ACETYLENIC DERIVATIVES OF THIOQUINOLINES [1]

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Abstract - Various 3,4-substituted quinoline sulfides possessing a propargylthio and/or propargyloxy groups at the 3- and 4- positions were prepared by the reaction of thioquinanthrene with alkoxides.

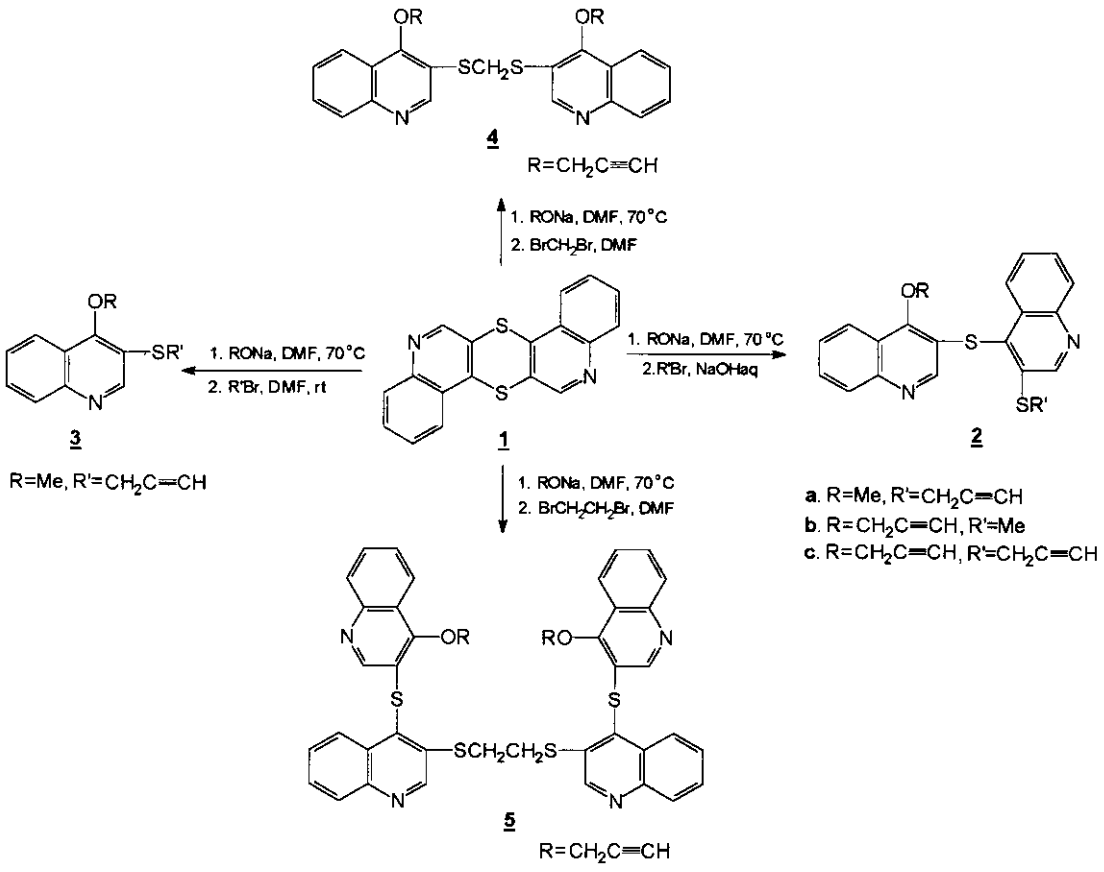
INTRODUCTION

Alkynylquinolines comprise a large and important class of biologically active compounds which have been considered for use as bactericides,[2] insecticides,[3] pesticides,[4] fungicides,[2] analgesics,[3] and intermediates for many synthetically transformations and in the pharmaceutical and cosmetic industries.[2,4-6] Synthetic methods for preparation of this class compounds are of an interest especially with regard to synthesis of biologically active enediyne systems or similar molecular models[7,8] and also 8-ethynylquinolones.[9] The biological properties of above mentioned compounds have motivated us to prepare new series of acetylenic derivatives of thioquinoline on the base of the reaction of thioquinanthrene (**1**) with alkoxides. Previously, we have reported that the functionalization of quinoline in 3 and 4 positions can be efficiently carried out by the reactions of thioquinanthrene (**1**) with alkoxides.[10-12] It was found that the reaction of **1** with sodium alkoxides followed by S-alkylation gave the 4-alkoxy-3'-methylthio-3,4'-diquinolinyl sulfides. Treatment of **1** with an excess of alkoxide in DMF followed by the addition of two moles of the alkylating agent run as one-pot process directly to 4-alkoxy-3-(alkylthio)quinolines. When the bifunctional alkylating agents such dibromoalkanes were used along the lines of the one-pot procedure mentioned above, thioquinanthrene (**1**) may be converted to the oligomers with four 3,4-quinolinediyl units of type *bis[4-(4-methoxy-3-quionlinylthio)-3-quinolinylthio]alkanes*.

In the present paper, we describe the extention of this methodology to the synthesis of new sulfur derivatives of quinoline with substituents of propargyloxy and/or propargylthio type in positions C-4 and C-3 of the quinoline molecule, which can exhibit a number of interesting biological activities.

RESULTS AND DISCUSION

The title compounds were prepared according to our previously reported method,[9-11] as illustrated in Scheme below. The starting material used in these reactions was thioquinanthrene (**1**) which is easily available in large scale.[13]

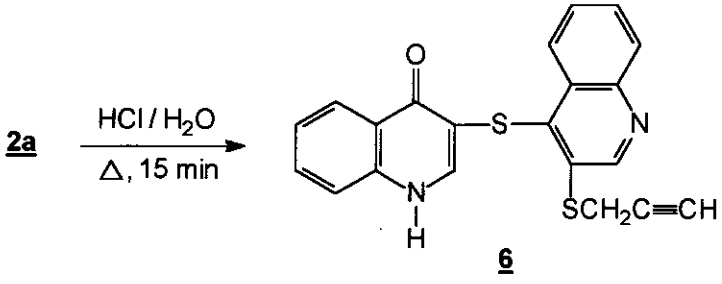


Reaction of **1** with sodium methoxide was performed in DMF solution at 70 °C and run by cleavage of one 4-quinolinyl-sulfur bond in 1,4-dithiin ring of **1** to form sodium 4-(4-methoxy-3-quinolinylthio)-3-quinolinylthiolate as primary product which was alkylated in aqueous solution by propargyl bromide to **2a** in the 86% yield. When **1** was treated with sodium propargyloxide followed by methyl bromide addition under experimental condition described above, the sulfide (**2b**) was obtained in the 82% yield. The use of the propargyl bromide as alkylating agent led to 3,4-diquinolinyl sulfide (**2c**) in the 75% yield. Reaction of **1** with excess of sodium methoxide followed by addition of two moles of propargyl bromide run with both 4-quinolinyl-sulfur bond cleavage steps and both S-alkylation ones and led directly to 4-methoxy-3-(propargylthio)quinoline (**3**) in the 66% yield. Treatment of **1** with excess of sodium propargyloxide followed by addition dibromomethane as bifunctional alkylating agent, according to previously reported

one-pot procedure,[11,12] gave bis(4-propargyloxy-3-quinolinylthio)methane (**4**) in the 77% yield. The same reaction with using 1,2-dibromoethane procceded to the tetramer (**5**) in the 85% yield.

The spectral properties of new compounds presented in this paper are very similar to those of sulfides of this class reported previously.[10-12] It is worth noting that signals of the H-2 proton in the compounds (**2a**), (**2c**) and (**3**) are shifted to the low field (δ=9.05 ppm, δ=9.01 ppm and δ=9.19 ppm , respectively) in comparison with the H-2 proton chemical shift in 4-methoxy-3'-methylthio-3,4'-diquinolinyl sulfide (δ=8.83 ppm) and 4-methoxy-3-(methylthio)quinoline (δ=8.82 ppm).[10] This H-2 chemical shift in above mentioned acetylenic compounds is a result of influence of the propargylthio substituent in position C-3 on the ortho proton (H-2).[14]

Due to their potent biological activity 4-quinolones are the important compounds. It has been previously reported that 4-alkoxy-3-(methylthio)quinolines and 4-alkoxy-3'-alkylthio-3,4'-diquinolinyl sulfides could be easily hydrolized in aqueous acidic medium to form corresponding 4-quinolones.[10] For these reason, our next attempt was to carry out the hydrolysis reaction of sulfides (**2a**) and (**3**) in order to obtain 4-quinolones containing propargylthio substituent at C-3.



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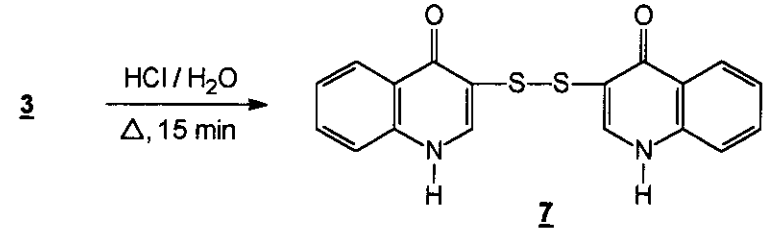
The acid hydrolysis of **2a** provided in good yield to 4-quinolone (**6**). However, the hydrolysis of **3** under experimental conditions similar to those used for **2a** afforded unexpected disulfide (**7**), whose structure was established by their analytical and spectroscopic data. At this stage it is difficult to say what is the mechanism of this reaction.



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In conclusion, the results described in this paper indicate that acetylenic derivatives of thioquinolines can be obtained from reaction of thioquinanthrene with alkoxides. The present method is experimentally simple and good in the yield, and practically seems to be available for the ready introduction of propargylthio and propargyloxy substituents to 3- and/or 4- positions of quinolinyl sulfides.

EXPERIMENTAL

Melting points were determined in open capillary tubes on a Boetius melting point apparatus and are uncorrected. The ^{1}H NMR spectra were recorded on a Bruker MSL 300 spectrometer at 300 MHz in deuteriochloroform or dimethyl sulfoxide-d_6 solvents with tetramethylsilane as the internal standard and chemical shifts are reported in ppm (δ) and *J* values in Hz. EI MS spectra were run on a LKB GC 2091 spectrometer at 70 eV and 15 eV. FAB MS spectra were recorded on Finnigan MAT 95 spectrometer in FAB mode (Cs^+, 13keV, nba). TLC was performed on silica gel 60 254F plates (Merck) using a mixture of chloroform and ethanol (15:1, v/v) as an eluant. Visualization was accomplished by UV light and iodine. Column chromatography was performed on silica gel 60, < 63 μm (Merck) using a mixture of chloroform and ethanol (15:1, v/v) as an eluant. Thioquinanthrene (**1**) was obtained by exhaustive sulfurization of quinoline with elemental sulfur and recrystallized from DMF, mp 314-315 °C.[13]

Preparation of 4-alkoxy-3'-alkylthio-3,4'-diquinolinyl sulfides (**2**): A suspension of thioquinanthrene (**1**) (795 mg, 2.5 mmol) and sodium methoxide or sodium propargyloxide (7.5 mmol) in dry DMF (12 mL) was stirred at 70 °C for 30 min. Clear solution was then cooled down to rt and poured into 35 mL of 10 % aqueous sodium hydroxide. Methyl bromide or propargyl bromide (2.5 mmol) was added dropwise to the aqueous layer and mixture was stirred for 15 min. The mixture was extracted with 3 x 10 mL of chloroform. The combined organic layer was washed with water, dried with anhydrous magnesium sulfate and evaporated *in vacuo* to give an oily residue. The crude product was purified by column chromatography and crystallized from ethanol to give pure product (**2**).

4-Methoxy-3'-propargylthio-3,4'-diquinolinyl sulfide (**2a**): mp 164-166 °C. EI MS (15 eV). m/z (rel. intensity) 388(M^+, 100), 357(M-OCH_3 , 34.3), 349(M-CH_2CCH, 18.8). ^{1}H NMR ($CDCl_3$) δ: 2.25(t, J=2.4 Hz, 1H, C**H**); 3.77(d, J=2.4 Hz, 2H, C**H**$_2$S); 4.19(s, 3H, C**H**$_3$O); 7.52-8.41(m, 8H, Ar-**H**); 8.16(s, 1H, **H-2**); 9.05(s, 1H, **H'-2**). *Anal.* Calcd for $C_{22}H_{16}N_2OS_2$: C 68.03, H 4.16, N 7.22, S, 16.48. Found: C 68.20, H 4.06, N 7.15, S 16.38.

4-Propargyloxy-3'-methylthio-3,4'-diquinolinyl sulfide (**2b**): mp 115-116 °C. EI MS (15 eV), m/z (rel. intensity) 388(M^+, 66.7), 302(M-SCH_3-CH_2CCH, 100). ^{1}H NMR ($CDCl_3$) δ: 2.58(t, J=2.5 Hz, 1H, C**H**); 2.60(s, 3H, C**H**$_3$S); 5.12(d, J=2.5 Hz, 2H, C**H**$_2$O); 7.46-8.41(m, 8H, Ar-**H**); 8.11(s, 1H, **H-2**); 8.82(s, 1H, **H'-2**). *Anal.* Calcd for $C_{22}H_{16}N_2OS_2$: C 68.03, H 4.16, N 7.22, S 16.48. Found: C 68.24, H 4.19, N 7.05, S 16.31.

4-Propargyloxy-3'-propargylthio-3,4'-diquinolinyl sulfide (**2c**): mp 152-154 °C (decomp). EI MS (15 eV), m/z (rel. intensity) 412(M^+, 49.9), 373(M-CH_2CCH, 15.5), 334(M-2 x CH_2CCH, 21.3). ^{1}H NMR ($CDCl_3$) δ: 2.25(t, J=2.4 Hz, 1H, C**H**); 2.61(t, J=2.5 Hz, 1H, C**H**); 3.76(d, J=2.4 Hz, 2H, C**H**$_2$S); 5.10(d, J=2.5

Hz, 2H, C**H**$_2$O); 7.51-8.31(m, 8H, Ar-**H**); 8.14(s, 1H, **H-2**); 9.01(s, 1H, **H'-2**). *Anal.* Calcd for $C_{24}H_{16}N_2OS_2$: C 69.88, H 3.91, N 6.79, S 15.54. Found: C 69.76, H 4.02, N 6.91, S 15.36.

4-Methoxy-3-(propargylthio)quinoline (**3**): A suspension of thioquinanthrene (**1**) (795 mg, 2.5 mmol) and sodium methoxide (810 mg, 15 mmol) in dry DMF (12 mL) was stirred at 70 °C for 30 min. Clear solution was then cooled to rt and propargyl bromide (618 mg, 5.2 mmol) was added dropwise during 30 min. The reaction mixture was stirred for 1 h and then poured into 35 mL of 10 % aqueous sodium hydroxide. The mixture was extracted with 3 x 10 mL of chloroform. The combined organic layer was washed with water and dried with anhydrous magnesium sulfate. After removal of the solvent, the residue was purified by column chromatography to give 760 mg (66%) of pure product (**3**), mp 73-75 °C (ethanol). *EI MS* (15 eV), m/z (rel. intensity) 229(M^+, 100), 214(M-CH_3 , 22.5). ^{1}H NMR ($CDCl_3$) δ: 2.11(t, J=2.5 Hz, 1H, C**H**); 3.71(d, J=2.5 Hz, 2H, C**H**$_2$S); 4.08(s, 3H, C**H**$_3$O); 7.54-7.67(m, 2H, **H-6** and **H-7**); 8.02-8.10(m, 2H, **H-5** and **H-8**); 9.11(s, 1H, **H-2**). *Anal.* Calcd for $C_{13}H_{11}NOS$: C 68.10, H 4.84, N 6.11, S 13.98. Found: C 67.95, H 4.89, N 6.15, S 14.16.

Bis(4-propargyloxy-3-quinolinylothio)methane (**4**): A suspension of thioquinanthrene (**1**) (795 mg, 2.5 mmol) and sodium propargyloxide (810 mg, 15 mmol) and dry DMF (12 mL) was stirred at 70 °C for 30 min. Clear solution was then cooled to rt and dibromomethane (469 mg, 2.7 mmol) was added dropwise during 30 min. The reaction mixture was stirred for 1 h and then poured into 35 mL of 10 % aqueous sodium hydroxide. The mixture was extracted with 3 x 10 mL of chloroform. The combined organic layer was washed with water and dried with anhydrous magnesium sulfate. After removal of the solvent, the residue was purified by column chromatography to give 850 mg (77%) of pure product (**4**), mp 113-114 °C (ethanol). EI MS (15 eV), m/z (rel. intensity) 442(M^+, 9.6), 228(M-$C_{12}H_8NOS$, 100), 214(M-$C_{13}H_{10}NOS$, 22.4). ^{1}H NMR ($CDCl_3$) δ: 2.45(t, J=2.5 Hz, 2H, 2 x C**H**); 4.51(s, 2H, SC**H**$_2$S); 4.96(d, J=2.5 Hz, 4H, 2 x C**H**$_2$O); 7.49-7.73(m, 4H, 2 x **H-6** and 2 x **H-7**); 7.99-8.18(m, 4H, 2 x **H-5** and 2 x **H-8**); 8.84(s, 2H, **H-2**). *Anal.* Calcd for $C_{25}H_{18}N_2O_2S_2$: C 67.85, H 4.10, N 6.33, S 14.49. Found: C 67.68, H 4.16, N 6.21, S 14.38.

1,2-Bis[4-(4-propargyloxy-3-quinolinylthio)-3-quinolinylthio]ethane (**5**): A suspension of thioquinanthrene (**1**) (795 mg, 2.5 mmol) and sodium propargyloxide (405 mg, 7.5 mmol) in dry DMF (12 mL) was stirred at 70 °C for 30 min. Clear solution was then cooled to rt and 1,2-dibromoethane (263 mg, 1.4 mmol) was added dropwise during 30 min. The reaction mixture was stirred for 1 h and then poured into 35 mL of 10 % aqueous sodium hydroxide. The mixture was extracted with 3 x 10 mL of chloroform. The combined organic layer was washed with water and dried with anhydrous magnesium sulfate. After removal of the solvent, the residue was purified by column chromatography to give 820 mg (85%) of pure product (**5**), mp 184-185 °C (DMF). *FAB MS* (+VE), m/z (rel. intensity) 775(M^++1, 39). ^{1}H NMR ($CDCl_3$) δ: 2.58(t,

2H, J=2.4 Hz, 2 x C**H**); 3.24(s, 4H, SC**H**$_2$C**H**$_2$S); 5.09(d, 4H, J=2.4 Hz, 2 x C**H**$_2$O); 7.50-8.38(m, 16H, Ar-**H**); 8.11(s, 2H, 2 x **H-2**); 8.81(s, 2H, 2 x **H'-2**). *Anal.* Calcd for $C_{44}H_{30}N_4O_2S_4$: C 68.21, H 3.91, N 7.24, S 16.52. Found: C 68.02, H 4.02, N 7.37, S 16.65.

Hydrolysis of 4-methoxy-3'-propargylthio-3,4'-diquinolinyl sulfide (**2a**) and 4-methoxy-3-(propargylthio)-quinoline (**3**) : A mixture of **2a** or **3** (1 mmol) and 10% hydrochloric acid (20 mL) was heated at reflux for 15 min. The solution was then evaporated *in vacuo* to dryness. The residue was neutralized with 5% aqueous sodium bicarbonate solution (20 mL). The resultant solid was filtered off and air-dried to give crude product which was crystallized from DMF to yield pure 330 mg (88%) of **6** or 160 mg (91%) of **7** respectively.

1,4-Dihydro-4-oxo-3'-(propargylthio)-3,4'-diquinolinyl sulfide (**6**) : mp 215-217 °C . FAB MS (+VE), m/z (rel. intensity) 375(M^++1, 52). ^{1}H NMR (DMSO-d_6) δ: 3.18(t, J=2.6 Hz, 1H, C**H**); 4.14(d, J=2.6 Hz, 2H, C**H**$_2$S); 7.30-8.45(m, 8H, Ar-**H**); 7.81(s, J=6.2 Hz, 1H, **H-2**); 8.97(s, 1H, **H'-2**); 12.09(d, J=6.2 Hz, 1H, N**H**). *Anal.* Calcd for $C_{21}H_{14}N_2OS_2$: C 67.36, H 3.77, N 7.48, S 17.12. Found: C 67.48, H 3.86, N 7.32, S 17.24.

3,3'-Bis(4-oxo-1,4-dihydroquinolinyl) disulfide (**7**) : mp>300 °C, lit.,[15] mp>300 °C. EI MS (15 eV), m/z (rel. intensity) 320(M^+-S, 23.7), 303(M-OH, 8.5), 177(M-C_9H_5NO, 100). ^{1}H NMR (DMSO-d_6) δ: 7.37-7.66(m, 6H, Ar-**H**); 8.11(d, J=8.1 Hz, 2H, 2 x **H-5**); 8.45(s, 1H, 2 x **H-2**); 12.21(br s, 2H, 2 x N**H**) *Anal.* Calcd for $C_{12}H_{12}N_2O_2S_2$: C 61.36, H 3.44, N 7.96, S 18.16. Found: C 61.48, H 3.36, N 7.88, S 18.02.

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