

THE PREPARATION OF 1-NONSUBSTITUTED AND 1-METHYL- (AND ETHYL)-1,4-DIHYDRO-4-OXO-3-QUINOLINESULFONAMIDES FROM 4-CHLORO-3-QUINOLINESULFONAMIDES ¹

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Abstract 4-Chloro-3-quinolinesulfonamides (1) were hydrolysed to 1,4-dihydro-4-oxo-3-quinolinesulfonamides (2) with boiling 18% hydrochloric acid. *N*-Alkyl-1,4-dihydro-4-oxo-3-quinolinesulfonamides (3) were prepared by quaternization of compounds (1) with dialkyl (methyl or ethyl) sulfate followed by hydrolysis of the quinolinium salt (4) formed.

INTRODUCTION

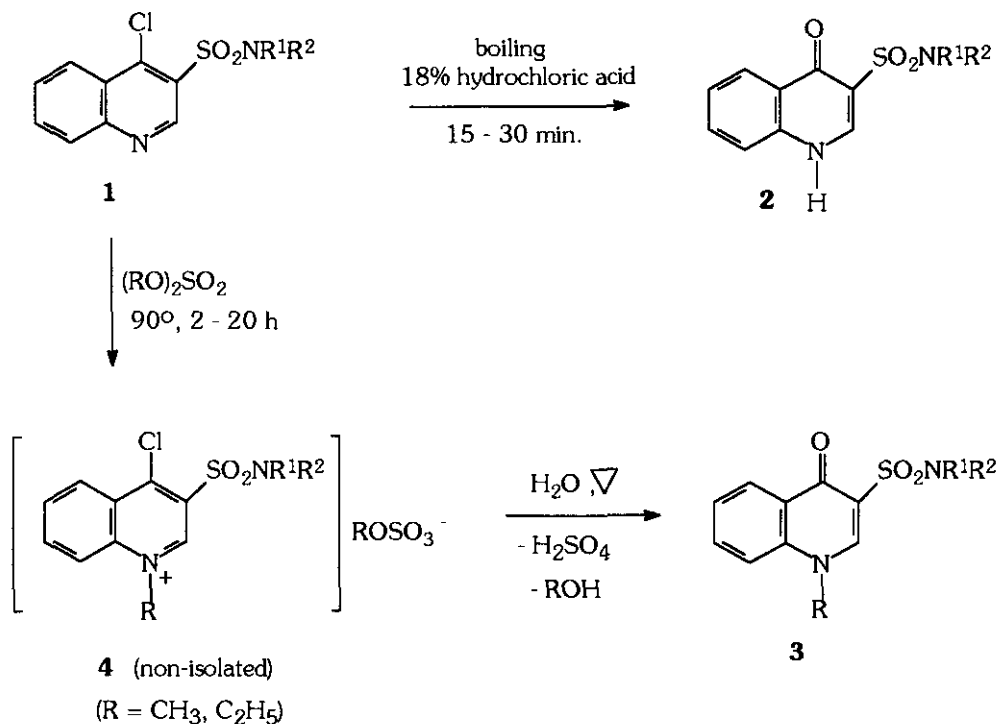
In the preceding paper we reported a two-step preparation of 4-chloro-3-quinolinesulfonyl chloride from quinoline.² Depending on the reaction procedure and amine structure, aminolysis of 4-chloro-3-quinolinesulfonyl chloride led to 4-amino-3-quinolinesulfonamides, 4-chloro-3-quinolinesulfonamides (1) (for ammonia and *N*-methylaniline) or the mixture of 4-amino-3-quinolinesulfonamide (the major product) and 4-chloro-3-quinolinesulfonamide (1) (the minor product).² The chloroquinolines (1) appeared to be unstable compounds and in the presence of atmospheric moisture they underwent partial hydrolysis to 4(1*H*)-quinolinones (2).

Literature search revealed that 1,4-dihydro-4-oxo-3-quinolinesulfonamides (2) could be prepared either *via* pyridine ring closure starting from appropriate benzene derivatives³⁻⁵ or by sulfonation of 4(1*H*)-quinolinones.⁴ *N*₁-Alkyl derivatives (3) were also prepared by *N*₁-alkylation of the corresponding 4(1*H*)-quinolinones.^{3,4}

In this paper we would like to present a new way of preparing 4-oxo-3-quinolinesulfonamides (2) by hydrolysis of 4-chloro-3-quinolinesulfonamides (1) as well as a new approach to endocyclic-nitrogen atom substituted 4(1*H*)-quinolinones (3) *via* alkylation of (1) followed by hydrolysis of the formed *N*-alkylquinolinium salt (4).

RESULTS AND DISCUSSION

4-Chlorine substituent in 4-chloro-3-quinolinesulfonamides (**1**) is strongly activated toward nucleophilic displacement both by ring nitrogen (aza-activation) and by ortho electron-withdrawing sulfonamide group. Thus, 4-chloroquinolines (**1**) undergo partial hydrolysis even in atmospheric moisture at room temperature. For preparative purposes, compounds (**1**) were treated with hot 18% hydrochloric acid. It causes complete hydrolysis of (**1**) to (**2**) within 15-30 min and 1,4-dihydro-4-oxo-3-quinolinesulfonamides (**2**) were obtained in high yields (79-91%) as well as with good purity.



Taking into account high nucleophilic susceptibility of chlorine substituent in (**1**) as well as nitrogen-base type properties of (**1**) we consider to prepare 4-quinolinone-3-sulfonamide (**3**) by means of quaternization of (**1**) followed by hydrolysis of the formed *N*-alkyl-quinolinium salt (**4**). In fact, the reactions of compounds (**1**) with dialkyl sulfates proceed (90°C , 2 h for $\text{R} = \text{CH}_3$ or 20 h for $\text{R} = \text{C}_2\text{H}_5$) with complete consumption of quinoline substrate (**1**) (except 4-chloro-3-quinolinesulfonanilide, see Experimental) to form the salt (**4**) almost quantitatively. However, due to instability of quinolinium methyl (or ethyl) sulfates (**4**), we could not isolate them in a pure state. The salts (**4**) were readily hydrolysed even in a weak aqueous acidic medium to form 1-methyl(ethyl)-4-quinolinone-3-sulfonamide (**3**). Yanagisawa *et al.* described that methylation of quinolinone-3-sulfonamide (**2a**) by means of methyl iodide / silver oxide system took place simultaneously both at endocyclic and at sulfonamide nitrogens.³ In the reaction of (**1**) with dialkyl sulfates no formation of products resulting from alkylation at sulfonamide nitrogen was observed.

Table

Product			Yield [%]
	R ¹	R ²	
2a	H	H	90
2b	H	CH ₃	87
2c	CH ₃	CH ₃	79
2d	H	CH ₂ CH ₃	89
2e	CH ₂ CH ₃	CH ₂ CH ₃	81
2f	-CH ₂ CH ₂ OCH ₂ CH ₂ -		93
2g	-CH ₂ (CH ₂) ₃ CH ₂ -		90
2h	H	Ph	91
2i	CH ₃	Ph	89

Product				Yield [%]
	R	R ¹	R ²	
3a	CH ₃	H	H	82
3b	CH ₂ CH ₃	H	H	81
3c	CH ₃	H	CH ₃	81
3d	CH ₂ CH ₃	H	CH ₃	80
3e	CH ₃	-CH ₂ CH ₂ OCH ₂ CH ₂ -		84
3f	CH ₂ CH ₃	-CH ₂ CH ₂ OCH ₂ CH ₂ -		83
3g	CH ₃	H	Ph	79
3h	CH ₂ CH ₃	H	Ph	ca. 20
3i	CH ₃	CH ₃	Ph	81
3j	CH ₂ CH ₃	CH ₃	Ph	88

EXPERIMENTAL

Melting points were determined in open capillary tubes on a Boetius melting point apparatus and are uncorrected. The ¹H NMR spectra were recorded on a Bruker MSL 300 (300 MHz) spectrometer in dimethyl sulfoxide-d₆ solutions with tetramethylsilane as the internal standard and chemical shifts are reported in ppm (δ) and *J* values in Hz. EIMS spectra were run on a LKB GC 2091 spectrometer at 70 eV and 15 eV. CIMS spectra were recorded with Finnigan MAT 95 spectrometer using isobutane as a reagent gas and temperature of ion source of 180 °C. TLC was performed on aluminium oxide using a mixture of chloroform - ethanol (10:1 v/v) as an eluent.

4-Chloro-3-quinolinesulfonamides (**1a-i**) were prepared by amination of 4-chloro-3-quinolinesulfonyl chloride with appropriate amine as described previously.²

1,4-Dihydro-4-oxo-3-quinolinesulfonamides (2)

The mixture of 4-chloro-3-quinolinesulfonamide (**1a-i**) (2 mmol) and 10 mL of 18% hydrochloric acid was refluxed for 0.5 h and cooled down to rt. The solid was filtered off, then washed twice with 2 mL of water and air-dried. It was recrystallized from ethanol or aqueous ethanol to give white crystals of 1,4-dihydro-4-oxo-3-quinolinesulfonamide (**2a-i**) (79-91%). The results are collected in the Table.

1,4-Dihydro-4-oxo-3-quinolinesulfonamide (2a)

mp 291-293 °C, lit.,³ mp 303-305 °C.

1,4-Dihydro-N-methyl-4-oxo-3-quinolinesulfonamide (2b)

mp 263-265 °C. EI MS (15 eV), (m/z): 238(M⁺, 78.28%), 145(100%). ¹H NMR, δ: 2.40(d, J=5.1 Hz, 3H, NHCH₃); 6.68(q, J=5.1 Hz, 1H, NHCH₃); 7.55-7.60(m, 1H, H-6); 7.78-7.81(m, 1H, H-8); 7.85-7.91(m, 1H, H-7); 8.27-8.30(m, 1H, H-5); 8.58(d, J=6.6 Hz, 1H, H-2); 12.66(d, J=6.3 Hz, 1H, N₁-H). *Anal.* Calcd for C₁₀H₁₀N₂O₃S: C 50.41; H 4.23; N 11.76; S 13.46. Found: C 50.52; H 4.41; N 11.64; S 13.54.

1,4-Dihydro-N,N-dimethyl-4-oxo-3-quinolinesulfonamide (2c)

mp 287-289 °C. EI MS (15 eV), (m/z): 252(M⁺, 45.0%). ¹H NMR, δ: 2.89(s, 6H, 2 x CH₃); 7.53-7.59(m, 1H, H-6); 7.76-7.79(m, 1H, H-8); 7.84-7.89(m, 1H, H-7); 8.24-8.27(m, 1H, H-5); 8.58(s, 1H, H-2). *Anal.* Calcd for C₁₁H₁₂N₂O₃S: C 52.37; H 4.79; N 11.10; S 12.71. Found: C 52.45; H 4.64; N 11.22.

1,4-Dihydro-N-ethyl-4-oxo-3-quinolinesulfonamide (2d)

mp 252-253 °C. EI MS (15 eV), (m/z): 252(M⁺, 77.89%), 145(100%). ¹H NMR, δ: 1.08(t, J=7.2 Hz, 3H, CH₂CH₃); 2.86-2.95(m, 2H, CH₂CH₃); 6.91(t, J=5.9 Hz, 1H, NHCH₂-); 7.54-7.59(m, 1H, H-6); 7.77-7.80(m, 1H, H-8); 7.85-7.90(m, 1H, H-7); 8.27-8.30(m, 1H, H-5); 8.59(s, 1H, H-2); 12.60(s, 1H, N₁-H). *Anal.* Calcd for C₁₁H₁₂N₂O₃S: C 52.37; H 4.79; N 11.10; S 12.71. Found: C 52.30; H 4.58; N 11.15; S 12.64.

1,4-Dihydro-N,N-diethyl-4-oxo-3-quinolinesulfonamide (2e)

mp 271-273 °C. EI MS (15 eV), (m/z): 280(M⁺, 100%). ¹H NMR, δ: 1.15(t, J=7.0 Hz, 6H, 2 x CH₂CH₃); 3.41(q, J=7.0 Hz, 4H, 2 x CH₂CH₃); 7.51-7.57(m, 1H, H-6); 7.76-7.82(m, 1H, H-8); 7.84-7.88(m, 1H, H-7); 8.24-8.27(m, 1H, H-5); 8.60(d, J=6.3 Hz, 1H, H-2); 12.59(d, J=6.3 Hz, 1H, N₁-H). *Anal.* Calcd for C₁₃H₁₆N₂O₃S: C 55.70; H 5.75; N 9.99; S 11.44. Found: C 55.60; H 5.84; N 10.06; S 11.24.

1,4-Dihydro-4-oxo-3-quinolinesulfonmorpholide (2f)

mp 297-298 °C. EI MS (15 eV), (m/z): 294(M⁺, 46.9%), 86(100%). ¹H NMR, δ: 3.27-3.30(m, 4H, CH₂-N-CH₂); 3.68-3.71(m, 4H, CH₂-O-CH₂); 7.54-7.60(m, 1H, H-6); 7.77-7.79(m, 1H, H-8); 7.85-7.91(m, 1H, H-7); 8.25-8.28(m, 1H, H-5); 8.59(s, 1H, H-2). *Anal.* Calcd for C₁₃H₁₄N₂O₄S: C 53.05; H 4.79; N 9.52; S 0.89. Found: C 53.18; H 4.65; N 9.72; S 10.99.

1,4-Dihydro-4-oxo-3-quinolinesulfonpiperidide (2g)

mp 295-297 °C. EI MS (15 eV), (m/z): 292(M⁺, 35.2%), 84(100%). ¹H NMR, δ: 1.54-1.64(m, 6H, C-CH₂-C); 3.24-3.27(m, 4H, CH₂-N-CH₂); 7.53-7.58(m, 1H, H-6); 7.75-7.78(m, 1H, H-8); 7.83-7.88(m, 1H, H-7); 8.24-8.27(m, 1H, H-5); 8.57(d, J=6.7 Hz, 1H, H-2); 12.61(d, J=6.3 Hz, 1H, N₁-H). *Anal.* Calcd for C₁₄H₁₆N₂O₃S: C 57.52; H 5.52; N 9.58; S 10.97. Found: C 57.64; H 5.61; N 9.48; S 11.03.

1,4-Dihydro-4-oxo-3-quinolinesulfonanilide (2h)

mp 264-265 °C. EI MS (15 eV), (m/z): 300(M⁺, 39.65%), 93(100%). ¹H NMR, δ: 6.95-7.20(m, 5H,

C_6H_5); 7.41-7.48(m, 1H, **H-6**); 7.63-7.66(m, 1H, **H-8**); 7.71-7.78(m, 1H, **H-7**); 8.14-8.17(m, 1H, **H-5**); 8.58(s, 1H, **H-2**); 9.91(s, 1H, NHPH); 12.57(s, 1H, N_1 -**H**). *Anal.* Calcd for $C_{15}H_{12}N_2O_3S$: C 59.99; H 4.03; N 9.33; S 10.67. Found: C 60.04; H 4.12; N 9.53; S 10.59.

1,4-Dihydro-*N*-methyl-4-oxo-3-quinolinesulfonanilide (2i)

mp 250-251 °C. EI MS (15 eV), (m/z): 314(M^+ , 11.96%), 107(100%). 1H NMR, δ : 3.50(s, 3H, NCH_3Ph); 7.12-7.31(m, 5H, C_6H_5); 7.44-7.50(m, 1H, **H-6**); 7.62-7.66(m, 1H, **H-8**); 7.72-7.78(m, 1H, **H-7**); 8.18-8.21(m, 1H, **H-5**); 8.32(s, 1H, **H-2**); 12.48(s, 1H, N_1 -**H**). *Anal.* Calcd for $C_{16}H_{14}N_2O_3S$: C 61.13; H 4.49; N 8.91; S 10.20. Found: C 61.01; H 4.31; N 8.84; S 10.31.

The reaction of 4-chloro-3-quinolinesulfonamides (1) with dialkyl sulfates

A suspension of 2.5 mmol of finely powdered 4-chloro-3-quinolinesulfonamide (**1**) and 10 mmol of dialkyl sulfate was heated at 90°C for 2 h (dimethyl sulfate) or 20 h (diethyl sulfate). The mixture was then cooled down to rt. An excess of dialkyl sulfate was removed by three-fold trituration with 3 mL of benzene followed by decantation. The oily residue was kept at 40 °C under vacuum to give, almost quantitatively, crude 1-alkyl-4-chloro-3-aminosulfonylquinolinium alkyl sulfate (**4**) as a solid or syrupy semi-solid material.

Determination of sulfate content, performed as presented below, indicates 97-98 % of salt (**4**) in crude material. In order to analyse sulfate content, the sample of alkyl sulfate (**4**) was hydrolysed [as presented for the preparation of (**3**)] to the mixture of quinolinone (**3**), sulfuric acid and alcohol. Quinolinone (**3**) was removed by filtration and washed with water. Aqueous filtrate and washings were combined and then neutralized with sodium bicarbonate solution and finally treated with 5 % barium chloride aqueous solution to precipitate barium sulfate.

Due to instability of quinolinium methyl (or ethyl) sulfates (**4**), they could not be isolated in a pure state. Crude salt (**4**) was used for the preparation of compound (**3**).

1,4-Dihydro-1-methyl(ethyl)-4-oxo-3-quinolinesulfonamides (3)

a) General procedure:

Quinolinium salt (**4**) (*ca.* 2.5 mmol) [prepared as above from compound (**1**)] was suspended in 10 mL of water. The mixture was refluxed for 1 h and then cooled down to rt. The solid was filtered off, washed with water and air-dried. It was recrystallized from ethanol or aqueous ethanol to give white crystals of 1,4-dihydro-1-methyl(ethyl)-4-oxo-3-quinolinesulfonamide (**3**) (79-88%). The results are collected in the Table.

b) Procedure for the conversion of 4-chloro-3-quinolinesulfonamide (**1f** or **1i** to **3e**, **3f** or **3i**, **3j**) without isolation of quinolinium salts (**4**).

The reaction of 4-chloro-3-quinolinesulfonamide (**1**) with dialkyl sulfate was performed as in procedure a). Salts (**4**) containing *N,N*-dialkylsulfonamide moiety are partially soluble in benzene. In these cases the mixture resulting from the reaction of (**1**) with excess of dialkyl sulfate was directly subjected to hydrolysis.

The compounds (**3**) were isolated as in procedure a).

c) Reaction of 4-chloro-3-quinolinesulfonanilide (**1h**) with diethyl sulfate.

The reaction of (**1h**) with diethyl sulfate proceeded very slowly, after 20 h only 10% conversion of (**1h**) was observed, 40% conversion of (**1h**) was reached after 100 h. The mixture was subjected to hydrolysis as in procedure b). 1-Ethyl-4-quinolinesulfonanilide (**3h**) was isolated by column chromatography on aluminium oxide and solution of chloroform - ethanol (20 : 1, v/v) as an eluent.

1,4-Dihydro-1-methyl-4-oxo-3-quinolinesulfonamide (**3a**)

mp 244-245 °C, lit.,⁴ mp 230-231 °C or lit.,³ mp 244-246 °C.

1-Ethyl-1,4-dihydro-4-oxo-3-quinolinesulfonamide (**3b**)

mp 228-230 °C. EI MS (15 eV), (m/z): 252(M⁺, 100%). ¹H NMR, δ: 1.37(t, J=6.9 Hz, 3H, CH₂CH₃); 4.49(q, J=6.9 Hz, 2H, CH₂CH₃); 6.85(s, 2H, NH₂); 7.52-7.57(m, 1H, H-6); 7.86-7.92(m, 1H, H-8); 7.86-7.92(m, 1H, H-7); 8.29-8.32(m, 1H, H-5); 8.69(s, 1H, H-2). Anal. Calcd for C₁₁H₁₂N₂O₃S: C 52.37; H 4.79; N 11.10; S 12.71. Found: C 51.81; H 4.46; N 10.86; S 12.60.

1,4-Dihydro-1,N-dimethyl-4-oxo-3-quinolinesulfonamide (**3c**)

mp 258-260 °C, lit.,⁴ mp 248-250 °C or lit.,³ mp 254-261 °C.

1-Ethyl-1,4-dihydro-N-methyl-4-oxo-3-quinolinesulfonamide (**3d**)

mp 196-197 °C. CI MS (m/z): 267(M⁺+1, 100%). ¹H NMR, δ: 1.38(t, J=7.1 Hz, 3H, CH₂CH₃); 2.41(d, J=5 Hz, 3H, NHCH₃); 4.48(q, J=7.1 Hz, 2H, CH₂CH₃); 6.74(q, J=5 Hz, 1H, NHCH₃); 7.50-7.58(m, 1H, H-6); 7.81-7.92(m, 2H, H-7, H-8); 8.26-8.30(m, 1H, H-5); 8.64(s, 1H, H-2). Anal. Calcd for C₁₂H₁₄N₂O₃S: C 54.12; H 5.30; N 10.53; S 12.02. Found: C 53.96; H 5.15; N 10.27; S 12.21.

1,4-Dihydro-1-methyl-4-oxo-3-quinolinesulfonmorpholide (**3e**)

mp 279-280 °C. CI MS (m/z): 309(M⁺+1, 100%). ¹H NMR, δ: 3.16-3.21(m, 4H, CH₂-N-CH₂); 3.59-3.62(m, 4H, CH₂-O-CH₂); 3.97(s, 3H, N₁-CH₃); 7.54-7.59(m, 1H, H-6); 7.79-7.81(m, 1H, H-8); 7.85-7.91(m, 1H, H-7); 8.24-8.27(m, 1H, H-5); 8.63(s, 1H, H-2). Anal. Calcd for C₁₄H₁₆N₂O₄S: C 54.53; H 5.23; N 9.08; S 10.40. Found: C 54.04; H 5.13; N 8.92; S 10.56.

1-Ethyl-1,4-dihydro-4-oxo-3-quinolinesulfonmorpholide (**3f**)

mp 186-188 °C. CI MS (m/z): 323(M⁺+1, 100%). ¹H NMR, δ: 1.39(t, J=7.0 Hz, 3H, CH₂CH₃); 3.16-3.21(m, 4H, CH₂-N-CH₂); 3.59-3.62(m, 4H, CH₂-O-CH₂); 4.47(q, J=7.0 Hz, 2H, CH₂CH₃); 7.52-7.57(m, 1H, H-6); 7.83-7.91(m, 2H, H-7, H-8); 8.26-8.29(m, 1H, H-5); 8.65(s, 1H, H-2). Anal. Calcd for C₁₅H₁₈N₂O₄S: C 55.89; H 5.63; N 8.69; S 9.94. Found: C 56.02; H 5.89; N 8.54.

1,4-Dihydro-1-methyl-4-oxo-3-quinolinesulfonanilide (**3g**)

mp 281-283 °C. EI MS (15 eV), (m/z): 314(M⁺, 100%). ¹H NMR, δ: 3.94(s, 3H, N₁-CH₃); 6.90-6.96(m, 1H, p-C₆H₅); 7.14-7.20(m, 4H, C₆H₄); 7.49-7.53(m, 1H, H-6); 7.71-7.74(m, 1H, H-8); 7.80-7.85(m, 1H,

H-7); 8.22-8.24(m, 1H, H-5); 8.73(s, 1H, H-2); 9.96(s, 1H, NHPh). *Anal.* Calcd for $C_{16}H_{14}N_2O_3S$: C 61.13; H 4.49; N 8.91; S 10.20. Found: C 61.31; H 4.67; N 9.11; S 10.40.

1-Ethyl-1,4-dihydro-4-oxo-3-quinolinesulfonanilide (3h)

mp 254-255 °C. EI MS (15 eV), (m/z): 328(M^+ , 100%). 1H NMR, δ : 1.29(t, $J=7.2$ Hz, 3H, CH_2CH_3); 4.47(q, $J=7.2$ Hz, 2H, CH_2CH_3); 6.91-6.96(m, 1H, p- C_6H_5); 7.12-7.16(m, 4H, C_6H_5); 7.50-7.54(m, 1H, H-6); 7.82-7.84(m, 1H, H-8); 7.82-7.85(m, 1H, H-7); 8.24-8.26(m, 1H, H-5); 8.74(s, 1H, H-2); 9.99(s, 1H, NHPh). *Anal.* Calcd for $C_{17}H_{16}N_2O_3S$: C 62.18; H 4.91; N 8.53; S 9.76. Found: C 62.40; H 4.70; N 8.67; S 9.84.

1,4-Dihydro-1,N-dimethyl-4-oxo-3-quinolinesulfonanilide (3i)

mp 178-180 °C. CI MS (m/z): 329(M^++1 , 100%). 1H NMR, δ : 3.89(s, 3H, N_1-CH_3); 3.48(s, 3H, NCH_3Ph); 7.26-7.31(m, 1H, p- C_6H_5); 7.12-7.16(m, 4H, C_6H_5); 7.53-7.58(m, 1H, H-6); 7.73-7.76(m, 1H, H-8); 7.83-7.88(m, 1H, H-7); 8.27-8.30(m, 1H, H-5); 8.52(s, 1H, H-2). *Anal.* Calcd for $C_{17}H_{16}N_2O_3S$: C 62.18; H 4.91; N 8.53; S 9.76. Found: C 61.42; H 4.88; N 8.37.p

1-Ethyl-1,4-dihydro-N-methyl-4-oxo-3-quinolinesulfonanilide (3j)

mp 187-189 °C. CI MS (m/z): 343(M^++1 , 100%). 1H NMR, δ : 1.23(t, $J=7.0$ Hz, 3H, CH_2CH_3); 3.47(s, 3H, NCH_3Ph); 4.39(q, $J=7.0$ Hz, 2H, CH_2CH_3); 7.13-7.19(m, 1H, p- C_6H_5); 7.25-7.30(m, 4H, C_6H_5); 7.51-7.57(m, 1H, H-6); 7.83-7.85(m, 2H, H-7, H-8); 8.28-8.30(m, 1H, H-5); 8.47(s, 1H, H-2). *Anal.* Calcd. for $C_{18}H_{18}N_2O_3S$: C 63.14; H 5.30; N 8.18; S 9.36. Found: C 62.94; H 5.51; N 8.27; S 9.46.

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