SYNTHESIS OF 3-ALKYL SULFINYL-4(1H)-QUINOLINONES FROM 4-METHOXY-3-ALKYLTHIOQUINOLINES

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Abstract - Reactions of 4-methoxy- or 1,4-dihydro-4-oxo-3-alkylthioquinolines (1) and (4, 5) with a nitrating mixture ran as the 3-alkylthio group S-monooxidation and led to the respective alkylsulfinyl derivatives (2, 3 or 6). Hydrolysis of 4-methoxy-3-alkylsulfinylquinolines (2) with hydrochloric acid (1:1) at 65-68 °C gave 3-alkylsulfinyl-4(1H)-quinolinones (3).

INTRODUCTION
Flosequinan, i.e. 7-fluoro derivative of 1-methyl-3-methylsulfinyl-4(1H)-quinolinone exhibits vasodilatory and antihypertensive activity. As broadly demonstrated for fluoroquinolinone antibacterial drugs, flosequinan may be prepared like other 4(1H)-quinolinones, via pyridine ring closure starting from respective benzene derivatives followed by sulfide group oxidation and N-methylation. However, our previous studies on the 3,4-difunctionalization of quinoline via thioquinanthrene demonstrate 4-alkoxy-3-alkylthioquinolines (1) and 3-alkylthio-4(1H)-quinolinones (4) to be easily available. Furthermore, cautious treatment of 4-substituted 3'-methylthio-3,4'-diquinolinyl sulfides with a nitrating mixture allows the methylthio group oxidation and gives high yield of corresponding 3'-methylsulfinyl-3,4'-diquinolinyl sulfides. One would therefore expect to find a new way of preparing 3-alkylsulfinyl-4(1H)-quinolinones (3) or (6) starting from 4-alkoxy-3-(alkylthio)quinolines (1) by combining monooxidation of 3-alkylthio group and transformations of 4-methoxy group, as shown in the Scheme.

RESULTS AND DISCUSSION
The key step in the preparation of 3-alkylsulfinyl-4(1H)-quinolinones (3) or (6) from 4-alkoxy-3-alkylthio quinolines (1) is oxidation of the 3-alkylthio function in 1, 4 or 5 to sulfoxide one in compounds (2, 3 or 6), respectively. However, in reactions with 4-substituted 3'-methylthio-3,4'-diquinolinyl sulfides, the nitrating mixture acts both as an oxidizing system and as a nitrating one. To avoid nitrataion we choose 4-methoxy-3-methylthioquinoline (1a) as a model compound since 4-methoxyquinoline is less reactive than
4(1H)-quinolinone toward nitration with nitric acid / conc. sulfuric acid mixture. In fact, treatment of sulfide (1a) with solution containing up to three molar equivalents of nitric acid (applied in the form of nitrating mixture) involved only S-monooxidation and gave mainly 4-methoxy-3-methylsulfinylquinoline (2a) (85%) accompanied by some amounts of 3-methylsulfinyl-4(1H)-quinolinone (3a) (as hydrolysis product of 2a). Similar results were obtained for sulfides (1b and 1c).

Scheme

The aza-activated ether linkage in 4-alkoxyquinolines could be easily splitted giving respective 4(1H)-quinolinones by the action of hydrochloric or hydrobromic acid. One would therefore expect hydrolysis of 4-methoxy-3-alkylsulfinylquinolines (2) into 3-alkylsulfinyl-4(1H)-quinolinones (3) by means of hydrochloric acid, as shown for transformation of 4-alkoxy-3-alkylthioquinolines (1) into 3-alkylthio-
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4(1H)-quinolinones (4). Easy deoxygenation of sulfoxides in the presence of hydrogen halides, both in aqueous and non-aqueous solutions has been, on the other hand, well documented.\textsuperscript{10-12} Furthermore, Connor and Strandtmann \textsuperscript{13} reported that the action of boiling 5N hydrochloric acid causes deoxygenation of 1-methyl-3-methylsulfanyl-4(1H)-quinolinone (6a) to 1-methyl-3-methylthio-4(1H)-quinolinone (5a), it even causes splitting of the whole methylsulfanyl group and formation of 1-methyl-4(1H)-quinolinone. Very close results, including transformation of methylsulfanyl group and hydrolysis of 4-methoxy group, were obtained in our studies concerning the behaviour of 4-methoxy-3-methylsulfanylquinoline (2a) in boiling hydrochloric acid (1:1) for 0.5 h. The main product was 3-methylthio-4(1H)-quinolinone (4a) (50\%) accompanied by small amounts of 4(1H)-quinolinone. Also, as reported by Connor and Strandtmann \textsuperscript{13} for 3a or 6a the balance of substrate-isolated products relation was below 60\%. Fortunately, treatment of 2a-c with hydrochloric acid (1:1) at 65-68°C causes selective splitting of the ether linkage, leaving the sulfanyl group almost unaffected and gives the expected 3-alkylsulfanyl-4(1H)-quinolinones (3a-c), with 85-90\% yield. Comparison of the acid catalyzed hydrolysis ability of 4-methoxy-3-alkylthioquinolines (1) versus 4-methoxy-3-alkylsulfanylquinolines (2) shows that in the case when sulfoxides (2) were completely used up and converted into quinolinones (3) with in 85-90\% yield, the consumption of 4-methoxy-3-alkylthioquinolines (1) (and the conversion of 1 to 3-alkylthio-4(1H)-quinolinones (4) ) amounted to 12 -14\% only.

Preparation of 3 presented above consists of oxidation step of 1 into 2 and hydrolysis of 2 into 3 (Scheme, route a). To avoid problems caused by instability of sulfoxides (2) in the presence of hydrochloric acid we decided to study a reverse reaction sequence starting from 1 but involving transformation of methoxyquinoline (1) to 4-quinolinones (4) or (5) and completing the process with oxidation of sulfides (4) or (5) to sulfoxides (3) or (6), respectively. However, the reaction of 3-methylthio-4(1H)-quinolinone (4a) with the mixture containing three molar equivalents of nitric acid proceeded as both S-oxidation and nitration to give 6-nitro-3-methylsulfanyl-4(1H)-quinolinone (7a) (R=Me) with 70\% yield. On the other hand, analogical reaction of compounds (4a-4c) or (5a-5c) performed with the use of one molar equivalent of nitric acid gave only the sulfide group oxidation products (3a-3c) or (6a-6c) with 85-90\% or 85-97\% yield, respectively.

The \textsuperscript{1}H NMR spectra of methoxy-sulfoxides (2) related to the spectral data of sulfides (1) show characteristic changes (cf. ref.\textsuperscript{7}) in the positions of H-2 protons shifted downfield by $\Delta \delta = 0.36$- 0.45 ppm. On the other hand, the differences in the chemical shifts values $\Delta \delta_{\text{sulfoxide-sulfide}}$ for $\text{SCH}_2$ protons ($\Delta \delta = ca. 0.02$ up to 0.40 ppm) and that for $\text{SCH}_3$ protons ($\Delta \delta$ up to 0.54 ppm) show non-identical spatial arrangement of alkylsulfanyl group in 3-methylsulfanylquinolines (2a), (3a) and (6a) and theirs higher alkyl
homologs (2b,c), (3b,c) and (6b,c), respectively. The assignment of the aromatic ring protons was performed by the use of COSY spectra as well as by $^1$H-$^1$H NOE experiments with methoxy group protons indicating the spectral position of H-5 proton signals.

**EXPERIMENTAL**

All melting points are uncorrected. The $^1$H NMR spectra were recorded on a Bruker MSL 300 spectrometer at 300 MHz in deuteriochloroform or in hexadeuteriodimethyl sulfoxide solutions with tetramethylsilane as internal standard. The COSY and NOE correlation spectra diagrams were performed on the same samples that were used to determine $^1$H NMR spectra at 500 MHz (on a Bruker AM 500 spectrometer). IR spectra were taken on a UR-10 apparatus (Carl Zeiss, Jena) in KBr pellets. El MS spectra were determined on a LKB 2091 spectrometer at 15 and 70 eV and Finnigan MAT 95 spectrometer at 70 eV.

TLC analyses were performed employing Merck's silicagel 60 F254 plates and a solution of chloroform-methanol (25 : 2, v/v) as an eluent (system I) or Merck's aluminium oxide 60 F254 neutral (type E) plates using mixture of chloroform - methanol (60:1, v/v) as an eluent (system II).

4-Methoxy-3-alkylthioquinolines (1a) (R=CH₃), (1b) (R=C₂H₅) and (1c) (R=n-C₃H₇) were prepared from thioquinanthrene and sodium methoxide followed by S-alkylation with alkyl iodide according to the "one pot" procedure reported previously.⁵

4-Methoxy-3-propylthioquinoline (1c)

This compound was obtained as an oil, bp 167-170 °C / 1 torr. $^1$H NMR (CDCl₃), $\delta$ : 1.01 (t, 3H, J = 7.3 Hz, CH₃CH₂), 1.59-1.66 (sextet, 2H, J = 7.3 Hz, CH₂CH₂CH₃), 2.95 (t, 2H, J = 7.3 Hz, SCH₂CH₂), 4.13 (s, 3H, CH₃O), 7.51-7.56 (m, 1H, H-6), 7.65-7.70 (m, 1H, H-7), 8.03-8.06 (m, 1H, H-8), 8.07-8.11 (m, 1H, H-5), 8.84 (s, 1H, H-2). El MS (70 eV) m/z (relative intensity): 233 (100, M⁺). Anal. Calc'd for C₁₃H₁₅NOS: C, 66.92; H, 6.48; N, 6.00; S, 13.74. Found: C, 67.00; H, 6.50; N, 5.90; S, 13.61.

1,4-Dihydro-4-oxo-3-alkylthioquinolines (4a) (R=CH₃), (4b) (R=C₂H₅), (4c) (R=n-C₃H₇) were prepared by hydrolysis of 4-methoxy-3-alkylthioquinolines (1) with boiling hydrochloric acid (1:1). The properties of 4a and 4b were the same as reported previously.⁶ 1,4-Dihydro-4-oxo-3-propylthioquinoline (4c) : mp 137-139 °C (ethanol), lit.¹⁵ mp 137-138 °C, yield 86%.

**Thermal rearrangement of 4-methoxy-3-alkylthioquinolines (1) to 1-methyl-3-alkylthio-4-oxo-1,4-dihydroquinolines (5)**

A glass test tube containing 100 mg of 4-methoxy-3-alkylthioquinoline (1) was inserted into a hot oil bath (200 °C) and then kept at this temperature for 0.5- 2 h. The products mixture was cooled down to rt. The
pure products (5a) (R=CH₃, 90%) and (5b) (R=C₂H₅, 96%) were obtained by recrystallization of crude material from 95% ethanol. n-Propyl derivative (5c) (R=n-C₃H₇) was isolated by means of column chromatography on silica gel (100-200 mesh) using a mixture of chloroform - 95% ethanol, 20 : 1, v/v, as an eluent and finally recrystallized from ethanol.

1-Methyl-3-methylthio-4-oxo-1,4-dihydroquinoline (5a) : mp 121-123 °C, lit.,¹³ mp 123-124 °C. ¹H NMR and TLC data of 5a were identical as those reported previously.¹⁶

1-Methyl-3-ethylthio-4-oxo-1,4-dihydroquinoline (5b) : mp 114-116 °C, lit., ⁴ mp 115-117 °C.

1-Methyl-3-propylthio-4-oxo-1,4-dihydroquinoline (5c) : mp 75-77 °C, lit., ⁴ mp 74-76 °C, yield 86 %.

4-Methoxy-3-alkylsulfinylquinolines (2)

4-Methoxy-3-alkylthioquinoline (1) (9 mmol) was dissolved upon stirring in 96% sulfuric acid (25 mL) at 0°C. The nitrating mixture (fuming nitric acid, d=1.50, 1.4 mL, ca. 31 mmol of HNO₃ and 1.4 mL of conc. sulfuric acid) was then added dropwise at 0-5 °C. The mixture was maintained at 0°C for 1.5 h, and then cautiously poured on 300 g of ice, and neutralized at 0 °C with conc. aqueous ammonia, up to pH 6. The solid (in the case of 2a) was filtered off, washed twice with cold water then with cold methanol, and air-dried. In the case of ethyl and propyl derivatives, the products (2b) or (2c) were isolated by extraction with chloroform (5 x 20 mL). Combined extracts were dried over anhydrous magnesium sulfate and then treated in a typical manner to give sulfoxides (2b) or (2c) as thick oils. Ethyl derivative (2b) (R=C₂H₅) and propyl one (2c) (R=n-C₃H₇) were separated by means of column chromatography on silica gel (100-200 mesh) using a mixture of chloroform (or methylene chloride) - 95% ethanol, 19 : 1, v/v, as an eluent.

4-Methoxy-3-methylsulfinylquinoline (2a).

This compound had mp 138-140 °C (ethanol), yield 85 %. ¹H NMR (CDCl₃) δ : 2.90 (s, 3H, CH₃SO), 4.13 (4asm, 3H, CH₃-0), 7.58 (ddd, 1H, ³J = 6.9 Hz, ⁴J = 8.4 Hz, ⁵J = 1.2 Hz, H-6), 7.68 (ddd, 1H, ³J = 6.9 Hz, ⁴J = 8.4 Hz, ⁵J = 1.5 Hz, H-7), 7.99 (ddd, 1H, ³J = 8.5 Hz, ⁴J = 1.2 Hz, ⁵J = 0.7 Hz, H-8). 8.05 (ddd, 1H, ³J = 8.5 Hz, ⁴J = 1.2 Hz, ⁵J = 0.7 Hz, H-5), 9.49 (s, 1H, H-2). IR (KBr pellet), vS=O = 1055 cm⁻¹. El MS (70 eV) m/z (relative intensity): 221 (10, M⁺), 204 (100, M - OH), 206 (51.1, M-CH₃). Anal. Calcd for C₁₁H₁₁NO₂S: C, 59.71; H, 5.02; N, 6.33; S, 14.46. Found: C, 59.63; H, 5.05; N, 6.18; S, 14.69.

4-Methoxy-3-ethylsulfinylquinoline (2b).

This compound was obtained as an oil, yield 89 %. ¹H NMR (CDCl₃), δ : 1.26 (t, 3H, J = 7.5 Hz, CH₃CH₂), 2.92-3.04 and 3.05-3.16 (2m, 2 x 1H, both from CH₃CH₂ group), 4.14 (s, 3H, CH₃-O), 7.62 (ddd, 1H, ³J = 6.9 Hz, ³J = 8.3 Hz, ⁴J = 1.1 Hz, H-6), 7.80 (ddd, 1H, ³J = 6.9 Hz, ³J = 8.4 Hz, ⁴J = 1.5 Hz, ⁵J = 1.4 Hz, H-5), 9.04 (s, 1H, H-2).
Hz, H-7), 8.09 (ddd, 1H, \( ^3J = 8.3 \text{ Hz} \), \( ^4J = 1.5 \text{ Hz} \), \( ^5J = 0.7 \text{ Hz} \), H-8), 8.17 (ddd, 1H, \( ^3J = 8.5 \text{ Hz} \), \( ^4J = 1.1 \text{ Hz} \), \( ^5J = 0.7 \text{ Hz} \), H-5), 9.19 (s, 1H, H-2). IR (KBr pellet), \( \nu_{\text{S=O}} = 1020, 1055 \) and 1075 cm\(^{-1} \). El MS (15 eV) m/z (relative intensity): 235 (12, M\(^+\)). Anal. Calcd for C\(_{12}\)H\(_13\)N\(_2\)O\(_2\)S: C, 61.25; H, 5.57; N, 5.96; S, 13.63. Found: C, 61.41; H, 5.40; N, 6.00; S, 13.79.

4-Methoxy-3-propylsulfinylquinoline (2c)

This compound was obtained as an oil, yield 88%; \(^1\)H NMR (CDCl\(_3\)), \( \delta \) : 1.05 (t, 3H, \( ^3J = 7.4 \text{ Hz} \), CH\(_2\)CH\(_3\)), 1.63-1.73 and 1.83-1.94 (2m, 2 x 1H, both from CH\(_2\)CH\(_2\)CH\(_3\) group), 2.94-3.03 (m, 2H, SC\(_2\)CH\(_2\)CH\(_3\)), 4.13 (s, 3H, CH\(_3\)O), 7.59-7.62 (m, 1H, H-6), 7.76-7.81 (m, 1H, H-7), 8.07-8.11 (m, 1H, H-8), 8.14-8.17 (m, 1H, H-5), 9.21 (s, 1H, H-2). IR (KBr pellet), \( \nu_{\text{S=O}} = 1025, 1041, 1061 \) and 1081 cm\(^{-1} \). El MS (15 eV) m/z (relative intensity): 249 (14, M\(^+\)), 207 (100, M - C\(_3\)H\(_5\)). Anal. Calcd for C\(_{13}\)H\(_27\)N\(_2\)O\(_2\)S: C, 62.63; H, 6.07; N, 5.62; S, 12.84. Found: C, 62.80; H, 6.01; N, 5.70; S, 12.72.

1.4-Dihydro-4-oxo-3-methylsulfinyl-6-nitroquinoline (7a)

This compound was prepared from quinolinone (4a) according to the procedure for the preparation of 2a followed by recrystallization from DMF to give 7a with mp 242-243 \(^{\circ}\)C in 70% yield. \(^1\)H NMR (DMSO-\( d_6 \)), \( \delta \) : 2.82 (s, 3H, CH\(_3\)SO), 7.82 (dd, 1H, \( ^3J = 9.1 \text{ Hz} \), \( ^4J = 0.5 \text{ Hz} \), H-8), 8.14 (s, 1H, H-2), 8.45 (dd, 1H, \( ^3J = 9.1 \text{ Hz} \), \( ^4J = 2.6 \text{ Hz} \), H-7), 8.78 (dd, 1H, \( ^4J = 2.6 \text{ Hz} \), \( ^5J = 0.5 \text{ Hz} \), H-5), 12.35 (s, 1H, N\(_1\)-H). IR (KBr pellet), \( \nu_{\text{S=O}} = 1030 \) and 1070 cm\(^{-1} \), \( \nu_{\text{N=O}} = 1360 \) and 1560 cm\(^{-1} \). El MS (15 eV) m/z (relative intensity): 252 (22.5, M\(^+\)). Anal. Calcd for C\(_{10}\)H\(_8\)N\(_2\)O\(_4\)S: C, 47.62; H, 3.2; N, 11.11; S, 12.69. Found: C, 47.90; H, 3.01; N, 11.42; S, 12.90.

Oxidation of 3-alkylthio-4-oxo-1,4-dihydroquinolines (4a-c) and 1-methyl-3-alkylthio-4-oxo-1,4-dihydroquinolines (5a-c) leading to sulfoxides (3) or (6) (route b, c)

3-Alkylthio-4-oxo-1,4-dihydroquinoline (4) or (5) (9 mmol) was dissolved with stirring in 96% sulfuric acid (25 mL) at 0 \(^{\circ}\)C. The nitrating mixture (fuming nitric acid, \( d = 1.50, 0.43 \text{ mL}, \) ca. 10 mmol of HNO\(_3\) and 1.4 mL of conc. sulfuric acid) was then added dropwise at 0-5 \(^{\circ}\)C. The addition of nitrating mixture was stopped when deep-cherry colored reaction mixture turned yellow. The mixture was then cautiously poured on 300 g of ice, and neutralized at 0 \(^{\circ}\)C with conc. aqueous ammonia, up to pH 6. The mixture (together with possible solid precipitates) was extracted with chloroform (4 \times 20 \text{ mL}). The combined extracts were washed with water and then dried over anhydrous sodium sulfate. Evaporation of the solvent left 3 or 6 as a solid. Crude product was recrystallized from ethyl acetate, ethyl acetate /hexane.
or ethanol. For analytical purposes, compounds (3a-c) were purified by column chromatography (aluminium oxide, methylene chloride / 95% ethanol - 1 : 1, v/v).

1.4-Dihydro-4-oxo-3-methylsulfinylquinoline (3a): mp 248-250 °C, lit., 13 mp 253-254 °C, yield 85 %; 1H NMR and IR data of 3a were identical with those reported previously. 13

1.4-Dihydro-4-oxo-3-ethylsulfinylquinoline (3b)
This compound had mp 65-66 °C (methanol), yield 90 %. 1H NMR (CDCl3): δ 1.28 (t, 3H, J = 7.4 Hz, CH2CH3), 3.03-3.18 and 3.33-3.45 (2m, 2 x 1H, both from CH3CH2 group), 7.43 (ddd, 1H, 3J = 7.0 Hz, 3J = 8.1 Hz, 4J = 1.1 Hz, H-6), 7.58 (ddd, 1H, 3J = 8.3 Hz, 4J = 1.1 Hz, 5J = 0.5 Hz, H-8), 7.69 (ddd, 1H, 3J = 7.0 Hz, 3J = 8.3 Hz, 4J = 1.2 Hz, H-7), 8.09 (d, 1H, 3J = 3.1 Hz, H-2), 8.32 (ddd, 1H, 3J = 8.1 Hz, 4J = 1.2 Hz, 5J = 0.5 Hz, H-5), 11.82 (br d, 1J = 3 Hz, 1H, N-H). IR (KBr pellet), νs=O = 1030 and 1058 cm⁻¹; El MS (15 eV) m/z (relative intensity): 221 (67.8, M'). Anal. Calcd for C11H11NO2S: C, 59.71; H, 5.02; N, 6.33; S, 14.46. Found: C, 59.60; H, 5.10; N, 6.18; S, 14.71.

1.4-Dihydro-4-oxo-3-n-propylsulfinylquinoline (3c)
This compound had mp 88-91 °C (ethanol), yield 88 %. 1H NMR (CDCl3): δ 1.08 (t, 3H, J = 7.4 Hz, CH2CH3), 1.69-1.79 and 1.87-1.97 (2m, 2 x 1H, both from CH2CH2CH3 group), 2.95-3.02 and 3.36-3.43 (2m, 2 x 1H, both from SCH2CH2 group), 7.41-7.45 (m, 1H, H-6), 7.61-7.64 (m, 1H, H-8), 7.67-7.71 (m, 1H, H-7), 8.13 (d, J = 6.3 Hz, 1H, H-2), 8.31-8.34 (m, 1H, H-5), 12.19 (br d, J = 6.2 Hz, 1H, N-H). IR (KBr pellet), νs=O = 1024 and 1057 cm⁻¹. El MS (15 eV) m/z (relative intensity): 235 (59, M⁺), 193 (100, M - C3H6). Anal. Calcd for C12H13NO2S: C, 61.26; H, 5.57; N, 5.96; S, 13.60. Found C, 61.01; H, 5.40; N, 6.10; S, 13.71.

1-Methyl-1,4-dihydro-4-oxo-3-methylsulfinylquinoline (6a)
This compound had mp 167-169 °C (ethanol / ethyl acetate), lit., 17 mp 168-170 °C, yield 85 %.

1-Methyl-1,4-dihydro-4-oxo-3-ethylsulfinylquinoline (6b)
This compound had mp 159-161 °C (ethanol / ethyl acetate), lit., 4 mp 160-163 °C, yield 97 %.

1-Methyl-1,4-dihydro-4-oxo-3-n-propylsulfinylquinoline (6c)
This compound had mp 154-155 °C (ethanol / ethyl acetate), lit., 4 mp 153-155 °C, yield 87 %.

Hydrolysis of 4-methoxy-3-alkylsulfinylquinolines (2) with hydrochloric acid to 1,4-dihydro-4-oxo-3-alkylsulfinyl-quinolines (3)
A mixture of 2 (1 mmol) and hydrochloric acid (1:1) (7 mL) was heated under stirring at 65-68 °C for 1-2 h. The solution was then evaporated to dryness under vacuum at 60 °C. The residue was triturated with 2
mL of water and neutralized with 5% aqueous sodium bicarbonate to pH 5.5-6. The resultant solid was filtered off, washed with water and air-dried to give crude 4(1H)-quinolinone derivatives (3). Compounds (3) were finally recrystallized from ethanol.

Results: Substrate Product (yield, mp)

(2a) (R=CH₃), (3a) (85, 238-240 °C)
(2b) (R=C₆H₅) (3b) (90, 65-6 °C)
(2c) (R=n-C₃H₇), (3c) (88, 136-8 °C)

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