

Using Two-Dimensional NMR Methods:
Phenanthro[3',4':3,4]phenanthro[2,1-*b*]thiophene
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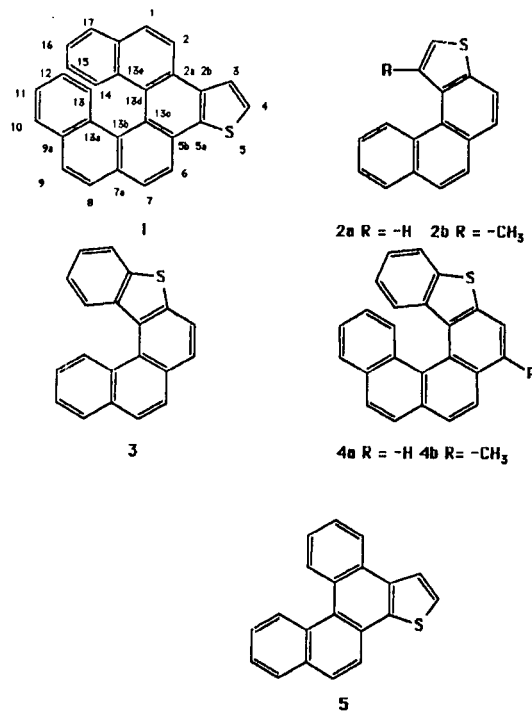
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Phenanthro[3',4':3,4]phenanthro[2,1-*b*]thiophene has been prepared and its highly congested proton and carbon nmr spectra assigned. The nmr assignments required concerted utilization of two-dimensional nmr techniques which included: COSY, direct and long range optimized heteronuclear chemical shift correlation and heteronuclear relayed coherence transfer.

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Introduction.

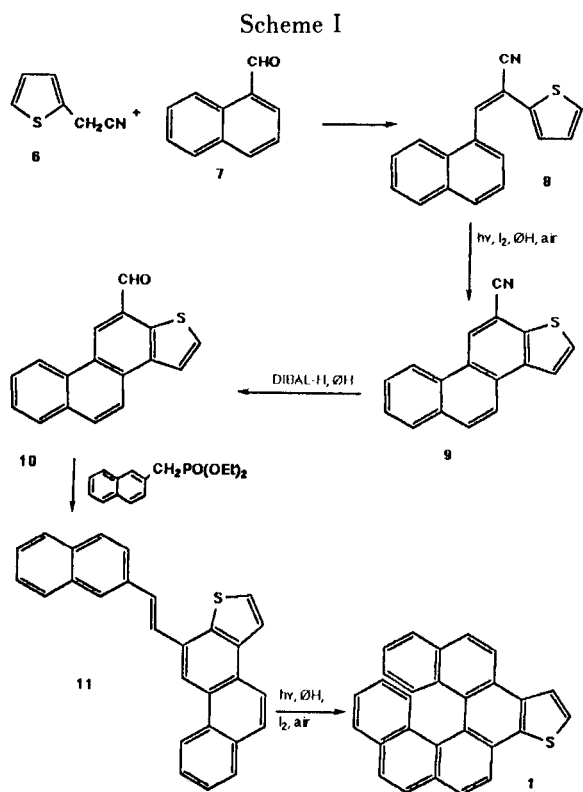
Total proton and carbon nmr assignments for several complex, helically distorted polynuclear aromatic heterocycles have appeared in the recent literature [1a-7]. Generally, because of the high degree of congestion inherent in the proton and carbon nmr spectra of these molecules, they are intractable to assignment by conventional techniques and chemical shift calculations, requiring instead that two-dimensional nmr methods be employed to provide unequivocal assignments. Earlier work on compounds in this series generally required the utilization of carbon-carbon double quantum techniques [1a,3,6-14] to provide an unequivocal assignment of the carbon spectrum. Thus, the carbon spectra of members of the homologous series including the mutagen phenanthro[3,4-*b*]thiophene (**2a**) [1a], benzo[*b*]phenanthro[4,3-*d*]thiophene (**3**) [6] and phenanthro[4,3-*a*]dibenzothiophene (**4a**) [2,3] were assigned using the autocorrelated carbon-carbon double quantum technique of Turner [13,14] with a modified read pulse [12] to improve sensitivity. More recently, total assignments have been based upon the use of long range optimized heteronuclear proton-carbon chemical shift correlation (LROCSCM), as in the case of 9-methylphenanthro[4,3-*a*]dibenzothiophene (**4b**) [5]. Practically, **4b** was chosen as an initial model system to evaluate the utilization of LROCSCM because of its very well characterized parent, **4a** [2,3]. Usefully, the LROCSCM technique provided an unequivocal assignment for all of the carbon resonances of **4b** including the quaternary carbons in the interior of the helix which can be difficult to obtain responses for in the carbon-carbon double quantum experiment because of their lengthy relaxation times. In the completely unrelated benzo[3,4]phenanthro[1,2-*b*]thiophene (**5**), the results obtained using both the LROCSCM



at 75 MHz and the conventional carbon-carbon double quantum INADEQUATE experiments [8-11] at 125 MHz were completely complementary, although the LROCSCM experiment exhibited far superior sensitivity even when the differences in sensitivity due to the observation frequencies were discounted.

Our interest in these complex heterocycles is many fold. First, they provide exceptionally challenging assignment problems because of their highly congested proton and

carbon spectra. Second, these systems are helically distorted, phenanthro[3,4-*b*]thiophene (**2a**) showing pronounced mutagenicity [15] which may, in part, be related to its helicity. Finally, the distorted bond lengths in the interior of the helical turn which are necessary to accommodate the non-planarity of these molecules [4,7,16] may have interesting consequences on the chemical shifts of these carbons. It is on these bases that we now wish to report the synthesis of phenanthro[3',4':3,4]phenanthro[2,1-*b*]thiophene (**1**) as shown in Scheme I and the total assignment of its proton and carbon nmr spectra by two-dimensional nmr methods.



The title compound, **1**, required the initial preparation of 1-cyano-1-(2'-thienyl)-2-(1"-naphthyl)ethene (**8**) which was obtained from the condensation of thiophene-2-acetonitrile (**6**) and 1-naphthalenecarboxaldehyde (**7**). Photocyclization of **8** in benzene afforded 11-cyanophenanthro[2,1-*b*]thiophene (**9**) which was converted to the corresponding aldehyde **10** by reaction with diisobutylaluminum hydride in hexane. Reaction of **10** with 2-naphthylmethyl diethylphosphonate under Wadsworth-Emmons conditions gave the requisite ethene **11** for the final photocyclization to the desired phenanthro[3,4:3':4']phenanthro[2,1-*b*]thiophene (**1**). Photocyclization of **11** in benzene in the presence of iodine and a stream of dry air for five hours gave the desired **1** in a 75% yield.

Results and Discussion.

The structural assignment of **1** was accomplished without the luxury of having downfield shifted bay region protons as a starting point. As a homolog of **5** and related systems which have been assigned by 2D-nmr methods [7] the lack of a bay region proton resonance to begin the assignment process necessitated the identification of another starting point. The ¹H-nmr spectrum of this compound is comprised of two AKMX, three AX and one AB spin systems. Due to the helical nature of the compound the furthest downfield resonances are not expected to be members of the two four spin systems. Rather, the proton constituents of the four spin systems are expected to be shifted upfield by the overlap of the terminal rings of the hexahelicene backbone of the molecule [16,17]. Confirmation of this premise was provided by the COSY spectrum (not shown). The two four spin systems were essentially in precise correspondence with only minimal differences in chemical shift as would be expected for the highly similar nature of the chemical environments of these spin systems. The COSY spectrum also identified the two downfield resonances as members of two separate two spin systems.

A heteronuclear chemical shift correlation experiment with broadband homonuclear decoupling (CSCMBB) [18] was performed to establish the direct proton-carbon connectivities in addition to providing precise proton chemical shifts. From the direct proton-carbon connectivities established with the CSCMBB spectrum a heteronuclear relayed coherence transfer (RCT2D) [2-7,24] experiment was next performed to establish the vicinal proton-proton coupling network hence providing the exact constitution of the four spin heteronuclear system. This operation was necessary since there is a chance of misordering the heteronuclear system if only the COSY data are utilized. The RCT2D experiment was, however, only partially successful since the connectivities between H11-H12 and H15-H16 could not be established with certainty from the experiment. Importantly, however, RCT2D did establish the H10-H11, H12-H13, H14-H15 and H16-H17 connectivities unequivocally. The remaining connectivities which were not established by the RCT2D spectrum can be established from either the long range optimized heteronuclear chemical shift correlation experiment (LROCSCM) [7,17,19] or a ¹³C-¹³C double quantum coherence experiment in one of its various forms [3,6,7,20,21].

Although direct proton-carbon connectivities have been deduced along with the proton-proton vicinal coupling network, the orientation of the various heteronuclear spin systems with respect to each other remains to be established. In order to orient the heteronuclear spin systems, the non-protonated carbon resonances must next be considered. Two alternative means of orienting the heteronuclear

spin systems and linking them to the quaternary carbons, thus completing the assignment, are available. The two methods available are the long range optimized heteronuclear chemical shift correlation (LROCSCM) [19], and ^{13}C - ^{13}C double quantum coherence (INADEQUATE) [20]. Although both experiments have been used with success in the total nmr spectral assignment of polycyclic aromatic heterocycles [3,6,7,21], the LROCSCM experiment offers several advantages with regard to acquisition time and the amount of compound needed. In addition, the relative information content of the LROCSCM experiment is potentially higher in many cases, allowing multiple coupling pathways into the same nucleus or spin system thereby providing alternative means of making a particular assignment or means of linking adjacent spin systems. In con-

trast, the ^{13}C - ^{13}C INADEQUATE experiment may fail to lead to a total assignment in those cases where there are too many breaks in the connectivity network due to AB ^{13}C - ^{13}C pairings.

A summary of the observed three bond couplings from the LROCSCM experiment (depicted as arrows) and the observed responses from the RCT2D experiment (depicted as double headed arrows) performed on **1** are shown in Figure 1. The quaternary carbon signals furthest downfield are clearly attributable to the thiophene ring [7]. Further, although it is not evident from the contour plot, Figure 2, the two furthest downfield proton resonances

Figure 1A.

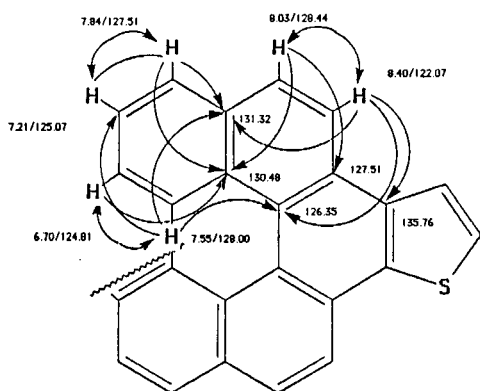


Figure 1B

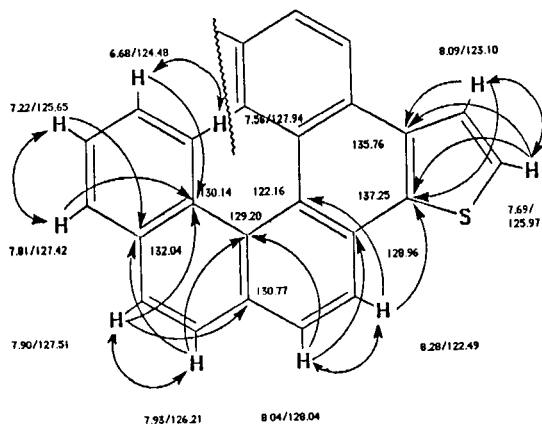


Figure 1. A) Long range connectivities for the "upper half" of **1** obtained using the LROCSCM experiment optimized for a 10 Hz transfer of magnetization. Couplings are illustrated using single headed arrows to indicate the coupling of a proton to the carbon to which the arrow points. Vicinal proton-proton spin couplings deduced from the RCT2D spectrum are presented as double headed arrows. B) Long range connectivities for the "lower half" of **1** using the same convention as above.

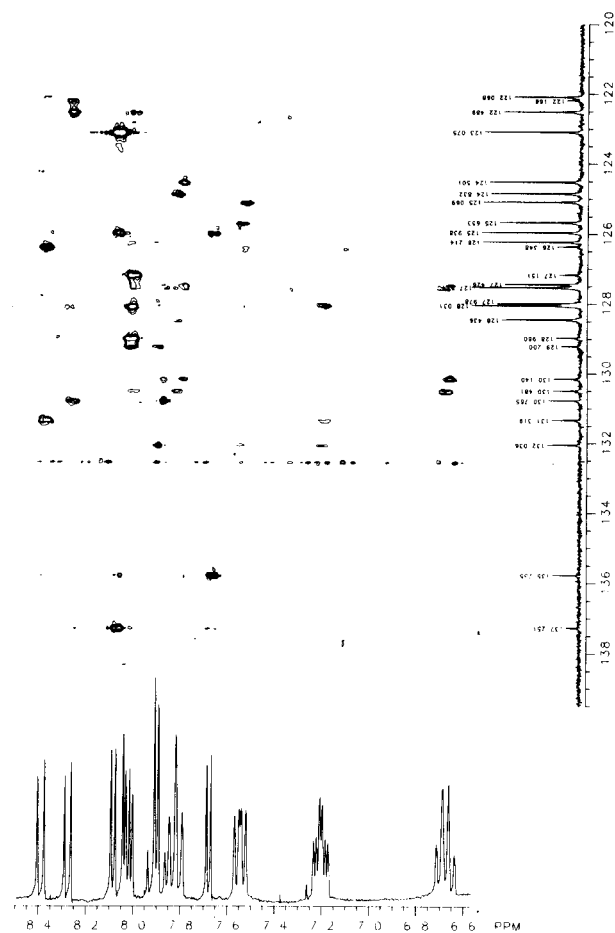


Figure 2. Long range optimized heteronuclear chemical shift correlation (LROCSCM) spectrum of **1** in deuteriochloroform at observation frequencies of 300.068/75.459 MHz at 303°K. The conventional high resolution proton spectrum is plotted along the F₁ axis (below) while the high resolution carbon spectrum is plotted along the F₂ axis (vertically).

have three bond couplings to the quaternary carbons of the thiophene ring. These couplings were visible when the individual slices from the data matrix of the LROCSCM experiment were plotted, as shown in Figure 3, for these quaternary carbons. The H2 proton can now be assigned

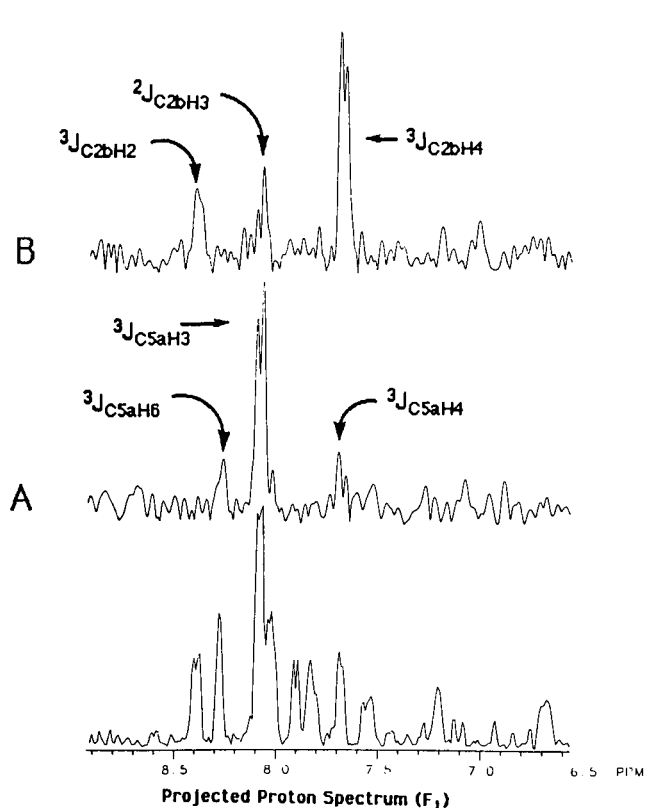


Figure 3. Slices taken from the LROCSCM contour plot showing the responses for A) C5a resonating at 137.25 ppm; B) C2b resonating at 135.76 ppm. Slices were plotted to confirm the long range connectivities from H6 and H2, respectively, which allow the proper orientation of the two AB spin systems flanking the fusion face where the thiophene ring is attached.

as the signal at $\delta_H = 8.40$, on the basis of its coupling to the carbon signal at $\delta_C = 135.76$, which is assigned as C2b from chemical shift considerations [7]. The other downfield proton is assignable as H6, resonating at $\delta_H = 8.28$, based upon coupling to the other downfield quaternary carbon signal at $\delta_C = 137.23$, which is assigned as C5a. The location of these signals furthest downfield is reasonable considering that each is in a "pseudo-bay" region. With these tentative assignments made, the remainder of the assignment can proceed. In the presumably rare case where the assignments of C2b and C5a are reversed, further extension of the connectivity network in both directions would eventually rectify the error.

Included in Figure 1A is the observed long range coupling network extending outward from the H2 signal at $\delta_H = 8.40$. In the case of H2, the assignment of C17a and C13d at $\delta_C = 131.32$ and 126.35, respectively, is possible, as shown by Figure 1A. Verification of the C17a signal assignment is provided by long range proton-carbon coupling to the H14 and H16 resonances of the adjacent four spin system. For C13d, the assignment is confirmed by coupling to only one of the protons, H14, from the four spin system. Importantly, once the assignment of the C17a

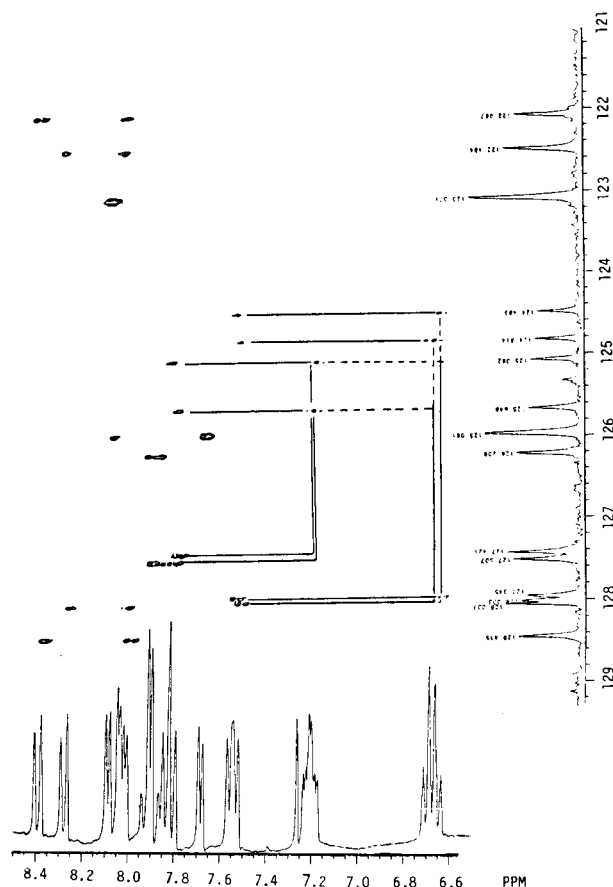


Figure 4. Heteronuclear relayed coherence transfer (RCT2D) spectrum of **1** recorded in deuteriochloroform at 303° K. The conventional high resolution proton spectrum is plotted along the F_1 axis (below) while the projected carbon spectrum containing only the protonated carbon resonances is plotted along the F_2 axis (vertically).

resonance has been established the assignment of the four spin system is also consequently completed because of the $^3J_{C17aH16}$ and $^3J_{C17aH14}$ couplings. Since the vicinal neighbors of the H14 and H16 signals, H15 and H17, respectively, have been determined from the RCT2D experiment, all members of one of the four spin systems have been assigned. The remainder of the quaternary carbons in this portion of the molecule, C2a and C13e, can also be assigned through long range coupling to H1 as shown in Figure 1A (although expected, the $^3J_{C2aH3}$ coupling was not visible).

Turning to the lower portion of the compound, the assignment process continues from H6 in much the same way. The $^3J_{CH}$ connectivity pathways from the LROCSCM experiment are included in Figure 1B. From H6 access is gained to both the C7a and C13c assignments. The assignment of C7a establishes the orientation of the remaining two two spin systems later this coupling sets the stage for the assignment of the remaining four spin system. The connectivity between the proton signal at 8.28 ppm, assigned as H6 and the signal at 8.04 ppm is provided by the

RCT2D experiment, Figure 4 and diagrammed in Figure 1B, thus it can be assigned as H7. This correlation allows the assignment of C13b (no connectivity between H7 and C8 was found however). This assignment is verified by the coupling of H8 to the C13b signal from the LROCSCM experiment. From the RCT2D experiment the H9 signal is next assigned. Once the assignment of the H9 signal is determined, entry into the four spin system is possible through mutual long range coupling to C9a and C13a by protons in both adjacent spin systems. Consequentially, the assignment process for the members of the four spin system is identical to that described for the upper portion of the molecule.

Table 1

Proton and Carbon Resonance Assignments for Phenanthro[3',4':3,4]-phenanthro[2,1-*b*]thiophene (**1**) in Deuteriochloroform at Observation Frequencies of 300.068 and 75.459 MHz

Position	δ_H (ppm)	δ_C (ppm)
1	8.03	128.44
2	8.40	122.07
2a		127.51
2b		135.76
3	8.09	123.10
4	7.69	125.97
5a		137.25
5b		128.96
6	8.28	122.49
7	8.04	128.04
7a		130.77
8	7.93	126.21
9	7.90	127.51
9a		132.04
10	7.81	127.42
11	7.22	125.65
12	6.68	124.48
13	7.56	127.94
13a		130.14
13b		129.20
13c		122.16
13d		126.35
13e		130.48
14	7.44	128.00
15	6.70	124.81
16	7.21	125.07
17	7.84	127.51
17a		131.32

Conclusions.

This work demonstrates the complexity of compounds that can be unequivocally assigned through the use of the two-dimensional nmr experiments; in this case the com-

pound had 28 carbon signals within a region 15 ppm wide with 16 of these carbons in a congested region less than 6 ppm wide. This work also substantiates the contention that the synergistic combination of LROCSCM with RCT2D is as powerful, if not more so, than the ^{13}C - ^{13}C double quantum INADEQUATE experiment. Conservatively, it can be stated that the combination of LROCSCM and RCT2D experiments provides connectivity information that is equivalent to the connectivity information generated by the ^{13}C - ^{13}C double quantum INADEQUATE experiment, assuming that the latter will be able to establish all possible connectivities; in many cases, however, the AB character of the carbon-carbon pairings precludes the establishment of the total connectivity network. It can be argued that the ^{13}C - ^{13}C double quantum INADEQUATE experiment, when combined with the RCT2D experiment, will usually, if not always, provide all the connectivities necessary to unequivocally assign the spectra and/or establish the structure. However, the instrument time required is much greater for the ^{13}C - ^{13}C double quantum INADEQUATE experiment than for any other two-dimensional nmr technique. Therefore, it is generally more time efficient to obtain the data in another manner, more specifically using the LROCSCM technique. Additionally, the LROCSCM experiment usually provides multiple couplings from each proton and thus, any missing connectivities can almost invariably be obtained from an alternative coupling pathway thereby completing the assignment despite the missing connectivity. Finally, a much higher sensitivity long range heteronuclear chemical shift correlation experiment utilizing heteronuclear multiple quantum coherence has recently been described by Bax and co-workers [25]. Their experiment provides further advantages over the INADEQUATE experiment, and should make it possible to successfully assign the ^1H and ^{13}C -nmr spectra of much smaller samples than were used in this work.

EXPERIMENTAL

Synthesis.

1-Cyano-1-(2'-thienyl)-2-(1"-naphthyl)ethene (**8**).

Condensation of thiophene-2-acetonitrile (**6**) and naphthalene-1-carboxaldehyde (**7**) (1:1 molar ratio) in the presence of sodium ethoxide (1 molar equivalent) in absolute ethanol afforded the required ethene **8** in a typical yield of ~75%, mp 112-113°.

Anal. Calcd. for $\text{C}_{17}\text{H}_{11}\text{NS}$: C, 78.12; H, 4.25; N, 5.36; S, 12.26. Found: C, 77.91; H, 4.27; N, 5.36; S, 12.31.

11-Cyanophenanthro[2,1-*b*]thiophene (**9**).

Photocyclization of 1.0 g (0.0038 mole) of **8** in 500 ml of dry benzene in the presence of 0.1 g of iodine for four hours in the presence of a stream of dry air afforded **9** in a yield of 80%, mp 190°.

Anal. Calcd. for $\text{C}_{17}\text{H}_9\text{NS}$: C, 78.73; H, 3.50; N, 5.40; S, 12.37. Found: C, 78.72; H, 3.68; N, 5.41; S, 12.54.

1-(11'-Phenanthro[2,1-*b*]thienyl)-2-(2"-naphthyl)ethene (**11**).

Reduction of 11-cyanophenanthro[2,1-*b*]thiophene (**9**) to the corresponding carboxaldehyde **10** was accomplished by adding an equimolar quantity of diisobutylaluminum hydride (DIBAL-H) in hexane to **9** dissolved in dry benzene under a dry nitrogen atmosphere. After stirring for two hours at room temperature, dilute hydrochloric acid was added after which the desired carboxaldehyde **10** was extracted into chloroform. After drying over anhydrous sodium sulfate the chloroform was removed *in vacuo* to afford an orange solid, **10** in 65% yield, mp 192° which was used directly without further characterization.

To 1.0 g (0.0037 mole) of **10** in dry dimethoxyethane was added equimolar quantities of 2-naphthylmethyldiethylphosphonate and sodium hydride with stirring under a dry nitrogen atmosphere. The reaction mixture was stirred for three hours and then poured over ice, the solid material which precipitated was collected by filtration and dried to afford **11** in 85% yield, mp 179-180°.

Anal. Calcd. for C₂₈H₁₈S: C, 87.00; H, 4.70. Found: C, 86.64; H, 4.74.

Phenanthro[3,4:3',4']phenanthro[2,1-*b*]thiophene (**1**).

Photocyclization of 1.0 g (0.0026 mole) of **11** in 500 ml of dry benzene in the presence of 0.1 g of iodine and a slow stream of dry air using a 450 Watt medium pressure Hanovia lamp for five hours afforded the desired phenanthro[3,4:3',4']phenanthro[2,1-*b*]thiophene (**1**) in a crude yield of 75%, mp 234-235°. Attempts at recrystallization from a variety of solvent systems failed to give material which would give satisfactory analysis. Sublimation of **1** at 225° and 0.5 mm Hg gave a pale yellow crystalline material, mp 236° which gave a satisfactory elemental analysis.

Anal. Calcd. for C₂₈H₁₈S: C, 87.46; H, 4.20. Found: C, 87.38; H, 4.41.

NMR Spectroscopy.

The experiments in this work were performed on 45 mg of **1** in 0.4 ml of deuteriochloroform. All the spectra were recorded using a Nicolet NT-300 spectrometer controlled by a Model 293-C pulse programmer and equipped with a 5 mm ¹H/¹³C dual tuned probe. The 90° ¹³C observed pulse was calibrated as 17.5 μseconds using the two-dimensional pulse calibration procedure as described by Lawn and Jones [22]. The 90° ¹H pulse from the decoupler was calibrated as 27.5 μseconds by taking ¼(γH₂/2π). The ¹³C-nmr reference spectrum digitized with 8K points was recorded using a 12 μsecond pulse and a 1 second interpulse delay. The data was processed to provide the reference spectrum shown in Figure 2 using a double exponential apodization.

Heteronuclear ¹H/¹³C Chemical Shift Correlation with Broadband Homonuclear Proton Decoupling (CSCMBB).

Due to the high degree of congestion of the proton nmr spectrum of **1** exact chemical shifts of the proton resonances were determined using the heteronuclear chemical shift correlation experiment with broadband homonuclear proton decoupling [23]. Broadband homonuclear proton decoupling was obtained using delays of 3.0 mseconds, based on an assumed 165 Hz one bond proton-carbon coupling constant. The data were collected using 128 acquisitions/block as 256 × 1K points and were processed using a double exponential apodization prior to both Fourier transforms to give a 256 × 512 matrix. Proton chemical shift locations were determined from the projected, broadband proton decoupled proton spectrum.

Heteronuclear Relayed Coherence Transfer (RCT2D).

The heteronuclear relayed coherence transfer experiment was performed using the pulse sequence and phase cycling reported previously [2]. The Δ₁ and Δ₂ delays were set as in the heteronuclear chemical correlation experiment with the exception that the Δ₁ delay was halved because of the 180° ¹³C refocusing pulse applied midway through the Δ₁ interval in this experiment [24]. The mixing time was set to 1/5³J_{HH} = 28.56 mseconds. A 1 second interpulse delay was employed. The data were collected using 160 acquisitions/block, as a 256 × 1K matrix. The processing gave a final matrix of 256 × 512 points, the data are presented as a six level contour plot in Figure 4.

Long Range Optimized Heteronuclear ¹H/¹³C Chemical Shift Correlation (LROCSCM).

The pulse sequence employed for the long range optimized chemical shift experiment was identical to that used for the conventional heteronuclear chemical shift correlation experiment, the only difference being the Δ₁ and Δ₂ delays were optimized for an assumed 10 Hz long range coupling constant giving durations of 50.0 mseconds and 33.3 mseconds, respectively [7,17,19]. The data were collected using 192 acquisitions/block as an initial 256 × 1K points. The data were processed using 2.5 Hz exponential broadening prior to the first Fourier transformation and double exponential apodization before the second Fourier transformation. The final matrix consisted of 256 × 512 points, shown in Figure 2 as a four level contour plot.

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