

SYNTHESIS OF 1-METHYL-3-METHYLTHIO- AND 1-METHYL-
3-METHYLSULFINYL-4-SUBSTITUTED 2(1*H*)-QUINOLINONES [#]

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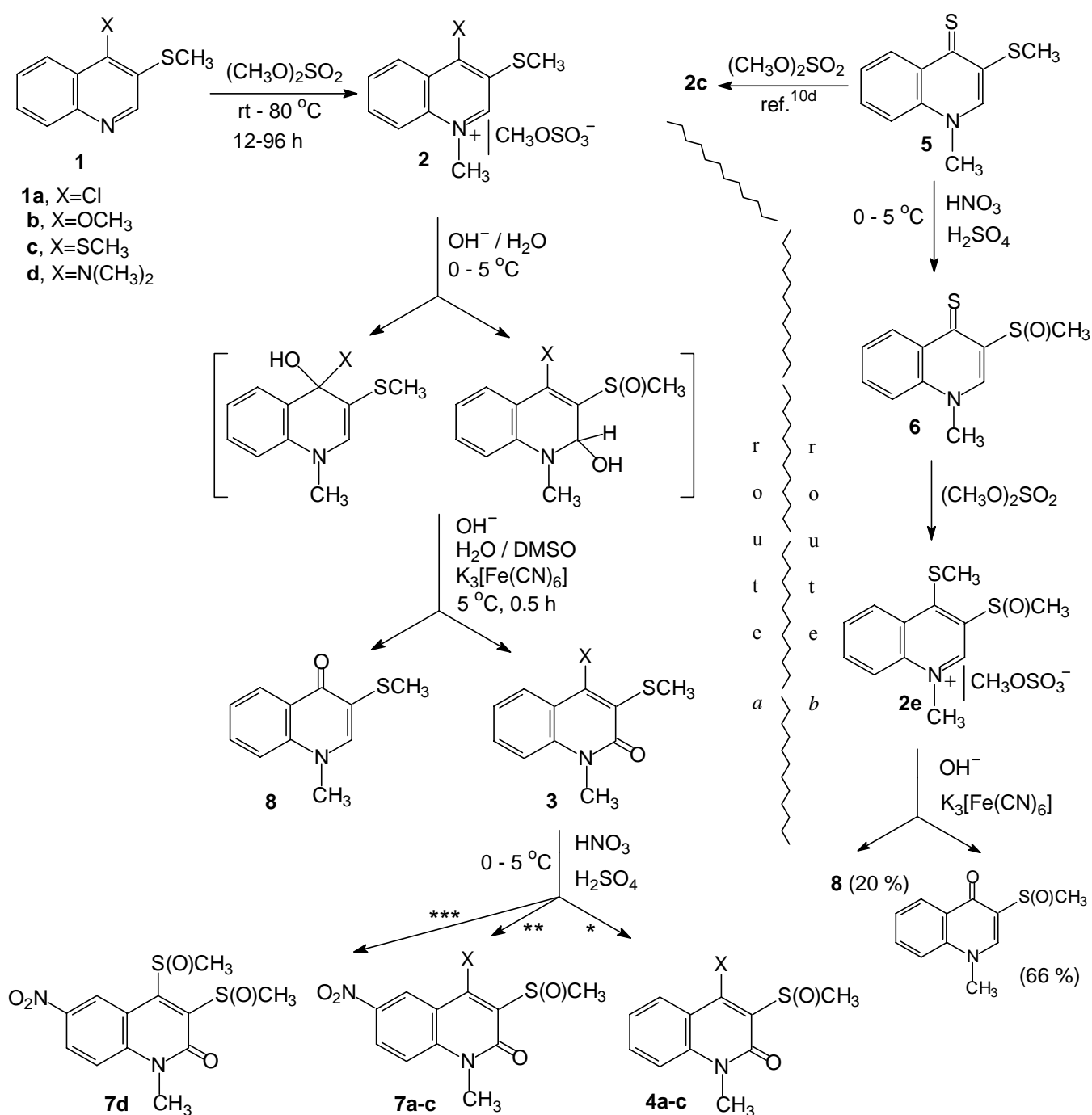
Abstract – Treatment of 4-substituted (X=Cl, OCH₃, SCH₃) quinolinium salts (**2**) in aqueous-DMSO solution with K₃[Fe(CN)₆] / NaOH system led to the respective 2-quinolinones (**3**) (60-69 %) which were accompanied by 1-methyl-3-methylthio-4-quinolinone (**8**) (*ca.* 20%). 3-Methylthio substituent in quinolines (**1**), 4-quinolinethione (**5**) and 2-quinolinones (**3**) underwent *S*-oxidation to a sulfinyl group when the compounds (**1**), (**3**) and (**5**) were treated with nitrating mixture (-5 °C, 1 mol. eqv. of HNO₃), but with an excess of nitric acid 2-quinolinones (**3**) were transformed to the respective 3-methylsulfinyl-6-nitro derivatives (**7**). The reaction of 4-chloroquinolines (**1a**), (**3a**) (at 140-160 °C) and (**4a**) (at 0 °C) with dimethylamine gave high yield of the 4-dimethylamino derivatives (**1d**), (**3d**) and (**4d**), respectively.

In spite of the fact that 2(1*H*)-quinolinones are not as ‘famous’ as 4-isomers, they also exhibit valuable modes of biological activity. They act *e.g.* as cytotoxic or anticancer agents,¹ cholesterol acyl-transferase inhibitors,² immunomodulators,³ gastric antiulcer agents,⁴ as well as a bronchospasmodic drug (*procaterol*).⁵ This paper was inspired by the Chinese report on the preparation of certain 1-alkyl-3,4-disubstituted 2(1*H*)-quinolinones as osteoporosis inhibitors.⁶ 2-Quinolinone derivatives, including those with 3-thio-substituents, are most often prepared by the cyclization reactions starting from the appropriate benzene derivatives.^{7,8} The reaction pathways leading from other quinolines or from other heterocyclic systems to 2(1*H*)-quinolinones are also known.^{7,9}

Since 4-substituted 3-quinolinyl sulfides (**1**) are easily available according to previously elaborated methodology,¹⁰ we consider using them for the preparation of the title 2-quinolinones (**3**) and (**4**). The conversion of **1** to **3** required the transformation of azamethin moiety of quinolines (**1**) to *N*-alkyllactam grouping in products (**3**). Literature review reveals that it could be achieved by classical but still important methodology based on the reaction sequence : azine → *N*-alkylazinium salt → *N*-alkylazinium

'pseudobase' \rightarrow *N*-alkyl-2(1*H*)-azinone.^{11,12} This methodology appeared to be useful for the preparation of 4-substituted 3-methylthio-2(1*H*)-quinolinones (**3a-c**) with 4-chloro-, 4-methoxy- and 4-methylthio-substituents, however the products (**3**) were accompanied by 1-methyl-3-methylthio-4(1*H*)-quinolinone (**8**). Synthesis of 4-dimethylamino-2(1*H*)-quinolinones (**3d**) and (**4d**) was achieved by the amination of 4-chloro-2(1*H*)-quinolinones (**3a**) or (**4a**), respectively, as presented below.

Scheme 1

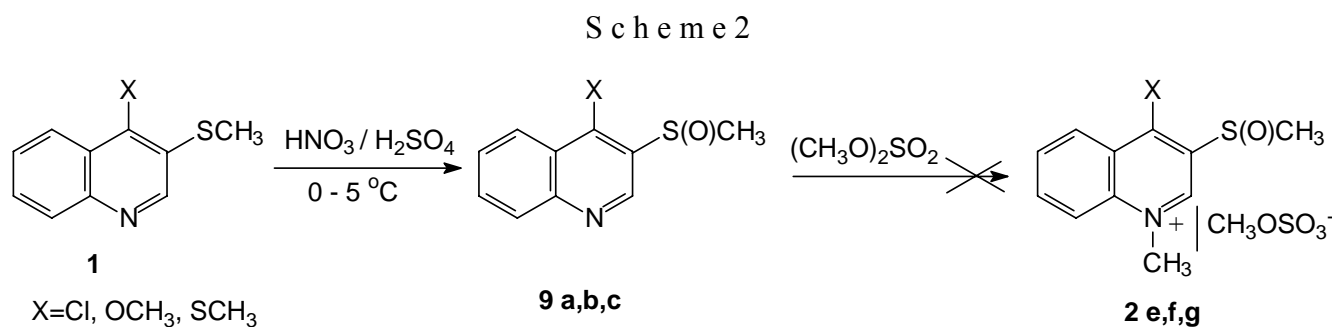


* 1 mol. eqv. of HNO₃ was used, ** 1.5 - 3 mol. eqv. of HNO₃ were used (see Table).

*** for dimethylthio derivative (**3c**), when 3 mol. eqv. of HNO₃ were used.

RESULTS AND DISCUSSION

The first part of our work was focused on the preparation of the title compounds (**3**) and (**4**) according to the routes *a* and *b*. (Scheme 1) The route *a* involves three steps : preparation of quinolinium salts (**2**), treatment of salts (**2**) with aqueous alkali and oxidation of the ‘1,2-pseudobases’ to 2(1*H*)-quinolinones (**3**) and finally *S*-oxidation of sulfides (**3**) to sulfoxides (**4**). Since sulfoxides (**9**) are easily available (as described below), and since we were encouraged by the Queguiner group report on the quaternization of 3-methylsulfinylquinoline to 1-methyl-3-methylsulfinylquinolinium iodide,¹³ we decided to shift the *S*-oxidation step to the beginning of the reaction sequence as shown with the route *b*. The quinolinyl sulfoxides (**9**) were prepared by the nitric acid oxidation of sulfides (**1**) as previously described for methoxy derivative (**1b**).¹⁴



The site of *S*-oxidation in **1c** (X=SCH₃), i.e. the structure of 4-methylthio-3-methylsulfinylquinoline (**9c**) was confirmed by the independent synthesis of **9c** from 4-chloro-3-methylsulfinylquinoline (**9a**) *via* thiouronium salt, alkaline hydrolysis of the latter and methylation. The same oxidation of thiono-sulfide (**5**) led to thiono-sulfoxide (**6**) (see Scheme 1) as it was deduced from the ¹H NMR spectrum of **6** which as compared to that of the substrate (**5**)¹⁶ exhibited changes only at the vicinity of CH₃S group (the signals of the CH₃S protons and that of H-2 proton were shifted by Δδ=0.69 ppm or Δδ=0.72 ppm, respectively). However, the positions of the ‘peri’ influenced H-5 protons at *ca.* 9 ppm in the ¹H NMR spectra of **5** and **6** were almost the same.

Preparation of quinolinium salts (**2**)

4-Substituted (chloro, methoxy, methylthio and dimethylamino) quinolines (**1**) were effectively quaternized with dimethyl (and diethyl) sulfates to the respective quinolinium salts (**2**). Contrary to quinolinyl sulfides (**1**), the corresponding sulfoxides (**9**) practically did not react with alkylating agents (benzene, acetonitrile, rt - 80 °C, up to 24 h) so we were not able to prepare the salts (**2e-g**) in this manner. Fortunately, the salt (**2e**) could be obtained by the treatment of thiono-sulfoxide (**6**) with dimethyl sulfate.

Transformation of quinolinium salts (**2**) to 2(1*H*)-quinolinones (**3**)

Nucleophiles are readily added to 1-alkylpyridinium and 1-alkylquinolinium salts.^{12,15} The reaction takes place at *aza*-activated positions to form 1,2- and 1,4-adducts.^{12,15} Fortunately, since hydroxide anion as

'hard base' adds mainly to α -position,^{12,15} transformations of the studied quinolinium salts (**2a-d**) under the action of aqueous-DMSO of NaOH / K₃Fe(CN)₆ system follow mainly the reactions sequence: **2** \rightarrow 1,2-pseudobase \rightarrow 4-substituted 2(1*H*)-quinolinone (**3**) (60-69 %). The competitive reaction pathway *via* 1,4-pseudobase (see Scheme 1) proceeded to a lesser extent to give finally 1-methyl-3-methylthio-4(1*H*)-quinolinone (**8**) (16-20 %). However, the same treatment of 4-dimethylamino derivate (**2d**) led only to 10-12 % of 2-quinolinone (**3d**) and 44 % of 4-quinolinone (**8**).

Quinolinium salt with 3-methylsulfinyl substituent (**2e**) treated with aqueous-DMSO solutions of NaOH / K₃Fe(CN)₆ system underwent decomposition to 1-methyl-3-methylsulfinyl-4(1*H*)-quinolinone (66%) and 1-methyl-3-methylthio-4(1*H*)-quinolinone (**8**) (20 %).

Treatment of 3-methylthio-2(1*H*)-quinolinones (**3**) with nitrating mixture

When 2-quinolinones (**3a-c**) (in the form of solutions in sulfuric acid) were subjected to the reaction with nitrating mixture (containing 0.8-1 mol. eqv. of HNO₃), the oxidation of 3-methylthio group took place and the reaction gave sulfoxides (**4**) (82-90 %). 3,4-Dimethylthio derivative (**3c**) was oxidized to 4-methylthio-3-methylsulfinyl-2-quinolinone (**4c**). Its structure was confirmed by NOE experiment because irradiation of the protons from 4-CH₃S group ($\delta=2.54$ ppm) induced enhancement (11 %) of the signal of H-5 proton ($\delta=8.42$ ppm). Treating of 4-dimethylamino derivative (**3d**) in the same manner as **3a-c** led to the multicomponent mixture of unstable products.

Table, Reactions of 3-methylthioquinolines (**1**), (**3**) and (**5**) with a nitrating mixture

Entry	Substrate	Molar ratio substrate : HNO ₃	Products (yield, %)
1	1a , (X=Cl)	1 : 1	9a (94)
2	1b , (X=OCH ₃)	1 : 1	9b (85) ¹⁴
3	1c , (X=SCH ₃)	1 : 1	9c (90)
4.1	3a , (X=Cl)	1 : 1	4a (82)
4.2		1 : 3	7a (94)
5.1	3b , (X=OCH ₃)	1 : 1	4b (86)
5.2		1 : 3	7b (98)
6.1	3c , (X=SCH ₃)	1 : 1	4c (90)
6.2		1 : 1.5	4c (50), 7c (32)
6.3		1 : 3	7d (65)
7	5	1 : 1	6 (65)

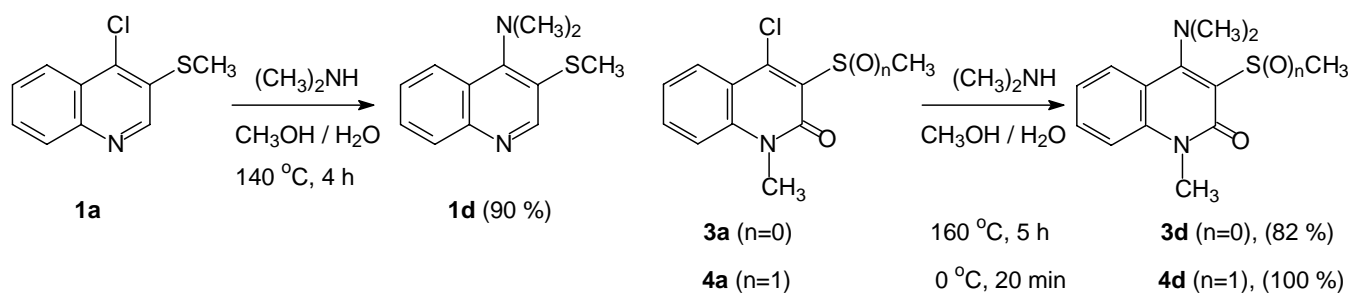
With an excess of nitric acid (up to 3 mol. eqv.) 2-quinolinones (**3a,b**) were converted directly to nitro sulfoxides (**7a,b**) (94-98 %). Furthermore, in the case of 3,4-dimethylthio-2-quinolinone (**3c**), with an

increasing amounts of nitric acid, the reaction proceeded from 3-quinolinylsulfoxide (**4c**) via nitrosulfoxide (**7c**) up to 3,4-dimethylsulfinyl-6-nitro-2-quinolinone (**7d**) (65 %).

Preparation of 4-dimethylamino-1-methyl-3-methylsulfinyl-2(1H)-quinolinone (**4d**)

The methodology presented above and depicted in the Scheme 2 was not effective for the preparation of 4-dimethylamino-2(1H)-quinolinones (**3d**) and (**4d**). Encouraged by effectiveness of *dimethylamino-dechlorination* of 4-chloro-3-methylthioquinoline (**1a**) to **1d** we successfully adopted it to the transformation of 4-chloro-2-quinolinones (**3a**) and (**4a**) into 4-dimethylamino derivatives (**3d**) and (**4d**), respectively.

Scheme 3



It should be noted that 4-chloro-2-quinolinone (**4a**) exhibited high nucleophilic susceptibility and **4d** was sensitive to acids and decomposed to multicomponent mixture even at room temperature. This may be the reason of low effectiveness in the preparation of **4d** by the oxidation of **3d** with nitrating mixture.

CONCLUSIONS

The title compounds (**3**) and (**4**) represent multifunctional structures. The best results in the conversion of **1** to **3** and **4** were obtained when the reaction sequence was performed according to the route *a* (Scheme 1). However, the key-step for the route *a* is the reaction of quinolinium salts (**2**) with sodium hydroxide. Despite the presence of labile, nucleophilic sensitive, 4-substituent, the compounds (**2**) reacted mainly with hydroxyl anion to form 1,2-adducts, which were then oxidized to 2-quinolinones **3**. The 1,4-adducts were formed to a lesser extent and finally converted to 4-quinolinone (**8**). 4-Dimethylamino-2-quinolinones (**3d**) and (**4d**) could be effectively prepared only by the amination of 4-chloroquinolines (**3a**) or (**4a**), respectively.

EXPERIMENTAL

Melting points were taken in open capillary tubes and are uncorrected. ¹H NMR spectra were recorded on a Varian Unity Inova spectrometer at 300 MHz in deuteriochloroform or in hexadeuteriodimethyl sulfoxide solutions with tetramethylsilane (δ 0.0 ppm) as internal standard. EIMS spectra were determined on a Finnigan Mat 95 spectrometer at 70 eV and at a temperature of 80-100 °C. IR spectra

were recorded with a Magma – IR 500 (Nicolet) spectrometer in potassium bromide pellets. TLC analyses were performed employing Merck's silicagel 60 F₂₅₄ plates and a solution of chloroform-ethanol (19 : 1, v/v) as an eluent (system I) or Merck's aluminium oxide 60 F₂₅₄ neutral (type E) plates using mixture of chloroform – ethanol (19 : 1, or 10 : 1, v/v) as an eluent (system II).

4-Substituted 3-methylthioquinolines (**1a**), (**1b**), (**1c**), 1-methyl-3-methylthio-4(1*H*)-quinolinethione (**5**) and 1-methyl-3-methylthio-4(1*H*)-quinolinone (**8**) were prepared as described previously.^{10a-d, 14}

Synthesis of 4-substituted 1-methyl-3-methylthioquinolinium methylsulfates (**2**)

b) from 4-substituted 3-methylthioquinolines (**1**)

A mixture of 4-substituted 3-methylthioquinoline (**1**) (2 mmol), fresh distilled dimethyl sulfate (0.21 mL, 2.2 mmol) and 3 mL of dried benzene was stirred at rt for 72 h (for **1d**), or 96 h (for **1b**) or at 80 °C (6 h) for **1a**. (The progress of the reaction was monitored by TLC, up to full consumption of **1**.) The product (**2**) was filtered off, washed with cold benzene and dried under vacuum at rt. Yields: 92-96%. Due to instability of salts (**2**), products were purified only by trituration with small amount of cold methanol.

4-Chloro-1-methyl-3-methylthioquinolinium methylsulfate (**2a**)

mp 194-196 °C (decomp). ¹H NMR (CDCl₃), δ: 3.01 (s, 3H, SCH₃), 3.77 (s, 3H, CH₃OSO₃), 4.96 (s, 3H, NCH₃), 8.01-8.06 (m, 1H, H_{arom}), 8.13-8.18 (m, 1H, H_{arom}), 8.25-8.35 (m, 1H, H_{arom}), 8.49-8.53 (m, 1H, H_{arom}), 9.77 (s, 1H, H-2). *Anal.* Calcd for C₁₂H₁₄NO₄ClS₂: C 42.92, H 4.20, N 4.17, Cl 10.56, S 19.09.

Found: C 42.70, H 4.12, N 4.27, Cl 10.26, S 19.39

1-Methyl-3-methylthio-4-methoxyquinolinium methylsulfate (**2b**)

mp 111-115 °C (decomp). ¹H NMR (CDCl₃), δ: 2.81 (s, 3H, CH₃S), 3.67 (s, 3H, CH₃OSO₃), 4.48 (s, 3H, CH₃O), 4.77 (s, 3H, CH₃N), 7.85-7.90 (m, 1H, H_{arom}), 8.08-8.14 (m, 1H, H_{arom}), 8.27-8.30 (m, 1H, H_{arom}), 8.36-8.39 (m, 1H, H_{arom}), 9.61 (s, 1H, H-2). *Anal.* Calcd for C₁₃H₁₇NO₅S₂: C 47.12, H 5.17, N 4.23, S 19.35. Found: C 46.94, H 5.06, N 4.52, S 19.28.

4-Dimethylamino-1-methyl-3-methylthioquinolinium methylsulfate (**2d**)

mp 164-166 °C (decomp). ¹H NMR (CDCl₃), δ: 2.72 (s, 3H, SCH₃), 3.52 (s, 6H, N(CH₃)₂), 3.71 (s, 3H, CH₃OSO₃), 4.52 (s, 3H, NCH₃), 7.72-7.76 (m, 1H, H_{arom}), 7.94-7.99 (m, 1H, H_{arom}), 8.03-8.06 (m, 1H, H_{arom}), 8.14-8.21 (m, 1H, H_{arom}), 9.08 (s, 1H, H-2). Not isolated in the pure state. Determination of the sulfate content after hydrolysis of salt **2d** (see procedure b), calcd for 1 mmol of C₁₃H₁₇N₂S⁽⁺⁾ x CH₃OSO₃⁽⁻⁾: 223 mg of BaSO₄, found: 222 mg of BaSO₄.

b) from 1-methyl-4(1*H*)-quinolinethiones (**5**) and (**6**) (as described previously for **5**)^{10d}

A mixture of 4-quinolinethione (10 mmol) and freshly distilled dimethyl sulfate (7.6 g, 60 mmol) was heated at 40 °C for 45 min. It was then cooled down to rt and triturated with ether (3 x 20 mL). The ether solution was decanted off leaving the quinolinium salt (**2c**) and (**2e**) as a yellow-orange or brown

colored solid, completely soluble in water. The properties of **2c** were the same as reported previously.^{10d} Due to instability of quinolinium methylsulfate (**2e**), it could not be isolated in the pure state.

Determination of the sulfate content The sample of alkyl sulfate (**2**) (*ca.* 1-2 mmol) was hydrolyzed with 10 parts of hot dil. hydrochloric acid (30 min.). The mixture was then cooled to rt, diluted with water up to 200 mL, partially neutralized with 5 % sodium bicarbonate solution (up to pH *ca.* 1.5) and finally treated on hot with hot 5% barium chloride aqueous solution to precipitate barium sulfate. It was then treated in the typical manner as for analysis of BaSO₄.

Crude salts (**2d** and **2e**) were used for the preparation of compounds (**3**).

1-Methyl-3-methylsulfinyl-4-methylthioquinolinium methylsulfate (**2e**)

mp 72-78 °C (decomp). ¹H NMR (DMSO-d₆), δ: 2.81 (s, 3H, SCH₃), 3.07 (s, 3H, S(O)CH₃), 3.36 (s, 3H, CH₃OSO₃), 4.75 (s, 3H, NCH₃), 8.16-8.21 (m, 1H, H_{arom}), 8.35-8.44 (m, 1H, H_{arom}), 8.61-8.64 (m, 1H, H_{arom}), 8.77-8.79 (m, 1H, H_{arom}), 9.5 (s, 1H, H-2). Determination of the sulfate content after hydrolysis of salt **2e**, calcd for 1 mmol of C₁₂H₁₄NOS₂⁽⁺⁾ x CH₃OSO₃⁽⁻⁾: 223 mg of BaSO₄, found: 257 mg of BaSO₄.

Reaction of quinolinium salts (**2**) with NaOH / K₃[Fe(CN)₆] system

Solution of sodium hydroxide (0.66 g, 16.5 mmol) in 2.5 mL of water was cooled to 0 °C and then the solutions of quinolinium salt (**2**) (2 mmol) in DMSO (12 mL) and the solution of 1.32 g (4 mmol) of K₃[Fe(CN)₆] in water (5.5 mL) was added dropwise simultaneously on stirring at 2-6 °C. The stirring was continued for 1 h. The solid was filtered off, air-dried, extracted with ethanol and after evaporation the solvent, first crop of 2-quinolinone (**3**) was obtained. Aqueous-DMSO layer was subjected to continuous extraction with methylene chloride. The extract was concentrated to give the second portion of product. Both crops of product were combined and separated by means of column chromatography (silica gel 60, chloroform-ethanol, 19:1, v/v as an eluent) to give 2-quinolinone (**3**) with higher R_f value and 1-methyl-3-methylthio-4(1H)-quinolinone (**8**) with lower R_f value.

Results :	substrate	products , yield (%)
	(2a)	(3a) (48), (8) (22)
		(3a) (62), (8) (16), water used as the only solvent
	(2b)	(3b) (60-69), (8) (19)
	(2c)	(3c) (66), (8) (20)
	(2d)	(3d) (10-12), (8) (44)

4-Chloro-1-methyl-3-methylthio-1,2-dihydro-2-oxoquinoline (**3a**)

mp 126-128 °C (ethanol). EIMS (70 eV) m/z: 239 (76, M⁺). ¹H NMR (CDCl₃), δ: 2.61 (s, 3H, SCH₃), 3.77 (s, 3H, NCH₃), 7.3-7.4 (m, 2H, 2 x H_{arom}), 7.58-7.62 (m, 1H, H_{arom}), 8.06-8.09 (m, 1H, H_{arom}). *Anal.* Calcd for C₁₁H₁₀NOCIS: C 55.11, H 4.20, N 5.84, S 13.37. Found: C 54.87, H 4.20, N 5.91, S 12.98.

4-Methoxy-1-methyl-3-methylthio-1,2-dihydro-2-oxoquinoline (3b)

mp 90-92 °C (ethanol). EIMS (70 eV) m/z: 235 (100, M⁺). ¹H NMR (CDCl₃), δ : 2.50 (s, 3H, SCH₃), 3.75 (s, 3H, NCH₃), 4.11 (s, 3H, OCH₃), 7.25-7.30 (m, 1H, H_{arom}), 7.35-7.38 (m, 1H, H_{arom}), 7.56-7.61 (m, 1H, H_{arom}), 7.91-7.94 (m, 1H, H_{arom}). *Anal.* Calcd for C₁₂H₁₃NO₂S: C 61.25, H 5.57, N 5.95, S 13.36. Found: C 61.02, H 5.70, N 6.01, S 13.11.

3,4-Dimethylthio-1-methyl-1,2-dihydro-2-oxoquinoline (3c)

mp 100-101 °C (ethanol). EIMS (70 eV) m/z: 251 (58, M⁺), 237 (100). ¹H NMR (CDCl₃), δ: 2.50 (s, 3H, SCH₃), 2.85 (s, 3H, SCH₃), 3.77 (s, 3H, NCH₃), 7.28-7.39 (m, 2H, 2x H_{arom}), 7.54-7.60 (m, 1H, H_{arom}), 8.40-8.43 (m, 1H, H_{arom}). *Anal.* Calcd for C₁₂H₁₃NOS₂: C 57.34, H 5.21, N 5.75, S 25.51. Found: C 57.13, H 5.07, N 5.76, S 25.31.

4-Dimethylamino-1-methyl-3-methylthio-1,2-dihydro-2-oxoquinoline (3d)

mp 79-81 °C (ethanol). EIMS (70 eV) m/z: 248 (100, M⁺). ¹H NMR (CDCl₃), δ: 2.45 (s, 3H, CH₃S), 3.08 [s, 6H, (CH₃)₂N], 3.74 (s, 3H, CH₃N), 7.21-7.23 (m, 1H, H_{arom}), 7.32-7.35 (m, 1H, H_{arom}), 7.51-7.56 (m, 1H, H_{arom}), 7.75-7.97 (m, 1H, H_{arom}). *Anal.* Calcd for C₁₃H₁₄N₂OS: C 62.87, H 6.49, N 11.28, S 19.91. Found: C 62.38, H 6.31, N 11.43, S 20.11.

Reactions of 3-methylthioquinolines (1), (3) and (5) with nitrating mixture :

a) Preparation of 3-methylsulfinylquinolines (4a-c), (6) and (9a-c):

The described procedure¹⁴ was modified as follows:

3-Methylthioquinoline (3a-c) (1 mmol) was dissolved upon stirring in conc. sulfuric acid (2.8 mL) at -10 °C. Then, ca. 0.41 mL of the nitrating mixture (prepared from 0.1 mL of fuming nitric acid and 0.9 mL of conc. sulfuric acid) was added dropwise at -5 °C. The addition of the nitrating mixture was stopped when deep-cherry colored reaction mixture turned to yellow and the reaction mixture was immediately poured on 40 g of crushed ice and then neutralized at 0 °C with conc. aqueous ammonia up to pH 6. The solid product was filtered off and the filtrate was extracted with chloroform (2 x 10 mL). Combined extracts were dried over anhydrous sodium sulfate. The solvent was stripped off to leave the second portion of product. Compounds (4a-c) were isolated only by extraction (4 x 10 mL of CHCl₃). Products were twice recrystallized from ethanol or purified by column chromatography (silicagel 60, a mixture chloroform/ethanol, 19 : 1, v/v).

1-Methyl-3-methylsulfinyl-1,4-dihydro-4-thiooxoquinoline (6)

mp 186-188 °C (became dark), up to 209 °C complete melting and decomposition. EIMS (70 eV) m/z: 237 (32.5, M⁺), 220 (100). ¹H NMR (CDCl₃), δ: 3.12 (s, 3H, S(O)CH₃), 4.10 (s, 3H, NCH₃), 7.57-7.66 (m, 2H, 2 x H_{arom}), 7.82-7.88 (m, 1H, H_{arom}), 7.96 (s, 1H, H-2), 8.98-9.01 (m, 1H, H_{arom}). IR (KBr pellet):

$\nu_{\text{S=O}}=1030\text{ cm}^{-1}$ and 1044 cm^{-1} . *Anal.* Calcd for $\text{C}_{11}\text{H}_{11}\text{NOS}_2$: C 55.67, H 4.67, N 5.90, S 27.02. Found: C 55.20, H 4.47, N 5.93, S 26.72

4-Chloro-3-methylsulfinylquinoline (9a)

mp 140-141 °C (ethanol-acetone). EIMS (15 eV) m/z: 225 (59.5), 227 (19.2). $^1\text{H NMR}$ (CDCl_3), δ : 2.96 (s, 3H, S(O)CH_3), 7.68-7.77 (m, 1H, H_{arom}), 7.83-7.91 (m, 1H, H_{arom}), 8.17-8.27 (m, 2H, H_{arom}), 9.30 (s, 1H, **H-2**). IR (KBr pellet): $\nu_{\text{S=O}}=1063\text{ cm}^{-1}$. *Anal.* Calcd for $\text{C}_{10}\text{H}_8\text{NOCIS}$: C 53.22, H 3.57, N 6.21, S 14.21. Found: C 53.26, H 3.50, N 6.13, S 14.02.

4-Methoxy-3-methylsulfinylquinoline (9b)

mp 138-140 °C, lit.,¹⁴ mp 138-140 °C.

4-Methylthio-3-methylsulfinylquinoline (9c)

mp 120-122 °C, (ethanol). EIMS (15 eV) m/z: 237 (4.8, M^+), 220 (100), 205(87.4). $^1\text{H NMR}$ (CDCl_3), δ : 2.53 (s, 3H, SCH_3), 2.99 (s, 3H, S(O)CH_3), 7.68-7.75 (m, 1H, H_{arom}), 7.84-7.87(m, 1H, H_{arom}), 8.22-8.25 (m, 1H, H_{arom}), 8.48-8.51 (m, 1H, H_{arom}), 9.39 (s, 1H, **H-2**). IR (KBr pellet): $\nu_{\text{S=O}}=1040\text{ cm}^{-1}$. *Anal.* Calcd for $\text{C}_{11}\text{H}_{11}\text{NOS}_2$: C 55.67, H 4.67, N 5.90, S 27.02. Found: C 55.73, H 4.60, N 5.85, S 26.91.

4-Chloro-1-methyl-3-methylsulfinyl-1,2-dihydro-2-oxoquinoline (4a)

mp 170-172 °C (ethanol). EIMS (70 eV) m/z: 255 (10.7, M^+), 234 (100%). $^1\text{H NMR}$ (CDCl_3), δ : 3.20 (s, 3H, S(O)CH_3), 3.75 (s, 3H, NCH_3), 7.38-7.46 (m, 2H, 2x H_{arom}), 7.72-7.77 (m, 1H, H_{arom}) 8.18-8.22 (m, 1H, H_{arom}). IR (KBr pellet), $\nu_{\text{S=O}}=1058\text{ cm}^{-1}$. *Anal.* Calcd for $\text{C}_{11}\text{H}_{10}\text{NO}_2\text{ClS}$: C 51.67, H 3.94, N 5.48, Cl 13.86, S 12.54. Found: C 51.37, H 3.85, N 5.50, Cl 13.70, S 12.23.

4-Methoxy-1-methyl-3-methylsulfinyl-1,2-dihydro-2-oxoquinoline (4b)

mp 137-140 °C (ethanol). EIMS (70 eV) m/z: 251 (40, M^+), 234 (100%). $^1\text{H NMR}$ (CDCl_3), δ : 3.20 (s, 3H, S(O)CH_3), 3.71 (s, 3H, NCH_3), 4.23 (s, 3H, OCH_3), 7.3-7.35 (m, 1H, H_{arom}), 7.39-7.42 (m, 1H, H_{arom}), 7.66-7.69 (m, 1H, H_{arom}), 7.96-7.99 (m, 1H, H_{arom}). IR (KBr pellet): $\nu_{\text{S=O}}=1032\text{ cm}^{-1}$. *Anal.* Calcd for $\text{C}_{12}\text{H}_{13}\text{NO}_3\text{S}$: C 57.35, H 5.21, N 5.57, S 12.76. Found: C 57.45, H 5.07, N 5.67, S 12.46.

1-Methyl-3-methylsulfinyl-4-methylthio-1,2-dihydro-2-oxoquinoline (4c)

mp 145-147 °C (ethanol). EIMS (70 eV) m/z: 267 (20, M^+), 234 (100). $^1\text{H NMR}$ (CDCl_3), δ : 2.55 (s, 3H, SCH_3), 3.25 (s, 3H, S(O)CH_3), 3.75 (s, 3H, NCH_3), 7.34-7.44 (m, 2H, 2 x H_{arom}), 7.66-7.72 (m, 1H, H_{arom}), 8.41-8.44 (m, 1H, H_{arom}). IR (KBr pellet): $\nu_{\text{S=O}}=1053\text{ cm}^{-1}$. *Anal.* Calcd for $\text{C}_{12}\text{H}_{13}\text{NO}_2\text{S}_2$: C 53.91, H 4.90, N 5.24, S 23.98. Found: C 53.71, H 4.72, N 5.20, S 23.68.

b) Preparation of 6-nitro-3-methylsulfinyl-2-quinolinones (**7a-d**)

The solution of 3-methylthioquinoline (**3**) in sulfuric acid was prepared as above (procedure a). Then, 0.26 mL (Table, Entry 6.2) or 0.52 mL (Table, Entries 4.2, 5.2 and 6.3) of nitrating mixture (prepared from 0.25 mL of fuming nitric acid and 0.75 mL of conc.sulfuric acid) was added dropwise at -5 °C and

kept at -5 °C for 15 min. The mixture was next treated as above but the product was isolated by filtration only and finally recrystallized from ethanol. The mixture of **4** and **7** was separated by column chromatography (silica gel 60, a mixture chloroform/ethanol, 19 : 1, v/v).

4-Chloro-1-methyl-3-methylsulfinyl-6-nitro-1,2-dihydro-2-oxoquinoline (7a)

mp 225-228 °C. EIMS (70 eV) m/z: 300 (4, M⁺), 254 (38), 252 (100). ¹H NMR (CDCl₃), δ: 3.20 (s, 3H, S(O)CH₃), 3.80 (s, 3H, NCH₃), 7.55-7.58 (m, J=9.3 Hz, 1H, H_{arom}), 8.53-8.56 (m, J=9.3 Hz, J=2.5 Hz, 1H, H_{arom}), 9.09-9.11 (m, J=2.5 Hz, 1H, H_{arom}). IR (KBr pellet): ν_{S=O}=1066 cm⁻¹, ν_{NO₂}=1337 cm⁻¹ and 1519 cm⁻¹. *Anal.* Calcd for C₁₁H₉N₂O₄ClS: C 43.94, H 3.02, N 9.32, S 10.66. Found: C 43.74, H 2.94, N, 9.02, S 10.36.

4-Methoxy-1-methyl-3-methylsulfinyl-6-nitro-1,2-dihydro-2-oxoquinoline (7b)

mp 186-188 °C. EIMS (70 eV) m/z: 296 (15, M⁺), 279 (100). ¹H NMR (CDCl₃), δ: 3.23 (s, 3H, S(O)CH₃), 3.75 (s, 3H, NCH₃), 4.34 (s, 3H, OCH₃), 7.48-7.51 (m, J=9.3 Hz, 1H, H_{arom}), 8.48-8.52 (m, J=9.3 Hz, J=2.7 Hz, 1H, H_{arom}), 8.87-8.88 (m, J=2.7 Hz, 1H, H_{arom}). IR (KBr pellet): ν_{S=O}=1057 cm⁻¹, ν_{NO₂}=1335 cm⁻¹ and 1515 cm⁻¹. *Anal.* Calcd for C₁₂H₁₂N₂O₅S: C 48.64, H 4.08, N 9.45, S 10.82. Found: C 48.24, H 3.95, N 9.28, S 10.60.

1-Methyl-3-methylsulfinyl-4-methylthio-6-nitro-1,2-dihydro-2-oxoquinoline (7c)

mp 203-205 °C. EIMS (70 eV) m/z: 312 (27, M⁺), 295 (100). ¹H NMR (CDCl₃), δ: 2.62 (s, 3H, SCH₃), 3.25 (s, 3H, S(O)CH₃), 3.80 (s, 3H, NCH₃), 7.51-7.54 (d, J=9.3 Hz, 1H, H-8), 8.49-8.53 (dd, J=9.3 Hz, J=2.4 Hz, 1H, H-7), 9.33-9.34 (d, J=2.4 Hz, 1H, H-5). IR (KBr pellet): ν_{S=O}=1057 cm⁻¹, ν_{NO₂}=1541 cm⁻¹. *Anal.* Calcd for C₁₂H₁₂N₂O₄S₂: C 46.14, H 3.87, N 8.97, S 20.53. Found: C 46.01, H 3.80, N 8.77, S 20.11

3,4-Dimethylsulfinyl-1-methyl-6-nitro-1,2-dihydro-2-oxoquinoline (7d)

mp 231-232 °C. EIMS (70 eV) m/z: 328 (23.7, M⁺). ¹H NMR (CDCl₃), δ: 3.26 (s, 3H, S(O)CH₃), 3.42 (s, 3H, S(O)CH₃), 3.81 (s, 3H, NCH₃), 7.58-7.61 (d, J=9.3 Hz, 1H, H-8), 8.52-8.56 (dd, J=9.3 Hz, J=2.4 Hz, 1H, H-7), 10.26-10.27 (d, J=2.4 Hz, 1H, H-5). IR (KBr pellet): ν_{S=O}=1039 cm⁻¹, ν_{NO₂}=1519 cm⁻¹. *Anal.* Calcd for C₁₂H₁₂N₂O₅S₂: C 43.89, H 3.68, N 8.53, S 19.53. Found: C 43.69, H 3.50, N 8.51, S 19.32.

Reactions of 4-chloroquinolines (1a), (3a) and (4a) with dimethylamine

4-Chloroquinoline (**1a** or **3a**) (5 mmol), 15 mL of methanol, 4 mL of 20% aqueous dimethylamine and one drop of conc. hydrochloric acid was placed in a steel autoclave. It was heated at 140-150 °C for 4 h (for **1a**) or 160 °C for 5 h for **3a**. The mixture was cooled to rt, transferred to distillation flask and the volatile compounds were evaporated under vacuum at 50 °C. The residue was neutralized with few drops of 10% aqueous sodium hydroxide and extracted with methylene chloride or chloroform (4 x 5 mL). The extracts were dried over anhydrous sodium sulfate and the solvent was removed to give 93 % of **1d** or 82 % of **3d**.

Amination of 4-chloro-3-methylsulfinyl-2-quinolinone (**4a**) to **4d** (100%) was performed in the same manner but at 0 °C, because at rt the reaction led to multicomponent mixture. 4-Dimethylamino-3-methylsulfinyl-2-quinolinone (**4d**) is unstable even at rt within few hrs.

4-Dimethylamino-3-methylthioquinoline (**1d**)

mp 86-88 °C (hexane). EIMS (70eV) m/z: 218 (100, M⁺). ¹H NMR (CDCl₃), δ: 2.51 (s, 3H, SCH₃), 3.13 (s, 6H, N(CH₃)₂), 7.48-7.51 (m, 1H, H_{arom}), 7.59-7.63 (m, 1H, H_{arom}), 8.02-8.08 (m, 2H, 2 x H_{arom}), 8.75 (s, 1H, H-2). *Anal.* Calcd for C₁₂H₁₄N₂S: C 66.02, H 6.46, N 12.83, S 14.69. Found: C 65.96, H 6.34, N 13.01, S 14.49.

4-Dimethylamino-1-methyl-3-methylthio-1,2-dihydro-2-oxoquinoline (**3d**)

mp 79-81 °C (ethanol). EIMS (70 eV) m/z: 248 (100, M⁺). ¹H NMR (CDCl₃), δ: 2.45 (s, 3H, CH₃S), 3.08 [s, 6H, (CH₃)₂N], 3.74 (s, 3H, CH₃N), 7.21-7.23 (m, 1H, H_{arom}), 7.32-7.35 (m, 1H, H_{arom}), 7.51-7.56 (m, 1H, H_{arom}), 7.75-7.97 (m, 1H, H_{arom}). *Anal.* Calcd for C₁₃H₁₅N₂OS: C 62.87, H 6.49, N 11.28, S 12.91. Found: C 62.48, H 6.31, N 11.43, S 13.01

4-Dimethylamino-1-methyl-3-methylsulfinyl-1,2-dihydro-2-oxoquinoline (**4d**)

semi-solid. ¹H NMR (CDCl₃), δ: 3.21 (s, 6H, N(CH₃)₂), 3.27 (s, 3H, S(O)CH₃), 3.68 (s, 3H, NCH₃), 7.22-7.26 (m, 1H, H_{arom}), 7.35-7.37 (m, 1H, H_{arom}), 7.58-7.63 (m, 1H, H_{arom}), 7.87-7.89 (m, 1H, H_{arom}). IR (KBr pellet or nujol suspension): ν_{S=O}=1058 cm⁻¹ and 1087 cm⁻¹. *Anal.* Calcd for C₁₃H₁₆N₂O₂S: C 59.07, H 6.10, N 10.60, S 12.13. Found: C 58.94, H 6.01, N 10.33, S 11.82.

Preparation of 4-methylthio-3-methylsulfinylquinoline (**9c**) from 4-chloro-3-methylsulfinylquinoline (**9a**)

A suspension of 4-chloroquinoline (**9a**) (2.25 g, 10 mmol), thiourea (0.78 g, 10 mmol) in 10 mL of 95% ethanol was stirred at rt for 18 h, or until the mixture became so dense that the magnetic stir bar was stopped. The mixture was cooled at 0 °C for several h, the isothiuronium salt was filtered off and dissolved in 60 mL of 10% aqueous sodium hydroxide. The solution was methylated on stirring with 0.5 mL (8 mmol) of methyl iodide for 30 min. Methylthio derivative (**9c**) was filtered off, washed with water and dried on air. It was finally recrystallized from ethanol to give the product (75 %) with mp 120-122 °C, identical as the oxidation product of (**1c**) described above.

REFERENCES AND NOTES

Part LXXXII in the Series of Azinyl Sulfides

1. a) B. Joseph, F. Darro, A. Bernard, B. Lesur, F. Collignon, C. Decaestecker, A. Frydman, G. Guillaumet, and R. Kiss, *J. Med. Chem.*, 2002, **45**, 2543. b) S. B. Chen, G. Y. Gao, Y. S. Li, S. C. Yu, and P. G. Xiao, *Planta Med.*, 2002, **68**, 554. c) S. Ratnayake, X. P. Fang, J. E. Anderson, J. L. Mc Laughlin, and D. R. Evert, *J. Nat. Prod.*, 1992, **55**, 1462.

2. H. Tawada, H. Natsugari, E. Ishikawa, Y. Sugiyama, H. Ikeda, and K. Meguro, *Chem. Pharm. Bull.*, 1995, **43**, 616.
3. G. W. Spears, K. Tsuji, T. Tojo, H. Nishimura, and T. Ogino, *J. Heterocycl. Chem.*, 2002, **39**, 799.
4. K. Otsubo, K. Morita, M. Uchida, K. Yamasaki, T. Kanabe, and T. Shimizu, *Chem. Pharm. Bull.*, 1991, **39**, 2906.
5. J. Elks and C. R. Ganellin [eds.], *Dictionary of Drugs*, Chapman and Hall, London, New York, Tokyo, Melbourne, Madras, 1990, p.1021.
6. M. X. Xu, W. X. Duan, and H. Zeng, *Yaoxue Xuebao*, 1995, **20**, 792 (*Chem. Abstr.*, 1996, **124**, 201978 c).
7. T. Eicher and S. Hauptman, "The Chemistry of Heterocycles", Thieme, Stuttgart-New York, 1995, chapter 6.
8. J. P. Chupp and S. Metz, *J. Heterocycl. Chem.*, 1978, **16**, 65.
9. W. Śliwa, *N-Substituted salts of pyridine and related compounds*, WSP, Częstochowa (Poland), 1996, chapter 2.3. H. Weber, *Adv. Heterocycl. Chem.*, 1987, **41**, 275.
10. a) A. Maślankiewicz and S. Boryczka, *Rec. Trav. Chim. Pays-Bas*, 1993, **112**, 519.
b) A. Maślankiewicz and S. Boryczka, *J. Heterocycl. Chem.*, 1993, **30**, 1623.
c) A. Maślankiewicz and A. Zięba, *Heterocycles*, 1992, **34**, 247.
d) A. Maślankiewicz and A. Zięba, *Polish J. Chem.*, 1994, **68**, 1957.
11. J. M. Barker, P. R. Hudleston, and D. Holmes, *J. Chem. Res. (S)*, 1985, 214; *J. Chem. Res. (M)*, 1985, 2501.
12. O. N. Nadein and A. V. Aksenov, *Khim. Geterotsykl. Soedin.*, 2001, 942.
13. N. Boussad, T. Trefouel, G. Dupas, J. Bourguignon, and G. Queguiner, *Phosphorus, Sulfur and Silicon*, 1992, **66**, 127.
14. M. Rudnik and A. Maślankiewicz, *Heterocycles*, 1999, **51**, 2731.
15. I. S. Poddubnyi, *Khim. Geterotsykl. Soedin.*, 1995, 774.
16. Significant distinctions between the values of δ_{H} in aromatic region of **5** (up to $\Delta\delta$ ca. 0.6 ppm) taken in DMSO- d_6 and CDCl₃ solutions were observed. Thus, in order to compare the spectral data of **6** and **5** the ¹H NMR spectrum of **5** in CDCl₃ was recorded [2.42 (CH₃S), 3.99 (CH₃N), 7.24 (H₂), 7.45-7.48 (m, H₆), 7.48-7.50 (m, H₈), 7.65-7.70 (m, H₇), 9.02-9.04 (m, H₅)].