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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**).

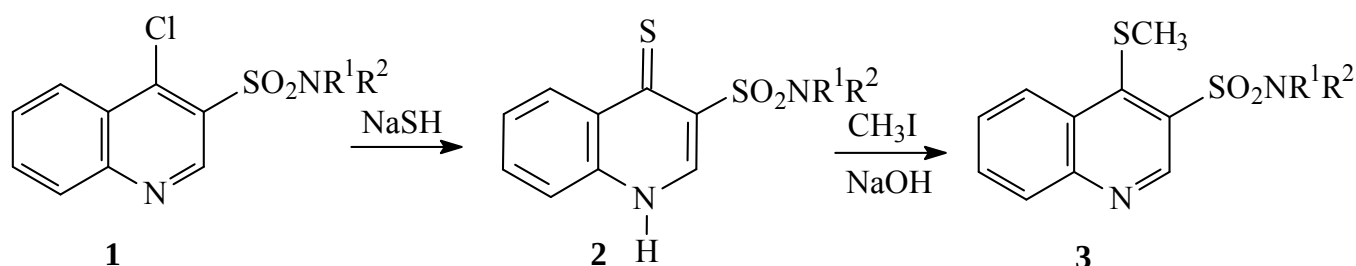
INTRODUCTION

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-quinolinesulfonamides (**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-quinolinesulfonic acids⁶ we synthesized the 4-S-substituted derivatives of 3-quinolinesulfonic acids.

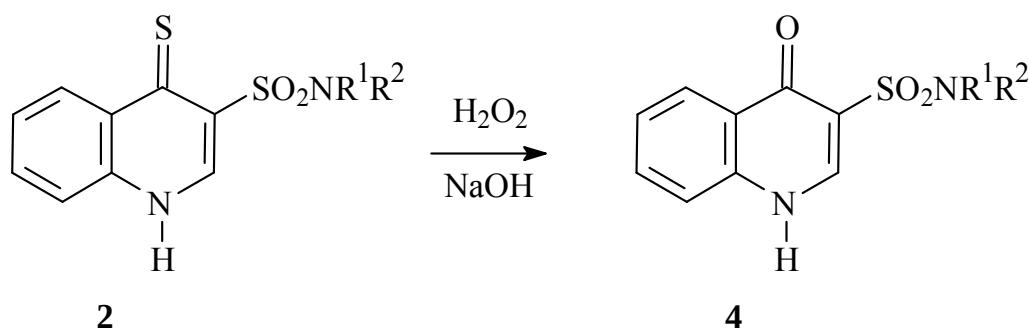
RESULTS AND DISCUSSION

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).

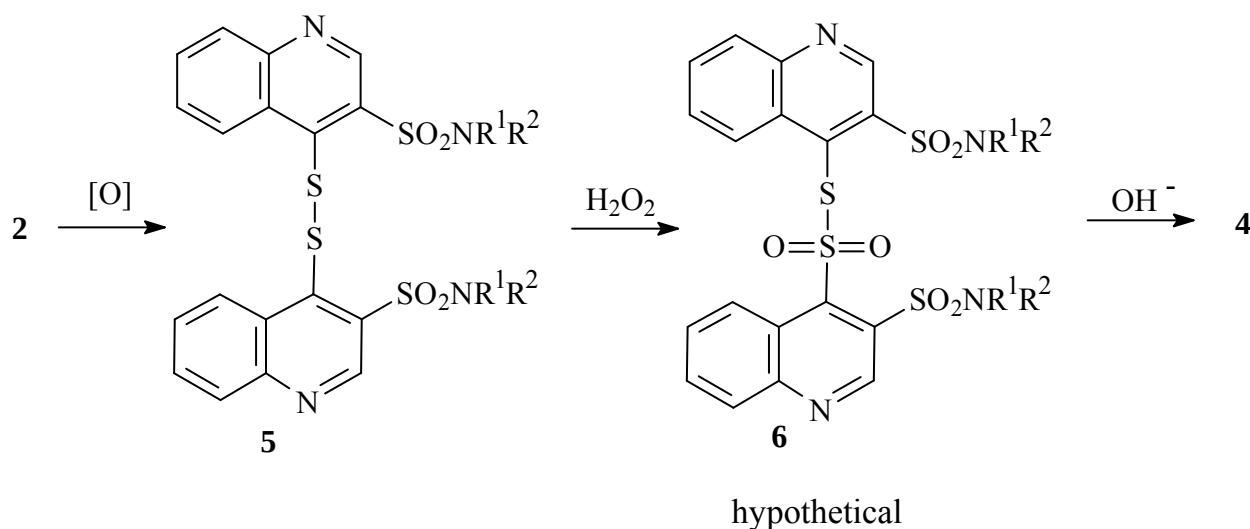


For some monosubstituted sulfonoamides, e.g., $\text{NR}^1\text{R}^2 = \text{NHCH}_3$ (**2b**), we observed the formation of some amount of the SO_2N -methylated products.

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-mercaptapurine under basic conditions gave hypoxanthine.^{7,8}



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



The sulfur atom in compound (**2**) can be oxidized to the sulfonic group (SO_3H).^{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 (SO_3Na) 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-quinoline-sulfonamides (**3**) and 1,4-dihydro-4-oxo-3-quinolinesulfamides (**4**).

R ¹	R ²	Yields of 2 (%)		Yields of 3 (%)		Yields of 4 (%)	
H	H	2a	83	3a	60	4a	56
H	CH ₃	2b	79	3b	75	4b	50
(CH ₂) ₂ O(CH ₂) ₂		2c	82	3c	83	4c	56
H	Ph	2d	87	3d	70	4d	67
CH ₃	Ph	2e	80	3e	92	4e	63

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-*d*₆) 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-*d*₆) 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-*d*₆) 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 $C_{13}H_{14}N_2O_3S_2$: 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- d_6) 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, H_{arom}), 6.97-6.99(m, 1H, H_{arom}), 9.84(s, 1H, NHPh), 13.47(s, 1H, H1). *Anal.* Calcd for $C_{15}H_{12}N_2O_2S_2$: 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- d_6) δ : 3.46(s, 3H, NCH_3), 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, H_{arom}), 13.24(s, 1H, H1). *Anal.* Calcd for $C_{16}H_{14}N_2O_2S_2$: C 58.16, H 4.27, N 8.48, 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 whole 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- d_6) δ : 2.52(2.61, $CDCl_3$)(s, 3H, SCH_3), 7.78(s, 2H, NH_2), 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 $C_{10}H_{10}N_2O_2S_2$: 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- d_6) δ : 2.57(2.56, $CDCl_3$)(s, 3H, SCH_3), 3.31-3.35(m, 4H, $-CH_2NCH_2-$), 3.63-3.66(m, 4H, $-CH_2OCH_2-$), 9.25(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 $C_{14}H_{16}N_2O_3S_2$: 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- d_6) δ : 2.53(2.63, $CDCl_3$)(s, 3H, SCH_3), 6.95-7.00(m, 1H, H_{arom}), 7.16-7.24(m, 4H, H_{arom}), 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 $C_{16}H_{14}N_2O_2S_2$: 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- d_6) δ : 2.56(2.51, $CDCl_3$)(s, 3H, SCH_3), 3.49(s, 3H, CH_3), 7.21-7.36(m, 5H,

H_{arom}), 9.03(s, 1H, H2), 8.58-8.61(m, 1H, H5), 8.14-8.17(m, 1H, H8), 7.97-8.03(m, 1H, H7), 7.85-7.90(m, 1H, H6). *Anal.* Calcd for C₁₇H₁₆N₂O₂S₂: C 59.28, H 4.68, N 8.13, S 18.62. Found: C 59.34, H 4.80, N 8.06, S 18.75.

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-d₆) δ: 2.52(2.60, CDCl₃)(s, 3H, SCH₃), 2.55(d, *J*=5.0 Hz, 3H, NHCH₃), 7.78(q, *J*=5.0 Hz, 1H, NHCH₃), 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 C₁₁H₁₂N₂O₂S₂: 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-d₆) δ: 2.54(s, 3H, SCH₃), 2.94(s, 6H, N(CH₃)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 C₁₂H₁₄N₂O₂S₂: 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.,² mp 291-293 °C.

1,4-Dihydro-4-oxo-*N*-methyl-3-quinolinesulfonamide (4b): mp 270-271 °C, lit.,² mp 263-265 °C.

1,4-Dihydro-4-oxo-3-quinolinesulfonmorpholide (4c): mp 298-299 °C, lit.,² mp 297-298 °C.

1,4-Dihydro-4-oxo-3-quinolinesulfonanilide (4d): mp 264-265 °C, lit.,² mp 264-265 °C.

1,4-Dihydro-4-oxo-*N*-methyl-3-quinolinesulfonanilide (4e): mp 249-250 °C, lit.,² mp 250-251 °C.

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