

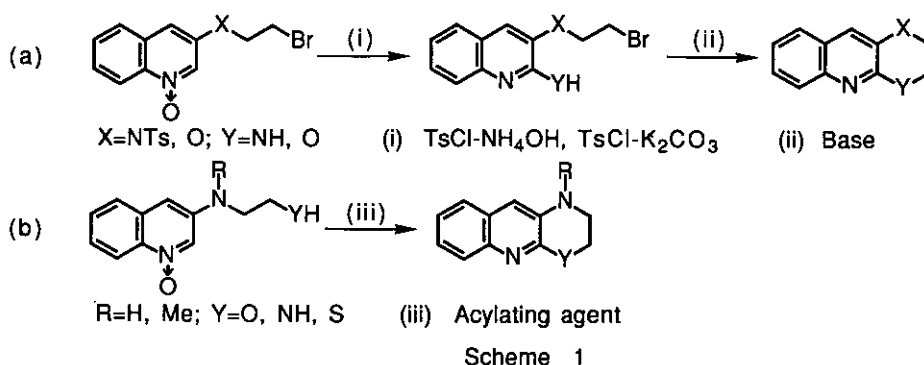
**SYNTHESIS OF 2,3-FUSED QUINOLINES FROM
3-SUBSTITUTED QUINOLINE 1-OXIDES. PART II.**

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Abstract — 3-Bromo-4-nitroquinoline 1-oxide (1) reacted with 2-methylaminoethanol, 1-amino-2-propanol and ethylenediamine to give the corresponding 3-amino-4-nitroquinoline 1-oxides (2, 4 and 7), which readily underwent the intramolecular cyclization, upon heating with Ac₂O in DMF, to afford the morpholino[2,3-b]quinolines (3 and 6) and the piperazino[2,3-b]quinoline (8). The reaction of 1 with N,N'-dimethylethylenediamine afforded directly the piperazinoquinoline (10), and that with 2-aminoethanethiol gave the thiomorpholino[2,3-b]quinoline (11) and its 10-oxide (12).

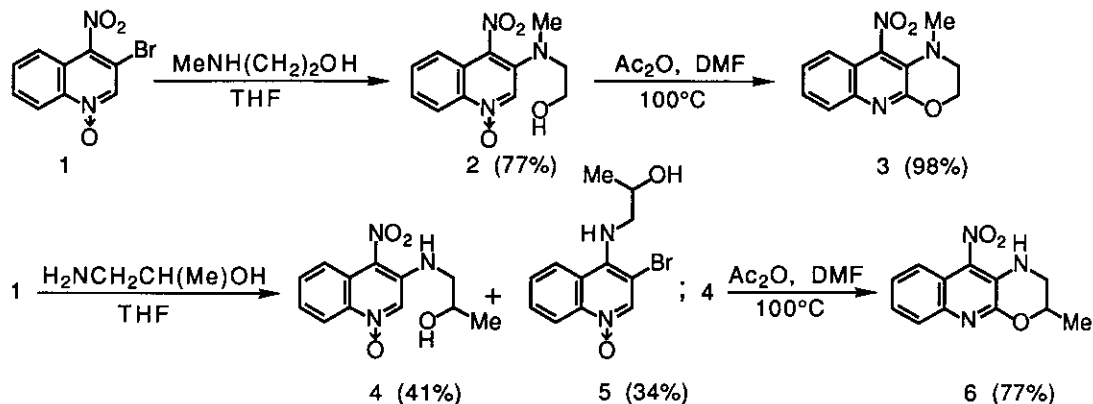
In a previous paper we described the synthesis of some 2,3-fused quinolines by the route (a) which involves the deoxygenative 2-substitution¹ of 3-(2-bromoethylamino)- and 3-(2-bromoethoxy)quinoline 1-oxides as the key step.² As a continuation of this work, we tried the cyclization by the deoxygenative intramolecular 2-substitution of 3-aminoquinoline 1-oxides having 2-hydroxyethyl, 2-aminoethyl- or 2-mercaptoethyl substituent on the 3-amino group (b) (Scheme 1).



3-Bromo-4-nitroquinoline 1-oxide³ (**1**) was chosen as the starting material because its 3-bromo substituent may reasonably be expected to be highly reactive toward nucleophilic displacement with amines and further the 4-amino group obtainable from the 4-nitro group of the quinoline ring is generally known to have a favorable effect on the biological activity against dementia of Alzheimer type.⁴

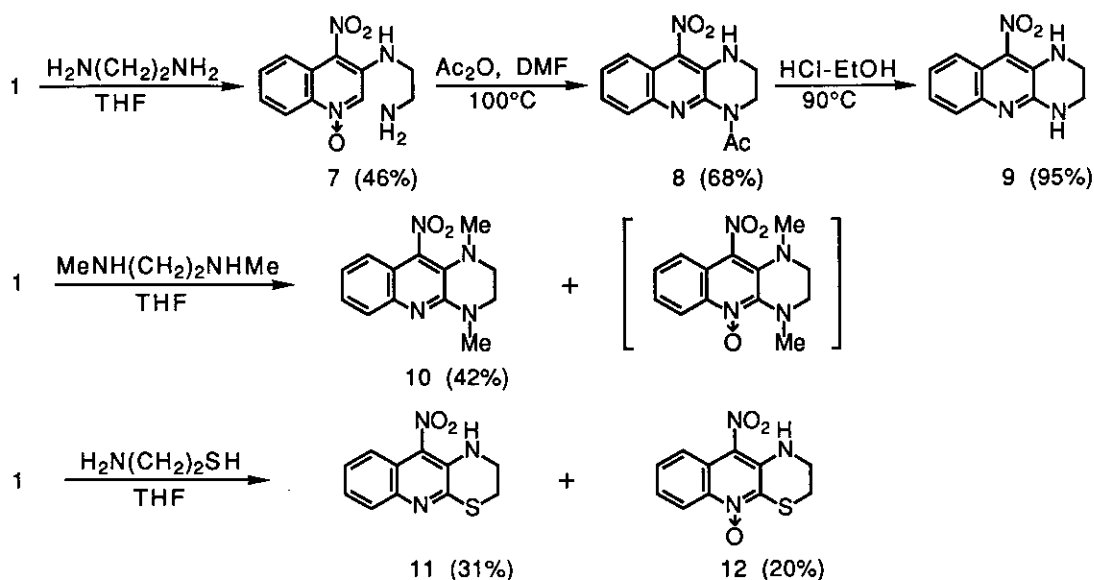
Treatment of **1** with excess 2-methylaminoethanol in tetrahydrofuran (THF) at room temperature overnight gave 3-(*N*-2-hydroxyethyl-*N*-methylamino)-4-nitroquinoline 1-oxide (**2**) as a sole product in 77% yield. The cyclization of **2** by means of an acylating agent was explored first using acetic anhydride (Ac₂O). Although no reaction was observed when **2** was treated with Ac₂O (3 equiv.) at room temperature in dimethylformamide (DMF), a reaction smoothly occurred upon heating with excess Ac₂O at 100°C for 0.5 h in DMF to afford 4-methyl-5-nitromorpholino[2,3-*b*]quinoline (**3**) in a high yield of 98%. In a similar reaction of **1** with 1-amino-2-propanol, however, 3-(2-hydroxypropylamino)-4-nitroquinoline 1-oxide (**4**) as well as 3-bromo-4-(2-hydroxypropylamino)quinoline 1-oxide (**5**) were formed in 41 and 34% yields, respectively. Although **5**, an orange oil, could not be purified enough for elemental analysis, its ¹H-nmr spectrum was consistent with the assigned structure, the alternative 4-(1-amino-2-propoxy)quinoline structure seeming to be excluded. Cyclization of **4** also smoothly occurred by heating with

Ac₂O at 100°C for 2 h in DMF to give 2-methyl-5-nitromorpholino[2,3-*b*]-quinoline (**6**) in 77% yield (Scheme 2).



Scheme 2

Subsequently the reaction of **1** with ethylenediamines was examined. Treatment of **1** with ethylenediamine in THF at room temperature gave 3-(2-aminoethylamino)-4-nitroquinoline 1-oxide (**7**) in a somewhat lower yield of 46%. Heating **7** with Ac₂O at 100°C for 10 min in DMF led to 4-acetyl-10-nitropiperazino[2,3-*b*]quinoline (**8**) in 68% yield. Deacetylation from **8** was readily effected by heating with 7% hydrochloric acid in ethanol at 90°C for 1.5 h to give the piperazinoquinoline (**9**) in 95% yield. On the other hand, the reaction of **1** with *N,N'*-dimethylethylenediamine or 2-aminoethanethiol was unexpectedly found to provide directly the cyclization products. Thus, when a THF solution of **1** and an excess of the diamine was stirred at room temperature for 2 h, 1,4-dimethyl-10-nitropiperazino[2,3-*b*]quinoline (**10**) was obtained in 42% yield accompanied with a minute amount of its 5-oxide, which structure was deduced from its behavior on thin layer chromatogram and by analogy with the reaction of **1** with 2-aminoethanethiol mentioned below. Treatment of **1** with 2-aminoethanethiol at room temperature for 12 h in THF gave 5-nitrothiomorpholino[2,3-*b*]quinoline (**11**) and its 10-oxide (**12**) in 31 and 20% yield, respectively (Scheme 3).



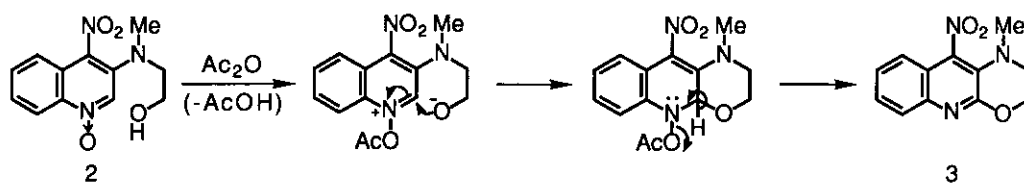
Scheme 3

The structures of these products were assigned on the basis of elemental analyses and spectral examinations. As it was found that Ac_2O served as an efficient agent for the desired cyclization, the employment of other acylating agents was not tried.

Kawazoe *et al.* reported that 3-fluoro-4-nitroquinoline 1-oxide is highly reactive toward nucleophilic substitution reaction and the corresponding 3-amino-4-nitroquinoline 1-oxides were obtained from reactions with various amines, including 2-aminoethanol, but 3,4-bis(carboxymethylthio)quinoline 1-oxide was formed with thioglycolic acid.⁵ However, there is no comparable study on such reactions of 3-bromo-4-nitroquinoline 1-oxide (1). The formation of 3-aminoquinoline derivatives (2, 4 and 7) from reactions of 1 with 2-methylaminoethanol, 1-amino-2-propanol and ethylenediamine, respectively, is apparently the same pattern with the reaction of 3-fluoro-4-nitroquinoline 1-oxide with amines. The reaction with N,N'-dimethylethylenediamine should be also considered to be initiated by the displacement of the 3-bromo substituent with the methylamino group. However,

the formation of the 4-amino-substituted quinoline 1-oxide (5) in the reaction with 1-amino-2-propanol is rather an unexpected result because the 4-nitro group of 4-nitroquinoline 1-oxides is known to be more readily displaced with alkoxy groups than with amines.⁶ The steric effect of the 3-methyl group of 1-amino-2-propanol as well as the reaction conditions (the absence of a strong base) seem to be responsible for this result, but its details are not yet clear. The reaction of 1 with 2-aminoethanethiol will be separately discussed below.

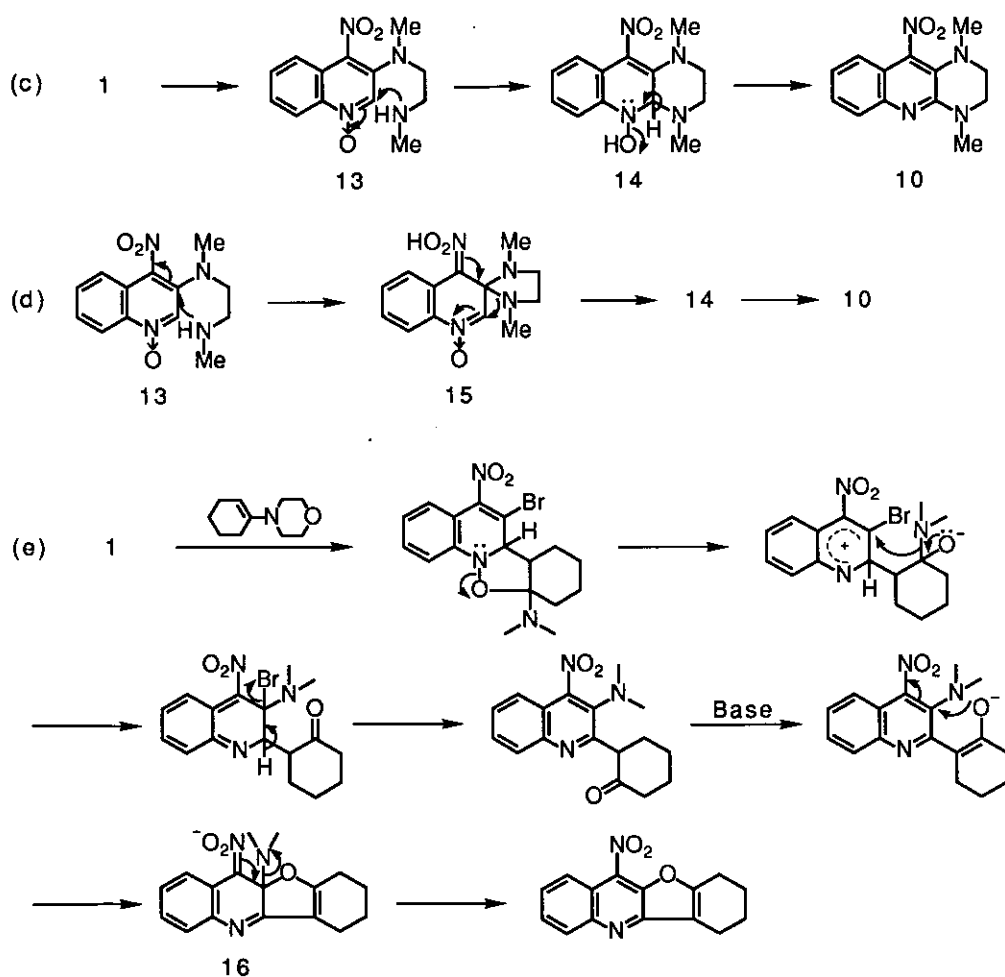
It is well known that the nucleophilic reaction of aromatic *N*-oxide in the presence of acylating agents is markedly governed by the nature of acylating agents.¹ Thus, 2-alkoxylation of quinoline 1-oxide with an alcohol in the presence of triethylamine progresses efficiently by means of tosyl chloride or ethyl chloroformate,⁷ and its 2-amination is promoted by tosyl chloride.⁸ In these cases Ac₂O is generally not effective. However, Issidorides *et al.* found that 3-(2-hydroxyphenyl)quinoxaline 1-oxide was readily transformed into benzofuro[2,3-*b*]quinoxaline upon heating with Ac₂O.⁹ Apparently, this intramolecular reaction is facilitated by the favorable steric environment, and this is also the case for the smooth cyclization of 2, 4 and 7, to 3, 6 and 8, respectively; Ac₂O is enough efficient as an acylating agent in these cases and the reaction can be explained by the addition-elimination mechanism as illustrated by the reaction of 2 in Scheme 4.



Scheme 4

Of particular interest is the direct formation of the cyclization products (10 or 11 and 12) from the reaction of 1 with *N,N'*-dimethylethylenediamine

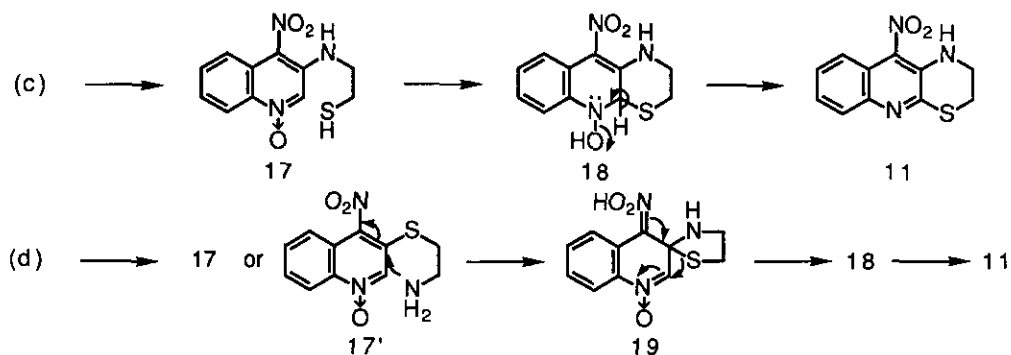
or 2-aminoethanethiol. As mentioned above, the initial step of the former reaction is the formation of 3-(*N*-2-aminoethyl-*N*-methylamino)-4-nitroquinoline 1-oxide (**13**) which is so highly reactive that cyclizes instantly to the piperazinoquinoline (**10**). Although the essential feature of this cyclization is not obvious yet, the following two courses might be conceivable. The first is the addition-elimination course (c) in the absence of an acylating agent through the 1,2-dihydroquinoline intermediate (**14**).



Scheme 5

This might be promoted by the highly nucleophilic reactivity of the dialkyl-amino group together with the isolated nitron-like character of the *N*-oxide function of 13 caused by the combined effect of the 3- and 4-substituents. The second course (d) involves the spiro intermediate (15), which might be formed by the strong electron-withdrawing effect of the 4-nitro group, and its cleavage might generate the highly reactive nitrogen anion which attacks at the 2-position to give the same dihydroquinoline intermediate (14). The possibility of the intermediacy of such a spiro compound (15) is supported by the mechanism of the reaction of 1 with 1-morpholinocyclohexene (e)¹⁰ involving the spiro intermediate (16) (Scheme 5).

Although it was reported that 4-nitroquinoline 1-oxide reacts with cysteine¹¹ or 2-aminoethanethiol¹² to give the respective 4-thio-substituted quinoline 1-oxide, the reaction of 1 with 2-aminoethanethiol is apparently initiated by the displacement of the 3-bromo substituent, the 4-nitro group being intact. Thus, the first step of course (c) in this case is the formation of the 3-amino-4-nitroquinoline 1-oxide (17), which consecutively transformed into 11 through the 1,2-dihydroquinoline intermediate (18). As for course (d), the spiro intermediate (19) may be formed through either the 3-aminoquinoline 1-oxide (17) or the 3-thio-substituted quinoline 1-oxide (17') (Scheme 6).



Scheme 6

It is difficult at present to rationalize the formation of the N-oxide (12) of 11. The formation of 10, 11 and 12 involves many interesting problems and should be explored in details by a number of means.

EXPERIMENTAL

All melting points are uncorrected. ^1H -Nmr spectra were recorded on a Hitachi RB-24 spectrometer using tetramethylsilane as an internal standard. X-Ray diffraction data were obtained from a Enraf-Nonius CAD 4 diffractometer.

3-(N-2-Hydroxyethyl-N-methylamino)-4-nitroquinoline 1-Oxide (2) — A solution of 3-bromo-4-nitroquinoline 1-oxide (1) (2 g, 7.4 mmol) and 2-methylaminoethanol (2 ml, 24.9 mmol) in THF (15 ml) was stirred at room temperature overnight, then concentrated. The residue was washed with 10% K_2CO_3 and dissolved in CHCl_3 . The CHCl_3 solution was washed with H_2O , dried over Na_2SO_4 and concentrated in vacuo. The residue was recrystallized from EtOH-ether to give 1.51 g (77%) of 2, orange granules, mp 151–155°C. Anal. Calcd for $\text{C}_{12}\text{H}_{23}\text{N}_3\text{O}_4$: C, 54.75; H, 4.94; N, 15.97. Found: C, 54.76; H, 4.89; N, 15.65. ^1H -Nmr (CDCl_3) δ : 2.96 (3H, s, CH_3), 3.30–3.59 (2H, m, N- CH_3), 3.61–3.97 (2H, m, O- CH_2), 4.64 (1H, br s, OH), 7.27–7.80 (3H, m, C_5 –7-H), 8.26–8.54 (1H, m, C_8 -H), 8.66 (1H, s, C_2 -H).

4-Methyl-5-nitromorpholino[2,3-b]quinoline (3) — A solution of 2 (1.2 g, 4.6 mmol) and Ac_2O (5 ml) in DMF (10 ml) was heated at 100°C for 0.5 h, then concentrated. The residue was dissolved in CHCl_3 , and the CHCl_3 solution was washed with 10% NaHCO_3 and H_2O , dried over Na_2SO_4 , and concentrated. The residue was recrystallized from CHCl_3 -hexane to give 1.1 g (98%) of 3, red prisms, mp 112–113°C. Anal. Calcd for $\text{C}_{12}\text{H}_{11}\text{N}_3\text{O}_3$: C, 58.77; H, 4.52; N, 17.13. Found: C, 58.68; H, 4.38; N, 17.20. ^1H -Nmr (CDCl_3) δ : 2.95 (3H, s,

CH₃), 3.47-3.66 (2H, m, C₃-H), 4.32-4.54 (2H, m, C₂-H), 7.20-8.05 (4H, m, C₆-9-H).

Reaction of 1 with 1-Amino-2-propanol -- A solution of 1 (2 g, 7.4 mmol) and 1-amino-2-propanol (2 ml, 25.9 mmol) in THF (10 ml) was stirred at room temperature overnight, then concentrated. The residue was dissolved in CHCl₃ and the CHCl₃ solution was washed with 10% K₂CO₃ and H₂O, dried over Na₂SO₄, and concentrated. The residue was chromatographed on silica gel with 3% MeOH-CHCl₃ to give successively 0.8 g (41%) of 3-(2-hydroxypropylamino)-4-nitroquinoline 1-oxide (4) and 0.76 g (34%) of 3-bromo-4-(2-hydroxypropylamino)quinoline 1-oxide (5).

4: orange needles, mp 173-174°C (MeOH). Anal. Calcd for C₁₂H₁₃N₃O₄: C, 54.75; H, 4.98; N, 15.96. Found: C, 54.70; H, 5.22; N, 16.08. ¹H-Nmr (CDCl₃) δ: 1.17 (3H, d, J=5.9 Hz, CH₃), 3.34-3.64 (2H, m, N-CH₂), 3.84 (1H, m, CH-OH), 5.15 (1H, d, J=4.9 Hz, OH), 7.51-7.80 (2H, m, C_{6,7}-H), 8.42-8.76 (2H, m, C_{5,8}-H), 8.74 (1H, s, C₂-H), 9.20 (1H, br s, NH).

5: an orange oil. ¹H-Nmr (CDCl₃) δ: 1.12 (3H, d, J=6.3 Hz, CH₃), 3.31-3.67 (2H, m, N-CH₃), 3.74-3.95 (1H, m, CH-OH), 5.01 (1H, d, J=4.9 Hz, OH), 5.69 (1H, br s, NH), 7.64-7.83 (2H, m, C_{6,7}-H), 8.28-8.54 (2H, m, C_{5,8}-H), 8.60 (1H, s, C₂-H).

2-Methyl-5-nitromorpholino[2,3-*b*]quinoline (6) -- A solution of 4 (0.7 g, 2.7 mmol) and Ac₂O (3 ml) in DMF (8 ml) was heated at 100°C for 2 h, then concentrated. The residue was dissolved in CHCl₃, and the CHCl₃ solution was washed with 10% NaHCO₃ and H₂O, dried over Na₂SO₄ and concentrated in vacuo. The residue was chromatographed on silica gel with 5% MeOH-CHCl₃ to give 0.5 g (77%) of 6, orange granules, mp 188-189°C (CHCl₃-hexane). Anal. Calcd for C₁₂H₁₁N₃O₃: C, 58.77; H, 4.52; N, 17.13. Found: C, 58.74; H, 4.39; N, 17.18. ¹H-Nmr (CDCl₃) δ: 1.69 (3H, d, J=6 Hz, CH₃), 3.34-3.80 (2H, m, C₃-H), 4.19-4.75 (1H, m, C₂-H), 7.11-7.85 (3H, m, C₆₋₈-H), 8.21-8.75 (2H, m, C₉-H, NH).
3-(2-Aminoethylamino)-4-nitroquinoline 1-Oxide (7) -- A solution of 1 (2 g,

7.4 mmol) and ethylenediamine (2 ml, 29.9 mmol) in THF (15 ml) was stirred at room temperature overnight, then concentrated in vacuo. The residue was dissolved in CHCl_3 , and the CHCl_3 solution was washed with H_2O , dried over Na_2SO_4 and concentrated in vacuo. The residue was recrystallized from ether to give 0.85 g (46%) of 7, red granules, mp 233-234°C. Anal. Calcd for $\text{C}_{11}\text{H}_{12}\text{N}_4\text{O}_3$: C, 53.22; H, 4.84; N, 22.58. Found: C, 53.05; H, 4.69; N, 22.58. $^1\text{H-Nmr}$ (CDCl_3) δ : 3.25 (2H, br s, NH_2), 3.30-3.75 (4H, m, $\text{N-CH}_2\text{CH}_2\text{-N}$), 7.04-8.40 (5H, m, Ar-H), 9.04 (1H, br s, NH).

4-Acetyl-10-nitropiperazino[2,3-b]quinoline (8) — A solution of 7 (0.8 g, 3.2 mmol) and Ac_2O (5 ml) in DMF (15 ml) was heated at 100°C for 10 min, then concentrated in vacuo. The residue was extracted with CHCl_3 , and the CHCl_3 solution was washed with H_2O and dried over Na_2SO_4 . The residue from the CHCl_3 extract was chromatographed on silica gel with 2% MeOH-CHCl_3 to give 0.60 g (68%) of 8, red prisms, mp 196-197°C (CHCl_3 -hexane). Anal. Calcd for $\text{C}_{13}\text{H}_{12}\text{N}_4\text{O}_3$: C, 57.34; H, 4.44; N, 20.58. Found: C, 57.23; H, 4.31; N, 20.62. $^1\text{H-Nmr}$ (CDCl_3) δ : 2.53 (3H, s, COCH_3), 3.45-3.85 (2H, m, $\text{C}_3\text{-H}$), 3.90-4.14 (2H, m, $\text{C}_2\text{-H}$), 7.23-7.82 (3H, m, $\text{C}_7\text{-}_9\text{-H}$), 8.16-8.45 (1H, m, $\text{C}_6\text{-H}$), 8.92 (1H, br s, NH).

10-Nitropiperazino[2,3-b]quinoline (9) — A solution of 8 (0.5 g, 2 mmol) in 7% HCl (5 ml) and EtOH (10 ml) was heated at 90°C for 1.5 h, then concentrated and neutralized with 7% NaHCO_3 . A precipitate formed was filtered, washed with H_2O and MeOH , and recrystallized from MeOH-ether to give 0.4 g (95%) of 9, red granules, mp 251-252°C. Anal. Calcd for $\text{C}_{11}\text{H}_{10}\text{N}_4\text{O}_2 \cdot \frac{1}{2}\text{H}_2\text{O}$: C, 55.23; H, 4.60; N, 22.43. Found: C, 55.18; H, 4.32; N, 22.99. $^1\text{H-Nmr}$ (CDCl_3) δ : 3.53 (4H, s, $\text{C}_{2,3}\text{-H}$), 6.80 (1H, br s, $\text{N}_4\text{-H}$), 7.04-7.56 (3H, m, $\text{C}_7\text{-}_9\text{-H}$), 7.96-8.35 (1H, m, $\text{C}_6\text{-H}$), 9.04 (1H, br s, $\text{N}_1\text{-H}$).

1,4-Dimethyl-10-nitropiperazino[2,3-b]quinoline (10) — A solution of 1 (2 g, 7.4 mmol) and N,N' -dimethylethylenediamine (2 ml, 18.9 mmol) in THF (10 ml) was stirred at room temperature for 2 h. The reaction mixture was

concentrated, and the residue was chromatographed on silica gel with CHCl_3 to give 0.8 g (42%) of **10**, red prisms, mp 251–253°C (CHCl_3 -ether). Anal. Calcd for $\text{C}_{13}\text{H}_{14}\text{N}_4\text{O}_2$: C, 60.45; H, 5.46; N, 21.69. Found: C, 60.49; H, 5.57; N, 21.77. $^1\text{H-Nmr}$ (CDCl_3) δ : 2.90 (3H, s, $\text{N}_1\text{-CH}_3$), 3.19 (3H, s, $\text{N}_3\text{-CH}_3$), 3.46 (4H, s, $\text{C}_{2,3}\text{-H}$), 7.04–7.65 (4H, m, $\text{C}_{6-9}\text{-H}$).

Reaction of 1 with 2-Aminoethanethiol — A solution of **1** (4 g, 15 mmol) and 2-aminoethanethiol (3.4 g, 44.0 mmol) in THF (100 ml) was stirred at room temperature overnight, then concentrated. The residue was dissolved in CHCl_3 , and the CHCl_3 solution was washed with 10% K_2CO_3 and H_2O , dried over Na_2SO_4 . The residue from the CHCl_3 solution was chromatographed on silica gel with 3% MeOH-CHCl_3 to give successively 1.2 g (31%) of 5-nitrothiomorpholino[2,3-*b*]quinoline (**11**) and 0.8 g (20%) of its 10-oxide (**12**).

11: red needles, mp 191–192°C (CHCl_3 -ether). Anal. Calcd for $\text{C}_{11}\text{H}_9\text{N}_3\text{O}_2\text{S}$: C, 53.43; H, 3.67; N, 17.13; S, 12.97. Found: C, 53.63; H, 3.49; N, 17.10; S, 12.54. $^1\text{H-Nmr}$ (CDCl_3) δ : 3.30–3.35 (2H, m, $\text{C}_3\text{-H}$), 3.74–3.81 (2H, m, $\text{C}_2\text{-H}$), 7.43–8.05 (4H, m, $\text{C}_{6-9}\text{-H}$), 8.50 (1H, br s, NH).

12: red granules, mp 245–247°C (decomp.) (CHCl_3 -ether). Anal. Calcd for $\text{C}_{11}\text{H}_9\text{N}_3\text{O}_3\text{S}$: C, 50.18; H, 3.45; N, 15.96; S, 12.18. Found: C, 50.00; H, 3.20; N, 15.93; S, 11.87. $^1\text{H-Nmr}$ (CDCl_3) δ : 3.23–3.28 (2H, m, $\text{C}_3\text{-H}$), 3.79–3.83 (2H, m, $\text{C}_2\text{-H}$), 7.48–7.70 (2H, m, $\text{C}_{7,8}\text{-H}$), 8.29–8.52 (2H, m, $\text{C}_{6,9}\text{-H}$), 9.39 (1H, br s, NH).

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