Structure Analysis of some α-(*N*-Methyl-*N*-formylaminomethyl)-quinolines

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Received July 8, 2002

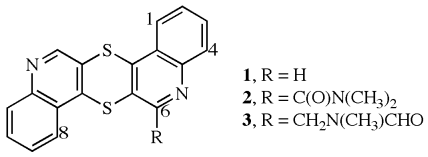
The ^{1}H and ^{13}C nmr spectra of the rotational isomers **3a** and **3b** of 6-(*N*-methyl-*N*-formylaminomethyl)-thioquinanthrene were completely assigned with a combination of 1D and 2D nmr techniques. The key-parts of this methodology were long-range proton-carbon correlations and NOE experiments with *N*-methyl-*N*-formylaminomethyl substituent. The X-ray study of 4-methyl-2-(*N*-methyl-*N*-formylaminomethyl)quinoline **4a** as well as ^{1}H and ^{13}C nmr spectra show that *N*-methyl-*N*-formylaminomethyl substituent in **4a** and **4b** has a different steric arrangement than the same substituent in **3a** and **3b**.

J. *Heterocyclic Chem*., **40**, 201 (2003).

Introduction.

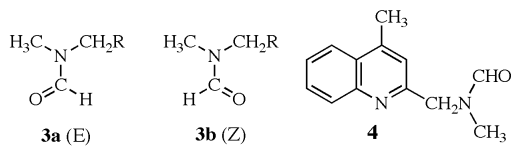
The reaction of protonated azine with DMF/hydroxylamine-*O*-sulfonic acid/Fe^{++} ion system led to α- and or γ-substituted azines with *N*,*N*-dimethylcarbamoyl and (or) *N*-methyl-*N*-formylaminomethyl substituents [1,2,3,4]. In the case of thioquinanthrene **1** both type of products, *i.e.*, compounds **2** and **3** were isolated [5].

Scheme 1



The structure of dimethylcarbamoyl derivative **2** was completely assigned both by ^{1}H and ^{13}C nmr study [5] and by X-ray diffraction examination [6]. In the case of 6-(*N*-methyl-*N*-formylaminomethyl)thioquinanthrene **3** a serious problem arose. Its ^{1}H and ^{13}C nmr spectra show resonances of the same functional groups of two species, having the same intensities and very similar coupling patterns [5]. This observation was interpreted in terms of restricted rotation about the C(O)-N bond in amides, taking into account that in the case of numerous unsymmetrical *N*,*N*-disubstituted amides [7] hindered rotation can give rise to *cis*- and *trans*- rotational isomers [8]. They often occur to an equal extent, as it was shown for *N*-methyl-*N*-ethylnicotinamide [9].

Scheme 2



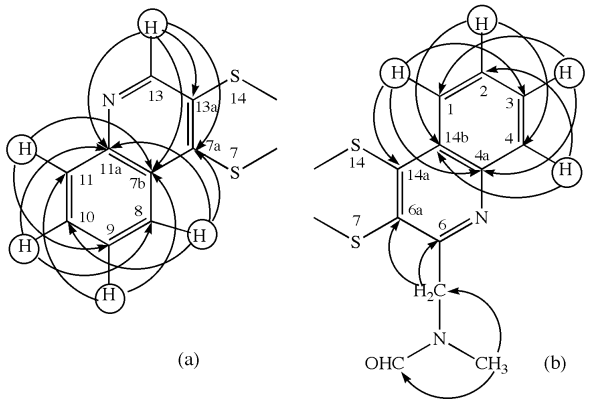
R = 6-thioquinanthrenyl

To confirm this hypothesis, the present study dealt with the complete ^{1}H and ^{13}C nmr assignment of **3a** and **3b** isomers. To evaluate spectroscopic effects observed for **3a** and **3b**, nmr and X-ray study of 4-methyl-2-(*N*-methyl-*N*-formylaminomethyl)quinoline **4** were also acquired.

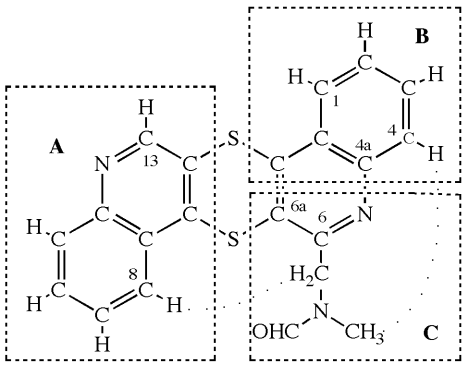
NMR Study of **3a** and **3b**.

The proton nmr spectrum of **3**, *i.e.*, of the mixture of **3a** and **3b** rotational isomers, shows two singlets of the *N*-methyl protons at δ=3.04 ppm and δ=2.92 ppm, two singlets of the *N*-methylene protons at δ=5.14 ppm and δ=5.01 ppm, two singlets of the formyl protons at δ=8.57 ppm and δ=8.93 ppm, two singlets of α-quinolinyl protons H13 (δ=8.93 ppm and δ=8.91 ppm) and multiplets of sixteen benzene-ring protons. A COSY ^{1}H-^{1}H experiment allowed the segregation of sixteen benzene ring protons into four ABMX systems of quinolinyl type. The next step was to find the correlation in the two 3,4-disubstituted quinoline moieties, *i.e.*, between α-quinolinyl proton H13 with benzene ring protons: H8, H9, H10, H11 for both **3a** and **3b** isomers. It could be achieved with the help of long-range ^{1}H-^{13}C correlations presented in Scheme 3 (formula a) and shows the spectral positions of protons and carbons being members of area A, (Scheme 4).

Scheme 3



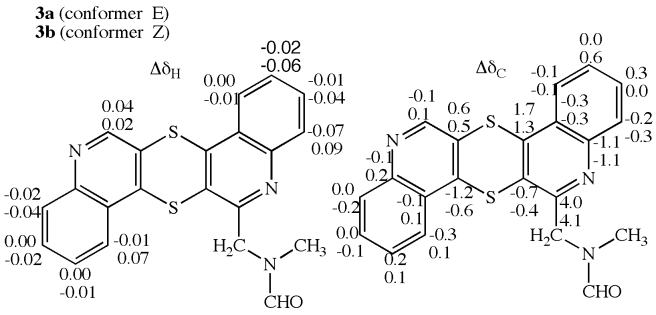
Scheme 4



The long-range proton-carbon correlations of benzene ring members of 2,3,4-trisubstituted quinoline moiety as well as those of *N*-methyl-*N*-formylaminomethyl substituent (Scheme 3, formula b) show connectivities between the carbon and proton atoms as depicted by areas B or C (Scheme 4), respectively. The ^{1}H-^{1}H NOE experiments proved **3a** to be conformer *E* and **3b** to be conformer *Z*. The positions of α-quinolinyl carbon C6 and β-quinolinyl carbon C6a were confirmed with ^{1}H-^{13}C long-range correlations (Tables 1, 2), they fit well with literature data as α-quinolinyl carbon was usually observed at 150 ppm but β-quinolinyl one near 130 ppm [10].

Due to the folded shape of **3a** and **3b** rotamers, distances between some protons of alkyl substituents and benzene rings protons of **3** are within the limit required for the occurrence of NOE (Tables 1, 2). Thus, connectivities between areas A, B and C for both rotamers could be deduced from NOE experiments indicating the interaction of methylene group protons with H8 proton and methyl group protons with H4 proton (see Scheme 4 and Figure 1). To evaluate the spatial requirement for the occurrence of NOE structure of **3a** and **3b** were simulated by means of AM1 and PM3 methods [11]. The calculations show that the H8/CH_2 protons distances are 3.54 Å or 3.67

Scheme 5
The values Δδ = δ(**3a** or **3b**) - δ(thioquinanthrene, **1**)



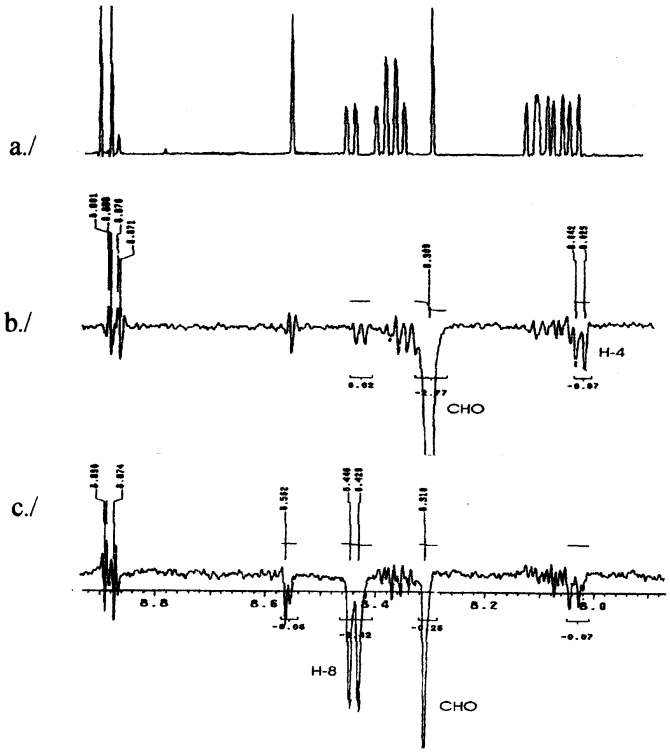


Figure 1. a./ ^{1}H nmr spectrum of **3a** and **3b** (500 MHz, $CDCl_3$) - region 7.90-8.90 ppm, b./ The NOE difference spectrum after irradiation of CH_3 group protons (δ=3.04 ppm), c./ The NOE difference spectrum after irradiation of CH_2 group protons (δ=5.12 ppm).

Table 1
Summary of the ^{1}H and ^{13}C correlations
(δ, ppm) and NOE enhancement recorded for **3a**

Position	Proton	Carbon	Long range proton–carbon couplings [a]	Proton enhancement (δ,ppm / %)
1	8.37	123.6 [a],[b]	C3 (130.6) C4a (146.1) C14a (145.9)	
2	7.67	128.0 [a],[b]	C4 (129.8) C14b (126.5)	
3	7.76	130.6 [a],[b]	C1 (123.6) C4a (146.1)	
4	8.06	129.8 [a],[b]	C2 (128.0) C14b (126.5)	
4a		146.1 [a]		
6		152.0 [a]		
6a		126.0 [a]		
7a		143.0 [a]		
7b		126.7 [a]		
8	8.36	123.4 [a],[b]	C7a (143.0) C10 (130.3) C11a (147.1)	
9	7.70	128.2 [a],[b]	C7b (126.7) C11 (130.0)	
10	7.77	130.3 [a],[b]	C8 (123.4) C11a (147.1)	
11	8.11	130.0 [a],[b]	C7b (126.7) C9 (128.2)	
11a		147.1 [a]		
13	8.93	147.9 [a]	C7a (143.0) C7b (126.7) C11a (147.1) C13a (127.3)	
13a		127.3 [a]		
14a		145.9 [a]		
14b		126.5 [a]		
CH_3	2.92	30.2 [a],[b]	CH_2 (54.3) CHO (163.8)	CH_2 (5.01) / 2.4 CHO (8.57) / 0.8 H4 (8.06) / 0.4
CH_2	5.01	54.3 [a],[b]	CH_3 (30.2) CHO (163.8) C6a(126.0) C6 (152.0)	CH_3 (2.92) / 6.0 CHO (8.57) / 20.6 H8 (8.36) / 1.3
CHO	8.57	163.8 [a],[b]	CH_3 (30.2) CH_2 (54.3)	

[a] From HMBC spectra (scheme 3). [b] From HSQC spectra.

Table 2
Summary of the ^{1}H and ^{13}C correlations (δ, ppm)
and NOE enhancement recorded for **3b**

Position	Proton	Carbon	Long range proton–carbon couplings [a]	Proton enhancement (δ, ppm / %)
1	8.36	123.6 [a], [b]	C3 (130.3) C4a (146.1) C14a (145.4)	
2	7.63	128.6 [a], [b]	C4 (129.7) C14b(126.5)	
3	7.73	130.3 [a], [b]	C1 (123.6) C4a (146.1)	
4	8.04	129.7 [a], [b]	C2 (128.6) C14b (126.5)	
4a		146.1 [a]		
6		152.1 [a]		
6a		126.3 [a]		
7a		143.6 [a]		
7b		126.9 [a]		
8	8.44	123.8 [a], [b]	C7a (143.6) C10 (130.2) C11a (147.0)	
9	7.68	128.1 [a], [b]	C7b (126.9) C11 (129.8)	
10	7.75	130.2 [a], [b]	C8 (123.8) C11a (147.0)	
11	8.09	129.8 [a], [b]	C7b (126.9) C9 (128.1)	
11a		147.0 [a]		
13	8.91	147.8 [a]	C7a (143.6) C7b (126.9) C11a (147.0) C13a (127.2)	
13a		127.2 [a]		
14a		145.4 [a]		
14b		126.5 [a]		
CH_3	3.04	34.9 [a], [b]	CH_2 (49.0) CHO (162.8)	CH_2 (5.14) / 2.5 CHO (8.31)
11.6				H4 (8.04) / 0.3
CH_2	5.14	49.0 [a], [b]	CH_3 (34.9) CHO (162.8) C6a (126.3) C6 (152.1)	CH_3 (3.04) / 5.0 CHO (8.31) / 0.3 H8 (8.44) / 1.7
CHO	8.31	162.8 [a], [b]	CH_3 (34.8) CH_2 (49.0)	

[a] From HMBC spectra (scheme 3). [b] From HSQC spectra.

A for **3a** and 3.34 A or 3.44 A for **3b**, but those of H4 /CH_3 are of the magnitude of 4.25 Å or 4.31 Å for **3a** and 4.06 Å or 3.91 Å for **3b**. Thus, taking into account the opinion found in the literature that: "the NOE enhancements can be used to connected protons up to about 4.5 Å apart" [12], our measurements of NOE for **3a** and **3b** gave correctly the correlations presented in Scheme 4. Differences between the respective δ_H and δ_C values of ring protons and carbons of **3a** and **3b** are close and do not exceed 0.09 ppm for $\Delta\delta_H$ and 0.6 ppm for $\Delta\delta_C$. (see Scheme 5)

Transmission of the steric hindrance effects induced by *E* or *Z* *N*-methyl-*N*-formylaminomethyl substituents on the values of δ_H and δ_C in **3a** or **3b** may be rationalized in terms of the changes in geometry of the 1,4-dithiin ring. It should act in a similar manner as it was concluded from X-ray diffraction study of compound **2** [6], where the presence of a bulky dimethylcarbamoyl substituent in the *ortho* position relative to 1,4-dithiin ring causes differentiation between respective bond lengths and bond angles in all heterocyclic rings of **2**. For example, in the case of non-planar, butterfly-type shaped, 1,4-dithiin moiety, the length of β-quinolinyl-sulfur bond (C6a-S7, 1.770(5) Å) being sterically affected by the dimethylcarbamoyl substituent is longer than the second β-quinolinyl-sulfur bond (C13a-S14, 1.726(5) Å) by

Table 3
Summary of the ^{1}H and ^{13}C correlations (δ, ppm) and NOE enhancement recorded for **4a**

Position	Proton	Carbon	Long range proton–carbon couplings [a]	Proton enhancement (δ, ppm / %)
2		155.9 [a]		
3	7.14	119.4 [a], [b]	C2 (155.9)	
			C4a (127.5)	
4		145.8 [a]		
4a		127.5 [a]		
5	8.00	123.7 [a], [b]	C4 (145.8)	
			C7 (129.7)	
6	7.58	126.6 [a], [b]	C4a (127.5)	
			C8 (129.7)	
7	7.73	129.7 [a], [b]	C5 (123.7)	
			C8a (147.6)	
8	8.06	129.7 [a], [b]	C4a (127.5)	
			C6 (126.6)	
8a		147.6 [a]		
CH_3	2.69	18.8 [a], [b]	C3 (119.4)	
			C4a (127.5)	
NCH_3	2.89	30.1 [a], [b]	NCH_2 (55.9)	CHO (8.38) / 0.9
			CHO (163.2)	CH_2 (4.65) / 1.5
NCH_2	4.65	55.9 [a], [b]	NCH_3(30.1)	CH_3 (2.89) / 1.2
			CHO (163.2)	CHO (8.38) / 12.3
			C3 (119.4)	H3 (7.14) / 3.1
CHO	8.38	163.2 [a], [b]	NCH_3 (30.1)	
			NCH_2 (55.9)	

[a] From HMBC spectra. [b] From HSQC spectra.

Table 4
Summary of the ^{1}H and ^{13}C correlations (δ, ppm) and NOE enhancement recorded for **4b**

Position	Proton	Carbon	Long range proton – carbon couplings [a]	Proton enhancement (δ, ppm / %)
2		156.4 [a]		
3	7.22	120.5 [a], [b]	C2 (156.4)	
			C4a (127.5)	
4		145.5 [a]		
4a		127.5 [a]		
5	7.98	123.8 [a], [b]	C4 (145.5)	
			C7 (129.4)	
6	7.56	126.3 [a], [b]	C4a (127.5)	
			C8 (129.6)	
7	7.71	129.4 [a], [b]	C5 (123.8)	
			C8a (129.6)	
8	8.05	129.6 [a], [b]	C4a (127.5)	
			C6 (126.3)	
8a		129.6 [a]		
CH_3	2.68	18.7 [a], [b]	C3 (120.5)	
			C4a (127.5)	
NCH_3	2.99	34.7 [a], [b]	NCH_2 (50.4)	CH_2 (4.79) / 1.6
			CHO (162.8)	CHO (8.24) / 7.6
NCH_2	4.79	50.4 [a], [b]	NCH_3 (34.7)	NCH_3 (2.99) / 1.2
			CHO (162.8)	CHO (8.24) / 1.0
			C3 (120.5)	H3 (7.22) / 3.4
CHO	8.24	162.8 [a], [b]	NCH_3 (34.7)	
			NCH_2 (50.4)	

[a] From HMBC spectra. [b] From HSQC spectra.

Table 5
Crystal Data and Structure Refinement for the Compound **4a**

Empirical formula	$C_{13}H_{14}N_2O$
Formula weight	214.26
Temperature, K	293(2)
Diffractometer	KUMA KM4CCD
Wavelength, Å	0.71073
Crystal system	orthorombic
Space group	Pbca
Unit cell dimensions:	
a, Å	8.217(2)
b, Å	8.917(2)
c, Å	28.162(2)
Volume, $Å^3$	2314.6(9)
Z	8
Cell measurement refl. number	1851
Cell measurement theta range, deg.	5 – 20
Density (calculated), mg/m^3	1.230
Density (measured), mg/m^3	1.22
Absorption coefficient , mm^{-1}	0.079
F(000)	912
Crystal size,mm	0.22x0.25x0.35
Data collection method	Hemisphere run
θ range for data collection, deg.	2.64 - 24.71
Index ranges	-10 10, -10 10,-32 33
Reflections collected	17931
Independent reflections	1971
Refinement method	Full-matrix least-squares on F^2
Data / restraints/parameters	1971/0/160
Goodness-of-fit on F^2	1.129
Final R indices [I>4σ(I)]	0.0531
Weighting Scheme:	$1/[sigma^2(Fo^2)+(0.0572*P)^2+0.90*P]$ where $P=(Max(Fo^2,0)+2*Fc^2)/3$
Largest diff. peak and hole	0.16, –0.13

9 σ. It means that the transmission of the steric effects induced by 6-substituent *via* 1,4-dithiin ring affects the environment of the positions C-13 and H-13. In the case of rotational isomers **3a** and **3b**, non-identical *E* or *Z* *N*-methyl-*N*-formylaminomethyl substituents should influence the environment of H-13 differently, therefore two signals of H13 attributed to **3a** and **3b** should be observed.

The Structural Study on 4-Methyl-2-(*N*-methyl-*N*-formylaminomethyl)-quinoline **4**.

To evaluate the structural and spectroscopic effect induced by *N*-methyl-*N*-formylaminomethyl substituent in the molecule of **3**, the same properties of 4-methyl-2-(*N*-methyl-*N*-formylaminomethyl)quinoline **4** were then studied. The ^{1}H and ^{13}C nmr assignment of **4** (Table 3,4) was performed in the same way as for **3** (Scheme 3). In a $CDCl_3$ solution two rotational isomers **4a** and **4b** were observed to an equal extent. The NOE data presented in Table 4 proved **4a** to be the conformer *E* and those for **4b** the conformer *Z*, respectively.

Table 6

Atomic Coordinates and Equivalent Isotropic Displacement Parameters for the Compound **4a**

Atom	x	y	z	Ueq
N1	0.5918(2)	0.2254(2)	0.6630(1)	0.048(1)
C24	0.6099(3)	0.5893(3)	0.5519(1)	0.069(1)
C23	0.5412(3)	0.6155(3)	0.6343(1)	0.065(1)
C4a	0.4076(2)	0.430(2)	0.6385(1)	0.042(1)
C4	0.4179(2)	0.964(2)	05910(1)	0.047(1)
C2	0.5961(2)	0.2738(2)	0.6189(1)	0.047(1)
N22	0.6166(2)	0.5393(2)	0.5964(1)	0.050(1)
C21	0.6965(2)	0.4039(2)	0.6087(1)	0.057(1)
C3	0.5118(2)	0.2117(2)	0.5821(1)	0.051(1)
C8a	0.4982(2)	0.1099(2)	0.6731(1)	0.043(1)
C5	0.3128(2)	-0.727(2)	0.6532(1)	0.055(1)
C8	0.4922(3)	0.0580(2)	0.7204(1)	0.058(1)
C6	0.3084(2)	-0.1187(2)	0.6991(1)	0.063(1)
C7	0.3989(3)	-0.0538(3)	0.7328(1)	0.067(1)
O25	0.5437(3)	0.7000(2)	0.5388(1)	0.0101(1)
C21	0.3293(3)	0.0290(3)	0.5515(1)	0.073(1)

U(eq) is defined as one third of the trace of the orthogonalized, Uij tensor.

Table 7

Selected Bond Lengths [Å] and Angles [°] for the Compound **4a**

bond lengths [Å]			bond lengths [Å]		
N1	C2	1.314(2)	C4	C41	1.504(3)
N1	C8a	1.374(2)	C2	C3	1.410(3)
C24	O25	1.219(3)	C2	C21	1.512(3)
C24	N22	1.331(3)	N5	C21	1.456(3)
C23	N22	1.444(3)	C4a	C4	1.423(3)
C4a	C8a	1.415(2)			

angles [°]				angles [°]			
C2	N1	C8a	117.44(16)	C24	N22	C2	121.65(19)
O25	C24	N22	125.5(2)	C23	N22	C21	117.24(18)
C3	C4	C4a	117.88(17)	N5	C21	C2	111.83(16)
C3	C4	C41	120.52(19)	C4	C3	C2	120.55(18)
C4a	C4	C41	121.61(19)	C3	C2	C21	119.89(18)
N1	C2	C3	123.34(18)	C24	N22	C23	121.1(2)
N1	C2	C21	116.76(18)				

X-ray Diffraction Study of **4a**.

Recrystallization of **4** from ethanol gave crystals of **4a** rotational isomer, *i.e.*, *E* isomer (see Figure 2). X-ray analysis data of **4a** are collected in Tables 5, 6 and 7. They show planarity around the amide bond in *N*-methyl-*N*-formylaminomethyl substituent of **4a**. Thus, taking into account the planarity of the quinoline unit, the molecule **4a** is composed of two planar moieties with the angles

Conclusion.

X-ray study of *E*-2-(*N*-methyl-*N*-formylaminomethyl)lepidine **4a** show that the molecule of **4a** is built from two planar moieties: quinoline moiety and *N*-methyl-*N*-formylaminomethyl group with the angle between them 112.3°. The calculation of this angle by means of AM1 method using X-ray parametrization gave the value 114.2°, and the H8 - CH_3 distance 4.83 Å. That explains the lack of NOE with H8 (δ=8.36 ppm) proton when CH_3 protons (δ= 2.92 ppm) of **4a** or **4b** were irradiated. On the other hand, the angle between the quinoline plane and *N*-methyl-*N*-formylaminomethyl group, which was calculated with AM1 method for *E*-isomer **3a** gave the value 84.1°. Thus, perpendicular arrangement of quinoline and *N*-methyl-*N*-formylaminomethyl planes in **3a**, caused by the 3-sulfide substituent, make the distance H8/CH_3 shorter (3.54 Å –from the calculation with AM1 method) and therefore, fortunately available for NOE.

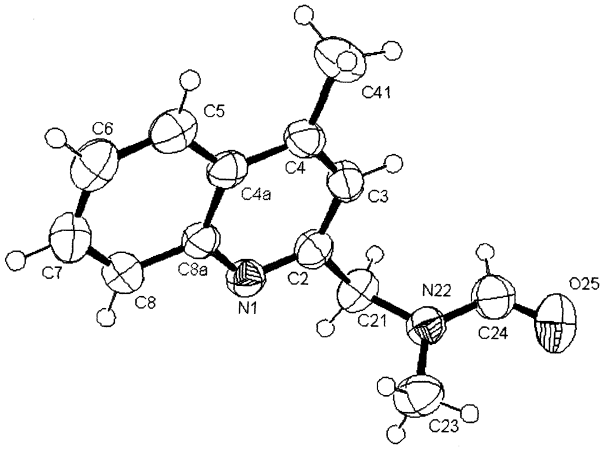


Figure 2. The ORTEP view for compound **4a**.

Differences between the respective δ_H and δ_C values of ring protons and carbons of **3a** and **3b** are close (see Scheme 5). This indicates that the dithiinodiquinoline moiety in **3a** and **3b** acts as a rigid system and that the hindered rotation in *N*-methyl-*N*-formylaminomethyl group leading to two non-identical *E* or *Z* 6-substituents slightly influences the 1,4-dithiin ring environment.

EXPRERIMENTAL

Materials.

Lepidine was purified by destillation, ^{1}H nmr spectrum ($CDCl_3$, 500 MHz, δ (ppm)]: 2.59 (CH_3), 7.12 (H3), 7.49 (m, H6), 7.65 (H7), 7.89 (H5), 8.10 (H8), 8.73 (H2).^{13}C nmr spectrum ($CDCl_3$, 126 MHz, δ (ppm)]: 149.8 (C2), 147.7 (C8), 143.9 (C4), 129.7 (C8), 128.8 (C7), 128.0 (C4a), 126.0 (C6), 123.5 (C5), 121.5 (C3).

6-(*N*-Methyl-*N*-formylaminomethyl)thioquinanthrene (**3**).

This compound was prepared from thioquinanthrene **1** and DMF as described previously [5].

4-Methyl-2-(*N*-formyl-*N*-methylaminomethyl)quinoline (**4**).

This compound was obtained according to the procedure of Minisci at al.[4]. The crystals of **4a** were grown from ethanol solution, mp. 73-75 °C.

Anal. Calcd. For $C_{13}H_{14}N_2$: C, 72.87; H, 6.59; N, 13.07; O, 7.47. Found: C, 72.83; H, 6.52; N, 13.11; O, 7.69.

Nmr Study.

The ^1H and ^{13}C nmr spectra of **3** and **4** were recorded on Bruker 500 MHz spectrometer at 500 MHz for ^1H nuclei and 126 MHz for ^{13}C nuclei in 0.1 *M* deuteriochloroform solution at 303 K, with tetramethylsilane as the internal standard. The 1D and 2D experiments were carried out with standard Bruker pulse programs.

The NOE spectra for compounds **3** and **4** were obtained using standard Bruker 500 MHz programs. The spectral widths were *ca*. 5000 Hz, power for NOE build up 84 dB, aquisition time 3.3 s, relaxation delay 1 s, overall irradiation time 3 s, pulse width 7.6 μs, number of scans 64 for each multiplet.

The crystallographic data were collected on four circle diffractometer KUMA KM4CCD using SHELXS 86 [13] and SHELXL 97 [14] programs.

The crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-184357. Copies of the available material can be obtained, free of the charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ UK. (Fax: +44-(0)1223-336033 or e-mail: deposit @ ccdc.cam.ac.uk.).

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