HETEROCYCLES, Vol. 57, No. 8, 2002, pp. 1433 - 1444, Received, 30th April, 2002

A SYNTHESIS OF OXYGENATED 1-AZAANTHRAQUINONES *VIA* DIELS-ALDER REACTION OF 2,4-DIOXYGENATED QUINOLINE-5,8-DIONES WITH 1-METHOXY-3-TRIMETHYLSILYLOXY-1,3-BUTADIENE

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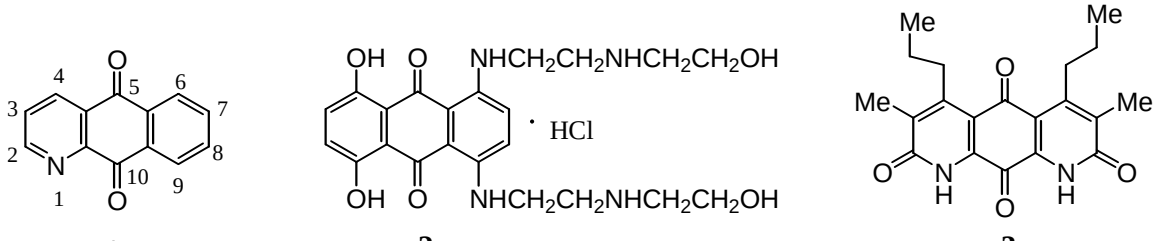
Abstract – Diels-Alder reaction of 2,4-dioxygenated quinoline-5,8-diones (**7a**, **b** and **8**) with 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (**11**) proceeded in a regio- and stereoselctive manner to give 2,4,6,8-tetraoxygenated 1-azaanthraquinoes (**12a**, **b** and **18**) in good to moderate yields, respectively. The results demonstrated that Diels-Alder reaction of the 2,4-dioxygenated quinolone-5,8-diones with the activated diene provides a useful method for synthesizing highly oxygenated 1-azaanthraquinones.

1-Azaanthraquinone (benzo[*g*]quinoline-5,10-dione) (**1**) derivatives, in particular, highly oxygenated ones, can be considered to have potential anticancer and anti-bacterial activities due to close structural analogies with metoxantrone (**2**)[1] and diazaquinomicin A (**3**).[2] Many compounds containing the similar ring systems were found in biologically active sea alkaloids.[3] Recently, Potts, *et al.* [4] and we[5] demonstrated that Diels-Alder (D-A) reaction of quinolinequinones (quinoline-5,8-diones) with 1,3-butadienes proceeded in a regioselective manner, providing an effective method for the construction of the ring system. This method has been successfully



1 **2** **3**

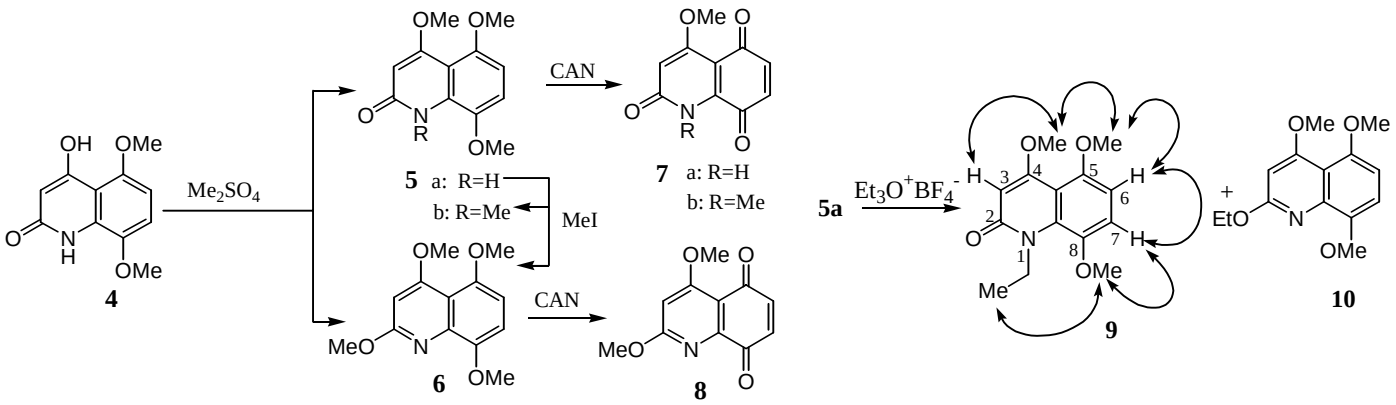
Scheme 1

applied to the syntheses of the similar polycyclic nitrogen heterocycles such as 1,8-diaza,[6] and 1,5-diazaanthraquinone,[7] and benz[*b*]acridone,[8] and pyrido[3,2-*b*]acridone[8] derivatives. In this paper we describe the D-A reaction of 2,4-dioxygenated quinolinequinones with 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (**11**) for preparation of highly oxygenated 1-azaanthraquinone derivatives and, at the same time, in an attempt to reveal the effect of oxy-substituents of the 2 and 4-positions on the reactivity of quinolinequinones and the regiochemistry of this reaction.

Preparation of 4-Methoxy-1*H*-quinoline-2,5,8-trione (7a), 4-Methoxy-1-methyl-1*H*-quinoline-2,5,8-trione (7b) and 2,4-Dimethoxyquinoline-5,8-dione (8)

2,4-Dioxygenated quinolinequinones (**7a-b** and **8**) were prepared as follows. Methylation of 4-hydroxy-5,8-dimethoxy-1*H*-quinolin-2-one (**4**)[9] with excess amount of dimethyl sulfate in the presence of potassium hydroxide in acetone gave 4-methoxy-1*H*-quinolin-2-one (**5a**), *N*-methyl-4-methoxy-1*H*-quinolin-2-one (**5b**) and 2,4-dimethoxyquinoline (**6**) in 46, 10 and 28% yields, respectively. When the methylation of **4** was carried out with equimolar amount of dimethyl sulfate in the presence of potassium carbonate, **5a** was selectively obtained in 76% yield. Reaction of **5a** with methyl iodide gave **5b** in 43% yield, together with **6** (30%).

In order to obtain the structural evidence of **5a** we carried out the ethylation reaction of **5a** with triethyloxonium fluoroborate (Meerwein reagent) which yielded *N*-ethyl-4,5,8-trimethoxy-1*H*-quinolin-2-one (**9**) (33% yield) and 2-ethoxy-4,5,8-trimethoxyquinoline (**10**) (9% yield). The 2D-nuclear Overhauser and exchange spectroscopy (NOESY) of **9** clearly revealed two groups of correlated cross peaks. One is between the 3-aromatic proton and the proton of 4-OMe group, and the other is between the methyl proton of the *N*-ethyl group and the proton of the 4-OMe group through the proton of 8-OMe, and the 7- and 6- aromatic protons, and 5-OMe as shown in Scheme 2.

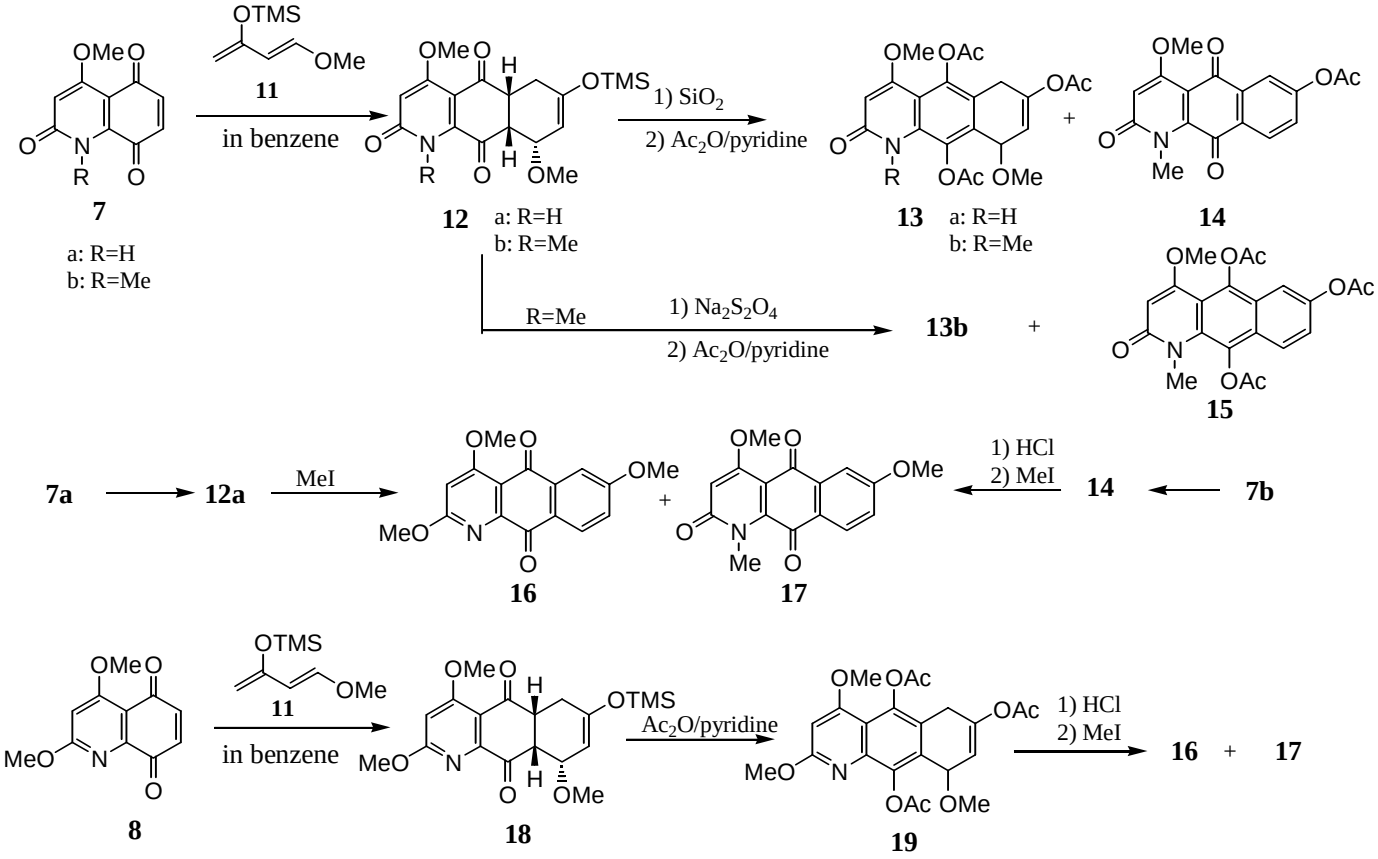


Scheme 2

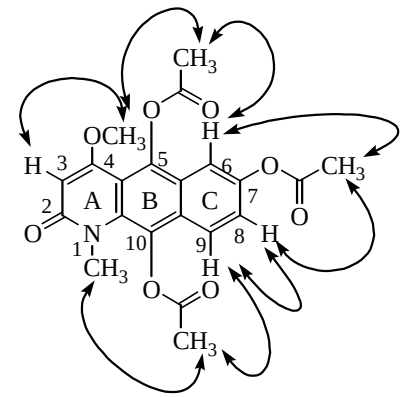
Oxidation of **5a**, **5b** and **6** with cerium ammonium nitrate (CAN) gave the corresponding quinolinequinones (**7a**, **7b**, and **8**) in 99, 91 and 97% yields, respectively.

Diels-Alder Reaction of 7b

A mixture of **7b** and **11** in benzene was heated at 80°C for 30 min in a sealed tube under an argon atmosphere to give the D-A adduct (**12b**) as a sole product in 81% yield. The ^{1}H-NMR spectrum exhibited the new signal originated from the diene of OTMS (δ 0.28), OMe (δ 3.05), two methylene protons (δ 2.12 and 2.99) and three methine protons (δ 3.26, 3.39, 4.20), indicating that the product (**12b**) was the desired [4+2] adduct. The coupling constants between the ring juncture protons ($J_{5a\text{-}9a}$=7 Hz) and between the 9 and 9a protons ($J_{9\text{-}9a}$=5 Hz) suggested that addition of the diene proceeded in an *endo*-manner.



Scheme 3



15 Figure 1

The regiochemistry of this addition was clarified as follows. Heating of **12b** in toluene in the presence of silica gel at 110°C for 2 h followed by acetylation of the crude product afforded the triacetoxy derivative (**13b**) and the C ring aromatized product (**14**) in 65 and 10% yields, respectively. Treatment of **12b** with sodium hydrosulfite followed by acetylation gave the other triacetate (**15**) (12%) together with **13b** (26%).

The cross peaks observed in the 2D-NOESY of **15** revealed a correlation between the 3-aromatic proton (δ 6.02) and the 7-OAc (δ 2.36), through the signal for 4-OMe (δ 3.92), 5-OAc (δ 2.48) and 6-aromatic proton (δ 7.64).

Further correlation was observed between 7-OAc and the *N*-Me proton (δ 3.73), through the signal for 8-aromatic proton (δ 7.37), 9-aromatic proton (δ 7.79) and 10-OAc (δ 2.51) as shown in Figure 1. The observations confirmed that the OAc group in C ring, originated from the diene moiety, was positioned at C-7.

Diels-Alder Reaction of 7a

D-A reaction of **7a** with the diene (**11**) was carried out in benzene at 80°C for 30 min to give the D-A adduct (**12a**) in 63% yield. The product (**12a**) was fairly unstable, and readily decomposed under heating in toluene in the presence of silica gel to give no characterizable product. However, the D-A reaction mixture was treated with sodium hydrosulfite followed by acetylation to give a triacetate (**13a**), though in only 2% yield. Methylation of **12a** with methyl iodide yielded 2,4,7-trimethoxy derivative (**16**) and *N*-methyl-4,7-dimethoxy derivative (**17**) in 14 and 6% yields, respectively.

Diels-Alder Reaction of 8

The reaction of **8** with **11** under similar reaction conditions gave the D-A adduct (**18**) in 56% yield. The product (**18**) was converted into the triacetate (**19**) by heating in toluene in the presence of silica gel followed by acetylation.

The evidence that the D-A reactions of **7a**, **7b** and **8** with the diene (**11**) proceeded in a same regiochemical manner, was obtained by chemical means, as shown in Scheme 3. The compound (**14**) obtained from **7b** was converted into **17** by hydrolysis with hydrochloric acid followed by methylation with methyl iodide. The product (**19**) derived from **8** was similarly converted into **16** and **17** by hydrolysis and methylation. The compounds (**16**) and (**17**) were identical with the products derived from **12a** described above, respectively.

D-A reaction of 2,4-dioxygenated quinolinequinones (**7a**, **b**) and (**8**) with 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (**11**) proceeded in a same regio- and stereoselctive manner to produce 2,4,6,8-tetraoxgenated 1-azaanthraquines (**12a**, **b**) and (**18**) in good to moderate yields. The regiochemistry in the D-A reaction of 1*H*-quinoline-2,5,8-triones (**7a**) and (**7b**) is identical with that of 2,4-dimethoxyquinolinequinone (**8**) and non-substituted quinolinequinone.[4] This result demonstrated that the carbonyl group at the 2-position of quinoline ring did not exert any effect on the regioselectivity of this D-A reaction. Thus, the D-A reaction of 2,4-dioxygenated quinolonequinone with the activated diene provides a useful method for synthesizing highly oxygenated 1-azaanthraquinones.

EXPERIMENTAL

Unless otherwise stated, the following procedures were adopted. All melting points were taken on

a Yanagimoto micro hot-stage melting point apparatus (Yanagimoto MP type) and are uncorrected. IR spectra were measured with a JASCO FT/IR-5000 as KBr disks and values are given in cm^{-1}. UV spectra were measured with a Hitachi U-3200 spectrophotometer in dioxane solution and values are given in ν_{max} nm (ε). NMR spectra were taken on a JEOL JNM-α500 (^1H; 500 MHz, ^{13}C; 125 MHz) or a JNM-AL-300 (^1H; 300 MHz, ^{13}C; 75 MHz) NMR spectrometer in $CDCl_3$ solution using tetramethylsilane (TMS) as an internal standard. The chemical shifts are given in δ values. Low-resolution MS spectra (LRMS) were taken on a JMS-AM20, and high-resolution MS spectra (HRMS) was taken on a JMS-D300 spectrometer at 70 eV or at 270 eV[chemical ionization MS (CIMS), reactant gas: *iso*-butane] using a direct inlet system. Elemental analyses were recorded on a Yanaco CHN-corder MT-3. For column chromatography, silica gel (Mallinckrodt type 150A or Wako-Gel C-200) was used. Thin layer chromatography (TLC) was performed on Merck precoated silica gel 60 F254 plates. Medium-pressure liquid chromatography (MPLC) was performed with Kusano CIG pre-packed silica gel columns, and peaks were detected with Shodex SE-12 RI detector. All organic extracts were washed with brine and dried over Na_2SO_4 before concentration *in vacuo*.

Methylation of 4-Hydroxy-5,8-dimethoxy-1*H*-quinolin-2-one (4)

i) A suspension of **4** (500 mg, 2.26 mmol), 10% NaOH solution(2 mL) and Me_2SO_4 (2.6 mL, 22.5 mmol), in acetone (50 mL) was stirred at rt for 24 h. The reaction mixture was extracted with $CHCl_3$. After removal of the solvent *in vacuo*, the residue was purified by column chromatography over silica gel. Elution with AcOEt-hexane (1:1) and crystallization from $CHCl_3$-Et_2O gave **5a** (244 mg, 46%), **6** (165 mg, 28%) and **5b** (59 mg, 10%).

ii) A suspension of **4** (500 mg, 2.26 mmol), K_2CO_3 (0.3 g, 2.26 mmol) and Me_2SO_4 (0.2 mL, 2.26 mmol), in acetone (50 mL) was stirred at rt for 2.5 h and further refluxed for 2 h. The reaction mixture was extracted with $CHCl_3$. After removal of the solvent *in vacuo*, and the residue was chromatographed over silica gel. Elution with AcOEt-hexane (1:1) and crystallization from $CHCl_3$-Et_2O gave **5a** (404 mg, 76%) and **6** (24 mg, 4%).

4,5,8-Trimethoxy-1*H*-quinolin-2-one (5a): Colorless prisms, mp 170-172°C. IR: 1686, 1649, 1638, 1562. UV: 236 (19300), 257 (16700), 277 (6600), 288 (7700), 298 (6200), 329 (2300). ^1H-NMR (300 MHz): 3.86 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 5.92 (1H, s, 3-H), 6.56 (1H, d, *J*=9 Hz, Ar-H), 6.90 (1H, d, *J*=9 Hz, Ar-H), 8.91 (1H, br s, NH). ^{13}C-NMR (300 MHz): 56.1 (OCH_3), 56.2 (OCH_3), 56.7 (OCH_3), 96.6 (C3), 103.5 (C6), 106.4 (C4a), 110.7 (C7), 130.3 (C8a), 139.6 (C8), 151.3 (C5), 162.9 (C4), 166.6 (C2). LRMS (*m/z*): 235 (M^+), 220 (base peak). *Anal.* Calcd for $C_{12}H_{13}NO_4 \cdot 1/4H_2O$: C, 60.12; H, 5.64; N, 5.85. Found: C, 59.98; H, 5.63; N, 5.90.

4,5,8-Trimethoxy-1-methyl-1*H*-quinolin-2-one (5b): Colorless prisms, mp 162-163°C. IR: 1692,

1578. UV: 232 (32000), 257 (17200), 293 (7100), 336 (2800). ^{1}H-NMR (90 MHz): 3.82 (6H, s, 5-OCH_3, NCH_3), 3.86 (3H, s, 8-OCH_3), 3.90 (3H, s, 4-OCH_3), 6.01 (1H, s, 3-H), 6.67 (1H, d, *J*=9 Hz, 7-H), 7.05 (1H, d, *J*=9 Hz, 6-H). ^{13}C-NMR (90 MHz) : 36.0 (NCH_3), 56.1 (OCH_3), 57.4 (OCH_3), 57.7 (OCH_3), 97.0 (C3), 106.2 (C6), 109.6 (C4a), 116.1(C7), 134.2 (C8a), 143.3 (C8), 152.4 (C5), 164.6 (C4), 164.9 (C2). LRMS (*m/z*):249 (M^+), 234 (base peak). *Anal.* Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.47; H, 6.12; N, 5.63.

1,4,5,8-Tetramethoxyquinoline (6): Colorless prisms, mp 145-149°C (lit.,[10] mp 146-147°C) . IR: 1603, 1522. UV: 247 (27800), 294 (4700), 323 (3600). ^{1}H-NMR (90 MHz): 3.90 (3H, s, OCH_3), 3.98 (3H, s, OCH_3), 4.00 (3H, s, OCH_3), 4.10 (3H, s, OCH_3), 6.28 (1H, s, 3-H), 6.68 (1H, d, *J*=9 Hz, Ar-H), 6.96 (1H, d, *J*=9 Hz, Ar-H). ^{13}C-NMR (90 MHz): 53.1 (OCH_3), 55.9 (OCH_3), 56.6 (OCH_3), 56.7 (OCH_3), 91.3 (C3), 104.4 (C6), 109.8 (C7), 111.5 (C4a), 140.5 (C8a), 148.4 (C5), 150.8 (C8), 163.1 (C4), 165.9 (C2). LRMS (*m/z*):249 (M^+), 234 (base peak). *Anal.* Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found : C, 62.83; H, 5.94; N, 5.46.

Methylation of 5a

A suspension of **5a** (500mg, 2.13 mmol) and K_2CO_3 (118 mg, 8.52 mmol) and MeI (120mg, 8.52 mmol), in DMF (4 mL) was stirred at room temperature for 3.5 h, under an Ar atmosphere. The reaction mixture was extracted with AcOEt. After removal of the solvent *in vacuo*, and the residue was chromatographed over silica gel. Elution with AcOEt-hexane (1:1) and crystallization from $CHCl_3$-Et_2O gave **5b** (228 mg, 43%) and **6** (159 mg, 30%).

Ethylation of 5a with Meerwein reagent

A suspension of **5a** (50 mg, 0.2 mmol) and Meerwein reagent (50 mg, 0.25 mmol), in dry $CHCl_3$ (5 mL) was stirred at rt for 18 h, under an Ar atmosphere. Cold 5% Na_2CO_3 solution was added to the reaction mixture, which was then extracted with $CHCl_3$. After removal of the solvent *in vacuo*, and the residue was purified by column chromatography (AcOEt) to gave 1-ethyl-4,5,8-trimethoxy-1*H*-quinolin-2-one (**9**) (19 mg, 33%) and 2-ethoxy-4,5,8-trimethoxyquinoline (**10**) (5 mg , 9%).

9: Colorless prisms from AcOEt-Et_2O, mp 118-120°C. IR: 1642, 1597, 1578. UV: 229 (29900), 258 (16900), 293 (6600), 336 (3000). ^{1}H-NMR (300 MHz): 1.38 (3H, t, *J*=7 Hz, $NCH_2C\underline{H}_3$), 3.85 (3H, s, 5-OCH_3), 3.87 (3H, s, 8-OCH_3), 3.89 (3H, s, 4-OCH_3), 4.46 (2H, q, *J*=7 Hz, $NC\underline{H}_2CH_3$), 6.02 (1H, s, 3-H), 6.68 (1H, d, *J*=9 Hz, 6-H), 7.03 (1H, d, *J*=9 Hz, 7-H). ^{13}C-NMR (300 MHz): 15.3 ($NCH_2\underline{C}H_3$), 43.0 ($N\underline{C}H_2CH_3$), 56.0 (OCH_3), 57.1 (OCH_3), 57.5 (OCH_3), 97.2 (C3), 106.1 (C6), 109.8 (C4a), 114.8 (C7), 133.2 (C8a), 143.0 (C8), 152.3 (C5), 164.4 (C4), 164.7 (C2). LRMS (*m/z*): 263 (M^+), 220 (base peak). HRMS *m/z* (M^+): Calcd for $C_{14}H_{17}NO_4$: 263.1155. Found: 263.1172.

10: Colorless prisms from AcOEt-Et_2O, mp 95-96°C. IR: 1612, 1600, 1527. UV: 212 (27700), 247

(25000), 288 (4000), 323 (3200). ^{1}H-NMR (300 MHz): 1.44 (3H, t, *J*=7 Hz, $OCH_2C\underline{H}_3$), 3.89 (3H, s, 5-OCH_3), 3.98 (3H, s, 8-OCH_3), 3.99 (3H, s, 4-OCH_3), 4.57 (2H, q, *J*=7 Hz, $OC\underline{H}_2CH3$), 6.28 (1H, s, 3-H), 6.67 (1H, d, *J*=9 Hz, 6-H), 6.90 (1H, d, *J*=9 Hz, 7-H). ^{13}C-NMR (300 MHz): 14.6 ($OCH_2\underline{C}H_3$), 56.1 (OCH_3), 56.8 (OCH_3), 56.9 (OCH_3), 61.6 ($O\underline{C}H_2CH_3$), 91.6 (C3), 104.3 (C6), 109.9 (C7), 111.6 (C4a), 140.7 (C8a), 148.5 (C8), 150.9 (C5), 163.0 (C4), 165.9 (C2). LRMS (*m/z*): 263 (M^+), 234 (base peak). HRMS *m/z* (M^+): Calcd for $C_{14}H_{17}NO_4$: 263.1155. Found: 263.1139.

CAN Oxidation of 5a-b and 6

To a solution of **5a-b** and **6** (0.4 mmol) in MeCN-H_2O (2:1, 15 mL) and CAN (1.1 g, 2 mmol) in MeCN-H_2O (2:1, 15 mL) was added with stirring at 0°C for 15 min. The reaction mixture was extracted with $CHCl_3$. After removal of the solvent *in vacuo*, the product was washed with Et_2O to give **7a**, **b** and **8.**

4-Methoxy-1*H*-quinoline-2,5,8-trione (7a) Yield, 99%. Yellow needles, mp 178-181°C. IR: 1654, 1646, 1637. UV: 260 (10000). ^{1}H-NMR (300 MHz): 3.97 (3H, s, 4-OCH_3), 6.16 (1H, s, 3-H), 6.85 (1H, d, *J*=10 Hz, 6-H), 6.92 (1H, d, *J*=10 Hz, 7-H). ^{13}C-NMR (300 MHz) : 56.8 (OCH_3), 102.5 (C3), 108.7 (C4a), 132.5 (C6), 138.8 (C8a), 140.5 (C7), 162.0 (C4), 166.5 (C2), 179.1 (s), 180.8 (s).

4-Methoxy-1-methyl-1*H*-quinoline-2,5,8-trione (7b) Yield, 91%. Yellow needles, mp 176-179°C. IR: 1649, 1622, 1586. UV: 215 (26700), 263 (10500). ^{1}H-NMR (90 MHz): 3.83 (3H, s, NCH_3), 3.91 (3H, s, OCH_3), 6.21 (1H, s, 3-H), 6.76 (2H, s, Ar-H). ^{13}C-NMR (300 MHz): 33.8 (NCH_3), 56.5 (OCH_3), 101.4 (C3), 111.3 (C4a), 134.7 (C6), 137.9 (C7), 142.2 (C8a), 163.2 (s), 164.7 (s), 181.7 (s), 182.0 (s). LRMS (*m/z*) : 219 ($M^{+\cdot}$ base peak). *Anal.* Calcd for $C_{11}H_9NO_4$: C, 60.27; H, 4.14; N, 6.39. Found: C, 59.99; H, 4.27; N, 6.39.

2,4-Dimethoxyquinoline-2,4-dione (8) Yield, 97%. Yellow prisms, mp 198-200°C. IR: 1654, 1589. UV: 249 (18200), 342 (2200). ^{1}H-NMR (300 MHz): 4.00 (3H, s, OCH_3), 4.12 (3H, s, OCH_3), 6.48 (1H, s, 3-H), 6.83 (1H, d, *J*=10 Hz, 6-H), 6.93 (1H, d, *J*=10 Hz, 7-H). ^{13}C-NMR (300 MHz): 54.6 (OCH_3), 56.6 (OCH_3), 97.2 (C3), 115.3 (C4a), 135.7 (C6), 139.6 (C7), 148.7 (C8a), 167.5 (s), 167.9 (s), 183.4 (s), 183.7 (s). LRMS (*m/z*): 219 (M^+, base peak). *Anal.* Calcd for $C_{11}H_9NO_4$: C, 60.27; H, 4.14; N, 6.39. Found: C, 60.05; H, 4.26; N, 6.32.

D-A reaction of 7b with 11

i) A solution of **7b** (180 mg, 0.82 mmol) and **11** (284 mg, 1.64 mmol) in benzene (20 mL) was heated at 80°C for 30 min in a sealed tube under an Ar atmosphere. After removal of the solvent *in vacuo*, the residue was crystallized from $CHCl_3$-Et_2O to give 5a,6,9,9a-tetrahydro-4,9-dimethoxy-1-methyl-7-trimethylsilyloxy-1*H*-benzo[*g*]quinoline-2,5,10-trione (**12b**) (259 mg, 81%), as colorless needles, mp 118-120°C. IR: 1698, 1659. UV : 252 (27200), 351 (4200). ^{1}H-NMR (500 MHz): 0.28 (9H, s, OTMS), 2.12 (1H, dd, *J*=18, 7 Hz, 6-H), 2.99 (1H, d, *J*=18 Hz, 6-H), 3.05

(3H, s, 9-OCH_3), 3.26 (1H, dd, *J*=7, 5 Hz, 9a-H), 3.39 (1H, t, *J*=7 Hz, 5a-H), 3.75 (3H, s, NCH_3), 3.86 (3H, s, 4-OCH_3), 4.20 (1H, t, *J*=5 Hz, 9-H), 5.14 (1H, d, *J*=5 Hz, 8-H), 6.15 (1H, s, 3-H). ^{13}C-NMR (500 MHz): 0.20 (OTMS), 26.4 (C6), 33.7 (C5a), 44.3 (C9a), 51.4 (OCH_3), 55.3 (OCH_3), 56.3 (OCH_3), 74.5 (C9), 100.6 (C3), 101.1 (C8), 117.2 (C7), 145.8 (C4a), 154.1 (C10a), 163.5 (C4), 164.2 (C2), 190.6 (C5), 193.8 (C10). CIMS (*m/z*): 392 (MH^+), 320 (base peak). *Anal.* Calcd for $C_{19}H_{25}NO_6Si$: C, 58.29; H, 6.43; N, 3.58. Found : C, 58.20; H, 6.36; N, 3.75.

ii) The product (**12b**) (242 mg, 0.62 mmol) was dissolved in dioxane (10 mL) and $Na_2S_2O_4$ (538 mg, 3.2 mmol) was added to the solution at 0°C and the whole was stirred for 10 min. Water was added to the reaction mixture and the mixture was extracted with $CHCl_3$. After removal of the solvent *in vacuo*, the residue was treated with acetic anhydride-pyridine (1:2) solution (3 mL) at rt for 16 h. The reaction mixture was diluted with $CHCl_3$ and washed with 5% $NaHCO_3$ solution and 5% HCl solution and the organic layer was dried over Na_2SO_4. After removal of the solvent *in vacuo*, the residue was purified by column chromatography (AcOEt-hexane=1:1) to give 5,7,10-triacetoxy-4-methoxy-1-methyl-1*H*-benzo[*g*]quinolin-2-one (**15**) (31 mg, 12 %) and 5,7,10-triacetoxy-6,9-dihydro-4,9-dimethoxy-1-methyl-1*H*-benzo[*g*]quinolin-2-one (**13b**) (72 mg, 26%).

15: Yellow prisms from $CHCl_3$-Et_2O, mp 191-193°C. IR: 2360, 1772, 1654. UV : 261 (31000), 270 (33000), 281 (24000), 302 (4600), 316 (4800), 331 (5100). ^{1}H-NMR (500 MHz) : 2.36 (3H, s, 7-$OCOCH_3$), 2.48 (3H, s, 5-$OCOCH_3$), 2.51 (3H, s, 10-$OCOCH_3$), 3.73 (3H, s, NCH_3), 3.92 (3H, s, 4-OCH_3), 6.02 (1H, s, 3-H), 7.37 (1H, dd, *J*=9, 2 Hz, 8-H), 7.64 (1H, d, *J*=2 Hz, 6-H), 7.79 (1H, d, *J*=9 Hz, 9-H). ^{13}C-NMR (300 MHz): 20.7 (OCO$\underline{C}H_3$), 20.8 (OCO$\underline{C}H_3$), 21.2 (OCO$\underline{C}H_3$), 35.3 (NCH_3), 56.6 (OCH_3), 98.5 (C3), 112.0 (C4a), 113.2 (C8), 122.6 (C6), 124.2 (C6), 124.9 (C7), 126.9 (C5a), 129.9 (C9a), 131.2 (C7), 133.0 (C5), 133.9 (C10), 148.7 (C10a), 161.9 (C2), 164.2 (C4), 168.2 (O$\underline{C}OCH_3$), 169.2 (O$\underline{C}OCH_3$). LRMS (*m/z*): 413 (M^+), 329 (base peak). HRMS *m/z* (M^+): Calcd for $C_{21}H_{19}NO_8$: 410.1140. Found: 413.1140.

13b: Colorless prisms from $CHCl_3$-Et_2O, mp 125-127°C. IR: 1769, 1747, 1653. UV: 264 (15000), 271 (14700). ^{1}H-NMR (500 MHz): 2.21 (3H, s, $OCOCH_3$), 2.35 (3H, s, $OCOCH_3$), 2.37(3H, s, $OCOCH_3$), 2.82 (2H, m, 6-H), 3.20 (3H, s, NCH_3), 3.66 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 4.72 (1H, m, 9-H), 6.02 (1H, s, 3-H), 6.39 (1H, br s, 8-H). ^{13}C-NMR: 20.4 (OCO$\underline{C}H_3$), 20.6 (OCO$\underline{C}H_3$), 21.9 (OCO$\underline{C}H_3$), 31.3 (C6), 34.9 (NCH_3), 56.4 (OCH3), 70.0 (OCH_3), 98.4 (C3 and C9), 106.2 (C8), 112.7 (C4a), 122.2 (C5a), 127.4 (C9a), 134.7 (C7), 134.9 (C5), 140.0 (C10), 149.3 (C10a), 162.1 (C2), 163.9 (C4), 168.0 (O$\underline{C}$OCH3), 168.5 (O$\underline{C}OCH_3$), 169.2 (O$\underline{C}OCH_3$). LRMS (*m/z*): 445 (M^+), 287 (base peak). HRMS m/z (M^+): Calcd for $C_{22}H_{23}NO_9$: 446.1360. Found: 445.1360. *Anal.* Calcd for $C_{22}H_{23}NO_9$ H_2O: C, 57.26; H, 5.02; N, 3.04. Found : C, 57.56; H, 5.15; N, 3.12.

ii) The crude product (**12b**) (150 mg, 0.38 mmol) in toluene (10 mL) was heated at 120°C in the

presence of small amount of silica gel for 4 h. After removal of the solvent *in vacuo*, the residue was treated with acetic anhydride-pyridine (1:2) solution (3 mL) at rt for 16 h. The reaction mixture was worked up in a similar manner as described above to give **13b** (111 mg, 65%) and 7-acetoxy-2-methyl-4-methoxy-1*H*-benzo[*g*]quinoline-2,5,10-trione (**14**)(12 mg, 10%).

14: Yellow prisms, mp 209-212°C. IR: 1765, 1667, 1595. UV: 281 (28500), 415 (1760). ^{1}H-NMR: 2.37 (3H, s, $OCOCH_3$), 3.90 (3H, s, NCH_3), 3.96 (3H, s, OCH_3), 6.25 (1H, s, 3-H), 7.47 (1H, dd, *J*=8, 2 Hz, 8-H), 7.83 (1H, dd, *J*=2 Hz, 6-H), 8.11 (1H, d, *J*=8 Hz, 9-H).

D-A reaction of 7a with 11

i) A solution of **7a** (167 mg, 0.81 mmol) and **11** (418 mg, 2.43 mmol) in benzene (20 mL) was heated at 80°C for 30 min in a sealed tube. After removal of the solvent *in vacuo*, the crystalline residue was washed by Et_2O to 5a,6,9,9a-tetrahydro-2,9-dimethoxy-7-trimethylsilyloxy-1*H*-benzo[*g*]quinoline-2,5,10-trione (**12a**) (193 mg, 63%) as yellow prisms, mp 162-164°C. IR : 1643. UV: 249 (20000), 286 (3300), 349 (2900). ^{1}H-NMR (500 MHz): 0.28 (9H, s, OTMS), 2.14 (1H, dd, *J*=18, 7 Hz, 6-H), 3.02 (3H, s, OCH_3), 3.0-3.1 (1H, m, 6-H), 3.31 (1H, dd, *J*=6, 4 Hz, 9a-H), 3.38 (1H, t, *J*=6 Hz, 5a-H), 3.89 (3H, s, OCH_3), 4.16 (1H, dd, *J*=5, 4 Hz, 9-H), 5.15 (1H, d, *J*=5 Hz, 8-H), 6.09 (1H, s, 3-H), 9.37 (1H, brs, NH). ^{13}C-NMR (500 MHz): 0.30 (OTMS), 26.3 (C6), 44.3 (C5a), 50.1 (C9a), 55.4 (C9-OCH_3), 56.7 (C4-OCH_3), 74.8 (C9), 100.9 (C8), 102.6 (C3), 114.9 (C4a), 141.8 (C10a), 154.3 (C7), 162.3 (C4), 166.3 (C2), 190.3 (s), 192.2 (s). LRMS (*m/z*): 377 (M^+), 343 (base peak). HRMS *m/z* (M^+): Calcd for $C_{18}H_{23}NO_6Si$: 377.1291. Found: 377.1271. *Anal.* Calcd for $C_{18}H_{23}NO_6Si$: C, 57.28; H, 6.14; N, 3.71. Found: C, 57.15; H, 5.86; N, 3.34.

ii) The crude **12a** (294 mg, 0.78 mmol) obtained from **7a** (247 mg, 1.20 mmol) was dissolved in dioxane (10 mL) and $Na_2S_2O_4$ (1.0 g, 5.70 mmol) was added to the solution at 0°C and the whole was stirred for 30 min. Water was added to the reaction mixture and this mixture was extracted with $CHCl_3$. After removal of the solvent *in vacuo*, the residue was treated with acetic anhydride-pyridine (1:2) solution (6 mL) at rt for 20 h. The reaction mixture was extracted with $CHCl_3$. After removal of the solvent *in vacuo*, the residue was purified by column chromatography (AcOEt-hexane=1:1) to gave 5,7,10-triacetoxy-6,9-dihydro-4,9-dimethoxy-1*H*-benzo[*g*]quinolin-2-one (**13a**) 10 mg (2% from **7a**) as colorless prisms from $CHCl_3$-Et_2O, mp 166-168°C. IR : 1774, 1762, 1654. UV : 239 (20300), 269 (20200). ^{1}H-NMR (500 MHz): 2.21 (3H, s, $OCOCH_3$), 2.36 (3H, s, $OCOCH_3$), 2.54 (3H, s, $OCOCH_3$), 2.6-2.7 (1H, m, 6-H), 2.8-2.9 (1H, m, 6-H), 3.24 (3H, s, 9-OCH_3), 3.90 (3H, s, 4-OCH_3), 4.50 (1H, m, 9-H), 5.92 (1H, s, 3-H), 6.3-6.4 (1H, m, 8-H), 10.41 (1H, br s, NH). LRMS (*m/z*): 431 (M^+), 273 (base peak). HRMS m/z (M^+): Calcd for $C_{21}H_{21}NO_9$: 431.1216. Found: 431.1211.

iii) The crude **12a** (145 mg, 0.38 mmol) obtained from **7a** (120 mg, 0.59 mmol) in DMF (4 mL), was

treated with K_2CO_3, (166 mg, 1.2 mmol) and MeI (170 mg, 1.2 mmol), at rt for 3.5 h. The reaction mixture was extracted with $CHCl_3$. After removal of the solvent *in vacuo*, the residue was chromatographed over silica gel. Elution with AcOEt-hexane (1:2) gave 4,7-dimethoxy-1-methyl-1*H*-benzo[*g*]quinoline-2,5,10-trione (**17**) (18 mg, 14%) and 2,4,7-trimethoxybenzo[*g*]quinoline-5,10-dione (**16**) 7 mg (6%).

16: Brown prisms from $CHCl_3$-Et_2O, mp 173-175°C. IR: 2919, 1675, 1654, 1590. UV: 272 (23300). ^{1}H-NMR (300 MHz): 3.97 (3H, s, OCH_3), 4.03 (3H, s, OCH_3), 4.17 (3H, s, OCH_3), 6.50 (1H, s, 3-H), 7.22 (1H, dd, *J*=9, 2 Hz, 8-H), 7.66 (1H, d, *J*=2 Hz, 6-H), 8.21 (1H, d, *J*=9 Hz, 9-H). ^{13}C-NMR (300 MHz) : 54.5 (OCH_3), 55.9 (OCH_3), 56.7 (OCH_3), 96.9 (C3), 109.7 (C6), 120.3 (C8), 125.7 (C4a), 129.6 (C9), 136.1 (C5a), 150.7 (C9a), 163.5 (C10a), 164.6 (C7), 168.0 (s), 168.3 (s), 181.6 (s), 186.8 (s). LRMS (*m/z*): 299 (M^+, base peak). HRMS *m/z* (M^+): Calcd for $C_{16}H_{13}NO_5$: 299.0791. Found: 299.0763.

17: Yellow prisms from $CHCl_3$-Et_2O, mp 235-237°C. IR: 1670, 1602. UV: 216 (25000), 288 (26000), 339 (5700). ^{1}H-NMR (300 MHz): 3.86 (3H, s, N-CH_3), 3.95 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 6.23 (1H, s, 3-H), 7.19 (1H, dd, *J*=9, 2 Hz, 8-H), 7.55 (1H, d, *J*=2 Hz, 6-H), 8.01 (1H, d, *J*=9 Hz, 9-H). ^{13}C-NMR (300 MHz): 34.7 (NCH_3), 56.0 (OCH_3), 56.5 (OCH_3), 101.1 (C3), 109.4 (C6), 113.0 (C4a), 120.4 (C8), 125.2 (C5a), 129.2 (C9), 134.9 (C9a), 145.0 (C10a), 163.6 (s), 164.9 (s), 165.3 (C2), 179.6 (s), 179.9 (s). LRMS (*m/z*): 299 (M^+), 284 (base peak). HRMS *m/z* (M^+): Calcd for $C_{16}H_{13}NO_5$: 299.0791. Found: 299.0778. *Anal.* Calcd for $C_{16}H_{13}NO_5 \cdot 3/4H_2O$: C, 61.44; H, 4.64; N, 4.48. Found : C, 61.41; H, 4.77; N, 4.35.

D-A reaction of 8 with 11

i) A solution of **8** (100 mg, 0.45 mmol) and **11** (157 mg, 0.91 mmol) in benzene (10 mL) was heated at 80°C for 1 h in a sealed tube. After removal of the solvent *in vacuo*, and the residue was chromatographed over silica gel. Elution with AcOEt gave 5a,6,9,9a-tetrahydro-2,4,9-trimethoxy-7-trimethylsilyloxybenzo[*g*]quinoline-5,10-dione (**18**) (100 mg, 56 %) as colorless prisms from AcOEt, mp 135-138°C. IR: 1705, 1671, 1601. UV: 250 (34800), 343 (4300). ^{1}H-NMR (90 MHz): 0.42 (9H, s, OTMS), 2.14 (1H, dd, *J*=18, 7 Hz, 6-H), 2.97 (3H, s, OCH_3), 3.2-3.5 (3H, m, 5a-H, 6-H and 9a-H), 3.94 (3H, s, OCH_3), 4.10 (3H, s, OCH_3), 4.02 (1H, dd, *J*=6, 4 Hz, 9-H), 5.14 (1H, dt, *J*=6, 1 Hz, 8-H), 6.42 (1H, s, 3-H). CIMS: m/z 392 (MH^+), 360 (base peak). HRMS *m/z* (M^+): Calcd for $C_{19}H_{25}NO_6Si$: 391.6448. Found: 391.1423.

ii) The compound (**18**) (125 mg, 0.32 mmol) was treated with acetic anhydride-pyridine (1:2) solution (3 mL) at rt for16 h. The reaction mixture was diluted with $CHCl_3$, and washed with 5% HCl solution, 5% $NaHCO_3$ solution and water and dried over Na_2SO_4. After removal of the solvent *in vacuo*, the residue was purified by column chromatography (AcOEt-hexane=1:1) gave

6,9-dihydro-5,7,10-triacetoxy-2,4,9-trimethoxybenzo[*g*]quinoline (**19**) (56 mg, 40%) as yellow prisms from $CHCl_3$-Et_2O, mp 215-220°C. IR: 1767, 1605, 1578. UV: 265 (48100), 324 (6000). ^{1}H-NMR (500 MHz): 2.21 (3H, s, $OCOCH_3$), 2.36 (3H, s, $OCOCH_3$), 2.46 (3H, s, $OCOCH_3$), 2.66 (1H, dd, *J*=18, 2 Hz, 6-H), 2.97 (1H, ddd, *J*=18, 5, 3 Hz, 6-H), 3.29 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.98 (3H, s, OCH_3), 4.79 (1H, dd, *J*=5, 2 Hz, 9-H), 6.24 (1H, s, 3-H), 6.51 (1H, d, *J*=3 Hz, 8-H).

Hydrolysis and methylation of 14

14 (16 mg, 0.05 mmol) in 10% HCl/dioxane-H_2O (2:1) (10 mL) was refluxed for 2 h. The reaction mixture was extracted with $CHCl_3$. After removal of the solvent *in vacuo*, the residue in DMF (4 mL) was treated with K_2CO_3 (28 mg, 0.2 mmol) and MeI (28 mg, 0.2 mmol) at rt for 3 h. The reaction mixture was extracted with $CHCl_3$. After removal of the solvent *in vacuo*, and the residue was chromatographed over silica gel. Elution with AcOEt-hexane (1:2) gave **17** (3 mg, 20%) .

Hydrolysis and methylation of 19

19 (56 mg, 0.13 mmol) in 10% HCl/dioxane-H_2O (2:1) (10 mL) was refluxed for 1.5 h. The reaction mixture was extracted with $CHCl_3$. After removal of the solvent *in vacuo*, the residue was in DMF (4 mL) was treated with K_2CO_3 (69 mg, 0.5 mmol) and MeI (71 mg, 0.5 mmol) at room temperature for 3 h. The reaction mixture was worked up in a similar manner as above to give **17** (15 mg, 41%) and **16** (3 mg, 8%).

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