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Synthesis of Renierone, 7-Methoxy-1,6-dimethyl-5,8-dihydroisoquinoline-5,8-dione and *N*-Formyl-1,2-dihydrorenierone, Antimicrobial Metabolites from a Marine Sponge, *Reniera* sp.[1]

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Three isoquinolinequinone antimicrobial metabolites, renierone (**3**), 7-methoxy-1,6-dimethyl-5,8-dihydroisoquinoline-5,8-dione (**4**) and *N*-formyl-1,2-dihydrorenierone (**6**), isolated from a marine sponge (*Reniera* sp.), were synthesized.

Keywords——synthesis; isoquinolinequinone; antimicrobial metabolite; renierone; *N*-formyl-1,2-dihydrorenierone; marine sponge; *Reniera* sp.; ceric ammonium nitrate; oxidative demethylation

There is much interest at present in the chemistry and biological activity of heterocyclic quinones.[2] In recent years, several naturally occurring monomeric and dimeric isoquinolinequinones have been isolated from Actinomycetes and from marine sponges.[3] In connection with our research on isoquinolinequinone antibiotics, *e.g.* mimosamycin (**1**) and mimocin (**2**) isolated from *Streptomyces lavendulae* No. 314,[4,5] we have described a general process for the synthesis of various heterocyclic quinones using the oxidative demethylation reaction with ceric ammonium nitrate (CAN).[6,7]

In 1979, McIntyre and Faulkner reported the isolation and the structural elucidation of renierone (**3**), the major antimicrobial metabolite of a marine sponge, *Reniera* sp.[8] It shows strong antimicrobial activity against *Staphylococcus aureus, Bacillus subtilis* and *Candida albicans*. The structural similarity between renierone (**3**) and mimocin (**2**) derived from *Streptomyces lavendulae* is striking: both have a common skeleton, *i.e.* 7-methoxy-6-methyl-5,8-dihydroisoquinoline-5,8-dione, and differ only in a side chain at C-1 of the isoquinoline. Furthermore, in 1982, Frincke and Faulkner described the isolation and the structural elucidation of mimosamycin (**1**), 7-methoxy-1,6-dimethyl-5,8-dihydroisoquinoline-5,8-dione (**4**), *O*-demethylrenierone (**5**), *N*-formyl-1,2-dihydrorenierone (**6**) and four dimeric isoquinolinequinones (renieramycins A—D) from the sponge *Reniera*.[9] The mass spectrum (MS) of **6** was almost identical with that of renierone (**3**) except for the presence of a small molecular ion peak *m*/*z* 345, and the proton and carbon-13 nuclear magnetic resonance (^{1}H- and ^{13}C-NMR) spectra indicated that **6** was a 2 : 1 mixture of two inseparable isomers, **6a** and **6b**.

The isoquinolinequinones are highly active, but are not readily available in quantity from natural sources. Thus, we undertook the synthesis of these compounds. We report here the full details[1] of the synthesis of renierone (**3**), 7-methoxy-1,6-dimethyl-5,8-dihydroisoquinoline-5,8-dione (**4**) and (±)-*N*-formyl-1,2-dihydrorenierone (**6**). (Chart 1).

We first studied the synthesis of renierone (**3**). We chose 5,7,8-trimethoxy-6-methylisoquinoline (**12**) as a common starting compound for the synthesis of the isoquinolinequinones **3**, **4** and **6**. According to the modified Pomeranz–Fritsch isoquinoline synthesis,[10] the isoquinoline **12** was prepared from 2,3,5-trimethoxy-4-methylbenzaldehyde[7] (**7**) in five

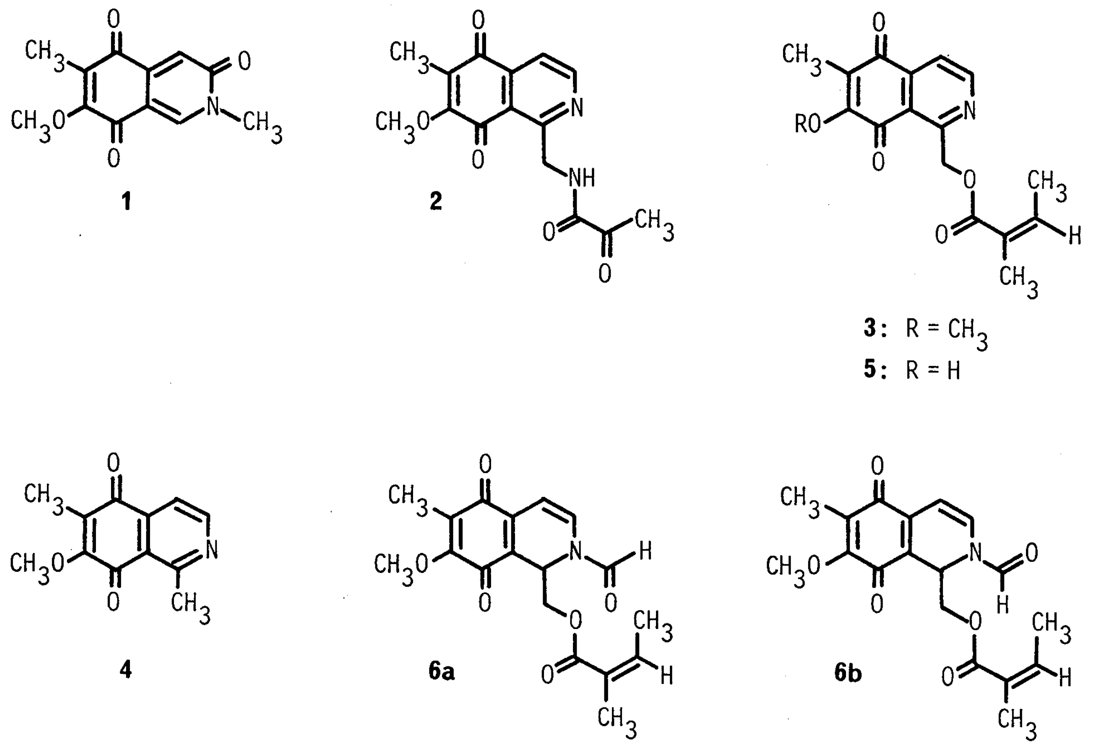

Chart 1

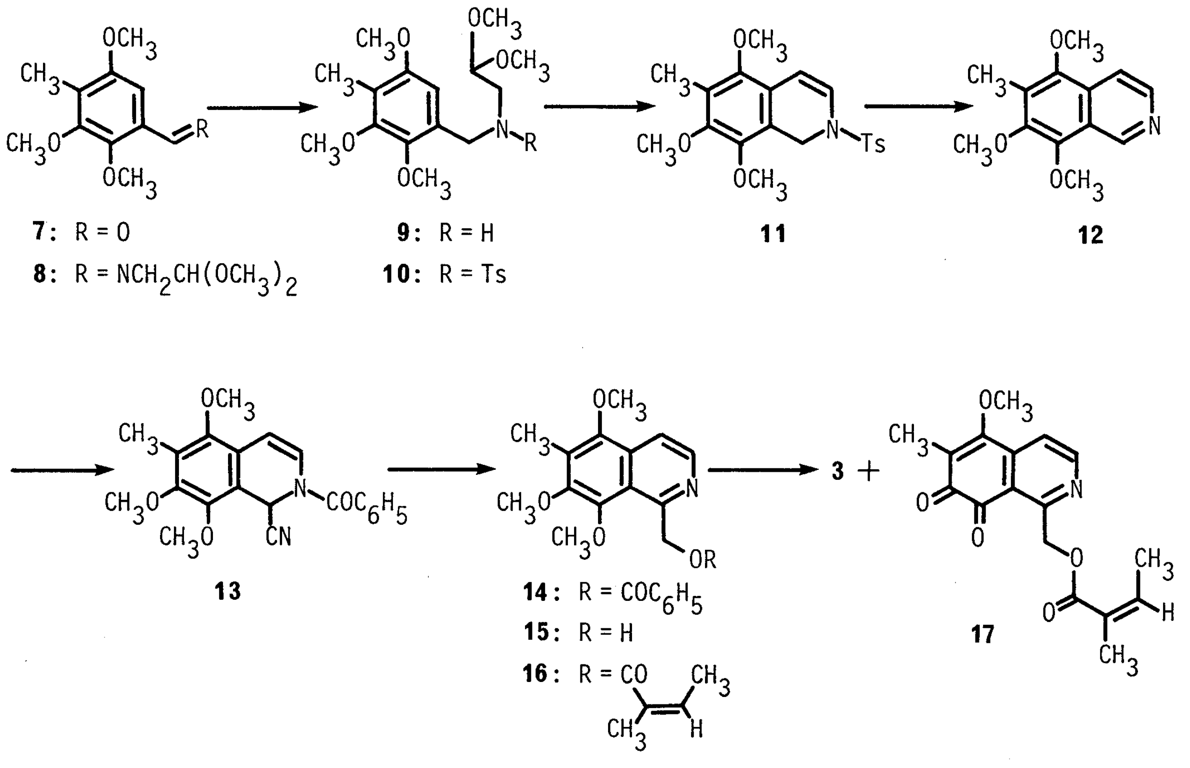

Chart 2

steps with 80% overall yield.

The isoquinoline **12** was treated with potassium cyanide and benzoyl chloride[11] to afford the Reissert compound **13** in 73% yield. The lithium salt of **13**, prepared by treatment with *n*-butyllithium in tetrahydrofuran (THF) at −40 °C, was treated with gaseous formaldehyde[12] to yield (5,7,8-trimethoxy-6-methyl-1-isoquinolyl)methyl benzoate (**14**) in 40% yield. On hydrolysis with potassium hydroxide in methanol, **14** was converted to **15** (93% yield), which was treated with phenyllithium in dioxane–ether followed by addition of angeloyl chloride[13] to afford the angelate ester **16** in 78% yield. The oxidative demethylation of **16** with CAN in aqueous acetonitrile containing pyridine-2,6-dicarboxylic acid *N*-oxide[14] furnished the desired *p*-quinone **3** (26% yield) and *o*-quinone isomer **17** (40% yield). The *o*-quinone **17** is known to be convertable to the *p*-quinone **3** in good yield.[15] Our synthetic *p*-quinone **3** was identical with renierone isolated from the sponge *Reniera* in terms of melting point, and infrared (IR), ^{1}H-NMR, ^{13}C-NMR[16] and MS spectra. (Chart 2).

The *p*-quinone structure for renierone (**3**) was confirmed by independent synthesis from 7-methoxy-6-methylisoquinoline[17] (**18**) in seven steps. The isoquinoline **18** was nitrated with potassium nitrate in sulfuric acid[18] to afford 7-methoxy-6-methyl-8-nitroisoquinoline[19] (**19**, 59% yield), which was converted to the Reissert compound **20** in 40% yield. Treatment of **20** with phenyllithium and then with gaseous formaldehyde afforded the benzoate **21** (61% yield), which was subsequently hydrolyzed with sodium hydroxide in ethanol to afford the isoquinolylmethanol **22** in 93% yield. Catalytic hydrogenation of **22** with 10% palladium on carbon in methanol afforded the aminoisoquinoline **23** in 92% yield. The oxidation of **23** with potassium nitrosodisulfonate (Fremy's salt)[20] furnished the *p*-quinone **24** in 64% yield. The quinone **24** was treated with phenyllithium in dioxane–ether, followed by addition of angeloyl

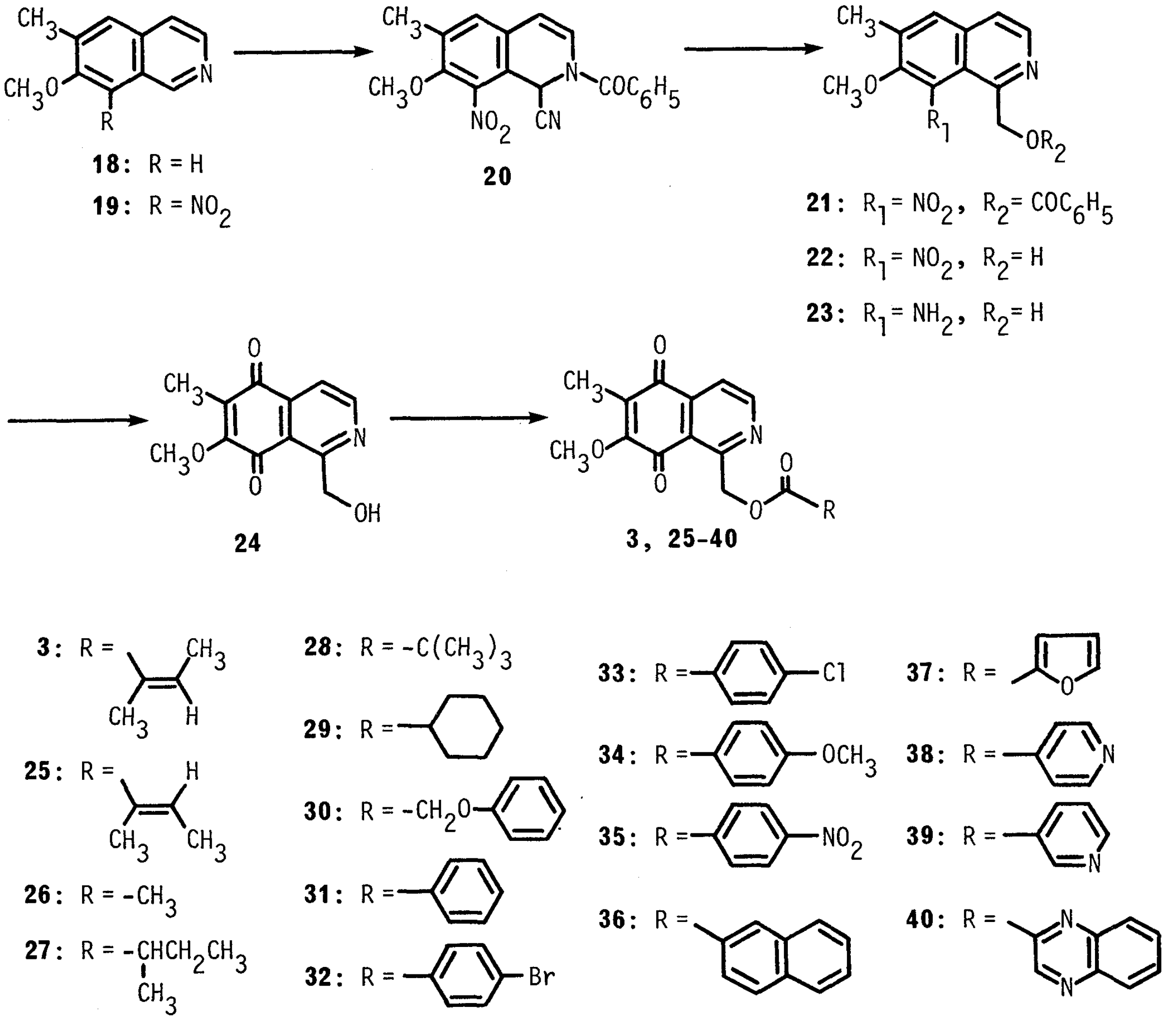

Chart 3

chloride to furnish the angelate ester **3** (38% yield), which was identical with the *p*-quinone obtained by the oxidative demethylation reaction of **16** (IR, ^{1}H-NMR, ^{13}C-NMR and MS spectra, and mixed melting point). However, attempted esterification of **24** with angeloyl chloride in pyridine failed, giving the tiglate ester **25** (32% yield), which was identical with the ester obtained by treatment of **24** with tigloyl chloride in pyridine.

The potent biological properties of renierone (**3**) led us to undertake the synthesis of derivatives of **3**, *i.e.* the (7-methoxy-6-methyl-5,8-dioxo-5,8-dihydro-1-isoquinolyl)methyl esters **26**—**40**. The esters were prepared by treatment of **24** with phenyllithium followed by the appropriate acyl chloride in dioxane–ether (method A) and/or by treatment of **24** with the appropriate acyl chloride in pyridine (method B). The biological properties will be reported separately. (Chart 3).

Next we studied the synthesis of 7-methoxy-1,6-dimethyl-5,8-dihydroisoquinoline-5,8-dione (**4**). The trimethoxyisoquinolylmethanol **15** was treated with phenyllithium followed by *p*-toluenesulfonyl chloride in dioxane–ether to afford the tosylate **41** (74% yield), which was reduced with lithium triethylborohydride[21] to give 5,7,8-trimethoxy-1,6-dimethylisoquinoline (**42**) in 69% yield. The isoquinoline **42** was also prepared directly from **15** by treatment with zinc in acetic anhydride in 90% yield. The oxidative demethylation of **42** with CAN yielded the desired *p*-quinone **4** (30% yield) and *o*-quinone isomer **43** (42% yield). The isoquinoline **42** was also oxidatively demethylated by using argentic oxide (AgO) in dioxane containing nitric acid[22] to afford the *p*-quinone **4** (31% yield) and *o*-quinone isomer **43** (28% yield). The *p*-quinone **4** thus obtained was identical with the natural product in spectral (^{1}H-NMR, ^{13}C-NMR[16] and MS spectra) properties, but not in melting point, reported as mp 188—190 °C (dec.)[9] (obsd. mp 137—138 °C).

The *p*-quinone structure for **4** was confirmed by the following independent synthesis. The nitroalcohol **22** was treated with phenyllithium and then *p*-toluenesulfonyl chloride in dioxane–ether to afford the tosylate **44** (85% yield), which was reduced with lithium triethylborohydride to afford 7-methoxy-1,6-dimethyl-8-nitroisoquinoline (**45**) in 57% yield. Catalytic hydrogenation of **45** with 10% palladium on carbon in methanol afforded the aminoisoquinoline **46** in 78% yield. Fremy's salt oxidation of **46** furnished the quinone **4** (83% yield), which was identical with the *p*-quinone obtained by the oxidative demethylation reaction of **42** with CAN or AgO (IR, ^{1}H-NMR, ^{13}C-NMR and MS spectra, and mixed melting point). The *p*-quinone **4** was also prepared from the quinone alcohol **24**. Treatment of **24** with zinc in acetic anhydride afforded the 5,8-diacetoxyisoquinoline **47** (65% yield), which

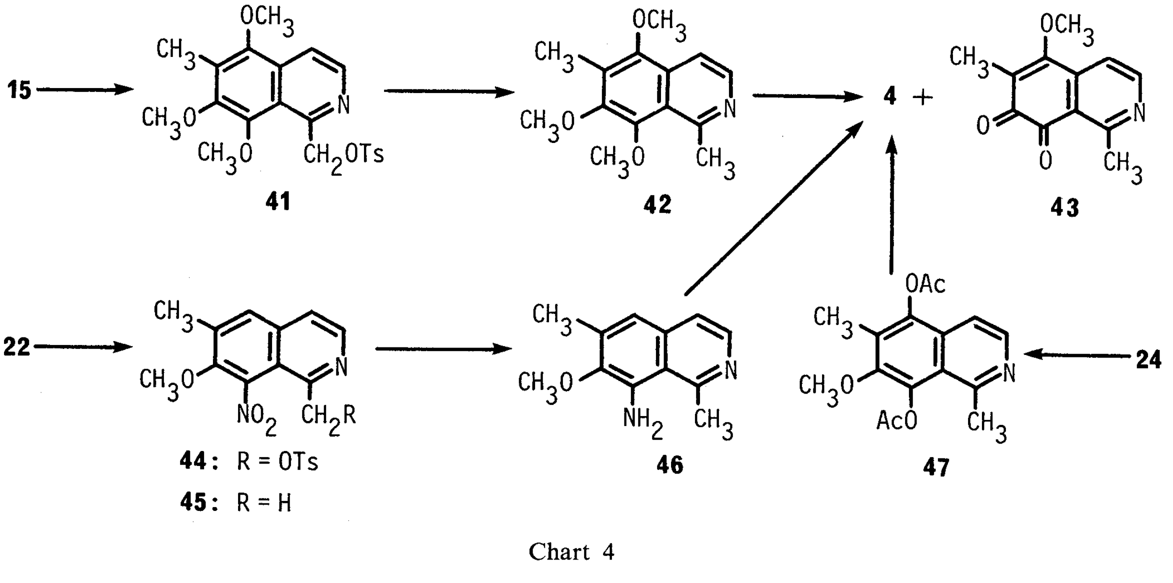

Chart 4

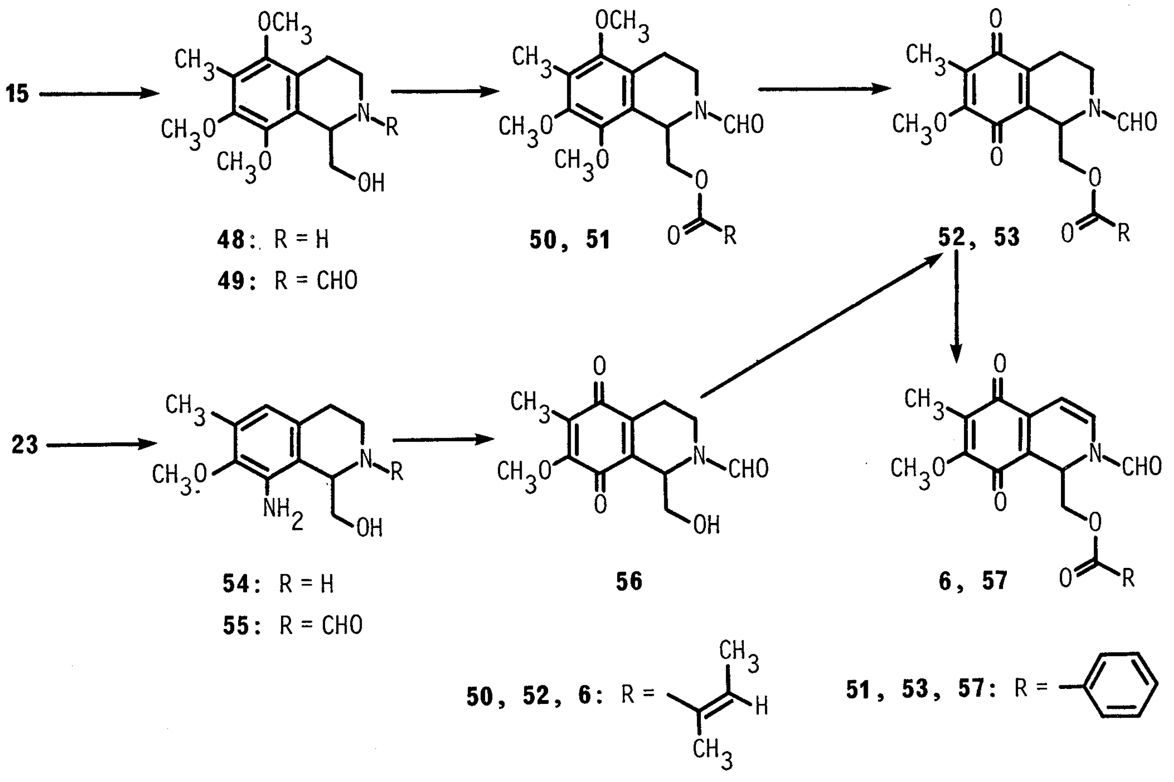

Chart 5

was deacetylated to the *p*-quinone **4** with sulfuric acid in methanol (74% yield). (Chart 4).

Finally we studied the synthesis of (±)-*N*-formyl-1,2-dihydrorenierone (**6**). Catalytic hydrogenation of (5,7,8-trimethoxy-6-methyl-1-isoquinolyl)methanol (**15**) with platinum (IV) dioxide in acetic acid afforded the tetrahydroisoquinoline **48**, which was *N*-formylated with ethyl formate to give **49** (77% yield from **15**). The *N*-formyltetrahydroisoquinoline **49** was treated with phenyllithium and then angeloyl chloride in dioxane–ether to afford the angelate ester **50** (66% yield), which was subsequently oxidized with CAN to give the *p*-quinone **52** (40% yield) but no *o*-quinone isomer. The *p*-quinone structure for **52** was confirmed by independent synthesis from **23**. The aminoisoquinoline **23** was catalytically reduced to **54**, which was subsequently *N*-formylated to give **55** (54% yield from **23**). Fremy's salt oxidation of **55** afforded the *p*-quinone **56** (74% yield), which was treated with phenyllithium and then angeloyl chloride to furnish the angelate ester **52** (70% yield). Dehydrogenation of **52** with 10% palladium on carbon in refluxing benzene afforded the desired (±)-*N*-formyl-1,2-dihydrorenierone (**6**, 59% yield), which was identical with the natural product in spectral (IR, ^{1}H-NMR, ^{13}C-NMR and MS spectra) properties. Furthermore, the benzoate analog **57** of **6** was prepared from **49** by the same procedure as used for the synthesis of **6**. Finally we confirmed that **6** was equilibrated in solution to a 2:1 mixture of **6a** and **6b** by ^{13}C-NMR spectroscopy in the gated decoupling non nuclear Overhauser effect (NOE) mode.[16] Other *N*-formylisoquinolines **49**—**53** and **55**—**57** were also equilibrated to a mixture of *cis* and *trans* rotamers[23] as judged from the ^{1}H-NMR and/or ^{13}C-NMR[16] spectra, which displayed characteristic chemical shift differences for the two rotamers. The chemical shift values for the pertinent protons are given in the experimental section. (Chart 5).

Experimental

All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. MS were taken on a JEOL JMS-D 300 instrument and the relative intensity of the ions is indicated in parenthesis as percent of the base peak. Ultraviolet (UV) spectra were recorded on a Hitachi 340 spectrophotometer. IR spectra were obtained with a JASCO DS-701G spectrometer. ^{1}H-NMR spectra were measured with a JEOL PS-100 (100 MHz) spectrometer, with tetramethylsilane as an internal standard.

2,2-Dimethoxy-*N*-(2,3,5-trimethoxy-4-methylbenzylidene)ethylamine (8)——Aminoacetaldehyde dimethylacetal (3.47 g, 33 mmol) was added to a solution of 2,3,5-trimethoxy-4-methylbenzaldehyde (**7**, 6.30 g, 30 mmol) in benzene (50 ml). The mixture was refluxed in a Dean–Stark apparatus until no further water appeared. Removal of the solvent under vacuum gave the required Schiff's base **8** (8.92 g, 100%) as a pale yellow oil, which was used without further purification. MS *m/z*: 297 (M$^+$, 6), 266 (3), 222 (4), 75 (100). High-resolution MS Calcd for $C_{15}H_{23}NO_5$: 297.1576. Found: 297.1544. IR ν_{max}^{neat} cm^{-1}: 1640 (C=N). ^{1}H-NMR (CDCl$_3$) δ: 2.11 (3H, s, Ar-CH$_3$), 3.38 (6H, s, -CH(OC$\underline{H}_3$)$_2$), 3.76 (2H, d, J=5 Hz, -C$\underline{H}_2$CH<), 3.81 (9H, s, 3×Ar-OCH$_3$), 4.64 (1H, t, J=5 Hz, -CH$_2$C$\underline{H}$<), 7.14 (1H, s, Ar-H), 8.60 (1H, s, CH=N).

2,2-Dimethoxy-*N*-(2,3,5-trimethoxy-4-methylbenzyl)ethylamine (9)——The Schiff's base **8** (8.92 g, 30 mmol) was dissolved in methanol (80 ml) and NaBH$_4$ (1.25 g, 33 mmol) was added in portions with stirring. The mixture was stirred for an additional 5 min, then diluted with water (400 ml), and extracted with CH$_2$Cl$_2$. The extract was washed with water and dried over Na$_2$SO$_4$. Removal of the solvent under reduced pressure gave the required *N*-benzylaminoacetal **9** (8.70 g, 97%) as a colorless oil, which was used without further purification. MS *m/z*: 299 (M$^+$, 8), 224 (22), 195 (100), 180 (52). High-resolution MS Calcd for $C_{15}H_{25}NO_5$: 299.1733. Found: 299.1743. IR ν_{max}^{neat} cm^{-1}: 3320 (NH). ^{1}H-NMR (CDCl$_3$) δ: 1.64 (1H, br s, NH), 2.08 (3H, s, Ar-CH$_3$), 2.70 (2H, d, J=5 Hz, -C$\underline{H}_2$CH<), 3.33 (6H, s, -CH(OC$\underline{H}_3$)$_2$), 3.79 (11H, s, 3×Ar-OCH$_3$ and Ar-CH$_2$-N<), 4.47 (1H, t, J=5 Hz, -CH$_2$C$\underline{H}$<), 6.53 (1H, s, Ar-H).

2,2-Dimethoxy-*N*-(2,3,5-trimethoxy-4-methylbenzyl)-*N*-tosylethylamine (10)——*p*-Toluenesulfonyl chloride (6.60 g, 34.6 mmol) was added to a solution of **9** (7.90 g, 26.4 mmol) in pyridine (40 ml). The solution was stirred at 20 °C for 16 h, then poured into ice-water (150 ml) and extracted with ether. The extract was washed with 5% HCl and water. Removal of the solvent under vacuum gave **10** as a solid (10.29 g, 86%), which was used without further purification. Recrystallization from ether–hexane gave an analytical sample as pale yellow prisms melting at 77—78 °C. *Anal.* Calcd for $C_{22}H_{31}NO_7S$: C, 58.26; H, 6.89; N, 3.09. Found: C, 58.01; H, 6.97; N, 3.14. MS *m/z*: 453 (M$^+$, 7), 421 (3), 298 (5), 75 (100). High-resolution MS Calcd for $C_{22}H_{31}NO_7S$: 453.1821. Found: 453.1820. IR ν_{max}^{KBr} cm^{-1}: 1350, 1165 (SO$_2$N<). ^{1}H-NMR (CDCl$_3$) δ: 2.04 (3H, s, C$_4$-CH$_3$), 2.36 (3H, s, C$\underline{H}_3$–C$_6$H$_4$–SO$_2$–), 3.20 (6H, s, -CH(OC$\underline{H}_3$)$_2$), 3.23 (2H, d, J=5 Hz, -C$\underline{H}_2$CH<), 3.64 (3H, s, Ar-OCH$_3$), 3.69 (3H, s, Ar-OCH$_3$), 3.72 (3H, s, Ar-OCH$_3$), 4.37 (1H, t, J=5 Hz, -CH$_2$C$\underline{H}$<), 4.46 (2H, s, Ar-CH$_2$-N<), 6.48 (1H, s, C$_6$-H), 7.24 (2H, d, J=8 Hz) and 7.70 (2H, d, J=8 Hz) for CH$_3$–C$_6\underline{H}_4$–SO$_2$–.

5,7,8-Trimethoxy-6-methyl-*N*-tosyl-1,2-dihydroisoquinoline (11)——The *N*-benzyl-*N*-tosylaminoacetal **10** (9.07 g, 20 mmol) in dioxane (180 ml) was treated with 6 N HCl (23 ml). The solution was boiled under reflux for 1 h, then poured into water (400 ml) and extracted with ether. The extract was washed with water and dried over Na$_2$SO$_4$; removal of the solvent under reduced pressure gave the *N*-tosyl-1,2-dihydroisoquinoline **11** as a solid (7.54 g, 97%), which was used without further purification. Recrystallization from ether–hexane gave an analytical sample as pale yellow prisms melting at 99—100 °C. *Anal.* Calcd for $C_{20}H_{23}NO_5S$: C, 61.71; H, 5.95; N, 3.60. Found: C, 61.91; H, 6.14; N, 3.73. MS *m/z*: 389 (M$^+$, 40), 234 (100), 204 (51), 203 (25). High-resolution MS Calcd for $C_{20}H_{23}NO_5S$: 389.1297. Found: 389.1306. IR ν_{max}^{KBr} cm^{-1}: 1345, 1170 (SO$_2$N<). ^{1}H-NMR (CDCl$_3$) δ: 2.06 (3H, s, C$_6$-CH$_3$), 2.32 (3H, s, C$\underline{H}_3$–C$_6$H$_4$–SO$_2$–), 3.56 (3H, s, OCH$_3$), 3.72 (6H, s, 2×OCH$_3$), 4.53 (2H, s, CH$_2$N<), 6.00 (1H, d, J=8 Hz, C$_4$-H), 6.68 (1H, d, J=8 Hz, C$_3$-H), 7.22 (2H, d, J=9 Hz) and 7.67 (2H, d, J=9 Hz) for CH$_3$–C$_6\underline{H}_4$–SO$_2$–.

5,7,8-Trimethoxy-6-methylisoquinoline (12)——Potassium *tert*-butoxide (11.0 g, 98 mmol) was added to a solution of **11** (8.5 g, 21.8 mmol) in *tert*-butyl alcohol (80 ml). The mixture was refluxed for 5 min and then the solvent was removed under reduced pressure; the residue was extracted into ether. The ether solution was washed with water, and extracted with 5% HCl (3×100 ml). The resulting yellow solution was made alkaline with conc. ammonium hydroxide and re-extracted with ether. The ether extract was washed with water, dried over Na$_2$SO$_4$ and evaporated. The residue was chromatographed on a silica gel column using CH$_2$Cl$_2$–acetone (9 : 1) as the eluent to give the desired isoquinoline **12** (5.02 g, 99%), which was used without further purification. Recrystallization from hexane gave an analytical sample as colorless prisms melting at 35 °C. *Anal.* Calcd for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48; N, 6.01. Found: C, 66.64; H, 6.48; N, 5.92. MS *m/z*: 233 (M$^+$, 100), 218 (72), 203 (17), 190 (42). High-resolution MS Calcd for $C_{13}H_{15}NO_3$: 233.1052. Found: 233.1033. ^{1}H-NMR (CDCl$_3$) δ: 2.34 (3H, s, CH$_3$), 3.84 (3H, s, OCH$_3$), 3.94 (3H, s, OCH$_3$), 4.00 (3H, s, OCH$_3$), 7.72 (1H, d, J=6 Hz, C$_4$-H), 8.47 (1H, d, J=6 Hz, C$_3$-H), 9.48 (1H, s, C$_1$-H).

***N*-Benzoyl-1-cyano-5,7,8-trimethoxy-6-methyl-1,2-dihydroisoquinoline (13)**——Benzoyl chloride (2.38 ml, 20 mmol) was added dropwise for 5 min to a stirred mixture of **12** (2.33 g, 10 mmol) in CH$_2$Cl$_2$ (10 ml) and KCN (1.95 g, 30 mmol) in water (3.85 ml). The resulting mixture was stirred for an additional 1 h, then diluted with water and extracted with CH$_2$Cl$_2$. The extract was washed with brine, dried over Na$_2$SO$_4$, and evaporated. The residue was chromatographed on a silica gel column using ethyl acetate–hexane (2 : 5) as the eluent to give **13** (2.65 g, 73%) as a colorless oil. MS *m/z*: 364 (M$^+$, 17), 233 (100), 218 (67), 105 (98). High-resolution MS Calcd for $C_{21}H_{20}N_2O_4$: 364.1423. Found: 364.1414. IR ν_{max}^{KBr} cm^{-1}: 1670 (C=O). ^{1}H-NMR (CDCl$_3$) δ: 2.19 (3H, s, CH$_3$), 3.72 (3H, s, OCH$_3$), 3.82 (3H, s, OCH_3), 3.98 (3H, s, OCH_3), 6.17 (1H, d, $J=8$ Hz, C_4-H), 6.55 (1H, d, $J=8$ Hz, C_3-H), 6.76 (1H, s, C_1-H), 7.4—7.7 (5H, m, C_6H_5).

(5,7,8-Trimethoxy-6-methyl-1-isoquinolyl)methyl Benzoate (14)——*n*-Butyllithium (1.30 ml of 1.16 M hexane solution, 1.51 mmol) was added to a solution of **13** (540 mg, 1.48 mmol) in dry THF (30 ml) at −40 °C under a nitrogen atmosphere; gaseous formaldehyde was passed through the solution with stirring and cooling at −25—−28 °C for about 10 min. The resulting suspension was warmed gradually to 18 °C for 1 h with stirring under a nitrogen atmosphere, then diluted with water and extracted with $CHCl_3$. The extract was washed with brine, dried over Na_2SO_4 and evaporated. The residue was recrystallized from methanol to give **14** (220 mg, 40%) as colorless columns melting at 138—139.5 °C. *Anal.* Calcd for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.80; H, 5.80; N, 3.80. MS *m*/*z*: 367 (M^+, 26), 262 (100), 105 (55), 77 (21). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1720 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.36 (3H, s, CH_3), 3.84 (6H, s, $2\times OCH_3$), 3.91 (3H, s, OCH_3), 6.00 (2H, s, CH_2O), 7.3—7.6 (3H, m) and 8.06 (2H, dd, $J=8$, 2 Hz) for C_6H_5, 7.74 (1H, d, $J=6$ Hz, C_4-H), 8.38 (1H, d, $J=6$ Hz, C_3-H).

(5,7,8-Trimethoxy-6-methyl-1-isoquinolyl)methanol (15)——A solution of **14** (577 mg, 1.57 mmol) in methanol (10 ml) containing KOH (200 mg) was refluxed for 5 min. The solvent was removed under reduced pressure and water was added. The precipitated crystals were collected and recrystallized from methanol to give the alcohol **15** (383 mg, 93%) as colorless prisms melting at 94—95 °C. *Anal.* Calcd for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.82; H, 6.61; N, 5.23. MS *m*/*z*: 263 (M^+, 100), 248 (41), 234 (37), 216 (27), 204 (37). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3400 (OH). ^{1}H-NMR ($CDCl_3$) δ: 2.36 (3H, s, CH_3), 3.85 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 5.27 (2H, s, CH_2O), 7.71 (1H, d, $J=6$ Hz, C_4-H), 8.34 (1H, d, $J=6$ Hz, C_3-H).

(5,7,8-Trimethoxy-6-methyl-1-isoquinolyl)methyl Angelate (16)——A solution of the alcohol **15** (278 mg, 1.1 mmol) in dry dioxane–ether (1 : 1, 12 ml) was cooled with ice-salt bath; phenyllithium (0.64 ml of 1.88 M benzene solution, 1.2 mmol) and then angeloyl chloride (130 mg, 1.1 mmol) in dry ether (1.2 ml) were added. The mixture was stirred for 5 min under cooling with an ice-salt bath, then diluted with water and extracted with ether. The extract was washed with brine, dried over Na_2SO_4 and evaporated. The residue was chromatographed on a silica gel column using benzene–ethyl acetate as the eluent to give the angelate ester **16** (285 mg, 78%) as an oil [the alcohol **15** (32 mg, 12%) was recovered]. MS *m*/*z*: 345 (M^+, 32), 262 (100), 83 (27), 55 (28). High-resolution MS Calcd for $C_{19}H_{23}NO_5$: 345.1576. Found: 345.1594. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1710 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.92 (3H, s, CH_3–C=), 1.96 (3H, d, $J=6$ Hz, $\underline{CH_3}$–CH=), 2.36 (3H, s, C_6-CH_3), 3.83 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 5.84 (2H, s, CH_2O), 6.01 (1H, q, $J=6$ Hz, CH_3–C$\underline{H}$=), 7.70 (1H, d, $J=6$ Hz, C_4-H), 8.32 (1H, d, $J=6$ Hz, C_3-H).

The Oxidative Demethylation of 16——A solution of CAN (1.64 g, 3 mmol) in acetonitrile–water (1 : 1, 6 ml) was added dropwise to an ice-cooled solution of **16** (207 mg, 0.6 mmol) in acetonitrile–water (1 : 1, 6 ml) containing suspended pyridine-2,6-dicarboxylic acid *N*-oxide (550 mg, 3 mmol) with stirring. The mixture was stirred for an additional 15 min below 5 °C, then diluted with water, adjusted to pH 7—8 with 2 N NaOH and extracted with $CHCl_3$. The extract was washed with brine, dried over Na_2SO_4 and evaporated. The residue was chromatographed on a silica gel column using benzene–ethyl acetate as the eluent to give the desired *p*-quinone **3** (less polar) and *o*-quinone isomer **17** (more polar). The crude quinones thus obtained were recrystallized from methanol.

(7-Methoxy-6-methyl-5,8-dioxo-5,8-dihydro-1-isoquinolyl)methyl Angelate (Renierone, **3**): Yield 48 mg (26%); mp 92—92.5 °C [lit.[8] mp 91.5—92.5 °C], (yellow needles). MS *m*/*z*: 315 (M^+, 62), 232 (18), 216 (25), 83 (77), 82 (100), 55 (55). High-resolution MS Calcd for $C_{17}H_{17}NO_5$: 315.1107. Found: 315.1110. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1715, 1670, 1640 (C=O), ^{1}H-NMR ($CDCl_3$) δ: 1.98 (3H, d, $J=1.5$ Hz, CH_3–C=), 2.04 (3H, dd, $J=7$, 1.5 Hz, $\underline{CH_3}$–CH=), 2.09 (3H, s, C_6-CH_3), 4.20 (3H, s, OCH_3), 5.84 (2H, s, CH_2O), 6.14 (1H, q, $J=7$ Hz, CH_3–C$\underline{H}$=), 7.87 (1H, d, $J=5$ Hz, C_4-H), 8.91 (1H, d, $J=5$ Hz, C_3-H).

(5-Methoxy-6-methyl-7,8-dioxo-7,8-dihydro-1-isoquinolyl)methyl Angelate (**17**): Yield 74 mg (40%); mp 140—141 °C (red needles). MS *m*/*z*: 315 (M^+, 9), 287 (25), 232 (71), 204 (27), 188 (43), 83 (94), 55 (100). High-resolution MS Calcd for $C_{17}H_{17}NO_5$: 315.1107. Found: 315.1110. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1710, 1695, 1640 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.97 (3H, br s, CH_3–C=), 1.98 (3H, m, $\underline{CH_3}$–CH=), 2.12 (3H, s, C_6-CH_3), 4.04 (3H, s, OCH_3), 5.70 (2H, s, CH_2O), 5.9—6.2 (1H, m, CH_3–C$\underline{H}$=), 7.54 (1H, d, $J=5$ Hz, C_4-H), 8.74 (1H, d, $J=5$ Hz, C_3-H).

7-Methoxy-6-methyl-8-nitroisoquinoline (19)——7-Methoxy-6-methylisoquinoline (**18**, 10 g, 58 mmol) and KNO_3 (10 g, 99 mmol) were added in portions to conc. H_2SO_4 with stirring. The mixture was stirred at 60 °C for an additional 5 h, then diluted with ice-water, made alkaline with conc. ammonium hydroxide and extracted with $CHCl_3$. The extract was washed with 10% NaOH and brine, dried over Na_2SO_4 and evaporated. The residual solid was recrystallized from benzene to give the nitroisoquinoline **19** (7.48 g, 59%) as pale yellow prisms melting at 84—85 °C. *Anal.* Calcd for $C_{11}H_{10}N_2O_3$: C, 60.54; H, 4.62; N, 12.84. Found: C, 60.57; H, 4.62; N, 12.81. MS *m*/*z*: 218 (M^+, 100), 158 (27), 142 (41). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1525, 1350 (NO_2). ^{1}H-NMR ($CDCl_3$) δ: 2.47 (3H, s, CH_3), 3.95 (3H, s, OCH_3), 7.52 (1H, d, $J=5$ Hz, C_4-H), 7.75 (1H, s, C_5-H), 8.52 (1H, d, $J=5$ Hz, C_3-H), 9.03 (1H, s, C_1-H).

***N*-Benzoyl-1-cyano-7-methoxy-6-methyl-8-nitro-1,2-dihydroisoquinoline (20)**——Benzoyl chloride (3.1 ml, 26 mmol) was added dropwise to a stirred mixture of **19** (2.83 g, 13 mmol) in CH_2Cl_2 (10 ml) and KCN (2.50 g, 39 mmol) in water (5 ml). The resulting mixture was stirred for an additional 1 h, then diluted with water and extracted with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4 and evaporated. The residue was recrystallized from methanol to give the Reissert compound **20** (1.80 g, 40%) as pale yellow prisms melting at 160—

161 °C. *Anal.* Calcd for $C_{19}H_{15}N_3O_4$: C, 65.32; H, 4.33; N, 12.03. Found: C, 65.29; H, 4.41; N, 12.12. MS *m/z*: 349 (M^+, 5), 218 (3), 105 (100), 77 (17). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1680 (C=O); 1535, 1330 (NO_2). ^{1}H-NMR ($CDCl_3$) δ: 2.40 (3H, s, CH_3), 3.95 (3H, s, OCH_3), 6.11 (1H, d, J=8 Hz, C_4-H), 6.54 (1H, s, C_1-H), 6.71 (1H, d, J=8 Hz, C_3-H), 7.24 (1H, s, C_5-H), 7.3—7.7 (5H, m, C_6H_5).

(7-Methoxy-6-methyl-8-nitro-1-isoquinolyl)methyl Benzoate (21)——Phenyllithium (5.42 ml of 1.88 M benzene solution, 10 mmol) was added to a solution of **20** (3.49 g, 10 mmol) in dry dioxane–ether (1 : 1, 200 ml) at −20 °C under a nitrogen atmosphere; gaseous formaldehyde was passed through the solution for 30 min with stirring and warming gradually to −5 °C. The resulting suspension was stirred at 10 °C for an additional 30 min under a nitrogen atmosphere, then diluted with water and extracted with ether. The extract was washed with brine, dried over Na_2SO_4 and evaporated. The residue was recrystallized from methanol to give **21** (2.15 g, 61%) as pale yellow prisms melting at 128—129 °C. *Anal.* Calcd for $C_{19}H_{16}N_2O_5$: C, 64.77; H, 4.58; N, 7.95. Found: C, 64.90; H, 4.46; N, 7.65. MS *m/z*: 352 (M^+, 7), 306 (31), 247 (56), 201 (26), 105 (100), 77 (55). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1730 (C=O); 1535, 1370 (NO_2). ^{1}H-NMR ($CDCl_3$) δ: 2.54 (3H, s, CH_3), 3.96 (3H, s, OCH_3), 5.76 (2H, s, CH_2O), 7.3—7.5 (3H, m) and 8.02 (2H, dd, J=8, 2 Hz) for C_6H_5, 7.53 (1H, d, J=5 Hz, C_4-H), 7.76 (1H, s, C_5-H), 8.45 (1H, d, J=5 Hz, C_3-H).

(7-Methoxy-6-methyl-8-nitro-1-isoquinolyl)methanol (22)——A solution of **21** (380 mg, 1.1 mmol) in ethanol (10 ml) containing NaOH (200 mg) was stirred at 45 °C for 5 min. The solvent was removed under reduced pressure, and the residue was diluted with water and extracted with $CHCl_3$. The extract was washed with brine, dried over Na_2SO_4 and evaporated. The residual solid was recrystallized from methanol to give the alcohol **22** (250 mg, 93%) as pale yellow prisms melting at 148—149 °C. *Anal.* Calcd for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.29. Found: C, 58.27; H, 4.95; N, 11.37. MS *m/z*: 249 (M^++1, 83), 231 (89), 201 (100), 173 (86). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3340 (OH); 1530, 1370 (NO_2). ^{1}H-NMR ($CDCl_3$) δ: 2.56 (3H, s, CH_3), 3.97 (3H, s, OCH_3), 4.3—4.5 (1H, br s, OH), 4.96 (2H, s, CH_2O), 7.56 (1H, d, J=6 Hz, C_4-H), 7.81 (1H, s, C_5-H), 8.44 (1H, d, J=6 Hz, C_3-H).

(8-Amino-7-methoxy-6-methyl-1-isoquinolyl)methanol (23)——The nitroisoquinoline **22** (100 mg) in methanol (30 ml) was hydrogenated at 1 atm for 30 min using 10% palladium on carbon (100 mg) as a catalyst. The catalyst was filtered off and the solvent was removed. The residue was recrystallized from $CHCl_3$ to give **23** (81 mg, 92%) as colorless prisms melting at 150—152 °C with decomposition. *Anal.* Calcd for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.47; N, 12.84. Found: C, 66.06; H, 6.47; N, 12.98. MS *m/z*: 218 (M^+, 96), 203 (58), 185 (100). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3390, 3320 (NH_2). ^{1}H-NMR (CD_3OD) δ: 2.49 (3H, s, CH_3), 3.92 (3H, s, OCH_3), 5.21 (2H, s, CH_2O), 7.10 (1H, s, C_5-H), 7.51 (1H, d, J=6 Hz, C_4-H), 8.10 (1H, d, J=6 Hz, C_3-H).

(7-Methoxy-6-methyl-5,8-dioxo-5,8-dihydro-1-isoquinolyl)methanol (24)——A solution of Fremy's salt (0.3 g, 1.11 mmol) in 1/15 M aq. KH_2PO_4 (12.5 ml) was added to the amine **23** (81 mg, 0.37 mmol) in acetone (3 ml). The mixture was stirred for 5 min, diluted with water, acidified with 10% HCl, then made alkaline with 10% NaOH and extracted with $CHCl_3$. The extract was washed with brine, dried over Na_2SO_4 and evaporated. The residue was chromatographed on a silica gel column using benzene–ethyl acetate as the eluent. The quinone **24** thus obtained was recrystallized from benzene to give 55 mg (64%) of yellow powder melting at 131—133 °C. MS *m/z*: 233 (M^+, 100), 190 (50), 162 (50). High-resolution MS Calcd for $C_{12}H_{11}NO_4$: 233.0688. Found: 233.0646. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3400 (OH); 1670 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.12 (3H, s, CH_3), 4.24 (3H, s, OCH_3), 4.6—5.1 (1H, br s, OH), 5.24 (2H, s, CH_2O), 7.87 (1H, d, J=5 Hz, C_4-H), 8.84 (1H, d, J=5 Hz, C_3-H).

General Procedure for the Synthesis of (7-Methoxy-6-methyl-5,8-dioxo-5,8-dihydro-1-isoquinolyl)methyl Esters (3, 25—40)——Method A: A solution of **24** (0.25 mmol) in dry dioxane–ether (1 : 1, 3 ml) was cooled with an ice-salt bath; phenyllithium (0.15 ml of 1.88 M benzene solution, 0.28 mmol) and then the appropriate acyl chloride (0.26 mmol) in dry ether (0.3 ml) were added. The mixture was stirred for 5 min under cooling with an ice-salt bath, then diluted with water and extracted with ether. The extract was washed with brine, dried over Na_2SO_4 and evaporated. The residue was chromatographed on a silica gel column using benzene–ethyl acetate as the eluent. The ester thus obtained was recrystallized.

Method B: The appropriate acyl chloride (0.12 mmol) was added to an ice-cooled solution of **24** (0.1 mmol) in dry pyridine (0.2 ml) with stirring. The mixture was stirred for an additional 10 min, then diluted with water and extracted with $CHCl_3$. The extract was washed with brine, dried over Na_2SO_4 and evaporated. The residue was chromatographed on a silica gel column using benzene–ethyl acetate as the eluent. The ester thus obtained was recrystallized.

(7-Methoxy-6-methyl-5,8-dioxo-5,8-dihydro-1-isoquinolyl)methyl Angelate (Renierone, **3**): Yield 38% (method A).

(7-Methoxy-6-methyl-5,8-dioxo-5,8-dihydro-1-isoquinolyl)methyl Tiglate (**25**): Yield 38% (method A), 76% (method B); mp 111—112.5 °C (yellow prisms from methanol). MS *m/z*: 315 (M^+, 27), 232 (12), 216 (12), 83 (100), 55 (93). High-resolution MS Calcd for $C_{17}H_{17}NO_5$: 315.1107. Found: 315.1090. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1715, 1670, 1650 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.82 (3H, dd, J=7, 1.5 Hz, $\underline{CH_3}$–CH=), 1.89 (3H, d, J=1.5 Hz, CH_3–C=), 2.09 (3H, s, C_6-CH_3), 4.20 (3H, s, OCH_3), 5.82 (2H, s, CH_2O), 7.01 (1H, q, J=7 Hz, CH_3–$\underline{CH}$=), 7.87 (1H, d, J=5 Hz, C_4-H), 8.90 (1H, d, J=5 Hz, C_3-H).

(7-Methoxy-6-methyl-5,8-dioxo-5,8-dihydro-1-isoquinolyl)methyl Acetate[16] (**26**): Yield 37% (method A), 87% (method B).

(7-Methoxy-6-methyl-5,8-dioxo-5,8-dihydro-1-isoquinolyl)methyl α-Methylbutyrate[16] (**27**): Yield 38% (method

A), 71% (method B).

(7-Methoxy-6-methyl-5,8-dioxo-5,8-dihydro-1-isoquinolyl)methyl Pivalate (**28**): Yield 70% (method B); mp 59—60 °C (yellow needles from hexane). *Anal.* Calcd for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.04; N, 4.41. Found: C, 64.22; H, 6.08; N, 4.37. MS *m*/*z*: 317 (M^+, 10), 233 (25), 232 (16), 216 (11), 85 (18), 57 (100). IR $\nu_{\max}^{\text{KBr}}\,\text{cm}^{-1}$: 1730, 1665, 1645 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.27 (9H, s, $(CH_3)_3C$–), 2.06 (3H, s, C_6-CH_3), 4.12 (3H, s, OCH_3), 5.65 (2H, s, CH_2O), 7.84 (1H, d, J=5 Hz, C_4-H), 8.86 (1H, d, J=5 Hz, C_3-H).

(7-Methoxy-6-methyl-5,8-dioxo-5,8-dihydro-1-isoquinolyl)methyl Cyclohexanecarboxylate (**29**): Yield 80% (method B); mp 85—86 °C (yellow needles from $CHCl_3$–methanol). *Anal.* Calcd for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.21; H, 6.17; N, 4.00. MS *m*/*z*: 343 (M^+, 9), 234 (17), 233 (100), 232 (13), 217 (21), 216 (12), 83 (93), 55 (26). IR $\nu_{\max}^{\text{KBr}}\,\text{cm}^{-1}$: 1740, 1665, 1655 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.0—2.1 (10H, m, –$(CH_2)_5$–), 2.05 (3H, s, C_6-CH_3), 2.2—2.6 (1H, m, $>$CH–CO), 4.11 (3H, s, OCH_3), 5.65 (2H, s, CH_2O), 7.84 (1H, d, J=5 Hz, C_4-H), 8.88 (1H, d, J=5 Hz, C_3-H).

(7-Methoxy-6-methyl-5,8-dioxo-5,8-dihydro-1-isoquinolyl)methyl Phenoxyacetate (**30**): Yield 98% (method B); mp 70—71 °C (yellow needles from $CHCl_3$–methanol). *Anal.* Calcd for $C_{20}H_{17}NO_6\cdot 1/10H_2O$: C, 65.07; H, 4.70; N, 3.79. Found: C, 64.99; H, 4.60; N, 3.72. MS *m*/*z*: 367 (M^+, 28), 274 (35), 260 (100), 217 (47). IR $\nu_{\max}^{\text{KBr}}\,\text{cm}^{-1}$: 1765, 1665, 1640 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.09 (3H, s, C_6-CH_3), 4.17 (3H, s, OCH_3), 4.87 (2H, s, OCH_2–CO), 5.87 (2H, s, C_1-CH_2O), 6.9—7.5 (5H, m, C_6H_5), 7.91 (1H, d, J=5 Hz, C_4-H), 8.91 (1H, d, J=5 Hz, C_3-H).

(7-Methoxy-6-methyl-5,8-dioxo-5,8-dihydro-1-isoquinolyl)methyl Benzoate[16] (**31**): Yield 65% (method A), 80% (method B).

(7-Methoxy-6-methyl-5,8-dioxo-5,8-dihydro-1-isoquinolyl)methyl *p*-Bromobenzoate (**32**): Yield 57% (method B); mp 163—164 °C (yellow needles from $CHCl_3$–methanol). *Anal.* Calcd for $C_{19}H_{14}BrNO_5\cdot 1/5H_2O$: C, 54.35; H, 3.46; N, 3.34. Found: C, 54.20; H, 3.27; N, 3.36. MS *m*/*z*: 417 (M^++2, 6), 415 (M^+, 6), 232 (26), 185 (99), 183 (100). IR $\nu_{\max}^{\text{KBr}}\,\text{cm}^{-1}$: 1715, 1670, 1650 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.08 (3H, s, C_6-CH_3), 4.14 (3H, s, OCH_3), 5.94 (2H, s, CH_2O), 7.59 (2H, d, J=9 Hz) and 7.97 (2H, d, J=9 Hz) for Br–C_6H_4–, 7.87 (1H, d, J=5 Hz, C_4-H), 8.85 (1H, d, J=5 Hz, C_3-H).

(7-Methoxy-6-methyl-5,8-dioxo-5,8-dihydro-1-isoquinolyl)methyl *p*-Chlorobenzoate (**33**): Yield 66% (method B); mp 165—166 °C (yellow needles from $CHCl_3$–methanol). *Anal.* Calcd for $C_{19}H_{14}ClNO_5$: C, 61.38; H, 3.79; N, 3.76. Found: C, 61.52; H, 3.67; N, 3.71. MS *m*/*z*: 371 (M^+, 8), 232 (17), 141 (34), 139 (100). IR $\nu_{\max}^{\text{KBr}}\,\text{cm}^{-1}$: 1715, 1670, 1645 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.08 (3H, s, C_6-CH_3), 4.13 (3H, s, OCH_3), 5.93 (2H, s, CH_2O), 7.42 (2H, d, J=9 Hz) and 8.05 (2H, d, J=9 Hz) for Cl–C_6H_4–, 7.87 (1H, d, J=5 Hz, C_4-H), 8.86 (1H, d, J=5 Hz, C_3-H).

(7-Methoxy-6-methyl-5,8-dioxo-5,8-dihydro-1-isoquinolyl)methyl *p*-Methoxybenzoate (**34**): Yield 68% (method B); mp 155—156 °C (yellow needles from $CHCl_3$–methanol). *Anal.* Calcd for $C_{20}H_{17}NO_6$: C, 65.39; H, 4.66; N, 3.81. Found: C, 65.22; H, 4.58; N, 3.70. MS *m*/*z*: 367 (M^+, 4), 136 (9), 135 (100). IR $\nu_{\max}^{\text{KBr}}\,\text{cm}^{-1}$: 1720, 1660, 1650 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.10 (3H, s, C_6-CH_3), 3.90 (3H, s, $C\underline{H}_3O$–C_6H_4–), 4.17 (3H, s, C_7-OCH_3), 5.96 (2H, s, CH_2O), 6.97 (2H, d, J=9 Hz) and 8.08 (2H, d, J=9 Hz) for CH_3O–$C_6\underline{H}_4$–, 7.89 (1H, d, J=5 Hz, C_4-H), 8.89 (1H, d, J=5 Hz, C_3-H).

(7-Methoxy-6-methyl-5,8-dioxo-5,8-dihydro-1-isoquinolyl)methyl *p*-Nitrobenzoate (**35**): Yield 80% (method B); mp 192—193 °C (yellow needles from $CHCl_3$–methanol). *Anal.* Calcd for $C_{19}H_{14}N_2O_7$: C, 59.69; H, 3.69; N, 7.33. Found: C, 59.50; H, 3.60; N, 7.27. MS *m*/*z*: 382 (M^+, 21), 233 (14), 232 (100), 215 (22), 204 (28), 150 (80). IR $\nu_{\max}^{\text{KBr}}\,\text{cm}^{-1}$: 1730, 1670, 1640 (C=O); 1520, 1345 (NO_2). ^{1}H-NMR ($CDCl_3$) δ: 2.09 (3H, s, C_6-CH_3), 4.15 (3H, s, OCH_3), 6.00 (2H, s, CH_2O), 7.90 (1H, d, J=5 Hz, C_4-H), 8.32 (4H, s, NO_2–C_6H_4–), 8.86 (1H, d, J=5 Hz, C_3-H).

(7-Methoxy-6-methyl-5,8-dioxo-5,8-dihydro-1-isoquinolyl)methyl 2-Naphthalenecarboxylate (**36**): Yield 74% (method B); mp 145—146 °C (yellow needles from $CHCl_3$–methanol). *Anal.* Calcd for $C_{23}H_{17}NO_5$: C, 71.31; H, 4.42; N, 3.62. Found: C, 71.04; H, 4.27; N, 3.53. MS *m*/*z*: 387 (M^+, 14), 156 (12), 155 (100), 127 (20). IR $\nu_{\max}^{\text{KBr}}\,\text{cm}^{-1}$: 1720, 1655 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.07 (3H, s, C_6-CH_3), 4.12 (3H, s, OCH_3), 6.00 (2H, s, CH_2O), 7.4—8.2 (6H, m) and 8.69 (1H, s) for 2-naphthyl, 7.86 (1H, d, J=5 Hz, C_4-H), 8.87 (1H, d, J=5 Hz, C_3-H).

(7-Methoxy-6-methyl-5,8-dioxo-5,8-dihydro-1-isoquinolyl)methyl 2-Furancarboxylate (**37**): Yield 83% (method B); mp 122—123 °C (yellow needles from $CHCl_3$–methanol). *Anal.* Calcd for $C_{17}H_{13}NO_6$: C, 62.38; H, 4.00; N, 4.28. Found: C, 62.47; H, 3.93; N, 4.33. MS *m*/*z*: 327 (M^+, 18), 232 (29), 95 (100). IR $\nu_{\max}^{\text{KBr}}\,\text{cm}^{-1}$: 1735, 1665 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.08 (3H, s, C_6-CH_3), 4.15 (3H, s, OCH_3), 5.93 (2H, s, CH_2O), 6.52 (1H, dd, J=4, 2 Hz, C_4-H of 2-furyl), 7.26 (1H, d, J=4 Hz, C_3-H of 2-furyl), 7.59 (1H, d, J=2 Hz, C_5-H of 2-furyl), 7.86 (1H, d, J=5 Hz, C_4-H), 8.87 (1H, d, J=5 Hz, C_3-H).

(7-Methoxy-6-methyl-5,8-dioxo-5,8-dihydro-1-isoquinolyl)methyl 4-Pyridinecarboxylate (**38**): Yield 89% (method B); mp 116—117 °C (yellow plates from ethanol). *Anal.* Calcd for $C_{18}H_{14}N_2O_5$: C, 63.90; H, 4.17; N, 8.28. Found: C, 63.88; H, 4.15; N, 8.29. MS *m*/*z*: 338 (M^+, 19), 232 (87), 106 (100), 78 (59). IR $\nu_{\max}^{\text{KBr}}\,\text{cm}^{-1}$: 1735, 1670, 1640 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.08 (3H, s, C_6-CH_3), 4.14 (3H, s, OCH_3), 5.94 (2H, s, CH_2O), 7.8—8.9 (6H, m, C_3-H, C_4-H, C_5H_4N–).

(7-Methoxy-6-methyl-5,8-dioxo-5,8-dihydro-1-isoquinolyl)methyl 3-Pyridinecarboxylate (**39**): Yield 77% (method B); mp 109—110 °C (yellow prisms from ethanol). *Anal.* Calcd for $C_{18}H_{14}N_2O_5$: C, 63.90; H, 4.17; N, 8.28. Found: C, 63.83; H, 4.15; N, 8.31. MS *m*/*z*: 338 (M^+, 10), 308 (37), 232 (48), 106 (100), 78 (49). IR $\nu_{\max}^{\text{KBr}}\,\text{cm}^{-1}$: 1725, 1665 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.09 (3H, s, C_6-CH_3), 4.15 (3H, s, OCH_3), 5.98 (2H, s, CH_2O), 7.41 (1H, dd, J=8, 4 Hz, C_5-H of 3-pyridyl), 7.87 (1H, d, J=5 Hz, C_4-H), 8.37 (1H, ddd, J=8, 2, 2 Hz, C_4-H of 3-pyridyl), 8.78 (1H, dd, J=4, 2 Hz, C_6-H of 3-pyridyl), 8.84 (1H, d, J=5 Hz, C_3-H), 9.28 (1H, d, J=2 Hz, C_2-H of 3-pyridyl).

(7-Methoxy-6-methyl-5,8-dioxo-5,8-dihydro-1-isoquinolyl)methyl 2-Quinoxalinecarboxylate (**40**): Yield 71% (method B); mp 211—213 °C (yellow needles from $CHCl_3$–methanol). *Anal.* Calcd for $C_{21}H_{15}N_3O_5$: C, 64.78; H, 3.88; N, 10.79. Found: C, 64.73; H, 3.79; N, 10.70. MS *m/z*: 389 (M^+, 40), 359 (26), 232 (77), 215 (54), 130 (100), 129 (96). IR ν_{max}^{KBr} cm^{-1}: 1750, 1665 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.10 (3H, s, C_6-CH_3), 4.17 (3H, s, OCH_3), 6.16 (2H, s, CH_2O), 7.8—8.4 (5H, m) and 9.58 (1H, s) for C_4-H and 2-quinoxalyl, 8.84 (1H, d, J=5 Hz, C_3-H).

(5,7,8-Trimethoxy-6-methyl-1-isoquinolyl)methyl Tosylate (41)——A solution of (5,7,8-trimethoxy-6-methyl-1-isoquinolyl)methanol (**15**, 132 mg, 0.5 mmol) in dry dioxane–ether (1 : 1, 7.5 ml) was cooled with an ice-water bath; phenyllithium (0.27 ml of 1.88 M benzene solution, 0.5 mmol) and then a solution of *p*-toluenesulfonyl chloride (120 mg, 0.63 mmol) in dry dioxane (0.25 ml) were added with stirring. The mixture was stirred for an additional 10 min and then diluted with water. The precipitated crystals were collected and recrystallized from hexane to give the tosylate **41** (154 mg, 74%) as colorless prisms melting at 107—108 °C. *Anal.* Calcd for $C_{21}H_{23}NO_6S$: C, 60.42; H, 5.55; N, 3.36. Found: C, 60.52; H, 5.60; N, 3.34. MS *m/z*: 417 (M^+, 73), 402 (22), 262 (15), 247 (52), 246 (38), 232 (61), 231 (100), 216 (57), 204 (61), 91 (52). IR ν_{max}^{KBr} cm^{-1}: 1365, 1170 (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 2.38 (3H, s, CH_3), 2.42 (3H, s, CH_3), 3.85 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 4.00 (3H, s, OCH_3), 5.78 (2H, s, CH_2O), 7.28 (2H, d, J=8 Hz) and 7.82 (2H, d, J=8 Hz) for CH_3–$C_6\underline{H}_4$–SO_2–, 7.75 (1H, d, J=5 Hz, C_4-H), 8.33 (1H, d, J=5 Hz, C_3-H).

5,7,8-Trimethoxy-1,6-dimethylisoquinoline (42)——Method A (from **41**): Lithium triethylborohydride $Li(C_2H_5)_3BH$ (1.36 ml of 1 M THF solution, 1.36 mmol) was added to a solution of **41** (287 mg, 0.68 mmol) in dry THF (15 ml) with stirring at 0 °C. The mixture was stirred at room temperature for an additional 30 min, then diluted with ice-water and extracted with ether. The extract was washed with brine, dried over Na_2SO_4 and evaporated. The residue was chromatographed on a silica gel column with benzene–ethyl acetate as the eluent to give **42** (118 mg, 69%) as an oil. MS *m/z*: 247 (M^+, 100), 232 (77), 204 (48). High-resolution MS Calcd for $C_{14}H_{17}NO_3$: 247.1208. Found: 247.1214. ^{1}H-NMR ($CDCl_3$) δ: 2.34 (3H, s, C_6-CH_3), 3.08 (3H, s, C_1-CH_3), 3.84 (3H, s, OCH_3), 3.94 (6H, s, $2\times OCH_3$), 7.59 (1H, d, J=5 Hz, C_4-H), 8.23 (1H, d, J=5 Hz, C_3-H).

Method B (from **15**): Zinc powder (65 mg, 1 mmol) was added in portions to a solution of **15** (26 mg, 0.1 mmol) in acetic anhydride (0.5 ml) with stirring at 60 °C for 5 min. The mixture was stirred at 60 °C for an additional 30 min, diluted with methanol (1 ml) and then water, and extracted with benzene. The extract was washed with brine, and dried over Na_2SO_4; removal of the solvent under reduced pressure gave **42** (22 mg, 90%) as an oil, which was used without further purification.

The Oxidative Demethylation of 42 with CAN——A solution of CAN (2.77 g, 5 mmol) in acetonitrile–water (1 : 1, 6 ml) was added dropwise with stirring to an ice-cooled solution of **42** (124 mg, 0.5 mmol) in acetonitrile–water (2 : 1, 12 ml) containing suspended pyridine-2,6-dicarboxylic acid *N*-oxide (916 mg, 5 mmol). The mixture was stirred at room temperature for an additional 1 h, then diluted with water, adjusted to pH 9 with saturated aq. $NaHCO_3$ solution and extracted with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4 and evaporated. The residue was chromatographed on a silica gel column with ethyl acetate–hexane as the eluent to give the less polar *p*-quinone **4** (33 mg, 30%) and the more polar *o*-quinone **43** (46 mg, 42%).

7-Methoxy-1,6-dimethyl-5,8-dihydroisoquinoline-5,8-dione (**4**): mp 137—138 °C (yellow powder from benzene) [lit.[9] mp 188—190 °C (dec.)]. *Anal.* Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.55; H, 5.04; N, 6.39. MS *m/z*: 217 (M^+, 100), 187 (21), 174 (19). High-resolution MS Calcd for $C_{12}H_{11}NO_3$: 217.0739. Found: 217.0735. IR ν_{max}^{KBr} cm^{-1}: 1675 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.09 (3H, s, C_6-CH_3), 3.00 (3H, s, C_1-CH_3), 4.20 (3H, s, OCH_3), 7.72 (1H, d, J=5 Hz, C_4-H), 8.72 (1H, d, J=5 Hz, C_3-H).

5-Methoxy-1,6-dimethyl-7,8-dihydroisoquinoline-7,8-dione (**43**): mp 149 °C (dec.) (red needles from methanol). *Anal.* Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.73; H, 5.02; N, 6.53. MS *m/z*: 217 (M^+, 0.2), 189 (84), 174 (100). IR ν_{max}^{KBr} cm^{-1}: 1690 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.08 (3H, s, C_6-CH_3), 2.88 (3H, s, C_1-CH_3), 4.00 (3H, s, OCH_3), 7.46 (1H, d, J=5 Hz, C_4-H), 8.74 (1H, d, J=5 Hz, C_3-H).

The Oxidative Demethylation of 42 with Argentic Oxide——Argentic oxide (100 mg, 0.8 mmol) and 6 M HNO_3 (0.2 ml) was added to a solution of **42** (50 mg, 0.2 mmol) in dioxane (5 ml) with stirring. The mixture was stirred at room temperature for an additional 1 h, then diluted with water and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4 and evaporated. The residue was chromatographed on a silica gel column with ethyl acetate–hexane as the eluent to give the less polar *p*-quinone **4** (14 mg, 31%) and the more polar *o*-quinone **43** (12 mg, 28%). The quinones **4** and **43** thus obtained were identical with the *p*-quinone and the *o*-quinone prepared by the oxidative demethylation of **42** with CAN, respectively, in terms of IR, ^{1}H-NMR and MS spectra, and mixed melting point.

(7-Methoxy-6-methyl-8-nitro-1-isoquinolyl)methyl Tosylate (44)——The tosylation of **22** was carried out by the same procedure as used for the synthesis of **41** to give **44** in 85% yield; mp 148—149 °C (pale yellow columns from ethanol). *Anal.* Calcd for $C_{19}H_{18}N_2O_6S$: C, 56.71; H, 4.51; N, 6.96. Found: C, 56.51; H, 4.43; N, 6.81. MS *m/z*: 356 (1), 338 (30), 247 (8), 231 ($[M-OTs]^+$, 82), 91 (100). IR ν_{max}^{KBr} cm^{-1}: 1535, 1370 (NO_2); 1170 (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 2.40 (3H, s, CH_3), 2.53 (3H, s, CH_3), 3.96 (3H, s, OCH_3), 5.45 (2H, s, CH_2O), 7.23 (2H, d, J=8 Hz) and 7.73 (2H, d, $J=8$ Hz) for CH_3–C_6H_4–, 7.54 (1H, d, $J=5$ Hz, C_4-H), 7.74 (1H, s, C_5-H), 8.45 (1H, d, $J=5$ Hz, C_3-H).

7-Methoxy-1,6-dimethyl-8-nitroisoquinoline (45)——The reduction of **44** was carried out by the same procedure as used for **41** to give **45**, which was recrystallized from ethanol. Yield 57%, mp 128—129 °C (pale yellow needles). *Anal.* Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 61.78; H, 5.11; N, 11.81. MS *m/z*: 232 (M^+, 100), 215 (66), 185 (37), 129 (38). IR ν_{max}^{KBr} cm^{-1}: 1530, 1370 (NO_2). ^{1}H-NMR ($CDCl_3$) δ: 2.56 (3H, s, C_6-CH_3), 2.85 (3H, s, C_1-CH_3), 3.99 (3H, s, OCH_3), 7.46 (1H, d, $J=5$ Hz, C_4-H), 7.73 (1H, s, C_5-H), 8.34 (1H; d, $J=5$ Hz, C_3-H).

8-Amino-7-methoxy-1,6-dimethylisoquinoline (46)——The nitroisoquinoline **45** (93 mg, 0.4 mmol) in methanol (100 ml) was hydrogenated at 1 atm for 1 h using 10% palladium on carbon (93 mg) as a catalyst. The catalyst was filtered off and the solvent was removed. The residue was recrystallized from benzene to give **46** (63 mg, 78%) as colorless prisms melting at 150—151 °C. *Anal.* Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.10; H, 7.05; N, 13.69. MS *m/z*: 202 (M^+, 49), 187 (100), 159 (72). IR ν_{max}^{KBr} cm^{-1}: 3360 (NH_2). ^{1}H-NMR ($CDCl_3$) δ: 2.41 (3H, s, C_6-CH_3), 3.14 (3H, s, C_1-CH_3), 3.79 (3H, s, OCH_3), 4.4—4.9 (2H, br, NH_2), 6.95 (1H, s, C_5-H), 7.19 (1H, d, $J=5$ Hz, C_4-H), 8.10 (1H, d, $J=5$ Hz, C_3-H).

7-Methoxy-1,6-dimethyl-5,8-dihydroisoquinoline-5,8-dione (4) from 46——A solution of Fremy's salt (0.60 g, 2.2 mmol) in 1/15 aq. KH_2PO_4 (25 ml) was added to the amine **46** (63 mg, 0.3 mmol) in acetone (6 ml). The mixture was stirred at 30—40 °C for 30 min, diluted with water, acidified with 10% HCl, then made alkaline with 10% NaOH and extracted with $CHCl_3$. The extract was washed with brine, dried over Na_2SO_4 and evaporated. The residue was recrystallized from benzene to give **4** (56 mg, 83%) as a yellow powder.

5,8-Diacetoxy-7-methoxy-1,6-dimethylisoquinoline (47)——Zinc powder (327 mg, 5 mmol) was added in portions to a solution of **24** (117 mg, 0.5 mmol) in acetic anhydride (3 ml) with stirring at 60 °C for 5 min. The mixture was stirred at 60 °C for an additional 30 min, then cooled, diluted with methanol (5 ml) and then water, and extracted with benzene. The extract was washed with brine, dried over Na_2SO_4 and evaporated. The residue was recrystallized from ether–hexane to give **47** (108 mg, 65%) as colorless prisms melting at 135—136 °C. *Anal.* Calcd for $C_{16}H_{17}NO_5$: C, 63.36; H, 5.65; N, 4.62. Found: C, 63.41; H, 5.61; N, 4.57. MS *m/z*: 303 (M^+, 10), 261 (27), 219 (100), 204 (36). IR ν_{max}^{KBr} cm^{-1}: 1765 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.25 (3H, s, C_6-CH_3), 2.45 (6H, s, 2 × CH_3CO), 2.95 (3H, s, C_1-CH_3), 3.83 (3H, s, OCH_3), 7.33 (1H, d, $J=6$ Hz, C_4-H), 8.30 (1H, d, $J=6$ Hz, C_3-H).

7-Methoxy-1,6-dimethyl-5,8-dihydroisoquinoline-5,8-dione (4) from 47——Conc. H_2SO_4 (50 μl) was added to a solution of **47** (15 mg, 0.05 mmol) in methanol (1.2 ml). The mixture was refluxed for 4 h, then cooled, diluted with water, made alkaline with 5% $NaHCO_3$ and extracted with $CHCl_3$. The extract was washed with brine, dried over Na_2SO_4 and evaporated. The residue was chromatographed on a silica gel column with benzene–ethyl acetate as the eluent. The quinone **4** thus obtained was recrystallized from benzene; yield 8 mg (74%).

(5,7,8-Trimethoxy-6-methyl-1,2,3,4-tetrahydro-1-isoquinolyl)methanol (48)——The isoquinoline **15** (500 mg, 1.9 mmol) in acetic acid (5 ml) was hydrogenated at 1 atm for 5 h using platinum (IV) dioxide (175 mg) as a catalyst. The catalyst was filtered off, then the filtrate was diluted with water, made alkaline with conc. ammonium hydroxide and extracted with $CHCl_3$. The extract was washed with brine, dried over Na_2SO_4 and evaporated. The residue was recrystallized from $CHCl_3$–ether to give **48** (411 mg, 81%) as a colorless powder melting at 120—121 °C. *Anal.* Calcd for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.24. Found: C, 63.07; H, 8.01; N, 5.18. IR ν_{max}^{KBr} cm^{-1}: 3370, 3320 (NH). ^{1}H-NMR ($CDCl_3$) δ: 2.14 (3H, s, CH_3), 2.50 (2H, s, exchangeable with D_2O, OH, NH), 2.5—3.1 (4H, m, –CH_2CH_2–), 3.3—4.2 (3H, m, $>$CHCH_2O–), 3.63 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.80 (3H, s, OCH_3).

(*N*-Formyl-5,7,8-trimethoxy-6-methyl-1,2,3,4-tetrahydro-1-isoquinolyl)methanol (49)——A solution of **48** (53 mg, 0.2 mmol) in ethyl formate–methanol (1 : 1, 2 ml) was stirred for 12 h. The solvent was removed under reduced pressure and the residue was recrystallized from benzene–ether to give **49** (56 mg, 95%) as colorless prisms melting at 130—131 °C. *Anal.* Calcd for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17; N, 4.74. Found: C, 61.29; H, 7.27; N, 4.75. MS *m/z*: 295 (M^+, 1), 277 (2), 264 (100). IR ν_{max}^{KBr} cm^{-1}: 3370 (OH); 1660 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.17 (3H, s, CH_3), 3.66 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 4.75, 5.61 (1H, dd, dd, $J=9$, 4 Hz, C_1-H), 8.21 (1H, s, CHO).

(*N*-Formyl-5,7,8-trimethoxy-6-methyl-1,2,3,4-tetrahydro-1-isoquinolyl)methyl Angelate (50)——The alcohol **49** was esterified by the same procedure as used for the synthesis of **16** to give **50** as a colorless oil; yield 66%. MS *m/z*: 377 (M^+, 2), 277 (3), 264 (100). High-resolution MS Calcd for $C_{20}H_{27}NO_6$: 377.1828. Found: 377.1850. IR ν_{max}^{KBr} cm^{-1}: 1715, 1670 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.6—2.1 (6H, m, $C\underline{H}_3$–CH=C($C\underline{H}_3$)–), 2.16 (3H, s, C_6-CH_3), 3.63 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.87, 3.91 (3H, s, s, OCH_3), 4.91, 5.79 (1H, dd, dd, $J=9$, 5 Hz, C_1-H), 6.08 (1H, q, $J=8$ Hz, CH_3–C$\underline{H}$=), 8.19, 8.23 (1H, s, s, CHO).

(*N*-Formyl-5,7,8-trimethoxy-6-methyl-1,2,3,4-tetrahydro-1-isoquinolyl)methyl Benzoate (51)——A solution of **49** (663 mg, 2.25 mmol) in dry THF (15 ml) was stirred at −40 °C; phenyllithium (1.25 ml of 1.88 M benzene solution, 2.35 mmol) and then benzoyl chloride (1.10 ml, 9.4 mmol) in dry THF (1 ml) were added. The mixture was stirred at −40 °C for 5 min, then diluted with water and extracted with $CHCl_3$. The extract was washed with brine, dried over Na_2SO_4 and evaporated. The residue was chromatographed on a silica gel column using benzene–ethyl acetate as the eluent. The crude ester **51** thus obtained was recrystallized from $CHCl_3$–ether to give 664 mg (74%) of colorless prisms melting at 140—141 °C. *Anal.* Calcd for $C_{22}H_{25}NO_6$: C, 66.15; H, 6.31; N, 3.51. Found: C, 66.25; H, 6.25; N, 3.51. MS *m/z*: 399 (M^+, 3), 369 (3), 264 (100), 234 (40), 105 (20). IR ν_{max}^{KBr} cm^{-1}: 1720, 1660 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.20 (3H, s, CH_3), 3.65, 3.67 (3H, s, s, OCH_3), 3.81 (3H, s, OCH_3), 3.93, 3.97 (3H, s, s, OCH_3), 7.1—7.4 (3H, m) and 7.9—8.1 (2H, m) for C_6H_5, 8.16, 8.27 (1H, s, s, CHO).

The Oxidative Demethylation of 50 and 51——A solution of CAN (2.06 g, 3.75 mmol) in acetonitrile–water (2 : 1, 12 ml) was added in portions to an ice-cooled solution of **50** (or **51**) (0.75 mmol) in acetonitrile–water (2 : 1, 12 ml) containing suspended pyridine-2,6-dicarboxylic acid *N*-oxide (687 mg, 3.75 mmol) with stirring. The mixture was stirred for an additional 20 min below 5 °C, then diluted with water, adjusted to pH 9 with 5% $NaHCO_3$, and extracted with $CHCl_3$. The extract was washed with brine, dried over Na_2SO_4 and evaporated. The residue was chromatographed on a silica gel column using benzene–ethyl acetate as the eluent to give **52** (or **53**) as an oil.

(*N*-Formyl-7-methoxy-6-methyl-5,8-dioxo-1,2,3,4,5,8-hexahydro-1-isoquinolyl)methyl Angelate (**52**): Yield 40%. MS *m*/*z*: 347 (M^+, 8), 234 (100), 206 (17), 191 (22), 83 (17), 55 (15). High-resolution MS Calcd for $C_{18}H_{21}NO_6$: 347.1366. Found: 347.1361. IR $\nu_{\max}^{\text{KBr}}\,\text{cm}^{-1}$: 1710, 1670, 1650 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.6—2.1 (6H, m, $C\underline{H}_3$–CH=C($C\underline{H}_3$)–), 1.90, 1.92 (3H, s, s, C_6-CH_3), 4.00, 4.02 (3H, s, s, OCH_3), 5.8—6.2 (1H, m, CH_3–C$\underline{H}$=), 8.14, 8.20 (1H, s, s, CHO).

(*N*-Formyl-7-methoxy-6-methyl-5,8-dioxo-1,2,3,4,5,8-hexahydro-1-isoquinolyl)methyl Benzoate (**53**): Yield 31%. MS *m*/*z*: 369 (M^+, 7), 234 (100), 206 (15), 191 (22), 105 (21), 77 (11). High-resolution MS Calcd for $C_{20}H_{19}NO_6$: 369.1212. Found: 369.1214. ^{1}H-NMR ($CDCl_3$) δ: 1.91, 1.93 (3H, s, s, CH_3), 4.01, 4.04 (3H, s, s, OCH_3), 7.3—7.7 (3H, m) and 7.8—8.1 (2H, m) for C_6H_5, 8.15, 8.28 (1H, s, s, CHO).

(8-Amino-7-methoxy-6-methyl-1,2,3,4-tetrahydro-1-isoquinolyl)methanol (54)——The reduction of **23** was carried out by the same procedure as used for the synthesis of **48** to give **54** in 56% yield; mp 158—159 °C (colorless prisms from $CHCl_3$). *Anal.* Calcd for $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.62; H, 8.40; N, 12.58. MS *m*/*z*: 222 (M^+, 2), 204 (6), 191 (100), 176 (46). IR $\nu_{\max}^{\text{KBr}}\,\text{cm}^{-1}$: 3440, 3320, 3300, 3210 (NH_2, NH, OH). ^{1}H-NMR ($CDCl_3$) δ: 2.16 (3H, s, CH_3), 3.66 (3H, s, OCH_3), 6.31 (1H, s, C_5-H).

(8-Amino-*N*-formyl-7-methoxy-6-methyl-1,2,3,4-tetrahydro-1-isoquinolyl)methanol (55)——The formylation of **54** was carried out by the same procedure as used for **48** to give **55** in 97% yield; mp 187.5—189.5 °C (colorless powder from $CHCl_3$). *Anal.* Calcd for $C_{13}H_{18}N_2O_3 \cdot 1/10H_2O$: C, 61.93; H, 7.28; N, 11.11. Found: C, 61.86; H, 7.38; N, 11.12. MS *m*/*z*: 250 (M^+, 8), 219 (100), 204 (15), 174 (59). IR $\nu_{\max}^{\text{KBr}}\,\text{cm}^{-1}$: 3470, 3440, 3350, 3240 (NH_2, OH). ^{1}H-NMR ($CDCl_3$) δ: 2.18 (3H, s, CH_3), 3.68 (3H, s, OCH_3), 6.30, 6.33 (1H, s, s, C_5-H), 8.22, 8.28 (1H, s, s, CHO).

(*N*-Formyl-7-methoxy-6-methyl-5,8-dioxo-1,2,3,4,5,8-hexahydro-1-isoquinolyl)methanol (56)——The oxidation of **55** with Fremy's salt was carried out by the same procedure as used for **46** to give the quinone **56** in 74% yield; mp 143—145 °C (dec.) (yellow powder from $CHCl_3$). *Anal.* Calcd for $C_{13}H_{15}NO_5 \cdot 1/10H_2O$: C, 58.47; H, 5.74; N, 5.25. Found: C, 58.51; H, 5.67; N, 5.15. IR $\nu_{\max}^{\text{KBr}}\,\text{cm}^{-1}$: 3420 (OH); 1670, 1650 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.92 (3H, s, CH_3), 3.99 (3H, s, OCH_3), 8.14, 8.19 (1H, s, s, CHO).

(*N*-Formyl-7-methoxy-6-methyl-5,8-dioxo-1,2,3,4,5,8-hexahydro-1-isoquinolyl)methyl Angelate (52) from 56—— The esterification of **56** with angeloyl chloride was carried out by the same procedure as used for the synthesis of **16** to give **52** as an oil; yield 70%.

(*N*-Formyl-7-methoxy-6-methyl-5,8-dioxo-1,2,5,8-tetrahydro-1-isoquinolyl)methyl Angelate (*N*-Formyl-1,2-dihydrorenierone, 6)——A solution of **52** (174 mg, 0.5 mmol) in benzene (15 ml) containing 10% palladium on carbon (696 mg) as a catalyst was refluxed for 48 h with stirring. The catalyst was filtered off and the solvent was removed. The residue was chromatographed on a silica gel column using benzene–ethyl acetate as the eluent to give the desired *N*-formyl-1,2-dihydrorenierone (**6**, 102 mg, 59%) as a dark red oil. MS *m*/*z*: 345 (M^+, 6), 315 (19), 245 (6), 232 (100), 204 (93), 83 (75), 55 (41). High-resolution MS Calcd for $C_{18}H_{19}NO_6$: 345.1212. Found: 345.1187. UV $\lambda_{\max}^{\text{MeOH}}$ nm (log ε): 268 (4.0), 340 (3.61), 500 (3.32). IR $\nu_{\max}^{\text{KBr}}\,\text{cm}^{-1}$: 1705, 1650 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.90, 1.92 (3H, s, s, C_6-CH_3), 4.01, 4.02 (3H, s, s, OCH_3), 5.98, 6.19 (1H, d, d, J=8 Hz, C_4-H), 6.88, 7.43 (1H, d, d, J=8 Hz, C_3-H), 8.22, 8.43 (1H, s, s, CHO).

(*N*-Formyl-7-methoxy-6-methyl-5,8-dioxo-1,2,5,8-tetrahydro-1-isoquinolyl)methyl Benzoate (57)——The dehydrogenation of **53** with 10% palladium on carbon was carried out by the same procedure as used for **52** to give **57** (59%) as an oil. MS *m*/*z*: 367 (M^+, 9), 337 (13), 232 (100), 204 (75), 105 (72), 77 (28). High-resolution MS Calcd for $C_{20}H_{17}NO_6$: 367.1056. Found: 367.1052. ^{1}H-NMR ($CDCl_3$) δ: 1.92, 1.94 (3H, s, s, CH_3), 4.02, 4.03 (3H, s, s, OCH_3), 6.05, 6.24 (1H, d, d, J=8 Hz, C_4-H), 8.31, 8.46 (1H, s, s, CHO). However, **53** was not dehydrogenated with chloranil or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in refluxing benzene; **53** was recovered quantitatively.

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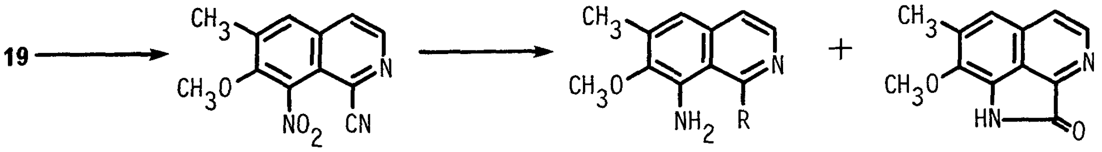

58

59: R = CN

60: R = CONH$_2$

61: R = H

62

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