HETEROCYCLES, Vol. 57, No. 7, 2002, pp. 1279 - 1286, Received, 27th March, 2002

5-(3-QUINOLINYLTHIO)METHYL-TETRAHYDRO-2-FURANONES FROM 3,3'-BIS(4-SUBSTITUTED QUINOLINYL) DISULFIDES [#]

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Abstract - The intramolecular lactonization of 4-pentenoic acid to the title tetrahydrofuranones (**12**) was performed by addition of electrochemically generated sulfenyl cations starting from 3,3'-bis(4-substituted quinolinyl) disulfides (**7a, b, c, d, e**) and 3,3'-bis(1-methyl-1,4-dihydro-4-oxo-quinolinyl) disulfide (**9b**) and using bromide as a redox catalyst. Two syntheses of diquinolinyl disulfide (**7e**) were described as well.

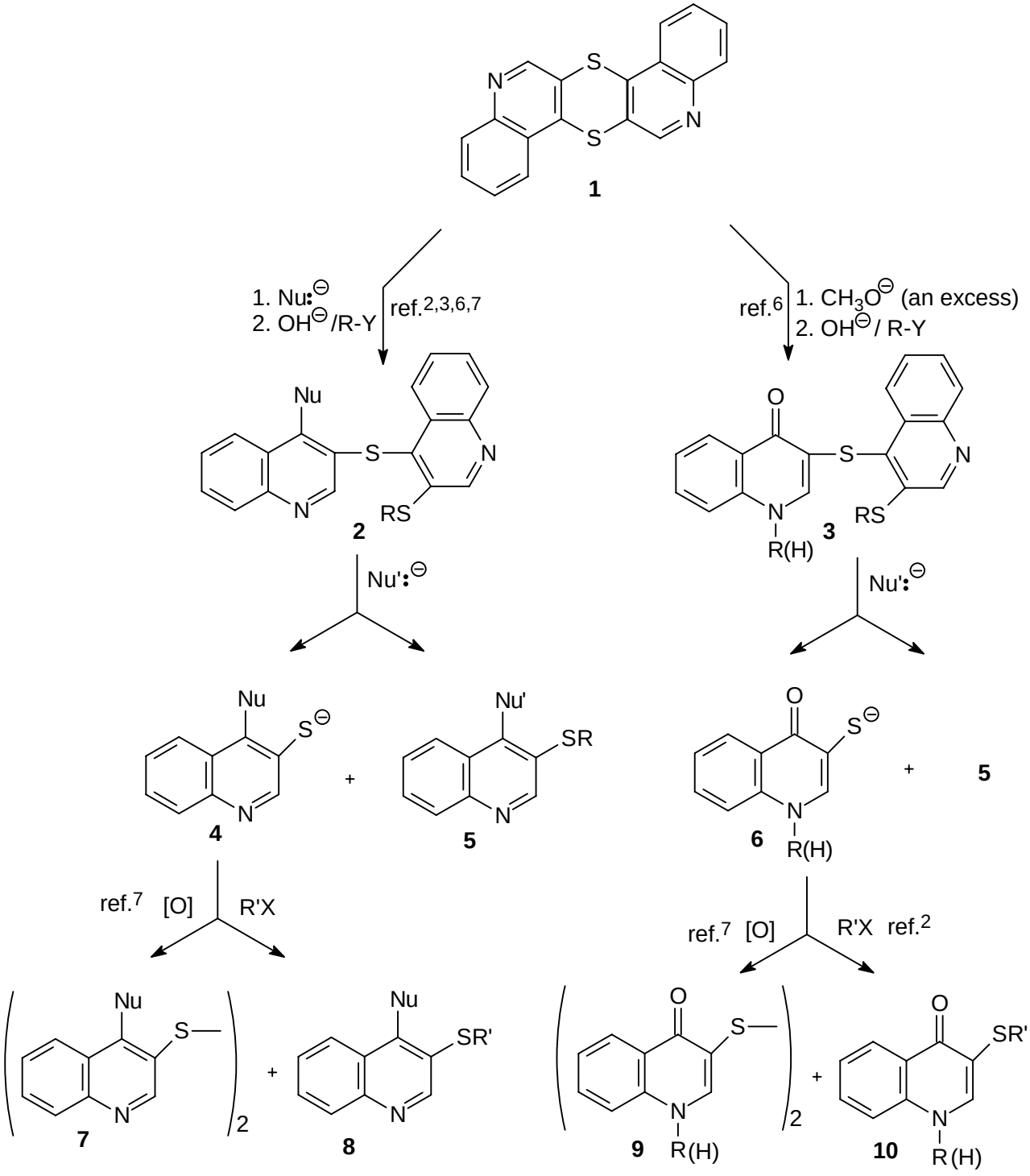
INTRODUCTION

Thioquinanthrene (**1**) (the main quinoline sulfurization product, 64%) [1] could be a source of numerous thioquinolines.[2-7] The reaction of thioquinanthrene (**1**) with nucleophiles gave 3'-quinolinethiolates of type (**2**) (R=Na) or (**3**) (R=Na), which were trapped in the form of 3'-alkylthio derivatives (**2**) or (**3**) (R=alkyl). [2,3] Alkylthio members of compounds (**2**) and (**3**) were subsequently split off in the reaction with the next molecules of nucleophile to form 4-nucleophilo-3-alkylthioquinolines (**5**) and 4-substituted 3-quinoline-thiolates (**4**) or 4-quinolinone-3-thiolate (**6**).[2,3,7] The latter were alkylated to alkylthioquinolines (**8**) or (**10**) or oxidized in alkaline aqueous-DMSO solution to respective 3,3'-bis(4-substituted quinolinyl) disulfides (**7**) or (**9**).[7] However, attempts to prepare and (or) to isolate free 3-quinolinethiols by acidification of the alkaline aqueous-DMSO solution of the parent 3-quinolinethiolates (**4**) or (**6**) have failed.[7]

In the methodology outlined in Scheme 1 the key role is played by nucleophilo-desulfidation of 4-quinolinyl sulfur bond, which is followed by *S*-alkylation of β-quinolinyl thiolates. The latter were effective in preparing n-alkyl derivative, but secondary 3'-alkylthio derivative of **2** and **3** were obtained with lower yields.[8] Furthermore, some alkylating agents e.g. derived from γ-halogenocarboxylic acids could not be easily available.[9]

These premises inspired the present study leading to the title γ-butyrolactone derivatives : i) alkyl-aryl sulfides could be prepared by sulfenylation of alkenes,[10] ii) diaryl disulfides, e.g. diphenyl disulfide, could be applied as a source of electrochemically generated arylsulfenyl cations,[11] iii) oxidation potentials of β,β'-diquinolinyl disulfides with alkoxy- or methylthio- substituents of type (**7**) are of the same order of magnitude as that of diphenyl disulfide.[12]

S c h e m e 1

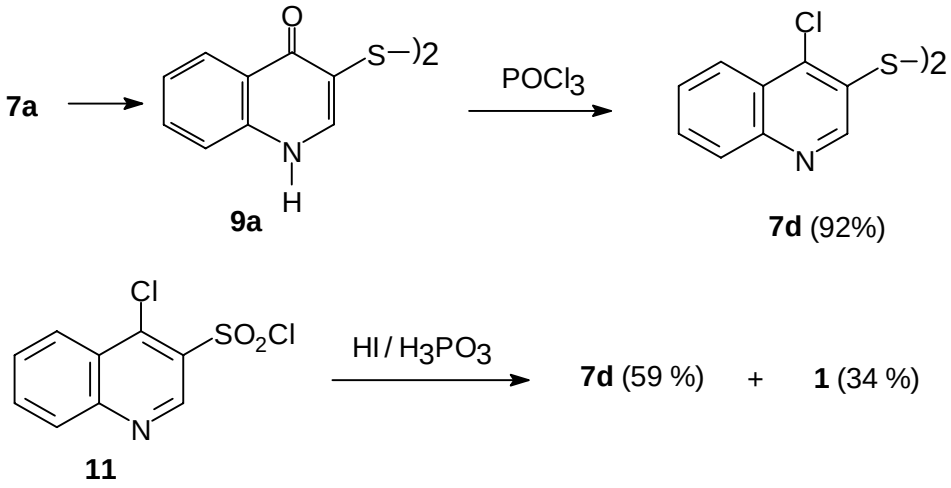


RESULTS AND DISCUSSION

Synthesis of 3,3'-diquinolinyl disulfides

Disulfides with alkoxy and alkylthio groups **7a** (Nu = OCH_3), **7b** (Nu=OC_3H_7), **7c** (Nu = SCH_3) and that with oxo function **9b** (R=CH_3) were prepared as presented in Scheme 1. Two route were followed in preparing the 4,4'-dichlorodisulfide (**7d**). The first route relies upon acidic hydrolysis of dimethoxy derivative (**7a**) to dioxo derivative (**9a**) (R=H) followed by chlorination of **9a** to **7d** with phosphoryl chloride. The second route has been inspired by the reduction procedure of arylsulfochlorides with HI / H_3PO_3 system to diaryl disulfides[13] and easy availability of sulfochloride (**11**) from "wet"-chlorination of thioquinanthrene (**1**).[14] When sulfochloride (**11**) was subjected to the reaction with HI / H_3PO_3 system, the reaction gave also bis-chloride (**7d**) (59%) accompanied by thioquinanthrene (**1**) (34%).

Scheme 2

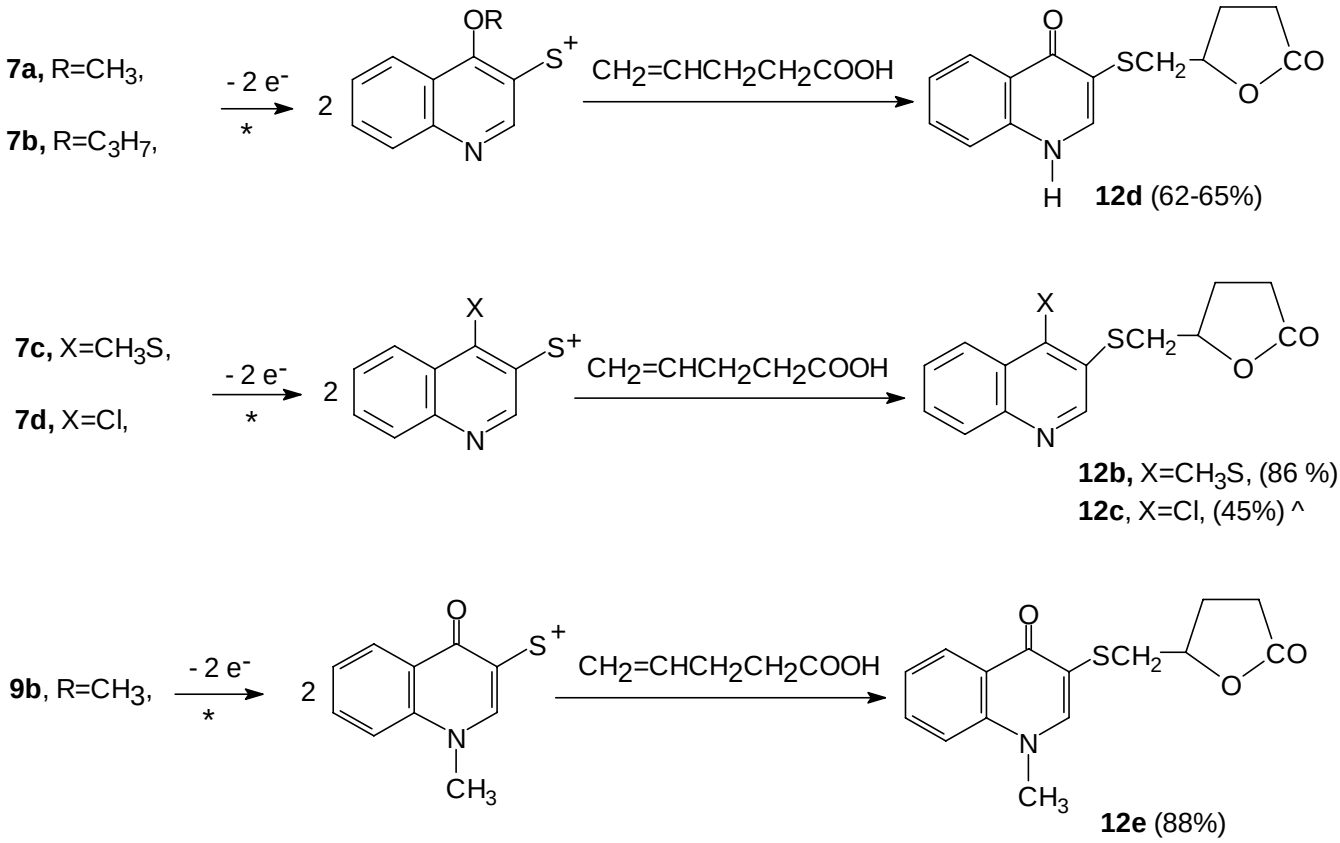


Diquinolinyl disulfides as a source of sulfenylating agents

Sulfenylation of alkenes follows the Markovnikoff rule and leads to β-substituted alkyl sulfides.[10] Literature data [11] show that the electrochemical generation of arenesulfenyl cations from disulfides may be carried out by either direct anodic oxidation or by indirect anodic oxidation using bromide ions as redox catalysts. The latter method was used in this study for the transformation of diquinolinyl disulfides (**7**) and (**9**). However, the bromide mediated electrolysis of disulfides performed in the presence of alkenes may lead to the β-bromosulfides.[11] To avoid formation of lacrimatory acting β-halogeno sulfides, the elegant concept of Töteberg-Kaulen and Steckhan [11] has been applied whereby 4-pentenoic acid is used as an acceptor of quinolinesulfenyl cations. In the case of bismethylthio- and bischloro derivatives (**7c**) and (**7d**) respectively, as well as for bisquinolinone (**9b**) the reaction gave the expected 5-(3-quinolinylthio)-methyltetrahydro-2-furanones (**12b, c, e**). However, in the case of bismethoxy- and bispropoxy derivatives (**7a, b**) the main product was quinolinonelactone (**12d**) (62-65 %).

Most probably in the course of electrolysis, the primarily formed bismethoxy derivative (**12a**) (X=OCH_3) underwent demethylation to **12d**.

Scheme 3



* electrolysis was performed in 0.1 M solution of tetrabutylammonium bromide in methylene chloride

^ as the second product, thioquinanthrene (**1**) (25 %) was isolated.

CONCLUSIONS

The formation of the $C_{quinolinyl}$-S-C bond in the title furanones may be achieved either by alkylation of quinolinethiolate (route a) or by quinolinesulfenation of alkenes (route b):

$C_{quinolinyl}$-S^- + R-X → C-S-R + X^- (route a) ; $C_{quinolinyl}$-S^+Y^- + C=C → C-S-C-C-Y (route b)

However, in the synthesis of 5-[(4,5-diphenyl-1*H*-imidazol-2-yl)thio]methyltetrahydro-2-furanone,[9] which was performed according to the route a, alkylating agent with tetrahydrofuranone moiety was obtained with yield below 30%, and alkylation at sulfur atom ran with *ca*. 42% yield, thus total yield of desired product was *ca.* 12 %.[9] Considering the synthesis of furanones (**12**) according to route a we should note that the respective 3-quinolinethiolates occurr only in aqueous DMSO (or DMF) solution and therefore the corresponding quinolinethiols remain unkown. Thus, taking into account availability and stability of both substrates, the preparation of the furanones (**12**) according to route b is more convenient and effective.

EXPERIMENTAL

All melting points are uncorrected. The ^{1}H NMR spectra were recorded on a INOVA 300 spectrometer at 300 MHz in deuteriochloroform or in hexadeuteriodimethyl sulfoxide solutions with tetramethylsilane as internal standard. EI MS spectra were determined on a LKB 2091 spectrometer at 15 and 70 eV and Finnigan MAT 95 spectrometer at 70 eV. TLC analyses were performed employing Merck's silicagel 60 F_{254} plates using a mixture of methylene chloride - ethanol (10:1, v/v) as an eluent. Column chromatography was performed on silica gel 60 (Merck) using a mixture of methylene chloride - ethanol (10:1, v/v) as an eluent.

3,3'-Diquinolinyl disulfides (**7a, b, c**) and (**9a, b**) were prepared as described previously.[7]

Synthesis of 3,3'-bis(4-chloroquinolinyl) disulfide (**7d**)

a) From 3,3'-bis(1,4-dihydro-4-oxo-quinolinyl) disulfide (**9a**)

A mixture of disulfide (**9a**) (0.35 g, 1 mmol) and 4 mL (43.7 mmol) of phosphoryl chloride was refluxed for 0.5 h. It was then cooled to rt and poured into 10 g of ice and neutralized at 5 °C with concd aqueous ammonia. The solid was filtered off, washed with water and air-dried. The crude product (0.36 g, mp 167-168 °C) was recrystallized from ethanol to give 0.33 g (92%) of disulfide (**7d**).

3,3'-Bis(4-chloroquinolinyl)-disulfide (**7d**): mp 172-173 °C (ethanol). EI MS (70 eV) m/z: 388 (61, M^+), 390 (36, M+2), 194 (100), ^{1}H NMR ($CDCl_3$), δ: 7.54-7.58 (m, 2H, 2 × $\mathbf{H}_{arom}$), 7.69–7.74 (m, 2H, 2 × $\mathbf{H}_{arom}$), 8.12-8.19 (m, 4H, 4 × $\mathbf{H}_{arom}$), 8.90 (s, 2H, 2 × **H**-2). *Anal*. Calcd for $C_{18}H_{10}N_2Cl_2S_2$: C 55.53; H 2.59; N 7.20; Cl 18.21; S 16.47. Found: C 55.25; H 2.35; N 7.41; Cl 18.02; S 16.50.

b) From 4-chloro-3-quinolinesulfonyl chloride (**11**)

A mixture of 4.2 g (51 mmol) of phosphorous acid (H_3PO_3), 0.2 mL (1.5 mmol) of 57% aqueous hydroiodic acid, 5 mL of water and 25 mL of benzene was strirred at the reflux for 2 h. Then sulfonyl chloride (**11**) (2.62 g, 10 mmol) was added portionwise through the reflux condenser within 2 h. Every next portion of **11** was added when the color of the reaction mixture turned from violet to yellow. The mixture was then cooled to rt, poured into 30 mL of water and neutralized at 5 °C with concd aqueous ammonia. The solid was filtered off and air-dried. It consisted of thioquinanthrene (**1**) and dichloride (**7d**) as concluded from TLC data. The filtrate was separated. The benzene layer was dried with anhydrous sodium sulfate, and the solvent was stripped off. The residue is also composed of thioquinanthrene (**1**) and dichloride (**7d**). Both solid products were combined and triturated with 10 mL of ethanol. Insoluble material was filtered off, air-dried and finally recrystallized from DMF to give 0.55 g (34%) of thioquinanthrene (**1**) with mp 314-315 °C lit.,[1] mp 314-315 °C. Ethanolic filtrate was evaporated to dryness. The residue was recrystallized from ethanol to give dichlorodisulfide (**7d**) (1.14 g, 59 %) with mp 171-172 °C and properties identical as those of the product prepared by procedure a).

General procedure for preparative electrolysis:

Electrolysis was carried out under controlled potential in three-compartment H-cell equipped with a platinium working electrode (area 10 cm^2), a carbon rod as counter electrode and a saturated calomel electrode as a reference. Electrodes were connected to an Atlas Sollich 9833 potentiostat in combination with Atlas DC 9933 computer program.

A solution of disulfide (**7**) or a suspension of disulfide (**9b**) (1 mmol) in 100 mL of 0.1 M solution of tetrabutylammonium bromide in methylene chloride was electrolyzed at working potential as shown in Table. After electric current consumption of 10^{-4} F, 4-pentenoic acid (0.2 g, 2 mmol) in 2 mL of methylene chloride was added to the reaction mixture and the electrolysis was continued up to complete consumption of the starting disulfide (as monitored by TLC).

Table: Electrolysis parameters:

Sulfide	Oxidation and working Potential (in CH_2Cl_2 solution)	Current consumption F / mol
7a, R= CH_3	1.85 V, ref.[12]	3
7b, R= C_3H_7	1.85 V, ref.[12]	3
7c, X=SCH_3	1.85 V, ref.[12]	4
7d, X=Cl	1.81 V	3
9b, R=CH_3	1.83 V	3

Isolation of electrolysis products:

i) After electrolysis of disulfides (**7c**) or (**9b**), the resulting mixture was evaporated up to the volume of 30 mL, washed with water (3 x 30 mL) and dried with anhydrous sodium sulfate. The solvent was stripped off. The residue was purified by column chromatography and recrystallized from acetone or DMF to give pure **12b** (0.51 g, 84 %) or **12e** (0.51 g, 88 %), respectively.

ii) In the case of disulfides (**7a**) or (**7b**) the reaction mixture was filtered off to give 0.29 g (or 0.27 g from disulfide **7b**) of furanone (**12d**). The filtrate was then worked up as above (procedure i) to give the second portion of **12d** (0.07 g). The total yield of **12d** reached 62-65 %.

iii) In the case of disulfide (**7d**) the reaction mixture was filtered off to give 0.08 g (25 %) of a solid with mp 314-315 °C which was identified as a thioquinanthrene (**1**). The filtrate was then worked up as above (procedure i) to give furanone (**12c**) (0.18 g, 31 %) as a thick oil.

5-(4-Methylthio-3-quinolinylthio)methyltetrahydro-2-furanone (**12b**): mp 71-72 °C (acetone). EI MS (70 eV) m/z: 305 (100, M^+). ^{1}H NMR ($CDCl_3$), δ: 1.36-1.45 (m, 2H, CHC**H**$_2$CH$_2$), 2.17-2.23 (m, 2H, CH$_2$C**H**$_2$CO), 2.52 (s, 3H, SC**H**$_3$), 2.62 (d, *J*=7.3, 2H, SC**H**$_2$), 4.19-4.30 (m, 1H, C**H**O), 7.62-7.67 (m, 1H, **H**$_{arom}$), 7.69–7.74 (m, 1H, **H**$_{arom}$), 8.10-8.17 (m, 1H, **H**$_{arom}$), 8.54-8.51 (m, 1H, **H**$_{arom}$), 8.88 (s, 1H, **H**$_{2\text{-quinolinyl}}$). *Anal.* Calcd for $C_{15}H_{15}NO_2S_2$: C 58.99; H 4.90; N 4.59; S 20.99. Found: C 58.78; H 4.80; N 4.65; S 20.23.

5-(4-Chloro-3-quinolinylthio)methyltetrahydro-2-furanone (**12c**): an oil. EI MS (70 eV) m/z: 293 (100, M^+), 295 (40, M+2). ^{1}H NMR ($CDCl_3$), δ: 1.20-1.29 (m, 2H, CHC**H**$_2$CH$_2$), 2.60-2.66 (m, 2H, CH$_2$C**H**$_2$CO), 2.91-2.93 (m, 2H, SC**H**$_2$), 4.70-4.81 (m, 1H, C**H**O), 7.66-7.71 (m, 1H, **H**$_{arom}$), 7.75-8.80 (m, 1H, **H**$_{arom}$), 8.10-8.17 (m, 1H, **H**$_{arom}$), 8.21-8.24 (m, 1H, **H**$_{arom}$), 8.63 (s, 1H, **H**$_{2\text{-quinolinyl}}$). *Anal.* Calcd for $C_{14}H_{12}NO_2ClS$: C 57.24; H 4.12; N 4.74; Cl 12.07; S 10.91. Found : C 57.46, H 4.03, N 4.58, Cl 12.34, S 10.70.

5-(1,4-Dihydro-4-oxo-3-quinolinylthio)methyltetrahydro-2-furanone (**12d**): mp 191-192 °C (DMF). EI MS (70 eV) m/z: 275 (100, M^+). ^{1}H NMR (DMSO-d_6), δ: 1.76-1.82 (m, 2H, CHC**H**$_2$CH$_2$), 2.62 (t, *J*=7.3, 2H, CH$_2$C**H**$_2$CO), 3.20 (d, *J*=7.3, 2H, SCH$_2$), 4.78-4.89 (m, 1H, C**H**O), 7.35-7.41 (m, 1H, **H**$_{arom}$), 7.56-7.59 (m, 1H, **H**$_{arom}$), 7.66-7.68 (m, 1H, **H**$_{arom}$), 8.13 (s, 1H, **H**$_{2\text{-quinolinyl}}$), 8.47-8.49 (m, 1H, **H**$_{arom}$), 12.35 (s, 1H, N**H**). *Anal.* Calcd for $C_{14}H_{13}NO_3S$: C 61.08; H 4.76; N 5.09; S 11.64. Found : C 61.38; H 4.35; N 5.36; S 11.23.

5-(1-Methyl-1,4-dihydro-4-oxo-3-quinolinylthio)methyltetrahydro-2-furanone (**12e**): mp 158-160 °C (DMF). EI MS (70 eV) m/z: 289 (59, M^+), 159 (100). ^{1}H NMR (DMSO-d_6), δ: 1.88-1.98 (m, 2H, CHC**H**$_2$CH$_2$), 2.52-2.57 (m, 2H, CH$_2$C**H**$_2$CO), 3.11 (d, *J*=7.3, 2H, SCH$_2$), 3.89 (s, 3H, NC**H**$_3$), 4.57- 4.68 (m, 1H, C**H**O), 7.91-7.96 (m, 2H, 2 x **H**$_{arom}$), 8.10–8.16 (m, 1H, **H**$_{arom}$), 8.31 (s, 1H, **H**$_{2\text{-quinolinyl}}$), 8.36-8.39 (m, 1H, **H**$_{arom}$). *Anal.* Calcd for $C_{15}H_{15}NO_3S$: C 62.27; H 5.23; N 4.84; S 11.08. Found: C 62.30; H 5.10; N 4.96; S 10.94.

ACKNOWLEDGEMENTS

The authors thank prof. G. Le Guillanton (Universite Catholique de l'Ouest, Angers, France) for determining the oxidation potentials of diquinolinyl disulfides (**7a, b, c**).

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