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1*H*- AND 1-ALKYL-1,4-DIHYDRO-4-OXO-3-ALKYLTHIOQUINOLINES FROM 1,4-DIHYDRO-4-OXO-3'-ALKYLTHIO-3,4'-DIQUINOLINYL SULFIDES[#]

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Abstract- Quinolinones (**1**) were *N*-alkylated with alkyl iodides in DMSO or DMF in the presence of potassium methoxide to *N*-alkyl derivatives (**3**) (78-98%). *One-pot* method was elaborated allowing to transform compound (**1a**) into the mixture of 1-alkyl-3-alkylthio-4(1*H*)-quinolinones (**8**) (55-76%) and 4-methoxy-3-methylthioquinoline (**4a**) (83-90 %).
Potassium methoxide in DMSO causes sequentially fission of diquinolinyl sulfide (**1**) to the mixture of dipotassium salt of 3-mercapto-4-quinolinone (**9**) and (**4**) and then *O*-demethylation of **4** to potassium salt of 3-alkylthio-4-quinolinone (**5**), which could be transformed after *S*-alkylation of **9** and neutralization to 3-alkylthio-4-quinolinones (**6**). This *one-pot* procedure permits to convert both quinoline-units of 3,4'-diquinolinyl sulfide (**1)** to **6** with total yield of 60-78%.

4(1*H*)-Quinolinones with 3-sulfide function of type (**8**) were used in the synthesis of 3-sulfinyl-4(1*H*)-quinolinones or 3-sulfonyl-4(1*H*)-quinolinones. [1-2] They exhibited significant vasodilatory activity or antihypertensive activity, respectively. [1-4]

Among compounds (**8**) only sulfide (**8a**) was previously prepared from *N*,*S*-dimethyl derivative of 3,4'-diquinolinyl sulfide (**3a**) [5] by the reaction with sodium methoxide followed by methylation (Scheme 1, route a). To extend this reaction to the preparation of other 1-alkyl-3-alkylthio-4(1*H*)-quinolinones (**8**) some improvements are required, i.e.: x) the preparation of **3** by N^1-alkylation of **1**, xx) two-stage convertion of compound (**1**) to obtain the expected product (**8**). Furthermore, in the preparation of quinolinones (**8**), from two quinoline parts of diquinolinyl sulfide (**3**) only the "left" one is consumed in the synthesis of **8**, remaining the "right"-methoxyquinoline part unsuitable. [5] Taking into account that

potassium methoxide causes simultanous splitting of 4'-quinolinyl-sulfide bond in **2** (i.e. potassium salt of **1**) as well in sulfide (**3**), and complete *O*-demethylation of 4-methoxyquinolines (**4**) to **5**, we successfully performed the reaction of diquinolinyl sulfides (**1**) with potassium methoxide leading (after *S*-alkylation and neutralization) to 3-alkylthio-4(1*H*)-quinolinones (**6**). (Scheme 2)

RESULTS AND DISCUSSION

N^1-Methylation of **1** has been performed previously by treatment of sodium (or potassium) salt (**2**) with methyl iodide. [5,6] In the first case the starting N^1-sodium salt of type (**2**) was prepared from quinolinone (**1a**) and sodium hydride in DMF and methylated to **3a** with 88% yield.[5] In the second case, sodium (or potassium) salts of type (**2**) in aqueous alkaline DMSO solution have been alkylated to **3a,b,d,e** in 26-36 %. [6] The newly elaborated procedure appears more convenient: it results in forming DMF (and DMSO) soluble potassium salts (**2**) by treatment of **1a-d** with potassium methoxide in DMF (or in DMSO) followed by the reaction with alkyl iodide to give the *N*-alkylquinolinones (**3a-f**) (78-97 %) (see Scheme 1, route a;Table 1).

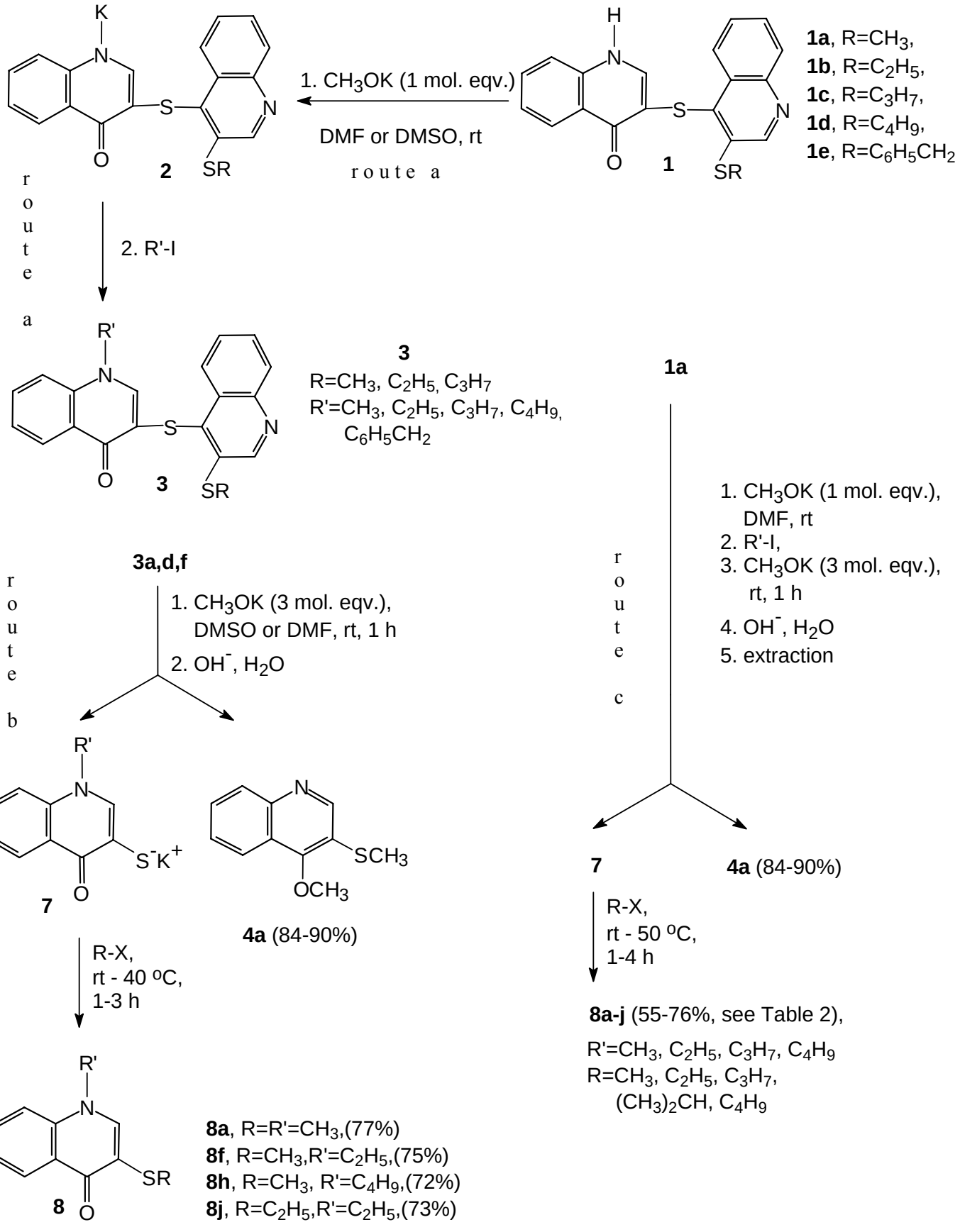
Table 1

Preparation of *N*-alkylquinolinones (**3**) from compounds (**1**)

Entry	Substrate, R	*N*-Alkylation Conditions	Product (Yield)
1	**1a**, CH_3	CH_3I, DMSO, rt, 1 h	**3a**, R=R'=CH_3, (93%)
2	**1a**, CH_3	CH_3I, DMF, rt, 1 h	**3a**, R=R'=CH_3, (98%)
3	**1b**, C_2H_5	CH_3I, DMF, rt, 1 h	**3b**, R=C_2H_5, R'=CH_3, (97%)
4	**1c**, C_3H_7	CH_3I, DMF, rt, 1 h	**3c**, R=C_3H_7, R'=CH_3, (96%)
5	**1a**, CH_3	C_2H_5I, DMF, rt, 2 h	**3d**, R=CH_3, R'=C_2H_5, (86%)
6	**1a**, CH_3	C_3H_7I, DMF, 40 °C, 3 h	**3e**, R=CH_3, R'=C_3H_7, (83%)
7	**1a**, CH_3	C_4H_9I, DMF, 50 °C, 4 h	**3f**, R=CH_3, R'=C_4H_9, (78%)
8	**1a**,CH_3	$C_6H_5CH_2Cl$, DMF, 50 °C, 4 h	**3g**, R=CH_3, R'=$C_6H_5CH_2$, (78%)

In order to utilize 3,4'-diquinolinyl sulfides (**3**) to the preparation of 4-quinolinones (**8**), (Scheme 1, route b), compounds (**3**) were treated with potassium methoxide (DMSO or DMF, rt, 0.5-1 h). The reaction proceeded *via* methoxy-desulfidation at 4'-quinolinyl sulfur bond and led to 3-quinolinethiolate (**7**) and 4-methoxy-3-methylthioquinoline (**4a**). After dilution with aqueous alkali, the neutral compound (**4a**) was removed by extraction and thiolate (**7**) was alkylated to 1-alkyl-3-alkylthio-4(1*H*)-quinolinones (**8a, f, h, j**) (72-77 %).

Scheme 1


1. CH3OK (1 mol. eqv.)
DMF or DMSO, rt
route a
1a, R=CH3,
1b, R=C2H5,
1c, R=C3H7,
1d, R=C4H9,
1e, R=C6H5CH2
2. R'-I
3
R=CH3, C2H5, C3H7
R'=CH3, C2H5, C3H7, C4H9,
C6H5CH2
3a,d,f
1. CH3OK (3 mol. eqv.),
DMSO or DMF, rt, 1 h
2. OH-, H2O
route b
4a (84-90%)
R-X,
rt - 40 oC,
1-3 h
8a, R=R'=CH3,(77%)
8f, R=CH3,R'=C2H5,(75%)
8h, R=CH3, R'=C4H9,(72%)
8j, R=C2H5,R'=C2H5,(73%)
1a
1. CH3OK (1 mol. eqv.),
DMF, rt
2. R'-I,
3. CH3OK (3 mol. eqv.),
rt, 1 h
4. OH-, H2O
5. extraction
route c
4a (84-90%)
R-X,
rt - 50 oC,
1-4 h
8a-j (55-76%, see Table 2),
R'=CH3, C2H5, C3H7, C4H9
R=CH3, C2H5, C3H7,
(CH3)2CH, C4H9

Since both reactions : **1** → **3** and **3** → **4** + **8** were performed in the same solvent and also with potassium methoxide as nucleophilic reagent, the transformation of **1** to the mixture of **4** + **8** was performed stepwise but as a "one-pot" process, without isolation of sulfide (**3**), making therefore the preparation of **8** more effective and more convenient (Scheme 1, route c and Table 2). In dry DMF, all three reactions i.e. formation of potassium salts (**2**), *N*-alkylation of **2** to **3** and methoxy-desulfidation of **3** to the mixture of quinolinethiolate (**7**) and methoxyquinoline (**4**) proceeded clean. Moreover, the thiolate (**7**) could be effectively *S*-alkylated in DMF to 3-alkylthio-4(1*H*)-quinolinones (**8**). (When the reactions were performed in DMSO solution both products (**4**) and (**8**) were obtained with lower yields and lower purity.) However, in order to prepare individually compound (**8**) it is more convient to remove the neutral compound (**4**) by dilution of the DMF reaction solution with aqueous alkali, followed by extraction of **4** with chloroform. In this case, final *S*-alkylation of thiolate (**7**) to **8** proceeded in alkaline aqueous-DMF solution.

Table 2

Preparation of 1-alkyl-3-alkylthio-4(1*H*)-quinolinones (**8**) from 3'-methylthioquinolinone (**1a**) **(**Scheme 1, route c)

Entry	Substrate	*N*-Alkylation Conditions [a)]	*S*-Alkylation Conditions [b)]	Products	
				Quinolinone (**8**)	**4a** (Yield)
1	**1a** R=CH_3	CH_3I, rt, 1 h	CH_3I, rt, 1 h	**8a**, R'=R=CH_3 (76%)	90%
2		CH_3I, rt, 1 h	C_2H_5I, 40 °C, 3 h	**8b**, R'=CH_3, R=C_2H_5 (74%)	89%
3		CH_3I, rt, 1 h	C_3H_7I, 40 °C, 3 h	**8c**, R'=CH_3, R=C_3H_7 (68%)	84%
4		CH_3I, rt, 1 h	$(CH_3)_2CHI$, 40 °C,3 h	**8d**, R'=CH_3, R= $(CH_3)_2CH$ (57%)	89%
5		CH_3I, rt, 1 h	C_4H_9I, 50 °C, 4 h	**8e**, R'=CH_3, R=C_4H_9 (61%)	90%
6		C_2H_5I, 40 °C, 3 h	CH_3I, rt, 1 h	**8f**, R'=C_2H_5, R=CH_3 (75%)	87%
7		C_3H_7I, 40 °C, 3 h	CH_3I, rt, 1 h	**8g**, R'=C_3H_7, R=CH_3 (68%)	90%
8		C_4H_9I, 50 °C, 4 h	CH_3I, rt, 1 h	**8h**, R'=C_4H_9, R=CH_3 (55%)	83%
9		C_4H_9I, 50 °C, 4 h	C_4H_9I, 50 °C, 4 h	**8i**, R'=R=C_4H_9 (55%)	88%
10		C_2H_5I, 40 °C, 3 h	C_2H_5I, 40 °C, 3 h	**8j**, R'=R=C_2H_5 (57%)	90%

[a)] The reactions were performed in dry DMF. [b)] The reactions were carried out after dilution the reaction mixture with aqueous sodium hydroxide and extraction of **4a** with chloroform.

Preparation of 3-alkylthio-4(1*H*)-quinolinones (**6**) from 3'-alkylthio-1,4-dihydro-4-oxo-3,4'-diquinolinyl sulfides (**1**)

When the reaction of **3a** with 3 molar equivalent of potassium methoxide was performed for a prolonged time (DMSO, rt, 1.5 h) according to route a (Scheme 1) it gave 71% of 1-methyl-3-methylthio-4(1*H*)-quinolinone (**8a**) and only 35 % of 4-methoxy-3-methylthioquinoline (**4a**). However, after neutralization of aqueous-DMSO layer 4-quinolinone (**6a**) (40%) could be isolated by extraction.Thus, the total amount of quinolinones (**6a**) and (**8a**) exceeded 100 % - calculated to the *quinolinone*-part of sulfide (**3**). It indicates that the "lacking" amount of 4-methoxyquinoline (**4a**) should be converted to 4-quinolinone (**6a**).The same treatment of the potassium salt (**2a**) proceeded with complete consumption of the starting sulfide (**1**) to give 64 % of 4-quinolinone (**6a**) and 30 % of 4-methoxy-3-methylthioquinoline (**4a**) (yields were calculated with respect to the whole molecule of **1**).This turned our attention to the reaction of **1** with an excess of potassium methoxide as a source of 3-alkylthio-4-quinolinones (**6**). According to the methodology presented in Scheme 2 both quinoline units of **1** were transformed to the same two molecules of 3-alkylthio-4(1*H*)-quinolinone (**6**) with total yields up to 78%.

Table 3

Preparation of 3-alkylthio-4(1*H*)-quinolinones (**6**) from 3,4'-diquinolinyl sulfides (**1**) (Scheme 2)

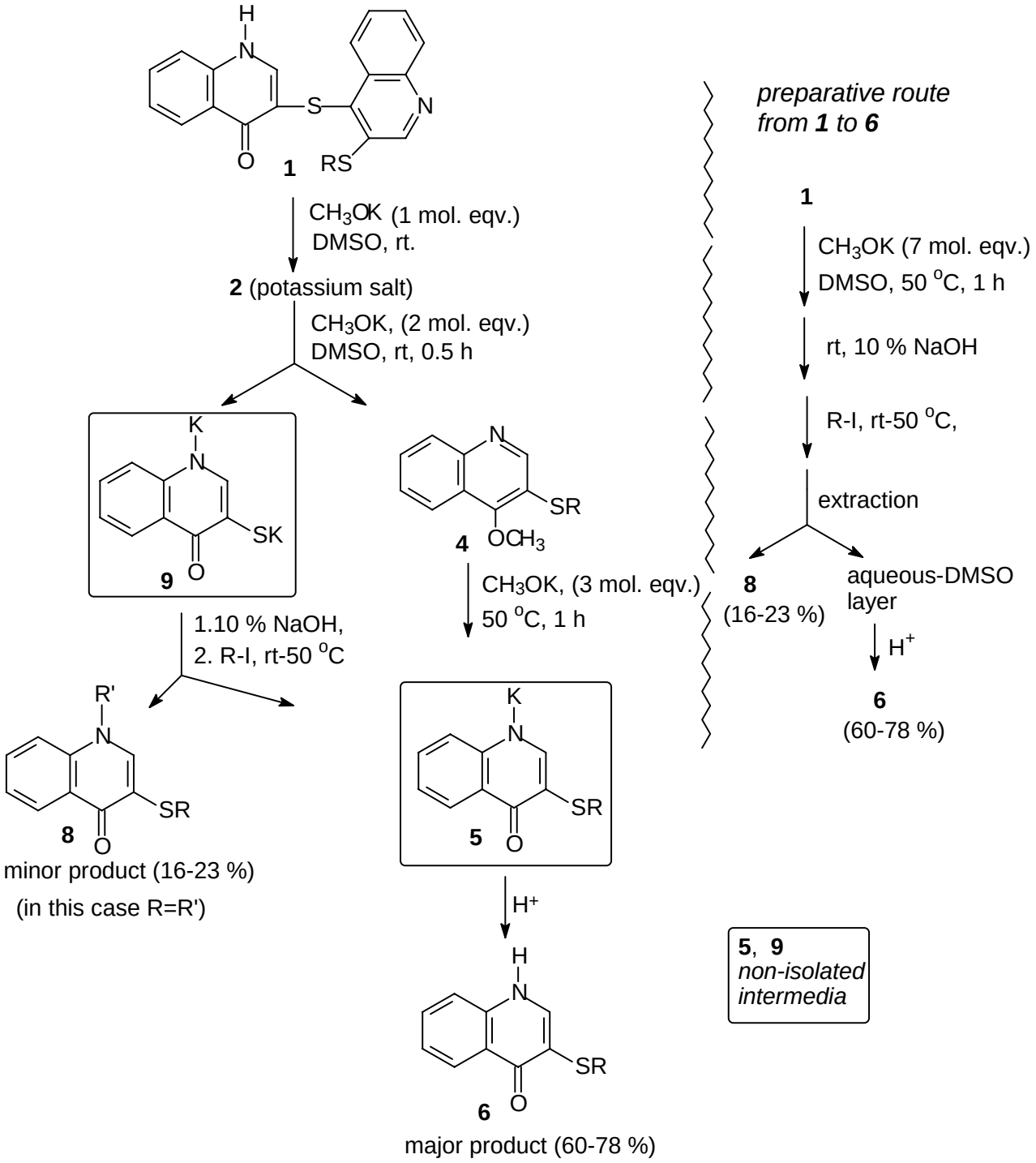
Entry	Substrate	*S*-Alkylation Conditions	Products (Yield)	
			6	**8**
1.	**1a**, R=CH_3	CH_3I, rt, 1 h	**6a**, R=CH_3, 78 %	**8a**, R=R'=CH_3, 22 %
2.	**1b**, R=C_2H_5	C_2H_5I, rt, 1 h	**6b**, R=C_2H_5, 77 %	**8j**, R=R'=C_2H_5, 18 %
3.	**1c**, R=C_3H_7	C_3H_7I, rt, 1 h	**6c**, R=C_3H_7, 73 %	**8k**, R=R'=C_3H_7, 16 %
5.	**1d**, R=C_4H_9	C_4H_9I, 50 ^oC, 4 h	**6e**, R=C_4H_9, 63 %	**8i**, R=R'=C_4H_9, 23 %
6.	**1e**, R=$C_6H_5CH_2$	$C_6H_5CH_2Cl$, 50 ^oC, 4 h	**6f**, R=$C_6H_5CH_2$, 60 %	**8l**, R=R'= $C_6H_5CH_2$, 20%

Findings presented below permit to formulate the final experimental procedure :

- Methoxy-desulfidation of potassium salt (**2**) (2 molar eqv. of potassium methoxide, DMSO, rt, 0.5 h) led to the mixture of dipotassium salt (**9**) and 4-methoxy-3-alkylthioquinoline (**4**).
- Methoxy-*O*-demethylation of **4a** (3 molar eqv. of potassium methoxide, DMSO, 50 °C, 1 h) to potassium salt (**5a**) (R=CH_3) gave after neutralization 3-methylthio-4(1*H*)-quinolinone (**6a**) (81%).
- To complete reaction sequence starting from **1** and finally producing the mixture of **9** and **5**, 7 molar eqv. of potassium methoxide (DMSO, 1 h, 50 °C) should be used.

- Direct *S*-alkylation of thiolates (**9**) in DMSO solution did not proceeded clean. Thus, before *S*-alkylation of thiolates (**9**) the solution of **9** and **5** in DMSO should be diluted with aqueous alkali.
- *S*-Alkylation of thiolate (**9**) to monopotassium salt (**5**) was accompanied in a small extent by *N*-alkylation leading to *N*,*S*-dialkyl derivative (**8**), which could be removed by extraction from alkaline DMSO-aqueous solution.
- Neutralization of salt (**5**) led to 3-alkylthio-4(1*H*)-quinolinone (**6**).

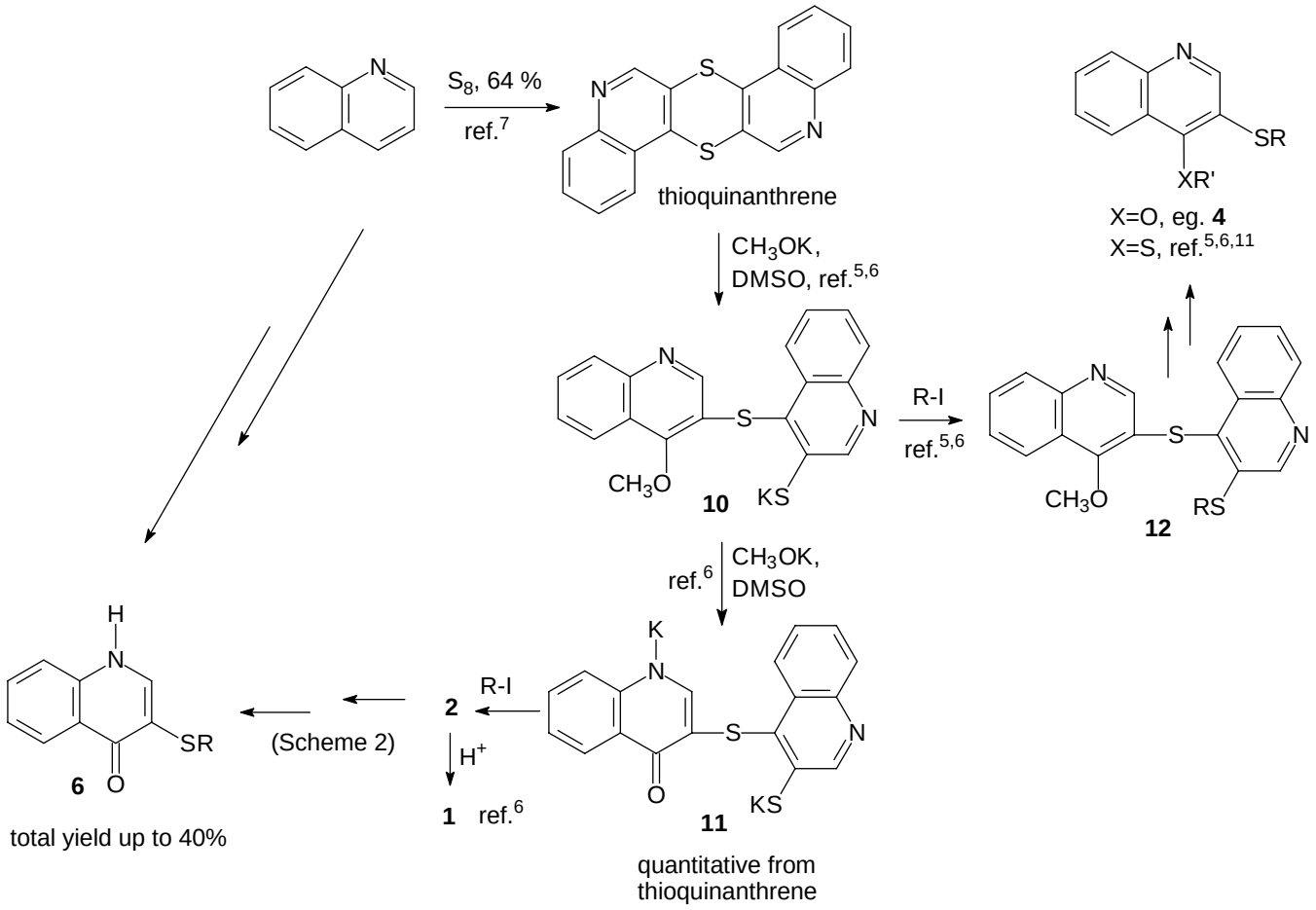
S c h e m e 2



CONCLUSIONS

In the preparation of diquinolinyl sulfides (**1**), from thioquinanthrene, (the main product of quinoline sulfurization [7]) the key parts are played by the cleavage of γ-quinolinyl-sulfur bond, followed by *O*-demethylation of thiolate (**10**) to dipotassium salt (**11**) and alkylation of salt (**11**) to monosalt (**2**) (finally converted to **1**). [5,6] Both of the 3'-quinolinethiolates (**10**) and (**11**) did not react with methoxide anion *via* fission of the 4'-quinolinyl sulfur bond. Thiolate (**10**) underwent *O*-demethylation to dipotassium salt (**11**),[6] the latter was resistant to potassium methoxide (DMSO, 90 °C) for 24 hrs. However, when 3'-thiolate function of **11** or **10** [5,8] (or theirs 4-alkylthio- analogs) [10,11] is alkylated to 3'-alkylthio one, 4'-quinolinyl-sulfur bond became sensitive to nucleophilic action and therefore both quinoline units of 3,4'-diquinolinyl sulfides of type (**12**) could be converted to 4-substituted (alkoxy, alkylthio)-3-alkylthioquinolines, e.g. (**4**). [5,8,11]

S c h e m e 3



In this paper, it was shown that potassium methoxide (7 mol. eqv) in DMSO (50 °C, 1.5 h) causes sequentially cleavage of diquinolinyl sulfide (**1**) to the mixture of dipotassium salt of 3-mercapto-4-quinolinone (**9**) and (**4**) and then *O*-demethylation of **4** to potassium salt of 3-alkylthio-4-quinolinone (**5**). The mixture of (**9**) and (**5**) could be transformed after *S*-alkylation of **9** and neutralization to 3-alkylthio-4-

quinolinones (**6**). This *one-pot* procedure permits to convert both quinoline-units of 3,4'-diquinolinyl sulfide (**1)** to two 4(1*H*)-quinolinone moieties in **6** with total yield of 60-78%.

EXPERIMENTAL

Melting points were taken in open capillary tubes and are uncorrected. ^{1}H 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. TLC analyses were performed employing Merck's silicagel 60 F_{254} plates and a solution of chloroform-ethanol (19 : 1, v/v) as an eluent (system I) or Merck's aluminium oxide 60 F_{254} neutral (type E) plates using mixture of chloroform - ethanol (19 : 1, or 10 : 1, v/v) as an eluent (system II).

3'-Alkylthio-3,4'-diquinolinyl sulfides (**1a-e**) were prepared from thioquinanthrene and potassium methoxide followed by *S*-alkylation with alkyl iodides or benzyl chloride as described previously for **1a-c** and **1e**.[6]

3'-Butylthio-1,4-dihydro-4-oxo-3,4'-diquinolinyl sulfide (**1d**): mp 195-197 ^{o}C (DMF). EIMS (70 eV) (m/z): 392 (29, M^+), 303 (100). ^{1}H NMR ($CDCl_3$), δ: 0.84 (t, *J*=7.2, 3H, C**H**$_3$CH$_2$), 1.30-1.47 (m, 2H, CH$_2$C**H**$_2$CH$_3$), 1.50-1.69 (m, 2H, CH$_2$C**H**$_2$CH$_2$), 3.20 (t, *J*=7.2, 2H, SC**H**$_2$), 7.32-7.37 (m, 1H, **H**$_{arom}$), 7.53-7.72 (m, 4H, 4 x **H**$_{arom}$), 7.75 (s,1H, **H**-2), 8.00-8.07 (m, 2H, 2 x **H**$_{arom}$), 8.49-8.52 (m, 1H, **H**$_{arom}$), 8.89 (s, 1H, **H**-2'), 12.10 (br s, 1H, N-**H**). *Anal.* Calcd for $C_{22}H_{20}N_2OS_2$: C 67.32; H 5.14; N 7.14; O 4.08; S 16.33. Found: C 67.12; H 5.04; N 7.01; S 16.42.

1-Alkyl -3'-alkylthio-1,4-dihydro-4-oxo-3,4'-diquinolinyl sulfides (**3**) (Scheme 1, route a)

0.37 g (5.25 mmol) of potassium methoxide was added to the suspension of quinolinone (**1**) (5 mmol) in 25 mL of dry DMF (or DMSO). The mixture was stirred for 25 min i.e. until the mixture became clear. Then, 0.75 g (5.25 mmol) of methyl iodide or 6.1 mmol of alkyl iodide or benzyl chloride was added dropwise for 0.5 h at rt and the mixture was stirred at 20-50 °C for 1-4 h as listed in Table 1. The mixture was then cooled to rt and diluted with 75 mL of 10 % aqueous sodium hydroxide. The solid was filtered off, washed with warm water and air-dried to give the pure sulfide (**3**). For analytical purposes, it was recrystallized from DMF. The properties of **3a** (R=R'=CH_3),[5] **3b** (R'=CH_3, R=C_2H_5), **3d** (R'=C_2H_5, R=CH_3), **3g** (R=CH_3, R'=$C_6H_5CH_2$),[13] **3f** (R=CH_3, R'=C_4H_9) [6] were the same as described previously.

1-Methyl -3'-propylthio-1,4-dihydro-4-oxo-3,4'-diquinolinyl sulfide (**3c**): mp 174-175 °C. EIMS (70 eV) m/z: 392 (0.5, M^+), 317 (100). ^{1}H NMR ($CDCl_3$), δ: 1.05 (t, *J*=7.3, 3H, C**H**$_3$CH$_2$), 1.73 (sextet, *J*=7.3, 2H, CH$_2$C**H**$_2$CH$_3$), 3.15 (t, *J*=7.3, 2H, SC**H**$_2$), 3.68 (s, 3H, NC**H**$_3$), 7.35-7.43 (m, 2H, 2 x **H**$_{arom}$), 7.47 (s, 1H, **H**-2), 7.56-7.65 (m, 3H, 3 x **H**$_{arom}$), 8.03-8.06 (m, 1H, **H**$_{arom}$), 8.45-8.48 (m,1H, **H**$_{arom}$), 8.68-8.71 (m, 1H,

H-2), 7.56-7.65 (m, 3H, 3 x $\mathbf{H}_{arom}$), 8.03-8.06 (m, 1H, $\mathbf{H}_{arom}$), 8.45-8.48 (m,1H, $\mathbf{H}_{arom}$), 8.68-8.71 (m, 1H, $\mathbf{H}_{arom}$), 8.83 (s, 1H, **H**-2'). *Anal*. Calcd for $C_{22}H_{20}N_2OS_2$: C 67.32; H 5.14; N 7.14; O 4.08; S 16.33. Found C 67.32; H 4.98; N 7.24; S 16.26.

1-Propyl -3'-methylthio-1,4-dihydro-4-oxo-3,4'-diquinolinyl sulfide (**3e**) : mp 195-197 ^{o}C. EIMS (70 eV) m/z: 392 (0.5,M^+), 345 (100). ^{1}H NMR ($CDCl_3$), δ : 0.79 (t, *J*=7.3, 3H, $CH_2C\mathbf{H}_3$), 1.75 (sextet, *J*=7.3, 2H, $C\mathbf{H}_2CH_3$), 2.63 (s, 3H, $SC\mathbf{H}_3$), 3.95 (t, *J*=7.3, 2H, $NC\mathbf{H}_2$), 7.34-7.38 (m, 3H, 2 x $\mathbf{H}_{arom}$), 7.43 (s, 1H, **H**-2), 7.56-7.67 (m, 3H, 3 x $\mathbf{H}_{arom}$), 8.04-8.07 (m, 1H, $\mathbf{H}_{arom}$), 8.45-8.48 (m, 1H, $\mathbf{H}_{arom}$), 8.67-8.69 (m, 1H, $\mathbf{H}_{arom}$), 8.78 (s, 1H, **H**-2). ***Anal.*** Calcd for $C_{22}H_{20}N_2OS_2$: C 67.32; H 5.14; N 7.14; O 4.08; S 16.33. Found: C 66.92; H 5.18; N 7.32; S 16.28.

Preparation of 1-alkyl-3-methylthio-1,4-dihydro-4-oxoquinolines (**8**) from sulfides (**3**) (Scheme 1, route b) The reaction was performed as described previously for compound (**3a**) [5] at rt within 20 min but using DMF as a solvent, potassium methoxide as a nucleophile and methyl or ethyl iodides as methylating agents. This procedure was applied to the preparation of quinolinones (**8a**) (77% from **3a**), (**8f**) (75% from **3d**), (**8j**) (73% from **3d**) and (**8h**) (72% from **3f**). For analytical data of quinolinones **8** obtained – see below.

Preparation of 1-alkyl-3-alkylthio-1,4-dihydro-4-oxoquinolines (**8**) from sulfide (**1a**) (Scheme 1, route c; Table 2)

Alkylation of **1a** to **3** was performed in DMF as described above (Scheme 1, route a) but omitting the isolation of **3**. The mixture was then cooled to rt and the next portion of potassium methoxide 1.05 g (15 mmol) was added and strirred at rt for 45 min. The resulting solution was poured into 50 mL of 5 % aqueous sodium hydroxide and 4-methoxy-3-methylthioquinoline (**4a**) was extracted with chloroform (5 x 10 mL). (Compound (**4a**) was isolated from combined extracts and purified by extraction with hot hexane.) The aqueous layer was alkylated on strirring with 5.25 mmol of alkyl iodide in the manner described in Table 2. Only the butylthio derivative (**8h**) was isolated directly by filtration. Other quinolinones (**8**) were isolated by continous extraction with chloroform. The extract was then concentrated and the residue was chromatographed on silica gel (100-200 mesh) using the mixture of chloroform-ethanol 19 : 1 v/v as an eluent. The fractions with quinolinone (**8**) were concentrated and the residue was recrystallized from ethyl acetate or ethanol. This procedure was applied for the preparation of quinolinones (**8a-j**) and the results are collected in Table 2.

1-Methyl-3-methylthio-1,4-dihydro-4-oxoquinoline (**8a**): mp 120-121 °C (ethyl acetate), lit.,[5] mp 121-122 °C. 1-Methyl-3-ethylthio-1,4-dihydro-4-oxoquinoline (**8b**) (R'=CH_3, R=C_2H_5): mp 115-117 °C (ethyl acetate), lit.,[3,12] mp 115-117 °C.

1-Methyl-3-propylthio-1,4-dihydro-4-oxoquinoline (**8c**) (R'=CH_3, R=C_3H_7): mp 74-76 °C (ethyl acetate), lit., [3,12] mp 74-76 °C.

1-Methyl-3-isopropylthio-1,4-dihydro-4-oxoquinoline (**8d**) [R'=CH_3, R=$CH(CH_3)_2$]: mp 105-107 °C (ethyl acetate). EIMS (70 eV) m/z: 233 (34, M^+), 191 (100). ^{1}H NMR ($CDCl_3$), δ: 1.22 [d, *J*=6.6, 6H, $CH(C\mathbf{H}_3)_2$], 3.6 (septet, *J*=6.6, 1H, SC**H**), 3.8 (s, 3H, NC$\mathbf{H}_3$), 7.35-7.40 (m, 2H, 2 x $\mathbf{H}_{arom}$) 7.62-7.68 (m, 1H, $\mathbf{H}_{arom}$), 7.87 (s, 1H, **H**-2), 8.42-8.45 (m, 1H, $\mathbf{H}_{arom}$). *Anal*. Calcd for $C_{13}H_{15}NOS$: C 66.92; H 6.48; N 6.00; S 13.74. Found C 66.59; H 6.51; N 6.14; S 13.22.

1-Methyl-3-butylthio-1,4-dihydro-4-oxoquinoline (**8e**) (R'=CH_3, R=C_4H_9); mp 54-56 °C(ethyl acetate), lit., [3,12] mp 53-55 °C.

1-Ethyl-3-methylthio-1,4-dihydro-4-oxoquinoline (**8f**) (R'=C_2H_5, R=CH_3); mp 91-94.5 °C(ethanol). EI MS (70 eV) m/z: 219 (88, M^+), 186 (100). ^{1}H NMR ($CDCl_3$), δ: 1.52 (t, *J*=7.3, 3H, $CH_2C\mathbf{H}_3$), 2.44 (s, 3H, SC$\mathbf{H}_3$), 4.21 (q, *J*=7.3, 2H, NC$\mathbf{H}_2$), 7.38-7.46 (m, 2H, $\mathbf{H}_{arom}$, 7.65-7.7 (m, 1H, $\mathbf{H}_{arom}$), 7.89 (s, 1H, **H**-2), 8.50-8.53 (m, 1H, $\mathbf{H}_{arom}$). ***Anal.*** Calcd for $C_{12}H_{13}NOS$: C 65.72; H 5.97; N 6.39; S 14.62. Found: C 65.49; H 5.88; N 6.67; S 14.41.

1-Propyl-3-methylthio-1,4-dihydro-4-oxoquinoline (**8g**) (R=CH_3, R'=C_3H_7): mp 113-115 °C (ethanol). EI MS (70 eV) m/z: 233 (63, M^+), 200 (100). ^{1}H NMR ($CDCl_3$), δ: 1.0 (t, *J*=7.4, 3H,$CH_2C\mathbf{H}_3$), 1.91 (sextet, *J*=7.4, 2H, $C\mathbf{H}_2CH_3$), 2.42 (s, 3H, SC$\mathbf{H}_3$), 4.08 (t, *J*=7.4, 2H, NC$\mathbf{H}_2$), 7.38-7.41 (m, 2H, 2 x $\mathbf{H}_{arom}$), 7.62 7.66 (m, 1H, $\mathbf{H}_{arom}$), 7.86 (s, 1H, **H**-2)8.48-8.5 (m, 1H, $\mathbf{H}_{arom}$). *Anal*. Calcd for $C_{13}H_{15}NOS$: C 66.92; H 6.48; N 6.00; S 13.74. Found: C 66.42; H 6.49; N 6.21; S 13.34.

1-Butyl-3-methylthio-1,4-dihydro-4-oxoquinoline (**8h**) (R=CH_3, R'=C_4H_9): mp 126-128 °C (ethanol). EIMS (70 eV) m/z: 247 (58, M^+), 214 (100). ^{1}H NMR ($CDCl_3$), δ: 1.00 (t, *J*=7.35, 3H, $CH_2C\mathbf{H}_3$), 1.44 (sextet, *J*=7.5, 2H, $CH_2C\mathbf{H}_2CH_3$), 1.81-1.91 (m, 2H, $CH_2C\mathbf{H}_2CH_2$), 2.43 (s, 3H, SC$\mathbf{H}_3$), 4.13 (t, *J*=7.35, 2H, NC$\mathbf{H}_2$), 7.37-7.43 (m, 2H, 2 x $\mathbf{H}_{arom}$), 7.63-7.71 (m, 1H, $\mathbf{H}_{arom}$), 7.87 (s, 1H, **H**-2), 8.50-8.53 (m, 1H, $\mathbf{H}_{arom}$). ***Anal.*** Calcd for $C_{14}H_{17}NOS$: C 67.98; H 6.93; N 5.66; S 12.96. Found: C 67.93; H 7.02; N 5.80; S 12.50.

1-Butyl-3-butylthio-1,4-dihydro-4-oxoquinoline (**8i**) (R'=R=C_4H_9): oil, EIMS (70 eV) m/z: 290 (29.5, M^+). ^{1}H NMR ($CDCl_3$), δ: 0.88 (t, *J*=7.2, 3H, $SCH_2CH_2CH_2C\mathbf{H}_3$), 0.99 (t, *J*=7.2, 3H, $NCH_2CH_2CH_2C\mathbf{H}_3$), 1.35-1.47 (m, 2 x 2H, $CH_2C\mathbf{H}_2CH_3$), 1.47-1.59 (m, 2H, $SCH_2C\mathbf{H}_2CH_2$), 1.81-1.91 (m, 2H, $NCH_2C\mathbf{H}_2CH_2$), 2.89 (t, *J*=7.35, 2H, SC$\mathbf{H}_2$), 4.13 (t, *J*=7.35, 2H, NC$\mathbf{H}_2$), 7.38-7.44 (m, 2H, 2 x $\mathbf{H}_{arom}$), 7.64-7.69 (m, 1H, $\mathbf{H}_{arom}$), 7.93 (s, 1H, **H**-2), 8.50-8.53 (m, 1H, $\mathbf{H}_{arom}$). ***Anal.*** Calcd for $C_{17}H_{23}NOS$: C 70.55; H 8.01; N 4.84; S 11.08. Found: C 70.55; H 8.14; N 4.81; S 11.00.

1-Ethyl-3-ethylthio-1,4-dihydro-4-oxoquinoline (**8j**) (R'=R=C_2H_5): mp 85-87 °C (ethanol). EIMS (70 eV) m/z: 233 (100, M^+), 205 (54). ^{1}H NMR ($CDCl_3$), δ: 1.22 (t, *J*=7.3, 3H, $SCH_2C\mathbf{H}_3$), 1.52 (t, *J*=7.3, 3H,

$NCH_2C\mathbf{H}_3$), 2.92 (q, *J*=7.3 2H, $SC\mathbf{H}_2$), 4.20 (q, *J*=7.3, 2H, $NC\mathbf{H}_2$), 7.38-7.45 (m, 2H, 2 x $\mathbf{H}_{arom}$), 7.64-7.70 (m, 1H, $\mathbf{H}_{arom}$), 7.96 (s, 1H, **H**-2), 8.50-8.53 (m, 1H, $\mathbf{H}_{arom}$). *Anal*. Calcd for $C_{13}H_{15}NOS$: C 66.92; H 6.48; N 6.00; S 13.74. Found: C 67.21; H 6.71; N 5.62; S 13.42.

1-Propyl-3-propylthio-1,4-dihydro-4-oxoquinoline (**8k**) (R'= R=C_3H_7): oil. EIMS (70 eV) m/z: 261 (37, M^+), 219 (100). ^{1}H NMR ($CDCl_3$), δ: 0.98 (t, *J*=7.3, 3H, $SCH_2CH_2C\mathbf{H}_3$), 1.02 (t, *J*=7.3, 3H, $NCH_2CH_2C\mathbf{H}_3$), 1.61 (sextet, *J*=7.3, 2H, $SCH_2C\mathbf{H}_2CH_3$), 1.9 (sextet, *J*=7.3, 2H, $NCH_2C\mathbf{H}_2CH_3$), 2.85 (t, *J*=7.35, 2H, $SC\mathbf{H}_2$), 4.09 (t, *J*=7.35, 2H, $NC\mathbf{H}_2$), 7.37-7.43 (m, 2H, 2 x $\mathbf{H}_{arom}$), 7.63-7.69 (m, 1H, $\mathbf{H}_{arom}$), 7.94 (s, 1H, **H**-2), 8.49-8.52 (m, 1H, $\mathbf{H}_{arom}$). *Anal*. Calcd for $C_{15}H_{19}NOS$: C 68.93; H 7.33; N 5.36; S 12.27. Found: C 69.11; H 7.21; N 5.62; S 12.02.

1-Benzyl-3-benzylthio-1,4-dihydro-4-oxoquinoline (**8l**) (R'=R= $C_6H_5CH_2$): mp 85-87 °C (ethanol). EIMS (70 eV) m/z: 357 (63, M^+), 324 (100). ^{1}H NMR ($CDCl_3$), δ: 4.11 (s, 2H, $SC\mathbf{H}_2C_6H_5$), 5.14 (s, 2H, $NC\mathbf{H}_2C_6H_5$), 6.87-6.90 (m, 2H, 2 x $\mathbf{H}_{arom}$), 7.08-7.56 (m, 11H, 11 x $\mathbf{H}_{arom}$), 7.65 (s, 1H, **H**-2), 8.51-8.55 (m, 1H, $\mathbf{H}_{arom}$). *Anal*. Calcd for $C_{23}H_{19}NOS$: C 77.28; H 5.36; N 3.92; S 8.97. Found: C 77.21; H 5.71; N 3.72; S 9.07.

Preparation of 3-alkylthio-1,4-dihydro-4-oxoquinolines (**6**) from sulfides (**1**)

A mixture of diquinolinyl sulfide (**1**) (5 mmol), potassium methoxide (2.45 g, 35 mmol) in 20 mL of dry DMSO was stirred at 50 °C for 1 h. It was then cooled to rt and poured into 50 mL of 5 % aqueous sodium hydroxide. The aqueous-DMSO solution was alkylated on strirring with 6.1 mmol of alkyl iodide at rt-50 °C for 1-4 h in the manner described in Table 3.

The mixture was then cooled to rt and dialkyl derivative (**8**) was extracted with chloroform (5 x 10 mL). Compound (**8**) was then isolated in a typical manner. The aqueous layer was neutralized at 10 °C with 20 % sulfuric acid up to pH 5.5. The solid deposited was filtered off and dried on air. The filtrate was then subjected to a continuous extraction with chloroform within 2 h. The chloroform extract was dried with anhydrous sodium sulfate. The solvent was then stripped off to give the second crop of quinolinone (**6**). Both crops of product (**6**) were combined and recrystallized from ethanol.

3-Methylthio-1,4-dihydro-4-oxoquinoline (**6a**): mp 171-173 °C, lit.,[14] mp 173-175 °C.

3-Ethylthio-1,4-dihydro-4-oxoquinoline (**6b**): mp 156-158 °C, lit., [9] mp 158-159 °C.

3-Propylthio-1,4-dihydro-4-oxoquinoline (**6c**): mp 137-139 °C, lit.,[15] mp 137-138 °C.

3-Butylthio-1,4-dihydro-4-oxoquinoline (**6d**): mp 143-145 °C. EIMS (70 eV) m/z: 233 (77, M^+), 177 (100). ^{1}H NMR ($CDCl_3$), δ: 0.83 (t, *J*=7.2, 3H, $CH_2C\mathbf{H}_3$), 1.36 (sextet, *J*=7.2, 2H, $C\mathbf{H}_2CH_3$), 1.53 (quintet, *J*=7.2, 2H, $C\mathbf{H}_2CH_2$), 2.83 (t, *J*=7.2, 2H, $SC\mathbf{H}_2$), 7.40-7.45 (m, 1H, $\mathbf{H}_{arom}$), 7.63-7.68 (m, 1H, $\mathbf{H}_{arom}$), 8.34 (s, 1H, **H**-2), 8.45-8.48 (m, 1H, $\mathbf{H}_{arom}$), 12.06 (br s,1H, N-**H**). *Anal*. Calcd for $C_{13}H_{15}NOS$: C 66.92; H 6.48; N 6.00; S 13.74. Found: C 67.07; H 6.21; N 6.12; S 13.38.

3-Benzylthio-1,4-dihydro-4-oxoquinoline (**6e**): mp 186-188 °C, lit.,[9] mp 186-188 °C.

O-Demethylation of 4-methoxy-3-methylthioquinoline (**4a**) to 3-methylthio-1,4-dihydro-4-oxoquinoline (**6a**)

A mixture of 1.02 g (*ca.* 5 mmol) of **4a**, 1.06 g (15 mmol) of potassium methoxide and 20 mL of DMSO was stirred at 50 °C for 1 h. It was then cooled to rt, diluted with 20 mL of water and neutralized up to pH 5.5 at rt with 10% sulfuric acid. The solid was filtered off and air dried. The filtrate was then subjected to a continuous extraction with chloroform within 2 h. The chloroform extract was dried with anhydrous sodium sulfate. The solvent was then stripped off to give the second crop of quinolinone (**6a**). Both crops were combined and boiled in 10 mL of ethanol and filtered in hot. The filtrate was evaporated to dryness to give 0.91 g (96 %) of 3-methylthio-4-oxoquinoline (**6a**) with mp 164-167 °C. It was recrystallized from ethanol to give the solid with mp 171-173 °C, lit.,[14] mp 173-175 °C.

REFERENCES

Part LXXVI. in the Series of Azinyl Sulfides

1. A. Birch, R. Davies, L. Maclean, and K. Robinson, *J. Chem. Soc., Perkin Trans. I*, 1994, 387.
2. K. Ikezono, S. Fujita, M. Umezato, E. Hosoki, Y. Toba, A. Kusunoki, and S. Shintani, *Arznei.-Forsch*., 1992, **42**, 1200.
3. R. V. Davies, J. Fraser, K. J. Nichol, R. Parkinson, M. F. Sim, and D .B. Yates, Ger. 30 11 994 A1 (16.10.1980) (*Chem. Abstr*., 1981, **94**, P 83968m).
4. R. V. Davies, J. Fraser, and K. J. Nichol, E P 0 206 616 A2 (1986) (*Chem. Abstr*., 1987, **107**, P 58881g).
5. S. Boryczka, A. Maślankiewicz, M. Wyszomirski, T. Borowiak, and M. Kubicki, *Rec. Trav. Chim. Pays-Bas*, 1990, **109**, 509.
6. A. Maślankiewicz and E. Bębenek, *Polish J. Chem.*, 1999, **73**, 1783.
7. A. Maślankiewicz, *Polish J. Chem.*, 1985, **59**, 511.
8. A. Maślankiewicz and S. Boryczka, *Rec. Trav. Chim. Pays-Bas,* 1993, **112**, 519.
9. A. Maślankiewicz and S. Boryczka, *J. Heterocycl. Chem*., 1993, **30**, 1623.
10. K. Pluta, *J. Heterocycl. Chem*., 1992, **29**, 1599.
11. K. Pluta, *J. Heterocycl. Chem*., 1995, **32**, 1245.
12. M. Rudnik and A. Maślankiewicz, *Heterocycles*, 1999, **51**, 2731.
13. S. Boryczka and A. Maślankiewicz, *Polish J. Chem*., 1997, **71**, 519.
14. D. T. Connor and M. von Strandtmann, *J. Heterocycl. Chem.,* 1978, **15**, 113.
15. R. J. Ife, T. H. Brown, D. J. Keeling, C. A. Leach, M. L. Meeson, M. E. Parsons, D. R. Reavill, C. J. Theobald, and K. J. Wiggall, *J. Med. Chem*., 1992, **35**, 3413.