

HETEROCYCLES, Vol. 81, No. 2, 2010, pp. 305 - 316. © The Japan Institute of Heterocyclic Chemistry
Received, 14th October, 2009, Accepted, 30th November, 2009, Published online, 1st December, 2009
DOI: 10.3987/COM-09-11855

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) occurred *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-chloroquinoliny) 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-quinolinesulfonyl 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 °C to chloroazine and sulfur dioxide,^{8,9,16,18,19} but freshly prepared samples could be successfully characterized with the ¹H and ¹³C NMR spectra^{8,9,19} and effectively 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.

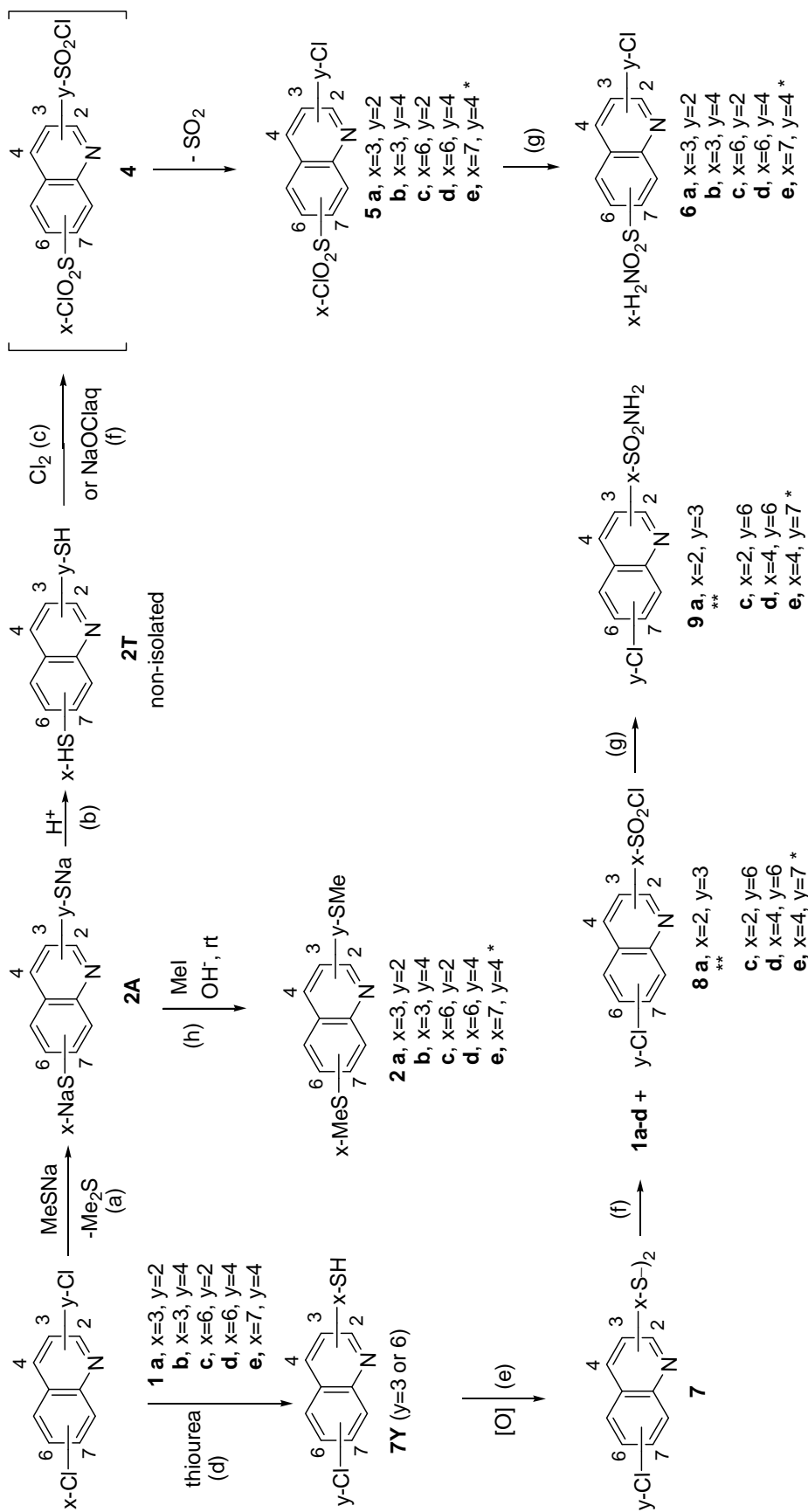
RESULTS AND DISCUSSION

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 oxidatively chlorinated to quinolinesulfonyl chlorides.^{8,9}

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

Synthesis of the γ -chloro- α -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:

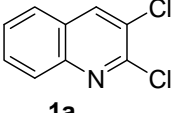
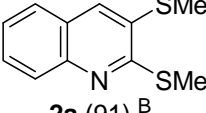
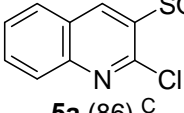
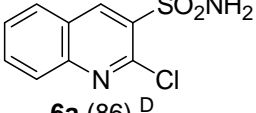
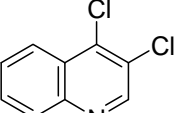
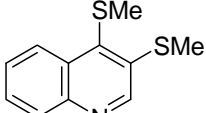
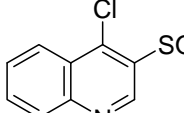
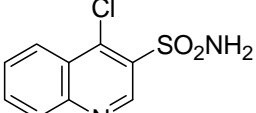
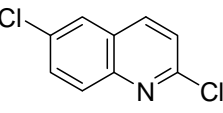
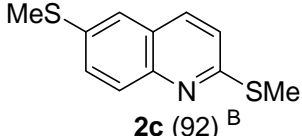
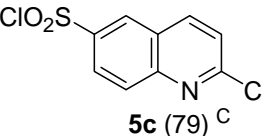
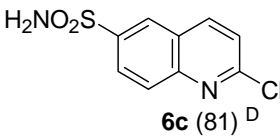
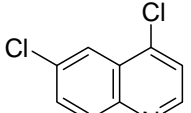
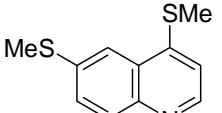
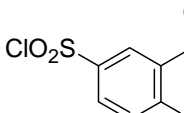
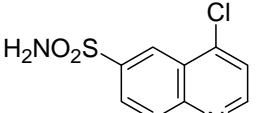
- i) Formation of dithiolates (**2A**) in the reaction of dichloroderivatives (**1**) with sodium methanethiolate. To confirm the structure of the expected x,y -quinolinedithiolates (**2A**), crude thiolate solution was methylated to x,y -dimethylsulfanylquinolines (**2a-d**).
- ii) Oxidative chlorination 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) Cl₂, 17 °C, 30 min- procedure C; (d) thiourea, rt, then H₂O, OH⁻, then H⁺; (e) aq. K₃Fe(CN)₆; (f) NaOClaq., conc. HClaq. - procedure E; (g) NH₃ 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 γ -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 γ -chloro-x-chlorosulfonyl-quinolines 5a-d.

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

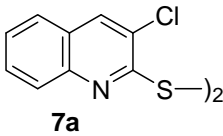
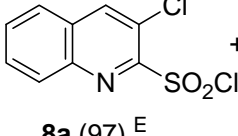
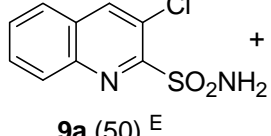
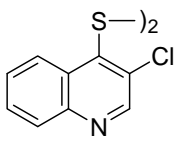
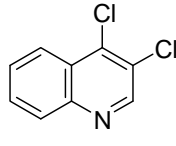
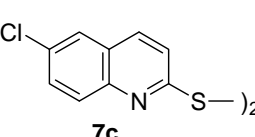
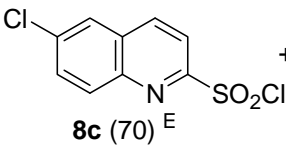
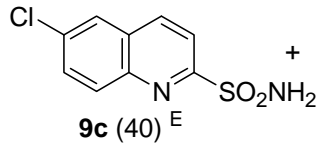
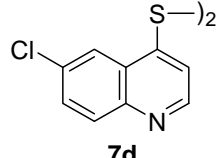
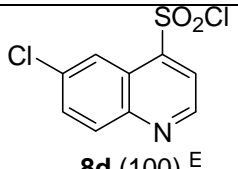
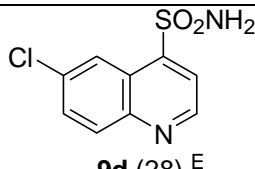
Entry	Substrate	Products, yield (%), ^{procedure}		
1	 1a	 2a (91) ^B	 5a (86) ^C	 6a (86) ^D
2	 1b	 2b (82) ^B	 5b (80) ^C	 6b (81) ^D
3	 1c	 2c (92) ^B	 5c (79) ^C	 6c (81) ^D
4	 1d	 2d (80) ^B	 5d (80) ^C	 6d (78) ^D

*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) CDCl₃ immediately after the synthesis and fully characterized (at 0 °C, up to 1 h) with ¹H and ¹³C NMR spectra. Moreover, both NMR spectra showed that the compounds **8a,c,d** in CDCl₃ 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**).

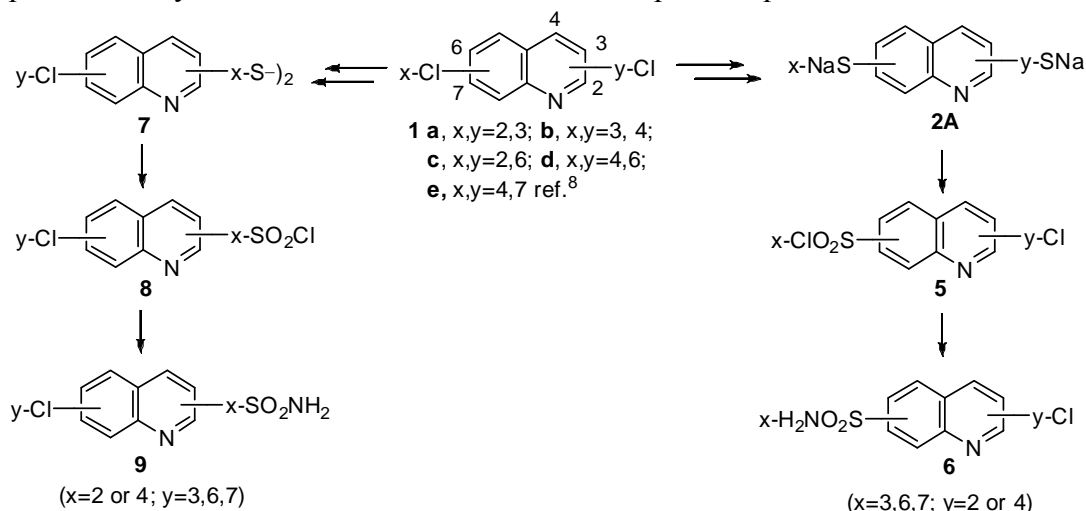
Table 2. Synthesis of chloroquinolinesulfonylchlorides **8** and chloroquinolinesulfonamides **9** from disulfides **7**.

Entry	Substrate	Products, yield (%), procedure	
1		 + 1a (3)	 + 1a (48)
		8a (97) ^E	9a (50) ^E
2			
		1b (100%) ^E	
3		 + 1c (30)	 + 1c (59)
		8c (70) ^E	9c (40) ^E
4			 + 1d (61)
		8d (100) ^E	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, starting 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 ^1H and ^{13}C nuclei, respectively, in deuteriochloroform (CDCl_3) or in hexadeuterodimethyl sulfoxide ($\text{DMSO}-d_6$) solutions with tetramethylsilane (δ 0.0 ppm) as internal standard. TLC analyses were performed employing Merck's silicagel 60 F₂₅₄ 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 F₂₅₄ 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 Cooper²¹ – 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 °C (hexane). EI MS (70eV) (m/z): 221 (100, M⁺). ¹H NMR (CDCl₃), δ: 2.57 (s, 3H, SCH₃), 2.72 (s, 3H, SCH₃), 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 C₁₁H₁₁NS₂ (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 °C (hexane), lit.,²² mp 93-94 °C. ¹H NMR spectrum (CDCl₃) was identical with the sample prepared previously.²²

2,6-Dimethylsulfanylquinoline (2c)

mp 104-105 °C (EtOH). EI MS (70eV) (m/z): 221 (100, M⁺). ¹H NMR (CDCl₃), δ: 2.57 (s, 3H, SCH₃), 2.69 (s, 3H, SCH₃), 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 C₁₁H₁₁NS₂ (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 °C (hexane). EI MS (70eV) (m/z): 221 (100, M⁺). ¹H NMR (CDCl₃), δ: 2.62 (s, 3H, SCH₃), 2.71 (s, 3H, SCH₃), 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 C₁₁H₁₁NS₂ (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* thiuronium 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 °C (EtOH). Yield 83%. EI MS (70eV) (m/z): 388 (3, M⁺), 390 (1.9, M⁺ + 2), 195 (100). ¹H NMR (CDCl₃), 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, H7 and 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 C₁₈H₁₀Cl₂N₂S₂ (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 °C (EtOH). Yield 86%. EI MS (70eV) (m/z): 388 (20, M⁺), 390 (16, M⁺ + 2), 195 (100). ¹H

NMR (CDCl₃), 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 C₁₈H₁₀Cl₂N₂S₂ (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 °C (EtOH). Yield 90%. EI MS (70eV) (m/z): 388 (20, M⁺), 390 (15, M⁺ + 2), 195 (100). ¹H NMR (CDCl₃), 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 C₁₈H₁₀Cl₂N₂S₂ (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 °C (EtOH), lit.,²³ mp 169-170 °C. Yield 89%.

Preparation of γ -chloro- α -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 α,γ -dimercaptoquinoline (**2T**) (ca. 4 mmol) (prepared from α,γ -dichloroquinoline according to procedure A), conc. hydrochloric acid (12 mL) and CHCl₃ (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 CHCl₃ (3 x 10 mL). The chloroform extracts were combined, washed with water and dried over anhydrous sodium sulfate. CHCl₃ was evaporated to leave solid residue. The residue was recrystallized from CCl₄ or from benzene to give γ -chloro- α -quinolinesulfonyl chloride (**5**) (79-86%).

2-Chloro-3-chlorosulfonylquinoline (5a)

mp 180-181 °C (CCl₄). EI MS (70eV) (m/z): 261 (33, M⁺), 263 (21, M⁺ + 2), 162 (100). ¹H NMR (CDCl₃), 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 C₉H₅Cl₂NO₂S (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 °C (benzene), lit.,⁵ mp 129-130 °C. ¹H NMR spectrum (CDCl₃) was identical with the sample prepared previously.⁵

2-Chloro-6-chlorosulfonylquinoline (5c)

mp 138-140 °C (CCl₄). EI MS (70eV) (m/z): 261 (34, M⁺), 263 (23, M⁺ + 2), 162 (100). ¹H NMR (CDCl₃), 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 C₉H₅Cl₂NO₂S (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 °C (CCl₄). EI MS (70eV) (m/z): 261 (43, M⁺), 263 (30, M⁺ + 2), 162 (100). ¹H NMR (CDCl₃), 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 C₉H₅Cl₂NO₂S (262.11): C 41.24, H 1.92, N 5.34. Found: C 41.24, H 2.09, N 5.53.

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

(Procedure D)

Crude γ-chloro-x-quinolinesulfonyl chloride (**5**) (0.65 g, 2.5 mmol) and conc. NH₄OH (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 °C (EtOH- water). EI MS (70eV) (m/z): 242 (100, M⁺), 244 (36, M⁺ + 2). ¹H NMR (DMSO-d₆), δ: 7.39 (s, 2H, NH₂), 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 C₉H₇ClN₂O₂S (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 °C (EtOH), lit.,⁵ mp 201-202 °C.

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

mp 213-214 °C (EtOH- water). EI MS (70eV) (m/z): 242 (100, M⁺). ¹H NMR (DMSO-d₆), δ: 7.58 (s, 2H, NH₂), 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 C₉H₇ClN₂O₂S (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 °C (EtOH- water). EI MS (70eV) (m/z): 242 (100, M⁺), 244 (37, M⁺ + 2). ¹H NMR (DMSO-d₆), δ: 7.69 (s, 2H, NH₂), 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 C₉H₇ClN₂O₂S (242.67): C 44.54; H 2.91; N 11.54. Found: C 44.41, H 3.10, N 11.65.

Synthesis of γ -chloro- α -quinolinesulfochloride (**8**)

Procedure E

Solution of α,α' -bis(γ -chloroquinolinyl disulfide (**7**)) (0.39g, 1 mmol) in conc. hydrochloric acid (10 mL) was cooled in an ice-salt bath down to $-10\text{ }^{\circ}\text{C}$. 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 $-10\text{ }^{\circ}\text{C}$. The mixture was poured into 60 g of ice and, due to instability of γ -chloro- α -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 α,γ -dichloroquinoline (**1**) (0.18-28 g, 48-68%). Further work-up^{8,9} of the filtrate resulted in γ -chloro- α -quinolinesulfonamide (**9**) (0.135-275 g, 28-50%).

For purpose of ^1H 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. ^1H 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 α,γ -dichloroquinoline (**1**) 0-30%. Amination of chloroform extract of **8** performed in above mentioned manner led to α,γ -dichloroquinoline (**1**) and γ -chloro- α -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. ^1H NMR (CDCl_3), δ : 7.61 (dd, 1H, $J=7.4\text{ Hz}$, $J=7.2\text{ Hz}$, H6), 7.74-7.79 (m, 2H, H5 and H7), 8.08 (d, 1H, $J=8.8\text{ Hz}$, 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 ^1H 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 ^1H NMR (CDCl_3), δ : 7.86 (dd, 1H, $J=9.04\text{ Hz}$, $J=8.8\text{ Hz}$, H7), 7.98 (d, 1H, $J=9.08\text{ Hz}$, H7), 8.15 (d, 1H, $J=8.6\text{ Hz}$, H3) 8.26 (d, 1H, $J=9.0\text{ Hz}$, H8), 8.44 (d, 1H, $J=8.6\text{ Hz}$, 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. ^1H NMR (CDCl_3), δ : 8.06 (d, 1H, $J=8.8\text{ Hz}$, H7), 8.11 (d, 1H, $J=5.6\text{ Hz}$, H3), 8.42 (s, 1H, H5), 8.84 (d, 1H, $J=8.8\text{ Hz}$, H8), 9.20 (d, 1H, $J=5.6\text{ Hz}$, 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 $234\text{--}235\text{ }^{\circ}\text{C}$ (EtOH- H_2O). EI MS (70eV) (m/z): 242 (33, M^+), 244 (12, $\text{M}^+ + 2$), 162 (100). ^1H 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, NH_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.

6-Chloro-2-quinolinesulfonamide (9c)

mp 213-214 °C (EtOH- water). EI MS (70eV) (m/z): 242 (40, M^+), 244 (15, $M^+ + 2$), 162 (100). 1H NMR (DMSO- d_6), δ : 7.58 (s, 2H, NH_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.

6-Chloro-4-quinolinesulfonamide (9d)

mp 211-212 °C (EtOH-water). EI MS (70eV) (m/z): 242 (34, M^+), 244 (13, $M^+ + 2$), 162 (100). 1H 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, NH_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.

REFERENCES (AND NOTES)

Part CXX in the series of Azinyl Sulfides

1. R. K. Smalley, *Haloquinolines*, in *Quinolines* part I [ed. by G. Jones], Interscience, Wiley and Sons, London-New York-Sydney-Toronto, 1977, chapter 3, pp. 319-786.
2. R. V. Davies, J. Fraser, and K. J. Nicol, European Pat. 0 206 616 A2, (09.06.1986) (*Chem. Abstr.* 1987, **107**, P 58881g).
3. F. Marsais, P. Bohn, V. Levacher, and N. le Fur, Patent WO 2006/103120 A2 (05. 10. 2006) (*Chem. Abstr.* 2006, **145**, P 377221y).
4. L. Skrzypek, J. Folwarczna, W. Janiec, I. Kaczmarczyk-Sedlak, A. Maślankiewicz, and M. Pytlik, *Polish J. Chem.*, 1998, **72**, 1127.
5. A. Maślankiewicz and L. Skrzypek, *Heterocycles*, 1994, **38**, 1317.
6. a) J. W. Malecha, S. A. Noble, B. M. Wiley, T. Z. Hoffman, C. Bonnefous, M. Sertic, P. L. Wash, N. D. Smith, Ch. A. Hassing, S. A. Scranton, J. E. Payne, and J. Hager, *U.S. Pat. Appl. Publ.* US **2007** 27,184 (*Chem. Abstr.*, 2007, **146**, 206220p). b) M. R. Becker, W. R. Ewing, R. S. Davis, H. W. Pauls, C. Ly, A. Li, H. J. Mason, Y. Choi-Sledeski, A. P. Spada, V. Chu, K. D. Brown, D. J. Colussi, R. J. Leadley, R. Bentley, J. Bostwick, Ch. Kasiewski, and S. Morgan, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 2753.
7. a) B. Riegel, G. R. Lappin, C. J. Albisetti, B. H. Adelson, R. M. Dodson, L. G. Ginger, and R. H. Baker, *J. Am. Chem. Soc.*, 1946, **68**, 1229. b) D. Zaruma and Yu. A. Bankovskii, *Latv. PSR Zinat.*

- Acad. Vestis. Kim. Ser.*, 1978, 110.
8. K. Marciniak and A. Maślankiewicz, *Heterocycles*, 2009, **78**, 93.
 9. A. Maślankiewicz, K. Marciniak, M. Pawłowski, and P. Zajdel, *Heterocycles*, 2007, **71**, 1975.
 10. S. Kubota and T. Akita, *Yakugaku Zasshi*, 1961, **81**, 511.
 11. R. H. Baker, R. M. Dodson, and B. Riegel, *J. Am. Chem. Soc.*, 1946, **68**, 2636.
 12. H. Kwart and L. J. Miller, *J. Am. Chem. Soc.*, 1958, **80**, 884.
 13. H. Kwart and R. W. Body, *J. Org. Chem.*, 1965, **30**, 1188.
 14. Typical examples of chlorinolysis of *aza*-activated azine-thiones and azine-thiols directed to respective chloroazines are summarized in ref. 13, p.1192.
 15. W. T. Caldwell and E. C. Kornfeld, *J. Am. Chem. Soc.*, 1942, **64**, 1695.
 16. Z. Talik and E. Płażek, *Acta Polon. Pharm.*, 1955, **12**, 5.
 17. E. Ager, B. Iddon, and H. Suschitzky, *J. Chem. Soc. (C)*, 1970, 1530.
 18. H. I. Skulnik, P. D. Johnson, P. A. Aristoff, J. K. Morris, K. D. Lovasz, W. J. Howe, K. D. Watenpaugh, M. N. Janakiraman, D. J. Anderson, R. J. Reischer, T. M. Schwartz, L. S. Banitt, P. K. Tomich, J. C. Lynn, M.-M. Horng, K.-T. Chong, R. R. Hinshaw, L. A. Dolak, E. P. Seest, F. J. Schwende, B. D. Rush, G. M. Howard, L. N. Toth, K. R. Wilkinson, T. J. Kakuk, C. W. Johnson, S. L. Cole, R. M. Zaya, G. L. Zipp, P. L. Possert, R. J. Dalga, W.-Zh. Zhong, M. G. Williams, and K. R. Romines, *J. Med. Chem.*, 1997, **40**, 1149.
 19. S. W. Wright and K. N. Hallstrom, *J. Org. Chem.*, 2006, **71**, 1080.
 20. L. Testaferri, M. Tiecco, M. Tingoli, D. Chianelli, and M. Montanucci, *Synthesis*, 1983, 751.
 21. G. B. Bachman and D. E. Cooper, *J. Org. Chem.*, 1944, **9**, 302.
 22. A. Maślankiewicz, *Polish J. Chem.*, 1980, **54**, 2069.
 23. E. Hayashi and N. Shimada, *Yakugaku Zasshi*, 1977, **97**, 627.
 24. M. Konishi, N. Fukuda, Y. Oku, H. Yamazaki, K. Imaizumi, and H. Kobayashi, *Japan PCT Int. Appl. WO 9623*, 1995, 774 (*Chem. Abstr.*, 1996, **125**, 247632h).
 25. NMR data of 2,6-dichloroquinoline (**1c**). ¹H NMR (CDCl₃), 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). ¹³C NMR (CDCl₃), δ: 123.3, 126.3, 127.4, 130.0, 131.5, 132.8, 137.9, 146.1, 150.9.