PREPARATION OF NEW 3-HYDROXYQUINOLINE ALKALOID, JINEOL AND ITS ETHER DERIVATIVES USING DIRECTED *ORTHO*-LITHIATION OF CHLOROQUINOLINE AS THE KEY STEP

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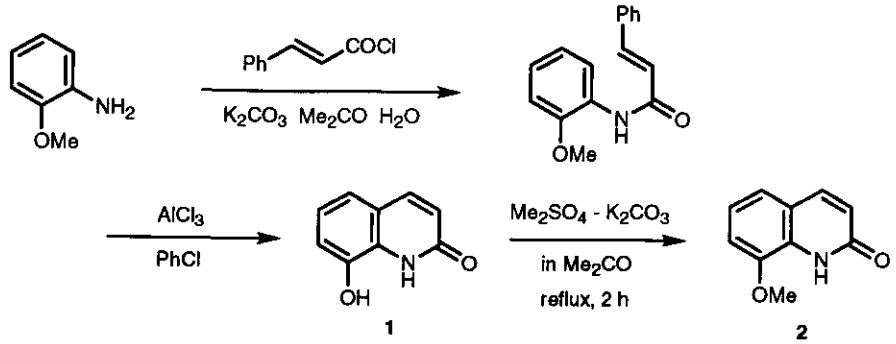
Abstract - A new alkaloid, jineol (3,8-dihydroxyquinoline) was conveniently prepared employing directed *ortho*-lithiation of chloroquinoline for 3-position of quinoline ring. Moreover, the ether derivatives of jineol were obtained by the reaction of jineol with alkyl halide in the presence of KOH in DMSO in 26-96% yields.

Jineol (3,8-dihydroxyquinoline), a new and cytotoxic alkaloid, was isolated from the centipede *Scolopendra subspinipes* in 1996.[1] It is disclosed that jineol has cytotoxic activity *in vitro* against the growth of human tumor cell lines.[1] It is of interest to investigate the unknown biological activities of this compound and its ether derivatives, however the present unsatisfying providing of this compound is limiting to the extract from live centipede. The present paper treats with the preparation of jineol and its ether derivatives using directed *ortho*-lithiation of chloroquinolines for 3-position of quinoline ring as the key step, which is in the course of our investigation of electrophilic reaction of aromatic *N*-oxides through base-induced deprotonation.[2]

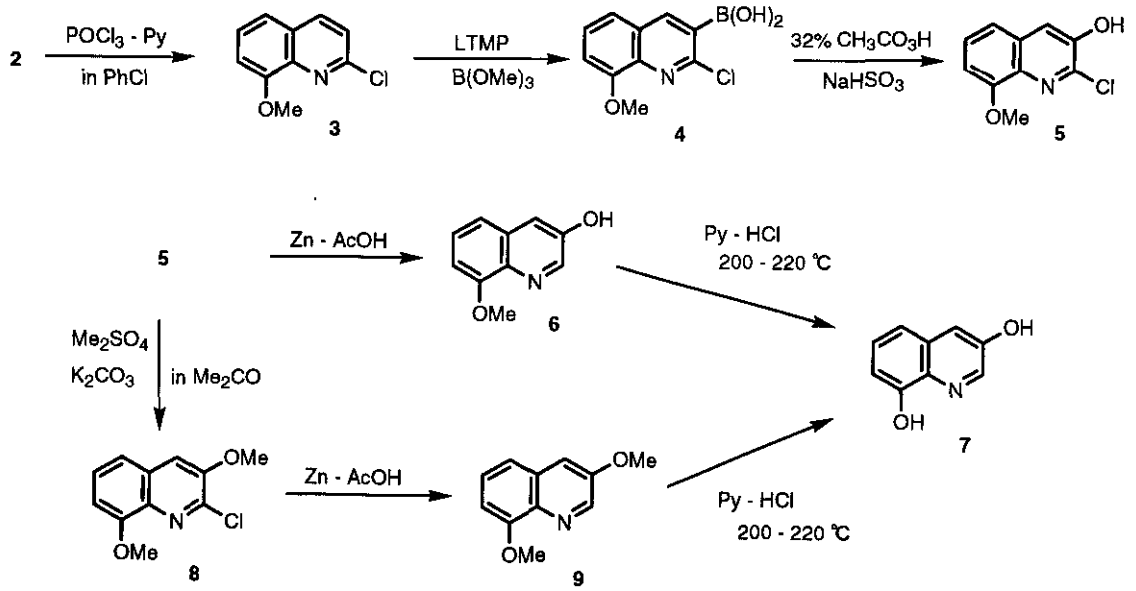
The selective *O*-methylation of 8-hydroxy-2(1*H*)-quinolone (**1**), which was easily prepared by intramolecular Friedel-Crafts reaction of 2-methoxycinnamanilide starting from Schotten-Baumann reaction of commercially available 2-methoxyaniline[3] using cinnamoyl chloride, was effected by using dimethyl sulfate-potassium carbonate and refluxing in acetone for 2 h to afford 8-methoxy-2(1*H*)-quinolone (**2**) in 95% yield (Scheme 1).

Scheme 1



2-Chloro-8-methoxyquinoline (**3**) was quantitatively obtained by the reaction of compound (**2**) with phosphorus oxychloride ($POCl_3$) in the presence of a catalytic amount of pyridine in chlorobenzene. It is well documented that chlorine of chloroquinolines is very useful for directed *ortho*-metalation (DoM) reaction.[4] Thus, the electrophilic reaction of compound (**3**) with trimethyl borate in the presence of LTMP (lithium tetramethylpiperidide) gave 2-chloro-8-methoxyquinolin-3-boronic acid (**4**) in 82% yield which was subsequently oxidized by 32% peracetic acid to give 2-chloro-3-hydroxy-8-methoxyquinoline (**5**) almost quantitatively. Compound (**5**) was subjected to reductive dechlorination employing Zn-AcOH to give 3-hydroxy-8-methoxy-quinoline (**6**) (84%) which was hydrolyzed to jineol (**7**) (25%) by heating with pyridine hydrochloride.[5] Alternatively, after compound (**5**) was selectively methylated to 2-chloro-3,8-dimethoxyquinoline (**8**) (95%) by the use of dimethyl sulfate-potassium carbonate in acetone, compound (**8**) was converted into 3,8-dimethoxyquinoline (**9**) (65%) and then into **7** (70%) by the treatment with Zn-AcOH and continuously pyridine hydrochloride (Scheme 2).

Scheme 2

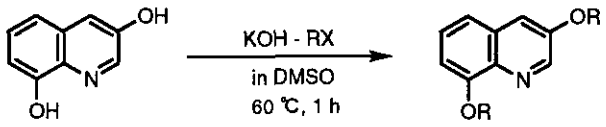


Thus, the prepared jineol was recrystallized from benzene to give brown prisms, mp 155-157 °C which is somewhat different from reported one.[1] However, the spectral data involving ^1H- and ^{13}C-NMR, EI-MS and IR spectra coincided with those reported in the literature.[1]

Furthermore, we prepared various types of the ether derivatives of jineol for biological screening test . These ether derivatives were basically prepared by the reaction of jineol with alkyl halide in the presence of powdered KOH in DMSO[6] in 26-96% yield as shown in Table 1. The biological screening test is under way using these ether derivatives.

Table 1.

Preparation of Jineol Ether by Reaction of Jineol with RX in the Presence of KOH in DMSO



7 **9 - 17**

Compound	RX	Yield (%)
9	MeI	60
10	EtBr	93
11	*n*-BuI	33
12	$Me(CH_2)_4Br$	82
13	$CH_2=CHCH_2Br$	87
14	$PhCH_2Br$	81
15	$PhCH_2CH_2Br$	26
16	PhCH(Br)Me	96
17	$BrCH_2COOEt$	71[a)]

a) Compound **17** was obtained as the carboxylic acid ($R=CH_2COOH$).

EXPERIMENTAL

Melting points were measured on a Yanagimoto micro melting points apparatus and are uncorrected. Spectral data were recorded on the following spectrophotometer and spectrometers : IR spectra, JASCO IR-810 ; ^{1}H-NMR spectra, JEOL GX-400 (400 MHz) and JEOL A-500 (500 MHz) ; ^{13}C-NMR spectra, JEOL GX-400 (100 MHz) and JEOL A-500 (125 MHz) ; MS spectra, JEOL JMS-DX300 for EI-MS and JMS-HX110 for FAB-MS. The H-COSY, CH-COSY, DEPT and HMQC experiments were also used for the assignments of the structures. The chemical shifts are given in the δ scale. Elemental analyses were performed on a Yanaco CHN CORDER MT-6 instrument. Medium pressure liquid chromatography(mplc) was carried out with Yamazen 540 FMI-C pump and Wakogel FC-40 (20-40μm, Wako). Column chromatography was carried out with Kieselgel 60 (70-230 mesh, Merck).

8-Methoxy-2(1*H*)-quinolone (2)

A mixture of 8-hydroxy-2(1*H*)-quinolone (**1**) (17.7 g, 110 mmol), dimethyl sulfate (16.6 g, 130 mmol) and potassium carbonate (30.4 g, 220 mmol) in acetone (1 L) was refluxed for 2 h

under stirring and then the resulting solution was filtered. After evaporation of the solvent, the residue from the filtrate was subjected to column chromatography on silica gel using a mixed solvent of chloroform-methanol (30:1) as the eluent to give 18.3 g (95%) of **2**. The mp and spectral data of this compound coincided with those of the authentic sample.[7]

2-Chloro-8-methoxyquinoline (3)

To a solution of 8-methoxy-2(1*H*)-quinolone (**2**) (21 g, 120 mmol) in chlorobenzene (500 mL), phosphorus oxychloride (17 mL, 180 mmol) and pyridine (3 mL, 36 mmol) were added dropwise and the resulting mixture was refluxed for 2 h. After evaporation of the solvent, a small amount of water was added to the residue and the residue was basified with saturated sodium carbonate solution and extracted with dichloromethane. The residue from the dichloromethane extract was chromatographed with chloroform to give 23 g (99%) of **3**. The mp and spectral data of this compound coincided with those of the authentic sample.[8]

2-Chloro-8-methoxyquinolin-3-boronic acid (4)

LTMP solution was prepared by mixing of 1.57M n-BuLi (8.2 mL, 12.8 mmol), 2,2,6,6,-tetramethylpiperidine (2.2 mL, 12.8 mmol) and THF (25 mL) at -20 °C under nitrogen and further stirring for 0.5 h at rt. Compound (**3**) (2.5 g, 12.8 mmol) in THF (20 mL) was added dropwise at -75 °C under nitrogen with stirring to the LTMP solution and the reaction mixture was further stirred for 1 h at -75 °C. Trimethyl borate (1.45 mL, 12.8 mmol) was then introduced all at once to the reaction mixture which was further stirred for 1 h at -75 °C followed by hydrolysis using aqueous THF (2 mL of water in 10 mL of THF). Water (10 mL) and diethylether (10 mL) were introduced at -10 °C and the resulting aqueous layer was acidified to pH 1 under cooling by 2*N*-hydrochloric acid to afford white precipitates which were filtrated and washed with water. This precipitate was recrystallized from hexane-ethyl acetate to give 2.50 g (82%) of **4** as pale yellow powder, mp >300 °C. *Anal.* Calcd for $C_{10}H_9NO_3BCl$: C, 50.58 ; H, 3.82 ; N, 5.90. Found : C, 50.70 ; H, 3.80 ; N, 5.87. IR (KBr) : 3400, 1578, 1466, 1261, 1116, 756 cm^{-1}. ^{1}H-NMR (DMSO-d_6) : δ 3.97(3H, s, CH_3), 7.22-7.26(1H, m, H-7), 7.51-7.56(2H, m, H-5 and H-6), 8.37(1H, s, H-4), 8.57(2H, br s, OH×2). ^{13}C-NMR (DMSO-d_6) : δ 55.64(q, CH_3), 109.55(d, C-7), 119.11(d, C-5), 127.13(d, C-6), 127.27(s, Ar), 138.60(s, Ar), 143.25(d, C-4), 150.79(s, Ar), 154.07(s, Ar). MS(EI) m/z (%): 192(M^+-$B(OH)_2$, 89), 164(88), 128(100).

2-Chloro-3-hydroxy-8-methoxyquinoline (5)

32% Peracetic acid (4.6 mL, 22.1 mmol) was added dropwise under ice cooling to a solution of compound (**4**) (2.5 g, 10.5 mmol) in acetic acid (40 mL) and then the resulting solution was stirred at rt for 2 h followed by the addition of saturated sodium hydrogen sulfite aqueous solution (10 mL) under ice cooling. After the solvent was evaporated, the residue was extracted with chloroform. This chloroform solution was chromatographed with chloroform to

give 2.0 g (90%) of **5**. This compound was recrystallized from chloroform to give colorless prisms, mp >300 °C. *Anal.* Calcd for $C_{10}H_8NO_2Cl$: C, 57.30 ; H, 3.85 ; N, 6.68. Found : C, 57.32 ; H, 3.84 ; N, 6.75. IR (KBr): 3150, 1364, 1314, 1227, 1125, 753 cm^{-1}. ^{1}H-NMR (DMSO-d_6) : δ 3.94(3H, s, CH_3), 7.01(1H, dd, J=1.1 and 8.1 Hz, H-7), 7.36(1H, dd, J=1.1 and 8.1 Hz, H-5), 7.44(1H, dd, J=7.9 and 7.9 Hz, H-6), 7.62(1H, s, H-4), 11.01(1H, s, OH). ^{13}C-NMR (DMSO-d_6) : δ 55.48(q, CH_3), 106.19(d, C-7), 117.70(d, C-5), 117.74(d, C-4), 127.65(d, C-6), 130.03(s, Ar), 132.72(s, Ar), 140.61(s, Ar), 147.31(s, Ar), 154.26(s, Ar). MS(EI) m/z (%): 209(M^+, 82), 180(100), 115(42), 102(24).

3-Hydroxy-8-methoxyquinoline (6)

Zinc powder (0.5 g, 7.65 mmol) was added all at once to a solution of compound (**5**) (0.75 g, 3.58 mmol), acetic acid (20 mL) and water (1.7 mL) at 70 °C and the mixture was heated at 70 °C for 2 h. After the insoluble materials were filtered, the filtrate was chromatographed by mplc with ethyl acetate and then a mixed solvent of chloroform-methanol (20:1) to give 0.53 g (84%) of **6**. This compound was recrystallized from ethyl acetate-methanol to give colorless prisms, mp 185 °C. *Anal.* Calcd for $C_{10}H_9NO_2 \cdot 0.8H_2O$: C, 63.35 ; H, 5.64 ; N, 7.39. Found : C, 63.26 ; H, 5.62 ; N, 7.36. ^{1}H-NMR (DMSO-d_6) : δ 3.93(3H, s, CH_3), 6.94(1H, dd, J=1.1 and 7.9 Hz, H-7), 7.31(1H, dd, J=1.1 and 7.9 Hz, H-5), 7.40(1H, dd, J=8.1 and 8.1 Hz, H-6), 7.46(1H, d, J=3.1 Hz, H-4), 8.51(1H, d, J=2.7 Hz, H-2), 10.25(1H, br s, OH). ^{13}C-NMR (DMSO-d_6) : δ 55.46(q, CH_3), 105.23(d, C-7), 115.52(d, C-4), 118.20(d, C-5), 127.19(d, C-6), 130.34(s, Ar), 134.03(s, Ar), 141.85(d, C-2), 151.29(s, Ar), 155.14(s, Ar). MS(EI) m/z (%): 175(M^+, 100), 174(83), 146(83), 145(52).

3,8-Dihydroxyquinoline (Jineol) (7)

A mixture of compound (**9**) (0.5 g, 2.65 mmol) and pyridine hydrochloride (1.85 g, 16 mmol) was heated at 200-220 °C for 1 h. After cooling, water was added to give the precipitate which was filtered and washed with water. The precipitate was recrystallized from benzene to give 0.3 g (70%) of **7** as brown prisms, mp 155-157 °C. Compound (**7**) was also obtained from compound (**6**) in a similar manner as from compound (**9**), but the yield was much lower (25%). *Anal.* Calcd for $C_9H_7NO_2$: C, 67.08 ; H, 4.38 ; N, 8.69. Found : C, 67.12 ; H, 4.44 ; N, 8.57. IR (KBr) : 3350-3200, 1578, 1453, 1345, 1218, 754 cm^{-1}. ^{1}H-NMR (CD_3OD) : δ 6.88(1H, dd, J=1.1 and 7.9 Hz, H-7), 7.16(1H, dd, J=1.1 and 7.9 Hz, H-5), 7.31(1H, dd, J=7.9 and 7.9 Hz, H-6), 7.43(1H, d, J=2.8 Hz, H-4), 8.48(1H, d, J=2.8 Hz, H-2). ^{13}C-NMR (CD_3OD) : δ 108.97(d, C-7), 117.22(d, C-4), 117.85(d, C-5), 129.03(d, C-6), 131.81(s, Ar), 134.88(s, Ar), 142.36(d, C-2), 153.01(s, Ar), 154.21(s, Ar). MS(FAB$^+$) : 161(M^++H).

2-Chloro-3,8-dimethoxyquinoline (8)

A mixture of compound (**5**) (0.5 g, 2.39 mmol), dimethyl sulfate (0.27 mL, 2.87 mmol) and potassium carbonate (0.66 g, 4.78 mmol) in acetone (50 mL) was refluxed for 1.5 h under

stirring and then the resulting solution was filtered. After evaporation of the solvent, the residue from the filtrate was recrystallized from hexane to give 0.51 g (95%) of **8** as colorless needles, mp 140-141 °C. *Anal.* Calcd for $C_{11}H_{10}NO_2Cl$: C, 59.07 ; H, 4.51 ; N, 6.26. Found : C, 59.06 ; H, 4.50 ; N, 6.28. IR (KBr) : 3072, 1571, 1362, 1234, 1006, 752 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : δ 4.00(3H, s, 3-OCH_3), 4.04(3H, s, 8-OCH_3), 6.93(1H, dd, J=1.1 and 7.8 Hz, H-7), 7.28(1H, dd, J=1.1 and 7.8 Hz, H-5), 7.38(1H, s, H-4), 7.42(1H, dd, J=8.1 and 8.1 Hz, H-6). ^{13}C-NMR ($CDCl_3$) : δ 55.93(q, 8-OCH_3), 56.14(q, 3-OCH_3), 106.37(d, C-7), 114.09(d, C-4), 118.06(d, C-5), 127.79(d, C-6), 129.88(s, Ar), 133.74(s, Ar), 142.11(s, Ar), 149.60(s, Ar), 154.71(s, Ar). MS(FAB$^+$) : 224(M^++H).

3,8-Dimethoxyquinoline (9)

A mixture of compound (**8**) (0.48 g, 2.29 mmol), zinc powder (0.22 g, 3.44 mmol), acetic acid (20 mL) and water (1.7 mL) was heated under stirring at 70-75 °C for 1.5 h. After filtration and evaporation of the solvents, the residue from the filtrate was purified by mplc with a mixed solvent of hexane-ethyl acetate (5:1-3:1) to give 0.28 g (65%) of **9** . This compound was recrystallized from hexane to give colorless needles, mp 98-99 °C. *Anal.* Calcd for $C_{11}H_{11}NO_2$: C, 69.83 ; H, 5.86 ; N, 7.40. Found : C, 69.93 ; H, 5.92 ; N, 7.41. IR (KBr) : 3450, 1614, 1361, 1213, 1022, 877, 759 cm^{-1}. ^{1}H-NMR (CD_3OD) : δ 3.94(3H, s, 3-OCH_3), 4.03(3H, s, 8-OCH_3), 6.99(1H, dd,J=0.8 and 8.0 Hz, H-7), 7.35(1H, dd, J=0.8 and 8.0 Hz, H-5), 7.45(1H, dd,J=7.9 and 7.9 Hz, H-6), 7.57(1H, d, J=2.8 Hz, H-4), 8.48(1H, d, J=2.8 Hz, H-2). ^{13}C-NMR (CD_3OD) : δ 56.24(q, 8-OCH_3), 56.29(q, 3-OCH_3), 106.89(d, C-7), 114.45(d, C-4), 119.81(d, C-5), 128.94(d, C-6), 131.66(s, Ar), 135.41(s, Ar), 143.04(d, C-2), 155.08(s, Ar), 156.20(s, Ar). MS(EI) m/z (%): 189(M^+, 100), 160(70), 116(51).

General procedure for preparation of jineol ether by reaction of jineol with RX in the presence of KOH in DMSO

A mixture of jineol (**7**) (0.2 g, 1.24 mmol) and powdered KOH (85%, 0.66 g, 9.9 mmol) in DMSO (7 mL) was stirred at rt for 0.5 h under nitrogen followed by the addition of alkyl halide (5.0 mmol) and further stirring at rt for 20 min. The resulting mixture was heated under stirring at 60 °C for 1 h after which the mixture was poured into water (50 mL) and extracted with dichloromethane. After removal of the solvent of the combined organic extracts, the residue was worked up in the manner as shown below, besides the case of 2, 2'- [3, 8-quinolinebis(oxy)]bis-acetic acid (**17**).

3,8-Dimethoxyquinoline (9)

The residue was purified by mplc (hexane : ethyl acetate=5:1) to give 0.14 g (60%) of **9**. The mp and spectral data of this compound coincided with the authentic sample obtained above.

3,8-Diethoxyquinoline (10)

The residue was purified by mplc (hexane : ethyl acetate=10:1) to give 0.25 g (93%) of **10**. This compound was recrystallized from hexane to give colorless prisms, mp 84-85 °C. *Anal.* Calcd for $C_{13}H_{15}NO_2$: C, 71.87 ; H, 6.96 ; N, 6.45. Found : C, 71.89 ; H, 7.04 ; N, 6.38. IR (KBr) : 2986, 1604, 1375, 1348, 1210, 1187, 1041, 764 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : δ 1.49(3H, t, J=7.0 Hz, 3-$OCH_2C\underline{H}_3$), 1.61(3H, t, J=7.0 Hz, 8-$OCH_2C\underline{H}_3$), 4.15(2H, q, J=7.0 Hz, 3-$OC\underline{H}_2CH_3$), 4.30(2H, q, J=7.0 Hz, 8-$OC\underline{H}_2CH_3$), 6.90(1H, dd, J=1.1 and 7.8 Hz, H-7), 7.26(1H, d, J=8.2 Hz, H-5), 7.34(1H, d, J=3.1 Hz, H-4), 7.39(1H, dd, J=7.9 and 7.9 Hz, H-6), 8.71(1H, s, H-2). ^{13}C-NMR ($CDCl_3$) : δ 14.51(q, 8-$OCH_2\underline{C}H_3$), 14.66(q, 3-$OCH_2\underline{C}H_3$), 63.88(t, 8-$O\underline{C}H_2CH_3$), 64.22(t, 3-$O\underline{C}H_2CH_3$), 106.33(d, C-7), 113.61(d, C-4), 118.36(d, C-5), 127.46(d, C-6), 134.84(s, Ar), 142.85(d, C-2), 154.64(s, Ar). MS(FAB$^+$) : 218(M^++H).

3,8-Dibutoxyquinoline (11)

The residue was purified by mplc (hexane : ethyl acetate=10:1) to give 0.11 g (33%) of **11**. This compound gradually crystallized, mp 53-54 °C. *Anal.* Calcd for $C_{17}H_{23}NO_2$: C, 74.69 ; H, 8.48 ; N, 5.12. Found : C, 74.45 ; H, 8.27 ; N, 5.18. IR (KBr) : 2956, 2872, 1610, 1466, 1352, 1215, 1104, 758 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : δ 0.99-1.02(6H, m, CH_3×2), 1.52-1.58(4H, m, CH_2×2), 1.81-1.87(2H, m, CH_2), 1.96-2.02(2H, m, CH_2), 4.06(2H, t, J=6.6 Hz, 3-$OC\underline{H}_2$-), 4.22(2H, t, J=7.0 Hz, 8-$OC\underline{H}_2$-), 6.89(1H, dd, J=1.1 and 8.0 Hz, H-7), 7.24(1H, dd, J=1.1 and 8.0 Hz, H-5), 7.32(1H, d, J=2.8 Hz, H-4), 7.38(1H, dd, J=7.9 and 7.9 Hz, H-6), 8.68(1H, d, J=2.8 Hz, H-2). ^{13}C-NMR ($CDCl_3$) : δ 13.76(q, 8-CH_3), 13.86(q, 3-CH_3), 19.19(t, 8-CH_2), 19.32(t, 3-CH_2), 31.07(t, 8-CH_2), 31.09(t, 3-CH_2), 68.05(t, 8-CH_2), 68.65(t, 3-CH_2), 106.37(d, C-7), 113.17(d, C-4), 118.37(d, C-5), 127.29(d, C-6), 130.43(s, Ar), 135.38(s, Ar), 143.22(d, C-2), 153.03(s, Ar), 155.13(s, Ar). MS(FAB$^+$) : 274(M^++H).

3,8-Dipentyloxyquinoline (12)

The residue was purified by mplc (hexane : ethyl acetate=10:1) to give 0.30 g (82%) of **12**. This compound was recrystallized from hexane to give colorless prisms, mp 56-57 °C. *Anal.* Calcd for $C_{19}H_{27}NO_2$: C, 75.71 ; H, 9.03 ; N, 4.65. Found : C, 75.69 ; H, 9.09 ; N, 4.64. IR (KBr) : 2942, 2870, 1607, 1466, 1356, 1207, 1018, 758 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : δ 0.93-0.96(6H, m, CH_3×2), 1.39-1.53(8H, m, CH_2×4), 1.84-1.89(2H, m, CH_2), 2.00-2.06(2H, m, CH_2), 4.08(2H, t, J=6.6 Hz, 3-$OC\underline{H}_2$-), 4.22(2H, t, J=7.0 Hz, 8-$OC\underline{H}_2$-), 6.91(1H, dd, J=1.1 and 7.8 Hz, H-7), 7.26(1H, d, J=7.9 Hz, H-5), 7.38(1H, s, H-4), 7.39(1H, dd, J=7.9 and 7.9 Hz, H-6), 8.72(1H, d, J=2.1 Hz, H-2). ^{13}C-NMR ($CDCl_3$) : δ 13.92(q, 8-CH_3), 13.95(q, 3-CH_3), 22.38(t, 8-CH_2), 22.46(t, 3-CH_2), 28.10(t, CH_2), 28.17(t, CH_2), 28.68(t, CH_2), 28.70(t, CH_2), 68.54(t, 8-$O\underline{C}H_2$-), 69.07(t, 3-$O\underline{C}H_2$-), 106.64(d, C-7), 114.16(d, C-4), 118.28(d, C-5), 127.62(d, C-6), 130.46(s, Ar), 134.47(s, Ar), 142.62(d, C-2), 153.06(s, Ar), 154.68(s, Ar). MS(FAB$^+$) : 302(M^++H).

3,8-Diallyloxyquinoline (13)

The residue was purified by mplc (hexane : ethyl acetate=10:1) to give 0.26 g (87%) of **13.** This pale yellow oil partly crystallized. *Anal.* Calcd for $C_{15}H_{15}NO_2 \cdot 0.1H_2O$: C, 74.11 ; H, 6.30 ; N, 5.76. Found : C, 74.07 ; H, 6.34 ; N, 5.49. IR (Nujol) : 1604, 1356, 1235, 1212, 1185, 1008, 913, 755 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : δ 4.66-4.68(2H, m, 3-OC$\underline{H}_2$-), 4.84-4.86(2H, m, 8-OC$\underline{H}_2$-), 5.31-5.37(2H, m, 3-CH_2=), 5.45-5.50(2H, m, 8-CH_2=), 6.06-6.13(1H, m, 3-CH=), 6.17-6.25(1H, m, 8-CH=), 6.93(1H, d, J=8.9 Hz, H-7), 7.27(1H, d, J=8.9 Hz, H-5), 7.38-7.41(2H, m, H-4 and H-6), 8.74(1H, d, J=2.4 Hz, H-2). ^{13}C-NMR ($CDCl_3$) : δ 69.15(t, 8-O$\underline{C}H_2$-), 69.84(t, 3-O$\underline{C}H_2$-), 107.37(d, C-7), 114.48(d, C-4), 118.20(t, 8-CH_2=), 118.44(t, 3-CH_2=), 118.75(d, C-5), 127.51(d, C-6), 130.29(s, Ar), 132.23(d, 8-CH=), 133.18(d, 3-CH=), 134.83(s, Ar), 142.74(d, C-2), 152.51(s, Ar), 154.19(s, Ar). MS(FAB$^+$) : 242(M^++H).

3,8-Dibenzyloxyquinoline (14)

The residue was purified by mplc (hexane : ethyl acetate=10:1) to give 0.34 g (81%) of **14**. This pale yellow oil gradually crystallized , mp 78-79 °C. *Anal.* Calcd for $C_{23}H_{19}NO_2$: C, 80.92 ; H, 5.61 ; N, 4.10. Found : C, 80.77 ; H, 5.73 ; N, 3.84. IR (KBr) : 3036, 1604, 1499, 1368, 1218, 1180, 754, 698 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : δ 5.18(2H, s, 3-CH_2), 5.41(2H, s, 8-CH_2), 6.90(1H, dd, J=0.9 and 7.6 Hz, H-7), 7.24-7.51(13H, m, Ar-H), 8.82(1H, s, H-2). ^{13}C-NMR ($CDCl_3$) : δ 70.43(t, 8-CH_2), 70.77(t, 3-CH_2), 108.07(d, C-7), 114.65(d, C-4), 118.92(d, C-5), 127.14(d, Ar), 127.53(d, Ar), 127.76(d, Ar), 128.33(d, Ar), 128.46(d, Ar), 128.55(d, Ar), 128.71(d, Ar), 130.31(s, Ar), 135.02(s, Ar), 135.85(s, Ar), 136.93(s, Ar), 142.86(d, C-2), 152.68(s, Ar), 154.25(s, Ar). MS(FAB$^+$) : 342(M^++H).

3,8-Diphenethyloxyquinoline (15)

The residue was purified by mplc (hexane : ethyl acetate=10:1) to give 0.12 g (26%) of **15**. This compound gradually crystallized, mp 90-91 °C. *Anal.* Calcd for $C_{25}H_{23}NO_2$: C, 81.27 ; H, 6.27 ; N, 3.79. Found : C, 81.24 ; H, 6.40 ; N, 3.75. IR (KBr) : 2868, 1602, 1497, 1365, 1211, 1184, 1025, 751, 700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : δ 3.18(2H, t, J=7.0 Hz, 3-$OCH_2C\underline{H}_2$-), 3.36(2H, t, J=7.9 Hz,8-$OCH_2C\underline{H}_2$-), 4.31(2H, t, J=7.0 Hz, 3-OC$\underline{H}_2$-), 4.42(2H, t, J=7.9 Hz, 8-OC$\underline{H}_2$-), 6.91(1H, dd, J=0.9 and 7.6 Hz, H-7), 7.22-7.40(13H, m, Ar-H), 8.74(1H, d, J=2.4 Hz, H-2). ^{13}C-NMR ($CDCl_3$) : δ 35.58(t, 8-$OCH_2\underline{C}H_2$-), 35.63(t, 3-$OCH_2\underline{C}H_2$-), 69.24(t, 3-O$\underline{C}H_2$-), 69.89(t, 8-O$\underline{C}H_2$-), 107.02(d, C-7), 114.43(d, C-4), 118.67(d, C-5), 126.54(d, Ar), 126.73(d, Ar), 127.72(d, Ar), 128.56(d, Ar), 128.62(d, Ar), 128.72(d, Ar), 128.84(d, Ar), 128.97(d, Ar), 129.07(d, Ar), 129.12(d, Ar), 130.41(s, Ar), 137.65(s, Ar), 137.88(s, Ar), 142.58(d, C-2), 152.82(s, Ar), 154.28(s, Ar). MS(FAB$^+$) : 370(M^++H).

3,8-Di-α-methylbenzyloxyquinoline (16)

The residue was purified by mplc (hexane : ethyl acetate=10:1) to give 0.44 g (96%) of **16** as yellow oil. *Anal.* Calcd for $C_{25}H_{23}NO_2$: C, 81.27 ; H, 6.27 ; N, 3.79. Found : C, 81.27 ; H, 6.51 ; N, 3.53. IR (Nujol) : 1604, 1453, 1345, 1206, 1182, 1069, 758, 698 cm^{-1}. ^{1}H-NMR ($CDCl_3$) : δ

1.49(3H, s, 3-CH_3), 1.50(3H, s, 8-CH_3), 1.72(1H, q, J=3.2 Hz, 3-C<u>H</u>-Ph), 1.84(1H, q, J=3.2 Hz, 8-C<u>H</u>-Ph), 6.70(1H, dd, J=0.8 and 7.8 Hz, H-7), 7.06(1H, d, J=7.9 Hz, H-5), 7.15(1H, dd, J=7.9 and 7.9 Hz, H-6), 7.18-7.46(11H, m, Ar-H), 8.83(1H, d, J=3.1 Hz, H-2). ^{13}C-NMR ($CDCl_3$) : δ 24.28(q, 8-CH_3), 24.32(q, 3-CH_3), 24.83(d, 8-<u>C</u>H-CH_3), 25.15(d, 3-<u>C</u>H-CH_3), 109.48(d, C-7), 116.80(d, C-4), 118.60(d, C-5), 125.35(d, Ar), 125.55(d, Ar), 127.32(d, Ar), 127.40(d, Ar), 127.88(d, C-6), 128.45(d, Ar), 128.58(d, Ar), 128.82(d, Ar), 128.84(d, Ar), 130.24(s, Ar), 141.92(s, Ar), 142.97(s, Ar), 143.03(s, Ar), 143.13(d, C-2), 145.87(s, Ar), 151.75(s, Ar). MS(FAB$^+$) : 370(M^++H).

2,2'-[3,8-quinolinebis(oxy)]bis-acetic acid (17)

The aqueous layer in General Procedure was evaporated off to give the residue which was washed with diethyl ether. The aqueous solution of the residue was made pH 4 using 15% hydrochloric acid solution to afford white precipitate which was recrystallized from water to give 0.24 g (71%) of **17** as colorless prisms. mp >250 °C. *Anal.* Calcd for $C_{13}H_{11}NO_6 \cdot 0.2H_2O$: C, 55.60 ; H, 4.09 ; N, 4.99. Found : C, 55.49 ; H, 4.14 ; N, 4.95. IR (KBr) : 3450, 1718, 1571, 1375, 1291, 1264, 1053, 802 cm^{-1}. ^{1}H-NMR (DMSO-d_6) : δ 3.00-4.00(2H, br s, OH×2), 4.89 (4H, s, CH_2×2), 6.96(1H, dd, J=3.5 and 5.6 Hz, H-7), 7.42-7.46(2H, m, H-5 and H-6), 7.70(1H, d, J=2.7 Hz, H-4), 8.64(1H, d, J=2.7 Hz, H-2). ^{13}C-NMR (DMSO-d_6) : δ 64.70(t, 8-CH_2), 65.37(t, 3-CH_2), 107.88(d, C-7), 113.98(d, C-4), 119.44(d, C-5), 127.39(d, C-6), 129.92(s, Ar), 134.77(s, Ar), 142.07(d, C-2), 151.70(s, Ar), 153.67(s, Ar), 169.58(s, C=O), 170.04(s, C=O). MS(FAB$^+$) : 278(M^++H).

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