Complete Assignment of the ^1H and ^{13}C NMR Spectra of 11,12-Dimethoxy[1]benzothieno[3,2-*a*]-4,7-phenanthroline and its 8-Chloro Analogue: Concerted Use of Two-Dimensional NMR Techniques [1]

M. J. Musmar and Raymond N. Castle* [2]

Department of Chemistry, University of South Florida,
Tampa, Florida 33620-5250

Received June 24, 1991

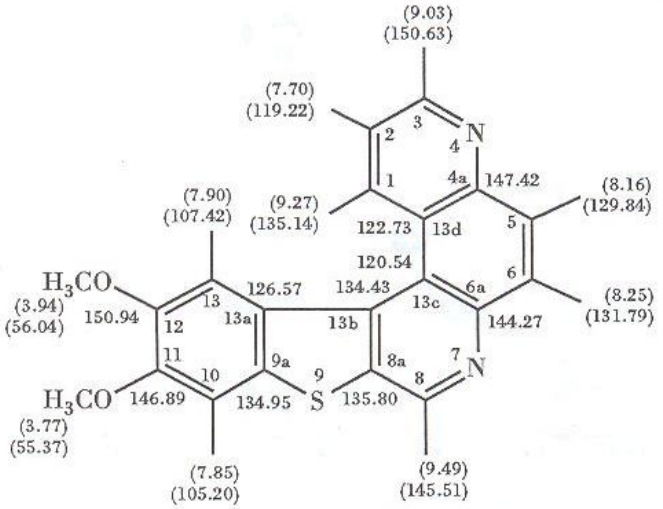
The ^1H and ^{13}C nmr spectra of 11,12-dimethoxy[1]benzothieno[3,2-*a*]-4,7-phenanthroline and its 8-chloro precursor were totally assigned using a combination of two-dimensional nmr techniques. After correlation of the majority of the proton signals by a COSY spectrum and one-bond heteronuclear correlation, the full assignment of the ^1H and ^{13}C nmr spectra of the novel heterocyclic compounds required the application of long-range CH coupling information particularly for quaternary carbon resonance assignments and the orientations of individual spin systems relative to one another. Key long-range heteronuclear couplings in both compounds served to confirm the one-bond heteronuclear correlations. Unequivocal interpretation of the spectral data leads to the complete assignments of the resonances.

J. Heterocyclic Chem., **28**, 1533 (1991).

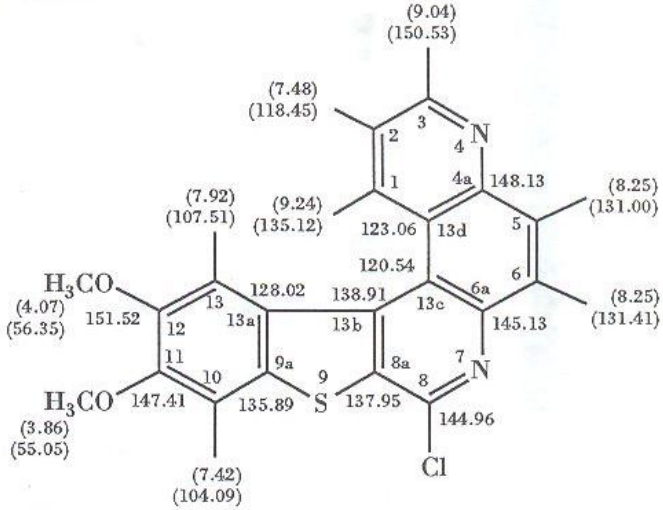
We have recently reported a novel pentacyclic heterocyclic ring system: namely, 12-methylbenzo[*h*][1]benzothieno[2,3-*c*][1,6]naphthyridine [3]. We would like to report another new pentacyclic heterocyclic ring system. In this communication, the complete assignment of ^1H and ^{13}C nmr spectra of 11,12-dimethoxy[1]benzothieno[3,2-*a*]-4,7-phenanthroline and the 8-chloro analogue is described. Two issues are important: first, the effect of the chlorine atom on the neighboring carbon resonances, if any, and second, the effect of the methoxy groups on the bay region proton and carbon resonances, the so-called *ortho* effect. Both questions may be analyzed for this particular heterocyclic ring system following the total assignment of the ^1H and ^{13}C nmr spectra. Some new information on these two issues can be found in two recent reports [4].

The COSY spectrum for compound **1** showed the expected two multi-spin systems, the three protons, H1, H2, H3 with their expected coupling pattern, and the two vicinal protons H5 and H6 as an AB spin system. The remaining protons all appeared as singlets. The protons at H5 and H6 in **2** appeared as a 2-proton singlet (J = 0). From the one-bond heteronuclear correlation experiment, several key assignments could easily be recognized. For example, in **1**, and based on precedent [1,3], the proton at H8 resonates at 9.49 ppm with its corresponding carbon, C8, resonating at 145.51 ppm. The bay region proton at H1 resonates at 9.27 ppm with its corresponding carbon, C1, resonating at 135.14 ppm. Similar correlations also were found for H2 and H3 with their corresponding carbon atoms resonating at 119.22 and 150.63, respectively. Unequivocal assignments of H5 and H6 cannot be made for these two resonances due to the lack of long-range couplings to these two carbon atoms resonating at 129.84 and 131.79 ppm.

At this stage preliminary assignments for all protonated carbons in the phenanthroline moiety had been worked out. The benzo[*b*]thiophene part of this molecule showed two singlets for two protons appearing at 7.90 ppm and



1



2

7.85 ppm along with their corresponding carbon atoms resonating at 107.42 ppm and 105.20 ppm, respectively. We observed the same correspondence between similar protons and carbon atoms for **2**. Furthermore, the two protons resonating at 8.25 ppm as a singlet showed correlations to the two carbon atoms, C5 and C6, resonating at 131.00 ppm and at 131.41 ppm, respectively. No extra information can be extracted from this one-bond heteronuclear correlation experiment.

In polycyclic heterocycles neither ^{1}H nor ^{13}C nmr by itself can give unambiguous assignments; thus neither type of spectroscopy, by itself, can confirm the identity of the molecules being studied. Bax, *et al.* [5] have provided some facile protocols for the complete assignments of polynuclear aromatic spectra. A variety of alternatives and newer or more effective techniques are now available, however, which should provide the means of dealing successfully with even more congested spectra than was previously possible. Only heteronuclear two-dimensional nmr experiments used in tandem to establish needed connectivities can successfully accomplish complete spectral assignments. One remarkable two-dimensional nmr experiment is the long-rang heteronuclear chemical shift correlation [6]. Protons which are coupled to carbon atoms *via* two or three bonds are observed. In this experiment a proton three-bond coupled to a carbon atom was observed. The optimization of the size of the three-bond couplings have a range of about 5-14 Hz [7]. The long-range heteronuclear chemical shift correlation provides a workable means of extending and confirming the assignments from key unequivocal starting points. During the writing of this communication a simple selective one-dimensional experiment, SIMBA, for the measurement of long-range heteronuclear coupling constants was published [8]. In this one-dimensional nmr experiment, each proton with a resolved long-range coupling to the selected carbon atom simultaneously appears in the resultant proton spectrum with an apparent additional splitting, which corresponds to the excited long-range heteronuclear coupling pathway. The major advantage of this experiment is the economy of time,

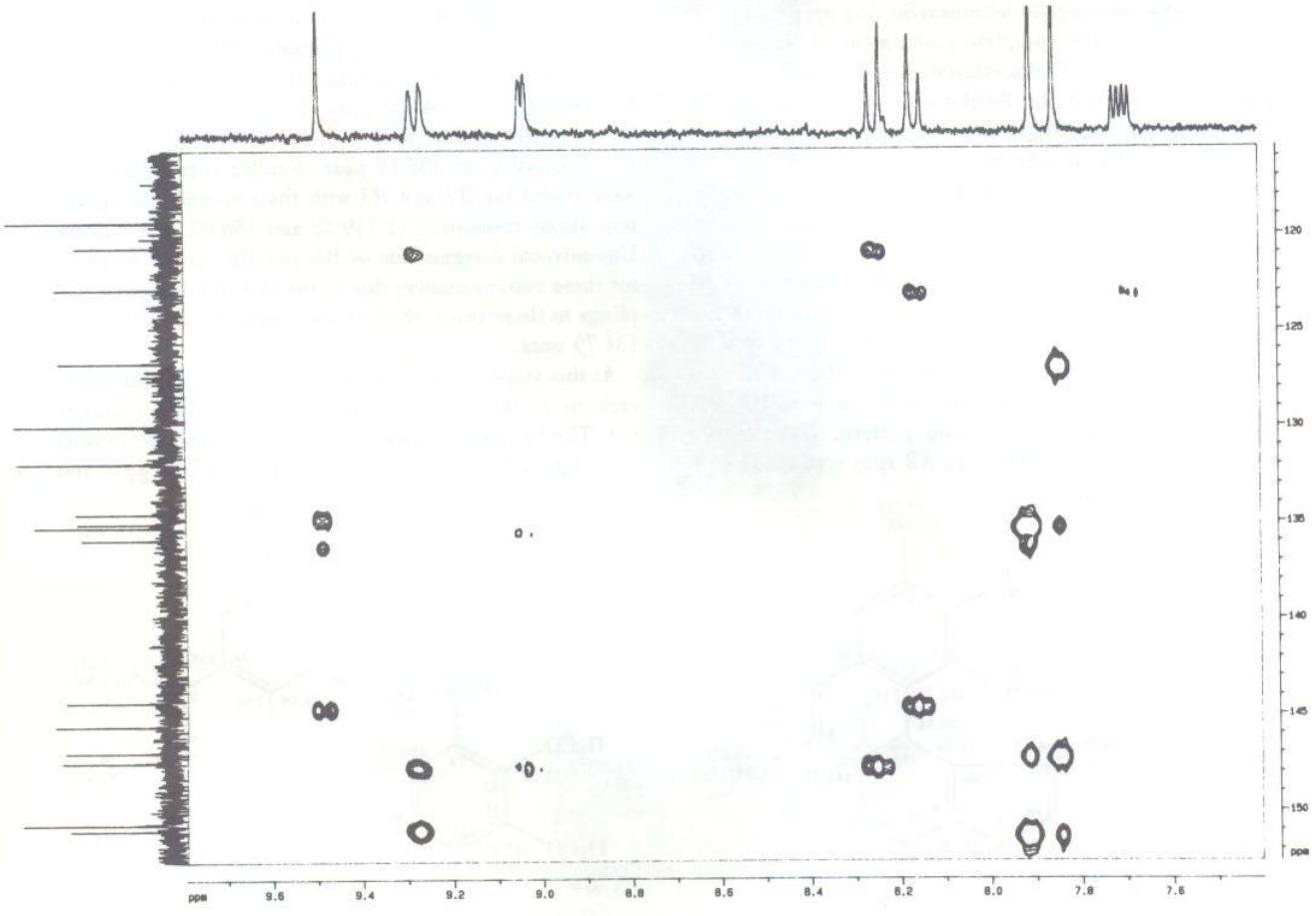


Figure 1. Long-range heteronuclear chemical shift correlation spectrum of **1** recorded in DMSO-d_6 at observation frequencies of 360.13/90.56 MHz for ^{1}H and ^{13}C nmr, respectively. The region 7-10 ppm on F_1 is shown.

i.e., a few minutes compared to several hours in the heteronuclear multiple-bond connectivity (HMBC) experiment. The necessary requirement for this experiment is that the carbon shifts must already be known before a selective carbon-pulsed experiment can be utilized. The two-dimensional HMBC experiment is undoubtedly superior in terms of resolving carbon atoms differing in chemical shift less than 1 ppm but if only a few heteronuclear couplings or connectivity pathways associated with well resolved carbons are to be determined, then the new one-dimensional SIMBA experiment is the attractive alternative.

The HMBC experiment was essential for the assignment of all the quaternary carbon atoms. In compound **1**, the quaternary carbon atoms C6a (144.27 ppm), C13b (134.43 ppm) and C8a (135.80 ppm) showed correlation with the proton at H8. On the other hand, the carbon atoms C3 (150.63 ppm), C4a (147.42 ppm) and C13c (120.54 ppm) were found to correlate with the proton at H1. The proton at H2 showed correlation with the quaternary carbon at C13d (122.73 ppm). The couplings of H3, H5 and H6 with their corresponding quaternary carbon atoms confirmed all the previous assignments. The chemical shifts and the correlations for C5, H5 and C6, H6 were found to be identical with their counterparts in the new naphtho[1',2':4,5]-thieno[3,2-*a*]-4,7-phenanthroline ring system. Considering the benzo[*b*]thiophene part of the molecule, the proton resonating at 7.90 ppm is the bay region proton H13, because it showed correlation with the quaternary carbon atom C13b (134.43 ppm). Therefore, from the bay-region proton H13, the correlations to C11 (146.89 ppm) and C9a (134.95 ppm) are clearly established. Assignments of the remaining quaternary carbon atoms, namely C13a (126.57 ppm), and C12 (150.94 ppm) follow from their correlation with the H10 proton. Furthermore, the methoxy protons (3.94 ppm) showed correlation with the C12 carbon atom, thus all protons and carbon atoms in compound **1** have been accounted for.

Concerning the chloro derivative **2**, the analysis of the long-range spectral data was more difficult. Some carbon atoms showed no correlations with key protons. The assignments for the quaternary carbon atoms C13d (123.06 ppm), C4a (148.14 ppm), C13c (120.54 ppm), and C6a (145.13 ppm) was carried out in the same manner as in compound **1**. The quaternary carbon atoms bearing the methoxy groups, C11 (147.41 ppm) and C12 (151.52 ppm) showed correlations with the H13 and the H10 protons, respectively. In order to balance the molecule for all low-field resonating quaternary carbon atoms attached to heteroatoms, then C8 must be the carbon atom resonating at 144.96 ppm. The assignments of C9a (135.89 ppm), C13a (128.02 ppm) and C13b (138.91 ppm) were very similar in analogy to those followed for compound **1**. The last quaternary carbon atom considered was the C8a, which appeared at 137.95 ppm and, as expected, showed no correlation to any proton in the molecule.

The presence of a chlorine atom in **2** caused minor *ipso* change (−0.55 ppm), a deshielding effect (2.15 ppm) on C8a and more deshielding effect on C13b (4.48 ppm). We observed no change on the C13c chemical shift (120.54 ppm in both **1** and **2**). Our depicted value for the C8 chemical shift change is compatible with reported values for pentachloro and tetrachloroquinoline, *i.e.*, −0.55 ppm *vs* −0.76 ppm [9]. By comparison, the typical *ipso* substituent chemical shift in benzene derivatives for a position not adjacent to nitrogen is 5-6 ppm downfield [10]. The substituent effects on the ^{13}C nmr chemical shifts at the *ortho* position, *i.e.*, (C8 *vs* C8a) can be broadly classified as electronic, steric and anisotropic, the former two being the most significant. Steric effects by definition may include all those phenomena which result in structural changes at the measured site, such as changes in bond lengths and angles. The relatively large size of the chlorine atom has some steric interaction with the *ortho* carbon C8a and therefore a deshielding effect was observed in this study.

The ^{13}C nmr spectrum of the 2,3,9,10-tetramethoxy[1]-benzothieno[2,3-*c*]quinoline showed that all four carbon atoms *ortho* to the methoxy groups resonate in the region 101-110 ppm, and their corresponding protons resonate in the region 7.38-7.98 ppm. These values compare favorably with the chemical shifts of protons and carbon atoms *ortho* to the methoxy groups in **1** and **2**.

EXPERIMENTAL

All the nmr spectra were measured in 5 mm tubes. Compound **1** was dissolved in DMSO-d_6 and compound **2** was dissolved in deuteriochloroform. Proton and carbon nmr spectra were acquired using a Bruker AMX 360 spectrometer at ambient temperature. A carbon frequency of 90.56 MHz was used with broad band decoupling, using a pulse flip angle of 35°. The one-dimensional carbon spectrum was obtained with a spectral width of 1500.5 Hz and 2 seconds between transients. Routine proton spectra were obtained at a proton frequency of 360.13 MHz, with a pulse flip angle of 48.6° and a 5 μs pulse. An acquisition time of 5 seconds was used between transients to ensure accurate integrals. The two-dimensional experiments were acquired using standard automation microprograms provided with the Bruker Aspect 3000 data system and a Bruker inverse geometry probe.

A typical proton-proton phase-sensitive double quantum filtered COSY experiment was acquired [11] using the spectral width 992.06 Hz in the F_2 domain. The spectra were acquired with 1K data points in F_2 (one order of zero filling in the F_1 domain) with four transients (two dummy scans) and 512 t_1 increments of 504 μs used to encode the second dimension. The delay between scans was 1.4 seconds. A 90° phase shifted sine-bell multiplication was applied to avoid truncation artifacts. The matrix was symmetrized about the diagonal. The experiment was acquired with 512 t_1 increments of 504 μs used to encode a second

dimension of 992.06 Hz. Proton-carbon correlation experiments were acquired using the proton-detected techniques of Bax [6]. Evolution times of 3.0 ms and 47.0 ms were used for direct and long-range methods, respectively. For the phase-sensitive direct correlation technique, 256 t_1 increments of 156 μs were used to encode a spectral width of 3205.13 Hz. For the long-range correlation experiment 256 t_1 increments of 312 μs were used to encode a spectral width of 3205.13 Hz. The t_1 interferograms were multiplied by a 90° phase-shifted (one bond) sine-bell (long-range) function before Fourier-transformation. Typically long-range CH correlation spectra were recorded with the same spectral widths (3205.13 Hz) as those used for the one-bond correlation spectrum. In the long-range CH correlation spectrum, the duration of Δ_1 low pass J filter and Δ_2 LR transfer were 3.2 ms and 46.8 ms, respectively. The t_2 data were collected and transformed after being exponentially weighted using a line broadening factor of 90° shifted sine-bell. The t_1 interferograms were multiplied with a phase shifted sine-bell function before Fourier-transformation and afforded a phase-sensitive spectrum.

The 11,12-dimethoxy[1]benzothieno[3,2-*a*]-4,7-phenanthroline (**1**) and 8-chloro-11,12-dimethoxy[1]benzothieno[3,2-*a*]-4,7-phenanthroline (**2**) were synthesized starting from 3,4-dimethoxybenzaldehyde following literature procedures [1,3].

REFERENCES AND NOTES

[1] Part **4**: J.-K. Luo, A. S. Zektzer and R. N. Castle, *J. Heterocyclic Chem.*, **28**, 737 (1991).

[2] To whom correspondence should be directed at the Department of Chemistry, University of South Florida, Tampa, FL 33620-5250.

[3] M. J. Musmar and R. N. Castle, *J. Heterocyclic Chem.*, **28**, 203 (1991).

[4] R. S. Mathews, M. Jones and J. Banks, *Magn. Reson. Chem.*, **27**, 841 (1989); R. R. Biekofsky, A. B. Pomilio, R. H. Contreras, D. G. deKowalewski and J. C. Facelli, *Magn. Reson. Chem.*, **27**, 158 (1989).

[5] A. Bax, J. A. Ferretti, N. Nashed and D. M. Jerina, *J. Org. Chem.*, **50**, 3029 (1985).

[6] A. Bax and M. F. Summers, *J. Am. Chem. Soc.*, **108**, 2093 (1986).

[7] G. E. Martin and A. S. Zektzer, *Magn. Reson. Chem.*, **26**, 631 (1988).

[8] R. C. Crouch and G. E. Martin, *J. Magn. Reson.*, **92**, 189 (1991).

[9] J. Su, E. Siew, E. V. Brown and S. L. Smith, *Org. Magn. Reson.*, **11**, 565 (1978).

[10] E. Breitmaier and W. Voelter, ^{13}C NMR Spectroscopy. Methods and Applications, Verlag Chimie, Weinheim, 1974.

[11] M. Piantini, O. W. Sorensen and R. R. Ernst, *J. Am. Chem. Soc.*, **104**, 6800 (1982).