A SYNTHESIS AND REACTIVITY OF 1,4-DIHYDRO-4-THIOXO-3-
QUINOLINESULFONAMIDES *

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Abstract - 4-Chloro-3-quinolinesulfonamides (1) were transformed to 1,4-dihydro-
4-thioxo-3-quinolinesulfonamides (2) which methylation gave 4-methylthio-3-
quinolinesulfonamides (3). Oxidation of sulfonamides (2) with hydrogen peroxide
provided 1,4-dihydro-4-oxo-3-quinolinesulfonamides (4).

INTRODUCTION

A number of 4-substituted 3-quinolinesulfonic acids and their analogs were described in literature.1-5 A
series of 1-alkyl-1,4-dihydro-4-thioxo-3-quinolinesulfonamides can be indicated here as the illustrative
example.5 The above mentioned compounds were obtained via the reaction of 4-chloro-3-quinoline-
sulfonamides (1) or 4-amino-3-quinolinesulfonamides via the respective 1-alkylquinolinium salts.
In order to prove the existence of the stable tautomeric forms of 4-thioxo- and 4-mercapto-3-quinol-
inesulfonic acids6 we synthesized the 4-S-substituted derivatives of 3-quinolinesulfonic acids.

RESULTS AND DISCUSSION

Reaction of 4-chloro-3-quinolinesulfonamides (1) with sodium hydrosulfide gave 1,4-dihydro-4-thioxo-3-
quinolinesulfonamides (2). Then thiones (2) were methylated with methyl iodide to 4-methylthio-3-
quinolinesulfonamides (3) (Table 1).
For some monosubstituted sulfonoamides, e.g., \( \text{NR}^1\text{R}^2 = \text{NHCH}_3 \) (2b), we observed the formation of some amount of the SO₂N-methylated products. We also tried to oxidize thiones (2). This reaction was performed with an excess of hydrogen peroxide in aqueous sodium hydroxide solution at ambient temperature. Unexpectedly, instead of the disulfides, we obtained hydrolysis products, i.e., 1,4-dihydro-4-oxo-3-quinolinesulfamides (4) (Table 1). It was observed previously that the oxidation of 6-mercaptopurine under basic conditions gave hypoxanthine.⁷,⁸

\[
\begin{align*}
\text{N} & \quad \text{S} & \quad \text{SO}_2\text{NR}^1\text{R}^2 \\
\text{H} & \quad \text{H}_2\text{O}_2 & \quad \text{NaOH}
\end{align*}
\]

4

We speculate that thiones (2) at first undergo oxidation to disulfides (5) and then to the thiosulfonyl compounds (6) (as was found in oxidation of thiols⁹) which can be hydrolyzed in alkali solution. A similar group to the thiosulfonyl one, the methylsulfonyl group in the aza-activated positions in quinoline, was found to be much more susceptible to nucleophilic displacement in alkali solution than the corresponding chlorine substituent.¹⁰-¹²

\[
\begin{align*}
\text{N} & \quad \text{S} & \quad \text{SO}_2\text{NR}^1\text{R}^2 \\
\text{H} & \quad \text{H}_2\text{O}_2 \\ & \quad \text{OH}^{-}
\end{align*}
\]

6

The sulfur atom in compound (2) can be oxidized to the sulfonic group \((\text{SO}_3\text{H})\) ⁹,¹³ The sulfonic group can be converted to the amino function but this reaction requires increased pressure and temperature over 100 °C.¹⁴,¹⁵ However, in our reaction conditions (room temperature and atmospheric pressure) the sodium sulfonate group \((\text{SO}_3\text{Na})\) seems not to exchange into the hydroxyl group in nucleophilic substitution.
Table 1. The yields of 1,4-dihydro-4-thioxo-3-quinolinesulfonamides (2), 4-methylthio-3-quinolinesulfonamides (3) and 1,4-dihydro-4-oxo-3-quinolinesulfamides (4).

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>Yields of 2 (%)</th>
<th>Yields of 3 (%)</th>
<th>Yields of 4 (%)</th>
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<tr>
<td>H</td>
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<td>2a 83</td>
<td>3a 60</td>
<td>4a 56</td>
</tr>
<tr>
<td>H</td>
<td>CH₃</td>
<td>2b 79</td>
<td>3b 75</td>
<td>4b 50</td>
</tr>
<tr>
<td>(CH₂)₂O(CH₂)₂</td>
<td>2c 82</td>
<td>3c 83</td>
<td></td>
<td>4c 56</td>
</tr>
<tr>
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<td>Ph</td>
<td>2d 87</td>
<td>3d 70</td>
<td>4d 67</td>
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<td>CH₃</td>
<td>Ph</td>
<td>2e 80</td>
<td>3e 92</td>
<td>4e 63</td>
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</table>

EXPERIMENTAL

Melting points were determined in open capillary tubes on an electronic mp apparatus and are uncorrected. The ¹H NMR spectra were recorded on a Bruker MSL 300 spectrometer at 300 MHz with tetramethylsilane as the internal standard. EI MS spectra were recorded on Finnigan MAT 95 spectrometer at 70 eV.

1,4-Dihydro-4-thioxo-3-quinolinesulfonamide (2). General procedure:

A solution of 4-chloro-3-quinolinesulfonamide (1) (2 mmol) and sodium hydroulfide (700 mg, ca. 7.5 mmol) in 50% ethanol (12 mL) was refluxed for 0.5 h. The reaction mixture was cooled, acidified with 10% hydrochloric acid to pH 3-4 and filtered to give thione (2) which were recrystallized from acetic acid (yields are given in Table 1).

1,4-Dihydro-4-thioxo-3-quinolinesulfonamide (2a): mp 227-228 °C. EI MS, (m/z): 240(M⁺, 51.3%), 161(100%). ¹H NMR (DMSO-d₆) δ: 7.16(s, 2H, NH₂), 7.70(s, 1H, H2), 8.80-8.83(m, 1H, H5), 7.80-7.85(m, 2H, H8, H7), 7.58-7.63(m, 1H, H6), 13.60(s, 1H, H1). Anal. Calcd for C₉H₈N₂O₂S₂: C 44.99, H 3.36, N 11.66, S 26.68. Found: C 45.15, H 3.50, N 11.70, S 26.48.

1,4-Dihydro-4-thioxo-N-methyl-3-quinolinesulfonamide (2b): mp 238-239 °C. EI MS, (m/z): 254(M⁺, 49.1%), 224(100%). ¹H NMR (DMSO-d₆) δ: 2.37(d, J=5.1 Hz, 3H, NHCH₃), 7.06(q, J=5.1 Hz, 1H, NHCH₃), 7.65(s, 1H, H2), 8.80-8.82(m, 1H, H5), 7.78-7.85(m, 2H, H8, H7), 7.57-7.62(m, 1H, H6), 13.63(s, 1H, H1). Anal. Calcd for C₁₀H₁₀N₂O₂S₂: C 47.23, H 3.96, N 11.01, S 25.21. Found: C 47.05, H 3.76, N 10.90, S 25.11.

1,4-Dihydro-4-thioxo-3-quinolinesulfonmorpholide (2c): mp 251-252 °C. EI MS, (m/z): 310(M⁺, 57.2%), 86(100%). ¹H NMR (DMSO-d₆) δ: 3.30-3.33(m, 4H, -CH₂NCH₂-), 3.55-3.57(m, 4H, -CH₂OCH₂-), 7.64(s, 1H, H2), 8.78-8.80(m, 1H, H5), 7.73-7.88(m, 2H, H8, H7), 7.54-7.58(m, 1H, H6), 13.42(s, 1H,
H1). Anal. Calcd for C_{13}H_{14}N_{2}O_{3}S_{2}: C 50.31, H 4.55, N 9.03, S 20.66. Found: C 50.47, H 4.31, N 9.23, S 20.72.

1,4-Dihydro-4-thioxo-3-quinolinesulfonanilide (2d): mp 243-244 °C. EI MS, (m/z): 316(M⁺, 30%), 93(100%). ¹H NMR (DMSO-d₆) δ: 7.67(s, 1H, H2), 8.72-8.74(m, 1H, H5), 7.71-7.84(m, 2H, H8, H7), 7.53-7.58(m, 1H, H6), 7.14-7.20(m, 4H, Harom), 9.84(s, 1H, NHPh), 13.47(s, 1H, H1). Anal. Calcd for C_{15}H_{12}N_{2}O_{2}S_{2}: C 56.94, H 3.82, N 8.85, S 20.27. Found: C 56.78, H 4.02, N 8.75, S 20.27.

1,4-Dihydro-4-thioxo-N-methyl-3-quinolinesulfonanilide (2e): mp 240-241 °C. EI MS, (m/z): 330(M⁺, 10%), 107(100%). ¹H NMR (DMSO-d₆) δ: 3.46(s, 3H, NCH₃), 7.47(s, 1H, H2), 8.69-8.72(m, 1H, H5), 7.62-7.76(m, 2H, H8, H7), 7.45-7.50(m, 1H, H6), 7.04-7.30(m, 5H, Harom), 13.24(s, 1H, H1). Anal. Calcd for C_{16}H_{14}N_{2}O_{2}S_{2}: C 58.16, H 4.32, N 8.24, S 19.41. Found: C 58.24, H 4.32, N 8.24, S 19.41.

4-Methylthio-3-quinolinesulfamide (3a, 3c, 3d and 3e). General procedure:

1,4-Dihydro-4-thioxo-3-quinolinesulfonamide (2) (0.5 mmol) was dissolved in 10% solution of sodium hydroxide (5 mL) and methyl iodide (0.1 mL, 1.61 mmol) was added and the whale was reacted for 0.5 h under mixing at ambient temperature. The reaction mixture was acidified with 10% hydrochloric acid to pH 3-4 and filtered to give products (3). 4-Methylthio-3-quinolinesulfonamides (3a, 3c, 3d and 3e) were recrystallized from aqueous ethanol (yields are given in Table 1).

4-Methylthio-3-quinolinesulfonamide (3a): mp 188-189 °C. EI MS, (m/z): 254(M⁺, 81.6%), 207(100%). ¹H NMR (DMSO-d₆) δ: 2.52(2.61, CDCl₃)(s, 3H, SCH₃), 7.78(s, 2H, NH₂), 9.32(s, 1H, H2), 8.60-8.63(m, 1H, H5), 8.17-8.19(m, 1H, H8), 7.95-8.00(m, 1H, H7), 7.85-7.90(m, 1H, H6). Anal. Calcd for C_{10}H_{10}N_{2}O_{2}S_{2}: C 47.23, H 3.96, N 11.01, S 25.21. Found: C 47.15, H 3.71, N 11.21, S 25.34.

4-Methylthio-3-quinolinesulfonmorpholide (3c): mp 101-102 °C. EI MS (70 eV), (m/z): 324(M⁺, 23.5%), 86(100%). ¹H NMR (DMSO-d₆) δ: 2.57(2.56, CDCl₃)(s, 3H, SCH₃), 3.31-3.35(m, 4H, -CH₂NCH₂-), 3.63-3.66(m, 4H, -CH₂OCH₂-), 2.57(2.61, CDCl₃)(s, 3H, S), 7.78(s, 2H, NH₂), 9.32(s, 1H, H2), 8.61-8.64(m, 1H, H5), 8.18-8.21(m, 1H, H8), 7.98-8.04(m, 1H, H7), 7.86-7.92(m, 1H, H6). Anal. Calcd for C_{14}H_{16}N_{2}O_{3}S_{2}: C 51.83, H 4.97, N 8.64, S 19.76. Found: C 51.68, H 5.11, N 8.52, S 19.84.

4-Methylthio-3-quinolinesulfonanilide (3d): mp 183-184 °C. EI MS, (m/z): 330(M⁺, 100%). ¹H NMR (DMSO-d₆) δ: 2.53(2.63, CDCl₃)(s, 3H, SCH₃), 6.95-7.00(m, 1H, Harom), 7.16-7.24(m, 4H, Harom), 9.30(s, 1H, H2), 8.54-8.57(m, 1H, H5), 8.13-8.15(m, 1H, H8), 7.95-8.00(m, 1H, H7), 7.83-7.88(m, 1H, H6), 10.68(s, 1H, NHPh). Anal. Calcd for C_{16}H_{16}N_{2}O_{3}S_{2}: C 58.16, H 4.27, N 8.48, S 19.41. Found: C 58.31, H 4.45, N 8.60, S 19.57.

4-Methylthio-N-methyl-3-quinolinesulfonanilide (3e): mp 95-96 °C. EI MS, (m/z): 344(M⁺, 35.3%), 106(100%). ¹H NMR (DMSO-d₆) δ: 2.56(2.51, CDCl₃)(s, 3H, SCH₃), 3.49(s, 3H, CH₃), 7.21-7.36(m, 5H,
4-Methylthio-3-quinolinesulfonamide (3b and 3f). General procedure:
1,4-Dihydro-4-thioxo-N-methyl-3-quinolinesulfonamide (2b) (200 mg, 0.78 mmol) was dissolved in 10% solution of sodium hydroxide (6 mL) and methyl iodide (0.15 mL, 2.42 mmol) was added and the whole was reacted for 0.5 h under stirring at ambient temperature. The reaction mixture was extracted with hexane (3 x 5 mL). The extract was evaporated to give 10 mg (5%) of sulfonamide (3f). Aqueous phase was acidified with 10% hydrochloric acid to pH 2-3 and filtered to give product (3b) which was recrystallized from aqueous ethanol.

4-Methylthio-N-methyl-3-quinolinesulfonamide (3b): mp 171-172 °C. EI MS, (m/z): 268(M+, 100%). 1H NMR (DMSO-d_6) δ: 2.52(2.60, CDCl_3)(s, 3H, SCH_3), 2.55(d, J=5.0 Hz, 3H, NHCH_3), 7.78(q, J=5.0 Hz, 1H, NHCH_3), 9.25(s, 1H, H2), 8.60-8.63(m, 1H, H5), 8.18-8.21(m, 1H, H8), 7.97-8.03(m, 1H, H7), 7.88-7.91(m, 1H, H6). Anal. Calcd for C_{11}H_{12}N_2O_2S_2: C 49.23, H 4.51, N 10.44, S 23.89. Found: C 49.41, H 4.64, N 10.49, S 23.74.

4-Methylthio-N,N-dimethyl-3-quinolinesulfonamide (3f): mp 81-82 °C. EI MS, (m/z): 282(M+, 79.7%), 238(100%). 1H NMR (DMSO-d_6) δ: 2.54(s, 3H, S, SCH_3), 2.94(s, 6H, N(CH_3)_2), 9.24(s, 1H, H2), 8.63-8.66(m, 1H, H5), 8.18-8.21(m, 1H, H8), 7.98-8.03(m, 1H, H7). 7.86-7.91(m, 1H, H6). Anal. Calcd for C_{12}H_{14}N_2O_2S_2: C 51.04, H 5.00, N 9.92, S 22.71. Found: C 50.85, H 5.21, N 9.79, S 22.87.

1,4-Dihydro-4-oxo-3-quinolinesulfamide (4). General procedure:
To 1,4-dihydro-4-thioxo-3-quinolinesulfamide (2) (0.5 mmol) dissolved in 5% solution of sodium hydroxide (5 mL) a 30% solution of hydrogen peroxide (0.15 mL, 1.5 mmol) was added dropwise. This was reacted for 24 h under stirring at ambient temperature. The reaction mixture was acidified with 5% hydrochloric acid to pH 2-3 and filtered to give 1,4-dihydro-4-oxo-3-quinolinesulfamides (4) which were recrystallized from aqueous ethanol. The yields are given in Table 1.

1,4-Dihydro-4-oxo-3-quinolinesulfonamide (4a): mp 291-292 °C, lit., mp 291-293 °C.
1,4-Dihydro-4-oxo-N-methyl-3-quinolinesulfonamide (4b): mp 270-271 °C, lit., mp 263-265 °C.
1,4-Dihydro-4-oxo-3-quinolinesulfonmorpholide (4c): mp 298-299 °C, lit., mp 297-298 °C.
1,4-Dihydro-4-oxo-3-quinolinesulfonanilide (4d): mp 264-265 °C, lit., mp 264-265 °C.
1,4-Dihydro-4-oxo-N-methyl-3-quinolinesulfonanilide (4e): mp 249-250 °C, lit., mp 250-251 °C.

REFERENCES
* Part LXXXIV in the series of Azinyl Sulfides.