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FROM 2,3-, 2,6-, 3,4- AND 4,6-DICHLOROQUINOLINES TO ISOMERIC CHLOROQUINOLINESULFONYL CHLORIDES

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Abstract – The action of sodium methanethiolate (in boiling DMF) on x,y-dichloroquinolines (**1**) (x=3 or 6, y=2 or 4) occured *via* chlorine *ipso*-substitution followed by *methanethiolato-S-demethylation* to yield x,y-quinolinedithiolates **2A** which were: i) subjected to *S*-methylation, ii) oxidatively chlorinated to y-chloro-x-quinolinesulfonyl chlorides (**5**). Oxidative chlorination of y,y'-bis(x-chloro-quinolinyl) disulfides (**7**) led to x-chloro-y-quinolinesulfonyl chlorides (**8**) accompanied by x,y-dichloroquinolines (**1**). Both quinolinesulfonyl chlorides **5** and **8** were efficiently converted to the corresponding quinolinesulfonamides **6** and **9**.

INTRODUCTION

2-Chloro- and 4-chloroquinoline moieties,[1] as well as quinolinesulfonyl chloride units[2,3,4,5] give broad access to further functionalization of quinolines. Co-occurrence of both functional groups in one quinoline molecule broaden the above potential, as was shown for 4-chloro-3-quinolinesulfonyl chloride (**5b**)[4,5] and 2-chloro-6-quinolinesulfonyl chloride (**5c**)[6] in studies directed at the preparation of biologically active compounds.[1-6] The 3- or 7-chlorosulfonyl-4-chloroquinolines (**5b**,**e**),[4,5,8] 8-chlorosulfonyl-4-chloroquinolines,[7] 4-chlorosulfonyl-7-chloroquinoline (**8e**),[8] and 2-chloro-6-quinoline-sulfonyl chloride (**5c**),[6] are well known but only the 4,7-isomers **5e** and **8e** were prepared from the respective dichloroquinoline (**1e**).[8]

Azinesulfonyl chlorides could be directly obtained by oxidative chlorination of thioazines – thiols[8,9,10] disulfides,[8,9] benzylsulfides[5,11] with a thio substituents at non-*aza*-activated positions. On the other hand, the results of the same treatment of thioazines with a thio substituent at *aza*-activated positions strongly depends on the experimental conditions. Since the oxidative chlorination when performed in acetic acid solution leads to the respective chloroazines,[8,9,12-14] but the oxidative chlorination of α- and γ-

thiopyridines and thioquinolines performed in conc. hydrochloric acid permits unstable α- and γ-azinesulfonyl chlorides[8,9,16,18,19] to be isolated. These underwent decomposition even below 0 ºC to chloroazine and sulfur dioxide,[8,9,16,18,19] but freshly prepared samples could be succesfully characterized with the ^{1}H and ^{13}C NMR spectra[8,9,19] and effective trapped (with yields up to 90%) in the form of the respective sulfonamides.[8,9,16,18,19] It is worth noting that structural modification may affect the stability of α- and γ-azinesulfonyl halides, as was exemplified for 5-acetylamino-2-pyridinesulfonyl chloride,[15] for tetrachloro-4-pyridinesulfonyl chloride,[17] and even for 2-pyrimidinesulfonyl fluoride.[19]

The starting point for this paper was the previously elaborated methodology based on formation of a quinolinethiolate function from chloroquinolines and an excess of sodium methanethiolate.[20] The final step of this approach was the transformation of the divalent-sulfur substituent to chlorosulfonyl group. To extend the above study concerning 4,7-dichloroquinoline (**1e**),[8] we turned our attention to other dichloroquinolines (isomers 2,3-, 2,6-, 3,4- and 4,6-) containing one chloro substituent at *aza*- and another one at *non-aza*-activated positions as a source of both isomeric chloroquinolinesulfonyl chlorides **5** and **8** with one substituent at *aza*- and the second one at *non-aza*-activated positions.

RESULTS AND DISCUSSION

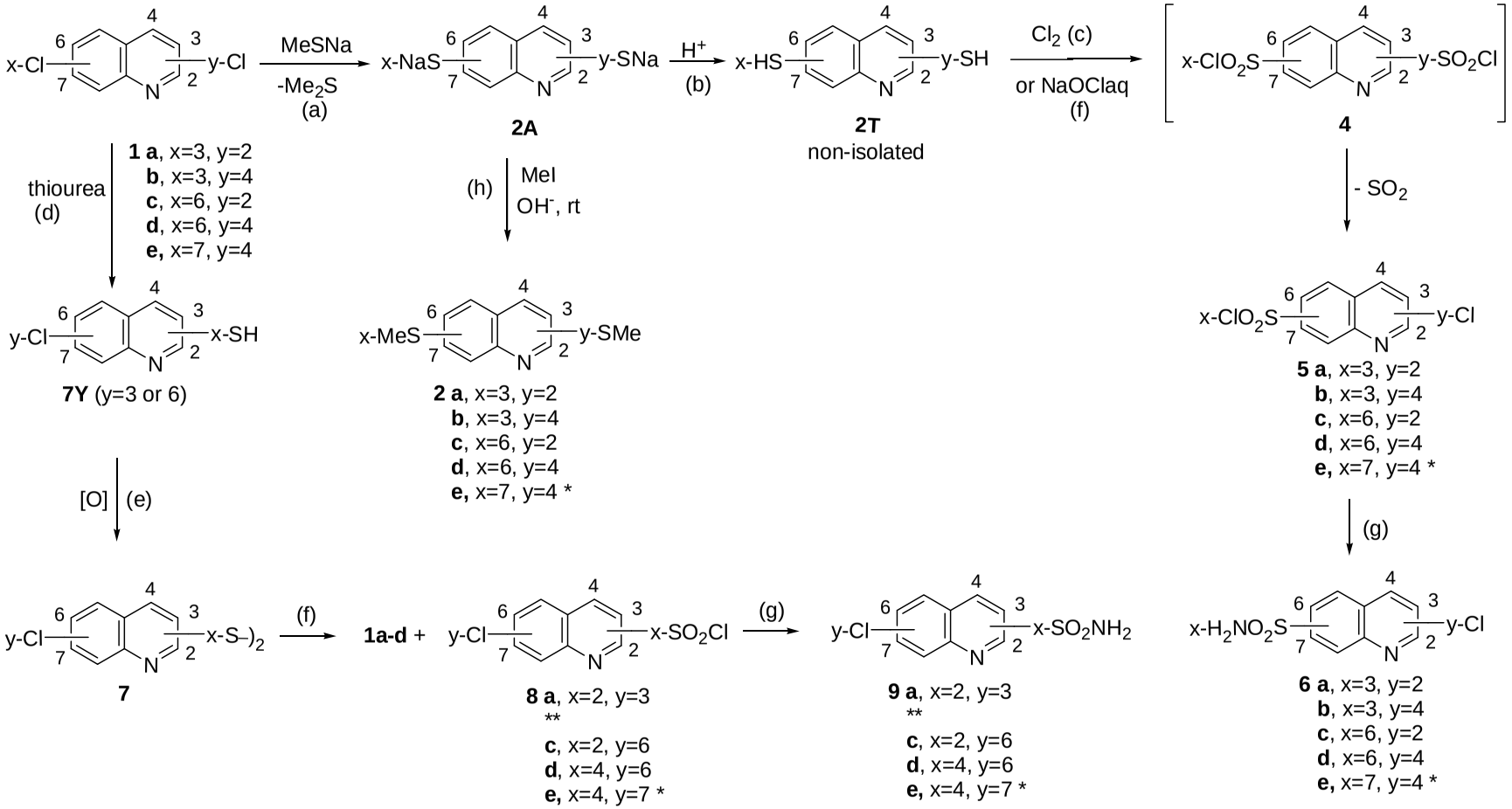
Quinoline- and pyridinethiolates are easily available from the respective chloro- or bromo-derivatives in a *one-pot* process performed with an excess of sodium methanethiolate.[8,20] This process proceeds stepwise by halogen *ipso*-substitution leading to the respective methylsulfanyl derivatives, which are then *S*-dealkylated to the respective azinethiolates.[8,20] They can be trapped by methylation to methylsulfanylazines[20,8] or by oxidation to disulfides[8,9] or they can be oxidative chlorinated to quinolinesulfonyl chlorides.[8,9]

Synthesis of quinoline derivatives **5a-d** with chlorosulfonyl a substituent at *non-aza*-activated position

Synthesis of the y-chloro-x-chlorosulfonylquinolines (**5**) (x=3 or 6, y=2 or 4) was performed using the previously elaborated methodology applied for the preparation of 4-chloro-7-chlorosulfonylquinoline (**5e**) from 4,7-dichloroquinoline (**1e**).[9] (see Scheme 1). It comprises three steps:

i) Formation of dithiolates (**2A**) in the reaction of dichloroderivatives (**1**) with sodium methanethiolate. To confirm the structure of the expected x,y-quinolinedithiolates (**2A**), crude thiolate solution was methylated to x,y-dimethylsulfanylquinolines (**2a-d**).

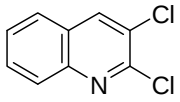
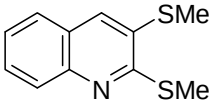
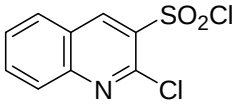
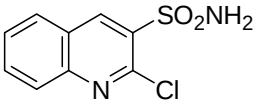
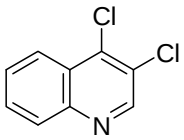
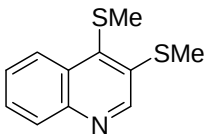
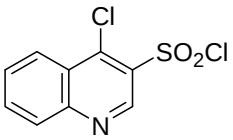
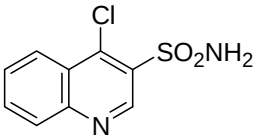
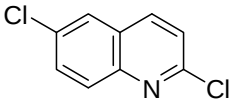
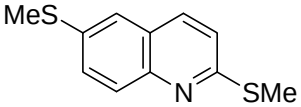
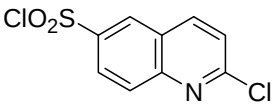
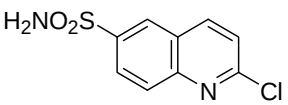
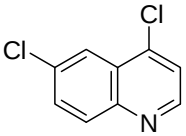
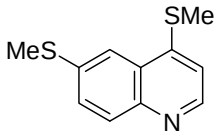
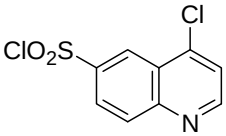
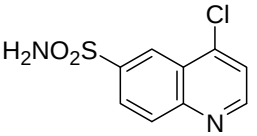
ii) Oxidative chlorination of quinolinedithiols **2T** to di(chlorosulfonyl)quinolines **4**. For this purpose dithiolates **2A** were acidified to non-isolated dithiols **2T**, which were then oxidatively chlorinated with sodium hypochlorite in conc. hydrochloric acid. This should lead to x,y-di(chlorosulfonyl)quinolines (**4**).



Scheme 1. Reagents and experimental procedures: (a) MeSNa (10 equivalents), DMF, boiling temp., 4h - procedure A; (b) rt, HClaq - procedure A; (c) Cl_2, 17 ^oC, 30 min- procedure C; (d) thiourea, rt, then H_2O, OH^-, then H^+; (e) aq. $K_3Fe(CN)_6$; (f) NaOClaq., conc. HClaq. - procedure E ; (g) NH_3 aq., rt. - procedure D; (h) MeI, 8% NaOHaq., rt. - procedure B; * reported previously in ref.[8]; **compounds **8b** and **9b** (x=4, y=3) were not obtained.

iii) The third step is decomposition of di(chlorosulfonyl)quinolines **4** to y-chloro-x-chlorosulfonyl-quinolines **5a-d**. It is well documented that α- and γ-azinesulfonyl chlorides undergo decomposition even at 0 °C to α- and γ-chloroazines and sulfur dioxide.[8,12-14,16,19] In the result the oxidative chlorination of **2T** *via* x,y-di(chlorosulfonyl)quinolines (**4**) led to y-chloro-x-chlorosulfonyl-quinolines **5a-d**.

Table 1. Synthesis of dimethylsulfanylquinolines **2**, chloroquinolinesulfonylchlorides **5** and chloroquinolinesulfonamides **6** from dichloroquinolines **1** *via* quinolinedithiolates **2A**.

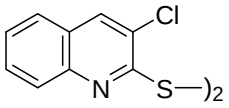
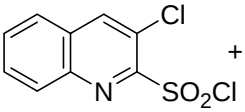
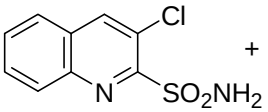
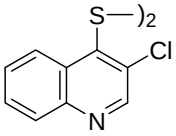
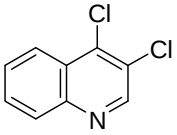
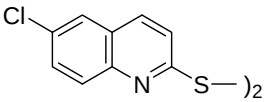
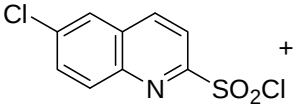
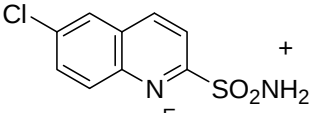
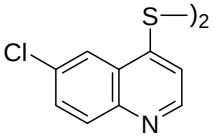
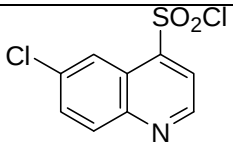
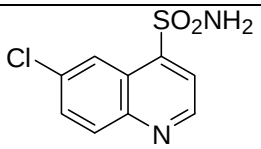
Entry	Substrate	Products, yield (%), procedure		
1	 **1a**	 **2a** (91) B	 **5a** (86) C	 **6a** (86) D
2	 **1b**	 **2b** (82) B	 **5b** (80) C	 **6b** (81) D
3	 **1c**	 **2c** (92) B	 **5c** (79) C	 **6c** (81) D
4	 **1d**	 **2d** (80) B	 **5d** (80) C	 **6d** (78) D

*procedure A,B,C,D, – see experimental

Synthesis of quinoline derivatives **8** with chlorosulfonyl substituent at *aza*-activated position

Synthesis of 7-chloro-4-chlorosulfonylquinoline (**8e**) from 4,7-dichloroquinoline (**1e**) was performed as outlined in Scheme 1.[8] This methodology was applied for the preparation of compounds **8** and **9.** The key-step was the chlorination of x,x'-bis (y-chloroquinolinyl) disulfides (**7**) (x=2 or 4, y=3 or 6) in conc. hydrochloric acid at -8 °C. Despite the instability of sulfonyl chlorides **8a,c,d**, they were extracted with cold (-5 °C) $CDCl_3$ immediately after the synthesis and fully characterized (at 0 °C, up to 1 h) with ^1H and ^{13}C NMR spectra. Moreover, both NMR spectra showed that the compounds **8a,c,d** in $CDCl_3$ solution are accompanied by the respective x,y-dichloroquinolines (Table 2). Due to the instability of the sulfonyl chlorides **8a,c,d**, they should be immediately consumed *e.g.* by amination to the respective sulfonamides **9**. Oxidative chlorination of disulfide **7b** performed even at -20 °C led directly to 3,4-dichloroquinoline (**1b**).

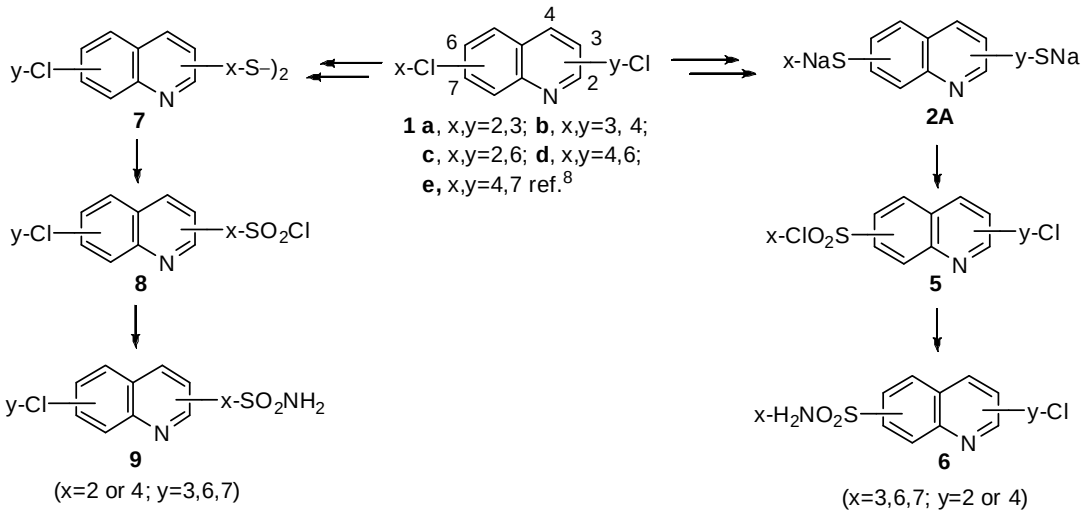
Table 2. Synthesis of chloroquinolinesulfonylchlorides **8** and chloroquinolinesulfonamides **9** from disulfides **7**.

Entry	Substrate	Products, yield (%), procedure
1	 **7a**	 + **1a** (3) **8a** (97) E |  + **1a** (48) **9a** (50) E
2	 **7b**	 **1b** (100 %)E
3	 **7c**	 + **1c** (30) **8c** (70) E |  + **1c** (59) **9c** (40) E
4	 **7d**	 **8d** (100) E |  + **1d** (61) **9d** (28) E

*procedure E – see experimental

CONCLUSIONS

A previously elaborated methodology based on formation of quinolinethiolate function from chloroquinolines and an excess of sodium methanethiolate followed by oxidative chlorination of quinolinethiolate or diquinolinyl disulfide to quinolinesulfonyl chlorides[8,9] could be successfully extended for the preparation of four pairs of isomeric chloroquinolinesulfonyl chlorides **5** and **8**, with one substituent at *aza*- and the second one at *non-aza*-activated positions**, s**tarting from x,y-dichloroquinolines (**1**). Both types of sulfonyl chlorides were converted to the respective quinolinesulfonamides **6** and **9**.



Scheme 2

EXPERIMENTAL

Melting points were taken in open capillary tubes and are uncorrected. All NMR spectra were recorded on a Bruker AVANCE 400 spectrometer operating at 400.22 MHz and 100.64 MHz for ^{1}H and ^{13}C nuclei, respectively, in deuterochloroform ($CDCl_3$) or in hexadeuterodimethyl sulfoxide (DMSO-d_6) solutions with tetramethylsilane (δ 0.0 ppm) as internal standard. TLC analyses were performed employing Merck's silicagel 60 F_{254} plates and a solution of $CHCl_3$-EtOH (19 : 1, v/v) as an eluent (system I) or a mixture of CH_2Cl_2/EtOH, (19 : 1, v/v) (system II) and Merck's aluminium oxide 60 F_{254} neutral (type E) plates using mixture of $CHCl_3$-EtOH (19 : 1, or 10 : 1, v/v) as an eluent (system III). Sodium methanethiolate was prepared from methanethiol and sodium methoxide (1 mol. eqv.) in methanol solution as reported previously.[9] 2,6- and 4,6-Dichloroquinolines (**1c** and **1d**) were prepared from 6-chloroquinoline *N*-oxide and phosphoryl chloride as reported by Bachman and Cooper[21] – the same experimental protocol was applied for the preparation of 2,3-dichloroquinoline (**1a**) from 3-chloroquinoline *N*-oxide. 3,4-Dichloroquinoline (**1b**) was prepared by pyrolysis of 4-chloro-3-quinolinesulfonyl chloride (**5b**).[5]

Reaction of dichloroquinoline (**1**) with sodium methanethiolate leading to x,y-quinolinedithiolate (**2A**) (Procedure A)

A mixture of dichloroquinoline (**1**) (0.794 g, 4 mmol), sodium methanethiolate (2.80 g, 40 mmol) and dry DMF (24 mL) was boiled with stirring under argon atmosphere for 4 h (or 6h for 4,6-dichloroquinoline **1d**). (The reaction must be carried out in hood as it proceeds with strong evolution of dimethyl sulfide). This mixture was assigned as solution A. It was then cooled to 70 °C and the volatile components were evaporated under vacuum from water bath. The residue was cooled down in an ice-water bath, (under argon atmosphere) carefully acidified with 20% hydrochloric acid (8 mL) and then kept at vacuum to remove methanethiol. This residue - assigned as solution **B** - contains crude (non-isolated) x,y-dimercaptoquinoline (**2T**) and could be used for the preparation of sulfonyl chlorides **5**.

Methylation of x,y-quinolinedithiolate (**2A**)

(Procedure B)

Methyl iodide (0.37 mL, 5.9 mmol) was added dropwise on stirring to a solution composed of 8% aqueous sodium hydroxide (15 mL) and solution **A** (3 mL, containing *ca*. 0.5 mmol of thiolate **2A** - prepared as described above in procedure A). The stirring was continued at rt for 1 h. The solid was filtered off, washed with water and dried on air. It was recrystallized from aqueous EtOH or from hexane to give x,y-dimethylsulfanylquinoline (**2**) (0.1 g, *ca*. 91%).

2,3-Dimethylsulfanylquinoline (**2a**)

mp 62-63 ºC (hexane). EI MS (70eV) (m/z): 221 (100, M^+). ^{1}H NMR ($CDCl_3$), δ: 2.57 (s, 3H, SC$\underline{H}_3$), 2.72 (s, 3H, SC$\underline{H}_3$), 7.40 (ddd, 1H, *J*=7.8 Hz, *J*=7.6 Hz, *J*=1.2 Hz, H6), 7.59 (ddd, 1H, *J*=8.4 Hz, *J*=7.8 Hz, *J*=0.8 Hz, H7), 7.67 (dd, 1H, *J*=7.6 Hz, *J*=0.8 Hz, H5), 7.76 (s, 1H, H4), 7.93, (dd, 1H, *J*=8.4 Hz, *J*=1.2 Hz, H8). *Anal.* Calcd for $C_{11}H_{11}NS_2$ (221.33): C 59.69, H 5.01, N 6.33. Found: C 59.58, H 4.91, N 6.23.

3,4-Dimethylsulfanylquinoline (**2b**)

Mp 92-93 ºC (hexane), lit.,[22] mp 93-94 ºC. ^{1}H NMR spectrum ($CDCl_3$) was identical with the sample prepared previously.[22]

2,6-Dimethylsulfanylquinoline (**2c**)

mp 104-105 ºC (EtOH). EI MS (70eV) (m/z): 221 (100, M^+). ^{1}H NMR ($CDCl_3$), δ: 2.57 (s, 3H, SC$\underline{H}_3$), 2.69 (s, 3H, SC$\underline{H}_3$), 7.21 (d, 1H, *J*=8.6 Hz, H3), 7.47 (d, 1H, *J*=2.1 Hz, H5), 7.54 (dd, 1H, *J*=8.8 Hz, *J*=2.1 Hz, H7), 7.78 (d, 1H, *J*=8.6 Hz, H4), 7.84 (d, 1H, *J*=8.8 Hz, H8). *Anal.* Calcd for $C_{11}H_{11}NS_2$ (221.33): C 59.69, H 5.01, N 6.33. Found: C 59.63, H 5.01, N 6.21.

4,6-Dimethylsulfanylquinoline (**2d**)

mp 51-52 ºC (hexane). EI MS (70eV) (m/z): 221 (100, M^+). ^{1}H NMR ($CDCl_3$), δ: 2.62 (s, 3H, SC$\underline{H}_3$), 2.71 (s, 3H, SC$\underline{H}_3$), 7.17 (d, 1H, *J*=4.8 Hz, H3), 7.69 (dd, 1H, *J*=8.8 Hz, *J*=2.0 Hz, H7), 8.10 (d, 1H, *J*=2.0 Hz, H5), 8.31 (d, 1H, *J*=8.8 Hz, H8), 8.62 (d, 1H, *J*=4.8 Hz, H2). *Anal.* Calcd for $C_{11}H_{11}NS_2$ (221.33): C 59.69, H 5.01, N 6.33. Found: C 59.51, H 5.12, N 6.32.

Preparation of x,x'-bis(y-chloroquinolinyl) disulfides (**7**)

Starting y-chloro-x-mercaptoquinolines **7Y** were prepared *via* thiouronium salts treating x,y-dichloroquinoline (**1**) with 1.1 molar eqvs. of thiourea in ethanol (1 mL / 1 mmol of **1**) at rt for 1 day. The mixture was then transferred on cold to 5% aqueous NaOH (1 mL / 1 mmol of **1**) and oxidized to disulfide **7** with 8% aqueous potassium ferricyanide (65 mL / 1 mmol of **1**) as reported previously for 4,4'-bis(7-chloroquinolinyl disulfide) (**7e**).[24]

2,2'-Bis(3-chloroquinolinyl) disulfide (**7a**)

mp 221-222 ºC (EtOH). Yield 83%. EI MS (70eV) (m/z): 388 (3, M^+), 390 (1.9, $M^+ + 2$), 195 (100). ^{1}H NMR ($CDCl_3$), δ: 7.43 (ddd, 2H, *J*=8.0 Hz, *J*=7.6 Hz, *J*=1.6 Hz, H6 and H6'), 7.55 (ddd, 2H, *J*=8.4 Hz, *J*=7.6 Hz, *J*=1.6 Hz, H7and H7'), 7.68 (dd, 2H, *J*=8.0 Hz, *J*=1.6 Hz, H5 and H5'), 7.83 (dd, 2H, *J*=8.4 Hz, *J*=1.4 Hz, H8 and H8'), 8.07 (s, 2H, H4 and H4'). *Anal.* Calcd for $C_{18}H_{10}Cl_2N_2S_2$ (389.31): C 55.53, H 2.59, N 7.20. Found: C 55.37, H 2.69, N 7.28.

4,4'-Bis(3-chloroquinolinyl) disulfide (**7b**)

mp 102-103 ºC (EtOH). Yield 86%. EI MS (70eV) (m/z): 388 (20, M^+), 390 (16, $M^+ + 2$), 195 (100). ^{1}H

NMR ($CDCl_3$), δ: 7.49 (ddd, 2H, *J*=8.4 Hz, *J*=7.6 Hz, *J*=1.2 Hz, H6 and H6'), 7.74 (ddd, 2H, *J*=8.4 Hz, *J*=7.6 Hz, *J*=1.2 Hz, H7 and H7'), 8.03 (dd, 2H, *J*=8.4 Hz, *J*=1.2 Hz, H5 and H5'), 8.12 (dd, 2H, *J*=8.4 Hz, *J*=1.2 Hz, H8 and H8'), 8.80 (s, 2H, H2 and H2'). *Anal.* Calcd for $C_{18}H_{10}Cl_2N_2S_2$ (389.31): C 55.53, H 2.59, N 7.20. Found: C 55.69, H 2.61, N 7.32.

2,2'-Bis(6-chloroquinolinyl) disulfide (**7c**)

mp 241-242 ºC (EtOH). Yield 90%. EI MS (70eV) (m/z): 388 (20, M^+), 390 (15, $M^+ + 2$), 195 (100). ^1H NMR ($CDCl_3$), δ: 7.65 (dd, 2H, *J*=9.0 Hz, *J*=2.3 Hz, H7 and H7'), 7.75 (d, 2H, *J*=2.3 Hz, H5 and H5'), 7.81 (d, 2H, *J*=8.7 Hz, H3 and H3'), 7.93 (d, 2H, *J*=9.0 Hz, H8 and H8'), 7.98 (d, 2H, *J*=8.7 Hz, H4 and H4'), *Anal.* Calcd for $C_{18}H_{10}Cl_2N_2S_2$ (389.31: C 55.53, H 2.59, N 7.20. Found: C 55.37, H 2.55, N 7.33.

4,4'-Bis(6-chloroquinolinyl) disulfide (**7d**)

mp 169-170 ºC (EtOH), lit.,[23] mp 169-170 ºC. Yield 89%.

Preparation of y-chloro-x-quinolinesulfonamides (**6**)

(Procedure C)

6% Aqueous solution of sodium hypochlorite (39.5 g, 38 mL, 26.6 mmol) was cooled down to 5 °C and then dropped within 30 min to a cold well-stirred mixture of hydrochloric acid solution of x,y-dimercaptoquinoline (**2T**) (*ca*. 4 mmol) (prepared from x,y-dichloroquinoline according to procedure A), conc. hydrochloric acid (12 mL) and $CHCl_3$ (12 mL) at such a rate that temperature was maintained below 10 °C. The mixture was poured into 60 g of ice. The chloroform layer was separated, and aqueous layer was extracted with $CHCl_3$ (3 x 10 mL). The chloroform extracts were combined, washed with water and dried over anhydrous sodium sulfate. $CHCl_3$ was evaporated to leave solid residue. The residue was recrystallized from CCl_4 or from benzene to give y-chloro-x-quinolinesulfonyl chloride (**5**) (79-86%).

2-Chloro-3-chlorosulfonylquinoline (**5a**)

mp 180-181 ºC (CCl_4). EI MS (70eV) (m/z): 261 (33, M^+), 263 (21, $M^+ + 2$), 162 (100). ^1H NMR ($CDCl_3$), δ: 7.94 (ddd, 1H, *J*=8.2 Hz, *J*=7.6 Hz, *J*=0.9 Hz, H6), 8.13 (ddd, 1H, *J*=8.5 Hz, *J*=7.6 Hz, *J*=1.3 Hz, H7), 8.17 (dd, 1H, *J*=8.2 Hz, *J*=1.3 Hz, H5), 8.31 (dd, 1H, *J*=8.5 Hz, *J*=0.9 Hz, H8), 9.22 (s, 1H, H4). *Anal.* Calcd for $C_9H_5Cl_2NO_2S$ (262.11): C 41.24, H 1.92, N 5.34. Found: C 41.34, H 1.98, N 5.54.

4-Chloro-3-chlorosulfonylquinoline (**5b**)

mp 129-130 ºC (benzene), lit.,[5] mp 129-130 ºC. ^1H NMR spectrum ($CDCl_3$) was identical with the sample prepared previously.[5]

2-Chloro-6-chlorosulfonylquinoline (**5c**)

mp 138-140 ºC (CCl_4). EI MS (70eV) (m/z): 261 (34, M^+), 263 (23, $M^+ + 2$), 162 (100). ^1H NMR ($CDCl_3$), δ: 7.61 (d, 1H, *J*=8.8 Hz, H3), 8.24-8.32 (m, 3H, H4, H7 and H8), 8.60 (d, 1H, *J*=2.0 Hz, H5).

Anal. Calcd for $C_9H_5Cl_2NO_2S$ (262.11): C 41.24, H 1.92, N 5.34. Found: C 41.05, H 1.88, N 5.50. Compound **5c** was mentioned in references[6a,b] but no analytical data was given.

4-Chloro-6-chlorosulfonylquinoline (**5d**)

mp 101-102 ºC (CCl_4). EI MS (70eV) (m/z): 261 (43, M^+), 263 (30, $M^+ + 2$), 162 (100). ^{1}H NMR ($CDCl_3$), δ: 7.69 (d, 1H, *J*=4.8 Hz, H3), 8.26 (dd, 1H, *J*=8.8 Hz, *J*=2.0 Hz, H7), 8.37 (d, 1H, *J*=8.8 Hz, H8), 8.93 (d, 1H, *J*=2.0 Hz, H5), 8.98 (d, 1H, *J*=4.8 Hz, H2). *Anal.* Calcd for $C_9H_5Cl_2NO_2S$ (262.11): C 41.24, H 1.92, N 5.34. Found: C 41.24, H 2.09, N 5.53.

Preparation of y-chloro-x-quinolinesulfonamides (**6**)

(Procedure D)

Crude y-chloro-x-quinolinesulfonyl chloride (**5**) (0.65 g, 2.5 mmol) and conc. NH_4OH (12.5 mL) was stirred at 45 °C for 0.5 h. An excess of ammonia was evaporated under vacuum. Then water was added up to the volume of 10 mL. The solid was filtered off and washed with cold water. It was finally recrystallized from 10% aqueous EtOH (78-86%).

2-Chloro-3-quinolinesulfonamide (**6a**)

mp 238-240 ºC (EtOH- water). EI MS (70eV) (m/z): 242 (100, M^+), 244 (36, $M^+ + 2$). ^{1}H NMR (DMSO-d_6), δ: 7.39 (s, 2H, N$\underline{H}_2$), 7.96 (ddd, 1H, *J*=7.6 Hz, *J*=7.0 Hz, *J*=1.0 Hz, H6), 8.12 (ddd, 1H, *J*=7.9 Hz, *J*=7.0 Hz, *J*=1.2 Hz, H7), 8.27 (dd, 1H, *J*=7.6 Hz, *J*=1.2 Hz, H5), 8.43 (dd, 1H, *J*=7.9 Hz, *J*=1.0 Hz, H8), 9.25 (s, 1H, H4). *Anal.* Calcd for $C_9H_7ClN_2O_2S$ (242.67): C 44.54; H 2.91; N 11.54. Found: C 44.41, H 3.10, N 11.65.

4-Chloro-3-quinolinesulfonamide (**6b**)

mp 201-202 ºC (EtOH), lit.,[5] mp 201-202 ºC.

2-Chloro-6-quinolinesulfonamide (**6c**)

mp 213-214 ºC (EtOH- water). EI MS (70eV) (m/z): 242 (100, M^+). ^{1}H NMR (DMSO-d_6), δ: 7.58 (s, 2H, N$\underline{H}_2$), 7.75 (d, 1H, *J*=8.6 Hz, H3), 8.13-8-19 (m, 2H, H7 and H8), 8.57 (d, 1H, *J*=1.8 Hz, H5), 8.70 (d, 1H, *J*=8.6 Hz, H4). *Anal.* Calcd for $C_9H_7ClN_2O_2S$ (242.67): C 44.54; H 2.91; N 11.54. Found: C 44.60, H 2.98, N 11.45.

4-Chloro-6-quinolinesulfonamide (**6d**)

mp 133-134 ºC (EtOH- water). EI MS (70eV) (m/z): 242 (100, M^+), 244 (37, $M^+ + 2$). ^{1}H NMR (DMSO-d_6), δ: 7.69 (s, 2H, N$\underline{H}_2$), 7.93 (d, 1H, *J*=4.8 Hz, H3), 8.22 (dd, 1H, *J*=8.8 Hz, *J*=2.0 Hz, H7), 8.30 (d, 1H, *J*=8.8 Hz, H8), 8.66 (d, 1H, *J*=2.0 Hz, H5), 8.99 (d, 1H, *J*=4.8 Hz, H2). *Anal.* Calcd for $C_9H_7ClN_2O_2S$ (242.67): C 44.54; H 2.91; N 11.54. Found: C 44.41, H 3.10, N 11.65.

Synthesis of y-chloro-x-quinolinesulfochloride (**8**)

Procedure E

Solution of x,x'-bis(y-chloroquinolinyl disulfide (**7**) (0.39g, 1 mmol) in conc. hydrochloric acid (10 mL) was cooled in an ice-salt bath down to - 10 °C. Then, cold 6% aqueous solution of sodium hypochlorite (8.2 g, 7.8 mL, 5.5 mmol) was added dropwise within 15 min to the above well-stirred mixture at such a rate that temperature was maintained between -8 to -10 °C. The mixture was poured into 60 g of ice and, due to instability of y-chloro-x-quinolinesulfonyl chloride (**8**), the solution was treated with cold ammonia as described previously for quinolinesulfonyl chlorides with chlorosulfonyl substituent in the *aza*-activated position.[9] Aqueous ammonia insoluble solid was filtered off and air-dried to give x,y-dichloroquinoline (**1**) (0.18-28 g, 48-68%). Further work-up[8,9] of the filtrate resulted in y-chloro-x-quinolinesulfonamide (**9**) (0.135-275 g, 28-50%).

For purpose of ^{1}H and ^{13}C NMR analysis of **8**, chlorination of disulfide **7** was performed in $CDCl_3$ solution (5 mL). Organic layer was separated, washed with ice-cold water and dried over anhydrous sodium sulfate. ^{1}H and ^{13}C NMR spectra showed that the content of compound **8** in $CDCl_3$ solution ranged from 70 to 100% and that **8** is accompanied by x,y-dichloroquinoline (**1**) 0-30%. Amination of chloroform extract of **8** performed in above mentioned manner led to x,y-dichloroquinoline (**1**) and y-chloro-x-quinolinesulfonamide (**9**) with close results to those of direct amination of **8**.

3-Chloro-2-chlorosulfonylquinoline (**8a**)

Isolated in the form of $CDCl_3$ solution. ^{1}H NMR ($CDCl_3$), δ: 7.61 (dd, 1H, *J*=7.4 Hz, *J*=7.2 Hz, H6), 7.74-7.79 (m, 2H, H5 and H7), 8.08 (d, 1H, *J*=8.8 Hz, H8), 8.27 (s, 1H, H4). ^{13}C NMR ($CDCl_3$), δ: 126.8, 127.4, 128.3, 130.2, 131.1, 133.8, 137.8.

6-Chloro-2-chlorosulfonylquinoline (**8c**)

Chlorination of **7c** resulted in the mixture of **8c** (ca. 70%) and **1c** (ca. 30%). Both ^{1}H and ^{13}C NMR data of **8** were extracted from the spectra ($CDCl_3$ solution) of the **8c** and **1c** mixture, taking into account spectral data of **1c**.[25] ^{1}H NMR ($CDCl_3$), δ: 7.86 (dd, 1H, *J*=9.04 Hz, *J*=8.8 Hz, H7), 7.98 (d, 1H, *J*=9.08 Hz, H7), 8.15 (d, 1H, *J*=8.6 Hz, H3) 8.26 (d, 1H, *J*=9.0 Hz, H8), 8.44 (d, 1H, *J*=8.6 Hz, H4). ^{13}C NMR ($CDCl_3$), δ: 118.0, 123.8, 126.7, 127.6, 133.3, 136.9, 139.1, 145.3, 158.1.

6-Chloro-4-chlorosulfonylquinoline (**8d**)

Isolated in the form of $CDCl_3$ solution. ^{1}H NMR ($CDCl_3$), δ: 8.06 (d, 1H, *J*=8.8 Hz, H7), 8.11 (d, 1H, *J*=5.6 Hz, H3), 8.42 (s, 1H, H5), 8.84 (d, 1H, *J*=8.8 Hz, H8), 9.20 (d, 1H, *J*=5.6 Hz, H2). ^{13}C NMR ($CDCl_3$), δ: 123.3, 124.2, 124.5, 125.9, 128.2, 130.2, 132.2, 134.8, 136.8.

3-Chloro-2-quinolinesulfonamide (**9a**)

mp 234-235 ºC (EtOH-H_2O). EI MS (70eV) (m/z): 242 (33, M^+), 244 (12, M^+ +2), 162 (100). ^{1}H NMR

(DMSO-d_6), δ: 7.80 (ddd, 1H, *J*=8.0 Hz, *J*=7.6 Hz, *J*=0.9 Hz, H6), 7.87 (s, 2H, N<u>H</u>$_2$), 7.94 (ddd, 1H, *J*=7.7 Hz, *J*=6.7 Hz, *J*=1.3 Hz, H7), 8.08-8.13 (m, 2H, H5 and H8), 8.84 (s, 1H, H4). ***Anal.*** Calcd for $C_9H_7ClN_2O_2S$ (242.67): C 44.54; H 2.91; N 11.54. Found: C 44.31, H 3.09, N 11.65.

<u>6-Chloro-2-quinolinesulfonamide (**9c**)</u>

mp 213-214 ºC (EtOH- water). EI MS (70eV) (m/z): 242 (40, M^+), 244 (15, M^+ +2), 162 (100). ^{1}H NMR (DMSO-d_6), δ: 7.58 (s, 2H, N<u>H</u>$_2$), 7.75 (d, 1H, *J*=8.8 Hz, H3), 8.13-8.19 (m, 2H, H7 and H8), 8.57 (d, 1H, *J*=1.8 Hz, H5), 8.70 (d, 1H, *J*=8.8 Hz, H4). ***Anal.*** Calcd for $C_9H_7ClN_2O_2S$ (242.67): C 44.54; H 2.91; Cl 14.61; N 11.54; S 13.21. Found: C 44.41, H 3.10, N 11.65.

<u>6-Chloro-4-quinolinesulfonamide (**9d**)</u>

mp 211-212 ºC (EtOH-water). EI MS (70eV) (m/z): 242 (34, M^+), 244 (13, M^+ +2), 162 (100). ^{1}H NMR (DMSO-d_6), δ: 7.93 (dd, 1H, *J*=9.0 Hz, *J*=2.3 Hz, H7), 8.01 (d, 1H, *J*=4.4 Hz, H3), 8.11 (s, 2H, N<u>H</u>$_2$), 8.20 (d, 1H, *J*=9.0 Hz, H8), 8.63 (d, 1H, *J*=2.3 Hz, H5), 9.13 (d, 1H, *J*=4.4 Hz, H2). ***Anal.*** Calcd for $C_9H_7ClN_2O_2S$ (242.67): C 44.54; H 2.91; N 11.54. Found: C 44.61, H 3.06, N 11.61.

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25. NMR data of 2,6-dichloroquinoline (**1c**). ^{1}H NMR ($CDCl_3$), δ: 7.42 (d, 1H, *J*=8.6 Hz, H3), 7.68 (dd, 1H, *J*=9.0 Hz, *J*=2.3 Hz, H7), 7.81 (d, 1H, *J*=2.3 Hz, H5), 7.97 (d, 1H, *J*=9.0 Hz, H8), 8.03 (d, 1H, *J*=8.6 Hz, H4). ^{13}C NMR ($CDCl_3$), δ: 123.3, 126.3, 127.4, 130.0, 131.5, 132.8, 137.9, 146.1, 150.9.