Tetrahedron Letters,Vol.24,No.44,pp 4801-4804,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

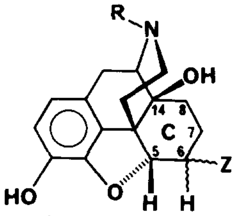
SOLUTION CONFORMATIONS OF THE 6α and 6β EPIMERS OF OXYMORPHAMINE

Ronald C. Crouch, Ashok V. Bhatia, and O. William Lever, Jr.

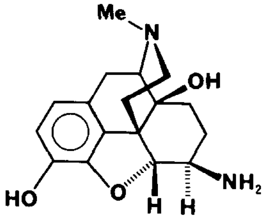
Department of Organic Chemistry, Wellcome Research Laboratories
Burroughs Wellcome Co., Research Triangle Park, NC 27709, U.S.A.

Abstract. High field (360 MHz) ^1H NMR studies have shown that the conformation of ring C in the oxymorphamines is dramatically influenced by the stereochemistry of the 6-amino group: ring C exists in a chair conformation in the 6β-epimer but adopts a twist boat conformation in the 6α-epimer.

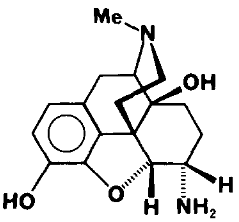
There is considerable current interest in the opioid properties of 17-alkyl-4,5α-epoxy-3,14-dihydroxymorphinanes which bear functionalized amino substituents at C-6 (cf. 1). A variety of ligands of this type have been developed as opiate receptor probes,[1-4] and understanding of the conformational preferences of these compounds is important for consideration of ligand-receptor interactions. Configurational assignments[2-4] at C-6 of the amino compounds have been derived from the coupling constants ($J_{5\text{-}6}$) between the protons at positions 5 and 6, by extrapolation from the couplings previously observed[5] for epimeric pairs of the related 6-hydroxy series 2. In the 6α-amino analogs, $J_{5\beta\text{-}6\beta}$ (3.2-4.0 Hz) is smaller than the $J_{5\beta\text{-}6\alpha}$ (6.8-7.6 Hz) observed in the epimeric 6β series.[2-4] This is in agreement with prior results for epimers of 2.[5] Similarly, considerations of ring C conformation in the 6-amino compounds[2-4] have also depended largely on earlier NMR analyses of the epimeric 6-hydroxy series,[6-9] which generally have been viewed as consistent with a preferential chair conformation for ring C in both the 6α and 6β alcohol epimers.[6-9] We wish to report that high field (360 MHz) ^1H NMR analysis of the α- and β-oxymorphamines[4] allows unambiguous assignment of the ring C conformation as a chair in the β-epimer 3 and as a twist boat in the α-epimer 4.



1 Z = NR_1R_2
2 Z = OH



3



4

J-correlation contour plots and water eliminated normal spectra for epimers 3 and 4 (as the dihydrochloride salts)[10] are shown in Figures 1 and 2 along with ring C connectivities and assignments.[11] Two dimensional J-correlation spectroscopy[12] at 360 MHz simplifies the assignment of these spectra since multiplets are separated into distinct spin systems. For both the 6α- and 6β-epimers, ring C configuration and conformation can be clearly established by considering only the couplings to H_6. Our results agree with earlier findings that $J_{5,6}$ provides an accurate evaluation of configuration;[2-5] however, $J_{5\text{-}6}$ alone does not allow a definitive assignment of conformation.[4] We have found that high field analysis provides access to $J_{6,7a}$ and $J_{6,7e}$ which permit an absolute conformational analysis of ring C. In each of these compounds both a large and a small coupling is observed between H_6 and the two H_7 protons: for 6α, $J_{6,7a}$ = 13.1 Hz and $J_{6,7e}$ = 4.1 Hz; for 6β, $J_{6,7a}$ = 12.0 Hz and $J_{6,7e}$ = 4.0 Hz. In each epimer H_6 is axial since vicinal couplings in the range of 12-13 Hz can only arise from diaxial interactions, and it follows from these observations that the C-ring conformation of the 6α-epimer 4 is a twist boat while the C-ring conformation of the 6β-epimer 3 is the expected chair. Inspection of Drieding models predicts

PROTON	SHIFT (ppm)	COUPLINGS
H(5)	4.79;	$J_{5,6}$ = 7.8Hz
H(6)	3.18;	$J_{6,7a}$=12.0Hz, $J_{6,7e}$ = 4.0Hz
H(7a)	1.99;	J_{gem}=-12.0Hz, $J_{7a,8a}$=10.0Hz
H(7e)	1.85;	$J_{7e,8a}$=2.0Hz, $J_{7e,8e}$ = 4.0Hz
H(8a)	1.61;	J_{gem}=-15.0Hz.
H(8e)	1.84;	$J_{8e,7a}$=3.0Hz.

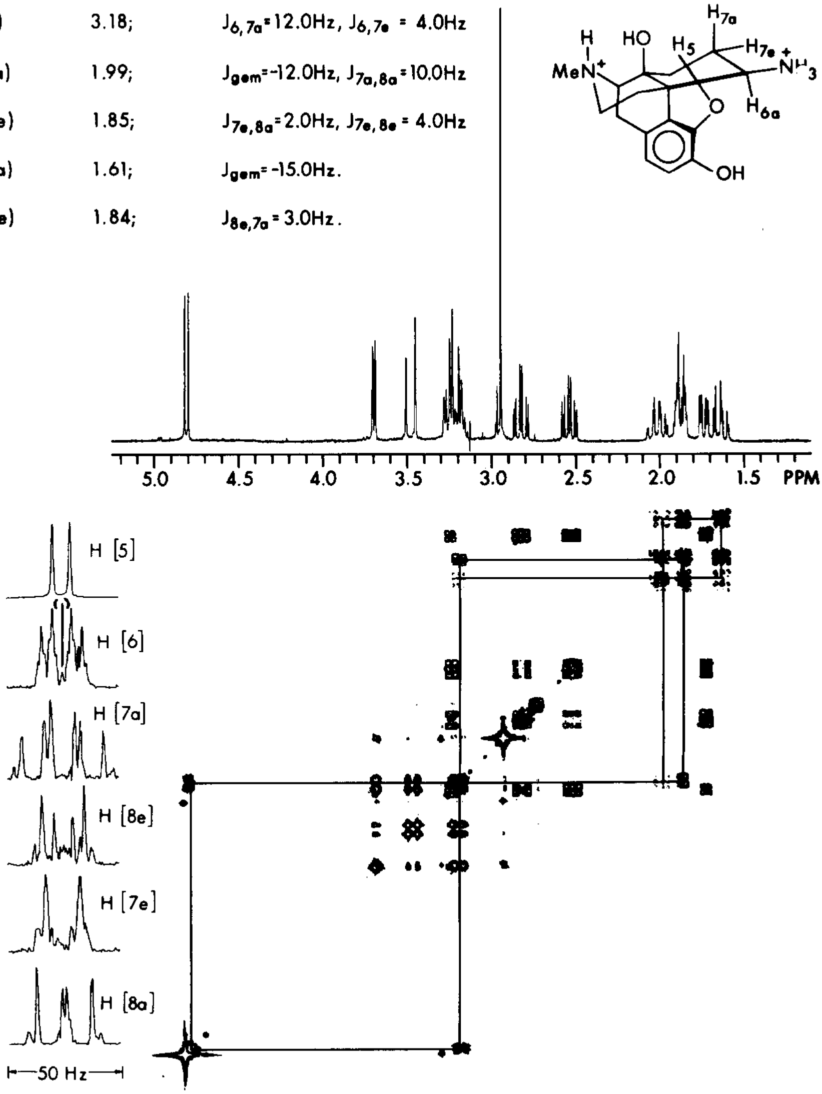


Figure 1. J-correlation spectrum of β-oxymorphamine (3) with J-resolved multiplets for ring C.

PROTON	SHIFT (ppm)	COUPLINGS
H(5)	4.92;	$J_{5,6}$ = 4.3Hz, $J_{5,7e}$ = 1.3Hz
H(6)	3.91;	$J_{6,7a}$ = 13.1Hz, $J_{6,7e}$ = 4.1Hz
H(7a)	1.19;	J_{gem} = -10.5Hz, $J_{7a,8a}$ = 7.0Hz
H(7e)	1.82;	$J_{7e,8a}$ = 8.0Hz, $J_{7e,8e}$ = 1.5Hz
H(8a)	1.89;	J_{gem} = -16.0Hz.
H(8e)	1.68;	$J_{8e,7a}$ = 9.5Hz.

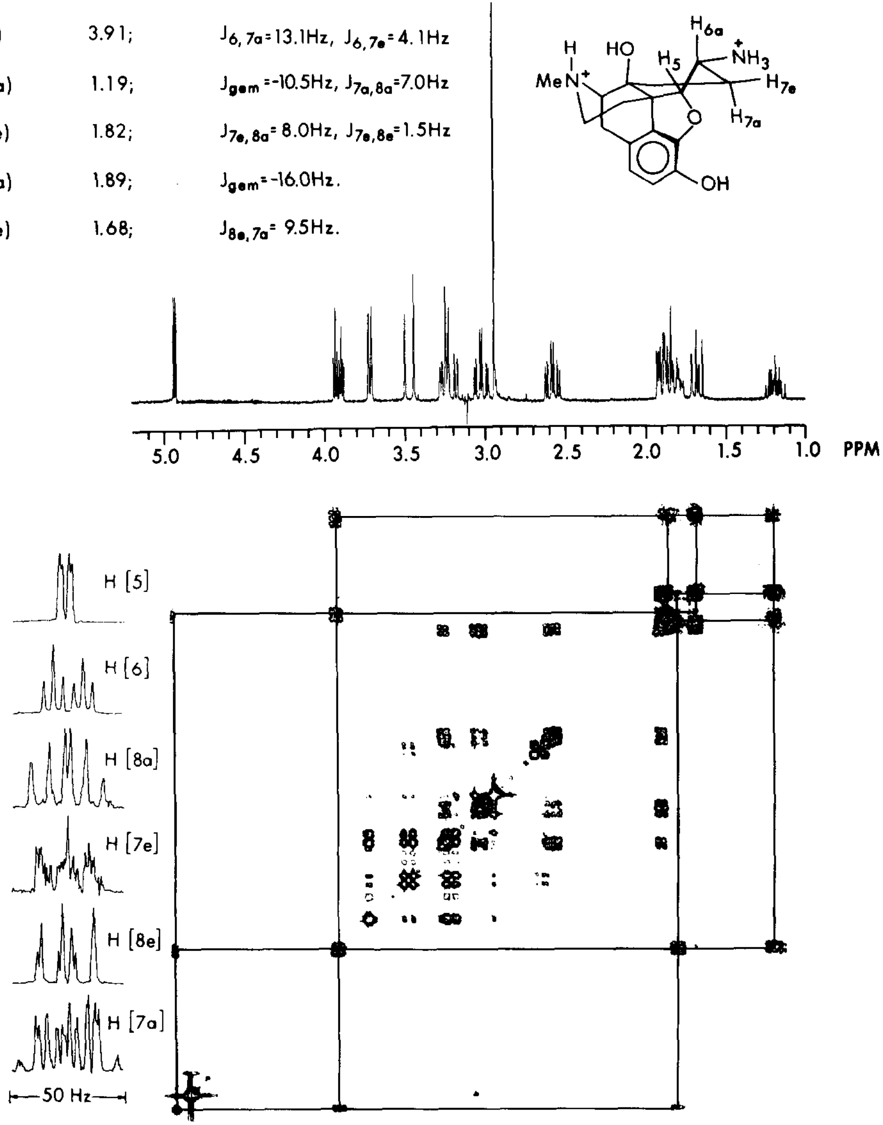


Figure 2. J-correlation spectrum of α-oxymorphamine (4) with J-resolved multiplets for ring C.

that if the 6α-epimer were a chair, the two $J_{6,7}$ values would be small and of nearly equal magnitude; this is clearly not the case. Further evidence of a ring C boat conformation for the 6α compound is obtained from the high field position of H_{7a} (1.19 ppm). A boat conformation would force H_{7a} into an orientation quite close to and above the plane of the aromatic ring. The observed upfield shift of 0.66 ppm agrees well with the shift predicted from measurement of Drieding models.[13,14]

Acknowledgement. The authors would like to thank the Department of Environmental Chemistry at NIEHS in Research Triangle Park, North Carolina , for the generous donation of instrument time which made this study possible. The authors also thank Professor P. S. Portoghese for providing reference samples of the oxymorphamine epimers.

References and Notes

1. (a) E. Hazum, K.-J. Chang, H.J. Leighton, O.W. Lever, Jr. and P. Cuatrecasas, Biochem. Biophys. Res. Commun., 104, 347 (1982); (b) M. Erez, A.E. Takemori and P.S. Portoghese, J. Med. Chem., 25, 847 (1982); (c) P.S. Portoghese, G. Ronsisvalle, D.L. Larson, C.B. Yim, L.M. Sayre and A.E. Takemori, Life Sci., 31, 1283 (1982).
2. (a) P.S. Portoghese, D.L. Larson, L.M. Sayre, D.S. Fries and A.E. Takemori, J. Med. Chem., 23, 233 (1980); (b) P.S. Portoghese, D.L. Larson, J.B. Jiang, T.P. Caruso and A.E. Takemori, J. Med. Chem., 22, 168 (1979); (c) T.P. Caruso, A.E. Takemori, D.L. Larson and P.S. Portoghese, Science, 204, 316 (1979).
3. J.B. Jiang, R.N. Hanson, P.S. Portoghese and A.E. Takemori, J. Med. Chem., 20, 1100 (1977).
4. L.M. Sayre and P.S. Portoghese, J. Org. Chem., 45, 3366 (1980).
5. (a) N. Chatterjie, C.E. Inturrisi, H.B. Dayton and H. Blumberg, J. Med. Chem., 18, 490 (1975); (b) E.F. Hahn and J. Fishman, J. Org. Chem., 40, 31 (1975); (c) N. Chatterjie, J.M. Fujimoto, C.E. Inturrisi, S. Roerig, R.I.H. Wang, D.V. Bowen, F.H. Field and D. D. Clarke, Drug Metab. and Dispos., 2, 401(1974); (d) L. Malspeis, M.S. Bathala, T.M. Ludden, H.B. Bhat, S.G. Frank, T.D. Sokoloski, B.E. Morrison and R.H. Reuning, Res. Commun. Chem. Pathol. Pharmacol., 12, 43 (1975).
6. T. Rull, Bull. Soc. Chim. Fr., 586 (1963).
7. S. Okuda, S. Yamaguchi, Y. Kawazoe and K. Tsuda, Chem. Pharm. Bull., 12, 104 (1964).
8. G.A. Brine, D. Prakash, C.K. Hart, D.J. Kotchmar, C.G. Moreland and F.I. Carroll, J. Org. Chem., 41, 3445 (1976).
9. F.I. Carroll, C.G. Moreland, C.A. Brine and J.A. Kepler, J. Org. Chem., 41, 996 (1976).
10. Spectra in $CDCl_3$ of the epimeric free bases of 3 and 4 also show ring C in chair and twist boat conformations, respectively; i.e. these conformations are independent of solvent and nitrogen protonation.
11. Spectra were obtained at 29° on a Nicolet 360 WB NMR. Chemical shifts and coupling constants were determined initially by double resonance experiments and were refined by using slices from tilted 2-D homonuclear J-spectra and spin simulation. Chemical shifts are reported relative to TSP = O for the dihydrochloride salts of 3 and 4 in D_2O (concentration: 2mg/ml). 2-D plots contain 512 x 512 real points.
12. A. Bax, R. Freeman and G. Morris, J. Magn. Reson., 42, 169 (1981).
13. F.A. Bovey, "Nuclear Magnegic Resonance Spectroscopy", Academic Press, New York, 1969, p. 64.
14. From ref. 13: Z corresponds to the measured distance in ring radii above the plane of the aromatic ring, and ρ is the distance in the plane of the aromatic ring. For H(7a) in the α epimer an eclipsed ring C boat conformer is found to have a Z = 2.6 and a ρ = 2.0 which gives a shielding term of 0.26 ppm. A twist boat results in Z = 2.0 and ρ = 1.2 which gives a shielding term of 1.0 ppm. A Z value of 2.2 and a ρ value of 1.5 correspond to a shielding of 0.67 ppm.

(Received in USA 8 July 1983)