# Synthesis of [1,4]Dioxino[2,3-*c*]quinolines and [1,4]Dioxepino-[2,3-*c*]quinolines and Their 1-Sulfur Analogues



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The synthesis of [1,4]dioxino[2,3-*c*]quinolines and [1,4]dioxepino[2,3-*c*]quinolines with restrained conformation of the piperidine ring, which represent 1,2,3,4-tetrahydroquinolines containing two heteroatom substituents at positions 3 and 4, is described. In addition, the application of this approach for the synthesis of 1-sulfur analogues is discussed. Both series are helpful tools for three-dimensional quantitative structure-activity relationship studies in the field of modulators of multidrug resistance.

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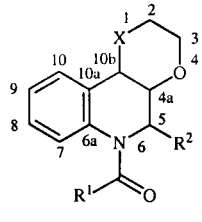
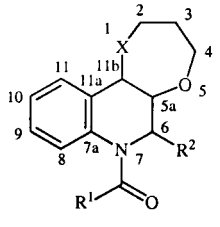
We have been interested in the synthesis of 3,4-diheteroatom substituted 1,2,3,4-tetrahydroquinolines with restricted conformation of the piperidine ring. Compounds with these structural features have attracted our interest as multidrug resistance modulators which are able to overcome the phenomenon of multiple drug resistance being an increasing problem in tumor therapy and in treatment of bacterial and viral infections [1,2]. Due to the enhanced rigid character of the molecules, these compounds represent a versatile tool for three-dimensional quantitative structure-activity relationship studies. To receive these target compounds we planned to introduce a two carbon link by ring closure producing [1,4]dioxino[2,3-*c*]quinolines **1a** and [1,4]oxathiino[2,3-*c*]quinolines **1b**, or a three carbon link leading to [1,4]dioxepino[2,3-*c*]quinolines **2a** and [1,4]oxathiepino[2,3-*c*]quinolines **2b**.



**1**

**a**, X = O, **b**, X = S

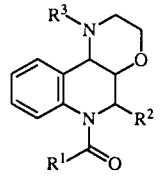


**2**

**a**, X = O, **b**, X = S

$R^1$ = alkyl, aryl
$R^2$ = alkyl, aryl

Recently, we reported on the synthesis of [1,4]oxazino-[2,3-*c*]quinolines **3** which contain a comparable rigidizing element and represent the (six-membered ring annullated) 1-*N*,4-*O*-analogues of the desired compounds [3]. The *trans*-epoxide **4**, which is easily available in three steps from quinoline, is cleaved by nucleophiles exclusively at the benzylic 4-position forming diastereoisomerically pure products [4,5]. To obtain the 4-ethers by alcoholysis of the oxirane ring the low reactivity of **4** has to be overcome by addition of cerium salts which have proved to be excellent catalysts in the cleavage step [5,6]. Applying this protocol, the epoxide cleavage should also be applicable to α,ω-diols, *e.g.*, 1,2-ethanediol in the simpliest case, yielding **5**. The cited reactions (and also the reaction sequences described



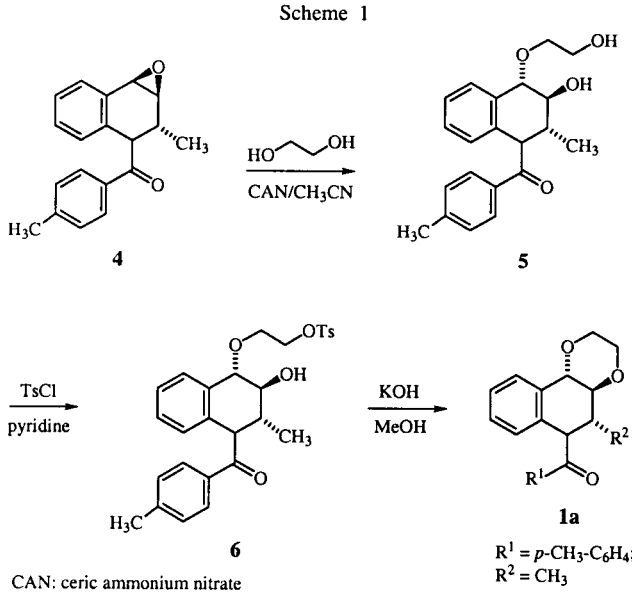
**3**

$R^1$ = alkyl, aryl
$R^2$ = alkyl, aryl
$R^3$ = H, alkyl, benzyl

in the following) can also be performed with analogues carrying other aryl or alkyl *N*-acyl groups, respectively. The reactions were exemplified using the *N*-*p*-toluoyl moiety due to its unambiguously spectroscopic properties.

To perform the ring closure preserving the relative configuration on C-3 we took the advantage that a sulfonyl chloride regioselectively reacts with the primary alcoholic function producing the sulfonyl ester, *e.g.*, **6** [7]. Finally, the 1,4-dioxine **1a** ($R^1$ = *p*-$CH_3$-$C_6H_4$, $R^2$ = $CH_3$) was prepared by reaction with potassium hydroxide in methanol (Scheme 1).

Scheme 1



CAN: ceric ammonium nitrate

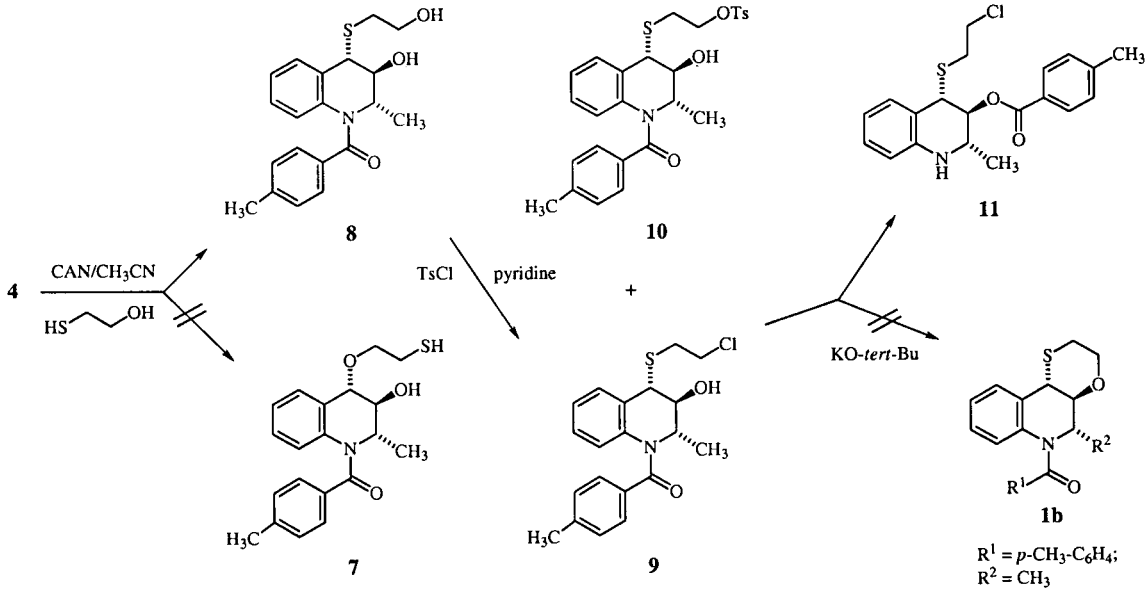
In the case of the formerly described *N,O*-congeners [3], which we have prepared using a similar strategy, we were unable to isolate the *O*-tosyl ester due to direct cyclization to the 1,4-oxazine during the tosylation step. This behavior might be explained by the basic functionality of the 1-*N*-analogue which could take the role of the base required for ring closure.

The *S*-analogous compounds **8** should be achieved in the same way opening the oxirane **4** with 2-mercaptoethanol which required heating over several hours. The dominating nucleophilicity of the mercapto group (in relation to the hydroxy function) aids in obtaining exclusively the 4-*S*-products **8** without formation of the 4-*O*-isomers **7**. Continuing the sequence by treatment of **8** with *p*-tosyl chloride in the presence of pyridine provided the chloro compound **9** while the tosyl product **10** was formed only in traces. Similar results have been obtained by Fujimoto and co-workers in the reaction of α-santonin derivatives with mesyl or tosyl chloride, respectively, obtaining the chloro compounds instead of the expected sulfonyl esters [8] (Scheme 2).

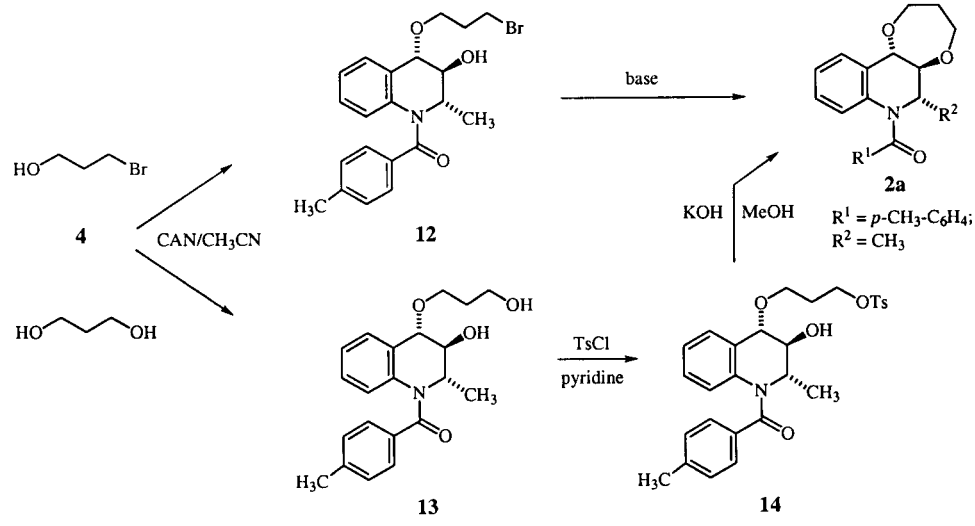
However, the lower reactivity of the chloride in comparison with the tosylate required more vigorous conditions in the cyclization step. This fact let dominate the formation of the ester **11** produced by the migration of the acyl group observed in our previous studies [3], instead of the heterocycle **1b** $R^1 = p\text{-}CH_3\text{-}C_6H_4$, $R^2 = CH_3$ (Scheme 2).

The reaction sequence can also be extended to the annullation of seven-membered rings. To obtain the 1,4-dioxepine **2a** ($R^1 = p\text{-}CH_3\text{-}C_6H_4$, $R^2 = CH_3$) it is obvious that one uses

Scheme 2



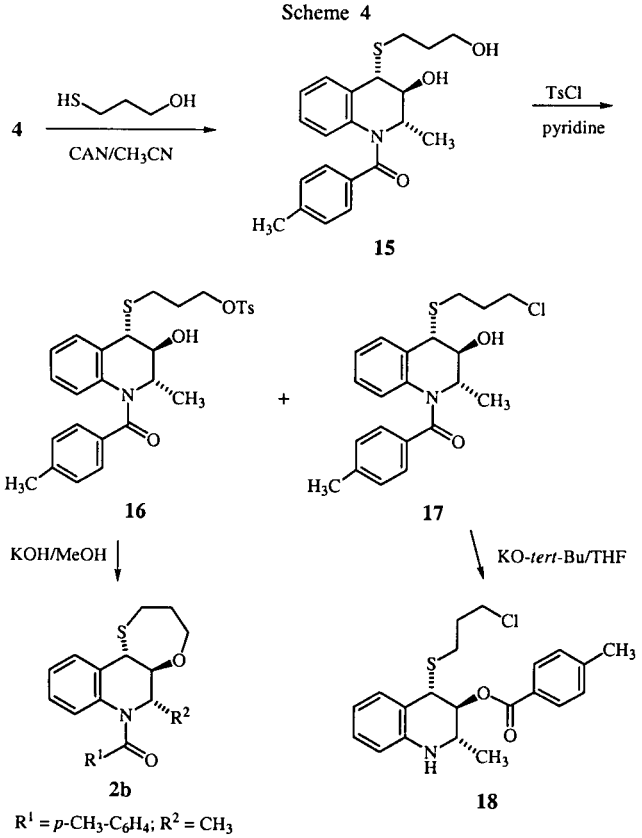

Scheme 3



3-bromo-1-propanol as the *O*-nucleophile. Though, the yields were moderate not only in the alcoholysis (→ **12**) but also in the cyclization step (→ **2a**; $R^1$ = *p*-$CH_3$-$C_6H_4$, $R^2$ = $CH_3$). Accordingly, we returned to the strategy shown before *via* epoxide cleavage with 1,3-propanediol to **13**, followed by tosylation of the primary hydroxy group to **14** and final ring closure to **2a** ($R^1$ = *p*-$CH_3$-$C_6H_4$, $R^2$ = $CH_3$) (Scheme 3).

The preparation of the 1-*S*-congeners of **2a** was accomplished as outlined for the planned synthesis of **1b**. Epoxide cleavage of **4** with 3-mercapto-1-propanol resulted in formation of the thioether **15**. Reaction of **15** with *p*-tosyl chloride, under the same conditions as above for **8**, provided tosyl compound **16** as the predominant product, however, chloro derivative **17** could be isolated in considerable yields. The cyclization product **2b** ($R^1$ = *p*-$CH_3$-$C_6H_4$, $R^2$ = $CH_3$), which is homologous to **1b**, was now obtained by treatment of the tosyl derivative with potassium hydroxide in methanol. The use of potassium *tert*-butoxide (in tetrahydrofuran) supported the acyl migration yielding the 3-*O*-ester as by-product. Compound **18** is obtained exclusively by allowing of **17** to rearrange under basic conditions (Scheme 4).

Scheme 4




## EXPERIMENTAL

Solvents and common reagents were obtained commercially and used as received. Solvents were dried as follows: dichloromethane was distilled under argon from phosphorus pentoxide, methanol was refluxed under argon over magnesium, and tetrahydrofuran was refluxed under argon over sodium benzophenone ketyl and distilled. The ir spectra were recorded as liquid films between potassium bromide disks using a Perkin Elmer model 298 spectrophotometer. The nmr spectra were determined on a Varian Unity-plus 300 spectrometer. All substances were measured in deuteriochloroform as the solvent. The $^1H$ nmr spectra were recorded with tetramethylsilane as the internal reference. The chemical shifts of the $^{13}C$ nmr spectra are given in ppm related to the resonance of deuteriochloroform (77.0 ppm). Mass spectra were recorded on Shimadzu QP 5000, Finnigan 8230 and Finnigan MAT 900S instruments. Column chromatography was conducted on Merck silica gel 60.

3-Hydroxy-4-(2-hydroxyethoxy)-2-methyl-1-*p*-toluoyl-1,2,3,4-tetrahydroquinoline (**5**).

To a suspension of 560 mg (2 mmoles) of **4** in 8 ml of acetonitrile, 2 ml of ethylene glycol and a catalytic amount of ceric ammonium nitrate (20 mg) were added. After stirring at room temperature overnight, the organic solvent was evaporated and the residue partitioned between water (10 ml) and ethyl acetate (3 x 10 ml]). The combined organic fractions were washed with brine, dried over sodium sulfate and evaporated *in vacuo* providing 590 mg (87%) of **5** as an oily residue, mp 143-145° (diethyl ether); ir (potassium bromide): ν 1630 $cm^{-1}$ (NCO); $^1H$ nmr (300 MHz): δ 1.28 (d, J = 6.6 Hz, 3H, 2-$CH_3$), 1.85 (br, 1H, OH), 2.28 (s, 3H, *p*-$CH_3$), 3.38 (br, 1H, OH), 3.51 (dd, J = 5.1, 8.4 Hz, 1H, 3-H), 3.86-4.02, 4.17-4.22 (each m, 1H, 3H, $OCH_2CH_2OH$), 4.39 (d, J = 8.4 Hz, 1H, 4-H), 4.59 (dq, J = 5.1, 6.6 Hz, 1H, 2-H), 6.51 (d, 1H, ArH, J = 7.8 Hz), 6.90-7.03 (m, 3H, ArH), 7.09-7.18 (m, 3H, ArH), 7.47 ppm (d, ArH, J = 7.5 Hz, 1H); $^{13}C$ nmr (75.43 MHz): δ 19.1 (2-$CH_3$), 21.4 (4-$CH_3$), 55.4 (2-C), 62.2 ($OCH_2CH_2OH$), 73.6 ($OCH_2CH_2OH$), 80.2, 80.3 (3-C, 4-C), 124.3, 125.5, 126.3, 127.1, 128.6, 128.8 (ArCH), 131.4, 132.4, 136.5, 140.6 (ArC), 169.5 (C=O); ms: m/z 341 ($M^+$).

*Anal.* Calcd. for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.26; H, 6.81; N, 3.95.

3-Hydroxy-2-methyl-1-*p*-toluoyl-4-[2-(*p*-tosyloxy)ethoxy]-1,2,3,4-tetrahydroquinoline (**6**).

To an ice-cooled solution of 340 mg (1 mmole) of **5** in 15 ml of dichloromethane, 380 mg (2 mmoles) of *p*-tosyl chloride and 1 ml of pyridine were added with stirring. After reaction at room temperature overnight the mixture was partitioned between 1 *N* hydrochloric acid (10 ml) and dichloromethane (3 x 10 ml). The combined organic layers were washed with saturated sodium bicarbonate solution (2 x 10 ml), dried over sodium sulfate and evaporated. Purification by column chromatography eluted with diethyl ether gave 360 mg (73%) of **6** as a pale yellow foam; ir (potassium bromide): ν 1640 (NCO), 1360, 1190, 1180 $cm^{-1}$ ($SO_2O$); $^1H$ nmr (300 MHz): δ 1.26 (d, J = 6.9 Hz, 3H, 2-$CH_3$), 2.32, 2.46 (each s, each 3H, *p*-$CH_3$), 3.42 (br, 1H, OH), 3.47 (dd, J = 2.7, 7.8 Hz, 1H, 3-H), 4.06-4.20 (m, 2H, $OCH_2CH_2OTs$), 4.31 (d, J = 7.8 Hz, 1H, 4-H), 4.38 (t, J = 4.8 Hz, 2H, $OCH_2CH_2OTs$), 4.59 (m, 1H, 2-H), 6.85 (d, J = 8.5 Hz, 1H, ArH), 6.94-7.04 (m, 3H, ArH), 7.08-7.18 (m, 3H, ArH), 7.38 (m, 3H, ArH), 7.86 (d, J = 8.5 Hz, 2H, ArH); $^{13}C$ nmr (75.43 MHz): δ 18.3 (2-$CH_3$), 21.3, 21.5 (*p*-$CH_3$), 55.0 (2-C), 69.3, 69.5 ($OCH_2CH_2OTs$), 79.0, 79.7 (3-C, 4-C), 125.0, 125.3, 126.0, 127.0, 127.8, 128.5, 128.7, 129.8 (ArCH), 130.4,

132.3, 132.7, 136.1, 140.5, 144.8 (ArC), 169.6 (C=O); ms: m/z 473/475 ($M^+$); hrms: Calcd. for $C_{27}H_{29}NO_6S$: m/z 475.172. Found: m/z 475.172.

5-Methyl-6-*p*-toluoyl-3,4a,5,10b-tetrahydro-2*H*-[1,4]dioxino-[2,3-*c*]quinoline (**1a**; $R^1 = p\text{-}CH_3\text{-}C_6H_4$, $R^2 = CH_3$).

To a stirred solution of 280 mg (0.57 mmole) of **6** in 4 ml of dry methanol a pellet of potassium hydroxide was added. After 15 minutes (tlc-control) the solvent was evaporated at low temperature. The residue was partitioned between water (10 ml) and dichloromethane (3 x 10 ml), the organic layers were dried over sodium sulfate and evaporated. Purification by column chromatography eluted with light petroleum-diethyl ether (1:2) afforded 160 mg (88%) of **1a** ($R^1 = p\text{-}CH_3\text{-}C_6H_4$, $R^2 = CH_3$), as colorless crystals from light petroleum-diethyl ether, mp 111-113°; ir (potassium bromide/liquid film): ν 1650 $cm^{-1}$ (NCO); $^1H$ nmr (300 MHz): δ 1.38 (d, J = 6.6 Hz, 3H, 5-$CH_3$), 2.26 (s, 3H, *p*-$CH_3$), 3.08 (dd, J = 2.9, 9.5 Hz dd, 1H, 4a-H), 3.70-3.82, 3.89, 3.99 (m, d, m, J = 11.2 Hz, 1H, 1H, 2H, 2-H, 3-H), 4.44, (d, J = 7.8 Hz, 1H, 10b-H), 4.45 (m, 1H, 5-H), 6.48 (d, J = 7.5 Hz, 1H, ArH), 6.86-6.98 (m, 3H, ArH), 7.04-7.15 (m, 3H, ArH), 7.43 (d, J = 7.5 Hz, 1H, ArH); $^{13}C$ nmr (75.43 MHz): δ 19.6 (5-$CH_3$), 21.3 (*p*-$CH_3$), 53.5 (5-C), 66.5, 66.6 (2-C, 3-C), 74.0 (4a-C), 85.2 (10b-C), 122.8, 125.5, 126.2, 126.8, 128.4, 128.7 (ArCH), 130.9, 132.4, 136.2, 140.3 (ArC), 168.9 (C=O); ms: m/z 323 ($M^+$).

*Anal.* Calcd. for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.54; N, 4.33. Found: 74.53; H, 6.61; N, 4.21.

3-Hydroxy-4-(2-hydroxyethylthio)-2-methyl-1-*p*-toluoyl-1,2,3,4-tetrahydroquinoline (**8**).

A suspension of 1.0 g (3.6 mmoles) of **4** in 10 ml of acetonitrile was treated with 310 mg (3.94 mmoles) of 2-mercaptoethanol. After addition of ceric ammonium nitrate (50 mg) the reaction mixture was heated under reflux for 4 hours. The resulting solution was evaporated *in vacuo,* redissolved in dichloromethane (20 ml) and washed with 1 *N* sodium hydroxide solution (1 x 10 ml) and brine (3 x 10 ml). The organic layer was dried over sodium sulfate, evaporated and purified by column chromatography eluted with light petroleum/ethyl acetate (1:3) to obtain 700 mg (55%) of **8** as a colorless oil; ir (potassium bromide/liquid film): ν 1620 $cm^{-1}$ (NCO); $^1H$ nmr (300 MHz): δ 1.28 (d, J = 6.6 Hz, 3H, 2-$CH_3$), 2.27 (s, 3H, *p*-$CH_3$), 2.41 (br, 1H, OH), 2.91 (m, 2H, S$CH_2$$CH_2$OH), 3.51 (m, 1H, 3-H), 3.86 (m, 2H, SCH$_2$$CH_2$OH), 3.92 (d, J = 8.4 Hz, 1H, 4-H), 4.68 (m, 1H, 2-H), 4.81 (br, 1H, OH), 6.56 (d, J = 8.0 Hz, 1H, ArH), 6.89-6.89 (m, 3H, ArH), 7.11-7.14 (m, 3H, ArH), 7.71 (d, J = 7.5 Hz, 1H, ArH); $^{13}C$ nmr (75.43 MHz): δ 18.7 (2-$CH_3$), 21.3 (*p*-$CH_3$), 34.6 (S$CH_2$$CH_2$OH), 50.4 (4-C), 56.4 (2-C), 61.7 (SCH$_2$$CH_2$OH), 79.0 (3-C), 125.5, 126.5, 126.9, 127.7, 128.6, 128.8 (ArCH), 130.1, 132.4, 137.6, 140.6 (ArC), 170.1 (C=O); ms: m/z 357 ($M^+$); hrms: Calcd. for $C_{20}H_{23}NO_3S$: m/z 357.140. Found: m/z 357.140.

4-(2-Chloroethylthio)-3-hydroxy-2-methyl-1-*p*-toluoyl-1,2,3,4-tetrahydroquinoline (**9**) and 3-Hydroxy-2-methyl-1-*p*-toluoyl-4-[2-(*p*-tosyloxy)ethylthio]-1,2,3,4-tetrahydroquinoline (**10**).

To a mixture of 400 mg (1.1 mmoles) of **8** and 320 mg (1.7 mmoles) of *p*-tosyl chloride dissolved in 20 ml of dry dichloromethane, 0.14 ml (1.7 mmoles) of pyridine were added at 0°. After 20 minutes the cooling bath was removed and the reaction mixture stirred for 48 hours. Then, the solution was treated with water (10 ml) and 6 *N* hydrochloric acid (5 ml) and stirred for further 10 minutes. The organic layer was separated, washed with 2 *N* hydrochloric acid (1 x 10 ml), 2 *N* sodium carbonate solution (2 x 10 ml) and brine (2 x 10 ml), dried over sodium sulfate and evaporated *in vacuo*. The resulting yellowish oil was purified by column chromatography (light petroleum-ethyl acetate (1:1). The *p*-tosyl ester **10** can be isolated only in traces. On the other hand, the yield of chloro compound **9** was 275 mg (65%), as colorless crystals, mp 138-140°; ir (potassium bromide): ν 1640 $cm^{-1}$ (NCO); $^1H$ nmr (300 MHz): δ 1.30 (d, J = 6.9 Hz, 3H, 2-$CH_3$), 2.31 (s, 3H, *p*-$CH_3$), 3.04-3.22 (m, 2H, SCH$_2$$CH_2$Cl), 3.45 (hidden, 1H, 3-H), 3.40-3.46 (br, 1H, OH), 3.70-3.84 (m, 2H, SCH$_2$$CH_2$Cl), 3.87 (d, J = 7.5 Hz, 1H, 4-H), 4.71 (m, 1H, 2-H), 6.57 (d, J = 7.5 Hz, 1H, ArH), 6.94 (t, J = 7.5 Hz, 1H, ArH), 7.00 (d, J = 7.5 Hz, 2H, ArH), 7.08-7.18 (m, 3H, ArH), 7.69 (d, J = 7.5 Hz, 1H, ArH); $^{13}C$ nmr (75.43 MHz): δ 18.7 (2-$CH_3$), 21.3 (*p*-$CH_3$), 34.7 (S$CH_2$$CH_2$Cl), 43.2 (SCH$_2$$CH_2$Cl), 51.2 (4-C), 56.0 (2-C), 79.1 (3-C), 125.4, 126.5, 127.2, 127.7, 128.6, 128.8 (ArCH), 129.2, 132.4, 137.7, 140.6 (ArC), 169.8 ppm (C=O); ms: m/z 375/377 ($M^+$).

Anal. Calcd. for $C_{20}H_{22}ClNO_2S$: C, 63.90; H, 5.90; N, 3.73. Found: 63.82; H, 5.78; N, 3.65.

4-(2-Chloroethylthio)-2-methyl-3-*p*-toluoyloxy-1,2,3,4-tetrahydroquinoline (**11**).

To a solution of 375 mg (1 mmole) of **9** in 10 ml of dry tetrahydrofuran, 115 mg (1 mmole) of potassium-*tert*-butoxide were added at room temperature. After stirring for 1 hour (tlc-control), the reaction mixture was evaporated *in vacuo* and directly subjected to a column chromatography eluted with petroleum ether-diethyl ether (1:1) to yield 270 mg (72%) of **11** as a colorless oil; ir (potassium bromide/liquid film): ν 1720 $cm^{-1}$ (COO). $^1H$ nmr (300 MHz): δ 1.20 (d, J = 7.0 Hz, 3H, 2-$CH_3$), 2.41 (s, 3H, *p*-$CH_3$), 2.70-2.85 (m, 2H, S$CH_2$$CH_2$Cl), 3.40-3.53 (m, 1H, 2-H), 3.48-3.60 (m, 2H, SCH$_2$$CH_2$Cl), 4.18 (d, J = 9.0 Hz, 1H, 4-H), 5.36 (t, J = 9.0 Hz, 1H, 3-H), 6.58 (d, J = 7.0 Hz, 1H, ArH), 6.77 (t, J = 7.5 Hz, 1H, ArH), 7.05 (m, 1H, ArH), 7.17- 7.28 (m, 2H, ArH), 7.61 (d, J = 8.0 Hz, 1H, ArH), 7.97 (m, 2H, ArH); ms: m/z 375/377 ($M^+$).

*Anal.* Calcd. for $C_{20}H_{22}ClNO_2S$: C, 63.90; H, 5.90; N, 3.73. Found: C, 63.68; H, 5.72; N, 3.58.

4-(3-Bromopropoxy)-3-hydroxy-2-methyl-1-*p*-toluoyl-1,2,3,4-tetrahydroquinoline (**12**).

To a suspension of 560 mg (2 mmoles) of **4** in 5 ml of dry acetonitrile, 0.75 ml (8.3 mmoles) of 3-bromo-1-propanol and a catalytic amount of ceric ammonium nitrate (20 mg) were added. After stirring at room temperature for 24 hours the solvent was evaporated and the residue partitioned between water (10 ml) and dichloromethane (3 x 10 ml). The combined organic fractions were washed with brine, dried over sodium sulfate and evaporated *in vacuo*. Purification of the residue by column chromatography eluted with light petroleum-diethyl ether (1:2) gave 360 mg (43%) of **12** as colorless crystals from diethyl ether, mp 135-136°; ir (potassium bromide): ν 1640 $cm^{-1}$ (NCO); $^1H$ nmr (300 MHz): δ 1.30 (d, J = 6.6 Hz, 3H, 2-$CH_3$), 2.30 (hidden, 2H, OCH$_2$$CH_2$CH$_2$Br), 2.31 (s, 3H, *p*-$CH_3$), 2.70 (br, 1H, OH), 3.55 (m, 1H, 3-H), 3.67 (t, J = 6.2 Hz, 2H, OCH$_2$CH$_2$$CH_2$Br), 3.97-4.06, 4.07-4.14 (each m, each 1H, OC$H_2$CH$_2$CH$_2$Br), 4.31 (d, J = 7.5 Hz, 1H, 4-H), 4.61 (m, 1H, 2-H), 6.55 (d, J = 7.5 Hz, 1H, ArH), 6.95 (t, J = 7.5 Hz, 1H, ArH), 7.01 (d, J = 7.5 Hz, 2H, ArH), 7.10-7.19 (m, 3H, ArH) 7.43 (d, J = 7.5 Hz, 1H, ArH); $^{13}C$ nmr (75.43 MHz): δ 18.1 (2-$CH_3$), 21.4 (*p*-$CH_3$), 30.6 (OCH$_2$$CH_2$CH$_2$Br), 32.8 (OCH$_2$CH$_2$$CH_2$Br), 54.9

(2-C), 69.0 ($OCH_2CH_2CH_2Br$), 78.5, 79.1 (3-C, 4-C), 125.3, 125.4, 126.2, 127.1, 128.6, 128.8 (ArCH), 130.5, 132.5, 136.3, 140.6 (ArC), 169.8 (C=O); ms: m/z 417/419 ($M^+$).

*Anal.* Calcd. for $C_{21}H_{24}BrNO_3$: C, 60.29; H, 5.78; N, 3.35; Br, 19.10. Found: C, 60.52; H, 5.78; N, 3.32; Br, 19.35.

3-Hydroxy-4-(3-hydroxypropoxy)-2-methyl-1-*p*-toluoyl-1,2,3,4-tetrahydroquinoline (**13**).

To a suspension of 840 mg (3 mmoles) of epoxide **4** in 10 ml of acetonitrile, 1 ml of 1,3-propanediol and a catalytic amount of ceric ammonium nitrate (50 mg) were added. After stirring at room temperature for 48 hours, the solvent was evaporated and the residue partitioned between water (10 ml) and dichloromethane (3 x 10 ml). The combined organic fractions were washed with brine (2 x 10 ml), dried over sodium sulfate and evaporated *in vacuo* to give 670 mg (63%) of **13** as colorless crystals from diethyl ether, mp 152-153°; ir (potassium bromide): ν 1650 $cm^{-1}$ (NCO); $^1H$ nmr (300 MHz): δ 1.31 (d, J = 6.9 Hz, 3H, 2-$CH_3$), 2.03 (m, 2H, $OCH_2CH_2CH_2OH$), 2.32 (s, 3H, *p*-$CH_3$), 2.73 (br, 1H, OH), 3.52 (dd, J = 3.3, 8.1 Hz, 1H, 3-H), 3.87-4.02 (m, 2H, $OCH_2CH_2CH_2OH$), 4.13 (br, 1H, OH), 4.04-4.12,4.15-4.23 (each m, each 1H, $OCH_2CH_2CH_2OH$), 4.34 (d, J = 8.1 Hz, 1H, 4-H), 4.62 (m, 1H, 2-H), 6.55 (d, J = 8.1 Hz, 1H, ArH), 6.96 (t, J = 8.1 Hz, 1H, ArH), 7.03 (d, J = 7.8 Hz, 2H, ArH), 7.12-7.22 (m, 3H, ArH), 7.47 (d, J = 7.8 Hz, 1H, ArH); $^{13}C$ nmr (75.43 MHz): δ 18.7 (2-$CH_3$), 21.4 (*p*-$CH_3$), 32.2 ($OCH_2CH_2CH_2OH$), 55.3 (2-C), 60.6 ($OCH_2CH_2CH_2OH$), 70.4 ($OCH_2CH_2CH_2OH$), 79.5, 79.7 (3-C, 4-C), 124.6, 125.4, 126.2, 127.0, 128.6, 128.8 (ArCH), 131.3, 132.4, 136.4, 140.5 (ArC), 169.6 (C=O); ms: m/z 355 ($M^+$).

*Anal.* Calcd. for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 71.21; H, 7.27; N, 3.98.

3-Hydroxy-2-methyl-1-*p*-toluoyl-4-[3-(*p*-tosyloxy)propoxyl-1,2,3,4-tetrahydroquinoline (**14**).

To an ice-cooled solution of 355 mg (1 mmole) of alcohol **13** in 10 ml of dichloromethane, 380 mg (2 mmoles) of *p*-tosyl chloride and 1 ml of pyridine were added with stirring. After reaction at room temperature overnight the mixture was partitioned between 1 *N* hydrochloric acid (10 ml) and dichloromethane (3 x 10 ml), the combined organic layers were washed with 1 *N* hydrochloric acid (1 x 10 ml) and saturated sodium bicarbonate solution (2 x 10 ml), dried over sodium sulfate and evaporated. Purification by column chromatography eluted with diethyl ether gave 400 mg (79%) of **14** as colorless crystals from diethyl ether, mp 80-82°; ir (potassium bromide): ν 1640 (NCO), 1390, 1360, 1190, 1180 $cm^{-1}$ ($SO_2O$); $^1H$ nmr (300 MHz): δ 1.20 (d, J = 6.6 Hz, 3H, 2-$CH_3$), 2.08 (m, 2H, $OCH_2CH_2CH_2OTs$), 2.33, 2.44 (each s, each 3H, 2 x *p*-$CH_3$), 3.51 (dd, J = 4.7, 6.6 Hz, 1H, 3-H), 3.87 (br, 1H, OH), 3.94 (dt, J = 1.0, 5.9 Hz, 2H, $OCH_2CH_2CH_2OTs$), 4.22-4.36 (m, 3H, 4-H, $OCH_2CH_2CH_2OTs$), 4.61 (m, 1H, 2-H), 6.53 (d, J = 7.8 Hz, 1H, ArH), 6.93 (t, J = 7.8 Hz, 1H, ArH), 7.01 (d, J = 7.8 Hz, 2H, ArH), 7.09 (d, J = 7.3 Hz, 1H, ArH), 7.17 (d, J = 8.1 Hz, 2H, ArH), 7.32-7.37 (m, 3H, ArH), 7.83 (d, J = 8.1 Hz, 1H, ArH); $^{13}C$ nmr (75.43 MHz): δ 18.0 (2-$CH_3$), 21.3, 21.5 (2 x *p*-$CH_3$), 29.5 ($OCH_2CH_2CH_2OTs$), 54.9 (2-C), 67.0, 67.3 ($OCH_2CH_2CH_2OTs$, $OCH_2CH_2CH_2OTs$), 78.4, 79.0 (3-C, 4-C), 125.1, 126.0, 126.9, 127.7, 128.5, 128.7, 129.8 (ArCH), 130.5, 132.4, 132.7, 136.2, 140.4, 144.8 (ArC), 169.7 (C=O); ms: m/z 509 ($M^+$); hrms: Calcd. for $C_{28}H_{31}NO_6S$: 509.187. Found: m/z 509.187).

6-Methyl-7-*p*-toluoyl-2,3,4,5a,6,11b-hexahydro[1,4]dioxepino[2,3-*c*]quinoline (**2a**; $R^1$ = *p*-$CH_3$-$C_6H_4$, $R^2$ = $CH_3$).

To a stirred solution of 340 mg (0.8 mmole) of tosylate in 4 ml of dry methanol a pellet of potassium hydroxide was added. After 1 hour the solvent was evaporated at low temperature. The residue was partitioned between water (10 ml) and dichloromethane (3 x 10 ml), the organic layers were dried over sodium sulfate and evaporated. Purification by column chromatography eluted with light petroleum-diethyl ether (1:2) gave 150 mg (67%) of **2a** ($R^1$ = *p*-$CH_3C_6H_4$, $R^2$ = $CH_3$) as colorless crystals from diethyl ether, mp 146-148°; ir (potassium bromide/liquid film): ν 1650 $cm^{-1}$ (NCO); $^1H$ nmr (300 MHz): δ 1.35 (d, J = 6.6 Hz, 3H, 6-$CH_3$), 2.04-2.22 (m, 2H, 3-H), 2.27 (s, 3H, *p*-$CH_3$), 3.09 (dd, J = 6.0, 9.3 Hz, 1H, 5a-H), 3.70-3.78, 3.97-4.05, 4.12-4.20, 4.22-4.30 (each m, each 1H, 2-H, 4-H), 4.47 (m, 1H, 6-H), 4.50 (d, J = 9.9 Hz, 1H, 11b-H), 6.47 (d, J = 7.8 Hz, 1H, ArH), 6.87-7.02 (m, 3H, ArH), 7.07-7.15 (m, 3H, ArH), 7.53 (d, J = 7.8 Hz, 1H, ArH); $^{13}C$ nmr (75.43 MHz): δ 19.6 (6-$CH_3$), 21.3 (*p*-$CH_3$), 32.3 (3-C), 54.3 (6-C), 67.8, 68.1 (2-C, 4-C), 80.4 (5a-C), 91.7 (11b-C), 123.5, 125.4, 126.0, 126.8, 128.4, 128.8 (ArCH), 131.9, 132.4, 136.1, 140.3 (ArC), 168.8 (C=O); ms: m/z 337 ($M^+$).

*Anal.* Calcd. for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.40; H, 6.74; N, 4.12.

3-Hydroxy-4-(3-hydroxypropylthio)-2-methyl-1-*p*-toluoyl-1,2,3,4-tetrahydroquinoline (**15**).

A suspension of 2.0 g (7.2 mmoles) of epoxide **4** in 20 ml of acetonitrile was treated with 0.7 ml (8 mmoles) of 3-mercapto-1-propanol after addition of ceric ammonium nitrate (100 mg). The reaction mixture was heated under reflux for 8 hours, then evaporated *in vacuo*, redissolved in dichloromethane (20 ml) and washed with 1 *N* sodium hydroxide solution (1 x 10 ml) and brine (3 x 10 ml). The organic layer was dried over sodium sulfate, evaporated and purified by column chromatography eluted with light petroleum-ethyl acetate (1:3) to yield 1.85 g (70%) of **15** as a colorless oil; ir (potassium bromide/liquid film): ν 1620 $cm^{-1}$ (NCO); $^1H$ nmr (300 MHz): δ 1.27 (d, J = 7.0 Hz, 3H, 2-$CH_3$), 1.90-1.96 (m, 2H, $SCH_2CH_2CH_2OH$), 2.28 (s, 3H, *p*-$CH_3$), 2.84-2.90 (m, 2H, $CH_2CH_2CH_2OH$), 3.10 (br, 1H, OH), 3.56 (dd, J = 5.0, 7.0 Hz, 1H, 3-H), 3.78 (m, 2H, $SCH_2CH_2CH_2OH$), 3.86 (d, J = 8.0 Hz, 1H, 4-H), 4.23 (br, 1H, OH), 4.70 (m, 1H, 2-H), 6.57 (d, J = 8.0 Hz, 1H, ArH), 6.91 (t, J = 8.0 Hz, 1H, ArH), 6.99 (d, J = 8.0 Hz, 2H, ArH), 7.09-7.16 (m, 3H, ArH), 7.69 (d, J = 7.5 Hz, 1H, ArH); $^{13}C$ nmr (75.43 MHz): δ 18.5 (2-$CH_3$), 21.3 (*p*-$CH_3$), 28.6 ($SCH_2CH_2CH_2OH$), 32.2 ($SCH_2CH_2CH_2OH$), 50.2 (4-C), 56.1 (2-C), 60.9 ($SCH_2CH_2CH_2OH$), 78.5 (3-C), 125.4, 126.4, 126.9, 127.9, 128.5, 128.7 (ArCH), 129.7, 132.5, 127.5, 140.5 (ArC), 170.1 (C=O); ms: m/z 371 ($M^+$); hrms: Calcd. for $C_{21}H_{25}NO_3S$: m/z 371.155. Found: m/z 371.156.

3-Hydroxy-2-methyl-1-*p*-toluoyl-4-[3-(*p*-tosyloxy)propylthiol-1,2,3,4-tetrahydroquinoline (**16**) and 4-(3-Chloropropylthio)-3-hydroxy-2-methyl-1-*p*-toluoyl-1,2,3,4-tetrahydroquinoline (**17**).

To a solution of 1.0 g (2.7 mmoles) of alcohol **15** and 700 mg (4 mmoles) of *p*-tosyl chloride, dissolved in 20 ml of dry dichloromethane, 0.3 ml (4 mmoles) of pyridine were added at 0°. After 20 minutes the cooling bath was removed and the reaction mixture stirred for 48 hours. Then, the solution was treated with water (10 ml) and 5 ml of 6 *N* hydrochloric acid and stirred for further 10 minutes. The organic layer was separated, washed

with 2 *N* hydrochloric acid (1 x 10 ml), 2 *N* sodium carbonate solution (2 x 10 ml) and brine (2 x 10 ml), dried over sodium sulfate and evaporated *in vacuo* to yield a red oil. The following separation by column chromatography eluted with light petroleum-ethyl acetate (1:1) afforded 880 mg (62%) of tosylate **16** and 155 mg (16%) of halide **17**.

Tosylate **16**: Colorless oil, ir (potassium bromide/liquid film): ν 1620 (NCO), 1385, 1355, 1190, 1180 $cm^{-1}$ ($SO_2O$); $^1H$ nmr (300 MHz): δ 1.25 (d, J = 6.6 Hz, 3H, 2-$CH_3$), 2.05 (m, 2H, $SCH_2CH_2CH_2OTs$), 2.28, 2.43 (each s, each 3H, 2 x *p*-$CH_3$), 2.80 (m, 2H, $SCH_2CH_2CH_2OTs$), 3.40 (br, 1H, OH), 3.50 (dd, J = 4.5, 7.5 Hz, 1H, 3-H), 3.78 (d, J = 7.5 Hz, 1H, 4-H), 4.21 (t, J = 6.0 Hz, 2H, $SCH_2CH_2CH_2OTs$), 4.67 (m, 1H, 2-H), 6.56 (d, J = 8.1 Hz, 1 H, ArH), 6.91 (t, J = 8.1 Hz, 1H, ArH), 6.99 (d, J = 7.8 Hz, 2H, ArH), 7.07-7.15 (m, 3H, ArH), 7.35 (d, J = 7.8 Hz, 2H, ArH), 7.60 (d, J = 7.8 Hz, 1H, ArH), 7.80 (d, J = 8.4 Hz, 2H, ArH); $^{13}C$ nmr (75.43 MHz): δ 18.4 (2-$CH_3$), 21.3, 21.6 (2 x *p*-$CH_3$), 28.1, 29.0 ($SCH_2CH_2CH_2OTs$ and $SCH_2CH_2CH_2OTs$), 50.2 (4-H), 56.0 (2-H), 68.5 ($SCH_2CH_2CH_2OTs$), 78.4 (3-C), 125.3, 126.4, 126.9, 127.8, 127.9, 128.5, 128.7, 129.2 (ArCH), 129.9, 132.5, 132.7, 137.5, 140.5, 144.9 (ArC), 170.0 (C=O); ms: m/z 525 ($M^+$); hrms: Calcd. for: $C_{28}H_{31}NO_5S_2$: m/z 525.164. Found: m/z 525.164.

Halide **17**: Colorless crystals from diethyl ether, mp 152-154°; ir (potassium bromide): ν 1615 $cm^{-1}$ (NCO); $^1H$ nmr (300 MHz): δ 1.28 (d, J = 6.6 Hz, 3H, 2-$CH_3$), 2.17 (quint, J = 6.3 Hz, 2H, $OCH_2CH_2CH_2Cl$), 2.29 (s, 3H, *p*-$CH_3$), 2.91-2.97 (m, 2H, $OCH_2CH_2CH_2Cl$), 3.53 (dd, J = 4.2, 7.5 Hz, 1H, 3-H), 3.65 (br, 1H, OH), 3.73 (t, J = 6.0 Hz, 2H, $OCH_2CH_2CH_2Cl$), 3.86 (d, J = 7.8 Hz, 1H, 4-H), 4.71 (m, 1H, 2-H), 6.57 (d, J = 8.1 Hz, 1H, ArH), 6.93 (t, J = 7.8 Hz, 1H, ArH), 6.99 (d, J = 7.8 Hz, 2H, ArH), 7.13 (m, 3H, ArH), 7.69 (d, J = 7.5 Hz, 1H, ArH); $^{13}C$ nmr (75.43 MHz): δ 18.6 (2-$CH_3$), 21.3 (*p*-$CH_3$), 29.3 ($SCH_2CH_2CH_2Cl$), 32.4 ($SCH_2CH_2CH_2Cl$), 43.3 ($SCH_2CH_2CH_2Cl$), 50.5 (4-C), 56.1 (2-C), 78.6 (3-C), 125.4, 126.5, 127.0, 127.8, 128.6 (ArCH), 128.8, 129.4, 132.5, 137.7 (ArC), 170.0 (C=O); ms: m/z 389/391 ($M^+$); hrms: Calcd. for $C_{21}H_{24}NO_2SCl$: m/z 389.122. Found: m/z 389.122.

6-Methyl-7-*p*-toluoyl-2,3,4,5a,6,11b-hexahydro[1,4]oxathiepino[2,3-*c*]quinoline (**2b**; $R^1$ = *p*-$CH_3$-$C_6H_4$, $R^2$ = $CH_3$).

To a stirred solution of 390 mg (0.74 mmole) of tosylate **16** in 5 ml of dry methanol a pellet of potassium hydroxide was added. The reaction mixture was stirred for 1 hour (tlc-control), evaporated *in vacuo*, and directly subjected to column chromatography eluted with light petroleum-diethyl ether (1:1) to afford 165 mg (63%) of **2b** ($R^1$ = *p*-$CH_3$-$C_6H_4$, $R^2$ = $CH_3$) as a colorless oil; ir (potassium bromide/liquid film): ν 1620 $cm^{-1}$ (NCO); $^1H$ nmr (300 MHz): δ 1.17 (d, J = 7.0 Hz, 3H, 2-$CH_3$), 2.05-2.18 (m, 2H, $SCH_2CH_2CH_2O$), 2.31 (s, 3H, *p*-$CH_3$), 2.84-2.98, 2.95-3.05 (each m, each 2H, $SCH_2CH_2CH_2O$, $SCH_2CH_2CH_2O$), 3.68 (t, J = 7.0 Hz, 1H, 3-H), 3.70 (d, J = 8.0 Hz, 1H, 4-H), 5.33 (m, 1H, 2-H), 6.60 (d, J = 8.0 Hz, 1H, ArH), 6.94 (t, J = 7.5 Hz, 1H, ArH), 7.02-7.13 (m, 2H, ArH), 7.18-7.28 (m, 3H, ArH), 7.65 (d, J = 9.0 Hz, 1H, ArH); $^{13}C$ nmr (75.43 MHz): δ 19.6 (6-$CH_3$), 21.2 (*p*-$CH_3$), 29.6 (3-C), 31.5 (2-C), 41.3 (11b-C), 54.3 (6-C), 67.9 (4-C), 78.5 (5a-C), 123.5, 125.4, 125.9, 126.8, 128.4, 128.5 (ArCH), 131.7, 132.4, 137.1, 140.3 (ArC), 168.2 (C=O); ms: m/z 353 ($M^+$).

*Anal.* Calcd. for $C_{21}H_{23}NO_2S$: C, 71.36; H, 6.56; N, 3.96. Found: C, 71.18; H, 6.42; N, 3.90.

4-(3-Chloropropylthio)-2-methyl-3-*p*-toluoyloxy-1,2,3,4-tetrahydroquinoline (**18**).

Using the same conditions as above 80 mg (0.2 mmol) of halide **17** yielded 60 mg (77%) of **18** as a colorless oil; ir (potassium bromide/liquid film): ν 1720 $cm^{-1}$ (COO); $^1H$ nmr (300 MHz): δ 1.24 (d, J = 7.0 Hz, 3H, 2-$CH_3$), 1.88-1.95 (m, 2H, $SCH_2CH_2CH_2Cl$), 2.42 (s, 3H, *p*-$CH_3$), 2.54, 2.62 (each m, each 1H, $SCH_2CH_2CH_2Cl$), 3.45-3.60 (each m, 2H, 1H, $SCH_2CH_2CH_2Cl$, 2-H), 4.15 (d, J = 9.0 Hz, 1H, 4-H), 5.34 (t, J = 8.5 Hz, 1H, 3-H), 6.58 (d, J = 8.5 Hz, 1H, ArH), 6.79 (t, J = 8.0 Hz, 1H, ArH), 7.04 (t, J = 8.0 Hz, 1H, ArH), 7.22-7.30 (m, 2H, ArH), 7.62 (d, J = 8.0 Hz, ArH), 7.98 (d, J = 8.5 Hz, 2H, ArH); ms: m/z 389/391 ($M^+$).

*Anal.* Calcd. for $C_{21}H_{24}ClNO_2S$: C, 64.68; H, 6.20; N, 3.59. Found: C, 64.45; H, 6.08; N, 3.50.

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