] In 12α-acetoxy steroids 5,[8b] $J_{a,e}$ is reported to be equal to $J_{e,e}$ (2.5 Hz). In both cases, the equatorial proton α to the oxygen bisects the angle between the adjacent methylene protons and the equatorial-axial coupling constants are very close to the diequatorial couplings. In view of these facts, the half chair conformation does not appear to be tenable.

The alternative explanation is that the difference in coupling between the C-11 proton and the two C-12 protons is due to a difference in dihedral angles. The C ring must be in an envelope conformation with the 10b carbon atom out of the plane of the other five carbon atoms in ring C (Figure 2, structure 6). A B/C half chair-envelope conformation is now indicated for chelidonine.

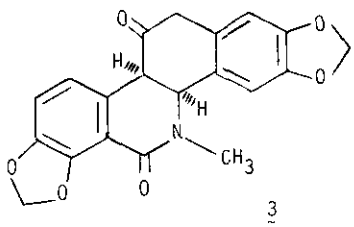
Table I. 360 MHz Spectra of Chelidonine and Chelidonine-6,6,11-d_3.

Chelidonine	Chelidonine-d_3	Assignment
δ 6.76 (d, 1H, J = 7.9 Hz)	δ 6.76 (d, 1H, J = 7.9 Hz)	Ar
6.73 (d, 1H, J = 7.9 Hz)	6.73 (d, 1H, J = 7.9 Hz)	Ar
6.66 (s, 1H)	6.66 (s, 1H)	Ar
6.64 (s, 1H)	6.64 (s, 1H)	Ar
5.99 (d, 1H, J = 1.5 Hz)	5.99 (d, 1H, J = 1.4 Hz)	Methylenedioxy
5.95 (d, 1H, J = 1.3 Hz)	5.95 (d, 1H, J = 1.4 Hz)	Methylenedioxy
5.934 (d, 1H, J = 1.5 Hz)	5.934 (d, 1H, J = 1.5 Hz)	Methylenedioxy
5.927 (d, 1H, J = 1.5 Hz)	5.927 (d, 1H, J = 1.5 Hz)	Methylenedioxy
4.23 (bs, 1H, W_H = 7.9 Hz)		11
4.08 (d, 1H, J = 15.7 Hz)		6β
3.57 (bs, 1H, W_H = 6.8 Hz)	3.57 (d, 1H, J = 3.0 Hz)	4b
3.43 (d, 1H, J = 15.7 Hz)		6α
3.21 (d, 1H, J = 17.5 Hz)	3.21 (d, 1H, J = 17.5 Hz)	12β
3.08 (d of d, 1H, J = 17.5, 4.3 Hz)	3.08 (d, 1H, J = 17.5 Hz)	12α
2.98 (t, 1H, J = 2.8 Hz)	2.98 (d, 1H, J = 3.0 Hz)	10b
2.27 (s, 3H)	2.27 (s, 3H)	N-CH_3



1, R=H

2, R=D



3

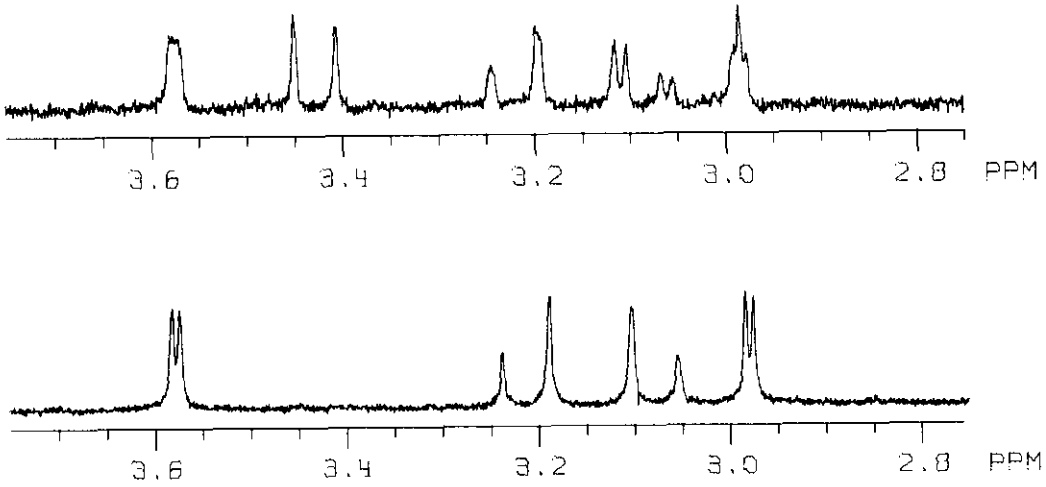
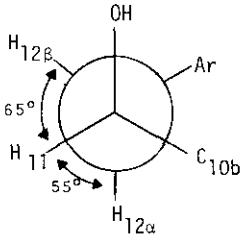
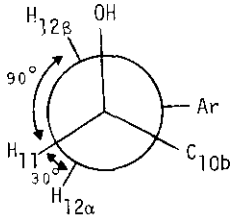


Figure 1. Partial 360 MHz spectra of (+)-chelidonine (upper) and (±)-chelidonine-6,6,11,d_3 (lower) in $CDCl_3$.



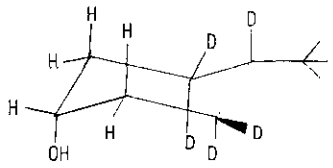
half chair ring C



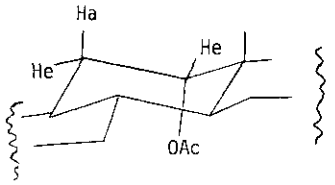
envelope ring C

(twist half chair)

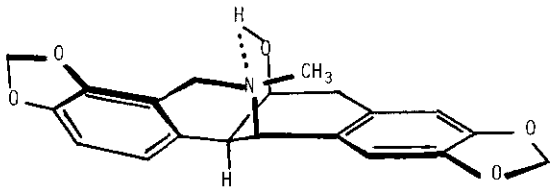
Figure 2. Newman projections of chelidonine conformers along the C-11, C-12 bond.



4



5



6

Acknowledgment. This investigation was supported by Grant CA19204, awarded by the National Cancer Institute, DHEW. We are grateful to Mr. John Kozlowski for obtaining the proton spectrum on the 360-MHz NMR instrument, which is supported by the National Institutes of Health, Research Grant Number RR01077, from the Department of Research Resources.

References and Notes

1. F. von Bruchhausen and H.-W. Bersch, Chem. Ber., 1930, 63, 2520; E. Späth and F. Kuffner, Chem. Ber., 1931, 64, 370.
2. H.-W. Bersch, Arch. Pharm. (Weinheim), 1958, 291, 491.
3. E. Seoane, Anales. Real. Soc. Espan. Fis. Quim. Madrid, Ser B, 1965, 61, 755.
4. C.-Y. Chen and D.B. MacLean, Can. J. Chem., 1967, 45, 3001.
5. S. Naruto, S. Arakawa, and H. Kaneko, Tetrahedron Lett., 1968, 1705.
6. Our total synthesis of (±)-chelidonine will be reported elsewhere.
7. H.P. Hamlow, S. Okuda, and N. Nakagawa, Tetrahedron Lett., 1964, 2553; M. Uskokovic, H. Bruderer, C. von Planta, T. Williams, and A. Brossi, J. Am. Chem. Soc., 1964, 86, 3364; F. Bohlmann, D. Schumann, and H. Schulz, Tetrahedron Lett., 1965, 173.
8. (a) H. Booth, Tetrahedron Lett., 1965, 411; (b) D.H. Williams and N.S. Bhacca, J. Am. Chem. Soc., 1964, 86, 2742.
9. F.A.L. Anet, J. Am. Chem. Soc., 1962, 84, 1053.

Received, 5th August, 1980