Opioid Conformations: The Remarkable Effect of C-14 Substituents on Ring C Conformations of 6α and 6β Epimers of 6-Substituted Epoxymorphinan Opioid Ligands

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High field ^{1}H nmr studies have shown that the nature of the C-14 substituents has a remarkable influence on ring C conformation of epoxymorphinan opioids which have a 6α-hydroxyl group. In sharp contrast to the ring C twist-boat conformation observed in those 6α-hydroxy compounds which also have a 14-hydroxyl group (α-naltrexol; α-oxymorphol), ring C exists predominantly as a chair conformer in 6α-hydroxy compounds which have a proton bound to C-14 (dihydromorphine; dihydrocodeine). The 6β-hydroxy compounds (β-naltrexol; β-oxymorphol) have a ring C chair conformation in agreement with earlier studies.

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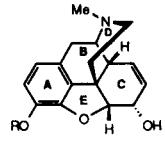
Introduction.

Opioid agonists such as morphine (**1**), codeine (**2**) and oxymorphone (**3**) are potent analgesics [1] and in recent years a variety of potential therapeutic roles have also emerged for opioid antagonists such as naltrexone (**4**) [2,3]. Metabolic studies have shown that conversion of naltrexone to the metabolites 6α-naltrexol (**5**) and 6β-naltrexol (**7**) is a species-dependent process [4,5], and the 6β-epimer, **7**, an active metabolite [3], is found as virtually the exclusive reduction product in man [3-5]. Conformational studies on these and related opioid agonist and antagonist ligands are of considerable interest as they provide a framework upon which to build a more accurate understanding of the interactions of agonist and antagonist opioid ligands at the receptor level.



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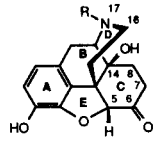

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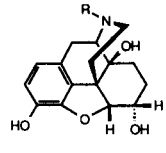
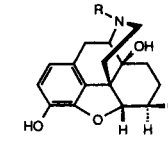
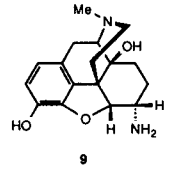


5 R = CH_2-c-C_3H_5
6 R = Me



7 R = CH_2-c-C_3H_5
8 R = Me



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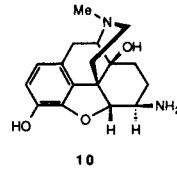

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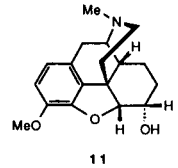

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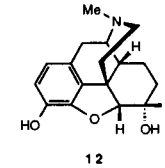

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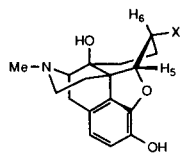
We have shown that the ring C solution conformation of 6-aminoepoxymorphinan opioid ligands is dramatically influenced by the configuration of the C-6 amino substituent [6]. Thus, 6α-oxymorphamine (**9**) exists primarily in a twist-boat conformation for ring C (*cf.* **13**, X = NH_2), while the corresponding 6β-epimer **10** has ring C in a chair conformation (*cf.* **14**, X = NH_2). A crystallographic study on **9** showed that ring C also adopts a twist-boat in the solid state [7]. In our continuing studies of opioid conformations, we have examined additional epoxymorphinan opioid ligands by high field nmr methods to explore the generality of these conformational observations. In the present paper we describe our findings that the α-**5** and β-**7** epimers of naltrexol and the corresponding α-**6** and β-**8** epimers of oxymorphol follow the ring C conformational trends (α epimer = twist-boat; β epimer = chair) that we had observed for the oxymorphamines. In contrast with the ring C twist-boat conformers which we observe for the α-epimers of naltrexol (**5**), oxymorphol (**6**) and oxymorphamine (**9**), we were intrigued to find that the α-hydroxy compounds dihydrocodeine (**11**) and dihydromorphine (**12**) predominantly adopt chair conformations for the C-ring. Since all five of the compounds **5**, **6**, **9**, **11**, and **12** have a 6-substituent of α-configuration, but the three, **5**, **6**, and **9**, with ring C twist-boat conformations have a 14-hydroxy group while the two, **11** and **12**, with ring C chair conformations have a proton bound to C-14, we feel that



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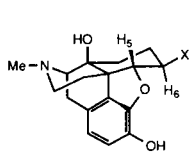

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disposition, boat versus chair, of the C-ring. As the primary focus of this work, each of the ring C assignments are described separately in the following discussions; however, all assignments were based upon a consistent strategy which will be briefly described as follows: Coupling these observations suggest that ring C conformational differences are determined by the presence or absence of the hydroxyl substituent at C-14.

Results.

The purpose of this study was to ascertain the relative pathways and initial estimates of chemical shifts were obtained from the COSY spectrum. Figure 1 is a representative COSY spectrum which is typical of what was obtained for each compound in this series. Table I summarizes the chemical shift assignments for all of these compounds. The highly overlapped proton multiplets from C-7 and C-8 were not deconvoluted by exhaustive spin simulations; rather, these methylene proton chemical shifts were estimated *via* interactive analysis with cursors on the zero-filled COSY datasets. The primary question of preferred C-ring configuration (boat *vs* chair) is unaffected by this incomplete analysis since in most cases it can be answered by a detailed analysis of all couplings to H-5 and H-6 alone. Expansions from 300 MHz 1D proton spectra (3.354 second acquisition time) detailing H-5 and H-6 assignments for each compound are presented in Figure 2. The coupling constants which are given in Figure 2 are the result of limited spin simulation studies in which the calculated spectra were fitted to the observed H-5 and H-6 transitions. The reported couplings are believed to be accurate to a precision of ± 0.15 Hz. While nOe measurements can provide a more detailed understanding of the precise nature of the C-ring conformation for each compound, no nOe results will be presented for these compounds. Interpretation of nOe data requires a rigorous assignment of each proton in the molecule before the results can be used for conformational arguments. The serious overlap of many of the protons on C-7 and C-8 makes the effective use of nOe very tedious towards the general goal of simply resolving the question of the preference for ring C boat *vs* ring C chair for this series of compounds.

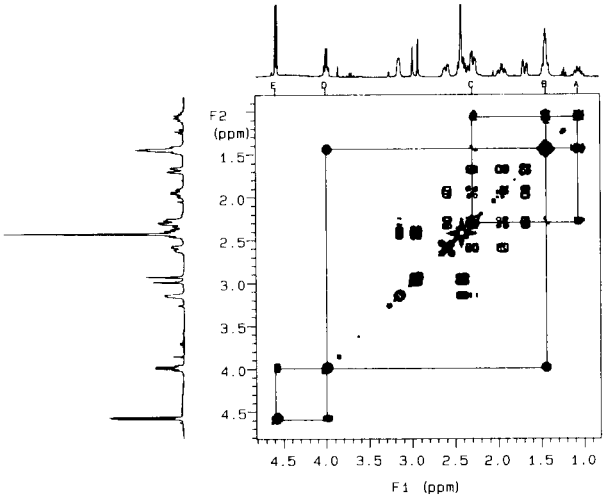

Figure 1. Representative COSY spectrum for dihydromorphine (**12**) in deuteriochloroform solution. Ring C couplings are shown with the following assignments (see text); A = H(8a), B = H(8e, 7a, 7e), C = H(14), D = H(6), E = H(5). Data were acquired at 300 MHz and plotted at a digital resolution of 0.86 pts/Hz.

Table I. Proton Chemical Shifts of the Epoxymorphinans[a]

	α-Naltrexol 5	α-Oxymorphol 6	β-Naltrexol 7	β-Oxymorphol 8	Dihydrocodeine 11	Dihydromorphine 12
H-1	6.680	6.685	6.678	6.682	6.707	6.639
H-2	6.508	6.535	6.536	6.556	6.618	6.520
H-5	4.645	4.639	4.487	4.493	4.582	4.573
H-6	4.235	4.220	3.554	3.548	4.031	3.984
H-7α	1.115	1.109	1.568	1.573	1.468	1.445
H-7β	1.695	1.716	1.949	1.946	1.585	1.436
H-8α	1.435	1.434	1.335	1.350	1.119	1.055
H-8β	1.615	1.636	1.591	1.614	1.412	1.427
H-9	3.070	2.749	3.074	2.759	3.181	3.141
H-10α	3.006	3.103	3.000	3.094	2.964	2.950
H-10β	2.563	2.549	2.567	2.547	2.460	2.413
H-14	-	-	-	-	2.356	2.282
H-15α	1.555	1.536	1.467	1.450	1.700	1.678
H-15β	2.225	2.217	2.117	2.140	1.998	1.943
H-16α	2.233	2.257	2.228	2.210	2.341	2.298
H-16β	2.633	2.396	2.615	2.379	2.630	2.587
H-17	2.328	2.333	2.340	2.339	2.471	2.419
H-18	0.825	-	0.819	-	-	-
H-19	0.51; 0.10	-	0.51; 0.10	-	-	-
OMe	-	-	-	-	3.845	-

[a] Chemical shifts obtained for 10 mM solutions at 299.942 MHz in deuteriochloroform (24 °C).

Although not the focus of this work, D-ring assignments are also presented. The relative disposition (α or β) for a given proton of the D-ring follows from inspection of the ^{1}H spectrum and the coupling patterns of the COSY assigned resonances. The couplings indicate a strong preference for a chair conformation for ring D in all cases. The precise assignments follow from an assumed D-ring chair with the 16α proton in an axial position. The relative configurations of the potentially inverting substituent on the ring D nitrogen (N-17) have not been addressed in this communication.

Naltrexols.

Syntheses and C-6 configurational assignments of the naltrexol epimers have been reported [5,8], and more extensive proton and carbon magnetic resonance studies of **5** and **7** led to the conclusion that ring C in each epimer adopts a chair conformation [9,10]. Our findings are in agreement with the ring C chair for β-naltrexol, but in contrast with the earlier work, our data confirm a ring C twist-boat conformation for α-naltrexol.

As we observed for the oxymorphamines [6], the ring C conformational assignments for the naltrexol epimers **5**

and **7** follow readily from the extraction of the couplings $J_{6,7\alpha}$ and $J_{6,7\beta}$ [11]. As indicated in Figure 2, the couplings $J_{6,7\alpha}$ = 11.3 Hz and $J_{6,7\beta}$ = 4.4 Hz are observed for α-naltrexol (**5**); for β-naltrexol (**7**) the couplings are $J_{6,7\beta}$ = 10.6 Hz and $J_{6,7\alpha}$ = 4.4 Hz. In each epimer, H-6 clearly is axial

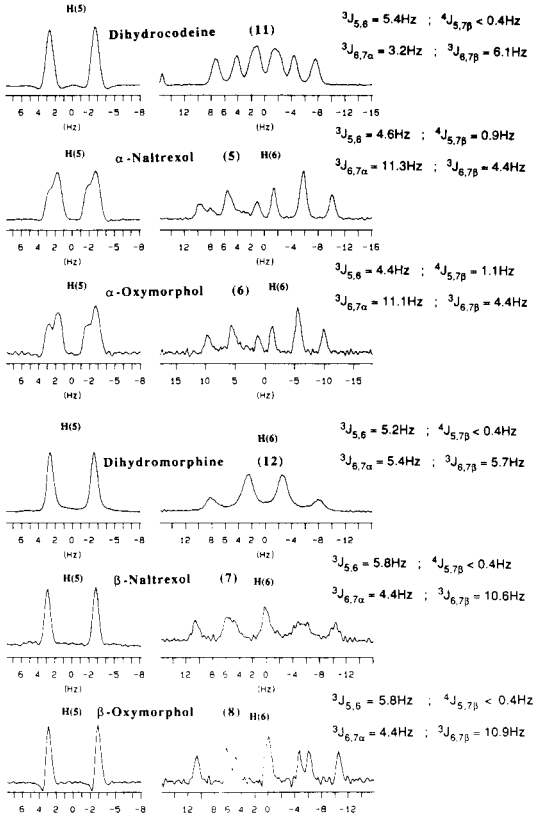

Figure 2. Expansions for the H(5) and H(6) multiplets of compounds **5-8**, **11**, and **12**. Data are from 1D proton spectra acquired at 300 MHz. Plots are scaled in hertz to facilitate coupling constant comparisons.

from consideration of the magnitudes of the couplings to the H-7 protons. The axial disposition of H-6 in each of the naltrexol epimers indicates that α-naltrexol (**5**) exists in a ring C twist-boat conformation while β-naltrexol (**7**) exists in a ring C chair conformation. The large magnitude of the observed axial-axial couplings suggests that the molar fractions of conformationally flipped contributors is relatively insignificant for either of these epimers.

Other spectral similarities between the oxymorphamines and the naltrexols have also been noted. In the twist-boat conformations of the α-epimers, **5** and **9**, H-7α is shifted to high field [6], probably from aromatic ring current effects. This shielding effect is consistent with the placement of the 7α proton directly over the aromatic ring that was observed crystallographically for **9** in the twist-boat [7]. In the β-epimers, **7** and **10**, which exist with ring C as a flattened chair, it is H-8α that is shifted to high field, presumably by a similar shielding mechanism. Also, the α-epimers of naltrexol and oxymorphamine display a small (1.1 Hz) W-coupling between the syn 1,3 protons, H-5 and H-7β. This coupling is absent, even in the COSY spectrum, for the β-epimers.

After establishing the ring C conformations for the naltrexols, we employed additional 2D methods to facilitate complete assignment of the spectra. $^{13}C/^1H$ chemical shift correlation data were acquired for each of the epimers. These heteronuclear chemical shift correlation studies permit the independent observation of all geminal pairs of protons while also allowing a direct link of our proton assignments to the published ^{13}C data [9,10]. Finally, in agreement with the large scalar couplings observed between the axial protons on H-6 and H-7, variable temperature ^{13}C studies (in deuteriomethanol to -90°) did not suggest significant populations of differing ring C conformers for the naltrexols. We therefore conclude that α-naltrexol exhibits a stable twist-boat ring C conformation which parallels that observed for the α-epimer of oxymorphamine.

As noted above, the twist-boat conformational assignment for ring C of α-naltrexol differs from the conclusion reached in a previous study in which ring C was assigned a chair conformation for both naltrexol epimers [10]. The previous workers [9,10] provided a thorough compilation of ^{13}C data, and our heteronuclear chemical shift experiments provide cross-correlations between COSY-assigned ^1H spectra and their ^{13}C assignments which are in total agreement. In the earlier study, however, chemical shifts appear to have interpreted in terms of assumed ring C chair conformations for both epimers [5,8b] rather than with consideration for the possibility of different ring C geometries for the two epimers.

Oxymorphols.

The data in Figure 1 demonstrate that the oxymorphol epimers follow exactly the spectroscopic and conformational trends we observed earlier for the oxymorphamines [6] and in the present study for the naltrexols. Once again, consideration of the magnitudes of couplings between H-6 and the H-7 protons indicates that H-6 is axially disposed in both the α-**6** and β-**8** epimers. Furthermore, the syn-1,3 W-coupling between H-5 and H-7β is readily observable in the twist-boat conformer which clearly must predominate for the α-epimer, **6**. Thus α-oxymorphol (**6**) adopts the ring C twist-boat conformation and β-oxymorphol (**8**) exists as a ring C chair.

The present observations for the naltrexols and the oxymorphols and our earlier studies on the oxymorphamines [6] support the generality of a stable twist-boat ring C disposition for 6α-substituted ligands with a hydroxyl group at C-14 and a chair ring C for the corresponding 6β com-

pounds. It is of interest that neither high field instrumentation nor 2D nmr spectroscopic methods are required to assign these ring C conformations. Inspection of proton spectra at 80 MHz allows an accurate estimation of all couplings to H-6. The presence or absence of a large diaxial coupling in the H-6 multiplets for each epimer, **5-10**, is the key observation in assigning ring C conformations. Furthermore, the characteristic four-bond coupling between H-5 and H-7β in the α-epimers **5**, **6**, and **9** that adopt C-ring twist-boat conformations is sufficiently large to be easily resolved. This observation is important for workers with limited access to high field nmr instrumentation.

Dihydromorphine and Dihydrocodeine.

Inspection of Figure 1 shows that the H-5 and H-6 multiplets for dihydrocodeine (**1**) and dihydromorphine (**12**) are distinctly different from the H-5 and H-6 multiplets for the other 6α-substituted ligands, which differ structurally in that they contain a hydroxyl at C-14 rather than the proton at C-14 in **11** and **12**. The relative width of H-6 is narrower for **11** and **12**, and the largest observed couplings to the geminal pair at C-7 are far too small (6.1 Hz for **11**, 5.7 Hz for **12**) to allow a predominantly axial H-6 for either compound. The four-bond coupling from H-7β to H-5 is not observed. These observations indicate a strong preference for ring C to exist in a chair form for both dihydrocodeine and dihydromorphine. The H-8α proton is observed as the highest field signal which is another trend we have observed for the chair-type ligands. For dihydrocodeine (**11**), the smaller coupling between H-6 and the H-7 proton is only 3.2 Hz. The magnitude of this coupling constant is not consistent with interconverting chair and boat conformers for **11**. Thus, if we assume that the 3.2 Hz coupling is between H-6 and H-7α, the H-6/H-7α diaxial configuration present in the twist-boat conformer should exhibit very large (10-12 Hz) couplings as we have previously observed, and any contributor of this type would have to be present in an insignificant molar fraction for the observed coupling constant to be as small as 3.2 Hz. Moreover, if we assume that this smallest coupling is between H-6 and H-7β, then we must assume a very small coupling between H-6 (equatorial) and H-7β (axial) in the chair form to suppress the 4.2 Hz coupling for these protons we have documented for compounds **5**, **6** and **9** in the twist-boat conformer; this is not consistent with the expected 3-4 Hz couplings between axial and vicinal equatorial protons. We therefore conclude that dihydrocodeine exists primarily with ring C as a flattened chair and that a boat conformer is either nonexistent or present as an exceedingly small contributor.

For dihydromorphine (**12**) the couplings for H-5, H-6, and H-7α,β are found to be potentially more averaged: $J_{5,6}$ = 5.2 Hz, while the couplings from H-6 to the H-7α/β protons are 5.4 Hz and 5.7 Hz respectively. As in the case of dihydrocodeine, a predominant boat conformer is precluded by the magnitude of these couplings, but the possibility for an interconverting mixture of chair and boat conformers is somewhat more likely for dihydromorphine than for dihydrocodeine. Based on our observed coupling parameters between H-6 and H-7α in the twist-boat isomers **5**, **6**, and **9**, axial-axial coupling should be at least 11 Hz in the boat conformer, and the equatorial-axial coupling between H-6 and H-7α in a chair form should be in the 3-4 Hz range. For a rapidly inverting spin system, the observed coupling is an average of the contributing forms, and the molar fraction of each form can be calculated from Equation 1, in which X represents the contributing fraction of each form [12].

$$J_{obs} = X_1 \cdot J_1 + X_2 \cdot J_2 \qquad \text{(Equation 1)}$$

Using Equation 1 and the predicted coupling constants between H-6 and H-7α for dominate chair and boat forms as given above, the observed couplings to H-6 for dihydromorphine suggest an equilibrium mixture containing a maximum of ca. 30% boat conformer could be possible. However, it is also possible that the observed couplings to H-6 simply reflect a specific chair conformer with little or no boat contributor. Low temperature proton nmr studies were undertaken in order to help resolve this question. Upon cooling to $-50°$, no significant changes are observed for the ring C protons of dihydromorphine; however, small changes were observed for ring D protons. From the insensitivity of ring C protons to cooling, and the observed coupling constants, we conclude that dihydromorphine (**12**) exists with ring C as a flattened chair in parallel to that observed for dihydrocodeine (**11**).

Conclusions.

Our earlier work on the oxymorphamines [6] and the present observations for the naltrexols and the oxymorphols lead to several potentially general conclusions that should have considerable predictive value concerning ring C conformation in epoxymorphinan opioid ligands. First, 6β-substituted ligands (**7**, **8**, and **10**) with a 14-hydroxy group exist in a flattened chair ring C conformation. Second, the epimeric 6α-substituted ligands **5**, **6**, and **9** with a hydroxyl group at C-14 adopt a stable twist-boat ring C conformation. Third, 6α-substituted ligands **11** and **12** with hydrogen rather than a hydroxy group at C-14 appear to preferentially adopt a chair-type conformation for ring C. These conclusions are based on experimental observation, but certainly have a basis in stereoelectronic and torsional effects. The origins of these conformational preferences may lie simply in the summation of through-space interaction (repulsion) that is present in each of the conformational possibilities. If this is the case, the net steric repulsions in those 6α-substituted compounds with a hydroxy group at C-14 must be significantly greater in the chair form than in the twist-boat form of these compounds,

and these α-isomers accordingly adopt the twist-boat conformation. Conversely, when there is a proton rather than a hydroxy group at C-14, the net repulsive effects of the chair must diminish to a level sufficiently below the twist-boat that these compounds preferentially adopt the flattened chair conformation. Molecular modeling studies are underway to explore relative conformational energies in these and related epoxymorphinan systems.

NMR EXPERIMENTAL

All nmr data were acquired with a Varian VXR 300 spectrometer at 299.942 MHz on approximately 10 m*M* solutions in deuteriochloroform. All reported ^1H chemical shifts are relative to the solvent resonance (chloroform) at 7.240 ppm. Scalar connectivities were established by some variant of a COSY experiment. Typical COSY parameters (as shown in Figure 1) are: spectral width = 1200 Hz with an acquisition time of 213 msec for 256 FIDs. Sinebell multiplication prior to fourier transformation was used in each dimension unless the experiment was a phase-sensitive double quantum filtered COSY [13,14]. Phase-sensitive datasets were apodized prior to fourier transformation to avoid truncation artifacts. Final data were symmetrized and zero filled to a size of 1K × 1K points. The data shown in Figure 2 were obtained from simple 1D proton spectra with a spectal width of 2442.7 Hz and an acquisition time of 3.354 seconds. Typical datasets were the result of 128 transients for 2mg/ml solutions. Each free induction decay was zero-filled to 64K points prior to fourier transformation. $^1H/^{13}C$ chemical shift correlation data was obtained by the method of Bax [15]. Typical parameters are: spectral width = 8250 Hz for the 13C window (80 msec acquisition time) and a 1200 Hz 1H window (128 FIDs).

REFERENCES AND NOTES

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[1] J. H. Jaffe and W. R. Martin, in The Pharmacological Basis of Therapeutics, 7th Ed, A. G. Gilman, L. S. Goodman, T. W. Rall, and F. Murad, eds, MacMillan, New York, NY, 1985, Chapter 22.

[2] L. F. McNicholas and W. R. Martin, *Drugs*, **27**, 81 (1984).

[3] M. S. Gold, C. A. Dackis, A. L. C. Pottash, H. H. Sternbach, W. J. Annitto, D. Martin and M. P. Dackis, *Med. Res. Rev.*, **2**, 211 (1982).

[4] E. J. Cone, *Tetrahedron Letters*, 2607 (1973); *J. Chromatog.*, **129**, 355 (1976).

[5] L. Malspeis, M. S. Bathala, T. M. Lidden, 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] R. C. Crouch, A. V. Bhatia and O. W. Lever, Jr., *Tetrahedron Letters*, **22**, 4801 (1983).

[7] O. W. Lever, Jr., A. V. Bhatia and K.-J. Chang, *J. Med. Chem.*, **28**, 1652 (1985).

[8a] N. Chatterjie, C. E. Inturrisi, H. B. Dayton and H. Blumbern, *J. Med. Chem.*, **18**, 490 (1975); [b] N. Chatterjie, J. M. Fujimoto, C. E. Inturrisi, S. Roerig, R. I. H. Wang, D. J. Bowen, F. H. Field and D. D. Clark, *Drug. Metab. Dispos.*, **2**, 401 (1974); [c] N. Chaterjie, J. G. Umans and C. E. Inturrisi, *J. Org. Chem.*, **41**, 3624 (1976).

[9] F. I. Carroll, C. G. Moreland, G. A. Brine and J. A. Kepler, *J. Org. Chem.*, **41**, 996 (1976).

[10] G. A. Brine, D. Prakash, C. K. Hart, D. J. Kotchmar, C. G. Moreland and F. I. Carroll, *J. Org. Chem.*, **41**, 3445 (1976).

[11] F. A. L. Anet, *J. Am. Chem. Soc.*, **84**, 1053 (1962).

[12] H. S. Gutowsky, G. G. Belford, and P. E. McMahon, *J. Chem. Phys.*, **36**, 3353 (1962).

[13] U. Piantini, Ø. W. Sorensen, and R. R. Ernst, *J. Am. Chem. Soc.*, **104**, 6800 (1982).

[14] M. Rance, Ø. W. Sorensen, E. G. Bodenhausen, G. Wagner, R. R. Ernst, and K. Wüthrich, *Biochem. Biophys. Res. Commun.*, **117**, 479 (1983).

[15] A. D. Bax, *J. Magn. Reson.*, **53**, 517 (1983).