SYNTHESIS AND AMINATION OF 4-CHLORO-3-QUINOLINESULFONYL CHLORIDE [1]

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Abstract -Chlorinolysis of 4-chloro-3-benzylthioquinoline (**2**) or thioquinanthrene (**1**) using chlorine gas in the presence of water gave 4-chloro-3-quinolinesulfonyl chloride (**3**). Amination of (**3**) performed in ether led to 4-chloro-3-quinolinesulfonamides (**4**). Reactions of compound (**3**) with an excess of primary or secondary amine in two phase (water/toluene or benzene) system gave 4-(substituted amino)-3-quinolinesulfonamides (**5**) with two identical amine rests. While 4-chloro-3-quinolinesulfonamides (**4**) were aminated with an excess of amine into aminosulfonamides (**5**) with two identical or two various amine rests.

INTRODUCTION

In the previous paper we described a four-stage procedure for the preparation of 4-substituted 3-quinolinyl sulfides from quinoline [2-5] In this synthesis, the key-steps were sulfurization of quinoline with elemental sulfur yielding thioquinanthrene i e. 1,4-dithiino[2,3-*c*:5,6-*c*']diquinoline (**1**) (60-64%) [6] and cleavage reaction of the 1,4-dithiin ring of (**1**) with nucleophiles.[2-8]

Another approach to the synthetic utilization of thioquinanthrene (**1**) could be based on its chlorinolysis taking into consideration literature data presented below. Chlorinolysis of γ- or α-azinyl sulfides (as well as thiols or thiones) proceeded with the cleavage of the γ- or α-azinyl-sulfur bond leading to the corresponding chloroazines. [9-11] On the other hand, chlorinolysis of other isomers with the non-*aza*-activated azinyl-sulfur bond (especially that of azinylbenzyl sulfides) did not affect the azinyl-sulfur bond producing azinesulfonyl chlorides. [12] It could therefore be expected that chlorinolysis of thioquinanthrene (**1**) as both γ- and β-quinolinyl sulfides would proceed with the cleavage of the γ-quinolinyl-sulfur bonds and oxidative chlorination of β-quinolinyl ones under the "wet-chlorination" -procedure [11] producing 4-chloro-3-quinolinesulfonyl chloride (**3**).

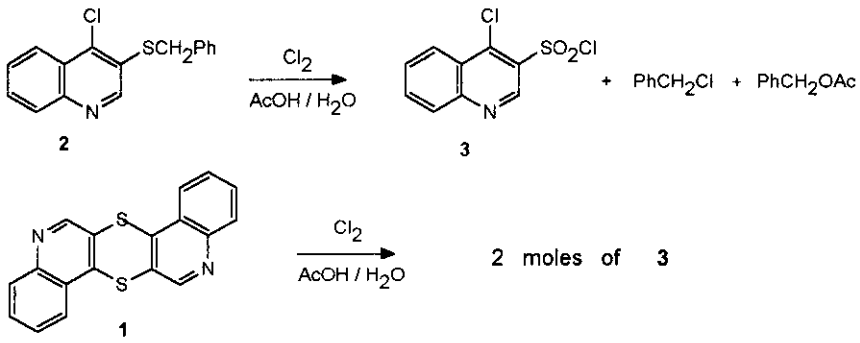
Compound (**3**) having an activated 4-chloro-substituent could be easily transformed into other derivatives of 3-quinolinesulfonic acid.

RESULTS AND DISCUSSION

4-Chloro-3-benzylthioquinoline (**2**) [5] was chosen as a model compound for our approach to the "wet-chlorination" of thioquinanthrene (**1**), since the chlorinolysis of 3-quinolinyl sulfides has not yet been studied. This reaction proceeded in acetic acid-water (80 : 1.8, v/v) solution at 15-17°C within 1 hour with complete consumption of quinolinyl sulfide (**2**) giving rise to high yields of the following products: 4-chloro-3-quinolinesulfonyl chloride (**3**) (89-91%) and benzyl chloride 50% and benzyl acetate 46%.

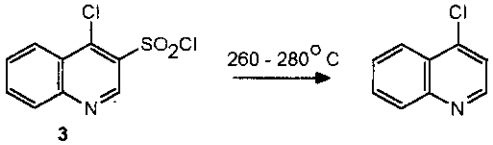
Chlorinolysis of thioquinanthrene (**1**) also proceeded in an exothermic reaction with complete consumption of the 1,4-dithiin-substrate, yielding 4-chloro-3-quinolinesulfonyl chloride (**3**), which could be isolated in a pure state in a maximum yield of 79%.

Scheme 1



4-Chloro-3-quinolinesulfonyl chloride (**3**) is a pale-yellow solid with mp 129-130°C, stable under the exclusion of moisture at room temperature for several days. Upon standing it partially undergoes transformation into 4-chloro-3-quinolinesulfonic acid (insoluble in benzene, tetrachloromethane and ether). The EI mass spectrum of the sulfonyl chloride (**3**) at 15 eV shows peaks of m/z 197 (5.5%) and 199 (3.2%) indicating the easy loss of sulfur dioxide and formation of 3,4-dichloroquinoline species. In fact, on heating at 260-280°C, 4-chloro-3-quinolinesulfonyl chloride (**3**) underwent decomposition with evolution of sulfur dioxide yielding 3,4-dichloroquinoline (25%).

Scheme 2

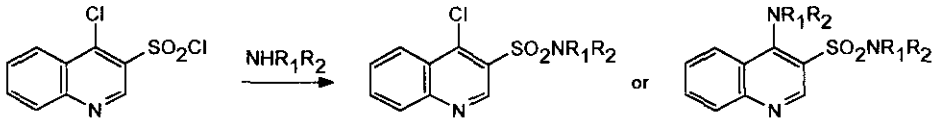


Amination of 4-chloro-3-quinolinesulfonyl chloride (**3**).

Some 3-quinolinesulfonamides exhibit interesting pharmacological mode of action [13] It induced the presented below study on the amination of 4-chloro-3-quinolinesulfonyl chloride (**3**) The molecule of compound (**3**) contains two reactive chlorine substituents: the first one in the chlorosulfonyl group and the second one in the 4-chloroquinoline group being simultanously aza-activated as well as ortho-activated by the electron-withdrawing group Thus, attempted dechloro-amination of the chlorosulfonyl chloride (**3**) may lead to mono- and (or) di-amination products.

In order to prepare 4-chloro-3-quinolinesulfonamides (**4**), amination of compound (**3**) was performed in ether using an excess of the amine as a hydrogen chloride acceptor. In the case of methylamine, dimethylamine, ethylamine and aniline substitution of only chlorine atom from the chlorosulfonyl group required low temperature (-70^{0}C) as well as removal of an amine excess below -20^{0}C (Table 1, Entries 2,4,5,8) In the other case reactions of compound (**3**) with amines mentioned above led to the mixtures of 4-chloro-3-quinolinesulfonamides (**4**) and 4-amino-3-quinolinesulfonamides (**5**) (Table 1, Entries 7,17,21). Reactions of ammonia, piperidine, morpholine, diethylamine and *N*-methylaniline with the chlorosulfonyl chloride (**3**) could be performed at room temperature or in boiling ether to give good yields of 4-chloro-3-quinolinesulfonamides of type (**4**) (Table 1, Entries 1,10-13)

Scheme 3



3 4 5

It should be noted that amination of compound (**3**) with methylamine, dimethylamine and aniline performed under the Schotten-Baumann reaction conditions, [14] i.e in aqueous 10% solution of sodium hydroxide, led to the expected 4-chloro-3-quinoline (*N*-mono-substituted or *N,N*-disubstituted) sulfonamides (**4b**, **4c**, **4d**) but in lower yields (28-54%, Table 1, Entries 3,6,9).

^{1}H Nmr spectral data of aromatic protons of compounds (**4**) are very close to those of parent compound (**3**) (see Table 3). It indicates that mono-dechloro-amination of the chlorosulfonyl chloride (**3**) proceeds as replacement of chlorine atom from chlorosulfonyl group leaving 4-chloroquinoline fragment unaffected. Also hydrolysis of 4-chloro-3-quinolinesulfonamides (**4**) give rise to 4-oxo-1,4-dihydro-3-quinolinesulfonamides but not to 4-amino-3-quinolinesulfonic acids[15] (see Scheme 4).

Table 1 4-Chloro-3-quinolinesulfonamides (**4**) and 4-amino-3-quinolinesulfonamides (**5**) prepared directly from 4-chloro-3-quinolinesulfonyl chloride (**3**)

Entry	Product		Reaction conditions					Properties of product					
		R	Procedure	Temp. °C	Time h	Molar ratio. amine/sulfochloride (3)	Yield %	mp °C	Ms 15 eV m/z M^+(%)	Formula	Analysis (Calcd/Found) C %	H %	N %	S %
1	**4a**	R_1=R_2=H	A-4	40-45	0.5	35/1	90	201-202 (decomp)	242 (100)	$C_9H_7N_2O_2ClS$	44 56 44 41	2.91 2.80	11 54 11.68	13.21 13.28
2	**4b**	R_1=H, R_2=Me	A-1	-70 up to -20	2	22/1	64	200-201	256 (100)	$C_{10}H_9N_2O_2ClS$	46.79 46 84	3.53 3 61	10.91 11.01	12 49 12.57
3	**4b**	R_1=H, R_2=Me	A-3	25	1.5	3/1	54							
4	**4c**	R_1=H, R_2=Et	A-1	-70 up to -20	2	12/1	78	186-188	270 (98.0)	$C_{11}H_{11}N_2O_2ClS$	48.80 48.72	4.10 4.19	10.35 10 27	11.84 11 72
5	**4d**	R_1=H, R_2=Ph	A-1	-70 up to +20	2	1/1 [a]	54	223-224 (decomp)	318 (84.1)	$C_{15}H_{11}N_2O_2ClS$	56.52 56 64	3.48 3.37	8.79 8.89	10.06 9.96
6	**4d**	R_1=H, R_2=Ph	A-3	25	1	1.1/1	42							
7	**4d**	R_1=H, R_2=Ph	A-2	36	1	1.1/1	a mixture of **4d** - 20% and **5d** - 40% [d]							
8	**4e**	R_1=R_2=Me	A-1	-70 up to -20	2	15/1	75	148-149	270 (100)	$C_{11}H_{11}N_2O_2ClS$	48.80 48.91	4.10 4 21	10.35 10.43	11 84 11.71
9	**4e**	R_1=R_2=Me	A-3	25	2	3/1	28							
10	**4f**	R_1=R_2=Et	A-2	36	0.25	12/1	76	104-105	298 (16.2)	$C_{13}H_{15}N_2O_2ClS$	52.26 52.17	5.06 5.21	9.38 9.31	10.73 10.84
11	**4g**	R_1+R_2= -$(CH_2)_5$-	A-2	room. temp.	1	2 25/1	80	147-148	310 (82.4)	$C_{14}H_{15}N_2O_2ClS$	54.10 54 23	4.86 4.75	9.01 8.92	10 32 10 39
12	**4h**	R_1+R_2=$(CH_2)_2O(CH_2)_2$-	A-2	room. temp.	1	2.25/1	84	185-186	312 (38.0)	$C_{13}H_{13}N_2O_3ClS$	49.92 49.84	4.19 4 30	8 96 8.81	10.25 10.18
13	**4i**	R_1=Me, R_2=Ph	A-2	36	2	1/1 [a]	71	123-124	332 (47 3)	$C_{16}H_{13}N_2O_2ClS$	57.74 57 86	3.94 3.81	8.42 8.38	9 63 9 51
14	**4i**	R_1=Me, R_2=Ph	B	c)	2	2.2/1 [b]	80							

Table 1 (continued)

Entry	Product	R	Reaction conditions: Procedure	Temp. °C	Time h	Molar ratio amine/sulfochloride (3)	Yield %	mp °C	Ms (15 eV) m/z. M^+(%)	Formula	Analysis (Calcd/Found) C %	H %	N %	S %
15	**5a**	R_1=R_2=H	-	180	2	-	90	277-279 (decomp.)	223 (100)	$C_9H_9N_3O_2S$	48.42	4.06	18.82	14.36
											48.34	4 01	18 71	14 47
16	**5b**	R_1=H, R_2=Me	B	c)	0.75	5 5/1	92	215-216	251 (100)	$C_{11}H_{13}N_3O_2S$	52.57	5.21	16 72	12.76
											52.61	5.18	16 64	12 58
17	**5b**	R_1=H, R_2=Me	A-1	-70 up to +20	2	5.5/1	a mixture of **5b** - 75% and **4b** - 5% [d]							
18	**5c**	R_1=H, R_2=Et	B	c)	1	15/1	83	149-150	279 (75.6)	$C_{13}H_{17}N_3O_2S$	55 89	6.13	15.04	11.48
											55.76	6.21	14.91	11.58
19	**5d**	R_1=H, R_2=Ph	B	c)	1 5	2.2/1 [b]	90	231-232 (decomp.)	375 (60 4)	$C_{21}H_{17}N_3O_2S$	7.18	4.56	11 19	8 54
											7 08	4 45	11 08	8 67
20	**5e**	R_1=R_2=Me	B	c)	0 75	6/1	92	45-48	279(17.3)	$C_{13}H_{17}N_3O_2S$	55 89	6 13	15.04	11 48
											55.78	6.02	15.20	11 38
21	**5e**	R_1=R_2=Me	A-1	-70 up to +20	2	6/1	a mixture of **5e** - 91% and **4e** - 2% [d]							
22	**5f**	R_1=R_2=Et	B	c)	2	6/1	93	oil	335(0.6)	$C_{17}H_{25}N_3O_2S$	60.87	7.51	12 53	9 56
											60.79	7.40	12.47	9.48
23	**5g**	R_1 +R_2= - $(CH_2)_5$ -	B	c)	2	5/1	87	108-109	359(0 4)	$C_{19}H_{25}N_3O_2S$	63.48	7.01	11.69	8.92
											63.51	7.11	11.57	8 84
24	**5h**	R_1+R_2= -$(CH_2)_2O(CH_2)_2$ -	B	c)	2	5/1	76	149-150	363(0 7)	$C_{17}H_{21}N_3O_4S$	56 18	5.82	11 56	8.82
											56 24	5.71	11.59	8.71

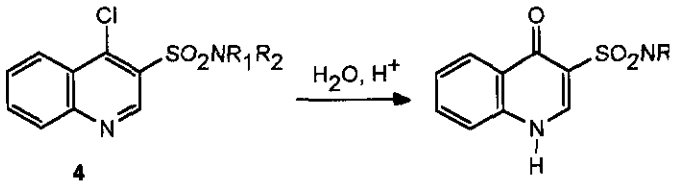
a) The reaction was performed in the presence of 1.25 equivs of triethylamine

b) The reaction was performed in the presence of 2.5 equivs. of sodium bicarbonate.

c) Reaction mixture boiling temperature

d) Calculated from ^{1}H nmr spectral data

Scheme 4



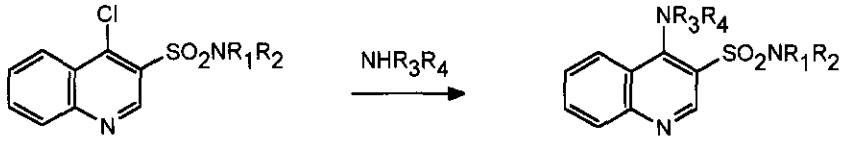
4

In order to obtain 4-amino-3-quinolinesulfonamides of type **5**, *aminolysis of chloride* (**3**) was also carried out with the use of an excess of amine but in the two-phase toluene (or benzene)-water system at its boiling temperature (*procedure* B). However, *in the case of ammonia* and *N*-methylaniline only 4-chloro-3-quinolinesulfonamides of type (**4**) were obtained (Table 1, Entry 14). We could not find any *satisfactory explanation* why *ammonolysis* of the chlorosulfonyl chloride (**3**) takes place only at the chlorosulfonyl group and leads to 4-chloro-3-quinolinesulfonamide (**4a**). That is why 4-*amino*-3-quinolinesulfonamide (**5a**) was prepared from (**4a**) by means of classical "phenol" method [16] in a yield of 90% (see procedure A-4)

4-Chloro-3-quinolinesulfonamides (**4**) were *easily transformed into* 4-*amino*-3-*quinolinesulfon*-amides (**5**) upon reaction with the appropriate amine / amine hydrochloride mixture in ethanolic solutions. *Similar reactions with the unprotonated amine proceeded much slower.*

Aminolysis of compounds (**4**) to yield 4-aminoquinoline derivatives (**5**) offers possibility to prepare *compounds containing various other combinations* of both amino substituents, as seen in Table 2

Scheme 5



4 **5**

4-Chlorine substituents in quinoline derivatives are activated towards nucleophilic displacement reactions with amines by protonation, [17] and results of the aminolysis of 4-chloro-3-quinolinesulfonamides (**4**) also confirm it. Thus, *one-pot* transformation of 4-chloro-3-quinolinesulfonyl chloride (**3**) into aminosulfonamides (**5**) should proceed through the stage of 4-chloro-3-quinoline-(*N*-substituted)sulfonamides (**4**) following by their transformation into 4-chloroquinolinium salts which at the end react with the amine giving rise to the final products (**5**).

CONCLUSIONS

As a conclusion we have shown that 4-(substituted amino)-3-quinolinesulfonamides can be produced in an effective three- or four-stage synthesis starting from quinoline via thioquinanthrene and 4-chloro-3-quinolinesulfonyl chloride (**3**). This synthetic strategy seems to be more convenient in comparison with previously reported synthesis of 3-quinolinesulfonic acid derivatives [13,18,19]

EXPERIMENTAL

Melting points were determined in open capillary tubes on a Boetius melting point apparatus and are uncorrected The ^{1}H nmr spectra were recorded on a Bruker MSL 300 (300 MHz) spectrometer in deuteriochloroform or dimethyl sulfoxide-d_6 solvents with tetramethylsilane as the internal standard and chemical shifts are reported in ppm (δ) and J values in Hz EI mass spectra were run on a LKB GC 2091 spectrometer at 70 eV i 15 eV CI mass spectra were recorded with Finnigan MAT 95 spectrometer using isobutane as a reagent gas and temperature of ion source of 180 ^{0}C Thin layer chromatography was performed on aluminium oxide or silica gel using a mixture of ethyl acetate-ethanol-conc. aqueous ammonia (17.3:1 v/v) as an eluent.

Preparation of 4-chloro-3-quinolinesulfonyl chloride (**3**) by chlorinolysis of 4-chloro-3-benzylthioquinoline (**2**). (Kwart and Miller procedure of chlorinolysis of 7-chloro-4-benzylthioquinoline [11] was adapted).

The reaction was carried out by passing chlorine gas into a well-stirred mixture composed of 4-chloro-3-benzylthioquinoline (**2**) (3 4 g, 12 mmol) and water (0.43 ml, 24 mmol) in glacial acetic acid (23 ml) cooled at 5 ^{0}C, at such a rate that temperature was maintained between 15-17°C. After 15 *min* no more heat seemed to be produced. The passage of chlorine gas was discontinued after 30 min The mixture was diluted with 20 ml of chloroform, and then poured into ice-water (120 ml). The chloroform layer was separated, and aqueous layer was extracted with chloroform (2 x 20 ml). The chloroform extracts were combined, washed with water and dried over anh. sodium sulfate. Chloroform was evaporated to leave semi-solid residue In order to remove benzyl acetate and benzyl chloride, the residue was triturated with ice-cold dry ether. After suction filtration 4-chloro-3-quinolinesulfonyl chloride (**3**) (2.8 g, 89%) with mp 127-130°C was obtained. Recrystallization from benzene gave product with mp 129-130°C

EI mass spectrum (15 eV) m/z (rel. intensity) 265 (6.3%), 263 (33.1%), 261 (M^+, 48.6%), 226 (31.6%), 201 (0.9 %), 199 (3.3%), 197 (5.5%), 162 (100%). ^{1}H Nmr ($CDCl_3$; δ [ppm]). 7.85-7.91 (m,1H,**H**-6), 8.05-8.08 (m,1H,**H**-7); 8.30-8 35 (m,1H,**H**-8); 8 50-8.53 (m,1H,**H**-5); 9 42 (s,1H,**H**-2) Anal. Calcd for $C_9H_5NO_2Cl_2S$: C, 41.24; H, 1.92; Cl, 27.05, N, 5 34; S, 12.23 Found C, 41.14; H, 1.80; Cl, 26.91; N, 5 29; S, 12.34.

Chlorinolysis of thioquinanthrene (**1**):

A mixture of thioquinanthrene (**1**) (4 g, 12.5 mmol), chloroform (40 ml) and 80% acetic acid (40 ml) was treated with chlorine gas as in the case of 4-chloro-3-benzylthioquinoline (**2**). The residue obtained after evaporation of chloroform was recrystallized from benzene to give 4-chloro-3-quinolinesulfonyl chloride (**3**) (5 2 g, 79%) with mp 127-130°C.

Separation of the mixture of 4-chloro-3-quinolinesulfonic acid and 4-chloro-3-quinolinesulfonyl chloride (**3**).

An old sample of 4-chloro-3-quinolinesulfonyl chloride (**3**) was boiled with dry ether or dry benzene (1 g/10 ml) The mixture was hot filtered to give 4-chloro-3-quinolinesulfonic acid. The filtrate was concentrated to dryness to give pure 4-chloro-3-quinolinesulfonyl chloride (**3**).

Analytical data of 4-chloro-3-quinolinesulfonic acid. mp 300-301 °C (decomp) EI mass spectrum, (15 eV) m/z (rel. intensity): 245 (35%), 243 (M^+,100%), 207 (72%), 208 (50%), 143 (52%), 115 (45%). ^{1}H Nmr (DMSO-d_6; δ [ppm]): 7.88-7.93 (m,1H,**H**-6); 8.13-8.19 (m,1H,**H**-7); 8.22- 8.24 (m,1H,**H**-8); 8.45-8.48 (m,1H,**H**-5); 9.27 (s,1H,**H**-2) Anal. Calcd for $C_9H_6NO_3ClS$: C, 44.36; H, 2.48; Cl, 14.55; N, 5.77. Found: C, 44.21; H, 2.41, Cl, 14.68; N, 5.84.

Pyrolysis of 4-chloro-3-quinolinesulfonyl chloride (**3**):

4-Chloro-3-quinolinesulfonyl chloride (**3**) (1.05 g, 4 mmol) was placed in short glass tube fitted with Hickman still The tube was heated at 260-280°C for 0.5 h. The reaction proceeded with sublimation of 3,4-dichloroquinoline accompanied by strong evolution of sulfur dioxide.The product was washed from Hickmann still with hot chloroform. The chloroform extract was concentrated to dryness. The residue from 12 pyrolysis runs was treated with 30 ml of 5% aqueous hydrochloric acid. Insoluble material was filtered off. The filtrate was alkalized with 5% aqueous sodium hydroxide. The solid precipitated was filtered off, washed with water and air-dried to give 2.4g (25%) of 3,4-dichloroquinoline with mp 68-69°C, lit., [20] mp 69-70°C.

Preparation of 4-chloro-3-quinolinesulfonamides (**4b**, **4c**, **4d**, **4e**). (Procedure A-1):

A suspension of 4-chloro-3-quinolinesulfonyl chloride (**3**) (524 mg, 2 mmol) in dry ether (15 ml) was cooled down to -70°C in dry ice-acetone bath. Then upon stirring, 2 ml (*ca*.30-44 mmol) of cold (-70°C) appropriate amine was added and the mixture was stirred for 2 h. Then the solvent was distilled off in vacuo at bath temperature below -20°C. The product resulted was washed with water, filtered off, dried on air and finally crystallized from ethanol. The results are presented in Table 1

Procedure for aniline: cold mixture of aniline (0.2 ml, *ca*. 2.1 mmol) and triethylamine (250 mg, 0.35 ml, 2 5 mmol) was introduced into a suspension of of 4-chloro-3-quinolinesulfonyl chloride (**3**) (524 mg, 2 mmol) in dry ether (15 ml) as above and then stirred at -70°C for 2 h and left for 2 h at room

temperature. The precipitate formed was filtered off, washed with water, dried on air and finally recrystallized from ethanol to give sulfonanilide (**4d**).

Preparation of 4-chloro-3-quinolinesulfonamides (**4f**, **4g**, **4h**, **4i**). (Procedure A-2):

To a solution of 4-chloro-3-quinolinesulfonyl chloride (**3**) (524 mg, 2 mmol) in dry ether (15 ml), appropriate amine (2.2-24 mmol, for details see Table 1) was added and then stirred at temperature indicated in the Table 1 for 2 h. Then the solvent was distilled off under vacuum. The residue was washed with water, filtered off. The solid was dried on air and finally recrystallized from methanol or ethanol.

Reactions of 4-chloro-3-quinolinesulfonyl chloride (**3**) with methylamine, dimethylamine and aniline in the presence of aqueous sodium hydroxide (Procedure A-3):

A mixture of 4-chloro-3-quinolinesulfonyl chloride (**3**) (524 mg, 2 mmol), 10 ml of 10% aqueous sodium hydroxide and 1 ml (6 mmol) of 30% aqueous solution of amine (methylamine or dimethylamine) or 0.2 ml (2.2 mmol) of aniline was stirred at 25°C for 1-6 h. The solid was then filtered off.

In the case of the reaction with dimethylamine, the solid was crystallized from ethanol to give pure 4-chloro-3-quinoline-*N,N*-dimethylsulfonamide (**4e**).

In order to isolate sulfonamides (**4b**) and (**4d**) from aqueous filtrate, it was extracted with chloroform (in the case of aniline) or concentrated in vacuo, both operations performed to remove non-converted amine. The aqueous layer was then acidified to pH 5 and sulfonamides (**4b**) or (**4d**) were isolated by suction filtration. They were finally recrystallized from ethanol.

Preparation of 4-chloro-3-quinolinesulfonamide (**4a**) (Procedure A-4):

A mixture of 4-chloro-3-quinolinesulfonyl chloride (**3**) (524 mg, 2 mmol), and 25% aqueous ammonia (10 ml) was stirred at 40-45°C until the mixture became clear (0 5 h). The excess of ammonia was removed in vacuo below 45°C. The residual mixture was diluted with water up to volume of 10 ml and the solid (440 mg, 90%) with mp 197-200°C (decomp.) was filtered off. For analytical purposes, product was recrystallized from ethanol to give 4-chloro-3-quinolinesulfonamide (**4a**) with mp 201-202°C (decomp.). ^{1}H Nmr and ms spectral data of (**4a**) are presented in Tables 2 and 3.

Acidification of aqueous fitrate which was obtained after isolation of (**4a**) up to pH value of 3 gave bis-(4-chloro-3-quinolinesulfonyl)imine without mp up to 320°C. Mass spectrum (chemical ionization) m/z (rel. intensity): 472 (2.3%), 470 (8.9%), 468 (M^+ +1, 11.7%), 245 (36.4 %), 243 (99.2%), 209 (100%), 166 (31.6 %), 164 (97 2%), 162 (46 9 %), 146 (53.9 %), 129 (99.1%). ^{1}H Nmr (DMSO-d_6, δ [ppm]): 7.81-7.87 (m,1H,**H**-6); 7.98-8 03 (m,1H,**H**-7); 8.09-8 12 (m,1H,**H**-8); 8.26-8.29 (m,1H,**H**-5); 9.10 (s,1H,**H**-2).

Preparation of 4-amino-3-quinolinesulfonamides (**5**) (with two identical amine rests). (Procedure B):

A mixture of 4-chloro-3-quinolinesulfonyl chloride (**3**) (1.05 g, 4 mmol), toluene or benzene (10 ml), water (10 ml), appropriate amine (8 8-30 mmol) (and in the case of aniline sodium bicarbonate 0.84 g, 10 mmol) was refluxed for 2 h (for experimental details see Table 1). The mixture was cooled down to room temperature

Eventual solid product was filtered off The organic layer was concentrated to dryness and combined with the solid product. The crude aminosulfonamides (**5b**, **5c**, **5d**, **5g**, **5h**) were purified by crystallization from ethanol or aqueous ethanol. Sulfonamides (**5e**, **5f**) were purified by extraction with hot hexane. Experimental parameters and properties of compounds (**5**) are collected in Tables 1 and 3.

Preparation of 4-amino-3-quinolinesulfonamides (**5**) (with two non-identical amine rests) from 4-chloro-3-quinolinesulfonamides (**4**). (Procedure C):

A mixture of 4-chloro-3-quinolinesulfonamide (**4**) (1 mmol), 25-30% aqueous solution of aliphatic amine (1 ml, *ca.* 6-8 mmol) or aromatic amine (1.2 mmol), ethanol (5 ml) and one drop of dilute ethanolic solution of hydrogen chloride was refluxed for 30 min. Then volatile components of reaction mixture were distilled off under vaccum.The residue containing non-substituted or mono-*N*-substituted sulfonamides was triturated with 5% aqueous sodium hydroxide (5 ml), filtered off and the solid was washed with cold water. The filtrate was acidified with 5% hydrochloric acid up to pH 4-5 to precipitate corresponding sulfonamide which was then isolated in a typical manner.

The residue containing *N,N*-disubstituted sulfonamides was triturated with 5% aqueous sodium hydroxide (5 ml), filtered off and the solid was washed with cold water to give *N,N*-disubstituted sulfonamides. Aminosulfonamides (**5**) were purified by recrystallization from methanol or ethanol.

Synthesis of 4-amino-3-quinolinesulfonamide (**5a**).

Ammonia was passed through a mixture of phenol (2 g), 4-chloro-3-quinolinesulfonamide (**4a**) (242 mg, 1 mmol) and ammonium chloride (10 mg) at 180°C for 2 h The mixture was cooled down and phenol was removed by steam distillation The residue was then concentrated to 4 ml, cooled down to room temperature and filtered off to give 200 mg (90%) of 4-amino-3-quinolinesulfonamide (**5a**) with mp 277-284°C (decomp).The solid was boiled with 10 ml of 95% ethanol and hot filtered. The filtrate was concentrated to dryness to give 4-amino-3-quinolinesulfonamide (**5a**) with mp 277-279 °C (decomp).

Table 2 4-Amino-3-quinolinesulfonamides (**5**) prepared from 4-chloro-3-quinolinesulfonamides (**4**).

Product					Analysis			
	Yield	mp	Ms (15 eV)	Formula	(Calcd/Found)			
R	%	°C	m/z· M⁺ (%)		C %	H %	N %	S %
5i R_1=R_2=R_3=H, R_4=Me	65	211-212	237(100)	$C_{10}H_{11}N_3O_2S$	50.62	4.67	17 71	13 51
					50 58	4 75	17 64	13 39
5j R_1=R_2=H, R_3=R_4=Me	86	172-174	251(23 4)	$C_{11}H_{13}N_3O_2S$	52.57	5 21	16.72	12 76
					52 37	5 29	16 64	12 68
5k R_1=R_2=R_3=H, R_4=Ph	72	209-210	299(54 4)	$C_{15}H_{13}N_3O_2S$	60.19	4 38	14 04	10 71
					60 08	4 47	13 93	10 61
5l R_2=R_3=R_4=Me, R_1=H	77	145-147	265(12 2)	$C_{12}H_{15}N_3O_2S$	54 32	5 70	15 84	12 08
					54 41	5 64	15 71	12 14
5m R_1=R_3=H, R_2=Me, R_4=Ph	75	169-170	313(100)	$C_{16}H_{15}N_3O_2S$	61 32	4 82	13 41	10 23
					61.47	4 74	13 49	10 18
5n R_1=R_3=H, R_2=Ph R_4=Me	82	229-230	313(100)	$C_{16}H_{15}N_3O_2S$	61 32	4 82	13 41	10 23
					61 47	4 77	13 48	10 19
5p R_1=R_2=R_3=Me, R_4=H	63	110-111	365(5 5)	$C_{12}H_{15}N_3O_2S$	54.32	5.70	15 84	12 08
					54 42	5 61	15 74	12 17
5r R_1=R_2=Me, R_3=H, R_4=Ph	84	147-148	327(100)	$C_{17}H_{17}N_3O_2S$	62 37	5.23	12 83	9 79
					62 34	5 19	12.66	9.87
5s R_1=R_2=Et, R_3=R_4=Me	92	oil	307(2 9)	$C_{15}H_{21}N_3O_2S$	58.61	6.89	13 63	10 43
					58 71	6.91	13 54	10 37
5t R_1+R_2= -$(CH_2)_2O(CH_2)_2$-	66	179-180	369(74 7)	$C_{19}H_{19}N_3O_3S$	61.77	5.18	11 37	8 68
R_3=H, R_4=Ph					61.79	5.14	11 19	8 74
5u R_1=R_3=Me, R_2=Ph, R_4=H	63	111-112	327(64 2)	$C_{17}H_{17}N_3O_2S$	62 37	5 23	12 83	9 79
					62 44	5.19	12.77	9.84
5w R_1=R_3=R_4=Me,	88	oil	341(27 4)	$C_{18}H_{19}N_3O_2S$	63 32	5.61	12 31	9 39
R_2= Ph					63.50	5.54	12.41	9.47
5x R_1=R_3=Ph, R_2=Me, R_4=H	65	146-147	389(44 0)	$C_{22}H_{19}N_3O_2S$	67 85	4 92	10 79	8 23
					67.78	4 81	10 89	8 14

Table 3. ^{1}H Nmr data (δ_H, ppm) of compounds (**4**) and (**5**).

Compound		Solvent	H-2	H-5	H-6	H-7	H-8	Other protons
3	4-Chloro-3-quinoline-sulfonyl chloride	$CDCl_3$	9.42	8.50-8.53	7 85-7.91	8 05-8 08	8.30-8.35	
4a	R_1=R_2=H	DMSO-d_6	9 39	8.48-8.51	7.94-8 00	8.07-8.13	8.25-8 28	8.14(s,2H,N**H**$_2$).
4b	R_1=H, R_2=Me	DMSO-d_6	9.32	8 51-8 54	7.97-8.02	8.11-8.16	*	2.60(d,J=4.8 Hz,3H,NHC**H**$_3$), * 8.24-8 30(m,2H, **H**-8 and NHC**H**$_3$)
4c	R_1=H, R_2=Et	$CDCl_3$	9.41	8.39-8.42	7.74-7.80	7 89-7 95	8.19-8.22	1.13(t,J=7 2 Hz,3H,CH$_2$C**H**$_3$); 3.05-3 14(m,2H, NHC**H**$_2$CH$_3$); 5.25(t,J=5.9 Hz, 1H,N**H**CH$_2$CH$_3$).
4d	R_1=H, R_2=Ph	DMSO-d_6	9.26	8.39-8.41	7.86-7 91	8 00-8 06	8 14-8.16	6 97-7.23(m,5H,C$_6$**H**$_5$); 11.00(s,1H,N**H**Ph).
4e	R_1=R_2=Me	$CDCl_3$	9.36	8 42-8 45	7.74-7 79	7 89-7.95	8.18-8 21	2.97[s,6H,N(C**H**$_3$)$_2$].
4f	R_1=R_2=Et	$CDCl_3$	9 40	8 40-8 44	7 72-7 77	7.87-7 93	8 17-8 20	1.16[t,J=7 1 Hz,6H,N(CH$_2$C**H**$_3$)$_2$]; 3.47[q,J=7.1 Hz, 4H,NC**H**$_2$CH$_3$)$_2$].
4g	R_1+R_2= -(CH$_2$)$_5$-	$CDCl_3$	9 36	8.42-8 46	7 73-7 79	7.88-7.93	8.17-8 20	1 49-1.68(m,6H,-C**H**$_2$C**H**$_2$C**H**$_2$-); 3.35(t,J=5 4 Hz, 4H, -C**H**$_2$NC**H**$_2$-).
4h	R_1+R_2=(CH$_2$)$_2$O(CH$_2$)$_2$	$CDCl_3$	9.34	8 43-8 46	7 75-7.81	7.91-7.96	8.18-8 21	3.36-3.39(m,4H,-C**H**$_2$NC**H**$_2$-), 3.75(t,J=4.7 Hz,4H, -CH$_2$OC**H**$_2$-).
4i	R_1=Me, R_2=Ph	$CDCl_3$	9.13	8 40-8.43	7 73-7.79	7 88-7 94	8.14-8.17	3 49(s,3H,C**H**$_3$); 7.18-7.28(m,5H,C$_6$**H**$_5$).
5a	R_1=R_2=H	DMSO-d_6	8.92	8.92-8.94	7.84-7.89	8 09-8 18	8 09-8.18	8 41(s,2H,SO$_2$N**H**$_2$); 10.34(s,2H,N**H**$_2$).
5b	R_1=H, R_2=Me	DMSO-d_6	8.64	8.41-8.44	7.47-7 53	*	7 84-7.87	2 43(d,J=4.9 Hz,3H,SO$_2$NHC**H**$_3$); 3.42(d,J=5 4 Hz, 3H,NHC**H**$_3$); 7.06(q,J=5.4 Hz,1H,N**H**CH$_3$); 7 73-7.78 (m,2H,SO$_2$N**H**CH$_3$,* and **H**-7)
5c	R_1=H, R_2=Et	$CDCl_3$	8 85	8.19-8 23	7.40-7 46	7.68-7.73	7.95-7 98	1 13(t,J=7.2 Hz,3H,CH$_2$C**H**$_3$); 1.40(t,J=7.1 Hz,3H, NHCH$_2$C**H**$_3$); 3 03(q,J=7.2 Hz,2H,NHC**H**$_2$CH$_3$), 3.81-3 91(m,2H, NHC**H**$_2$CH$_3$), 5 24(t,J=5.9 Hz,1H, N**H**CH$_2$CH$_3$); 7.04-7.10 (m,1H,N**H**CH$_2$CH$_3$).
5d	R_1=H, R_2=Ph	DMSO-d_6	8 93	7.89-7 91	*	7.68-7 73	7.50-7 53	6.83-7.30[m,11H,2 x (C$_6$**H**$_5$), * and **H**-6]; 8 35(s,1H, N**H**Ph), 10,73(s,1H,SO$_2$N**H**Ph).

Table 3. (continued)

Compound		Solvent	H-2	H-5	H-6	H-7	H-8	Other protons
5e	R_1=R_2=Me	$CDCl_3$	9.06	8.07-8 13	7 54-7.59	7.73-7.78	8 07-8 13	2 94[s,6H,$SO_2N(CH_3)_2$]; 3.22[s,6H,$N(CH_3)_2$].
5f	R_1=R_2=Et	$CDCl_3$	8.93	8.11-8.14	7.51-7.59	7.70-7.76	8.02-8.06	1.17[t,J=7.1 Hz,6H,$SO_2N(CH_2CH_3)_2$, 1.25[t,J= 7.1 Hz,6H, $N(CH_2CH_3)_2$]; 3 42[q,J=7.1 Hz,4H, SO_2N-$(CH_2CH_3)_2$], 3.61[q,J=7 1 Hz,4H, $N(CH_2CH_3)_2$].
5g	R_1 +R_2= -$(CH_2)_5$-	$CDCl_3$	8.98	7 24-7.27	7 53-7 58	7 72-7.77	8.04-8.07	1 56-1.72(m,6H,3Q-$CH_2CH_2CH_2$-); 1.76-1.82(m, 6H,-$CH_2CH_2CH_2$-), 3.32-3.35(m,4H,-CH_2NCH_2-); 3 50-3.53(m,4H,-CH_2NCH_2-).
5h	R_1 +R_2=$(CH_2)_2O(CH_2)_2$	$CDCl_3$	9.11	8 27-8 30	7.60-7.66	7 79-7.84	8.12-8.16	3.38-3.41(m,4H,-CH_2NCH_2-); 3 52-3.56(m,4H, -CH_2NCH_2-); 3.78-3.81(m,4H,-CH_2OCH_2-); 3 94-3.97(m,4H,-CH_2OCH_2-).
5i	R_1=R_2=R_3=H, R_4=Me	DMSO-d_6	8 86	8 50-8 53	7 56-7 62	7 81-7.86	7.94-7.97	3 52(d,J=5.5 Hz,3H,$NHCH_3$); 7 09(q,J=5.5 Hz,1H, $NHCH_3$), 7.72(s,2H,NH_2).
5j	R_1=R_2=H, R_3=R_4=Me	$CDCl_3$	9 36	8 18-8 21	7.61-7.67	7.79-7 85	8 11-8 15	3 21[s,6H,$N(CH_3)_2$]; 5.47(s,2H,NH_2).
5k	R_1=R_2=R_3=H, R_4=Ph	DMSO-d_6	9.17	8 07-8 10	7.42-7.47	7 81-7 86	7 70-7 74	7.02-7.40(m,5H,C_6H_5); 8 02(s,2H,NH_2).
5l	R_2=R_3=R_4=Me, R_1=H	$CDCl_3$	9 33	8.20-8 23	7 60-7 66	7.80-7.85	8.10-8 14	2.68(d,J=5.4 Hz,3H,$NHCH_3$), 3.20[s,6H,$N(CH_3)_2$]; 5.28(q,J=5.4 Hz,1H, $NHCH_3$).
5m	R_1=R_3=H, R_2=Me, R_4=Ph	DMSO-d_6	9 09	*	7 42-7 47	7.83-7.88	7 69-7.72	2.58(d,J=4 9 Hz,3H,$NHCH_3$), 7.04-7.41(m,5H, C_6H_5); * 8.08-8.12(m,2H,H-5 and $NHCH_3$); 8 48(s,1H,NHPh).
5n	R_1=R_3=H, R_2=Ph, R_4=Me	$CDCl_3$	8 77	8 16-8 19	7.38-7.44	7 67-7 73	7 94-7.97	3.14(d,J=5.4 Hz,3H,$NHCH_3$), 4.24-4.30(m,1H, $NHCH_3$), 7.10-7 38(m,6H,C_6H_5, and NHPh).
5p	R_1=R_2=R_3=Me, R_4=H	$CDCl_3$	8.78	8.28-8.31	7.42-7 48	7.70-7 76	7 97-8 00	2.78[s,6H,$N(CH_3)_2$], 3 45(d,J=5.5 Hz,3H,$NHCH_3$), 7.55(q,J=5 5 Hz,1H,$NHCH_3$)
5r	R_1=R_2=Me, R_3=H, R_4=Ph	$CDCl_3$	9 03	8.02-8.05	*	7.67-7 77	7.67-7.77	2.74[s,6H,$N(CH_3)_2$]; 6.90-7.30(m,6H,C_6H_5, * and H-6), 8.64(s,1H,NHPh).

Table 3. (continued)

Compound		Solvent	H-2	H-5	H-6	H-7	H-8	Other protons
5r	R_1=R_2=Me, R_3=H, R_4=Ph	DMSO-d_6	9.27	8 17-8.20	7.56-7 64	8.03-8 08	*	2 95[s,6H,N(C**H**$_3$)$_2$], 7.42-7 55(m,7H,C_6**H**$_5$.N**H**Ph,* and **H**-8)
5s	R_1=R_2=Et, R_3=R_4=Me	$CDCl_3$	9.05	8 06-8.12	7.52-7.58	7.71-7.77	8 06-8.12	1 21[t,J=7 1 Hz,6H,N(CH$_2$C**H**$_3$)$_2$]; 3.21[s,6H, N(C**H**$_3$)$_2$], 3 41[q,J=7 1 Hz,4H,(C**H**$_2$CH$_3$)$_2$].
5t	R_1+R_2=(CH$_2$)$_2$O(CH$_2$)$_2$, R_3=H, R_4=Ph	$CDCl_3$	9.02	8 04-8 08	*	7.71-7.76	7 71-7.76	3 06-3.09(m,4H,-C**H**$_2$NC**H**$_2$-); 3.62-3.65(m,4H, -C**H**$_2$OC**H**$_2$-), 6.92-7 32(m,6H,C_6**H**$_5$, * and **H**-6) 8 57(s,1H,N**H**Ph)
5u	R_1=R_3=Me, R_2=Ph, R_4=H	$CDCl_3$	8 75	8 10-8 13	7 36-7 42	7 68-7 73	7 94-7.98	2.90(d,J=5 6 Hz,3H,NHC**H**$_3$); 3 25(s,3H,NC**H**$_3$Ph); 6.88(q,J=5 6 Hz,1H, N**H**CH$_3$);7 18-7.32(m,5H, C_6**H**$_5$).
5w	R_1=R_3=R_4=Me, R_2=Ph	$CDCl_3$	9 05	8 10-8 12	7 54-7.59	7 73-7 78	8.07-8 09	3 16[s,6H,N(C**H**$_3$)$_2$], 3.42(s,3H,NC**H**$_3$Ph), 7.18-7.31(m,5H,C_6**H**$_5$)
5x	R_1=R_3=Ph, R_2=Me, R_4=H	$CDCl_3$	8.9	8 00-8 03	7 25-7 25	7 66-7.71	7.60-7.63	3 26(s,3H,NC**H**$_3$Ph); 6 66-7.19[m,10H,2 x (C_6**H**$_5$)]; 8 27(s,1H,N**H**Ph)

* non-assigned - see column "other protons"

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