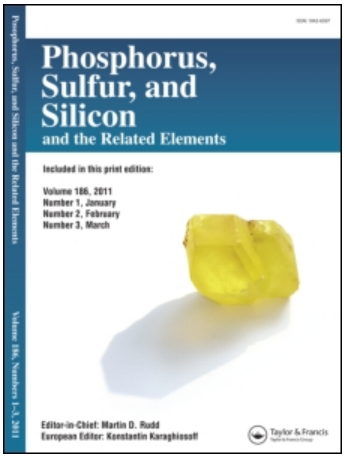

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Synthesis and Transformations of Substituted 3,3'-Diquinolinyl Sulfides

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Synthesis and Transformations of Substituted 3,3′-Diquinolinyl Sulfides

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*Reactions of the 1,4-dithiin ring opening in 1,4-dithiinodiquinoline **1** with selected oxygen nucleophiles followed by S- and N-alkylation led to sulfides possessing one or two quinolinyl or quinolonyl units. Diquinolinyl sulfides **2** were transformed into quinolinyl-quinolonyl sulfides **3** or diquinolonyl sulfides **9** via thermal rearrangement (the O-N alkyl migration) or hydrolysis of the alkoxy and alkylthio groups with the hydrochloric acid-ethanol mixture.*

Keywords 1,4-dithiinodiquinoline; 4(1H)-quinolones; diquinolyl sulfides; ring opening

INTRODUCTION

Substituted 4-quinolones are the quinoline derivatives of great interest because of a broad spectrum of activity, mainly antibacterial[1] and recently anticancer activity.[2–4] Some substituted quinolinyl sulfides and disulfides exhibit antibacterial,[5–8] antidepressant,[9] and very recently, antiproliferative activity.[10,11] Whereas 2,2′- and 4,4′-diquinolinyl sulfides most often were synthesized from substituted 2- and 4-haloquinolines, synthesis of other x,x-diquinolinyl sulfides (x = 2–4) is fatiguing and troublesome.[12] Our original conception of the 1,4-dithiin ring opening reactions in isomeric 1,4-dithiinodiquinolines with various O-, S-, Se-, N- and C-nucleophiles have brought very convenient and efficient synthesis of 2,3′-, 3,3′- and 3,4′-diquinolinyl sulfides.[13] Very recently we found 2,2′-disubstituted -3,3′-diquinolinyl sulfides to be excellent substrates for the synthesis of heteropentacenes.[14]

In continuation we would like to report the synthesis of the title compounds by the 1,4-dithiin ring opening reactions in

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LXXXIII in the series of Azinyl Sulfides.
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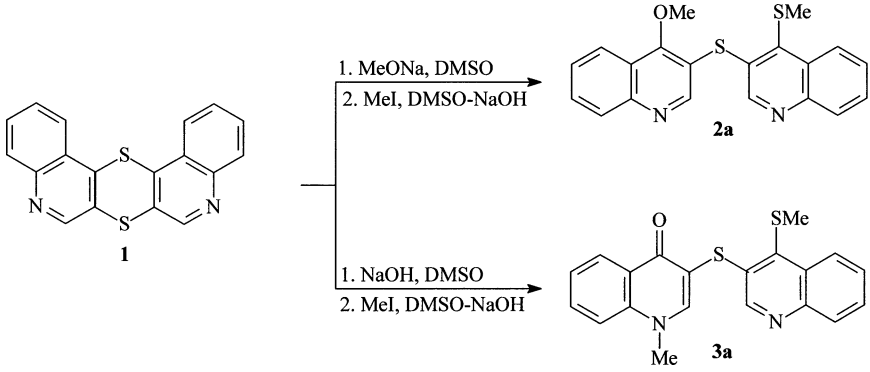
1,4-dithiinodiquinoline (common name: isothioquinanthrene) **1** with selected O-nucleophiles and further transformations to sulfides possessing one or two 4(1H)-quinolone units.

RESULTS AND DISCUSSION

The dithiin ring opening reactions in isothioquinanthrene **1** with sodium methanolate and sodium hydroxide led, after the methylation stage, to two isomeric 3,3′-diquinolinyl sulfides (**2a** and **3a**, Scheme 1).[13d] Both sulfides showed unexpected ^{1}H NMR spectroscopic effects (a significant shielding and deshielding of some protons) being a result of the conformations with donor–acceptor interactions of the heteroatoms as concluded from their X-ray analysis.[15,16]

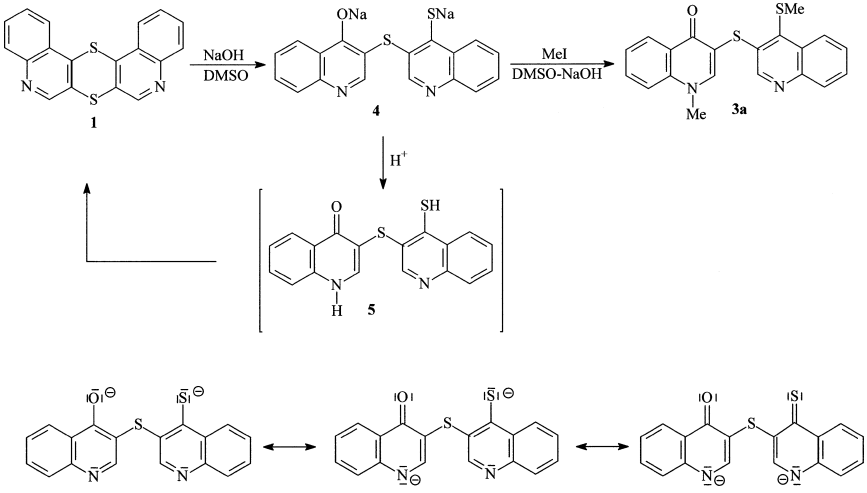


SCHEME 1

The unexpected sulfide **3a**, possessing one 4(1H)-quinolone unit, prompted us to further study the reactions of isothioquinanthrene **1** with O-nucleophiles such as sodium and potassium hydroxides and sodium alkoxides.

The 1,4-dithiin ring opening reactions in isothioquinoline **1** with O-nucleophiles were carried out in DMSO at 70°C. The progress of the reaction was followed by observation of a color of the reaction mixture (a change of yellow to deep red) and dissolution of a suspension of isothioquinanthrene **1** into a solution during the course of the reaction (in the end of this stage the reaction mixture became a transparent solution). The reaction mixture was poured into a threefold volume of 15% aqueous sodium hydroxide solution and was alkylated with alkyl halides to form the final product. All of the discussed reactions proceeded with a cleavage of only one $C_{quinolinyl}$–S bond.

The reaction of isothioquinanthrene **1** with powdered sodium hydroxide led to a disodium salt of 4-hydroxy-4′-mercapto-3,3′-diquinolinyl sulfide **4** as a primary product, which was soluble in DMSO. The DMSO-aqueous NaOH solution of sulfide **4**, when alkylated with methyl iodide, gave the final product as an insoluble solid. The final product was identified as 1-methyl-1,4-dihydro-4-oxo-4′-methylthio-3,3′-diquinolinyl sulfide **3a**. Direct acidification of the salt **4** with diluted hydrochloric acid to pH = 7 to obtain free 1,4-dihydro-4-oxo-4′-mercapto-3,3′-diquinolinyl sulfide **5** was unsuccessful because of a tendency of intramolecular cyclization to form back to isothioquinanthrene **1**. The unexpected structure of sulfide **3a** was the result of the alkylation of sodium salt **4** possessing three nucleophilic centers, i.e., the oxygen, nitrogen, and sulfur atoms (Scheme 2).



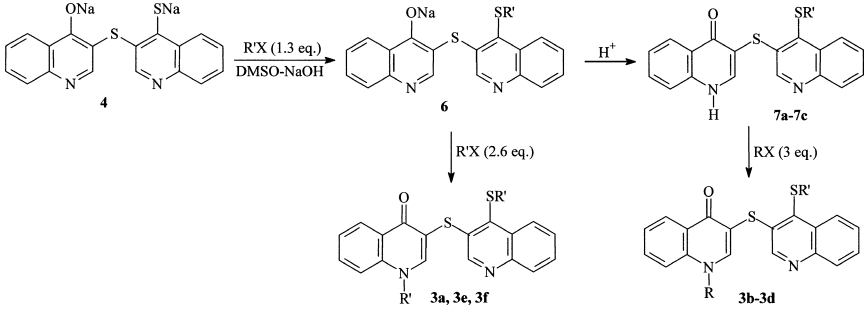
SCHEME 2

Since the most nucleophilic center is at the sulfur atom the alkylation stage with only 1.3 equivalents of alkylating agents (methyl iodide, ethyl iodide, and benzyl chloride) proceeded mainly as an S-alkylation. Such a product can be isolated after acidification of the reaction mixture with diluted hydrochloric acid to pH = 9 as sulfides **7a–7c**, possessing one quinolinyl and one 4(1H)-quinolonyl units. Only an excess of the alkylating agent enables further alkylation of the quinolonyl unit to form the N-alkyl derivatives **3a–3f**. When 2.6 equivalents of the alkylating agent (methyl iodide) were used, both sulfide **3a** (49%) and sulfide **7a** (34%) were obtained. Only 4 equivalents of the alkylating

TABLE I Reactions of Isothioquinanthrene 1 With Selected Oxygen Nucleophiles in DMSO at 70°C

No.	Nucleophile	Alkylating Agent (Equivalents)	Products (%) R, R′
1	EtONa	EtI (1.3)	**2c** R = R′ = Et (87)
2	$PhCH_2ONa$	MeI (1.3)	**2d** R = $PhCH_2$, R′ = Me (92)
3	$PhCH_2ONa$	$PhCH_2Cl$ (1.3)	**2e** R = R′ = $PhCH_2$ (90)
4	NaOH	MeI (1.3)	**7a** R = H, R′ = Me (88)
5	NaOH	MeI (4)	**3a** R = R′ = Me (85)
6	NaOH	MeI (2.6)	**3a** R = R′ = Me (49), **7a** R = H, R′ = Me (34)
7	NaOH	EtI (1.3)	**7b** R = H, R′ = Et (85)
8	NaOH	EtI (4)	**3e** R = R′ = Et (76)
9	NaOH	$PhCH_2Cl$ (1.3)	**7c** R = H, R′ = $PhCH_2$ (89)
10	NaOH	$PhCH_2Cl$ (4)	**3f** R = R′ = $PhCH_2$ (87)
11	KOH	MeI (4)	**3a** R = R′ = Me (11), **7a** R = H, R′ = Me (11), **8** R = R′ = Me (63)

agents gave sulfides **3a**, **3e**, and **3f** in good yields (76–87%; Table I, Scheme 3).



SCHEME 3

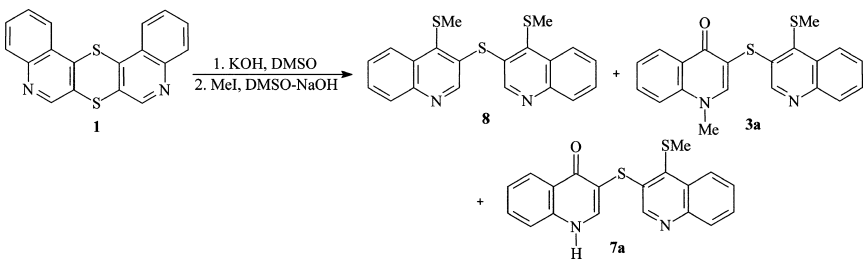
In the literature one can find procedures of alkylation of 4(1H)-quinolones but they need a boiling ethanolic solution of sodium or potassium hydroxides,[17,18] anhydrous aprotic solvent and sodium hydride,[19] trialkyl phosphate,[20] or a ten-fold amount of alkylating agent.[18] Our procedure of alkylation in the mixture of DMSO-15% aqueous NaOH (1:3) at room temperature, which was widely verified during synthesis of quinolinyl sulfides from quinolinethiolates and alkylating agents (alkyl halides, dialkyl sulfates and alkylene ditosylates),[13a,13c–13f,21] is very simple and efficient and enables direct observation of the alkylation progress and direct separation of insoluble alkylated products from a soluble acidic substrate by filtration.

TABLE II Alkylations of Sulfides 7 With Alkylating Agents in the DMSO-15% NaOH Mixture

No.	Sulfide	Alkylating Agent (Equivalents)	Products (%) R, R′
1	**7a**	MeI (3)	**3a** R = R′ = Me (88)
2	**7a**	EtI (3)	**3b** R = Et, R′ = Me (79)
3	**7a**	$PhCH_2Cl$ (3)	**3c** R = $PhCH_2$, R′ = Me (86)
4	**7b**	MeI (3)	**3d** R = Me, R′ = Et (87)
5	**7b**	EtI (3)	**3e** R = R′ = Et (76)
6	**7c**	$PhCH_2Cl$ (3)	**3f** R = R′ = $PhCH_2$ (89)

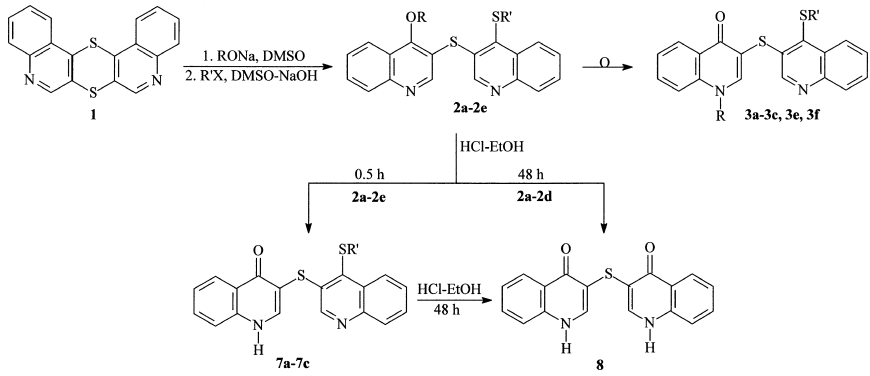
The isolated sulfides **7a–7c** after acidification can be further alkylated in the mixture of DMSO-15% aqueous NaOH (1:3) with the same or another alkylating agent. This method enables us to obtain substituted quinolonyl-quinolinyl sulfides **3** with the same (**3a**, **3e**, and **3f**) or different alkyl groups R and R′ (**3b–3d**) attached to the sulfur and nitrogen atoms in good yields (76–89%) (Tables I and II).

Because of hydroscopic properties of sodium hydroxide we tried to use the less hydroscopic potassium hydroxide in the dithiin ring opening reaction. Reaction of isothioquinanthrene **1** with potassium hydroxide in DMSO proceeded very smoothly and led unexpectedly, after methylation, to 4,4′-dimethylthio-3,3′-diquinolinyl sulfide **8** (63%) together with sulfide **3a** (11%) and sulfide **7a** (11%; Scheme 4).



SCHEME 4

Since the reactions of isothioquinanthrene **1** with sodium alkoxides run faster than with sodium hydroxide,[13d] we examined reactions with sodium ethoxide and sodium benzyloxide in DMSO at 70°C. After alkylation with alkyl halides (ethyl iodide and benzyl chloride), 4-alkoxy-4′-alkylthio-3,3′-diquinolinyl sulfides **2c–2e** were isolated in 87–92% yield (Scheme 5).



SCHEME 5

We reported the thermal O–N migration of the methyl group in 4-methoxy-3-methylthioquinoline to give 1-methyl-3-methylthio-4(1H)-quinolone in high yield[22] and this result prompted us to examine 4-alkoxy-4′-methylthio-3,3′-diquinolinyl sulfides **2a–2e**, possessing the methoxy, ethoxy, and benzyloxy groups. These sulfides heated at 200°C in or without a solvent and underwent the thermal rearrangement to give the products of the alkyl group migration, i.e., 1-alkyl-quinolonyl-quinolinyl sulfides **3a–3c**, **3e**, and **3d** (alkyl = methyl, ethyl, and benzyl) in a 55–90% yield (Table III).

This rearrangement is the evidence for the 4-alkoxyquinoline structure of sulfides **2** and 1-alkyl-4(1H)-quinolone structure of sulfides **3**. Structures of isomeric sulfides **2a** and **3a** were determined on the basis of the ^{1}H NMR experiments (COSY, HETCOR, and NOE) and finally confirmed by the X-ray analysis of their monocrystals.[15,16] We observed a characteristic downfield shift of the H-5 proton signal in sulfides **2** and **3** but we observed only an upfield shift of the H-8 proton in sulfides **3** in comparison with the appropriate signals in unsubstituted quinoline.

TABLE III The Thermal Rearrangement of Sulfide 2 to Sulfide 3. EEDG = Monoethyl Ether of Diethylene Glycol

No.	Sulfide R, R′	Conditions (°C/min.)	Products (%)
1	**2a** R = R′ = Me	200/60, in EEDG	**3a** (61)
2	**2a** R = R′ = Me	200/30 neat	**3a** (90)
3	**2b** R = Et, R′ = Me	200/30 neat	**3b** (55)
4	**2c** R = $PhCH_2$, R′ = Me	200/30 neat	**3c** (58)
5	**2d** R = R′ = Et	200/30 neat	**3e** (60)
6	**2e** R = R′ = $PhCH_2$	200/30 neat	**3f** (56)

The shielding and deshielding of these protons are the results of the peri interactions between the hydrogen atoms and the 4-and 1-substituents.

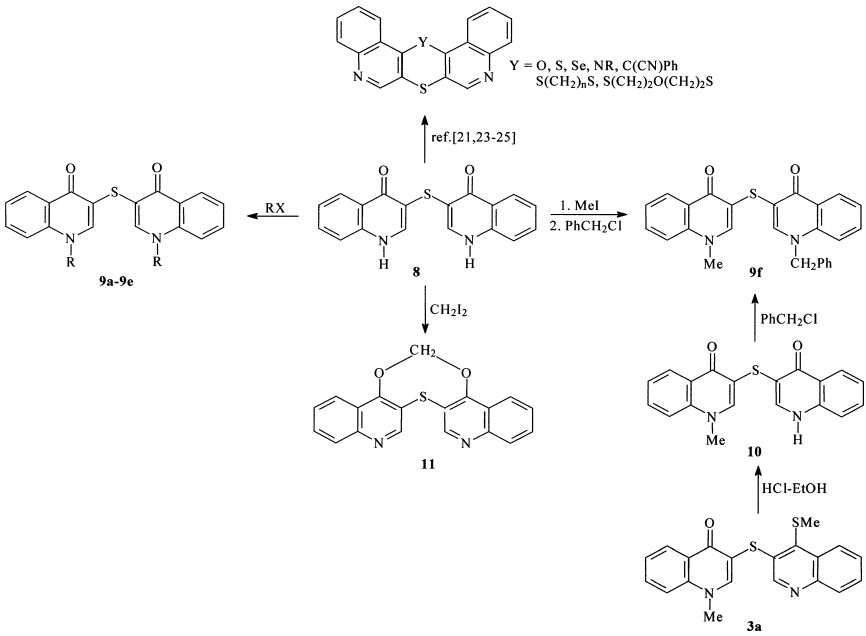
We found the alkoxy groups in 4-alkoxy-4′-alkylthio-3,3′-diquinolinyl sulfides **2a–2e** to be susceptible to hydrolysis in acidic conditions. Heating these sulfides in the hydrochloric acid-ethanol mixture (1:1) for 0.5 h led directly to hydrochlorides of N-unsubstituted quinolonyl-quinolinyl sulfides **7a–7c**. When the heating of sulfides **2a–2c** was carried for 48 h, not only the hydrolysis of the alkoxy group but also the hydrolysis of the alkylthio group was observed followed by an evolution of alkanethiol. After cooling we isolated hydrochloride of diquinolonyl sulfide (hydrochloride of 3,3′-bis(1,4-dihydro-4-oxoquinolinyl) sulfide) **8**[23] in a high yield (Table IV, Scheme 5). To avoid the emission of odorous volatile alkanethiol to the atmosphere, we trapped this thiol in an aqueous sodium hydroxide solution and oxidized it with potassium permangante.

The hydrochloride function in hydrochlorides of sulfides **7a–7c** and **8** can be easily withdrawn to give free sulfides **7a–7c** and **8** by dissolving in the mixture of DMSO-15% aqueous NaOH (1:3) and precipitating with hydrochloric acid. As expected, sulfides **7a** and **7b** underwent the reaction with the hydrochloric acid-ethanol mixture (1:1) for 48 h to give sulfide **8** in an 87% and 94% yield (Table IV).

It is worth noting that N-unsubstituted diquinolonyl sulfide **8** is an excellent initial compound in the synthesis of various pentacyclic heterocyclodiquinolines.[21,23–25] Sulfide **8** as a 4(1H)-quinolone derivative can be alkylated with selected alkyl halides. Alkylation in the same conditions as described above but with more equivalents of alkyl halides and longer reaction time proceeded as the N-alkylation, giving

TABLE IV Reactions of Sulfides 2, 3a, and 7 With the Hydrochloric Acid-Ethanol Mixture

No.	Sulfide R, R′	Conditions (h)	Products (%)
1	**2a** R = R′ = Me	0.5	**7a** (91)
2	**2b** R = Et, R′ = Me	0.5	**7a** (87)
3	**2c** R = $PhCH_2$, R′ = Me	0.5	**7a** (80)
4	**2d** R = R′ = Et	0.5	**7b** (88)
5	**2e** R = R′ = $PhCH_2$	0.5	**7c** (77)
6	**2a** R = R′ = Me	48	**8** (94)
7	**2b** R = Et, R′ = Me	48	**8** (94)
8	**2c** R = $PhCH_2$, R′ = Me	48	**8** (91)
9	**2d** R = R′ = Et	48	**8** (94)
10	**7a** R = H, R′ = Me	48	**8** (94)
11	**7b** R = H, R′ = Et	48	**8** (87)
12	**3a** R = R′ = Me	48	**10** (87)



SCHEME 6

symmetrical N,N-disubstituted diquinolonyl sulfides (bis(1-alkyl-1,4-dihydro-4-oxo-3-quinolinyl) sulfides) **9a–9e**, possessing two identical alkyl groups, in good yield (Table II, Scheme 6). In order to obtain unsymmetrical N,N-disubstituted diquinolonyl sulfides (possessing two different alkyl groups), we carried out consecutive alkylation with two different alkyl halides in the mixture of DMSO-15% aqueous NaOH. Sulfide **8** was first alkylated with 1.5 equivalents of methyl iodide to give the monomethyl derivative, i.e., 1-methylbis(1,4-dihydro-4-oxo-3-quinolinyl) sulfide **10** as the main product, which was soluble in the reaction mixture, and a small amount of the dimethyl derivative, i.e., sulfide **9a** (11%, insoluble, isolated by filtration). Sulfide **10** next was alkylated with 3 equivalents of benzyl chloride to give the final product as an insoluble compound—1-methyl-1′-benzylbis(1,4-dihydro-4-oxo-3-quinolinyl) sulfide **9f** in a good yield (71%, Table V).

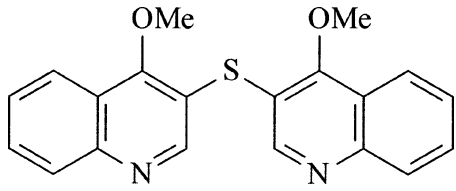
An alternative way to obtain sulfide **9f** is based on the observation of a behavior of the substituents in sulfides **2** and **3** during the reaction with the hydrochloric acid-ethanol mixture. Whereas the alkoxy and alkylthio groups in position 4 are susceptible to hydrolysis (a cleavage of the C—O and C—S bonds) during the reaction, the alkyl group in position 1 is quite stable (a stability of the C—N bond). The reaction of

TABLE V Alkylations of Sulfides 8 and 10 With Alkylating Agents in the DMSO-15% NaOH Mixture

No.	Sulfide	Alkylating Agent (Equivalents)	Conditions (°C/h)	Products (%) R R′
1	**8**	MeI (6)	20/24	**9a** R = R′ = Me (86)
2	**8**	EtI (6)	20/24	**9b** R = R′ = Et (22)
3	**8**	EtI (6)	60/24	**9b** R = R′ = Et (59)
4	**8**	PrI (6)	60/24	**9c** R = R′ = Pr (55)
5	**8**	AllBr (6)	20/24	**9d** R = R′ = All (76)
6	**8**	$PhCH_2Cl$ (6)	20/24	**9e** R = R′ = $PhCH_2$ (86)
7	**8**	MeI (1.5), $PhCH_2Cl$ (3)	20/48	**9a** (11), 9fR = Me, R′ = $PhCH_2$ (71)
8	**8**	CH_2I_2 (3)	60/24	**11** (54)
9	**8**	$BrCH_2CH_2CH_2Br$ (3)	60/24	**9d** R = R′ = All (40)
10	**10**	$PhCH_2Cl$ (3)	20/24	**9f** R = Me, R′ = $PhCH_2$ (87)

sulfide **3a** with the hydrochloric acid-ethanol mixture for 48 h led to sulfide **10** (in an 87% yield), which when alkylated in the DMSO-NaOH mixture with benzyl chloride gave sulfide **9f** in a good yield (87% yield, Scheme 6).

Sulfide **8** as a two-functional substrate can be alkylated with two-functional alkylating agents to form crown ethers containing two or four 4-quinolone moieties, similar to those crown thioethers containing two or four quinoline moieties obtained from dithiinodiquinolines.[21] The reaction of sulfide **8** with diiodomethane in the DMSO-NaOH mixture at 60°C for 24 h led to a product of intramolecular bisalkylation (the substrate/methylene group ratio 1:1, m/z = 332 (M, 100% in a 54% yield. Steric requirements in sulfide **8** excluded an intramolecular N,N-bisalkylation to form an N-CH_2-N fragment. The ^{1}H NMR spectrum analysis revealed an absence of the upfield shift of the H-8 proton (δ = 8.04 ppm), which was typical for 1-alkyl-4(1H)-quinolones and a weaker downfield shift of the H-5 proton (δ = 8.28 ppm) instead of the expected values (δ = 7.36–7.41 ppm and δ = 8.41–8.43 ppm, respectively, in compounds **9a–9d**). The methylene protons are strongly shifted downfield (δ = 7.10 ppm), even more than for the $ArOCH_2OAr$ region (δ = 6.1–6.7 ppm) and much more than in the $ArNCH_2NAr$ region (δ = 4–4.5 ppm).[26] More evidence came from the ^{13}C NMR spectrum. We observed the C_4 carbon at 158.90 ppm, which is close to the carbon signal of C_4-OCH_3 at 162.7 ppm[27] in 4,4′-dimethoxy-3,3′-diquinolinyl sulfide **12** (Scheme 7), but is unlike the carbon C_4=O signal at 177.7 ppm[28] in sulfide **9a**. Also the C_8 carbon signal at 130.73 ppm is similar to the appropriate signal at 130.2 ppm[27] in sulfide **12** but unlike the signal in sulfide **9a** (116.2 ppm).[28] The ^{1}H and ^{13}C NMR effects suggest the



12

SCHEME 7

formation of an O-CH_2-O fragment with some steric strains and the structure of compound **11** as dioxathia-8-crown-3 (Scheme 6). Reaction of sulfide **8** with 1,2-dibromoethane led to a polymeric product and with 1,3-dibromopropane led mainly to a product of subsequent elimination of hydrobromic acid instead of further alkylation, i.e., sulfide **9d**.

In conclusion we report a simple method of synthesis of selected substituted diquinolinyl **2**, quinolinyl-quinolonyl **3**, diquinolonyl sulfides **9**, and dioxathia-8-crown-3 **11** via 1,4-dithiin ring opening in 1,4-dithiinodiquinoline **1** followed by the S-, O-, and N-alkylation; the O-N alkyl migration; and the transformation of the alkoxy and alkylthio substituents.

EXPERIMENTAL

Melting points were determined in open capillary tubes on a Boetius melting point apparatus and are uncorrected. The ^1H and ^{13}C NMR spectra were recorded on a Varian Unity-Inova-300 spectrometer at 300 MHz and 75 MHz in deuteriochloroform and dimethyl sulphoxide-d_6 with tetramethylsilane as the internal standard. Electron impact mass spectra (EI MS) were run on a LKB 9000S at 70 eV and a chemical ionization mass spectrum (CI MS) was run on a Finnigan MAT 95 spectrometer.

Isothioquinanthrene (**1**) was obtained from thioquinanthrene (the exhaustive sulfuration product of quinoline with elemental sulfur)[29] via ring opening–ring closure reactions.[30] Sulfides **2a** and **2b** were obtained from reactions of isothioquinanthrene **1** with sodium alkoxides followed by the S-alkylation with alkyl halides according to the described procedure.[13d]

Reactions of Isothioquinanthrene 1 with Sodium Alkoholates

To a suspension of isothioquinanthrene **1** (0.32 g, 1 mmol) in 10 mL of dry DMSO at 70°C, sodium ethoxide (0.20 g, 3 mmol) or sodium

benzyloxide (0.39 g, 3 mmol) was added. The mixture was stirred for 30 min, then cooled and poured into 30 mL of 15% aqueous sodium hydroxide. Residual dithiin **1** was filtered and the filtrate was stirred with alkyl halides (methyl iodide, ethyl iodide, and benzyl chloride, 1.3 mmols, Table I). The resulting solid was collected by filtration, washed with water, and air-dried. The crude product was purified by column chromatography (silica gel 60, chloroform) to give sulfides **2c–2e**.

4-Ethoxy-4′-ethylthio-3,3′-diquinolinyl Sulfide 2c, Viscous Oil

^{1}H NMR ($CDCl_3$) δ 1.31 (t, 3H, J = 7.4 Hz, $SCH_2\mathbf{CH_3}$), 1.44 (t, 3H, J = 7.4 Hz, $OCH_2\mathbf{CH_3}$), 3.09 (q, 2H, J = 7.4 Hz, SCH_2), 4.46 (q, 2H, J = 7.4 Hz, OCH_2), 7.61, 7.65, 7.67 and 7.78 (4 m, 4H, H-6, H-6′, H-7 and H-7′), 8.01 and 8.12 (2dd, 2H, H-8 and H-8′), 8.20 and 8.55 (2dd, 2H, H-5 and H-5′), 8.28 and 8.85 (2s, 2H, H-2 and H-2′). EI MS (70 eV) m/z: 392 (M, 100), 363 (M-C_2H_5,30.0), 302 (M-$(C_2H_5)_2S$, 53.7). Anal. Calcd. for $C_{22}H_{20}N_2OS_2$ (392.53): C,67.32; H, 5.14; N, 7.14. Found: C, 67.22; H, 5.19; N, 7.01.

4-Benzyloxy-4′-methylthio-3,3′-diquinolinyl Sulfide 2d, Viscous Oil

^{1}H NMR ($CDCl_3$) δ: 2.50 (s, 3H, SCH_3), 5.43 (s, 2H, OCH_2) 7.27 and 7.35 (2 m, 5H, C_6H_5), 7.56, 7.64, 7.68 and 7.77 (4 m, 4H, H-6, H-6′, H-7 and H-7′), 8.02 and 8.14 (2dd, 2H, H-8 and H-8′), 8.12 and 8.50 (2dd, 2H, H-5 and H-5′), 8.33 and 8.87 (2s, 2H, H-2 and H-2′). CI MS (70 eV) m/z: 441 (M+1, 100), 393 (M-CH_3S, 24.1). Anal. Calcd. for $C_{26}H_{20}N_2OS_2$ (440.57): C, 70.88; H, 4.58; N,6.36: Found: C, 70.52; H, 4.62; N, 6.11.

4-Benzyloxy-4′-benzylthio-3,3′-diquinolinyl Sulfide 2e, Viscous Oil

^{1}H NMR ($CDCl_3$) δ: 4.14 (s, 2H, SCH_2), 5.39 (s, 2H, OCH_2), 7.08–7.38 (m, 10H, $2C_6H_5$), 7.56, 7.57, 7.65 and 7.77 (4 m, 4H, H-6, H-6′, H-7 and H-7′), 7.99 and 8.13 (2dd, 2H, H-8 and H-8′), 8.12 and 8.40 (2dd, 2H, H-5 and H-5′), 8.26 and 8.72 (2s, 2H, H-2 and H-2′). CI MS (70 eV) m/z: 517 (M+1, 4.0), 426 (M+1-$C_6H_5CH_2$, 22.9) 410 (M+1-$C_6H_5CH_2O$, 19.1), 358 (M+I-C_9H_5NS, 10.2), 319 (M+1-$(C_6H_5CH_2)_2O$, 71.3), 303 (M+1-$(C_6H_5CH_2)_2S$, 100). Anal. Calcd. for $C_{32}H_{24}N_2OS_2$ (516.67): C, 74.39; H, 4.68; N, 5.42. Found: C, 74.19; H, 4.58; N, 5.22.

Reactions of Isothioquinanthrene 1 with Sodium Hydroxide

To a suspension of isothioquinanthrene **1** (0.32 g, 1 mmol) in 10 mL of dry DMSO at 70°C, powdered sodium hydroxide (0.12 g, 3 mmol) was added. The mixture was stirred for 60 min, cooled, and poured into

30 mL of 15% aqueous sodium hydroxide. Residual dithiin **1** was filtered and the filtrate was stirred with alkyl halides (methyl iodide, ethyl iodide, and benzyl chloride, 2.6 and 4 equivalents at once, 1.3 equivalents in 1 mL of DMSO solution added drop by drop during 1 h, Table I). The resulting solid was collected by filtration, washed with water, and air-dried. The crude product was purified by column chromatography (silica gel 60, chloroform) to give sulfides **3a**, **3e**, and **3f** (Table I). The filtrate was acidified with diluted hydrochloric acid to pH = 9 and the resulting solid was collected by filtration, washed with water, and air-dried to give sulfides **7a–7c**.

1-Methyl-1,4-dihydro-4-oxo-4′-methylthio-3,3′-diquinolinyl sulfide **3a**, mp 252–253°C, lit.[13d] m.p. 252–253°C. ^{1}H NMR ($CDCl_3$) δ: 2.59 (s, 3H, SCH_3), 3.88 (s, 3H, NCH_3), 7.47, 7.60 and 7.74 (3m, 5H, H-6, H-6′, H-7, H-7′ and H-8), 7.98 (dd, 1H, H-8′), 8.17 and 8.42 (2s, 2H, H-2 and H-2′), 8.45 and 8.50 (2dd, 2H, H-5 and H-5′).

1-Ethyl-1,4-dihydro-4-oxo-4′-ethylthio-3,3′-diquinolinyl Sulfide 3e, m.p. 155–156°C

^{1}H NMR ($CDCl_3$) δ: 1.32 (t, 3H, J = 7.3 Hz, $SCH_2\mathbf{CH}_3$), 1.56 (t, 3H, J = 7.3 Hz, $NCH_2\mathbf{CH}_3$), 3.13 (q, 2H, J = 7.3 Hz, SCH_2), 4.26 (q, 2H, J = 7.3 Hz, NCH_2), 7.44, 7.58, 7.61 and 7.73 (4m, 4H, H-6, H-6′, H-7 and H-7′), 7.51 and 7.97 (2dd, 2H, H-8 and H-8′), 8.18 and 8.43 (2s, 2H, H-2 and H-2′), 8.49 and 8.53 (2dd, 2H, H-5 and H-5′). EI MS (70 eV) m/z: 392 (M, 13.9), 331 (M-C_2H_5S, 100), 302 (M-$(C_2H_5)_2S$, 17.4). Anal. Calcd. for $C_{22}H_{20}N_2OS_2$ (392.53): C, 67.32; H, 5.14; N, 7.14. Found: C, 67.18; H, 5.20; N, 7.03.

1-Benzyl-1,4-dihydro-4-oxo-4′-benzylthio-3,3′-diquinolinyl Sulfide 3f, m.p. 146–147°C

^{1}H NMR ($CDCl_3$) δ: 4.29 (s, 2H, SCH_2), 5.40 (s, 2H, NCH_2), 7.14–7.62 (m, 15H, $2C_6H_5$, H-6; H-6′, H-7, H-7′ and H-8), 7.95 (dd, 1H, H-8′), 8.20 and 8.50 (2s, 2H, H-2 and H-2′), 8.33 and 8.48 (2dd, 2H, H-5 and H-5′). CI MS (70 eV) m/z: 517 (M+1, 4.0), 426 (M+1-$C_6H_5CH_2$, 7.1) 410 (M+1-$C_6H_5CH_2O$, 13.5), 358 (M+1-C_9H_5NS, 100), 319 (M+1-$(C_6H_5CH_2)_2O$, 65.7), 303 (M+1-$(C_6H_5CH_2)_2S$, 22.1). Anal. Calcd. for $C_{32}H_{24}N_2OS_2$ (516.67): C, 74.39; H, 4.68; N, 5.42. Found: C, 74.30; H, 4.62; N, 5.26.

1,4-Dihydro-4-oxo-4′-methylthio-3,3′-diquinolinyl Sulfide 7a, m.p. 267–268°C, lit.[31] m.p. 268–269°C.

1,4-Dihydro-4-oxo-4′-ethylthio-3,3′-diquinolinyl sulfide **7b**, m.p. 262–263°C, lit.[31] m.p. 263–264°C.

1,4-Dihydro-4-oxo-4′-benzylthio-3,3′-diquinolinyl sulfide **7c**, m.p. 215–216°C.

^{1}H NMR (DMSO-d_6) δ: 4.42 (s, 2H, SCH_2), 7.22 and 7.32 (2m, 5H, C_6H_5), 7.48, 7.59, 7.68 and 7.76 (4m, 4H, H-6, H-6′, H-7 and H-7′), 7.78 and 7.94 (2dd, 2H, H-8 and H-8′), 8.21 and 8.30 (2dd, 2H, H-5 and H-5′), 8.36 and 8.63 (2s, 2H, H-2 and H-2′), 12.2 (broad, 1H, NH). CI MS (70 eV) m/z: 427 (M+1, 3.4), 319 (M+1-$C_6H_5CH_2OH$, 19.2), 303 (M+1-$C_6H_5CH_2SH$, 100). Anal. Calcd. for $C_{25}H_{18}N_2OS_2$ (426.55): C, 70.40; H, 4.25; N, 6.57. Found: C, 70.19; H, 4.35; N, 6.32.

Reactions of Isothioquinanthrene 1 with Potassium Hydroxide

To a suspension of isothioquinanthrene **1** (0.32 g, 1 mmol) in 10 mL of dry DMSO at 70°C, pellets of potassium hydroxide (0.17 g, 3 mmol) were added. The mixture was stirred for 20 min, cooled, and poured into 30 mL of 15% aqueous sodium hydroxide. Residual dithiin **1** was filtered off and the filtrate was stirred with methyl iodide (0.25 mL, 4 mmols). The resulting solid was collected by filtration, washed with water, and air-dried. The crude product was purified by column chromatography (silica gel 60, chloroform) to give 4,4′-dimethylthio-3,3′-diquinolinyl sulfide **8** (0.24 g, 63%, m.p. 142–143°C, lit.[13a] m.p. 142–143°C) and sulfide **3a** (0.04 g, 11%). The filtrate was acidified with diluted hydrochloric acid to pH = 9 and the resulting solid was collected by filtration, washed with water, and air-dried to give sulfides **7a** (0.04 g, 11%, m.p. 267–268°C, lit.[31] m.p. 268–269°C).

Alkylations of Sulfides 7 with Alkylating Agents

To a stirred solution of sulfide **7a–7c** (1 mmol) in the mixture of 2 mL of DMSO and 6 mL of 15% aqueous sodium hydroxide at 20°C, an alkyl halide (methyl iodide, ethyl iodide, and benzyl chloride, 3.6 mmol, Table II) was added. The mixture was stirred for 24 h. The resulting solid was collected by filtration, washed with water, and air-dried. The crude product was purified by column chromatography (silica gel 60, chloroform, chloroform-ethanol) to give sulfide **3b–3d** (Table II).

1-Ethyl-1,4-dihydro-4-oxo-4′-methylthio-3,3′-diquinolinyl Sulfide 3b, m.p. 149–150°C

^{1}H NMR ($CDCl_3$) δ: 1.56 (t, 3H, J = 7.3 Hz, CH_3), 2.60 (s, 3H, SCH_3), 4.27 (t, 2H, J = 7.3 Hz, NCH_2), 7.44, 7.59, 7.62 and 7.73 (4m, 4H, H-6, H-6′, H-7 and H-7′), 7.50 and 7.97 (2dd, 2H, H-8 and H-8′), 8.20 and 8.44 (2s, 2H, H-2 and H-2′), 8.48 and 8.51 (2dd, 2H, H-5 and H-5′). EI MS (70 eV) m/z: 378 (M, 5.6), 363 (M-CH_3, 5.6), 331 (M-CH_3S, 100), 302

(M-$C_2H_5SCH_3$, 15.3). Anal. Calcd. for $C_{21}H_{18}N_2OS_2$ (378.50): C, 66.64; H, 4.79; N, 7.40. Found: C, 66.49; H, 4.81; N, 7.24.

1-Benzyl-1,4-dihydro-4-oxo-4′-methylthio-3,3′-diquinolinyl Sulfide 3c, m.p. 201–202°C

^{1}H NMR ($CDCl_3$) δ: 2.60 (s, 3H, SCH_3), 5.41 (s, 2H, NCH_2) 7.20, 7.37 and 7.60 (3m, 10H, C_6H_5, H-6, H-6′, H-7, H-7′ and H-8), 7.99 (dd, 1H, H-8′), 8.28 and 8.52 (2s, 2H, H-2 and H-2′), 8.47 and 8.52 (2dd, 2H, H-5 and H-5′). CI MS (70 eV) m/z: 441 (M+1, 100), 393 (M+1-CH_3S, 18.2), 303 (M+1-$C_6H_5CH_2SCH_3$, 1.8). Anal. Calcd. for $C_{26}H_{20}N_2OS_2$ (440.67): C, 70.88; H, 4.58; N, 6.36. Found: C, 70.59; H, 4.62; N, 6.22.

1-Methyl-1,4-dihydro-4-oxo-4′-ethylthio-3,3′-diquinolinyl Sulfide 3d, m.p. 225–226°C

^{1}H NMR ($CDCl_3$) δ: 1.32 (t, 3H, J = 7.3 Hz, CH_3), 3.13 (t, 2H, J = 7.3 Hz, SCH_2), 3.87 (s, 3H, NCH_3), 7.46, 7.58, 7.60 and 7.74 (4m, 4H, H-6, H-6′, H-7 and H-7′), 7.45 and 7.96 (2dd, 2H, H-8 and H-8′), 8.14 and 8.42 (2s, 2H, H-2 and H-2′), 8.47 and 8.52 (2dd, 2H, H-5 and H-5′). EI MS (70 eV) m/z: 378 (M, 7.5), 349 (M-C_2H_5, 3.6), 317 (M-C_2H_5S, 100), 302 (M-$C_2H_5SCH_3$, 5.5). Anal. Calcd. for $C_{21}H_{18}N_2OS_2$ (378.50): C, 66.64; H, 4.79; N, 7.40. Found: C, 66.23; H, 4.84; N, 7.19.

The Thermal Rearrangement of Sulfides 2 to Sulfides 3

(a) Sulfide **2a–2e** (0.5 mmol) was heated in a test tube at 200°C for 30 min. After cooling the rearrangement product was extracted with chloroform and purified by column chromatography (silica gel 60, chloroform, chloroform-ethanol) to give sulfide **3a–3c**, **3e**, and **3f** (Table III).

(b) Sulfide **2a** (0.18 g, 0.5 mmol) was heated in 1 mL of boiling monoethyl ether of diethylene glycol for 1 h. After cooling the solution was poured into 5 mL of water and the resulting solid was collected by filtration, washed with water, and air-dried. The crude product was purified by column chromatography (silica gel 60, chloroform, chloroform-ethanol) to give sulfide 3a (0.11 g, 61%).

Reactions of Sulfides 2 and 3 with the Hydrochloric Acid-Ethanol Mixture

(a) A solution of sulfide, **2a–2e** (1 mmol) in 3 mL of the mixture of concentrated hydrochloric acid-ethanol (1:1) was refluxed for 30 min. After cooling the resulting solid was collected by filtration, washed with ethanol, and air-dried. The product was identified

as hydrochloride of sulfide **7a–7c** (m.p. 187–188°C, Belstein test, elementary analysis for hydrochloride of sulfide **7a**: calcd. for $C_{19}H_{14}N_2OS_2 \cdot 2HCl \cdot H_2O$ (441.39) C, 51.70; H, 4.11; N, 6.35; Cl, 16.06; S, 14.53. Found: C, 51.63; H, 3.93; N, 6.34; Cl, 16.06; S, 14.31). Neutral sulfides **7a–7c** were obtained from their hydrochlorides by dissolving in 6 mL of the mixture DMSO-15% aqueous sodium hydroxide (1:3) and precipitating with 10% hydrochloric acid to pH = 9. The resulting solid was collected by filtration, washed with water, and air-dried (Table IV).

(b) A solution of sulfide, **2**, **3a**, or **7** (1 mmol) in 10 mL of the mixture of concentrated hydrochloric acid-ethanol (1:1) was refluxed for 48 h. The volatile odorous alkanethiol leaking out of the condenser was trapped in a container with an aqueous solution of potassium permanganate and sodium hydroxide. After cooling the resulting solid was collected by filtration, washed with ethanol, and air-dried. The product was identified as hydrochloride of sulfide **8** (Belstein test, m.p. >300°C, lit.[23] m.p. >300°C, ^{1}H NMR spectrum as described in ref.[23]). Neutral sulfide **8** was obtained from its hydrochloride by dissolving in 2 mL of the mixture DMSO-15% aqueous sodium hydroxide (1:3) and precipitating with 10% hydrochloric acid to pH = 9. The resulting solid was collected by filtration, washed with water, and air-dried to give sulfide **8**, m.p. >300°C, lit.[23] m.p. >300°C (Table IV).

(c) A solution of sulfide **3a** (0.36 g, 1 mmol) in 5 mL of the mixture of concentrated hydrochloric acid-ethanol (1:1) was refluxed for 48 h. After cooling the resulting solid was collected by filtration, washed with ethanol, and air-dried. The product was identified as hydrochloride of sulfide **10** (m.p. 208–209°C, Belstein test, elementary analysis calcd. for $C_{19}H_{14}N_2O_2S \cdot HCl \cdot 2H_2O$ (406.88) C, 56.09; H, 4.71; N, 6.88; Cl, 8.71; S, 7.88. Found: C, 55.28; H, 4.58; N, 6.69; Cl, 9.03; S, 7.53). Neutral sulfide **10** was obtained from its hydrochloride by dissolving in 2 mL of the mixture DMSO-15% aqueous sodium hydroxide (1:3) and precipitating with 10% hydrochloric acid to pH = 9. The resulting solid was collected by filtration, washed with water, and air-dried to give sulfide **10** (0.29 g, 87%).

1-Methyl-bis(1,4-dihydro-4-oxo-3-quinolinyl) Sulfide 10, m.p. > 300°C

^{1}H NMR (DMSO-d_6) δ: 3.87 (s, 3H, NCH_3), 7.36, 7.46, 7.58 and 7.70 (4m, 4H, H-6, H-6′, H-8 and H-8′), 7.66 and 7.79 (2m, 2H, H-7 and H-7′), 7.95 and 8.27 (2s, 2H, H-2 and H-2′), 8.11 and 8.20 (2dd, 2H, H-5 and H-5′), 12.2 (broad, 1H, NH). EI MS (70 eV) m/z: 334 (M, 100), 317 (M-OH,

17.7), 302 (M-CH_3OH, 13.1). Anal. Calcd. for $C_{19}H_{14}N_2OS_2$ (334.39); C, 68.25, H, 4.22; N, 8.38. Found: C, 68.03; H, 4.24; N, 8.19.

Alkylations of Sulfides 8 and 10 with Alkylating Agents

(1) Sulfide **8** (0.32 g, 1 mmol) or hydrochloride of sulfide **8** (0.39 g, 1 mmol) was disolved in a mixture of 2 mL of DMSO, 6 mL of 15% aqueous sodium hydroxide, and stirred with an alkylating agent (methyl iodide, ethyl iodide, propyl iodide, allyl bromide, benzyl chloride, methylene iodide, and 1,3-dibromopropane) at 20°C or 60°C for 24 (Table V). The resulting solid was collected by filtration, washed with water, and air-dried. The crude product was purified by column chromatography (silica gel 60, chloroform, chloroform-ethanol) to give sulfides **9a–9e**.

(2) Sulfide **8** (0.32 g, 1 mmol) was disolved in the mixture of 2 mL of DMSO, 6 mL of 15% aqueous sodium hydroxide, and stirred with methyl iodide (0.21 g, 1.5 mmol) at 20°C for 24 h. The resulting solid was collected by filtration, washed with water, and air-dried. The crude product was purified by column chromatography (silica gel 60, chloroform, chloroform-ethanol) to give sulfides **9a** (0.04 g, 11%). The filtrate was stired with benzyl chloride (0.38 g, 3 mmol) at 20°C for 24 h. The resulting solid was collected by filtration, washed with water, and air-dried. The crude product was purified by column chromatography (silica gel 60, chloroform, chloroform-ethanol) to give sulfides **9f** (0.30 g, 71%).

(3) Sulfide **10** (0.33 g, 1 mmol) was disolved in the mixture of 2 mL of DMSO, 6 mL of 15% aqueous sodium hydroxide, and stirred with benzyl chloride (0.38 g, 3 mmol) at 20°C for 24 h. The resulting solid was collected by filtration, washed with water, and air-dried. The crude product was purified by column chromatography (silica gel 60, chloroform, chloroform-ethanol) to give sulfide **9f** (0.36 g, 87%).

Bis(1-Methyl-1, 4-dihydro-4-oxo-3-quinolinyl) Sulfide 9a, m.p. >310°C, lit.[28] m.p. 321°C

^{1}H NMR ($CDCl_3$) δ: 3.85 (s, 6H, $2NCH_3$), 7.38 (m, 4H, 2H-6 and 2H-8), 7.65 (m, 2H, 2H-7), 8.41 (dd, 2H, 2H-5), 8.56 (s, 2H, 2H-2).

Bis(1-Ethyl-1, 4-dihydro-4-oxo-3-quinolinyl) Sulfide 9b, m.p. 221–222°C, lit.[28] m.p. 213°C

^{1}H NMR ($CDCl_3$) δ: 1.51 (t, J = 7.2 Hz, 6H, $2CH_3$), 4.24 (q, J = 7.2 Hz, 4H, $2NCH_2$), 7.35 (m, 2H, 2H-6), 7.41 (dd, 2H, 2H-8), 7.62 (m, 2H, 2H-7), 8.43 (dd, 2H, 2H-5), 8.61 (s, 2H, 2H-2).

Bis(1-Propyl-1, 4-dihydro-4-oxo-3-quinolinyl) Sulfide 9c, m.p. 207–208°C

^{1}H NMR ($CDCl_3$) δ: 1.01 (t, J = 7.4 Hz, 6H, $2CH_3$), 1.90 (q, J = 7.4 and J = 7.2 Hz, 4H, $2CH_2$), 4.13 (t, J = 7.2 Hz, 4H, $2NCH_2$), 7.34 (m, 2H, 2H-6), 7.38 (dd, 2H, 2H-8), 7.61 (m, 2H, 2H-7), 8.42 (dd, 2H, 2H-5), 8.58 (s, 2H, 2H-2). EI MS (70 eV) m/z: 404 (M, 100), 386 M-H_2O, 18.1), 371 (M-SH, 25.8), 361 (M-C_3H_7, 38.6). Anal. Calcd. for $C_{24}H_{24}N_2O_2S$ (404.52): C, 71.26; H, 5.98; N, 6.92. Found: C, 71.13; H-5.94; N, 6.73.

Bis(1-Allyl-1, 4-dihydro-4-oxo-3-quinolinyl) Sulfide 9d, m.p. 200–201°C

^{1}H NMR ($CDCl_3$) δ: 4.78 (d, J = 7.3 Hz, 4H, $2NCH_2$), 5.24 (m, 4H, $2CH_2$), 6.00 (m, 2H, 2CH), 7.35 (m, 2H, 2H-6), 7.36 (dd, 2H, 2H-8), 7.59 (m, 2H, 2H-7), 8.41 (dd, 2H, 2H-5), 8.56 (s, 2H, 2H-2). EI MS (70 eV) m/z: 400 (M, 100), 385 M-CH_3, 34.9), 367 (M-SH, 18.0), 359 (M-C_3H_5, 21.5), 326 (M-C_3H_5SH, 11.3). Anal. Calcd. for $C_{24}H_{20}N_2O_2S$ (400.49): C, 71.98; H, 5.03; N, 6.99. Found: C, 71.73; H, 4.89; N, 6.89.

Bis(1-Benzyl-1, 4-dihydro-4-oxo-3-quinolinyl) Sulfide 9e, m.p. 226–227°C

^{1}H NMR ($CDCl_3$) δ: 5.38 (s, 4H, $2CH_2$), 7.21 and 7.31 (2m, 14H, 2H-6, 2H-8 and $2C_6H_5$), 7.49 (m, 2H, 2H-7), 8.42 (dd, 2H, 2H-5), 8.72 (s, 2H, 2H-2). CI MS (70 eV) m/z: 501 (M+1, 100), 425 (M+1-C_6H_5 + H, 30.3), 411 (M+1-$C_6H_5CH_2$ + H, 29.9), 335 (M+1-$C_6H_5CH_2C_6H_5$ + 2H, 17.8). Anal. Calcd. for $C_{32}H_{24}N_2O_2S$ (500.61): C, 76.78; H, 4.83; N, 5.60. Found: C, 76.53; H, 4.84; N, 5.39.

1-Methyl-1′-benzylbis(1, 4-dihydro-4-oxo-3-quinolinyl) Sulfide 9f, m.p. 209–210°C

^{1}H NMR ($CDCl_3$) δ: 3.83 (s, 3H, CH_3), 5.36 (s, 2H, CH_2), 7.20 and 7.32 (2m, 9H, C_6H_5, H-6, H-6′, H-8 and H-8′), 7.47 and 7.65 (2m, 2H, H-7 and H-7′), 8.41 and 8.42 (2dd, 2H, H-5 and H-5′), 8.51 and 8.71 (s, 2H, H-2 and H-2′). CI MS (70 eV) m/z: 425 (M+1, 100), 335 (M+1-$C_6H_5CH_2$ + H, 30.7). Anal. Calcd. for $C_{26}H_{20}N_2O_2S$ (424.51): C, 73.56; H, 4.75; N, 6.60. Found: C, 73.29; H, 4.71; N, 6.41.

4,4′-(Methylenedioxy)-3,3′-diquinolinyl Sulfide 11 m.p. 240–241°C (dec.)

^{1}H NMR ($CDCl_3$) δ: 7.10 (s, 2H, CH_2), 7.58 (m, 2H, 2H-6), 7.74 (m, 2H, 2H-7), 8.04 (dd, 2H, 2H-8), 8.28 (dd, 2H, 2H-5), 8.91 (s, 2H, 2H-2). ^{13}C NMR ($CDCl_3$) δ: 90.37 (CH_2), 110.18 (C-3), 122.12 (C-5), 122.37 (C-4a), 126.96 (C-6), 129.08 (C-7), 130.73 (C-8), 149.52 (C-8a), 154.81 (C-2),

158.90 (C-4). EI MS (70 eV) m/z: 332 (M, 100), 302 M-CH_2O, 12.8). Anal. Calcd. for $C_{19}H_{12}N_2O_2S$ (332.37): C, 68.66; H, 3.64; N, 8.43. Found: C, 68.43; H, 3.54; N, 8.27.

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