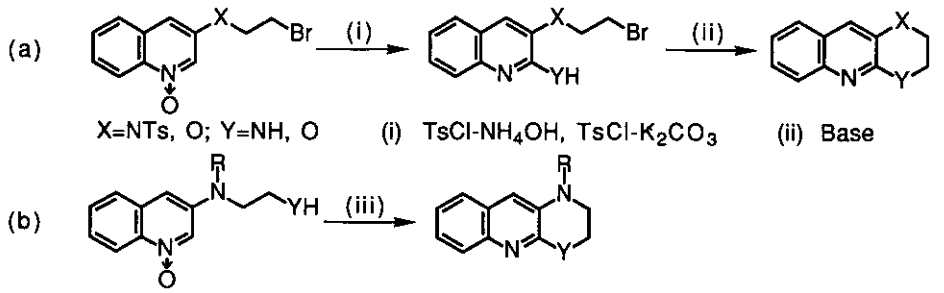
SYNTHESIS OF 2,3-FUSED QUINOLINES FROM 3-SUBSTITUTED QUINOLINE 1-OXIDES. PART II.

Yutaka Miura,* Mitsutaka Yoshida, and Masatomo Hamana

Exploratory Laboratories, Chugai Pharmaceutical Co., Ltd.
1-135 Komakado, Gotemba, Shizuoka Prefecture 412, Japan

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 Ac_2O 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-substitution[1] 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).

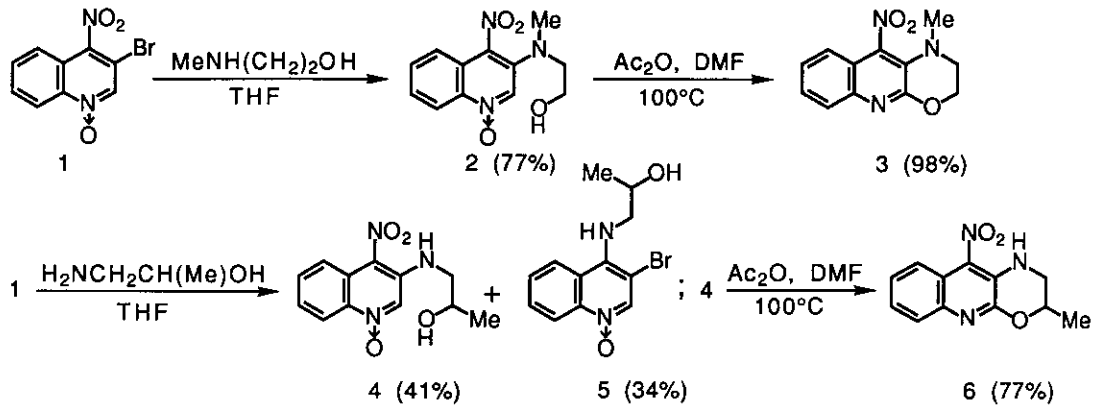


Scheme 1

3-Bromo-4-nitroquinoline 1-oxide[3] (**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]

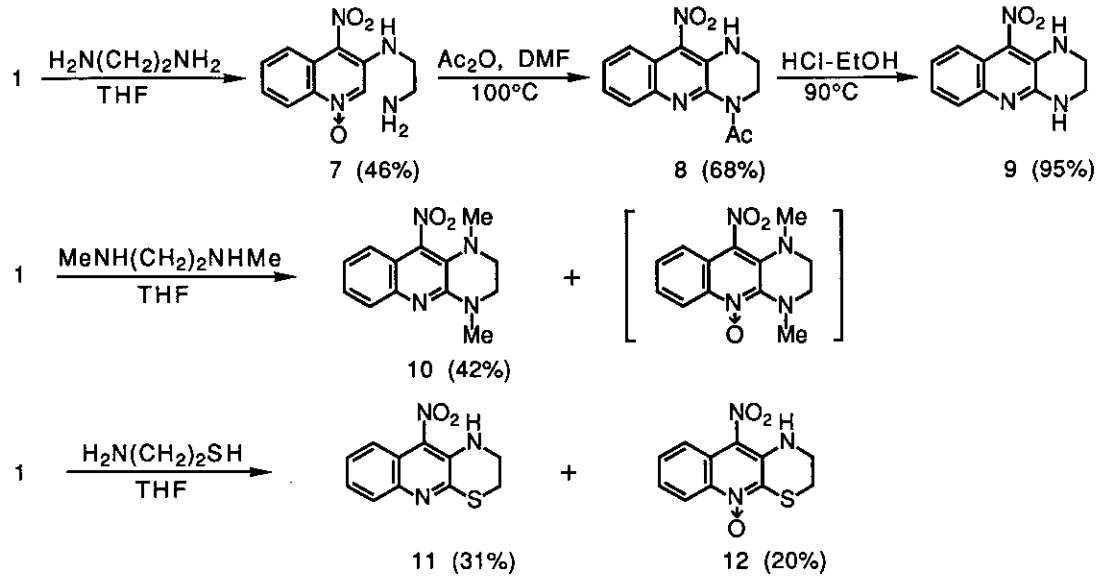
Treatment of **1** with excess 2-methylaminoethanol in tetrahydrofuran (THF) at room temperature overnight gave 3-(N-2-hydroxyethyl-N-methylamino)-4-nitroquinoline 1-oxide (**2**) as a sole product in 77% yield. The cyclization of **2** by means of an acylating agent was explored first using acetic anhydride (Ac_2O). Although no reaction was observed when **2** was treated with Ac_2O (3 equiv.) at room temperature in dimethylformamide (DMF) , a reaction smoothly occurred upon heating with excess Ac_2O 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 elmental analysis, its ^{1}H-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

Ac_2O 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 Ac_2O 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).



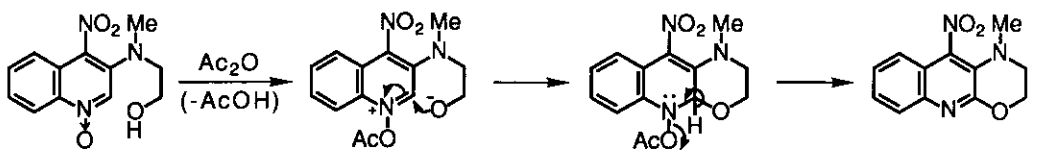
Scheme 3

The sturctures 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.

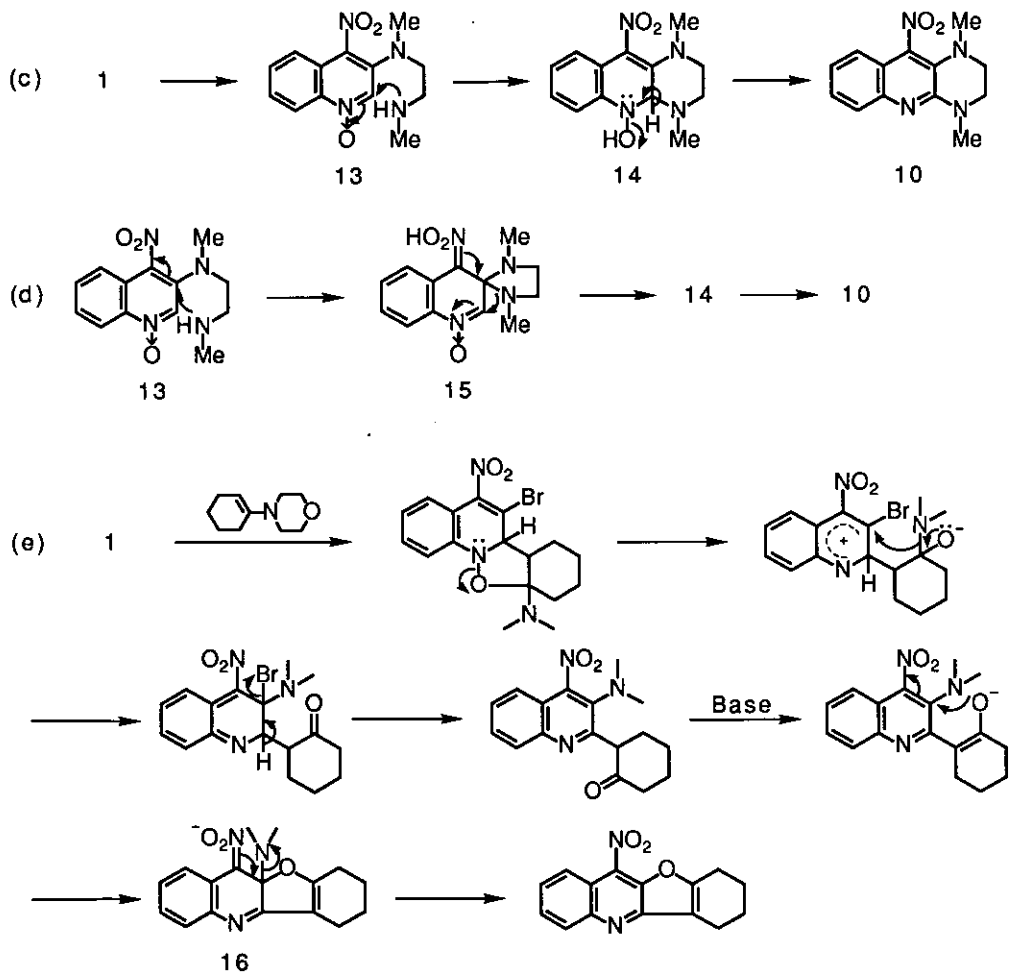
It is well known that the nucleophilic reaction of aromatic N-oxide in the presence of acylating agents is markedly governed by the nature of acylating agents.[1] Thus, 2-alkoxylation of quinoline 1-oxide with an alcohol in the presence of triethylamine progresses efficiently by means of tosyl chloride or ethyl chloroformate,[7] and its 2-amination is promoted by tosyl chloride.[8] In these cases Ac_2O 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 Ac_2O.[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; Ac_2O 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

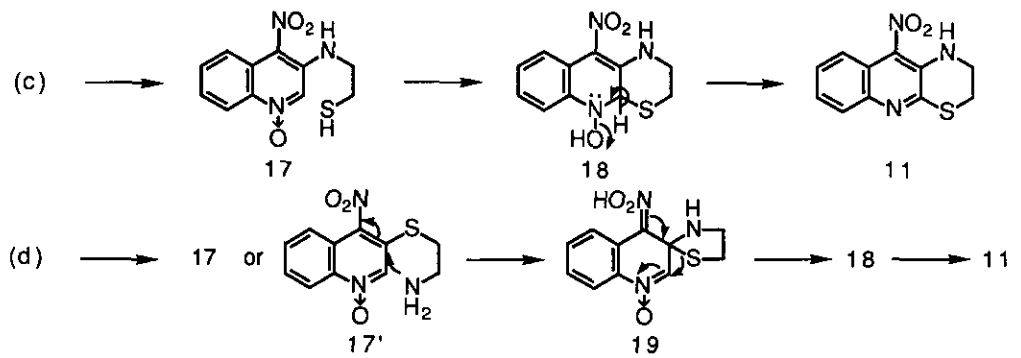
or 2-aminoethanethiol. As mentioned above, the initial step of the former reaction is the formation of 3-(N-2-aminoethyl-N-methylamino)-4-nitroquinoline 1-oxide (**13**) which is so highly reactive that cyclizes instantly to the piperazinoquinoline (**10**). Although the essential feature of this cyclization 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 dialkylamino group together with the isolated nitrone-like character of the N-oxide function of **13** caused by the combined effect of the 3- and 4-substitutents. 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 cysteine[11] or 2-aminoethanethiol[12] 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. ^{1}H-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 $C_{12}H_{23}N_3O_4$: C, 54.75; H, 4.94; N, 15.97. Found: C, 54.76; H, 4.89; N, 15.65. ^{1}H-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 $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.52; N, 17.13. Found: C, 58.68; H, 4.38; N, 17.20. ^{1}H-Nmr ($CDCl_3$) δ: 2.95 (3H, s,

CH_3), 3.47-3.66 (2H, m, C_3-H), 4.32-4.54 (2H, m, C_2-H), 7.20-8.05 (4H, m, C_{6-9}-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 $CHCl_3$ and the $CHCl_3$ solution was washed with 10% K_2CO_3 and H_2O, dried over Na_2SO_4, and concentrated. The residue was chromatographed on silica gel with 3% MeOH-$CHCl_3$ 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 $C_{12}H_{13}N_3O_4$: C, 54.75; H, 4.98; N, 15.96. Found: C, 54.70; H, 5.22; N, 16.08. ^{1}H-Nmr ($CDCl_3$) δ:1.17(3H, d, J=5.9 Hz, CH_3), 3.34-3.64 (2H, m, N-CH_2), 3.84 (1H, m, C<u>H</u>-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, C_2-H), 9.20 (1H, br s, NH).

5: an orange oil. ^{1}H-Nmr ($CDCl_3$) δ: 1.12 (3H, d, J=6.3 Hz, CH_3), 3.31-3.67 (2H, m, N-CH_3), 3.74-3.95 (1H, m, C<u>H</u>-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, C_2-H).

2-Methyl-5-nitromorpholino[2,3-b]quinoline (**6**) — A solution of **4** (0.7 g, 2.7 mmol) and Ac_2O (3 ml) in DMF (8 ml) was heated at 100°C for 2 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 *in vacuo*. The residue was chromatographed on silica gel with 5% MeOH-$CHCl_3$ to give 0.5 g (77%) of **6**, orange granules, mp 188-189°C ($CHCl_3$-hexane). Anal. Calcd for $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.52; N, 17.13. Found: C, 58.74; H, 4.39; N, 17.18. ^{1}H-Nmr ($CDCl_3$) δ: 1.69 (3H, d, J=6 Hz, CH_3), 3.34-3.80 (2H, m, C_3-H), 4.19-4.75 (1H, m, C_2-H), 7.11-7.85 (3H, m, C_{6-8}-H), 8.21-8.75 (2H, m, C_9-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 $C_{11}H_{12}N_4O_3$: C, 53.22; H, 4.84; N, 22.58. Found: C, 53.05; H, 4.69; N, 22.58. ^{1}H-Nmr ($CDCl_3$) δ: 3.25 (2H, br s, NH_2), 3.30-3.75 (4H, m, N-CH_2CH_2-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 $C_{13}H_{12}N_4O_3$: C, 57.34; H, 4.44; N, 20.58. Found: C, 57.23; H, 4.31; N, 20.62. ^{1}H-Nmr ($CDCl_3$) δ: 2.53 (3H, s, $COCH_3$), 3.45-3.85 (2H, m, C_3-H), 3.90-4.14 (2H, m, C_2-H), 7.23-7.82 (3H, m, C_{7-9}-H), 8.16-8.45 (1H, m, C_6-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 $C_{11}H_{10}N_4O_2$ $^1/_2H_2O$: C, 55.23; H, 4.60; N, 22.43. Found: C, 55.18; H, 4.32; N, 22.99. ^{1}H-Nmr ($CDCl_3$) δ: 3.53 (4H, s, $C_{2,3}$-H), 6.80 (1H, br s, N_4-H), 7.04-7.56 (3H, m, C_{7-9}-H), 7.96-8.35 (1H, m, C_6-H), 9.04 (1H, br s, N_1-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 $C_{13}H_{14}N_4O_2$: C, 60.45; H, 5.46; N, 21.69. Found: C, 60.49; H, 5.57; N, 21.77. ^{1}H-Nmr ($CDCl_3$) δ: 2.90 (3H, s, N_1-CH_3), 3.19 (3H, s, N_3-CH_3), 3.46 (4H, s, $C_{2,3}$-H), 7.04-7.65 (4H, m, C_{6-9}-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 $C_{11}H_9N_3O_2S$: 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}H-Nmr ($CDCl_3$) δ: 3.30-3.35 (2H, m, C_3-H), 3.74-3.81 (2H, m, C_2-H), 7.43-8.05 (4H, m, C_{6-9}-H), 8.50 (1H, br s, NH).

12: red granules, mp 245-247°C (decomp.)($CHCl_3$-ether). Anal. Calcd for $C_{11}H_9N_3O_3S$: 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}H-Nmr ($CDCl_3$) δ: 3.23-3.28 (2H, m, C_3-H), 3.79-3.83 (2H, m, C_2-H), 7.48-7.70 (2H, m, $C_{7,8}$-H), 8.29-8.52 (2H, m, $C_{6,9}$-H), 9.39 (1H, br s, NH).

REFERENCES

1. M. Hamana, Croat. Chem. Acta, 1986, **59**, 89.
2. Y. Miura, S. Takaku, Y. Fujimura, and M. Hamana, Heterocycles, 1992, **34**, 1055.
3. T. Okamoto, Yakugaku Zasshi, 1950, **70**, 376.
4. W. K. Summers, L. V. Majovski, G. M. Marsh, K. Tachiki, and A. Kling, N. Engl. J. Med., 1986, **315**, 1241.

5. M. Arai, M. Saneyoshi, H. Harada, and Y. Kawazoe, Chem. Pharm. Bull., 1968, **16**, 1742.

6. E. Ochiai, "Aromatic Amine Oxides," Elsevier Publishing Co., Amsterdam, 1967, pp. 374-382.

7. M. Hayashida, H. Honda, and M.Hamana, Heterocycles, 1990, **31**, 1325.

8. M. Hamana and O. Hoshino, Yakugaku Zasshi, 1962, **84**, 35.

9. a) M.J. Haddadin, J.-J. Zamet, and C.H. Issidorides, Tetrahedron Lett., 1972, 3653; b) J.-J. Zamet, M.J. Haddadin, and C.H. Issidorides, J. Chem. Soc., Perkin Trans. I, 1947, 1687.

10. Y. Miura, Y. Fujimura, S. Takaku, and M. Hamana, Heterocycles, 1990,**30**, 779.

11. T. Okabayashi, Yakugaku Zasshi, 1953, **73**, 946.

12. M. Hamana and S.Kumadaki, Yakugaku Zasshi, 1968, **88**, 665.

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