6-Substituted Thioquinanthrenes. Reaction of Thioquinanthrene with Radicals Formed From DMF [a]

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Reaction of bis-hydrogen sulfate of thioquinanthrene with DMF-ferrous sulfate-hydroxylamine-*O*-sulfonic acid system took place at the α-quinolinyl position and led to 6-monosubstituted thioquinanthrene derivatives **1** (42%) and **2** (11%).

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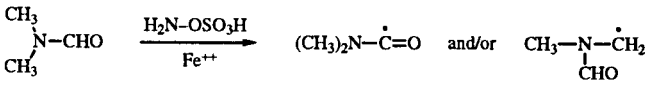
Introduction.

The Minisci reaction offers the possibility of transforming six-membered aza-hetarenes to their α- or γ-substituted derivatives *via* homolytic alkylation- or acylation-type processes [1,2]. Experimental procedures include the reactions of aza-hetarenium cations in aqueous medium with several types of C-radicals [1,2]. The latter ones are usually prepared *in situ* from carboxylic acids [1,3,5], aldehydes [2,3,5], α-ketoacids esters [1,2], amides [1,2,3,5,6,7], ethers [1,5] and acetals [3,5], alkyl iodide [1,4], olefines [1,5] and alcohols [2,3,5]. Under the Minisci reaction conditions also some quinolines were converted into respective α- or γ-substituted derivatives [6,7].

On the other hand, functionalization of the quinoline *via* thioquinanthrene (*i.e.* 1,4-dithiino [2,3-*c*:5,6-*c'*]diquinoline) as its sulfurization product following by the reactions of thioquinanthrene with nucleophiles opened a convenient way to the preparation of 3,4-disubstituted quinolines being mainly 4-substituted 3-quinolinyl sulfides [8-15,17]. Treatment of the latter ones under the Minisci reaction conditions may lead to 2,3,4-trisubstituted quinolines. Thus, 2,3,4-trisubstituted quinolines could be obtained in the sequence of two or three reactions starting from quinoline.

To extend previous studies on nucleophilic splitting [8-13], quaternization [15], oxidation [16], and "wet chlorination" [17] of thioquinanthrene, we would like to present now a preliminary study on homolytic heteroaromatic substitution of thioquinanthrene with free radical species formed from *N,N*-dimethylformamide. Taking into consideration the experimental data of Minisci group on the reactions of quinoline and lepidine with DMF/Fe^{++} ions/peroxides system or DMF/Fe^{++} ions/hydroxylamine-*O*-sulfonic acid [6,7] and the very poor solubility of thioquinanthrene, we chose DMF both as a solvent and as a source of radicals.

Scheme 1

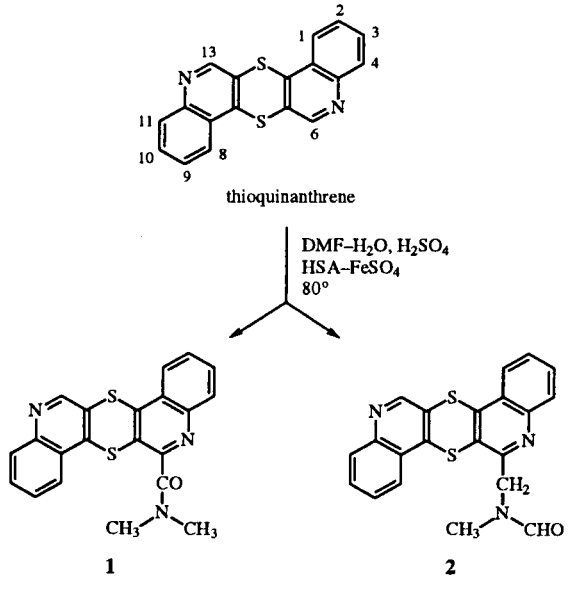


Results and Discussion.

The treatment of DMF with the Fe^{++} salt/hydroxylamino-*O*-sulfonic acid system generates carbamoyl and α-*N*-amidoalkyl radicals [7] (see Scheme 1).

They may then react with protonated azines in the heteroaromatic homolytic substitution to give α-substituted azine derivatives when the position γ is not free [7]. Thioquinanthrene with two potentially reactive α-quinolinyl sites could be therefore transformed into two monosubstitution products such as **1** and **2** (see Scheme 2), and three bisubstitution products.

Scheme 2



Both thioquinanthrene and its salts with protic acids do not form homogenous solutions with water-DMF mixtures at concentrations typical for Minisci reaction conditions [6,7]. In order to perform the reaction in homogenous solution, a large volume of DMF (more than 250 ml per 1 g of thioquinanthrene) should be used. On the other hand, when the reaction was carried out with a thioquinanthrene suspension, a more complex product mixture than that in homogenous solution was obtained.

Treatment of thioquinanthrene in the form of bis-hydrogen sulfate with the DMF/ferrous sulfate/hydroxylamine-*O*-sulfonic acid system in large volumes of DMF gave the mixture consisting of two main isomeric products **1** (42%) and **2** (11%) accompanied by 34% unreacted thioquinanthrene. After tlc separation and crystallisation, both products were obtained as analytically pure samples. Due to limited stability of the reaction products, *i.e.* 6-substituted thioquinanthrenes such as **1** and **2**, during isolation, the balance of the amounts of substrate and products was unsatisfactory and did not reach 70%.

Elemental analysis data as well as EI ms data showed the same molecular weight (389.49) of compounds **1** and **2** indicating for the introduction of one group C_3H_6NO to the molecule of thioquinanthrene.

The most diagnostic data in the structure assignment of **1** comes from its ^1H nmr spectra. They showed two singlets of *N*-methyl group protons at δ = 3.32 ppm and δ = 2.91 ppm, the presence of only one α-quinolinyl type proton recorded as a singlet at δ = 8.89 ppm and eight aromatic protons (see Figure 1) as well-separated multiplets at δ = 8.34-8.41 ppm (2H), δ = 8.09-8.12 ppm (2H) and δ = 7.74-7.80 ppm (2H) and δ = 7.65-7.72 ppm (2H). (For

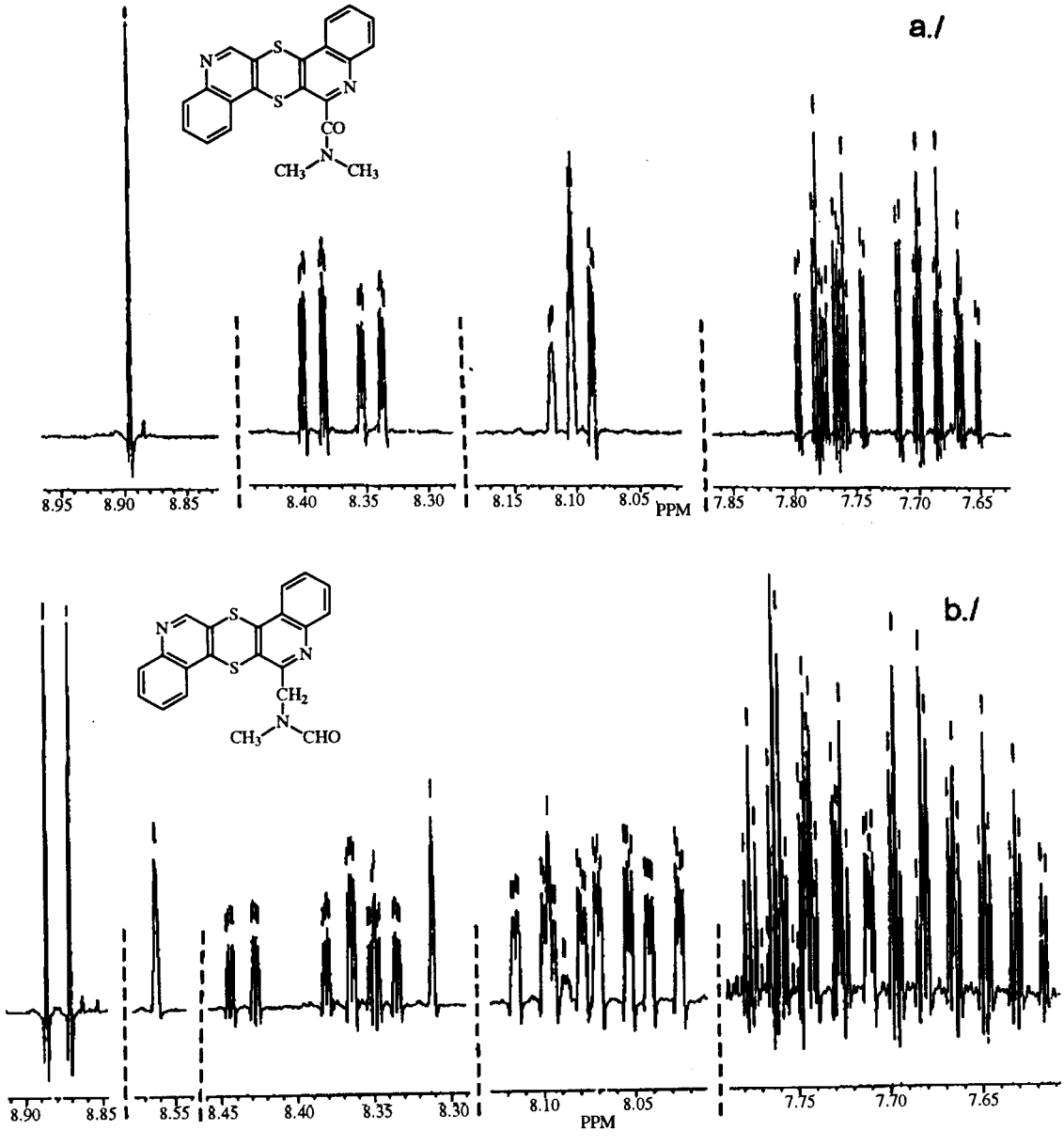


Figure 1. Aromatic part of ^1H nmr spectra of a./ 6-(*N,N*-dimethylcarbamoyl)thioquinanthrene **1** and b./ 6-(*N*-methyl-*N*-formylaminomethyl)thioquinathrene **2**.

nmr assignment details - see below). It proves for **1** the structure of 6-(*N,N*-dimethylcarbamoyl)thioquinanthrene.

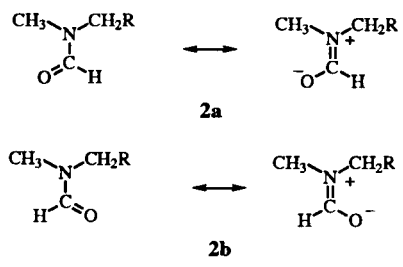
In the case of proton nmr spectra of product **2**, serious problems arose since the spectrum (see Figure 1) contained the spectral lines of the same functional groups of two species with the same intensities and very close shapes, despite the fact that the product seems to be chromatographically homogenous. There are two singlets of *N*-methyl group protons at δ = 3.04 ppm and δ = 2.92 ppm, two singlets of *N*-methylene group protons at δ = 5.14 ppm and δ = 5.01 ppm, two singlets of methine protons of the formyl groups at δ = 8.57 ppm, and δ = 8.31 ppm, two singlets of the α-quinolinyl protons at δ = 8.91 ppm and δ = 8.93 ppm, and multiplets of aromatic protons (see Figure 1) at δ = 8.33-8.45 ppm, δ = 8.02-8.12 ppm, δ = 7.61-7.78 ppm with intensity $(3:3)_{CH_3}$:$(2:2)_{CH_2}$:$(1:1)_{CH}$:$(1:1)_{\alpha\text{-quinolinyl}}$:$(2:2)_{arom.}$, $(2:2)_{arom.}$,$(4:4)_{arom.}$ respectively. It shows that product **2** contains two species with the 6-*N*-methyl-*N*-formyl aminomethyl substituent.

Taking into account literature data [18,19] concerning the restricted rotation-spectroscopic effects relation in *N,N'*-dialkylcarbonamides one would describe for both species of **2** the formulas as **2a** and **2b** (Scheme 3).

In fact, the 2D ^{1}H-^{1}H (COSY) spectrum of **2** showed four independent four proton (ABMX) systems indicating two independent molecules. Decoupled ^{13}C nmr spectrum of **2** exhibited double amounts of carbon atom signals. Very close proton nmr spectroscopic effects were observed for *N*-ethyl-*N*-methylnicotinamide existing "as a mixture of *cis* and *trans* methyl isomers both being present to an equal extent" [20,21].

The complex nature of the system of compound **2** seems to be a result from the presence of two pairs of two

Scheme 3



R = 6-thioquinanthrenyl

quinoline moieties being in the molecules of **2a** or **2b**, we started studies with some model compounds containing reduced amount of the quinoline fragment. They are now in progress.

NMR Study on Compound **1**.

To complete the nmr assignment of **1** as 6-(*N,N*-dimethylcarbamoyl)thioquinanthrene and in order to evaluate spectroscopic effects induced by the dimethylcarbamoyl substituent a further study was done. The 2D ^{1}H-^{1}H experiments allowed for the segregation of eight benzene ring protons in two ABMX systems of the quinolinyl type. To our surprise, a simple proton nmr spectrum at 500 MHz of **1** contains well separated multiplets, the assignments of both ABMX systems could be easily performed with support of LAOCOON-3 calculation.

The next question was how to prove correlation in the 3,4-disubstituted quinoline moiety, *i.e.* between α-quinolinyl proton (H-13) and benzene-ring protons (H-8, H-9, H-10 and H-11). It could be reached indirectly with the help of long-range proton-carbon correlations as presented in Figure 2 applying in part the methodology described by

Table 1

Summary of INEPT Long-range Proton-carbon and Hetcor Single-bond Correlations

Proton	Carbon single bond coupling [ppm]	Carbon three bond coupling [ppm]	Carbon two bond coupling [ppm]	Carbon four bond coupling [ppm]
H-1 (δ_H8.39)	C-1 (δ_C123.6)	C-14a (δ_C145.8) C-4a (δ_C145.5) C-3 (δ_C130.8)		
H-2 (δ_H7.70)	C-2 (δ_C128.4)	C-14b (δ_C126.6) C-4 (δ_C129.8)		
H-3 (δ_H7.78)	C-3 (δ_C130.8)		not determined [a]	
H-4 (δ_H8.10)	C-4 (δ_C129.8)		not determined [b]	
H-8 (δ_H8.35)	C-8 (δ_C123.4)	C-7a (δ_C144.0) C-11a (δ_C147.0) C-10 (δ_C130.2)		
H-9 (δ_H7.67)	C-9 (δ_C127.9)	C-7b (δ_C126.9) C-11 (δ_C129.9)		
H-10 (δ_H7.76)	C-10 (δ_C130.2)		not determined [a]	
H-11 (δ_H8.11)	C-11 (δ_C129.9)		not determined [b]	
H-13 (δ_H8.89)	C-13 (δ_C147.8)	C-11a (δ_C147.0) C-7a (δ_C144.0)	C-13a (δ_C127.1)	C-7b (δ_C126.9)

The INEPT experiment could not be performed due to very small differences between chemical shift values of H3 and H10 protons Δδ = 0.02 ppm [a], H11 and H4 protons Δδ = 0.01 ppm [b].

R. N. Castle and co-workers [22]. Therefore, the use of ^{13}C-^{1}H-two dimensional (Hetcor) spectrum, ^{13}C-nmr-^{1}H-coupled spectrum and an INEPT experiment are necessary to generate a total nmr assignment of compound **1**. The singlet resonating at δ = 8.89 ppm is assigned to H-13 on the basis of chemical shift and multiplicity. In the Hetcor spectrum, a single-bond correlation is observed between the resonance corresponding to H-13 and the carbon resonating at δ = 147.8 ppm (C-13). In the same way on the basis of Hetcor there are recorded proton-carbon correlations at positions 1, 2, 3, 4, 8, 9, 10 and 11 (Table 1).

Long-range couplings with H-9 (δ = 7.67 ppm) are observed in INEPT experiment at δ = 126.9 ppm, δ = 129.1 ppm. From the structure of compound **1**: H-9 should show correlations with carbon resonances corresponding with C-7b and C-11. The correlation at δ = 126.9 ppm is assigned to C-7b and the correlation at δ = 129.9 ppm is assigned to C-11, because quaternary carbon C-7b should have a lower intensity in ^{13}C nmr. Long-range couplings with H-8 (δ = 8.35 ppm) are observed in the INEPT experiment at δ = 130.2 ppm, δ =144.0 ppm and δ = 147.0 ppm. Tertiary carbon C-10 is assigned to δ = 130.2 ppm, because of its higher intensity. At ^{13}C nmr-^{1}H coupled spectrum C-7a is a doublet of doublet and C-11a is a multiplet. The correlation at δ = 144.0 ppm is assigned to C-7a and the correlation at δ = 147.0 ppm is assigned to C-11a.

From the structure of compound **1**, H-13 (δ = 8.89 ppm) should show $^{3}J_{C\text{-}H}$ correlations with quaternary carbon resonances corresponding to C-7a, C-11a. However, long-range couplings with H-13 are observed in the INEPT experiment at δ = 147.0 ppm, δ = 144.0 ppm, δ = 127.1 ppm, δ = 126.9 ppm. According to the above deduction, the correlation at δ = 147.0 ppm is assigned to C-11a, at δ = 144.0 ppm to C-7a, and that at δ = 126.9 ppm as a four-bond coupling $^{4}J_{C\text{-}H}$ to C-7b. The correlation at δ = 127.1 ppm is assigned to C-13a. The ^{13}C nmr-^{1}H coupled spectrum shows the doublet at δ = 127.1 ppm, it is the only doublet for these four carbons. Thus, although C-H two bond couplings are usually small, the two-bond H13/C13a coupling $^{2}J_{C\text{-}H}$ is comparable with $^{3}J_{C\text{-}H}$ one. Additionally, even a four-bond coupling $^{4}J_{C\text{-}H}$ (between H-13 and C-7b) was also observed. Similar effects were noted in the case of some polycyclic arenes [23,24] and six-membered aza-hetarenes [22-24], and also in the case of thienopyridines [23].

Long-range couplings with H-2 (δ = 7.70 ppm) are observed in the INEPT experiment at δ = 126.6 ppm and δ = 129.8 ppm. Analogous to C-9 the correlation at δ = 126.6 ppm is assigned to C-14b and δ = 129.8 ppm to C-4. Long-range couplings with H-1 (δ = 8.39 ppm) are observed in the INEPT experiment at δ = 145.8 ppm, δ = 145.5 ppm, δ = 130.8 ppm. Tertiary carbon C-3 is assigned to δ = 130.8 ppm, because of its higher intensity. At ^{13}C nmr-^{1}H coupled spectrum C-14a is a doublet and C-4a is a doublet of doublets and correlation at δ = 145.8 ppm is assigned to C-14a and δ = 145.5 ppm to C-4a. The carbonyl carbon atom of the carbon resonances occurs at δ = 167.0 ppm. At ^{13}C nmr-^{1}H coupled spectrum this is the second carbon which is observed as a multiplet.

The assignment of tertiary carbons C-6 (δ = 152.3 ppm) and C-6a (δ = 125.0 ppm) could not be supported with $^{3}J_{C\text{-}H}$ coupling. They are assigned as α- and β-quinolinyl carbons on the basis of the chemical shift being close to those of carbons C-13 (δ = 147.8 ppm) and C-13a (δ = 127.1 ppm) respectively in the "left" part of compound **1**.

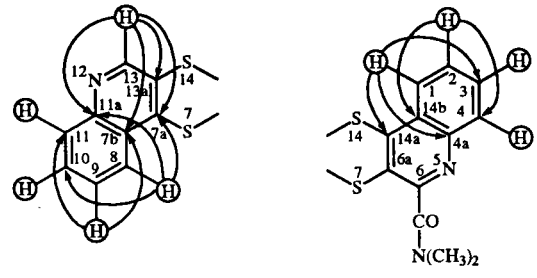


Figure 2. Set of long-range correlations used in nmr assignment of **1** (Table 1).

In spite of well documented nmr non-equivalency of the methyl groups in *N,N*-dimethylcarbonamides, we noticed very high differences in proton chemical shift values of the methyl groups in **1** as $\Delta\delta_H = \delta_{(N\text{-}CH3)a} - \delta_{(N\text{-}CH3)b}$ = 0.4 ppm, as compared to $\Delta\delta_H$ = 0.31 ppm for *o*-nitro-*N,N*-dimethylbenzamide, $\Delta\delta_H$ = 0.11 ppm for *p*-nitro-*N,N*-dimethylbenzamide in [18,19].

Conclusion.

The reactions of thioquinanthrene with radicals formed from DMF in the presence of hydroxy-*O*-sulfonic acid and Fe^{++} ions took place as a mono-substitution at the α-quinolinyl C_6 position and led to mono-carbamoylation product **1** and *N*-amidomethylation product **2** in the ratio of 4:1, since the reaction conditions applied were different from those of typical carbamoylation (97% of carbamoylation product) or *N*-amidoalkylation (98% of *N*-amidoalkylation product) for lepidine [3].

EXPERIMENTAL

Melting points were determined in open capillary tubes on a Boetius melting point apparatus and are uncorrected.

The ^{1}H nmr and ^{13}C nmr spectra of **1** and **2** were recorded on a Bruker MSL 500 spectrometer at 500 MHz for ^{1}H nuclei and at 126 MHz for ^{13}C nuclei in deuteriochloroform solutions with tetramethylsilane as the internal standard. Pulse width (60°) for ^{1}H nmr spectra was 8 μs. Pulse width (45°) for ^{13}C nmr spectra was 3 μs. The spectral width was 5495 Hz for ^{1}H nmr and

29412 Hz for ^{13}C nmr experiments. The COSY ^{1}H-^{1}H nmr spectrum of the compound **1** was acquired with $64t_1$ increments of 2044 μs to encode F1 spectral width of 245 Hz. The F2 dimension was acquired at 256 data points for a spectral width of 489 Hz. The 2D ^{1}H-^{13}C (Hetcor) nmr spectrum of the compound **1** was acquired with $128t_1$ increments of 1448 μs to encode F1 spectral width of 345 Hz. The F2 dimension was acquired at 4096 data points for a spectral width of 3788 Hz. The COSY ^{1}H-^{1}H nmr spectrum of compound **2** was acquired with $128t_1$ increments of 1474 μs to encode F1 spectral width of 339 Hz. The F2 dimension was acquired at 512 data points for a spectral width of 678 Hz. INEPT experiments were acquired with the soft pulse 90° (the spectral width was 29412 Hz, selectivity 12.5 Hz).

The El mass spectra were run on a LKB GC 2091 spectrometer at 70 eV and 15 eV. Thin layer chromatography was performed on silica gel 60 254F plates (Merck) using a mixture of chloroform and ethanol (19:1 v/v) as an eluent.

Thioquinanthrene was obtained by exhaustive sulfurization of quinoline with elemental sulfur [25].

Reaction of thioquinanthrene with Radicals Formed from *N,N*-Dimethylformamide.

Concentrated sulfuric acid (3 ml) was placed in the reaction flask fitted with a magnetic stirrer. Thioquinanthrene (0.95 g, 3 mmoles) was added portionwise and the mixture was heated gently to complete dissolution of thioquinanthrene. During the stirring, 250 ml of DMF containing 2 ml of water was introduced. Nitrogen was then passed through the reaction mixture and ferrous sulfate (3 mmoles, 0.83 g) and hydroxylamine-*O*-sulfonic acid (6 mmoles, 0.68 g) were added at once. The mixture was stirred at 80° for two hours and then concentrated to 30 ml by vacuum distillation. The residue was poured into 200 ml of water. The solid formed was filtered off, washed with water, and air dried to give 0.8 g of yellow solid containing three main compounds with spots of R_f value 0.59 for thioquinanthrene, 0.48 for product **1** and 0.41 for product **2**. Composition of a mixture determined by quantitive thin layer chromatography indicated: 42% **1** and 10% **2** accompanied by 34% of unreacted thioquinanthrene.

The products **1** and **2** were separated by tlc on aluminium oxide using methylene chloride as an eluent followed by tlc separation on silica gel with a mixture of chloroform/ethanol 19:1 v/v as an eluent. Both compounds were finally recrystallized from ethanol.

6-(*N,N*-Dimethylcarbamoyl)thioquinanthrene **1**.

This compound had mp 163-165°, yield 42%; ^{1}H nmr (deuteriochloroform): δ 2.91 (s, 3H, NCH_3), 3.32 (s, 3H, NCH_3), 7.67 (m, 1H, H9), 7.76 (m, 1H, H10), 7.70 (m, 1H, H2), 7.78 (m, 1H, H3), 8.10 (m, 1H, H4), 8.11 (m, 1H, H11), 8.35 (m, 1H, H8), 8.39 (m, 1H, H1), 8.89 (s, 1H, H13); ^{13}C nmr (deuteriochloroform): δ 123.4 (C8), 123.6 (C1), 125.0 (C6a), 126.6 (C14b), 126.9 (C7b), 127.1 (C13a), 127.9 (C9), 128.4 (C2), 129.8 (C4), 129.9 (C11), 130.2 (C10), 130.8 (C3), 144.0 (C7a), 145.5 (C4a), 145.8 (C14a), 147.0 (C11a), 147.8 (C13), 152.3 (C6), 167.0 (C=O); ms: EI (15 eV) m/z (relative intensity) 390 (12.63, M+1), 389 (49.64, M^+), 332 (11.79), 318 (100).

Anal. Calcd. for $C_{21}H_{15}N_3S_2O$: C, 64.76; H, 3.88; N, 10.79; S, 16.46. Found: C, 65.01; H, 3.61; N, 10.8; S, 16.58.

6-(*N*-Methyl-*N*-formylaminomethyl)thioquinanthrene **2**.

This compound had mp 107-110°, yield 11%; ^{1}H nmr (deuteriochloroform): δ 2.92 (s, 3H, NCH_3), 3.04 (s, 3H, NCH_3), 5.01 (s, 2H, NCH_2), 5.14 (s, 2H, NCH_2), 7.61-7.78 (m, 8H, Ar-H), 8.02-8.12 (m, 4H, Ar-H), 8.31 (s, 1H, NCHO), 8.33-8.45 (m, 4H, Ar-H), 8.57 (s, 1H, NCHO), 8.91 (s, 1H, Ar-H), 8.93 (s, 1H, Ar-H); ms: EI (15 eV) m/z (relative intensity) 390 (10.40, M+1), 389 (42.16, M^+), 332 (100), 318 (82.9).

Anal. Calcd. for $C_{21}H_{15}N_3S_2O$: C, 64.76; H, 3.88; N, 10.79; S, 16.46. Found: C, 64.85; H, 3.68; N, 10.68; S, 16.60.

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