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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**).

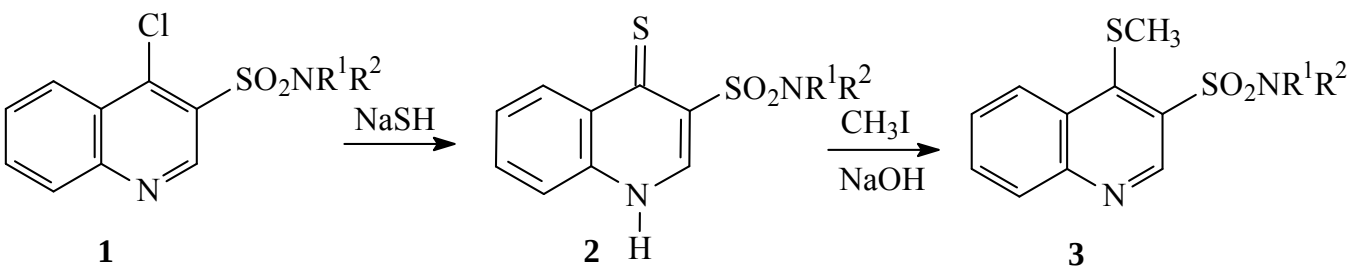
INTRODUCTION

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-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-quino-linesulfonic acids [6] we synthesized the 4-*S*-substituted derivatives of 3-quinolinesulfonic acids.

RESULTS AND DISCUSSION

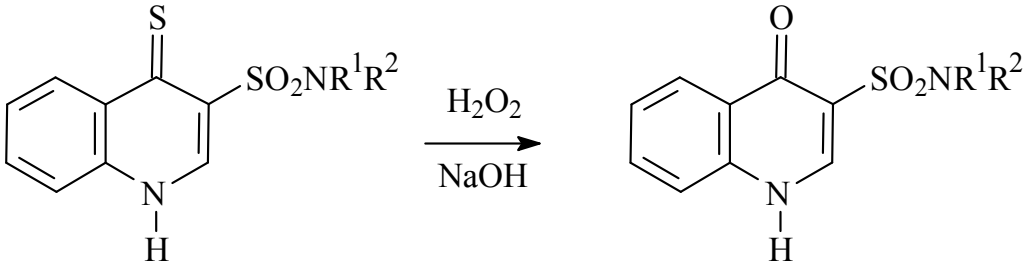
Reaction of 4-chloro-3-quinolinesulfonamides (**1**) with sodium hydrosulfide gave 1,4-dihydro-4-thioxo-3-quinolinesulfonamides (**2**). Then thiones (**2**) were methylated with methyl iodide to 4-methylthio-3-quinolinesulfonamides (**3**) (Table 1).



1 **2** **3**

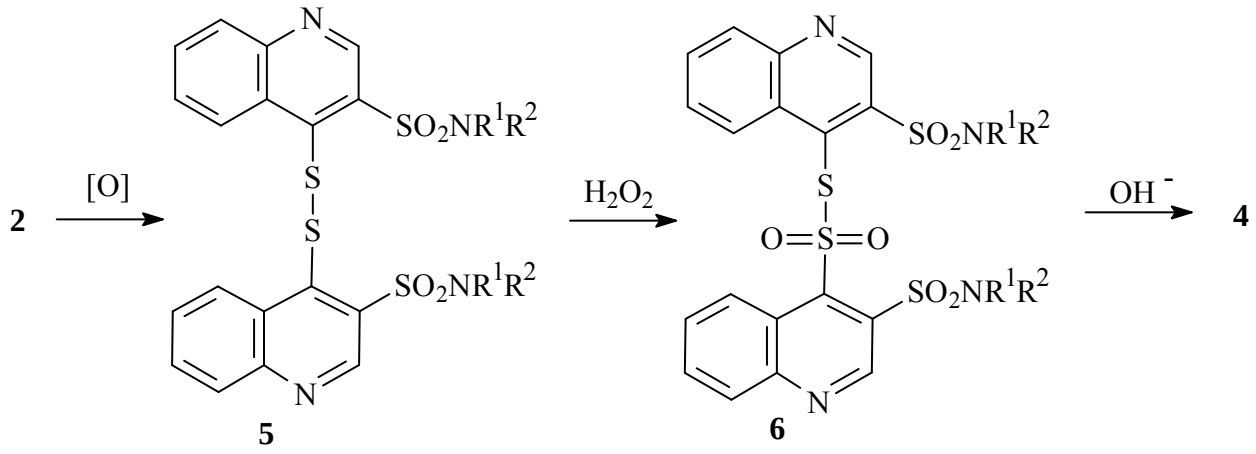
For some monosubstituted sulfonoamides, e.g., NR^1R^2 = $NHCH_3$ (**2b**), we observed the formation of some amount of the SO_2N-methylated products.

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-mercaptopurine under basic conditions gave hypoxanthine.[7,8]



2 **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 thiols[9]) 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]



5 **6**

hypothetical

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
$(CH_2)_2O(CH_2)_2$		**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 ^{1}H 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 ^{o}C. EI MS, (m/z): 240(M^+, 51.3%), 161(100%). ^{1}H NMR (DMSO-d_6) δ: 7.16(s, 2H, NH_2), 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 $C_9H_8N_2O_2S_2$: 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 ^{o}C. EI MS, (m/z): 254(M^+, 49.1%), 224(100%). ^{1}H NMR (DMSO-d_6) δ: 2.37(d, *J*=5.1 Hz, 3H, $NHCH_3$), 7.06(q, *J*=5.1 Hz, 1H, $NHCH_3$), 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 $C_{10}H_{10}N_2O_2S_2$: 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 ^{o}C. EI MS, (m/z): 310(M^+, 57.2%), 86(100%). ^{1}H NMR (DMSO-d_6) δ: 3.30-3.33(m, 4H, -CH_2NCH_2-), 3.55-3.57(m, 4H, -CH_2OCH_2-), 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%). ^{1}H 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%). ^{1}H 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 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-quinolinesufonamides (**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%). ^{1}H 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%). ^{1}H 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%). ^{1}H 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%). ^{1}H 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 $C_{17}H_{16}N_2O_2S_2$: 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-Methyltio-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 whale 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 ^{o}C. EI MS, (m/z): 268(M^+, 100%). ^{1}H 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 ^{o}C. EI MS, (m/z): 282(M^+, 79.7%), 238(100%). ^{1}H NMR (DMSO-d_6) δ: 2.54(s, 3H, 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 ^{o}C, lit.,[2] mp 291-293 ^{o}C.

1,4-Dihydro-4-oxo-*N*-methyl-3-quinolinesulfonamide (**4b**): mp 270-271 ^{o}C, lit.,[2] mp 263-265 ^{o}C.

1,4-Dihydro-4-oxo-3-quinolinesulfonmorpholide (**4c**): mp 298-299 ^{o}C, lit.,[2] mp 297-298 ^{o}C.

1,4-Dihydro-4-oxo-3-quinolinesulfonanilide (**4d**): mp 264-265 ^{o}C, lit.,[2] mp 264-265 ^{o}C.

1,4-Dihydro-4-oxo-*N*-methyl-3-quinolinesulfonanilide (**4e**): mp 249-250 ^{o}C, lit.,[2] mp 250-251 ^{o}C.

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