The Synthesis of Novel Polycyclic Heterocyclic Ring Systems *via* Photocyclization. 13 [1,2]. Dibenzo-[*f,h*]phenanthro[9',10':4,5]thieno[2,3-*c*]quinoline

Jiann-Kuan Luo and Raymond N. Castle* [3]

Department of Chemistry, University of South Florida,
Tampa, FL 33620-5250
Received July 12, 1993

Dedicated to the memory of Dr. Roland K. Robins

The synthesis of a previously unknown polycyclic heterocyclic ring system, dibenzo[*f,h*]phenanthro-[9',10':4,5]thieno[2,3-*c*]quinoline (4), was accomplished *via* photocyclization of the appropriate amide followed by chlorination. Substitution of the chlorine atom with hydrazine followed by removal of the hydrazine moiety with 10% copper sulfate solution afforded the parent ring system 4. The unequivocal assignment of its highly congested ^{1}H and ^{13}C spectra was accomplished by utilizing two-dimensional nmr methods.

Recently we reported the synthesis of three novel ring systems [4], phenanthro[9',10':4,5]thieno[2,3-*c*]quinoline (1), benzo[*f*]phenanthro[9',10':4,5]thieno[2,3-*c*]quinoline (2), and benzo[*h*]phenanthro[9',10':4,5]thieno[2,3-*c*]quinoline (3) and their total assignments of ^{1}H and ^{13}C spectra [5,6]. The unequivocal assignments of their ^{1}H and ^{13}C nmr spectra were not possible without the concerted usage of the HMQC [7], HMBC [8], HMQC-TOCSY [9], and HMQC-NOESY [5,10-13] due to the pseudo-symmetric nature of these compounds containing three four-spin systems. It is conceivable that the four four-spin systems of the title compound, dibenzo[*f,h*]phenanthro[9',10':4,5]thieno[2,3-*c*]quinoline (4), with a greater symmetric nature than 1 will make the differentiation of the spin systems even more difficult. To this end, we synthesized the novel ring system, dibenzo[*f,h*]phenanthro[9',10':4,5]thieno[2,3-*c*]quinoline (4) *via* photocyclization.

[17], 3-chloro-*N*-(9-phenanthryl)phenanthro[9,10-*b*]thiophene-2-carboxamide (8) was obtained in 61% yield. Photocyclization of 8 in benzene provided dibenzo[*f,h*]phenanthro[9',10':4,5]thieno[2,3-*c*]quinolin-10(9*H*)-one (9) in 75% yield. Chlorination of the lactam 9 with phosphorus oxychloride gave 10-chlorodibenzo[*f,h*]phenanthro[9',10':-
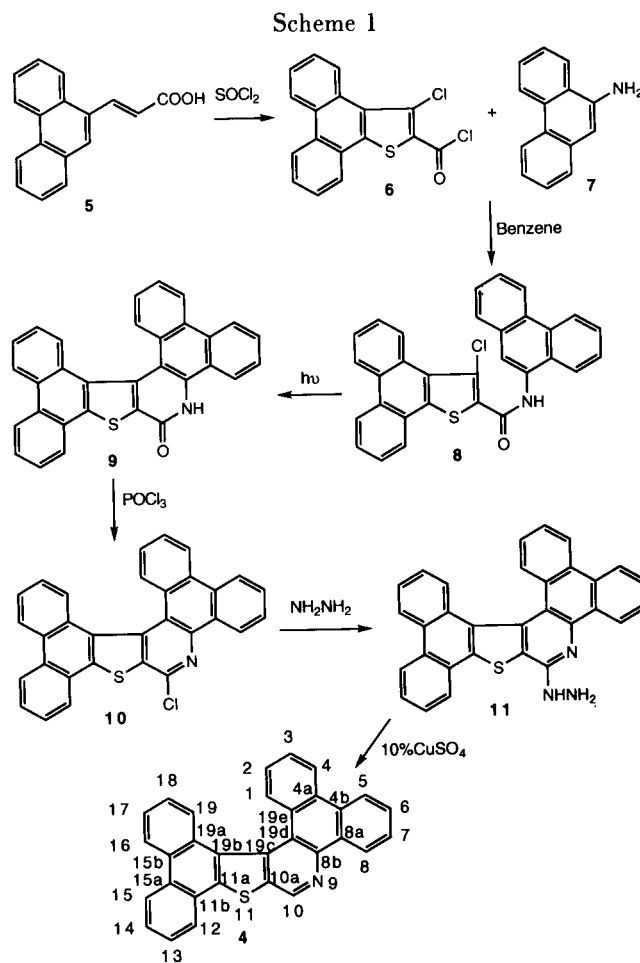
The synthetic pathway to 4 is illustrated in Scheme 1. The carbonyl chloride 6 [4,14] was obtained by treatment of 3-(9-phenanthryl)propenoic acid (5) [15] with thionyl chloride in chlorobenzene in the presence of pyridine [16]. When 6 was allowed to react with 9-phenanthrenamine (7)

Scheme 1

4,5]thieno[2,3-c]quinoline (**10**) in 24% yield. Reaction of **10** with anhydrous hydrazine in a mixture of benzene and ethanol gave 10-hydrazinodibenzo[f,h]phenanthro[9',10':-4,5]thieno[2,3-c]quinoline (**11**) in 76% yield. Upon removal of the hydrazine moiety by refluxing **11** with a 10% solution of copper sulfate and aqueous acetic acid, the parent ring system **4** was obtained in 25% yield.

NMR Spectroscopy.

Inspection of structure **4** shows that it consists of four four-spin systems and an isolated spin, H10. The congestion of the ^{1}H and ^{13}C spectra is expected due to the greater symmetric nature of **4** compared to **1**. The isolated spin, H10, serves as an entry point and it leads to the assignment of the four-spin system of H5, H6, H7 and H8 through common couplings H10/C8b and H8/C8b, which in turn makes the assignment of the four-spin system of H1, H2, H3 and H4 possible (Figure 1). Unfortunately, the long-range proton-carbon correlation of H8/C8b was not observed in the HMBC spectrum (Figure 2). Therefore, the connectivity must rely solely on the assignment of H8, which fortunately is well resolved and resonates furthest downfield at 9.36 ppm as a function of the location of H8 in a bay region and its proximity to the nitrogen atom.
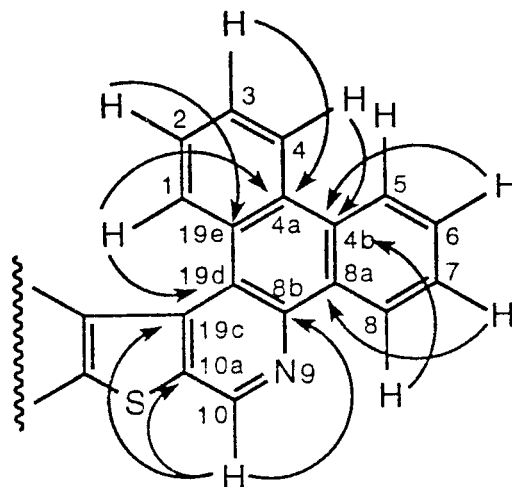

Figure 1. Diagram of long-range correlations observed on the HMBC spectrum for the protons 1-10.

Thus, the assignment of H1 through H10, the respective protonated carbon atoms and the quaternary carbon atoms can be achieved by concerted usage of HMQC (not shown), HMBC (Figure 2) and further confirmed by the
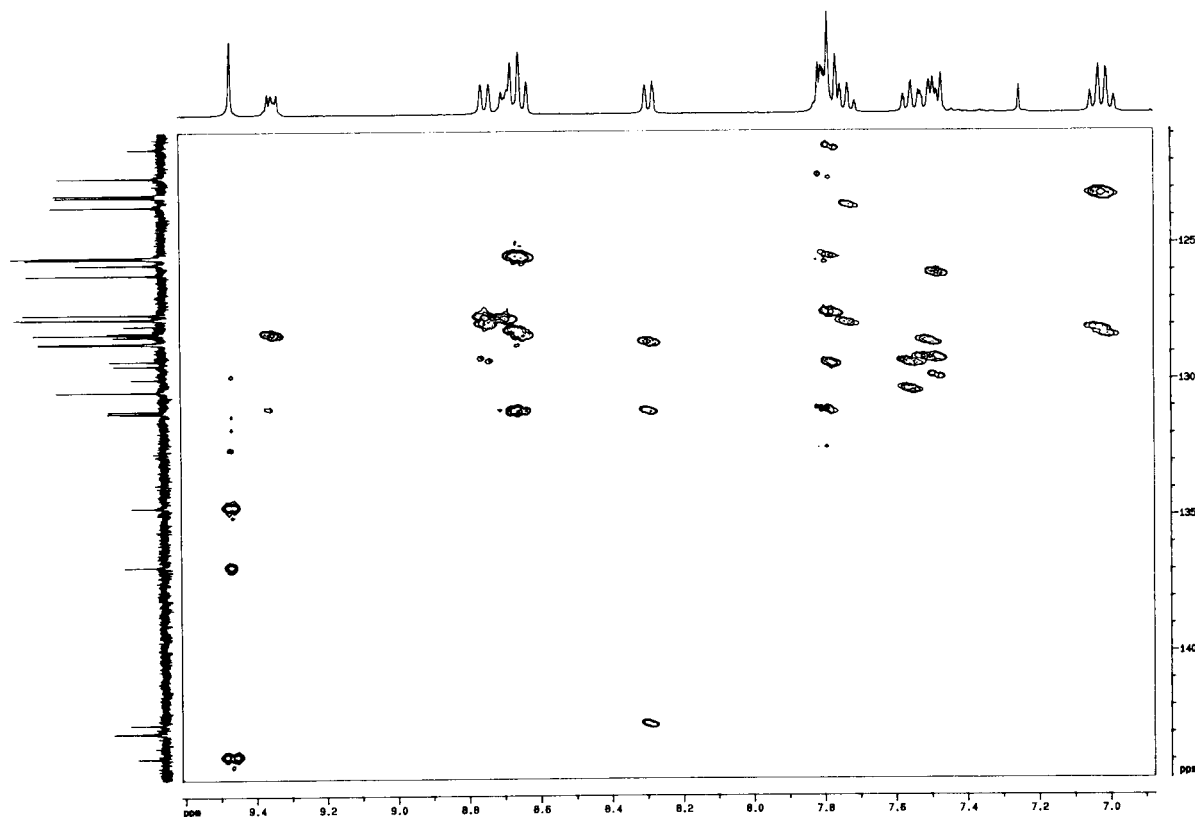

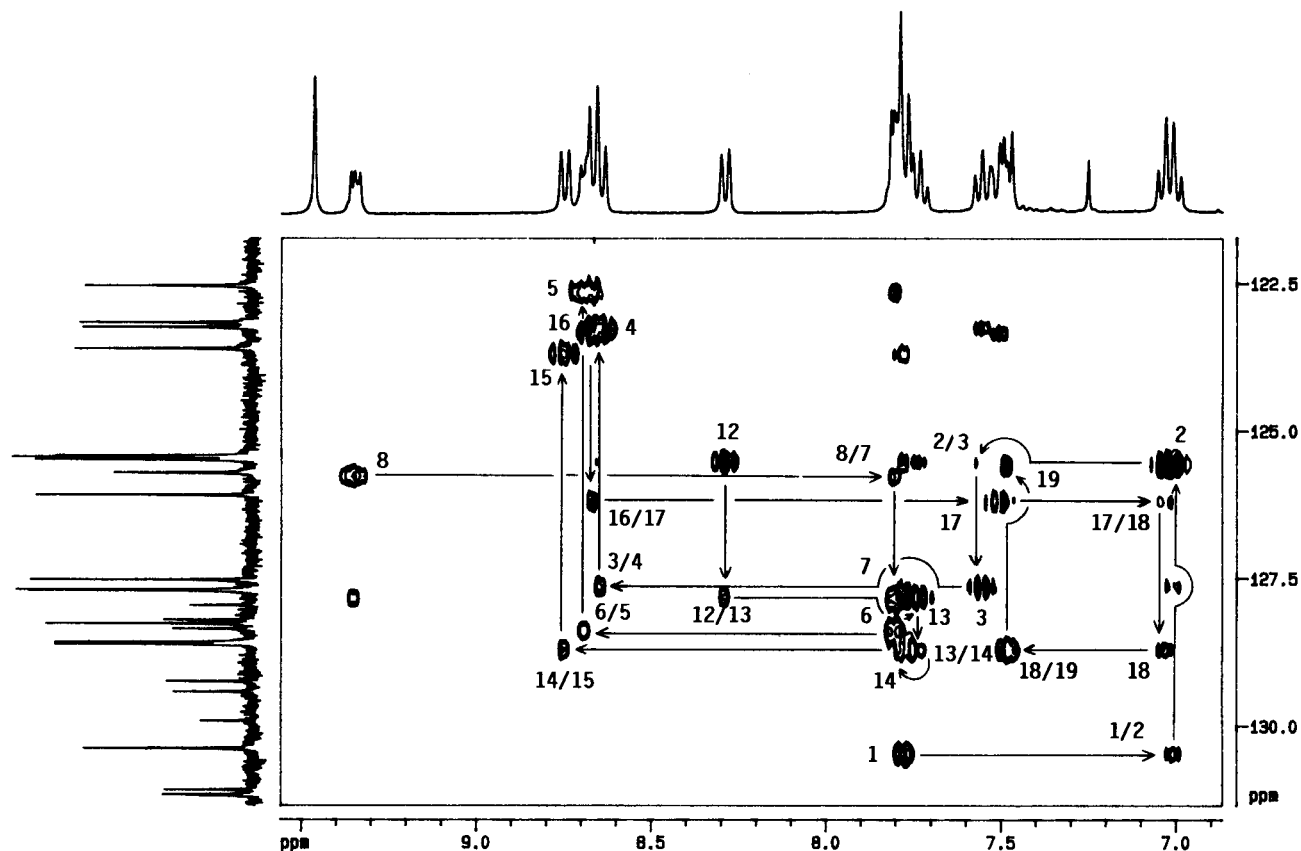Figure 2. The HMBC spectrum of **4**.

Figure 3.   The HMQC-TOCSY spectrum of **4**. Note that the direct responses from the proton carbon pairs at positions 6 and 7 are overlapped with the relayed responses between the proton pair at those positions.

Table 1

¹H and ¹³C Chemical Shifts of Dibenzo[*f,h*]-phenanthro[9′,10′:4,5]thieno[2,3-*c*]quinoline (**4**)

Position	δH	δC	Long-range Correlation
1	7.79	130.6	H3
2	7.02	125.7	H4
3	7.57	127.2	H1
4	8.66	123.2	H2
4a		129.3	H1, H3
4b		131.2	H4, H6, H8
5	8.70	122.7	H7
6	7.81	128.1	H8
7	7.82	127.9	H5
8	9.36	125.8	H6
8a		131.2	H5, H7
8b		143.7	H10
10	9.48	143.0	
10a		136.9	H10
11a		142.6	H12
11b		128.0	H13, H15
12	8.30	125.6	H14
13	7.75	127.9	H15
14	7.79	128.8	H12
15	8.76	123.8	H13
15a		131.0	H12, H14, H16
15b		129.1	H15, H17, H19
16	8.68	123.3	H18
17	7.52	126.0	H19
18	7.04	125.7	H16
19	7.50	128.8	H17
19a		128.1	H16, H18
19b		130.1	H19
19c		134.4	H10
19d		121.4	H1
19e		128.3	H2, H4

HMQC-TOCSY spectrum (Figure 3) (Table 1) as reported previously [1,5].

Due to the proximity of H1/H19 and H15/H16, the observation of nuclear Overhauser enhancement (nOe) may be utilized to identify H19 and differentiate the remaining two four-spin systems. Thus, an HMQC-NOESY (Figure 4) was acquired without heteronuclear decoupling during acquisition [6,13]. From this experiment a weak but prominent nOe response was observed between H1 and H19 on the opposite sides of the helical turn of **4**. The nOe between H1 and H19 provides the means of differentiating
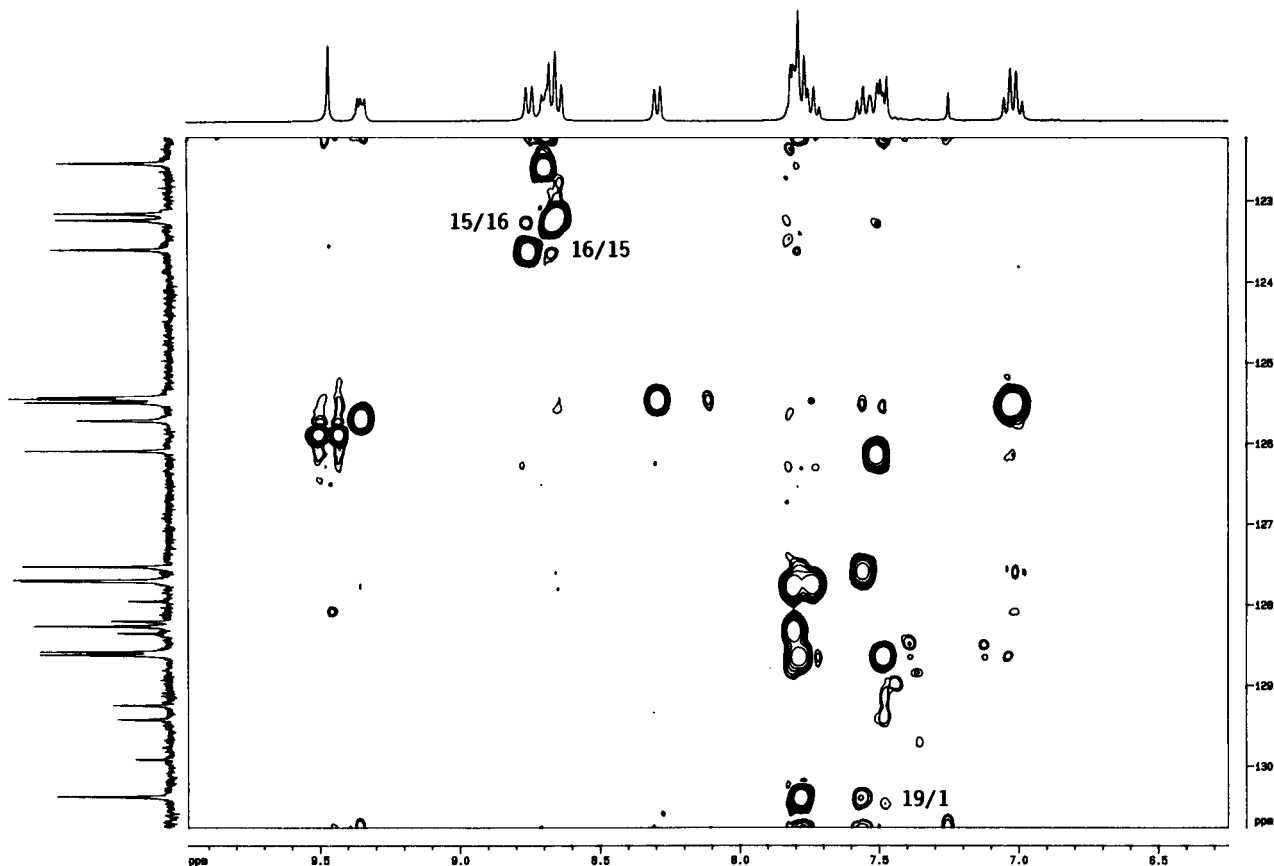
Figure 4. The HMQC-NOESY spectrum of **4** acquired without decoupling during the acquisition period. The responses of interest are the C1/H1 (130.6/7.79 ppm), C15/H15 (123.8/8.76 ppm) and C16/H16 (123.3/8.68 ppm) direct responses and the nOe responses at the chemical shifts of H19 (7.50 ppm), H16 (8.68 ppm) and H15 (8.76 ppm), respectively.

and assigning H19 unequivocally. The assignment of H19 orients the four-spin system which contains it. Ultimately, the nOe between H15 and H16 orients the spin system containing the former thereby completing the spectral assignment of **4** (Figure 5).
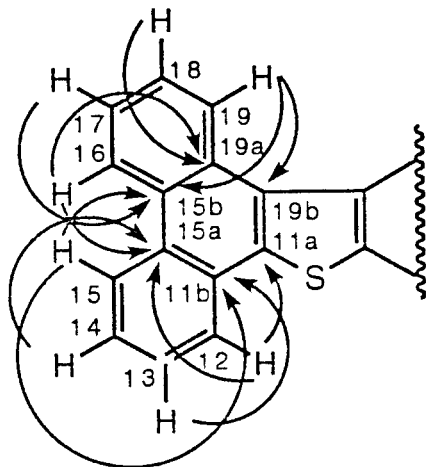

Figure 5. Diagram of long-range correlations observed on the HMBC spectrum for the protons 12-19.

In conclusion, we have synthesized the novel heterocyclic ring system, dibenzo[f,h]phenanthro[9',10':4,5]thieno-[2,3-c]quinoline (**4**). The complete assignments of the highly congested ¹H and ¹³C spectra of **4** were assigned by concerted usage of HMQC, HMBC, HMQC-TOCSY, and HMQC-NOESY two-dimensional nmr techniques.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. The ir spectra were recorded on a Beckman FT1100 spectrometer as potassium bromide pellets and frequencies are expressed in cm⁻¹. The ¹H nmr spectra of the intermediates except compound **8** were obtained on a JEOL FX-90Q spectrometer in the solvent indicated with TMS as the internal standard and chemical shifts are reported in ppm (δ) and J values in Hz. Column chromatography was performed utilizing Aldrich silica gel, 70-230 mesh. Elemental analyses were performed by M-H-W Laboratories, Phoenix, Arizona.

The ¹H and ¹³C spectra of **4** were acquired on a Bruker AMX 360 MHz NMR spectrometer operating at an observation frequency of 360.13 MHz for ¹H and 90.56 for ¹³C. All experiments were performed using an inverse-geometry 5 mm broad band probe. Pulse widths (90°) for ¹H and ¹³C were 7.2 and 14.4 μsec,

respectively. The spectral width was 3876 Hz for the ^{1}H nmr experiment and 1340 Hz for the HMQC, HMBC, HMQC-TOCSY, and HMQC-NOESY experiments. The carbon spectral width for the ^{13}C nmr experiment was 27773 Hz, 2463 Hz for the HMQC, HMBC, HMQC-TOCSY experiments, and 774 Hz for the HMQC-NOESY experiment.

Heteronuclear Multiple Quantum Coherence (HMQC).

The HMQC experiment was performed using the Bruker pulse program (*invbdgtp*) with the BIRD sequence optimized for direct couplings (165 Hz $^1J_{CH}$) [7]. The data were recorded as 1024 by 256 complex points with 256 transients/increment of the evolution time with a 1.0 second interpulse delay giving a total accumulation time of approximately 4.5 hours. Data were processed to give a final real matrix consisting of 512 by 512 real points.

Heteronuclear Multiple Bond Correlation (HMBC).

The HMBC experiment of **4** was obtained using the Bruker pulse program (*inv4lplrnd*) [8] optimized for 10.6 Hz $^3J_{CH}$ couplings and a delay for one bond suppression of 47 mseconds. The spectrum was acquired as 1024 by 256 data points, was zero-filled and subjected to cosine squared multiplication prior to both Fourier transforms to achieve a real data matrix of 512 by 512 points. A 2.5 second interpulse delay was employed. Total experiment time was approximately 13.5 hours.

HMQC-TOCSY.

The HMQC-TOCSY spectrum of **4** was acquired using the standard Bruker pulse program (*invbmltp*) [9] with a mixing time of 12 mseconds. The spectrum was acquired at a digital resolution of 1024 points for F_2 and 256 for F_1 in a phase-sensitive fashion with 256 transients/increment. A relaxation delay of 1.0 second was used between scans. Total accumulation time was approximately 4.5 hours. The data was zero-filled to achieve a real data matrix of 512 by 512 points and processed with cosine squared multiplication prior to both Fourier transformations.

HMQC-NOESY.

The HMQC-NOESY spectrum of **4** was acquired using the Bruker pulse program (*invbnotp*) modified such that the decoupler was off during acquisition [6,10,12]. F_2 was acquired with 1024 points and F_1 with 256 points and upon processing F_1 was zero-filled to achieve a data matrix of 512 by 512 points. Both dimensions were subjected to cosine squared multiplication prior to Fourier transformation. A mixing time of 250 mseconds was used for the generation of nOe. The null interval was 1.75 seconds and the interpulse delay was 1.0 second.

3-Chloro-*N*-(9-phenanthryl)phenanthro[9,10-*b*]thiophene-2-carboxamide (**8**).

A mixture of 2.5 g (7.55 mmoles) of 3-chlorophenanthro[9,10-*b*]thiophene-2-carbonyl chloride (**6**) [4,14] and 1.46 g (7.56 mmoles) of 9-phenanthrenamine (**7**) [17] in 80 ml of benzene was heated under reflux for 4 hours. After cooling the solid was collected by filtration and recrystallized from benzene to afford 2.23 g (4.57 mmoles, 61%) of amide **8** as short yellowish needles, mp 276-278°; ir (potassium bromide): 3422 (NH stretching), 1653 (C=O stretching); ^{1}H nmr (DMSO-d$_6$): 360 MHz, δ 7.67-7.80 (m, 8H, ArH), 8.05 (d, J = 7.20 Hz, ArH), 8.18 (s, 1H, H10'), 8.29-8.32 (m, 4H, ArH), 9.51 (m, 1H, ArH), 10.81 (br s, 1H, NH).

Anal. Calcd. for $C_{31}H_{18}ClNOS$: C, 76.30; H, 3.72; N, 2.87; S, 6.57. Found: C, 76.36; H, 3.71; N, 2.77; S, 6.51.

Dibenzo[*f,h*]phenanthro[9',10':4,5]thieno[2,3-*c*]quinolin-10(9*H*)-one (**9**).

A mixture of 0.5 g (1.03 mmoles) of **8**, 0.11 g of triethylamine and 450 ml of benzene was irradiated with a 450 watt Hanovia medium pressure mercury vapor lamp for 4 hours. A slow stream of air was passed through the solution during the course of the reaction. The solid was collected by filtration and washed with water to give 0.35 g (0.78 mmole, 76%) of **9**, mp >300°; ir (potassium bromide): 3145 (NH stretching), 1635 (C=O stretching). This compound is neither soluble in DMSO-d$_6$, nor in deuterated trifloroacetic acid at elevated temperature, therefore, no nmr spectrum was determined. Compound **9** was used in the next step without further purification because of low solubility.

10-Chlorodibenzo[*f,h*]phenanthro[9',10':4,5]thieno[2,3-*c*]quinoline (**10**).

A mixture of 1.42 g (3.14 mmoles) of lactam **9** and 60 ml of phosphorus oxychloride was heated at 110-115° for 4 hours. After cooling, the mixture was cautiously poured into 500 ml of ice-water. The solid was collected by filtration and recrystallized from benzene to afford 0.35 g (0.74 mmoles, 24%) of **10** as yellow crystals, mp >320°; ir (potassium bromide): 3068 (aromatic CH stretching); ^{1}H nmr (deuteriochloroform): 50°, δ 6.91-7.11 (m, 2H, ArH), 7.43-7.66 (m, 3H, ArH), 7.72-7.89 (m, 5H, ArH), 8.29-8.39 (m, 1H, H12), 8.63-8.81 (m, 4H, ArH), 9.25-9.36 (m, 1H, H8).

Anal. Calcd. for C, 79.22; H, 3.43; N, 2.98; S, 6.82. Found: C, 79.50; H, 3.70; N, 2.91; S, 6.56.

10-Hydrazinodibenzo[*f,h*]phenanthro[9',10':4,5]thieno[2,3-*c*]quinoline (**11**).

To a refluxing mixture of 0.32 g (0.68 mmole) of **10** in 25 ml of benzene and 25 ml of ethanol was added dropwise 10 ml of anhydrous hydrazine over a period of one hour. The resulting mixture was refluxed for 24 hours. An additional 5 ml of anhydrous hydrazine was added dropwise and the reflux was continued for an additional 24 hours. After cooling the solid was collected by filtration and washed thoroughly with water to give 0.24 g (0.52 mmole, 76%) of hydrazine **11** as a yellow powder, mp >280°; ir (potassium bromide): 3307, 3253 (NH stretching), 3065 (aromatic CH stretching); ^{1}H nmr (DMSO-d$_6$): 130°, δ, 6.87-7.10 (m, 2H, ArH), 7.36-7.93 (m, 8H, ArH), 8.33-8.43 (m, 1H, H12), 8.65-8.94 (m, 4H, ArH), 9.18-9.28 (m, 1H, H8). The hydrazino resonances were not observed in the ^{1}H nmr spectrum. The compound was used for the next step without further purification because of low solubility.

Dibenzo[*f,h*]phenanthro[9',10':4,5]thieno[2,3-*c*]quinoline (**4**).

To a refluxing mixture of 0.2 g (0.43 mmole) of **11** in 15 ml of water and 15 ml of glacial acetic acid was added 10 ml of 10% copper sulfate solution and the mixture was heated under reflux for 20 hours. After cooling the mixture was basified with 2*N* sodium hydroxide solution. The mixture was extracted with dichloromethane (3 x 50 ml), washed with water (1 x 100 ml) and dried over anhydrous magnesium sulfate. After filtration, the filtrate was evaporated to dryness *in vacuo*. The resulting solid was dissolved in 8 ml of chloroform and was chromatographed over silica gel eluting with a cyclohexane-benzene mixture to give 47 mg (0.108 mmole, 25%) of **4** as brownish crystals after recrystallization from cyclohexane, mp 255-258°; ir (potassium bromide):

3068 (aromatic CH stretching).

Anal. Calcd. for $C_{31}H_{17}NS \cdot 2/3\ C_6H_{12} \cdot 1/2\ H_2O$: C, 83.96; H, 5.24; N, 2.80. Found: C, 83.95; H, 5.49; N, 2.67.

Acknowledgement.

REFERENCES AND NOTES

[1] Part **1**: S. L. Castle, J.-K. Luo, H. Kudo and R. N. Castle, *J. Heterocyclic Chem.*, **25**, 1363 (1988); Part **2**: J.-K. Luo and R. N. Castle, *J. Heterocyclic Chem.*, **27**, 1031 (1990); Part **3**: M. J. Musmar and R. N. Castle, *J. Heterocyclic Chem.*, **28**, 203 (1991); Part **4**: J.-K. Luo, A. S. Zektzer and R. N. Castle, *J. Heterocyclic Chem.*, **28**, 737 (1991); Part **5**: J.-K. Luo and R. N. Castle, *J. Heterocyclic Chem.*, **28**, 1825 (1991); Part **6**: R. N. Castle, S. Pakray and G. E. Martin, *J. Heterocyclic Chem.*, **28**, 1997 (1991); Part **7**: K. Sasaki and R. N. Castle, *J. Heterocyclic Chem.*, **29**, 963 (1992); Part **8**: K. Sasaki and R. N. Castle, *J. Heterocyclic Chem.*, **29**, 1631 (1992); Part **9**: Ch. Camoutsis and R. N. Castle, *J. Heterocyclic Chem.*, **30**, 153 (1993); Part **10**: M. J. Musmar, A. S. Zektzer, R. N. Castle and N. K. Dalley, *J. Heterocyclic Chem.*, **30**, 487 (1993); Part **11**: J.-K. Luo, A. S. Zektzer, R. N. Castle, R. C. Crouch, J. P. Shockcor and G. E. Martin, *J. Heterocyclic Chem.*, **30**, 453 (1993); Part **12**: J.-K. Luo, S. L. Castle and R. N. Castle, *J. Heterocyclic Chem.*, **30**, 653 (1993).

[2] Presented at the 14th International Congress of Heterocyclic Chemistry, Antwerp, Belgium, August 1-6, 1993.

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

[4] C. L. Camoutsis and R. N. Castle, *J. Heterocyclic Chem.*, **30**, 153 (1993).

[5] L. W. Castle, M. D. Johnston, Jr., C. L. Camoutsis and R. N. Castle, *J. Heterocyclic Chem.*, **29**, 1805 (1992).

[6] L. W. Castle, M. D. Johnston, Jr., C. L. Camoutsis and R. N. Castle, *J. Heterocyclic Chem.*, **29**, 1869 (1992).

[7] A. Bax and S. Subramanian, *J. Magn. Reson.*, **67**, 565 (1986).

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

[9] L. Lerner and A. Bax, *J. Magn. Reson.*, **69**, 375 (1986).

[10] K. Sohn and S. J. Opella, *J. Magn. Reson.*, **82**, 193 (1989).

[11] R. C. Crouch, R. B. McFadyen, S. M. Daluge and G. E. Martin, *Magn. Reson. Chem.*, **28**, 792 (1990).

[12] G. E. Martin and R. C. Crouch, *J. Nat. Prod.*, **54**, 1 (1991).

[13] J. Kawabata, E. Fukushi and J. Mizutani, *J. Am. Chem. Soc.*, **114**, 1115 (1992).

[14] T. N. Sidorenko, G. A. Tecent'eva and V. S. Aksenov, *Chem. Heterocyclic Compd. (USSR).*, **19**, 161 (1983).

[15] W. E. Bachmann and M. C. Kloetzel, *J. Am. Chem. Soc.*, **59**, 2207 (1937).

[16] W. B. Wright, Jr. and H. J. Brabander, *J. Heterocyclic Chem.*, **8**, 711 (1971).

[17] L. F. Fieser, R. P. Jocobsen and C. C. Price, *J. Am. Chem. Soc.*, **58**, 2163 (1936).