Synthesis and NMR Assignment of 1,4-Oxathiino[3,2-*c*;5,6-*c*']diquinoline*

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1,4-Oxathiinodiquinoline **3** was obtained in three ways from 1,4-dithiinodiquinolines **1** and **2** *via* ring opening-ring closure reactions with total yield of 19, 46 and 77%. Through-space interactions between the H-$5_{quinolinyl}$ atoms and oxygen atom were discussed on the basis of ^{1}H nmr spectrum.

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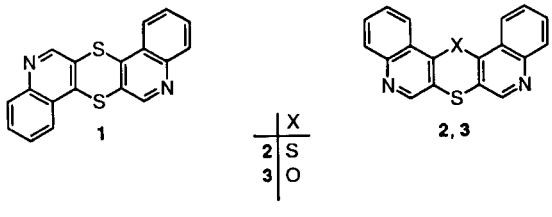
Introduction.

It has been previously reported that thioquinanthrene **1** (easy to obtain in 60% yield by exhaustive sulfurization of quinoline with elemental sulfur [1]) is a very useful substrate to obtain various bifunctional quinoline derivatives, for example *o,o'*-disubstituted 3,3'- and 3,4'-diquinolinyl sulfides and 4-substituted 3-alkylthioquinolines in the nucleophilic opening of the 1,4-dithiin ring [2-8]. Some of them exhibit nontypical and unexpected ^{1}H nmr spectral properties [3,9-11]. The isomer of dithiin **1**, isothioquinanthrene **2** was obtained in high yield from thioquinanthrene **1** *via* ring opening-ring closure reactions through a stage of the Smiles rearrangement of primary reaction products [5].

Scheme 1



The monoxygen analogue of dithiin **2**, 1,4-oxathiino[3,2-*c*;5,6-*c'*]diquinoline **3** was obtained in multistep synthesis from *o*-tosylaminoacetophenone with overall yield less than 7% [12].

It prompted us to use both readily available dithiins **1** and **2** as substrates to obtain oxathiin **3** in the series of ring opening ring closure reactions.

Results and discussion.

Synthesis.

It has been reported [5,6] that both dithiins **1** and **2** reacted with sodium methanethiolate or with *S*-methylisothiouronium sulfate (in the presence of alkali) to give 4,4'-dimethylthio-3,3'-diquinolinyl sulfide **4** in high yield (90%). The key-step of synthesis of oxathiin **3** is transformation of a methylthio group into a methoxy or a hydroxy group and cyclization of the obtained compounds to the desired oxathiin **3**.

A methylthio group is not a good leaving group in the nucleophilic substitution and there are only a few reports [13,14] involving substitution of a methylthio group by an alkoxy group in 2- and 4-methylthioazines (pyridines and quinolines).

Based on the results of transformation of sulfide **4** into oxycompounds we propose three methods of the synthesis of oxathiin **3**. (Scheme 2).

Method A.

Reaction of sulfide **4** with sodium methoxide in DMF or DMSO at 80° gave unexpectedly sulfide **5** with yield (100% and 97%, respectively). In our opinion a primary product dimethoxy compound was easily dealkylated by methanethiolate anion liberated from the reaction mixture. The same effect of dealkylation was observed by Testafferi and co-workers [13] in the reactions of substituted 2-methylthiopyridine with sodium methoxide and 2-methoxypyridine with sodium methanethiolate in DMF. The same compound **5** was obtained in 81% yield when powdered sodium hydroxide was used. Compound **5** was used by Kietzmann [12] in the cyclization to oxathiin **3** with yield of 21%. Thus overall yield by method A of the synthesis dithiins→oxathiin **3** is no more than 19%.

Method B.

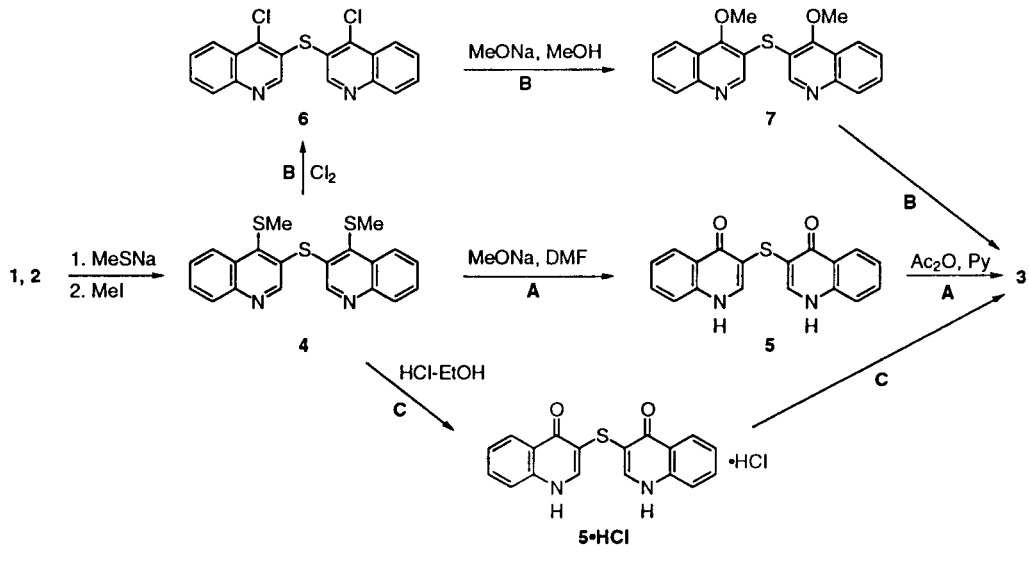
One of a few examples of transformation of an alkylthio group is substitution of a benzylthio group by chlorine in chlorinolysis ("wet chlorination") of substituted 3- and 4-benzylthioquinolines [15-18]. We succeeded in substitution of a methylthio group in chlorinolysis of sulfide **4** to give 4,4'-dichloro-3,3'-diquinolinyl sulfide **6** in good yield (75%). When chlorinolysis was continued 30 minutes after the exothermic effect disappeared we found 4,4'-dichloro-3,3'-diquinolinyl sulfoxide **6a** instead

of sulfide **6**. The desired dimethoxy compound **7** was obtained in 93% yield from sulfide **6** in the reaction with an excess of sodium methoxide in methanol. The oxathiin ring closure reaction was achieved in 73% yield in the reaction of sulfide **7** with acetic anhydride and pyridine. The overall yield of method B of the synthesis dithiins→oxathiin **3** is 46%.

Method C.

When substituted 2-methylthiopyrimidines were heated in strongly acidic alcoholic solution the 2-thio function was selectively hydrolysed with the formation of substituted 2-pyrimidones [19,20]. Encouraged by this result we tried to modify the synthesis of sulfide **5** without using dry aprotic solvents and sodium methoxide. Heating sulfide **4** in the mixture of concentrated hydrochloric acid and ethanol (1:1) under reflux gave unexpectedly after cooling long bright yellow needles of monohydrochloride of sulfide **5** in 94% yield. The latter compound **5•HCl** turned to be an excellent substrate in the oxathiin ring closure reaction giving oxathiin **3** in 91% yield. Method C became the best route to oxathiin 3 from dithiins **1** and **2** in overall yield of 77%.

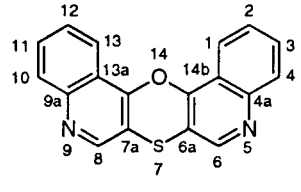
Scheme 2



^1H and ^{13}C NMR Study.

4-Substituted 3,3'- and 3,4'-diquinolinyl sulfides exhibit unusual ^1H nmr spectral properties. The signals of the H-$5_{quinolinyl}$ and H-$5'_{quinolinyl}$ protons in deuteriochloroform are shifted downfield due to through-space interaction with the 4-hetero-substituent (for example 4-methylthio and 4-methoxy groups) even by 0.87 ppm in comparison to the signal of the H-5 proton in quinoline (7.68 ppm) [9]. The deshielding of "peri" H-5 protons is not a result of a kind of the 4-heteroatom but also depends on the stereoelectronic interaction between the 3- and 4-substituents. For example, the chemical shifts of the H-$5_{quinolinyl}$ protons caused by the oxygen atom in 4-methoxy-3'-methylthio-3,4'-diquinolinyl sulfide and in 4-methoxy-4'-methylthio-3,3'-diquinolinyl sulfide are 8.07 ppm [4] and 8.18 ppm [21] (the "peri" effects are 0.39 and 0.50 ppm, respectively). Thus the signals of the H-$5_{quinolinyl}$ protons in these 4-methoxyquinolines were found more downfield (0.06-0.11 ppm) than the signals of the H-$8_{quinolinyl}$ protons (8.05 in quinoline [22], 7.96 and 8.12 in the 4-methoxyquinolines, respectively [4,21]). On the other hand, the conformations of reported 3,3'- and 3,4'-diquinolinyl sulfides have an effect on the chemical shift of the H-$2_{quinolinyl}$ protons, which are sometimes shifted upfield up to 1 ppm [10,21]. The ^1H nmr spectrum of oxathiin **3** in deuteriochloroform (at 300 MHz) showed one signal as a singlet at 8.52 ppm which is attributed to the H-6 and H-8 protons (*i.e.* the H-$2_{quinolinyl}$ protons). The assignment of ABCD system of benzene ring protons was accomplished by the LAOCOON-3 simulation. The most downfield signal at 8.31 ppm was assigned to the H-1 and H-13 protons (*i.e.* the H-$5_{quinolinyl}$ protons). The "peri" effect caused by oxygen atom is 0.63 ppm and is greater than we expected.

Scheme 3



The signal of the H-4 and H-10 protons (*i.e.* the $H\text{-}8_{quinolinyl}$ protons) was found at 8.04 ppm and practically was unchanged in comparison with the signal of the H-8 proton in quinoline (8.05 ppm).

The greater "peri" effect than expected seems to be not only a result of through-space interaction of the H-5 atom with oxygen atom but also a consequence of the geometry of the whole molecule. The shorter length of the C-O bond than the C-S bond causes both the H-1 and H-13 atoms to be relatively close to each other and the interaction between them additionally shifted the signal of these protons. The similar effects were found in ^1H nmr spectra of phenanthrene (where the signals of the closest protons are shifted downfield by 0.82 ppm [23]) and very lately in a similar polynuclear aromatic heterocycle, phenanthro [9',10';4,5]thieno[2,3-*c*]quinoline [24], where the signal of the $H\text{-}5_{quinolinyl}$ proton is shifted downfield by 1.08 ppm (in comparison with the appropriate signal in quinoline) owing to the steric interaction between the $H\text{-}5_{quinolinyl}$ atom and the equivalent of the H-5 atom in phenanthrene moiety.

The reported [12] ^1H nmr spectrum of oxathiin **3** in DMSO-d_6 showed signals of the H-1 and H-13 protons (the $H\text{-}5_{quinolinyl}$ protons) at 7.80 ppm, and the H-4 and H-10 protons (the $H\text{-}8_{quinolinyl}$ protons) at 8.43 ppm. This reverse order assignment did not take the "peri" effect into consideration.

Whereas the deshielding of the signal of the H-1 and H-13 protons was observed in ^1H nmr spectrum, in ^{13}C nmr spectrum the signal of the carbon atoms bonded with these protons *i.e.* the C-1 and C-13 atoms was shifted upfield (119.9 ppm vs 128.4 ppm found for the appropriate signal in quinoline [25]). This shielding effect ($\Delta\ \delta$ = -8.5 ppm) in oxathiin **3** was greater than found in 4-methoxyquinoline mentioned above ($\Delta\ \delta$ = -7.0 ppm [4] and $\Delta\ \delta$ = -6.1 ppm [20]) and phenothio[9',10';4,5]thieno-[2,3-*c*]quinoline ($\Delta\ \delta$ = -3.1 ppm [24]).

EXPERIMENTAL

Melting points were determined in capillary tubes on a Boetius melting point apparatus and are uncorrected. The ^1H nmr spectra were recorded on a Bruker MSL 300 (300 MHz) spectrometer in deuteriochloroform or DMSO-d_6 solutions. The ^{13}C nmr spectrum was recorded on a Bruker AC 200 (50.3 MHz) spectrometer in deuteriochloroform solution. Mass spectra were run on a LKB spectrometer using the electron impact method. Thin layer chromatography was performed on aluminium oxide (type E) and silica gel 60 254 F plates (Merck) using methylene chloride and benzene-ethyl acetate (1:1) solution as eluents. Silica gel (100-200 mesh) Merck Kiesel gel 60 was employed for column chromatography.

Thioquinanthrene **1** was obtained by exhaustive sulfurization of quinoline with elemental sulfur [1]. Isothioquinanthrene **2** was obtained from thioquinanthrene **1** *via* ring opening-ring closure reactions [5]. 4,4'-Dimethylthio-3,3'-diquinolinyl sulfide **4** was obtained from the reaction of dithiins **1** and **2** with sodium methanethiolate or *S*-methylisothiouronium sulfate followed by methylation with methyl iodide as described in reference [6].

3,3'-Bis(4-oxo-1,4-dihydroquinolinyl) Sulfide **5**.

To a solution of sulfide **4** (0.38 g; 1 mmole) in 10 ml of dry DMF at 80° sodium methoxide (0.27 g; 5 mmoles) was added. The mixture was stirred at 80° for 2 hours. After cooling the reaction mixture was poured into 50 ml of water and extracted with chloroform (3 x 20 ml). A white solid was precipitated from aqueous solution. The solid was filtered off and air-dried to give 0.32 g of sulfide **5** (100%), mp >300°, lit [12] mp >300°; ^1H nmr spectrum in DMSO-d_6 as in ref [12]; ms: (15 eV) m/z (relative intensity) 320 (M^+, 72.5), 303 (M-OH, 10), 44 (CS, 100).

Hydrochloride of 3,3'-Bis(4-oxo-1,4-dihydroquinolinyl) Sulfide **5•HCl**.

A solution of sulfide **4** (7.6 g; 20 mmoles) in 200 ml of concentrated hydrochloric acid and 200 ml of ethanol was refluxed for 48 hours. After cooling bright yellow needles precipitated. The precipitate was filtered off and air-dried to give 7.4 g of sulfide **5•HCl** (94%), mp >300°; ^1H nmr (DMSO-d_6): δ 7.38-7.80 (m, $6H_{arom}$), 8.23 (d, 2H, 2H-5, J = 8 Hz), 8.43 (s, 2H, 2H-2), 13.12 (s, br, 2H, 2NH).

Anal. Calcd. for $C_{18}H_{12}N_2O_2S$•HCl•$2H_2O$: C, 55.03; H, 4.36; N, 7.13; S, 8.16; Cl, 9.02. Found: C, 55.43; H, 4.30; N, 7.45; S, 8.37; Cl, 8.67.

4,4'-Dichloro-3,3'-diquinolinyl Sulfide **6**.

A solution of sulfide **4** (0.76 g; 2 mmoles) in a mixture of 8 ml of 80% acetic acid and 8 ml of chloroform was cooled down to 6-10° with an ice-water bath. Chlorine was passed into the solution until the exothermic effect disappeared (about 30 minutes). The temperature should be kept below 10°. The progress of chlorination was monitored by tlc. Chloroform was evaporated on a rotatory evaporator and the residue was neutralized with 15% aqueous sodium hydroxide. The resulting solid was filtered off, washed with water, air-dried and purified by column chromatography (silica gel 60, chloroform) to give 0.56 g of sulfide **6** (78%), mp 129-130°, lit [12] mp 129°; ^1H nmr (deuteriochloroform): δ 7.65-8.26 (m, $8H_{arom}$), 8.66 (s, 2H, 2H-2); ms: (15 eV) m/z (relative intensity) 356 (M^+, 100), 358 (M+2, 62.4), 321 (M-Cl, 18.7).

4,4'-Dichloro-3,3'-diquinolinyl Sulfoxide **6a**.

The chlorinolysis of sulfide **4** was carried out as described above passing chlorine for 1 hour. The crude product was crystallized from ethanol to give 0.56 g of sulfoxide **6a** (75%), mp 220-222°, lit [12] mp 225-227°; ^1H nmr spectrum in DMSO-d_6 as in ref [12]; ms: (15 eV) m/z (relative intensity) 372 (M^+, 40.2), 374 (M+2, 32.9), 356 (M-O, 100)7 358 (M+2-O, 65.2).

4,4'-Dimethoxy-3,3'-diquinolinyl sulfide **7**.

A solution of sulfide **6** (0.71 g; 2 mmoles) and sodium methoxide (1.08 g; 20 mmoles) in 20 ml of anhydrous methanol was refluxed for 3 hours. Methanol was evaporated, 5 ml of water was added to the residue and then extracted with chloroform (2 x 10 ml). The chloroform extract was dried with anhydrous sodium sulfate and then chloroform was evaporated and

the residue was purified by column chromatography (silica gel 60, chloroform) to give 0.65 g of sulfide **7** (93%), mp 83-84°, ^{1}H nmr (deuteriochloroform): 4.19 (s, 6H, 2OCH$_3$), 7.54-8.14 (m, 8H$_{arom}$), 8.67 (s, 2H, 2H-2); ms: (15 eV) m/z (relative intensity) 348 (M$^+$, 100), 318 (M-2CH$_3$, 8.8), 302 (M-CH$_3$OCH$_3$, 28.9).

Anal. Calcd. for $C_{20}H_{16}N_2O_2S$: C, 68.95; H, 4.63; N, 8.04; S, 9.20. Found: C, 68.76; H, 4.71; N, 8.07; S, 9.05.

1,4-Oxathiino[3,2-*c*;5,6-*c*']diquinoline **3**.

A. From Sulfide **5** in 21% yield according to reference [12].

B. From Sulfide **7**.

A solution of sulfide **7** (0.70 g; 2 mmoles) in the mixture of 20 ml of acetic anhydride and 20 ml of pyridine was refluxed for 6 hours. After cooling, the solution was poured into ice (40 g). A resulting solid was filtered off, washed with water, air-dried and purified by column chromatography (silica gel 60, chloroform and chloroform-ethanol (100:1)) to give 0.44 g of oxathiin **3** (73%), mp 207-208°, lit [12] mp 207°; ^{1}H nmr (deuteriochloroform): δ 7.66 (m, 2H, H-2, H-12), 7.73 (m, 2H, H-3, H-11), 8.04 (dd, 2H, H-4, H-10), 8.31 (dd, 2H, H-1, H-13), 8.52 (s, 2H, H-6, H-8), the values of aromatic coupling constants [Hz] are $J_{1,2}$ = 8.4; $J_{1,3}$ = 1.3; $J_{1,4}$ = 0.6; $J_{2,3}$ = 6.9; $J_{2,4}$ = 1.0; $J_{3,4}$ = 8.4; ^{13}C nmr (deuteriochloroform): δ 109.4 (C-6a, C-7a), 119.3 (C-13a, C-14b), 119.9 (C-1, C-13), 127.4 (C-2, C-12), 129.3 (C-3, C-11), 129.8 (C-4, C-10), 147.6 (C-6, C-8), 148.6 (C-4a, C-9a), 151.6 (C-13b, C-14a), ms: (15 eV) m/z (relative intensity) 302 (M$^+$, 100), 274 (M-CO, 3.7), 270 (M-S, 9.5), 258 (M-CS, 3.5).

C. From Sulfide **5•HCl**.

A solution of sulfide **5•HCl** (0.79 g, 2 mmoles) in the mixture of 20 ml of acetic anhydride and 20 ml of pyridine was refluxed for 2 hours. After cooling the reaction mixture was worked-up as described above to give 0.55 g of oxathiin **3** (91%).

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