SYNTHESIS OF 5,8-QUINOXALINEDIONES AND 5,8-QUINAZOLINEDIONES

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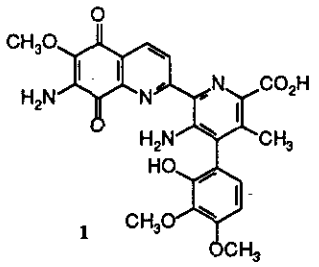
Abstract —— 5,8-Quinoxalinediones (**3a-c, 12, 13**), dibenzo[*a*,*c*]phenazine-10,13-diones (**5a, b**), 5,8-quinazolinediones (**17, 23**), and 4,5,8(3*H*)-quinazolinetrione (**21**) were prepared using oxidative demethylation of the corresponding 5,8-dimethoxy compounds with cerium (IV) ammonium nitrate.

Streptonigrin (**1**), a highly substituted 5,8-quinolinedione, was originally reported as an antitumor antibiotic in 1960.[1] It was later found to be a potent inhibitor of avian myeloblastosis virus reverse transcriptase (AMV-RT), though its marked cytotoxicity was disadvantageous with respect to a specific inhibitor of a retrovirus.[2] The 7-amino-6-methoxy-5,8-quinolinedione moiety in **1** was proved to be the minimum entity inhibiting AMV-RT.[2] The synthetic 6-methoxy-5,8-quinolinedione was as potent as inhibitors of AMV-RT as **1**, and much less toxic.[3] Further efforts to discover specific inhibitors of RT have continued employing various quinones. Now, we report the synthesis of aza-quinoline quinones, *i.e.* 5,8-quinoxalinediones and 5,8-quinazolinediones.



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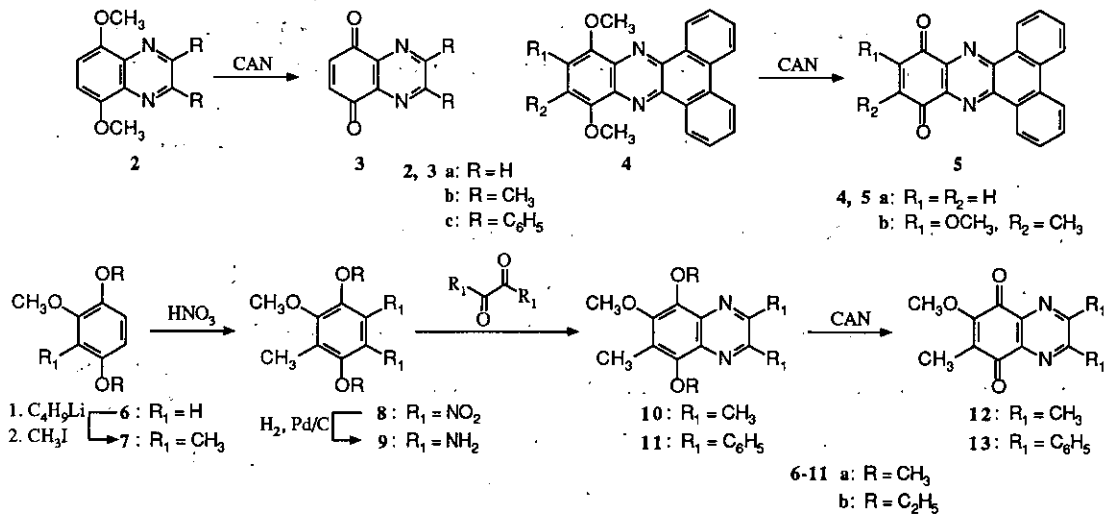
5,8-Dimethoxyquinoxalines (**2a-c**)[4] were oxidatively demethylated with cerium (IV) ammonium nitrate (CAN) in aqueous acetonitrile to afford the corresponding 5,8-quinoxalinediones (**3a-c**) in 49-70% yields. Oxidative demethylation of 10,13-dimethoxydibenzo[*a*, *c*]phenazine (**4a**)[4c] was carried out in acetic acid because of its low solubility in acetonitrile to give dibenzo[*a*, *c*]phenazine-10,13-dione (**5a**) in 77% yield.

Next, oxidative demethylation of 5,6,8-trimethoxyquinoxalines (**10a, 11a**) and 10,11,13-trimethoxydibenzo[*a*, *c*]phenazine (**4b**) with CAN was examined (formation of the *p*-quinones and/or the *o*-quinones is possible). The *o*-phenylenediamine (**9a**), obtained by catalytic hydrogenation of **8a**,[5] was condensed with diacetyl or benzil to give the corresponding 5,6,8-trimethoxyquinoxalines (**10a, 11a**). The quinoxalines (**10a, 11a**) were oxidized with CAN in acetonitrile-water to furnish the corresponding *p*-quinones (**12, 13**) in 68-75% yields, but furnished no *o*-quinones. The *p*-quinone (**12**) was also obtained by oxidative

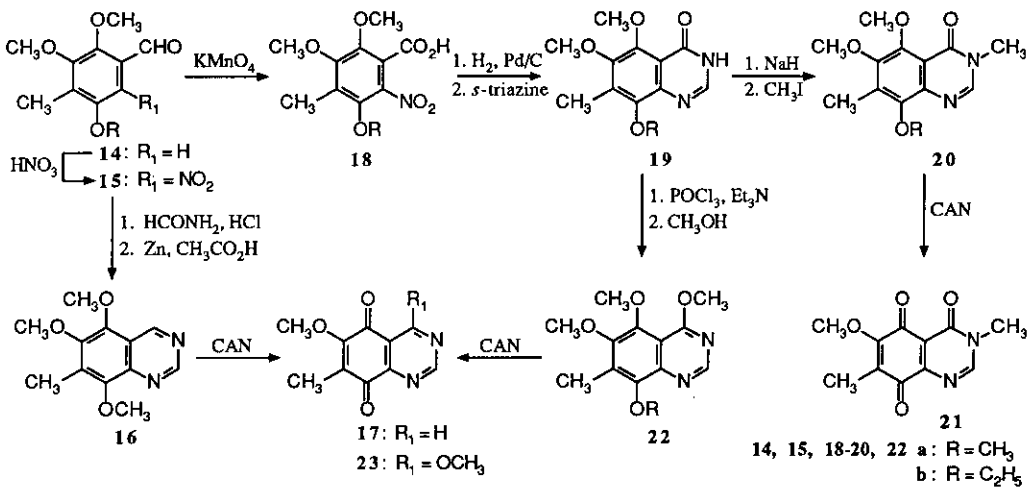
demethylation of **10a** with silver (II) oxide-nitric acid in dioxane[6] in 56% yield. The reaction of **9a** with 9,10-phenanthrenedione afforded 10,11,13-trimethoxydibenzo[*a*,*c*]phenazine (**4b**), which was oxidized to the *p*-quinone (**5b**) in 65% yield. The structure for the methoxy *p*-quinone (**12**) was further confirmed by the following synthesis. 3,6-Diethoxy-2-methoxytoluene (**7b**) prepared from **6b**[7] was converted to 5,8-diethoxy-6-methoxy-2,3,7-trimethylquinoxaline (**10b**) by the same procedure as used for **10a**. Oxidation of **10b** with CAN afforded 6-methoxy-2,3,7-trimethyl-5,8-quinoxalinedione (65% yield), which was identical with the quinone (**12**) obtained from **10a** in terms of ir, ^{1}H-nmr, and mass spectra, and mixed melting point.



We then examined oxidative demethylation of 5,6,8-trimethoxyquinazolines. 2,3,5-Trimethoxy-4-methyl-6-nitrobenzaldehyde (**15a**) prepared by nitration of **14a**,[8] was treated with hydrogen chloride in formamide followed by zinc in aqueous acetic acid[9] to give 5,6,8-trimethoxy-6-methylquinazoline (**16**) in 48% yield. Oxidative demethylation of **16** with CAN furnished 6-methoxy-7-methyl-5,8-quinazolinedione (**17**) in 23% yield, but again no *o*-quinone. The *o*-nitrobenzoic acid (**18a**) prepared by oxidation of **15a** with potassium permanganate was catalytically reduced in methanol, and then cyclized with *s*-triazine in ethanol[10] to give 5,6,8-trimethoxy-7-methyl-4(3*H*)-quinazolinone (**19a**) in 82% yield. The quinazolinone (**19a**) was treated with sodium hydride followed by methyl iodide to furnish the corresponding *N*-methylquinazolinone (**20a**) in 86% yield. Oxidative demethylation of **20a** with CAN in acetonitrile-water afforded the *p*-quinone (**21**) in 13% yield. Furthermore, treatment of **19a** with phosphoryl oxychloride-triethylamine in benzene followed by methanol gave the corresponding *O*-methylated quinazoline (**22a**, 65% yield). The quinazoline (**22a**) was oxidatively demethylated with CAN to give 4,6-dimethoxy-7-methyl-5,8-quinazolinedione (**23**) in 31% yield. The structure for the *p*-quinones (**21** and **23**) was further confirmed as follows. The oxidation of 8-

ethoxy-5,6-dimethoxy-3,7-dimethyl-4(3*H*)-quinazolinone (**20b**) and 8-ethoxy-4,5,6-trimethoxy-7-methylquinazoline (**22b**) with CAN gave the corresponding *p*-quinones (**21** and **23**), which were identical to the quinones obtained from **20a** and **22a**, respectively.

We have examined the effects of 5,8-quinoxalinedione (**12**) on the growth of mouse lymphoblastoma L5178Y cells and inhibition of AMV-RT of the quinone.[3b] Extensive biological studies are in progress.



EXPERIMENTAL

All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. ^{1}H-Nmr spectra were measured at 270 MHz in $CDCl_3$ with tetramethylsilane as an internal standard. All reactions were run with magnetic stirring. Anhydrous sodium sulfate was used for drying organic solvent extracts, and the solvent was removed with a rotary evaporator and finally under high vacuum. Column chromatography (flash chromatography)[11] was performed with silica gel 60 (230-400 mesh).

5,8-Quinoxalinediones (3a-c) A solution of CAN (1.37 g, 2.5 mmol) in acetonitrile-water (20:1, 10 ml) was added dropwise to **2** (1 mmol) dissolved in acetonitrile-water (1:1, 5 ml for **2a, b**; or 4:1, 50 ml for **2c**) at 20°C. The mixture was left at 20°C for 20 min, poured into ice-water (50 ml), and extracted with $CHCl_3$ (3 x 30 ml). The extract was washed with water, dried and evaporated. The residue was recrystallized. **3a**: Yield 49%. mp 157-159°C (CH_2Cl_2-ether; lit.,[12] mp 155-160°C). Ms *m/z* (%): 160 (M^+, 100). Ir (KBr): 1676 cm^{-1}. ^{1}H-Nmr δ: 7.28 (2H, s, C_6-H, C_7-H), 9.09 (2H, s, C_2-H, C_3-H). **3b**: Yield 61%. mp 203-205°C (decomp.) (petroleum ether; lit.,[4b] mp 206-208°C (decomp.)). Ms *m/z* (%): 188 (M^+, 100). Ir (KBr): 1672 cm^{-1}. ^{1}H-Nmr δ: 2.80 (6H, s, C_2-CH_3, C_3-CH_3), 7.15 (2H, s, C_6-H, C_7-H). **3c**: Yield 70%. mp 230-232°C (ethyl acetate-hexane; lit.,[13] mp 230-232°C). Ms *m/z* (%): 312 (M^+, 100). Ir (KBr): 1680 cm^{-1}. ^{1}H-Nmr δ: 7.24 (2H, s, C_6-H, C_7-H), 7.3-7.7 (10H, m, $2C_6H_5$).

10,11,13-Trimethoxy-12-methyldibenzo[*a*,*c*]phenazine (4b) 2,3,6-Trimethoxy-4,5-dinitrotoluene (**8a**, 1.36 g, 5 mmol; see below) in ethyl acetate (240 ml) was hydrogenated at 1 atm for 24 h using 10% palladium on carbon (0.68 g) as a catalyst. The catalyst was filtered off, and the filtrate was evaporated. The residue was dissolved in ethanol (10 ml), and 9,10-phenanthrenedione (1.04 g, 5 mmol) in acetic acid (35 ml) was added. The whole was heated at 90°C for 30 min, and cooled. The precipitated crystals were

collected by filtration, washed with cold ethanol (2 x 50 ml), dried, and recrystallized from acetic acid. Yield 1.25 g (65%). mp 208-209°C (yellow needles). *Anal.* Calcd for $C_{24}H_{20}N_2O_3$: C, 74.98; H, 5.24; N, 7.29. Found: C, 74.90; H, 5.33; N, 7.26. Ms *m/z* (%): 384 (M^+, 93), 369 (100). ^{1}H-Nmr δ: 2.49 (3H, s, C_7-CH_3), 4.18 (3H, s, OCH_3), 4.34 (6H, s, $2OCH_3$), 7.7-7.9 (4H, m, C_2-H, C_3-H, C_6-H, C_7-H), 8.55-8.65 (2H, m, C_4-H, C_5-H), 9.3-9.5 (2H, m, C_1-H, C_8-H).

Dibenzo[*a,c*]phenazine-10,13-dione (5a) A solution of CAN (1.37 g, 2.5 mmol) in water (5 ml) was added dropwise to **4a** (0.34 g, 1 mmol) dissolved in acetic acid (100 ml) at 25°C. The mixture was left at 25°C for 2 h, poured into water (200 ml), and extracted with CH_2Cl_2 (3 x 100 ml). The extract was washed with water (150 ml), dried and evaporated. The residue was chromatographed (eluting with CH_2Cl_2) to afford **5a** (239 mg, 77%). mp 261-263°C (orange needles from CH_2Cl_2-ether). *Anal.* Calcd for $C_{20}H_{10}N_2O_2 \cdot 2/5H_2O$: C, 75.66; H, 3.43; N, 8.82. Found: C, 75.72; H, 3.47; N, 8.80. Ms *m/z* (%): 310 (M^+, 100). Ir (KBr): 1680 cm^{-1}. ^{1}H-Nmr δ: 7.32 (2H, s, C_{11}-H, C_{12}-H), 7.7-8.0 (4H, m, C_2-H, C_3-H, C_6-H, C_7-H), 8.63 (2H, br d, *J*=7.9 Hz, C_4-H, C_5-H), 9.43 (2H, dd, *J*=7.9, 1.6 Hz, C_1-H, C_8-H).

11-Methoxy-12-methyldibenzo[*a,c*]phenazine-10,13-dione (5b) A solution of CAN (357 mg, 0.65 mmol) in water (3 ml) was added dropwise to **4b** (100 mg, 0.26 mmol) dissolved in acetonitrile (50 ml) containing suspended pyridine-2,6-dicarboxylic acid *N*-oxide[14] (119 mg, 0.65 mmol) at 25°C. The mixture was left at 25°C for 30 min, poured into water (150 ml), and extracted with CH_2Cl_2 (3 x 50 ml). The extract was washed with water (80 ml), dried and evaporated. The residue was chromatographed (eluting with CH_2Cl_2) to afford **5b** (60 mg, 65%). mp 252-255°C (decomp.) (red needles from CH_2Cl_2-ether). *Anal.* Calcd for $C_{22}H_{14}N_2O_3 \cdot 1/10H_2O$: C, 74.19; H, 4.02; N, 7.87. Found: C, 74.10; H, 4.09; N, 7.71. Ms *m/z* (%): 354 (M^+, 100). Ir (KBr): 1678, 1660 cm^{-1}. ^{1}H-Nmr δ: 2.27 (3H, s, C_{12}-CH_3), 4.33 (3H, s, OCH_3), 7.7-8.0 (4H, m, C_2-H, C_3-H, C_6-H, C_7-H), 8.5-8.7 (2H, m, C_4-H, C_5-H), 9.39 and 9.42 (each 1H, dd, *J*=7.9, 1.3 Hz, C_1-H, C_8-H).

3,6-Diethoxy-2-methoxytoluene (7b) *n*-Butyllithium (10 ml of 1.64 M hexane solution) was added dropwise to a solution of **6b** (1.96 g, 10 mmol) in dry tetrahydrofuran (10 ml) at 0-5°C. The whole was kept at room temperature for 1 h, and methyl iodide (2.13 g, 15 mmol) was added dropwise at 0-5°C. The mixture was allowed to warm to room temperature for 30 min, kept for 1 h, quenched with water (40 ml), and extracted with ether (3 x 20 ml). The extract was washed with brine, dried and evaporated. The residue was recrystallized from hexane to afford 1.98 g (94%) of **7b** as colorless prisms, mp 54-55°C. *Anal.* Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.37; H, 8.51. Ms *m/z* (%): 210 (M^+, 100). ^{1}H-Nmr δ: 1.39 and 1.41 (each 3H, t, *J*=6.9 Hz, $2CH_2C\underline{H}_3$), 2.15 (3H, s, Ar-CH_3), 3.81 (3H, s, OCH_3), 3.96 and 4.01 (each 2H, q, *J*=6.9 Hz, $2C\underline{H}_2CH_3$), 6.51 (1H, d, *J*=8.9 Hz, C_5-H), 6.67 (1H, d, *J*=8.9 Hz, C_4-H).

3,6-Diethoxy-2-methoxy-4,5-dinitrotoluene (8b) A solution of **7b** (210 mg, 1 mmol) in a mixture of acetic acid (0.4 ml) and concentrated HNO_3 (60-62%, 0.8 ml) was kept at 75-80°C for 5 min, then cooled, and diluted with water (10 ml). The precipitated crystals of **8b** were collected and recrystallized from $CHCl_3$-hexane. Yield 93 mg (31%). mp 84-85°C (colorless prisms). *Anal.* Calcd for $C_{12}H_{16}N_2O_7$: C, 48.00; H, 5.37; N, 9.33. Found: C, 47.93; H, 5.33; N, 9.24. Ms *m/z* (%): 300 (M^+, 100). ^{1}H-Nmr δ: 1.40 and 1.41 (each 3H, t, *J*=6.9 Hz, $2CH_2C\underline{H}_3$), 2.27 (3H, s, Ar-CH_3), 3.93 (3H, s, OCH_3), 4.05 and 4.19 (each 2H, q, *J*=6.9 Hz, $2C\underline{H}_2CH_3$).

5,6,8-Trimethoxy- (or 5,8-Diethoxy-6-methoxy-)2,3,7-trimethylquinoxaline (10a, b) The dinitrotoluene (**8**, 4.4 mmol) in acetic acid (18 ml) was hydrogenated at 1 atm for 3 h using 10% palladium

on carbon (500 mg) as a catalyst. The catalyst was filtered off, and the filtrate was diluted with water (18 ml) and treated with diacetyl (0.72 ml, 8.2 mmol). The resulting solution was kept for 30 min, then poured into water (70 ml) and extracted with $CHCl_3$ (3 x 30 ml). The extract was successively washed with water (2 x 20 ml), saturated aqueous $NaHCO_3$ solution (2 x 20 ml) and brine, and dried. The solvent was evaporated, and the residue was chromatographed (eluting with ethyl acetate-hexane 1:5) to afford **10**, which was recrystallized from hexane. **10a**: Yield 68%. mp 95-97°C (colorless prisms). *Anal.* Calcd for $C_{14}H_{18}N_2O_3$: C, 64.11; H, 6.92; N, 10.68. Found: C, 64.12; H, 7.02; N, 10.70. Ms *m/z* (%): 262 (M^+, 72), 247 (100). ^{1}H-Nmr δ: 2.38 (3H, s, C_7-CH_3), 2.73 and 2.74 (each 3H, s, C_2-CH_3, C_3-CH_3), 4.01, 4.04 and 4.08 (each 3H, s, $3OCH_3$). **10b**: Yield 66%. mp 64-65°C (colorless prisms). *Anal.* Calcd for $C_{16}H_{22}N_2O_3$: C, 66.18; H, 7.64; N, 9.65. Found: C, 66.06; H, 7.59; N, 9.61. Ms *m/z* (%): 290 (M^+, 64), 275 (49), 261 (30), 233 (100). ^{1}H-Nmr δ: 1.47 (6H, t, *J*=7.3 Hz, $2CH_2C\underline{H}_3$), 2.37 (3H, s, C_7-CH_3), 2.70 and 2.71 (each 3H, s, C_2-CH_3, C_3-CH_3), 4.02 (3H, s, OCH_3), 4.29 (4H, q, *J*=7.3 Hz, $2C\underline{H}_2CH_3$).

5,6,8-Trimethoxy-7-methyl-2,3-diphenylquinoxaline (11a) 2,3,6-Trimethoxy-4,5-dinitrotoluene (**8a**, 1.36 g, 5 mmol) in ethyl acetate (240 ml) was hydrogenated at 1 atm for 24 h using 10% palladium on carbon (0.68 g) as a catalyst. The catalyst was filtered off, and the filtrate was evaporated. A solution of the residue and benzil (1.05 g, 5 mmol) in ethanol (30 ml) was refluxed for 20 min, and evaporated. The residual solid was chromatographed (eluting with ethyl acetate-hexane 4:1) to afford **11a** (1.13 g, 70%). mp 145-147°C (pale yellow needles from ethanol). *Anal.* Calcd for $C_{24}H_{22}N_2O_3$: C, 74.59; H, 5.74; N, 7.25. Found: C, 74.59; H, 5.79; N, 7.23. Ms *m/z* (%): 386 (M^+, 78), 371 (100). ^{1}H-Nmr δ: 2.42 (3H, s, C_7-CH_3), 4.08, 4.18 and 4.19 (each 3H, s, $3OCH_3$), 7.25-7.60 (10H, m, $2C_6H_5$).

6-Methoxy-2,3,7-trimethyl-5,8-quinoxalinedione (12) Method A: Oxidative demethylation of **10** with CAN was carried out by the same procedure as used for **2a, b**. Yield 75% from **10a**, 65% from **10b**. mp 181.5-183°C (yellow needles from methanol). *Anal.* Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 62.24; H, 5.20; N, 11.82. Ms *m/z* (%): 232 (M^+, 100), 217 (23). ^{1}H-Nmr δ: 2.16 (3H, s, C_7-CH_3), 2.77 (6H, s, C_2-CH_3, C_3-CH_3), 4.21 (3H, s, OCH_3).

Method B: 6 M HNO_3 (0.5 ml) was added dropwise to a solution of **10a** (131 mg, 0.5 mmol) containing suspended AgO (372 mg, 3 mmol) in dioxane (5 ml) with stirring at 0-5°C. The whole was kept at 0-5°C for 20 min, diluted with water (30 ml), adjusted to pH 8-9 with saturated aqueous $NaHCO_3$ solution, and extracted with $CHCl_3$ (3 x 10 ml). The extract was washed with water, dried, and evaporated. The residue was chromatographed (eluting with ethyl acetate-hexane 2:1) to afford **12** (65 mg, 56%).

6-Methoxy-7-methyl-2,3-diphenyl-5,8-quinoxalinedione (13) A solution of CAN (1.37 g, 2.5 mmol) in water (10 ml) was added dropwise to **11a** (193 mg, 0.5 mmol) dissolved in acetonitrile-water (8:1, 45 ml) containing suspended pyridine-2,6-dicarboxylic acid *N*-oxide (462 mg, 2.5 mmol) at 0-5°C. The mixture was left at 0-5°C for 30 min, poured into ice-water (100 ml), and extracted with $CHCl_3$ (3 x 70 ml). The extract was washed with water, dried and evaporated. The residue was chromatographed (eluting with ethyl acetate-hexane 1:9-3:7) to afford **13**. Yield 121 mg (68%). mp 221-224°C (yellow needles from CH_2Cl_2-ether). *Anal.* Calcd for $C_{22}H_{16}N_2O_3 \cdot 1/10H_2O$: C, 73.77; H, 4.56; N, 7.82. Found: C, 73.75; H, 4.69; N, 7.81. Ms *m/z* (%): 356 (M^+, 100), 341 (35). Ir (KBr): 1680, 1666 cm^{-1}. ^{1}H-Nmr δ: 2.21 (3H, s, C_7-CH_3), 4.25 (3H, s, OCH_3), 7.3-7.7 (10H, m, $2C_6H_5$).

2,3,5-Trimethoxy- (or 5-Ethoxy-2,3-dimethoxy-)4-methyl-6-nitrobenzaldehyde (15a, b) Concentrated HNO_3 (60-62%, 0.35 ml) was added dropwise to a solution of **14**[8] (1 mmol) in acetic acid

(0.35 ml) at 5-8°C with stirring. The mixture was kept at 5-8°C for 20 min, diluted with water (6 ml) and extracted with ethyl acetate (3 x 2 ml). The extract was successively washed with water (3 ml), saturated aqueous $NaHCO_3$ solution (3 ml) and brine, dried and evaporated. The residue was chromatographed (eluting with ethyl acetate-hexane 5:1) to afford **15**. **15a**: Yield 51%.. mp 90-91°C (light yellow prisms from $CHCl_3$-hexane). *Anal.* Calcd for $C_{11}H_{13}NO_6$: C, 51.77; H, 5.13; N, 5.49. Found: C, 51.72; H, 5.10; N, 5.39. Ms *m/z* (%): 255 (M^+, 88), 238 (100), 195 (54). Ir (KBr): 1688, 1544, 1328 cm^{-1}. ^{1}H-Nmr δ: 2.31 (3H, s, C_4-CH_3), 3.81, 3.92 and 4.00 (each 3H, s, $3OCH_3$), 10.24 (1H, s, CHO). **15b**: Yield 60%. mp 49-50°C (colorless powder from $CHCl_3$-hexane). *Anal.* Calcd for $C_{12}H_{15}NO_6$: C, 53.53; H, 5.62; N, 5.20. Found: C, 53.40; H, 5.57; N, 5.10. Ms *m/z* (%): 269 (M^+, 100), 224 (81), 180 (47). Ir (KBr): 1694, 1544, 1326 cm^{-1}. ^{1}H-Nmr δ: 1.37 (3H, t, *J*=6.9 Hz, $CH_2C\underline{H}_3$), 2.29 (3H, s, C_4-CH_3), 3.90 and 3.99 (each 3H, s, $2OCH_3$), 3.97 (2H, q, *J*=6.9 Hz, $C\underline{H}_2CH_3$), 10.25 (1H, s, CHO).

5,6,8-Trimethoxy-7-methylquinazoline (16) Dry HCl was bubbled into a solution of **15a** (199 mg, 0.78 mmol) in formamide (5 ml) at 0-5°C for 5 min. The solution was heated at 80°C for 1 h, cooled and diluted with water (10 ml). The precipitated needles of the crude *N,N'*-diformamido acetal of **15a** (214 mg) were collected by filtration, washed with water, and suspended in H_2O-acetic acid (2:1, 3 ml). Zinc powder (641 mg) was added in small portions at 0-5°C during 20 min. The whole was kept at 0-5°C for 30 min, allowed to rise to room temperature for an additional 30 min, and filtered directly into a solution of 50% NaOH (5 ml). The mixture was diluted with water (25 ml). The precipitated crystals of **16** were collected by filtration and recrystallized from $CHCl_3$-hexane. Yield 87 mg (48%). mp 84-85°C (colorless prisms). *Anal.* Calcd for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.40; H, 6.01; N, 11.90. Ms *m/z* (%): 234 (M^+, 55), 219 (100). ^{1}H-Nmr δ: 2.44 (3H, s, C_7-CH_3), 3.98, 4.04 and 4.08 (each 3H, s, $3OCH_3$), 9.26 (1H, s, C_4-H), 9.60 (1H, s, C_2-H).

2,3,5-Trimethoxy- (or 5-Ethoxy-2,3-dimethoxy-)4-methyl-6-nitrobenzoic acid (18a, b) A solution of $KMnO_4$ (0.4 g, 2.53 mmol) in water (4 ml) was added dropwise to a solution of **15** (2.05 mmol) in acetone (8.3 ml) at 15-20°C with stirring. The mixture was kept at 20°C for 3 h, and the precipitate was filtered off. The filtrate was diluted with water, acidified with 10% HCl, and extracted with ethyl acetate (3 x 10 ml). The extract was washed with brine, dried and evaporated. The residue was recrystallized from $CHCl_3$-hexane to afford **18**. **18a**: Yield 81%. mp 138-139°C (colorless needles). *Anal.* Calcd for $C_{11}H_{13}NO_7$: C, 48.71; H, 4.83; N, 5.16. Found: C, 48.69; H, 4.78; N, 4.97. Ms *m/z* (%): 271 (M^+, 100), 256 (11). Ir (KBr): 1706, 1534, 1332 cm^{-1}. ^{1}H-Nmr δ: 2.29 (3H, s, C_4-CH_3), 3.86, 3.92 and 3.97 (each 3H, s, $3OCH_3$), 7.1-7.4 (1H, br, CO_2H). **18b**: Yield 79%. mp 159-160°C (colorless prisms). *Anal.* Calcd for $C_{12}H_{15}NO_7$: C, 50.53; H, 5.30; N, 4.91. Found: C, 50.42; H, 5.24; N, 4.85. Ms *m/z* (%): 285 (M^+, 100), 257 (82). Ir (KBr): 1702, 1538, 1332 cm^{-1}. ^{1}H-Nmr δ: 1.31 (3H, t, *J*=6.9 Hz, $CH_2C\underline{H}_3$), 2.19 (3H, s, C_4-CH_3), 3.84 and 3.89 (each 3H, s, $2OCH_3$), 3.93 (2H, q, *J*=6.9 Hz, $C\underline{H}_2CH_3$), 10.64 (1H, br, CO_2H).

5,6,8-Trimethoxy- (or 8-Ethoxy-5,6-dimethoxy-)7-methyl-4(3*H*)-quinazolinone (19a, b) The *o*-nitrobenzoic acid (**18**, 0.2 mmol) in methanol (3 ml) was hydrogenated at 1 atm for 2 h using 10% palladium on carbon as a catalyst. The catalyst was filtered off, and the filtrate was evaporated. A mixture of the resulting solid, *s*-triazine (48 mg, 0.6 mmol) and piperidine (1 drop) in dry ethanol (1.5 ml) was refluxed for 21 h. The solvent was evaporated, and the residue was chromatographed (eluting with ethyl acetate-hexane 1:2) to afford **19**. **19a**: Yield 82%. mp 232-233°C (colorless prisms from ethanol). *Anal.* Calcd for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.19. Found: C, 57.52; H, 5.63; N, 11.16. Ms *m/z* (%): 250 (M^+,

100), 235 (70). Ir (KBr): 3192, 1684 cm^{-1}. ^{1}H-Nmr δ: 2.37 (3H, s, C_7-CH_3), 3.95 (6H, s, $2OCH_3$), 3.97 (3H, s, OCH_3), 8.16 (1H, br s, C_2-H). **19b**: Yield 76%. mp 171-172°C (colorless needles from ethyl acetate). *Anal.* Calcd for $C_{13}H_{16}N_2O_4$: C, 59.08; H, 6.10; N, 10.60. Found: C, 58.98; H, 6.06; N, 10.56. Ms *m/z* (%): 264 (M^+, 99), 249 (100), 235 (42), 221 (69). Ir (KBr): 3172, 1682 cm^{-1}. ^{1}H-Nmr δ: 1.45 (3H, t, *J*=6.9 Hz, $CH_2C\underline{H}_3$), 2.36 (3H, s, C_7-CH_3), 3.95 and 3.96 (each 3H, s, $2OCH_3$), 4.18 (2H, q, *J*=6.9 Hz, $C\underline{H}_2CH_3$), 8.06 (1H, s, C_2-H), 11.55 (1H, br, NH).

5,6,8-Trimethoxy- (or 8-Ethoxy-5,6-dimethoxy-)3,7-dimethyl-4(3*H*)-quinazolinone (20a, b) Sodium hydride (72 mg, 3 mmol) was added to a solution of **19** (2 mmol) in *N*,*N*-dimethylformamide (15 ml) at 12°C with stirring. The whole was kept at 12°C for 30 min, and methyl iodide (426 mg, 3 mmol) was added dropwise. The mixture was kept at 12-14°C for 30 min, quenched with water (30 ml), and extracted with $CHCl_3$ (3 x 10 ml). The extract was washed with brine, dried and evaporated. The residue was chromatographed (eluting with ethyl acetate) to afford **20**. **20a**: Yield 86%. mp 136-137°C (colorless needles from $CHCl_3$-hexane). *Anal.* Calcd for $C_{13}H_{16}N_2O_4$: C, 59.08; H, 6.10; N, 10.60. Found: C, 59.02; H, 6.10; N, 10.60. Ms *m/z* (%): 264 (M^+, 100), 249 (59). Ir (KBr): 1676 cm^{-1}. ^{1}H-Nmr δ: 2.34 (3H, s, C_7-CH_3), 3.54 (3H, s, NCH_3), 3.93 (9H, s, $3OCH_3$), 7.96 (1H, s, C_2-H). **20b**: Yield 78%. mp 83-84°C (colorless prisms from $CHCl_3$-hexane). *Anal.* Calcd for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.25; H, 6.49; N, 9.99. Ms *m/z* (%): 278 (M^+, 100), 263 (96), 249 (45), 235 (48). Ir (KBr): 1678, 1660 cm^{-1}. ^{1}H-Nmr δ: 1.44 (3H, t, *J*=7.3 Hz, $CH_2C\underline{H}_3$), 2.34 (3H, s, C_7-CH_3), 3.54 (3H, s, NCH_3), 3.93 and 3.94 (each 3H, s, $2OCH_3$), 4.16 (2H, q, *J*=7.3 Hz, $C\underline{H}_2CH_3$), 7.94 (1H, s, C_2-H).

4,5,6,8-Tetramethoxy- (or 8-Ethoxy-4,5,6-trimethoxy-)7-methylquinazoline (22a, b) A mixture of **19** (0.2 mmol), phosphoryl oxychloride (34 mg, 0.22 mmol), and triethylamine (51 mg, 0.5 mmol) in dry benzene (2 ml) was heated at 80°C for 23 h. The reaction mixture was cooled, diluted with methanol (1 ml), kept at room temperature for 2.5 h, diluted with water (10 ml), and extracted with $CHCl_3$ (3 x 2 ml). The extract was washed with brine, dried and evaporated. The residue was chromatographed (eluting with ethyl acetate-hexane 1:5)[15] to afford **22**. **22a**: Yield 65%. mp 66-67°C (colorless needles from hexane). *Anal.* Calcd for $C_{13}H_{16}N_2O_4$: C, 59.08; H, 6.10; N, 10.60. Found: C, 58.83; H, 6.04; N, 10.51. Ms *m/z* (%): 264 (M^+, 55), 249 (100). ^{1}H-Nmr δ: 2.32 (3H, s, C_7-CH_3), 3.83, 3.88, 3.94 and 4.12 (each 3H, s, $4OCH_3$), 8.64 (1H, s, C_2-H). **22b**: Yield 61%. Oil. High-resolution ms: Calcd for $C_{14}H_{18}N_2O_4$: 278.1266. Found: 278.1264. Ms *m/z* (%): 278 (M^+, 45), 263 (100), 249 (19), 235 (39). ^{1}H-Nmr δ: 1.47 (3H, t, *J*=7.3 Hz, $CH_2C\underline{H}_3$), 2.40 (3H, s, C_7-CH_3), 3.91, 3.96 and 4.19 (each 3H, s, $3OCH_3$), 4.25 (2H, q, *J*=7.3 Hz, $C\underline{H}_2CH_3$), 8.70 (1H, s, C_2-H).

6-Methoxy-7-methyl-5,8-quinazolinedione (17), 6-Methoxy-3,7-dimethyl-4,5,8(3*H*)-quinazolinetrione (21), and 4,6-Dimethoxy-7-methyl-5,8-quinazolinedione (23) A solution of CAN (548 mg, 1 mmol) in acetonitrile-water (1:1, 1 ml) was added dropwise to **16**, **20** or **22** (0.2 mmol) dissolved in acetonitrile-water (20:1, 2.1 ml) containing pyridine-2,6-dicarboxylic acid *N*-oxide (183 mg, 1 mmol) at 15°C. The mixture was kept at 15°C for 15 min, diluted with water (10 ml), and extracted with $CHCl_3$ (4 x 2 ml). The extract was washed with brine, dried and evaporated. The residue was chromatographed (eluting with ethyl acetate) to afford **17**, **21** or **23**. **17**: Yield 23%. mp 112-113°C (yellow prisms from ether-hexane). *Anal.* Calcd for $C_{10}H_8N_2O_3$: C, 58.82; H, 3.95; N, 13.72. Found: C, 58.58; H, 4.00; N, 13.53. Ms *m/z* (%): 204 (M^+, 100), 189 (41). Ir (KBr): 1674 cm^{-1}. ^{1}H-Nmr δ: 2.18 (3H, s, C_7-CH_3), 4.24 (3H, s, OCH_3), 9.46 (1H, s, C_4-H), 9.63 (1H, s, C_2-H). **21**: Yield 13% from **20a**, 15%

from **20b**. mp 217-219°C (red needles from methanol). *Anal.* Calcd for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.30; N, 11.96. Found: C, 56.32; H, 4.35; N, 11.83. Ms *m/z* (%): 234 (M^+, 100), 176 (29), 148 (26). Ir (KBr): 1710, 1648 cm^{-1}. ^{1}H-Nmr δ: 2.05 (3H, s, C_7-CH_3), 3.65 (3H, s, NCH_3), 4.16 (3H, s, OCH_3), 8.51 (1H, s, C_2-H). **23**: Yield 31% from **22a**, 20% from **22b**. mp 182-183°C (yellow needles from methanol). *Anal.* Calcd for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.30; N, 11.96. Found: C, 56.38; H, 4.36; N, 11.71. Ms *m/z* (%): 234 (M^+, 100), 219 (43), 204 (31). Ir (KBr): 1670 cm^{-1}. ^{1}H-Nmr δ: 2.10(3H, s, C_7-CH_3), 4.17 and 4.22 (each 3H, s, $2OCH_3$), 9.08 (1H, s, C_2-H).

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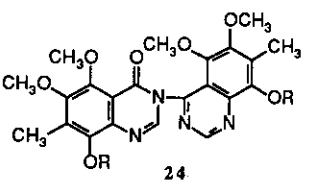
15. Further elution with ethyl acetate-hexane (3:2) gave a more polar "dimeric" product (**24**). **24a** (R = CH_3): Yield 16%. mp 209-210°C (light yellow needles from $CHCl_3$-hexane). *Anal.* Calcd for $C_{24}H_{26}N_4O_7$: C, 59.74; H, 5.43; N, 11.61. Found: C, 59.69; H, 5.43; N, 11.39. Ms *m/z* (%): 482 (M^+, 100), 451 (88), 249 (58). Ir (KBr): 1694 cm^{-1}. ^{1}H-Nmr δ: 2.40 and 2.44 (each 3H, s, 2Ar-CH_3), 3.59, 3.86, 3.89, 3.96, 4.01 and 4.10 (each 3H, s, $6OCH_3$), 8.16 and 9.26 (each 1H, s, 2Ar-H). **24b** (R = C_2H_5): Yield 9%. mp 185-186°C (colorless prisms from $CHCl_3$-hexane). *Anal.* Calcd for $C_{26}H_{30}N_4O_7$: C, 61.17; H, 5.92; N, 10.97. Found: C, 61.15; H, 5.91; N, 10.77. Ms *m/z* (%): 510 (M^+, 100), 495 (72), 479 (45), 263 (27). Ir (KBr): 1696 cm^{-1}. ^{1}H-Nmr δ: 1.48 and 1.51 (each 3H, t, J=6.9 Hz, $2CH_2\underline{CH_3}$), 2.39 and 2.43 (each 3H, s, 2Ar-CH_3), 3.57, 3.85, 3.89 and 3.96 (each 3H, s, $4OCH_3$), 4.12-4.47 (4H, m, $2\underline{CH_2}CH_3$), 8.14 and 9.22 (each 1H, s, 2Ar-H).



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