SYNTHESIS OF 2,3-FUSED QUINOLINES FROM 3-SUBSTITUTED QUINOLINE 1-OXIDES. PART 1.

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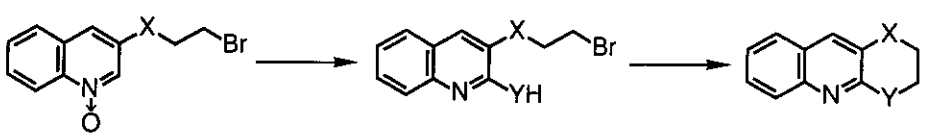
Abstract — 3-(2-Bromoethyltosylamino)quinoline 1-oxide (**4**) reacted with TsCl-NH_4OH and TsCl-K_2CO_3 to afford the 2-aminoquinoline (**5**) and the 2-quinolinone (**8**). Cyclization of **5** and **8** under basic conditions gave the piperazino-quinoline (**6**) and the morpholino-quinoline (**9**). Similar reactions of 3-(2-bromoethoxy)quinoline 1-oxide (**13**) in the presence of TsCl gave also the 2-aminoquinoline (**14**) and the 2-hydroxyquinoline (**16**), but accompanied with fair amounts of by-products (**15** and, **15** and **17**). Cyclization of **14** and **16** gave the morpholino-quinoline (**18**) and the 1,4-dioxano-quinoline (**19**) in somewhat lower yields.

In connection with studies directed toward development of medicines for dementia of Alzheimer type, we undertook the synthesis of 2,3-fused quinolines. This paper deals with the synthesis of 2,3-fused quinolines with piperazine, morpholine and 1,4-dioxane rings from 2-amino and 2-hydroxy derivatives of 3-(2-bromoethyltosylamino)quinoline and 3-(2-bromoethoxy)quinoline. The 2-aminoquinolines and 2-hydroxyquinolines were prepared by the deoxygenative 2-substitution reactions[1] of the corresponding 3-substituted quinoline 1-oxides with tosyl chloride (TsCl)-10% ammonium hydroxide (NH_4OH)[2] and TsCl-10% potassium carbonate (K_2CO_3),[3] respectively.

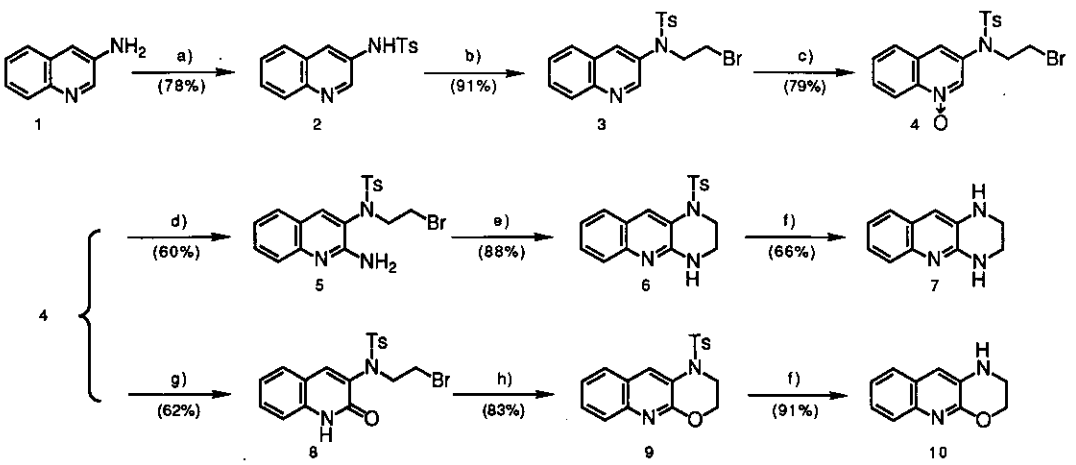


X=NTs, O Y=NH, O

3-(2-Bromoethyltosylamino)quinoline 1-oxide (**4**) required as the starting material was prepared as follows. 3-Aminoquinoline (**1**) was first derived to 3-tosylamino-quinoline (**2**) by means of TsCl and pyridine. Heating **2** with 1,2-dibromoethane at 100°C for 1 h in the presence of sodium hydride (NaH) in N,N-dimethylformamide (DMF) gave 3-(2-bromoethyltosylamino)quinoline (**3**) in 91% yield. Oxidation of **3** with m-chloroperbenzoic acid (m-CPBA) in chloroform afforded **4** in 79% yield.

When a solution of **4** and TsCl in chloroform was stirred with 10% NH_4OH at room temperature for 4 h, the 2-aminoquinoline (**5**) was obtained as a sole product in 60% yield. Cyclization of **5** to 1-tosylpiperazino[2,3-b]quinoline (**6**) was effected in 88% yield by heating at reflux with K_2CO_3 in n-butanol. The tosyl group was successfully removed by heating at reflux with 80% sulfuric acid (H_2SO_4) to give the desired piperazino[2,3-b]quinoline (**7**) in 66% yield.

The deoxygenative 2-hydroxylation of **4** readily proceeded upon treatment with TsCl-10% K_2CO_3 in chloroform to give the 2-quinolinone (**8**) in 62% yield. Cyclization of **8** to the morpholino[2,3-b]quinoline (**9**) smoothly occurred with NaH in DMF (83%), and its tosyl group was removed by heating with 80% H_2SO_4 in a similar way to give



a) TsCl-py ; b) $Br(CH_2)_2Br$, NaH, DMF, 100°C, 1 h ; c) m-CPBA, $CHCl_3$, room temperature, 2 h ;
d) TsCl-$CHCl_3$, 10% NH_4OH, room temperature, 4 h ; e) K_2CO_3, n-BuOH, reflux, 5 h ;
f) 80% H_2SO_4, Δ, 1 h ; g) TsCl-$CHCl_3$, 10% K_2CO_3, room temperature, 3 h ; h) NaH, DMF, 1 h

Scheme 1

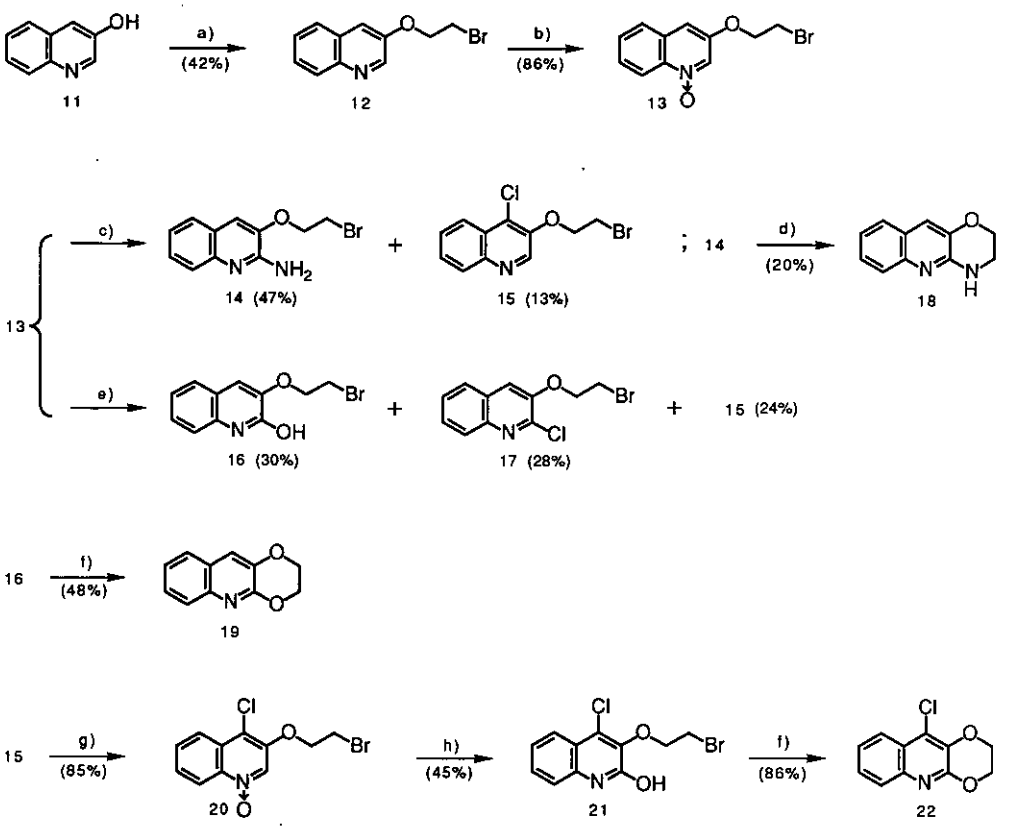
morpholino[2,3-b]quinoline (**10**) in a high yield of 91%. These reactions are formulated in Scheme 1.

Next the synthesis starting from 3-hydroxyquinoline (**11**) was carried out (Scheme 2). Treatment of **11** with 1,2-dibromoethane at 80-90°C for 2 h in the presence of K_2CO_3 in DMF gave 3-bromoethoxyquinoline (**12**) in a somewhat lower yield of 42%. Oxidation of **13** with m-CPBA in chloroform provided 3-(2-bromoethoxy)quinoline 1-oxide (**13**) in 86% yield.

The reaction of **13** in the presence of TsCl did not produce a single product, but fair amounts of by-products were formed. Thus, when a chloroform solution of **13** and TsCl was stirred with 10% NH_4OH, the desired 2-aminoquinoline (**14**) was obtained in 47% yield, but accompanied with the 4-chlorination product (**15**, 13%). Further, the reaction with 10% K_2CO_3 was found to give a mixture of three kinds of products, the 2-hydroxyquinoline (**16**, 30%), the 2-chloroquinoline (**17**, 28%) and the 4-chloroquinoline (**15**, 24%). These results agree with our previous observations[4] that reactions of some 3-substituted quinoline 1-oxides with TsCl afforded 2- or/and 4-chloroquinolines instead of, or in addition to, 2-hydroxyquinolines. Especially, the reaction of **13** with TsCl-K_2CO_3 is closely similar to that of 3-methoxyquinoline 1-oxide under the same conditions.[4]

Treatment of the 2-aminoquinoline (**14**) with K_2CO_3 in 3-methylbutanol under reflux led to the cyclization product, morpholino[3,2-b]quinoline (**18**), but in a rather low yield of 20%. Cyclization of the 2-hydroxyquinoline (**16**) occurred by means of NaH-DMF at room temperature to give [1,4]dioxano[2,3-b]quinoline (**19**) in 48% yield. Further we tried cyclization of 3-(2-bromoethoxy)-4-chloro-2-hydroxyquinoline (**21**) obtainable from **15** via its N-oxide (**20**). The reaction of **20** with TsCl-10% K_2CO_3 provided only **21** without the 2-chlorination product being formed, and cyclization of **21** took place under similar conditions as noted for **16** to give the 10-chloro derivative of **19** (**22**) in 86% yield. The rather lower yields of cyclization of **14** and **16** may be due to their poor solubilities in reaction media.

Although optimal conditions of each of the above-mentioned reactions were not explored, it may be concluded that the reaction sequence described in this paper is useful for the preparation of 2,3-fused quinolines.



a) $Br(CH_2)_2Br$, K_2CO_3, DMF, 80-90°C, 2 h; b) m-CPBA, $CHCl_3$, room temperature, 2 h; c) TsCl-$CHCl_3$, 10% NH_4OH, room temperature, 2 h; d) K_2CO_3, $Me_2CHCH_2CH_2OH$, reflux, 6 h; e) TsCl-$CHCl_3$, 10% K_2CO_3, room temperature, 3 h; f) NaH, DMF, room temperature, 1 h; g) m-CPBA, $CHCl_3$, room temperature, 3 h; h) TsCl-$CHCl_3$, 10% K_2CO_3, room temperature, 4 h

Scheme 2

EXPERIMENTAL

All melting points are uncorrected. ^{1}H-Nmr spectra were recorded on Hitachi RB-24 spectrometer using tetramethylsilane as an internal standard.

3-Tosylaminoquinoline (2) —— To a solution of 3-aminoquinoline (1) (25 g, 0.173 mol) in pyridine (100 ml) was added TsCl (34.63 g, 0.182 mol) at room temperature, and the whole was stirred for 1 h. The reaction mixture was poured into H_2O (100

ml), and precipitates formed were filtered and washed with H_2O. Recrystallization from $CHCl_3$-MeOH gave 40.5 g (78%) of **2**, colorless prisms, mp 173-174.5°C. Anal. Calcd for $C_{16}H_{14}N_2O_2S$: C, 64.41; H, 4.73; N, 9.39. Found: C, 64.25; H, 4.71; N, 9.51. ^{1}H-Nmr ($CDCl_3$) δ: 2.35 (3H, s, CH_3), 7.48-7.94 (9H, m, Ar-H), 8.69 (1H, s, Q_2-H), 10.47 (1H, br s, NH).

3-(2-Bromoethyltosylamino)quinoline (**3**) — Sodium hydride (1.74 g, 0.046 mol) was added to an ice-cooled solution of **2** (10.8 g, 0.029 mol) in DMF (100 ml) and the whole was stirred for 10 min. 1,2-Dibromoethane (28.63 g, 0.152 mol) was added, and the mixture was heated at 100°C for 1 h and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with H_2O and dried over anhyd. Na_2SO_4. The residue from the $CHCl_3$ solution was chromatographed on silica gel with $CHCl_3$ to give 10.50 g (91%) of **3**, colorless needles, mp 102-103°C (MeOH). Anal. Calcd for $C_{18}H_{17}N_2O_2BrS$: C, 53.34; H, 4.23; N, 6.91. Found: C, 53.63; H, 4.24; N, 6.95. ^{1}H-Nmr ($CDCl_3$) δ: 2.40 (3H, s, CH_3), 3.40 (2H, t, J=6.5 Hz, NCH_2), 3.98 (2H, t, J=6.5 Hz, CH_2Br), 7.10-8.10 (9H, m, Ph-4H, Q_{4-8}-5H), 8.47 (1H, d, J=2.0 Hz, Q_2-H).

3-(2-Bromoethyltosylamino)quinoline 1-Oxide (**4**) — To a solution of **3** (10 g, 0.024 mol) in $CHCl_3$ (100 ml) was added m-CPBA (5.36 g, 0.034 mol) with ice-cooling, and the whole was stirred at room temperature for 2 h, and then shaken with aq. $NaHCO_3$. The $CHCl_3$ layer was washed with H_2O, dried over anhyd. Na_2SO_4, and concentrated *in vacuo*. The residue was washed with ether-hexane and recrystallized from EtOH to give 8.60 g (79%) of **4**, colorless scales, mp 149-151°C. Anal. Calcd for $C_{18}H_{17}N_2O_3BrS$: C, 51.32; H, 4.07; N, 6.65. Found: C, 51.67; H, 4.00; N, 6.75. ^{1}H-Nmr ($CDCl_3$) δ: 2.42 (3H, s, CH_3), 3.40 (2H, t, J=6.0 Hz, NCH_2), 3.92 (2H, t, J=6.0 Hz, CH_2Br), 7.10-7.92 (8H, m, Ph-4H, Q_{4-7}-4H), 8.12 (1H, d, J=1.7 Hz, Q_2-H), 8.60 (1H, m, Q_8-H).

2-Amino-3-(2-bromoethyltosylamino)quinoline (**5**) — To an ice-cooled solution of **4** (4.21 g, 0.01 mol) in $CHCl_3$ (60 ml) was added TsCl (2.10 g, 0.011 mol), and the solution was stirred for 5 min and then stirred with 10% NH_4OH (30 ml) at room temperature for 4 h. The $CHCl_3$ layer was washed with H_2O, dried and concentrated. The residue was washed with EtOH and recrystallized from MeOH to give 2.50 g (60%) of **5**, colorless needles, mp 144-145°C. Anal. Calcd for $C_{18}H_{18}N_3O_2BrS$: C, 51.44; H, 4.32; N, 10.00. Found: C, 51.71; H, 4.17; N, 9.98. ^{1}H-Nmr ($CDCl_3$) δ: 2.41 (3H, s, CH_3), 3.15-4.40 (4H, m, NCH_2CH_2Br), 5.40 (2H, br s, NH_2), 7.15-7.65 (9H, m, Ar-H).

1-Tosylpiperazino[2,3-b]quinoline (**6**) —— A solution of **5** (2.26 g, 0.0054 mol) in n-BuOH (100 ml) was heated at reflux for 5 h in the presence of K_2CO_3 (0.88 g). Excess n-BuOH was evaporated and the residue was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried and concentrated. The residue was chromatographed on silica gel with 20% acetone-benzene to give 1.60 g (88%) of **6**, colorless needles, mp 205-207°C (MeOH). Anal. Calcd for $C_{18}H_{17}N_3O_2S$: C, 63.70; H, 5.05; N, 12.38. Found: C, 63.76; H, 5.05; N, 12.26. ^{1}H-Nmr ($CDCl_3$) δ: 2.33 (3H, s, CH_3), 3.12 (2H, t, J=5.0 Hz, C_3-2H), 3.88 (2H, t, J=5.0 Hz, C_2-2H), 6.33 (1H, br s, NH), 7.10-7.75 (8H, m, Ph-4H, C_{6-9}-4H), 8.28 (1H, s, C_{10}-H).

Piperazino[2,3-b]quinoline (**7**) —— A solution of **6** (1.30 g) in 80% H_2SO_4 (10 ml) was heated at 100 °C for 1 h. The solution was made alkaline with aq. NaOH and extracted with $CHCl_3$. The extract was washed with H_2O, dried and concentrated, and the residue was chromatographed on silica gel with 0.2% MeOH-$CHCl_3$ to give 0.47 g (66%) of **7**, colorless needles, mp 225-230°C (decomp.) (benzene). Anal. Calcd for $C_{11}H_{11}N_3$: C, 71.33; H, 5.99; N, 22.69. Found: C, 71.58; H, 5.95; N, 22.76. ^{1}H-Nmr ($CDCl_3$) δ: 3.23-3.63 (4H, m, $C_{2,3}$-4H), 5.47 (1H, br s, N_1-H), 6.68 (1H, br s, N_4-H), 6.80 (1H, s, C_{10}-H), 6.90-7.45 (4H, m, C_{6-9}-4H).

3-(2-Bromoethyltosylamino)quinolin-2-one (**8**) —— A solution of **4** (18 g, 0.043 mol) and TsCl (9.83 g, 0.052 mol) in $CHCl_3$ (200 ml) was stirred with 10% K_2CO_3 (200 ml) at room temperature for 3 h to give slowly precipitates. After evaporation of the $CHCl_3$ and addition of H_2O, precipitates were filtered, washed with EtOH and recrystallized from $CHCl_3$-EtOH to give 11.2 g (62%) of **8**, colorless needles, mp 216-221°C. Anal. Calcd for $C_{18}H_{17}N_2O_3BrS$: C, 51.32; H, 4.07; N, 6.65. Found: C, 51.51; H, 3.88; N, 6.48. ^{1}H-Nmr ($CDCl_3$-DMSO-d_6) δ: 2.37 (3H, s, CH_3), 3.35-3.55 (2H, m, NCH_2), 3.95-4.26 (2H, m, CH_2Br), 7.13-8.00 (9H, m, Ar-H), 11.61 (1H, br s, NH).

1-Tosylmorpholino[2,3-b]quinoline (**9**) —— To an ice-cooled suspension of **8** (11 g, 0.026 mol) in DMF (120 ml) was added NaH (1.57 g, 0.039 mol), and then the whole was stirred at room temperature for 1 h to give gradually a homogeneous solution. This solution was poured into H_2O (200 ml) to give precipitates which were filtered and recrystallized from EtOH to give 7.4 g (83%) of **9**, colorless needles, mp 163-165°C. Anal. *Calcd for* $C_{18}H_{16}N_2O_3S$: *C, 63.51; H, 4.74; N, 8.23. Found:* C, 63.37; H, 4.58; N, 8.10. ^{1}H-Nmr ($CDCl_3$) δ: 2.33 (3H, s, CH_3), 3.96 (4H, br s, C_{2-3}-4H), 7.06-7.97 (8H, m, Ph-4H, C_{6-9}-4H), 8.57 (1H, s, C_{10}-H).

Morpholino[2,3-b]quinoline (**10**) — A suspension of **9** (9.0 g, 0.026 mol) in 80% H_2SO_4 (60 ml) was heated on a steam bath for 1 h, then cooled and made alkaline with 10% NaOH. Precipitates formed were filtered and dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with H_2O, dried and concentrated. The residue was recrystallized from EtOH to give 4.5 g (91%) of **10**, colorless scales, mp 201-202°C. Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 71.21; H, 5.42; N, 14.97. ^{1}H-Nmr ($CDCl_3$-DMSO-d_6) δ: 3.40 (2H, t, J=4.5 Hz, C_2-2H), 4.40 (2H, t, J=4.5 Hz, C_3-2H), 5.71 (1H, br s, NH), 7.04-7.63 (5H, m, Ar-H).

3-(2-Bromoethoxy)quinoline (**12**) — 1,2-Dibromoethane (170 g, 0.90 mol) and K_2CO_3 (250 g) were added to a solution of 3-hydroxyquinoline (**11**) (33 g, 0.227 mol) in DMF (300 ml) and the whole was heated at 80-90°C for 2 h. Precipitates formed were filtered and the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel with benzene-$CHCl_3$ (1:1) to give 24 g (42%) of **12**, colorless needles, mp 59°C (acetone-hexane). Anal. Calcd for $C_{11}H_{10}NOBr$: C, 52.41; H, 4.00; N, 5.56. Found: C, 52.64; H, 3.93; N, 5.62. ^{1}H-Nmr ($CDCl_3$) δ: 3.65 (2H, t, J=6.0 Hz, OCH_2), 4.35 (2H, t, J=6.0 Hz, CH_2Br), 7.28-8.12 (5H, m, C_{4-8}-5H), 8.67 (1H, d, J=3.0 Hz, C_2-H).

3-(2-Bromoethoxy)quinoline 1-Oxide (**13**) — Oxidation of **12** (7.50 g, 0.03 mol) with m-CPBA (6.16 g, 0.036 mol) was carried out in $CHCl_3$ (100 ml) as described for the preparation of **4** to give 6.93 g (86%) of **13**, colorless scales, mp 113-114°C (acetone). Anal. Calcd for $C_{11}H_{10}NO_2Br$: *C, 49.28; H, 3.76; N, 5.22. Found: C, 49.49; H,* 3.61; N, 5.23. ^{1}H-Nmr ($CDCl_3$) δ: 3.63 (2H, t, J=6.0 Hz, CH_2Br), 4.37 (2H, t, J=6.0 Hz, OCH_2), 6.98 (1H, d, J=2.0 Hz, C_4-H), 7.30-7.70 (3H, m, C_{5-7}-3H), 8.25 (1H, d, J=2.0 Hz, C_2-H), 8.40-8.65 (1H, m, C_8-H).

Reaction of **13** with TsCl-10% NH_4OH — A solution of **13** (6.63 g, 0.025 mol) and TsCl (6.13 g, 0.032 mol) in $CHCl_3$ (60 ml) was stirred at room temperature for 10 min. To this solution was added 10% NH_4OH (60 ml) and the whole was stirred overnight at room temperature. The $CHCl_3$ solution was washed with H_2O, dried and concentrated. The residue was chromatographed on silica gel with 1% MeOH-$CHCl_3$ to give 3.09 g (41%) of 2-amino-3-(2-bromoethoxy)quinoline (**14**) and then 0.95 g (13%) of 3-(2-bromoethoxy)-4-chloroquinoline (**15**).

14: Colorless prisms, mp 82-84°C (EtOH). Anal. Calcd for $C_{11}H_{11}N_2OBr$: C, 49.46; H, 4.15; N, 10.49. Found: C, 49.57; H, 4.02; N, 10.55. ^{1}H-Nmr ($CDCl_3$) δ: 3.68 (2H, t,

J=6.0 Hz, OCH_2), 4.37 (2H, t, J=6.0 Hz, CH_2Br), 5.40 (2H, br s, NH_2), 7.80 (1H, s, C_4-H), 7.15-7.90 (4H, m, C_{5-8}-4H).

15: Colorless needles, mp 71-72°C (ether). Anal. Calcd for $C_{11}H_9NOBrCl$: C, 46.11; H, 3.17; N, 4.89. Found: C, 46.26; H, 3.09; N, 4.85. ^{1}H-Nmr ($CDCl_3$) δ: 3.65 (2H, t, J=6.0 Hz, OCH_2), 4.51 (2H, t, J=6.0 Hz, CH_2Br), 7.45-8.20 (4H, m, C_{5-8}-4H), 8.70 (1H, s, C_2-H).

Morpholino[3,2-b]quinoline (**18**) — A solution of **14** (3.0 g, 0.011 mol) in 3-methylbutanol (40 ml) was heated with K_2CO_3 (3.1 g) under reflux for 6 h. The solvent was evaporated and the residue was extracted with $CHCl_3$. The $CHCl_3$ solution was washed with H_2O, dried and concentrated. The residue was chromatographed on silica gel with 0.5% MeOH-$CHCl_3$ to give 0.41 g (20%) of **18**, colorless needles, mp 167-169°C (EtOH). Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 70.76; H, 5.53; N, 15.05. ^{1}H-Nmr ($CDCl_3$) δ: 3.55-3.70 (2H, m, C_3-2H), 4.20-4.35 (2H, m, C_2-2H), 7.10-7.70 (6H, m, NH, Ar-H).

Reaction of **13** with TsCl-10% K_2CO_3 — A solution of **13** (15 g, 0.056 mol) and TsCl (16 g, 0.084 mol) in $CHCl_3$ (200 ml) was stirred with 10% K_2CO_3 (200 ml) at room temperature for 3 h. The $CHCl_3$ layer was washed with H_2O, dried and concentrated. The residue was chromatographed on silica gel with $CHCl_3$ to give successively 4.5 g (28%) of 3-(2-bromoethoxy)-2-chloroquinoline (**17**), 3.9 g (24%) of **15** and 4.5 g (30%) of 3-(2-bromoethoxy)-2-hydroxyquinoline (**16**).

16: Colorless powder, mp 162-163°C (EtOH). Anal. Calcd for $C_{11}H_{10}NO_2Br$: C, 49.34; H, 3.76; N, 5.22. Found: C, 49.57; H, 3.76; N, 5.14. ^{1}H-Nmr ($CDCl_3$-DMSO-d_6) δ: 3.74 (2H, t, J=6.0 Hz, OCH_2), 4.36 (2H, t, J=6.0 Hz, CH_2Br), 5.30 (1H, br s, OH), 7.00-8.15 (5H, m, Ar-H).

17: Colorless needles, mp 82-83°C (ether). Anal. Calcd for $C_{11}H_9NOBrCl$: C, 46.11; H, 3.17; N, 4.89. Found: C, 46.41; H, 3.13; N, 4.98. ^{1}H-Nmr ($CDCl_3$) δ: 3.65 (2H, t, J=6.0 Hz, OCH_2), 4.32 (2H, t, J=6.0 Hz, CH_2Br), 7.15-8.15 (5H, m, Ar-H).

[1,4]Dioxano[2,3-b]quinoline (**19**) — To an ice-cooled solution of **16** (4.5 g, 0.017 mol) in DMF (50 ml) was added NaH (0.8 g, 0.02 mol), and then the solution was stirred at room temperature for 1 h. Precipitates formed on addition of H_2O were dissolved in ether. The ether solution was washed with H_2O, dried and concentrated. The residue was chromatographed on silica gel with $CHCl_3$ to give 1.5 g (48%) of **19**, colorless needles, mp 84-85°C (EtOH). Anal. Calcd for $C_{11}H_9NO_2$: C, 70.58; H, 4.85;

N, 7.48. Found: C, 70.57; H, 4.82; N, 7.42. ^{1}H-Nmr ($CDCl_3$) δ: 4.12-4.60 (4H, m, $C_{2,3}$-4H), 7.10-7.98 (5H, m, Ar-H).

3-(2-Bromoethoxy)-4-chloroquinoline 1-Oxide (**20**) — A solution of **15** (17 g, 0.06 mol) and m-CPBA (12.4 g, 0.072 mol) in $CHCl_3$ (300 ml) was stirred at room temperature for 3 h, and worked up as described for the preparation of **4** to give 15.2 g (85%) of **20**, colorless crystals, mp 164-166°C (MeOH). Anal. Calcd for $C_{11}H_9NO_2BrCl$: C, 43.67; H, 3.00: N, 4.63. Found: C, 43.96; H, 2.81; N, 4.68. ^{1}H-Nmr ($CDCl_3$-DMSO-d_6) δ: 3.65 (2H, t, J=6.0 Hz, CH_2Br), 4.43 (2H, t, J=6.0 Hz, OCH_2), 7.50-8.19 (3H, m, C_{5-7}-3H), 8.42 (1H, s, C_2-H), 8.48-8.65 (1H, m, C_8-H).

3-(2-Bromoethoxy)-4-chloro-2-hydroxyquinoline (**21**) — A solution of **20** (17 g, 0.056 mol) and TsCl (16 g, 0.084 mol) in $CHCl_3$ (200 ml) was stirred with 10% K_2CO_3 (200 ml) at room temperature for 4 h. The $CHCl_3$ layer was washed with H_2O, dried and concentrated. The residue was chromatogrphed on silica gel with $CHCl_3$ to give 7.5 g (45%) of **21**, colorless needles, mp 203-205°C (MeOH-ether). Anal. Calcd for $C_{11}H_9NO_2BrCl$: C, 43.67; H, 3.00; N, 4.63. Found: C, 43.94; H, 2.90; N, 4.69. ^{1}H-Nmr ($CDCl_3$) δ: 3.21-4.40 (4H, m, OCH_2CH_2Br), 6.90-7.29 (5H, m, Ar-H, OH).

10-Chloro-[1,4]dioxano[2,3-b]quinoline (**22**) — To an ice-cooled solution of **21** (6.7 g, 0.022 mol) in DMF (100 ml) was slowly added NaH (1.2 g, 0.033 mol) , and the whole was stirred at room temperature for 1 h. Precipitates formed on addition of H_2O were filtered and dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with H_2O, dried and concentrated to give 4.2 g (86%) of **22**, colorless needles, mp 139-140°C (MeOH-ether). Anal. Calcd for $C_{11}H_8NO_2Cl$: C, 59.61; H, 3.64; N, 6.32. Found: C, 59.56; H, 3.59; N, 6.28. ^{1}H-Nmr ($CDCl_3$) δ: 4.30-4.70 (4H, m, $C_{2,3}$-4H), 7.20-8.10 (4H, m, Ar-H).

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