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Synthesis of Mimocin, an Isoquinolinequinone Antibiotic from *Streptomyces lavendulae*, and Its Congeners

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Mimocin, an isoquinolinequinone antibiotic from *Streptomyces lavendulae* No. 314, and its congeners were synthesized.

Keywords——mimocin; antibiotic; *Streptomyces lavendulae*; isoquinolinequinone; synthesis; oxidative demethylation; ceric ammonium nitrate; congener

In recent years several naturally occurring isoquinolinequinones have been isolated from Actinomycetes and from marine sponges.[1)]

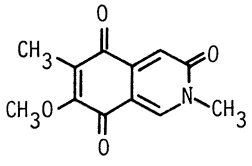
Arai and co-workers reported the isolation and the structural elucidation of satellite antibiotics, named mimosamycin[2)] (**1**) and saframycins A[3)] (**2**), B (**3**) and C[4)] (**4**) from *Streptomyces lavendulae* No. 314. In 1977, the structure of mimosamycin was determined as 2,6-dimethyl-7-methoxy-2,3,5,8-hexahydroisoquinoline-3,5,8-trione (**1**) by an X-ray crystallographic study and synthesis.[5)] Further studies of the minor metabolites led to the isolation of a new antibiotic, mimocin (**5a**) which exhibited strong antimicrobial activity against *Bacillus subtilis* and *Candida albicans*.[6)] The structure of mimocin was determined as 1-pyruvoylaminomethyl-7-methoxy-6-methyl-5,8-dihydroisoquinoline-5,8-dione (**5a**) by synthesis.[6,7)]

In 1983, new isoquinolinequinone antibiotics, safracins A (**6**) and B (**7**) having an alanylaminomethyl ($CH_3CH(NH_2)CONHCH_2$–) group, were isolated from *Pseudomonas fluorescens*.[8)] Even more interesting is the recent discovery of saframycin Y3 (**8**) from *Streptomyces lavendulae*.[9)] It has a very similar structure to saframycin A (**2**) and differs only in a side chain: **8** has an alanylaminomethyl group instead of a pyruvoylaminomethyl group.

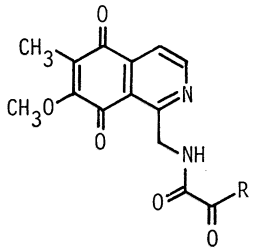
Faulkner and co-workers reported the isolation and structural determination of renierone (**9**), the major antimicrobial metabolite of a marine sponge, *Reniera* sp.[10)] It also showed strong activity against *B. subtilis* and *C. albicans*. The structural similarity between mimocin (**5a**) and renierone (**9**) 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. Further studies of the sponge led to the isolation of mimosamycin (**1**), *O*-demethylrenierone (**10**), 7-methoxy-1,6-dimethyl-5,8-dihydroisoquinoline-5,8-dione, *N*-formyl-1,2-dihydrorenierone and renieramycins A—D.[11)] We have reported the total synthesis of renierone (**9**), 7-methoxy-1,6-dimethyl-5,8-dihydroisoquinoline-5,8-dione and *N*-formyl-1,2-dihydrorenierone.[12)]

Now we report here the full details of the synthesis of **5a** and its congeners (**5b** and **5c**).

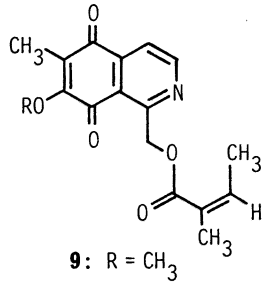
We chose 7-methoxy-6-methyl-8-nitroisoquinoline[12c)] (**11**) as a starting compound, which was catalytically reduced to the 8-aminoisoquinoline **12** in quantitative yield. The oxidation of **12** with potassium nitrosodisulfonate (Fremy's salt)[13)] furnished the isoquinolinequinone **13**



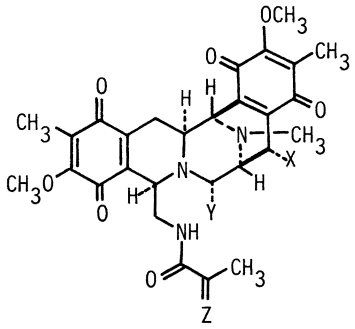
1



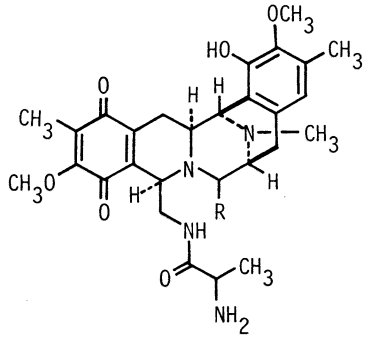
5a: R = CH_3
5b: R = CH_2CH_3
5c: R = $CH_2CH_2CH_3$



9: R = CH_3
10: R = H

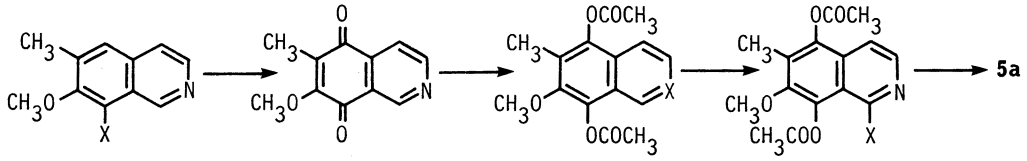


2: X = H, Y = CN, Z = O
3: X = Y = H, Z = O
4: X = OCH_3, Y = H, Z = O
8: X = H, Y = CN, Z = H, NH_2



6: R = H
7: R = OH

Chart 1



11: X = NO_2
12: X = NH_2
13
14: X = N
15: X = N→O
16: X = CN
17: X = $CH_2NH_2 \cdot 2HCl$

Chart 2

in 64% yield. The reductive acetylation of **13** with zinc in acetic anhydride[5c] afforded the 5,8-diacetoxyisoquinoline **14** in 89% yield. The *N*-oxide **15**, prepared by the oxidation of **14** with *m*-chloroperoxybenzoic acid, was treated with trimethylsilyl cyanide in *N*-methyl-2-pyrrolidone[14] to afford the 1-cyanoisoquinoline **16** in 84% yield. Catalytic hydrogenation of **16** over 10% palladium on carbon in methanol containing hydrochloric acid afforded the sensitive 1-aminomethylisoquinoline dihydrochloride **17**. Treatment of **17** with pyruvic acid in α,α-dichloromethyl methyl ether[15] furnished the desired **5a**, which was identical to the natural product in terms of mixed melting point, and infrared (IR), proton nuclear magnetic

resonance (^{1}H-NMR) and mass (MS) spectra. However, the yield of **5a** from **16** was very low, and a more efficient method was required.

Recently oxidative demethylation of hydroquinone dimethyl ethers with ceric ammonium nitrate (CAN) has been proved to be an efficient synthetic method for the preparation of various *p*-quinones.[16] We described a general process for the synthesis of various heterocyclic quinones using this reaction.[7b] Now, we have applied this reaction to the synthesis of **5a** from 5,7,8-trimethoxy-6-methylisoquinoline[12c] (**18**) (Chart 3). The *N*-oxide **19**, prepared by the oxidation of **18** with *m*-chloroperoxybenzoic acid, was treated with potassium cyanide and benzoyl chloride[17] to afford 1-cyano-5,7,8-trimethoxy-6-methylisoquinoline (**20**) in 96% yield. Catalytic hydrogenation of **20** over 10% palladium on carbon in methanol containing hydrochloric acid afforded 1-aminomethyl-5,7,8-trimethoxy-6-methylisoquinoline dihydrochloride (**21**) in quantitative yield. The free base of **21** was treated with pyruvic acid in α,α-

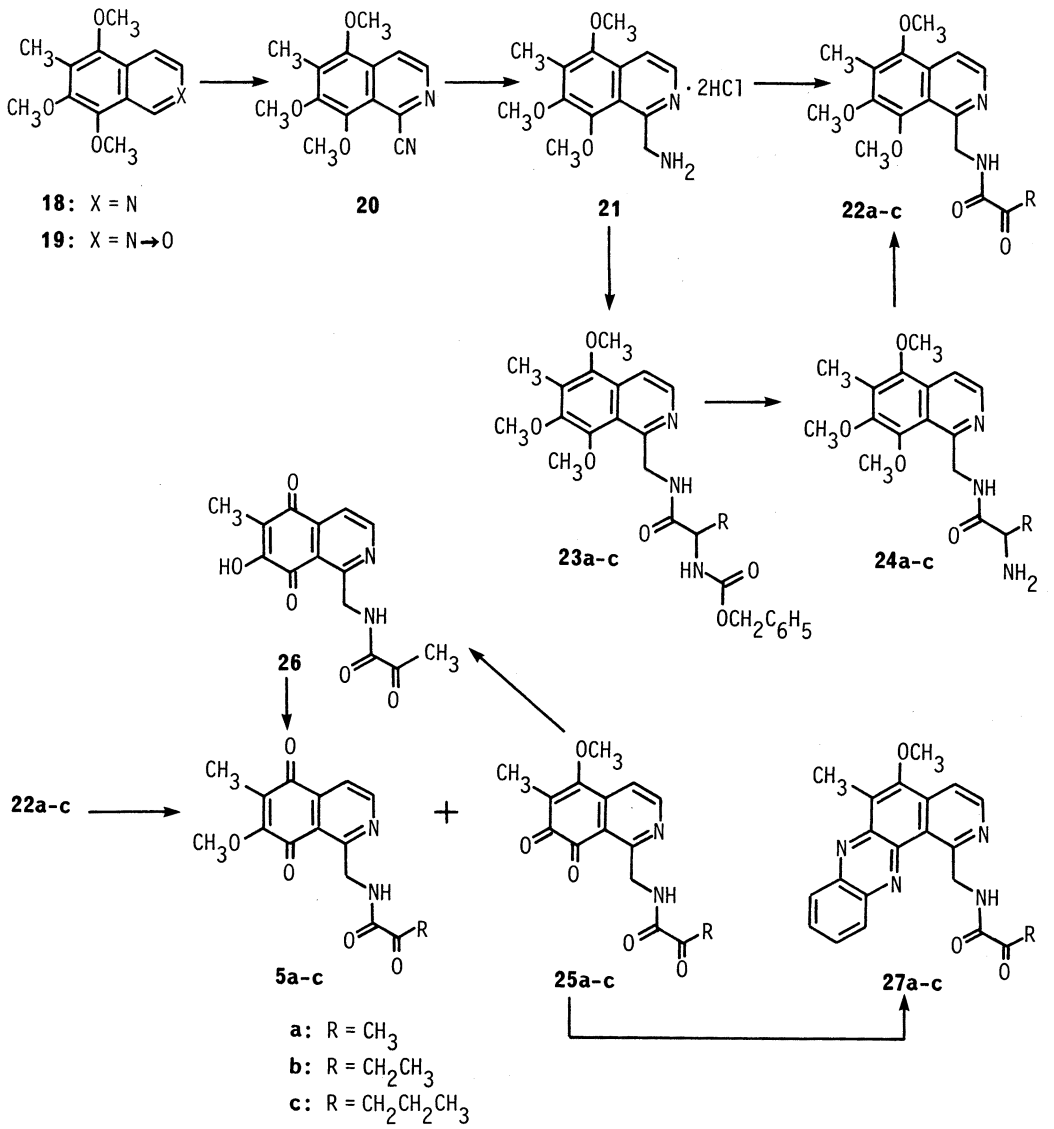


Chart 3

dichloromethyl methyl ether to afford the 1-pyruvoylaminomethylisoquinoline **22a** in 37% yield.

In 1985, Arai and co-workers reported that **2** is produced from **8** by an enzymatic deamination reaction.[9] We tried to synthesize the pyruvamide (**22a**) using a deamination reaction of the corresponding alanyl ($CH_3CH(NH_2)CO$–) group. The free base of **21** was condensed with *N*-carbobenzyloxy-DL-alanine in the presence of *N*,*N'*-dicyclohexylcarbodiimide (DCC)[18] to give **23a** (75% yield), which was converted to **24a** in the usual manner. The oxidation of **24a** with 3,5-di-*tert*-butyl-1,2-benzoquinone[19] in methanol furnished the 1-pyruvoylaminomethylisoquinoline **22a** (29% yield), which was identical to the isoquinoline obtained directly from the free base of **21**.

The oxidative demethylation of **22a** with CAN in aqueous acetonitrile containing pyridine-2,6-dicarboxylic acid *N*-oxide[16b] at 0—5 °C furnished **5a** (36% yield) and the corresponding *o*-quinone isomer **25a** (52% yield). The *p*-quinone **5a** thus obtained was identical to the natural product and the *p*-quinone derived from **16** in terms of mixed melting point, and IR, ^{1}H-NMR and MS spectra. The *o*-quinone **25a** was converted to the *p*-quinone, *i.e.* **5a**, in two steps. Treatment of **25a** with sulfuric acid[20] afforded *O*-demethylmimocin (**26**, 65% yield), which was subsequently methylated with methyl iodide in the presence of argentous oxide[21] to furnish **5a** in 39% yield.

Similarly the congeners (**5b** and **5c**) of **5a** were prepared from **21** *via* **22b** and **22c**, respectively. The oxidative demethylation of **22b** and **22c** with CAN furnished the desired *p*-quinone (**5b** and **5c**, respectively) and the corresponding *o*-quinone isomers (**25b** and **25c**, respectively). In order to confirm the *o*-quinone structure for **25a**—**c**, they were condensed with *o*-phenylenediamine to afford the corresponding pyrido[3,4-*a*]phenazines **27a**—**c**, respectively.

Experimental

All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Mass spectra 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 spectrometer (100 MHz) with tetramethylsilane as an internal standard. Microanalytical data were obtained by using a Perkin-Elmer 240B elemental analyzer.

8-Amino-7-methoxy-6-methylisoquinoline (12)——7-Methoxy-6-methyl-8-nitroisoquinoline (**11**, 9.73 g, 45 mmol) in methanol (400 ml) was hydrogenated at 1 atm for 3 h using 10% palladium on carbon (3.0 g) as a catalyst. The catalyst was filtered off and the solvent was removed under reduced pressure. The residue was recrystallized from hexane to give **12** (8.38 g, 100%) as a colorless powder melting at 78—79 °C. *Anal.* Calcd for $C_{11}H_{12}N_2O \cdot 1/5H_2O$: C, 68.87; H, 6.52; N, 14.60. Found: C, 69.07; H, 6.51; N, 14.69. MS *m/z*: 188 (M^+, 45), 173 (100), 145 (92). ^{1}H-NMR ($CDCl_3$) δ: 2.46 (3H, s, Ar-CH_3), 3.86 (3H, s, OCH_3), 4.64 (2H, br s, NH_2), 6.97 (1H, s, C_5-H), 7.39 (1H, d, J=5 Hz, C_4-H), 8.28 (1H, d, J=5 Hz, C_3-H), 9.22 (1H, s, C_1-H).

7-Methoxy-6-methyl-5,8-dihydroisoquinoline-5,8-dione (13)——A solution of Fremy's salt (25 g, 93 mmol) in 1/15 M aqueous KH_2PO_4 (1115 ml) was added dropwise to the amine **12** (8.38 g, 45 mmol) in acetone (45 ml) with stirring. The mixture was stirred at room temperature for an additional 2 h, 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 ethyl acetate–hexane as the eluent. The quinone **13** thus obtained was recrystallized from benzene to give 5.83 g (64%) of yellow needles melting at 130—131 °C. *Anal.* Calcd for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 65.08; H, 4.53; N, 6.98. MS *m/z*: 203 (M^+, 100), 173 (20), 117 (14). UV λ_{max}^{EtOH} nm ($\log \varepsilon$): 245 (4.15), 311 (3.62), 360 (3.26). IR ν_{max}^{KBr} cm^{-1}: 1658, 1670 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.08 (3H, s, C_6-CH_3), 4.18 (3H, s, OCH_3), 7.82 (1H, d, J=5 Hz, C_4-H), 8.97 (1H, d, J=5 Hz, C_3-H), 9.24 (1H, s, C_1-H).

5,8-Diacetoxy-7-methoxy-6-methylisoquinoline (14)——Zinc powder (3.74 g, 57 mmol) was added in portions to a solution of **13** (5.83 g, 29 mmol) in acetic anhydride (170 ml) with stirring at room temperature. The whole was stirred at room temperature for an additional 30 min. Then the insoluble materials were filtered off, and the filtrate was evaporated under reduced pressure and diluted with water. The precipitated crystals were collected and recrystallized from ethyl acetate to give **14** (7.40 g, 89%) as colorless needles melting at 142—143 °C. *Anal.* Calcd for

$C_{15}H_{15}NO_5$: C, 62.28; H, 5.23; N, 4.84. Found: C, 61.94; H, 5.23; N, 5.21. MS *m/z*: 289 (M^+, 7), 247 (25), 205 (100), 190 (34), 162 (58), 43 (40). IR ν_{max}^{KBr} cm^{-1}: 1760 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.31 (3H, s, C_6-CH_3), 2.49 (3H, s, $COCH_3$), 2.53 (3H, s, $COCH_3$), 3.97 (3H, s, OCH_3), 7.47 (1H, d, J=5 Hz, C_4-H), 8.48 (1H, d, J=5 Hz, C_3-H), 9.14 (1H, s, C_1-H).

5,8-Diacetoxy-7-methoxy-6-methylisoquinoline *N*-Oxide (15)——A solution of 80% *m*-chloroperoxybenzoic acid (5.52 g, 26 mmol) in CH_2Cl_2 (130 ml) was added dropwise to **14** (7.40 g, 26 mmol) in CH_2Cl_2 (50 ml) with stirring. The mixture was stirred at room temperature for 12 h, then washed with 2% aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4 and evaporated. The residue was recrystallized from $CHCl_3$ to give the *N*-oxide **15** (6.17 g, 79%) as a colorless powder melting at 188—189 °C. *Anal.* Calcd for $C_{15}H_{15}NO_6$: C, 59.02; H, 4.95; N, 4.59. Found: C, 59.23; H, 5.03; N, 4.77. MS *m/z*: 305 (M^+, 7), 263 (17), 221 (65), 220 (20), 43 (100).

5,8-Diacetoxy-1-cyano-7-methoxy-6-methylisoquinoline (16)——Trimethylsilyl cyanide (0.40 ml, 3 mmol) was added to a suspension of the *N*-oxide **15** (305 mg, 1 mmol) in *N*-methyl-2-pyrrolidone (2 ml). The mixture was stirred at 50—60 °C for 20 min, and then at room temperature for 20 h. The reaction mixture was diluted with water, and precipitated crystals were collected and recrystallized from acetone to give **16** (263 mg, 84%) as colorless prisms melting at 153—154 °C. *Anal.* Calcd for $C_{16}H_{14}N_2O_5$: C, 61.14; H, 4.49; N, 8.91. Found: C, 60.85; H, 4.60; N, 8.66. MS *m/z*: 314 (M^+, 0.8), 272 (48), 230 (100), 215 (25), 43 (70). IR ν_{max}^{KBr} cm^{-1}: 2230 (CN), 1770 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.25 (3H, s, C_6-CH_3), 2.40 (3H, s, $COCH_3$), 2.52 (3H, s, $COCH_3$), 3.88 (3H, s, OCH_3), 7.71 (1H, d, J=5 Hz, C_4-H), 8.58 (1H, d, J=5 Hz, C_3-H).

1-Pyruvoylaminomethyl-7-methoxy-6-methyl-5,8-dihydroisoquinoline-5,8-dione [Mimocin] (5a)——The 1-cyanoisoquinoline (**16**, 63 mg, 0.2 mmol) in methanol (20 ml) containing concentrated HCl (0.2 ml) was hydrogenated at 1 atm for 3 h using 10% palladium on carbon (63 mg) as a catalyst. The catalyst was filtered off and the solvent was removed under reduced pressure. The residue was washed with ether and benzene, and dried *in vacuo* to give the 1-aminomethylisoquinoline dihydrochloride **17**. Pyruvic acid (176 mg, 2 mmol) and α,α-dichloromethyl methyl ether (229 mg, 2 mmol) was added to **17** thus obtained. The whole was stirred at 50 °C for 10 min, diluted with ice-water (100 ml), adjusted to pH 8 with 10% aqueous $NaHCO_3$ solution, and extracted with ethyl acetate. The extract was washed with brine, dried over Na_2SO_4 and evaporated. The residue was chromatographed on a silica gel column using ethyl acetate–benzene as the eluent to afford mimocin (**5a**, 3 mg, 5% from **16**), which was recrystallized from ether–hexane as yellow needles; mp 189—191 °C (dec.) [lit.[6] mp 189—191 °C (dec.)]. *Anal.* Calcd for $C_{15}H_{14}N_2O_5$: C, 59.60; H, 4.67; N, 9.27. Found: C, 59.47; H, 4.60; N, 9.21. MS *m/z*: 302 (M^+, 1.2), 260 (23), 259 (100), 216 (56). UV λ_{max}^{EtOH} nm (log ε): 242 (4.23), 320 (3.65); λ_{min}^{EtOH} nm (log ε): 219 (4.11), 286 (3.17). IR ν_{max}^{KBr} cm^{-1}: 1663, 1680, 1720 (C=O), 3380 (NH). ^{1}H-NMR ($CDCl_3$) δ: 2.08 (3H, s, C_6-CH_3), 2.50 (3H, s, $COCH_3$), 4.18 (3H, s, OCH_3), 5.08 (2H, d, J=5 Hz, CH_2NH), 7.88 (1H, d, J=5 Hz, C_4-H), 8.6 (1H, br s, NH), 8.89 (1H, d, J=5 Hz, C_3-H).

5,7,8-Trimethoxy-6-methylisoquinoline *N*-Oxide (19)——A solution of 80% *m*-chloroperoxybenzoic acid (5.29 g, 24 mmol) in CH_2Cl_2 (130 ml) was added dropwise to 5,7,8-trimethoxy-6-methylisoquinoline (**18**, 2.86 g, 12 mmol) in CH_2Cl_2 (270 ml) with stirring. The mixture was stirred at room temperature for 2 h, and evaporated under reduced pressure. The residue was chromatographed on an alumina column using CH_2Cl_2 as the eluent to give the *N*-oxide **19** (3.06 g, 100%). Recrystallization from CH_2Cl_2–hexane afforded colorless needles, mp 106—107 °C. *Anal.* Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.78, H, 6.25; N, 5.77. MS *m/z*: 249 (M^+, 100), 234 (78), 206 (27), 191 (25). ^{1}H-NMR ($CDCl_3$) δ: 2.30 (3H, s, C_6-CH_3), 3.84 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 7.76 (1H, d, J=8 Hz, C_4-H), 8.02 (1H, dd, J=8, 2 Hz, C_3-H), 8.95 (1H, d, J=2 Hz, C_1-H).

1-Cyano-5,7,8-trimethoxy-6-methylisoquinoline (20)——Sodium cyanide (1.17 g, 24 mmol) and benzoyl chloride (2.51 g, 18 mmol) were added to a suspension of the *N*-oxide **19** (2.97 g, 12 mmol) in water (45 ml) with stirring. The mixture was stirred at room temperature for an additional 30 min, and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4 and evaporated. The residue was chromatographed on an alumina column using $CHCl_3$ as the eluent to give the 1-cyanoisoquinoline **20** (2.94 g, 96%). Recrystallization from ether–hexane afforded pale yellow plates, mp 99—100 °C. *Anal.* Calcd for $C_{14}H_{14}N_2O_3$: C, 65.10; H, 5.46; N, 10.85. Found: C, 64.85; H, 5.43; N, 10.76. MS *m/z*: 258 (M^+, 100), 243 (82), 215 (49). IR ν_{max}^{KBr} cm^{-1}: 2230 (CN). ^{1}H-NMR ($CDCl_3$) δ: 2.36 (3H, s, C_6-CH_3), 3.84 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 4.04 (3H, s, OCH_3), 7.97 (1H, d, J=6 Hz, C_4-H), 8.56 (1H, d, J=6 Hz, C_3-H).

1-Aminomethyl-5,7,8-trimethoxy-6-methylisoquinoline Dihydrochloride (21)——The 1-cyanoisoquinoline **20** (1.0 g, 3.9 mmol) in methanol (400 ml) containing concentrated HCl (2.0 ml) was hydrogenated at 1 atm for 2 h using 10% palladium on carbon (0.5 g) as a catalyst. The catalyst was filtered off and the solvent was removed under reduced pressure. The residual oil was dried at 50 °C *in vacuo* to give **21** (1.29 g, 100%). Recrystallization from methanol–ether afforded yellow needles, mp 180—185 °C. *Anal.* Calcd for $C_{14}H_{18}N_2O_3 \cdot 2HCl$: C, 50.16; H, 6.01; N, 8.36. Found: C, 49.88; H, 6.04; N, 8.27. MS *m/z*: 262 (M^+ of free base, 76), 234 (100). ^{1}H-NMR (CD_3OD) δ: 2.45 (3H, s, C_6-CH_3), 3.89 (3H, s, OCH_3), 3.98 (3H, s, OCH_3), 4.10 (3H, s, OCH_3), 4.92 (2H, s, CH_2), 8.28 (1H, d, J=7 Hz, C_4-H), 8.45 (1H, d, J=7 Hz, C_3-H).

1-Pyruvoylaminomethyl-5,7,8-trimethoxy-6-methylisoquinoline (22a)——An ice-cooled solution of **21** (0.45 g, 1.34 mmol) in water (20 ml) was adjusted to pH 9 with saturated aqueous $NaHCO_3$ solution, and extracted with CH_2Cl_2. The extract was washed with water, dried over Na_2SO_4 and evaporated under reduced pressure to give the

free base of **21**. A mixture of pyruvic acid (0.73 ml, 10.5 mmol) and α,α-dichloromethyl methyl ether (0.95 ml, 10.5 mmol) was stirred at 50 °C for 30 min, then cooled and added dropwise to a solution of the free base of **21** in CH_2Cl_2 (10 ml). The whole was stirred at room temperature for 10 min, then diluted with ice-cooled water (20 ml), adjusted to pH 9 with saturated aqueous $NaHCO_3$ solution, and extracted with CH_2Cl_2. The extract was washed with water, dried over Na_2SO_4 and evaporated. The residue was chromatographed on a silica gel column using benzene–ethyl acetate (8 : 2) as the eluent to give **22a** (167 mg, 37%). Recrystallization from ether–hexane afforded colorless needles, mp 156—157 °C. *Anal.* Calcd for $C_{17}H_{20}N_2O_5$: C, 61.43; H, 6.07; N, 8.43. Found: C, 61.16; H, 6.15; N, 8.21. MS *m/z*: 332 (M^+, 44), 289 (100), 261 (24), 259 (28), 231 (36), 216 (18). IR ν_{max}^{KBr} cm^{-1}: 1680, 1720 (C=O), 3350 (NH). ^{1}H-NMR ($CDCl_3$) δ: 2.37 (3H, s, C_6-CH_3), 2.52 (3H, s, $COCH_3$), 3.84 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 4.01 (3H, s, OCH_3), 5.16 (2H, d, J=5 Hz, CH_2), 7.72 (1H, d, J=6 Hz, C_4-H), 8.36 (1H, d, J=6 Hz, C_3-H), 9.1 (1H, br, NH).

1-(α-Oxo-*n*-butyrylaminomethyl)-5,7,8-trimethoxy-6-methylisoquinoline (22b)——A mixture of α-oxo-*n*-butyric acid (0.99 g, 9.7 mmol) and α,α-dichloromethyl methyl ether (0.88 ml, 9.7 mmol) was stirred at 50 °C for 20 min, and then cooled. Triethylamine (4.85 ml) and the above solution were added dropwise to an ice-cooled solution of **21** (1.63 g, 4.85 mmol) in CH_2Cl_2 (20 ml) with stirring. The whole was stirred at 0—5 °C for 1 h, then diluted with water, and extracted with $CHCl_3$. The extract was washed with 5% aqueous $NaHCO_3$ solution and water, dried over Na_2SO_4 and evaporated. The residue was chromatographed on a silica gel column using benzene–ethyl acetate (50 : 1) as the eluent to give **22b** (1.08 g, 64%). Recrystallization from benzene–ether afforded pale yellow prisms, mp 152—154 °C. *Anal.* Calcd for $C_{18}H_{22}N_2O_5$: C, 62.41; H, 6.40; N, 8.09. Found: C, 62.37; H, 6.46; N, 7.99. MS *m/z*: 346 (M^+, 21), 289 (100), 261 (14), 259 (20), 231 (28). IR ν_{max}^{KBr} cm^{-1}: 1680, 1720 (C=O), 3380 (NH). ^{1}H-NMR ($CDCl_3$) δ: 1.16 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.40 (3H, s, C_6-CH_3), 3.02 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 3.88 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 4.04 (3H, s, OCH_3), 5.19 (2H, d, J=6 Hz, $C\underline{H}_2NH$), 7.71 (1H, d, J=5 Hz, C_4-H), 8.34 (1H, d, J=5 Hz, C_3-H), 9.06 (1H, br, NH).

1-(α-Oxo-*n*-valerylaminomethyl)-5,7,8-trimethoxy-6-methylisoquinoline (22c)——A mixture of α-oxo-*n*-valeric acid (0.47 g, 4 mmol) and α,α-dichloromethyl methyl ether (0.36 ml, 4 mmol) was stirred at 50 °C for 20 min, and then cooled. Triethylamine (2 ml) and the above solution were added dropwise to an ice-cooled solution of **21** (0.67 g, 2 mmol) in CH_2Cl_2 (10 ml) with stirring. The whole was stirred at 0—5 °C for 1 h, then diluted with water, and extracted with $CHCl_3$. The extract was washed with 5% aqueous $NaHCO_3$ solution and water, dried over Na_2SO_4 and evaporated. The residue was chromatographed on a silica gel column using benzene–ethyl acetate (50 : 1) as the eluent to give **22c** (0.24 g, 34%). Recrystallization from benzene afforded yellow prisms, mp 140—142 °C. *Anal.* Calcd for $C_{19}H_{24}N_2O_5$: C, 63.32; H, 6.71; N, 7.77. Found: C, 63.29; H, 6.67; N, 7.68. MS *m/z*: 360 (M^+, 14), 342 (17), 289 (100), 261 (10), 259 (18), 231 (26). IR ν_{max}^{KBr} cm^{-1}: 1690, 1720 (C=O), 3380 (NH). ^{1}H-NMR ($CDCl_3$) δ: 0.99 (3H, t, J=7 Hz, $CH_2CH_2C\underline{H}_3$), 1.68 (2H, sextet, J=7 Hz, $CH_2C\underline{H}_2CH_3$), 2.39 (3H, s, C_6-CH_3), 2.96 (2H, t, J=7 Hz, $C\underline{H}_2CH_2CH_3$), 3.87 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 4.03 (3H, s, OCH_3), 5.18 (2H, d, J=4 Hz, $C\underline{H}_2NH$), 7.73 (1H, d, J=6 Hz, C_4-H), 8.38 (1H, d, J=6 Hz, C_3-H), 9.1 (1H, br, NH).

1-(*N*-Carbobenzyloxy-DL-alanylaminomethyl)-5,7,8-trimethoxy-6-methylisoquinoline (23a) and Its Congeners 23b—c——A solution of triethylamine (1.0 ml) in $CHCl_3$ (10 ml) was added dropwise to a suspension of **21** (1.0 g, 3 mmol) in $CHCl_3$ (20 ml) at 0 °C with stirring. Then *N*-carbobenzyloxy-DL-alanine, *N*-carbobenzyloxy-DL-α-amino-*n*-butyric acid or *N*-carbobenzyloxy-DL-norvaline (3.9 mmol), and DCC (0.80 g, 3.9 mmol) were added at 0 °C with stirring. The mixture was stirred at 0 °C for an additional 15 min, and then evaporated under reduced pressure. The residue was dissolved in ethyl acetate (60 ml), and the insoluble material was filtered off. The filtrate was washed successively with 5% aqueous citric acid solution, saturated aqueous $NaHCO_3$ solution and water, 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 corresponding product, **23a**—**c**.

1-(*N*-Carbobenzyloxy-DL-alanylaminomethyl)-5,7,8-trimethoxy-6-methylisoquinoline (**23a**): Yield 75%, mp 60—62 °C (colorless prisms from ether–hexane). *Anal.* Calcd for $C_{25}H_{29}N_3O_6$: C, 64.22; H, 6.25; N, 8.99. Found: C, 64.01; H, 6.33; N, 8.95. MS *m/z*: 467 (M^+, 33), 359 (37), 289 (100), 261 (23), 232 (48). IR ν_{max}^{KBr} cm^{-1}: 1660, 1720 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.47 (3H, d, J=7 Hz, $CHC\underline{H}_3$), 2.37 (3H, s, C_6-CH_3), 3.84 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 3.98 (3H, s, OCH_3), 4.22 (1H, q, J=7 Hz, $C\underline{H}CH_3$), 5.12 (2H, s, OCH_2), 5.14 (2H, d, J=7 Hz, $C\underline{H}_2NH$), 5.6 (1H, br d, J=7 Hz, NH), 7.32 (5H, br s, C_6H_5), 7.70 (1H, d, J=6 Hz, C_4-H), 8.3 (1H, br, NH), 8.28 (1H, d, J=6 Hz, C_4-H).

1-(*N*-Carbobenzyloxy-α-amino-*n*-butyrylaminomethyl)-5,7,8-trimethoxy-6-methylisoquinoline (**23b**): Yield 52%, mp 121.5—122.5 °C (colorless plates from benzene–ether). *Anal.* Calcd for $C_{26}H_{31}N_3O_6$: C, 64.85; H, 6.49; N, 8.73. Found: C, 64.75; H, 6.60; N, 8.51. MS *m/z*: 481 (M^+, 36), 373 (11), 289 (100), 261 (24), 232 (31), 91 (38). IR ν_{max}^{KBr} cm^{-1}: 1660, 1705 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.00 (3H, t, J=7 Hz, $CHCH_2C\underline{H}_3$), 1.6—2.1 (2H, m, $CHC\underline{H}_2CH_3$), 2.40 (3H, s, C_6-CH_3), 3.88 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 4.02 (3H, s, OCH_3), 4.2—4.5 (1H, m, $C\underline{H}CH_2CH_3$), 5.15 (2H, s, CH_2O), 5.17 (2H, d, J=7 Hz, $C\underline{H}_2NH$), 5.68 (1H, br d, J=7 Hz, NH), 7.33 (5H, br s, C_6H_5), 7.71 (1H, d, J=5 Hz, C_4-H), 8.26 (1H, br, NH), 8.28 (1H, d, J=5 Hz, C_3-H).

1-(*N*-Carbobenzyloxy-DL-norvalylaminomethyl)-5,7,8-trimethoxy-6-methylisoquinoline (**23c**): Yield 84%, mp 129—131 °C (colorless needles from CH_2Cl_2–ether). *Anal.* Calcd for $C_{27}H_{33}N_3O_6$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.21; H, 6.78; N, 8.40. MS *m/z*: 495 (M^+, 28), 387 (49), 289 (100), 261 (22), 232 (74), 91 (48). IR ν_{max}^{KBr} cm^{-1}:

1655, 1700 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, t, J=7 Hz, $CH_2CH_2C\underline{H}_3$), 1.1—2.0 (4H, m, $C\underline{H}_2C\underline{H}_2CH_3$), 2.39 (3H, s, C_6-CH_3), 3.87 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 4.00 (3H, s, OCH_3), 4.2—4.6 (1H, m, $C\underline{H}CH_2CH_2CH_3$), 5.14 (2H, s, CH_2O), 5.16 (2H, d, J=5 Hz, $C\underline{H}_2NH$), 5.57 (1H, br d, J=7 Hz, NH), 7.32 (5H, br s, C_6H_5), 7.70 (1H, d, J=6 Hz, C_4-H), 8.2 (1H, br, NH), 8.27 (1H, d, J=6 Hz, C_3-H).

1-(DL-Alanylaminomethyl)-5,7,8-trimethoxy-6-methylisoquinoline (24a) and Its Congeners 24b—c——Each of the isoquinolines **23a—c** (500 mg) in methanol (40 ml) was hydrogenated at 1 atm for 2 h using 10% palladium on carbon (500 mg) as a catalyst. The catalyst was filtered off, and the solvent was removed under reduced pressure to give the corresponding product, **24a—c** (100% yield), which was used without further purification.

1-Pyruvoylaminomethyl-5,7,8-trimethoxy-6-methylisoquinoline (22a) from 24a——A solution of 3,5-di-*tert*-butyl-1,2-benzoquinone (51 mg, 0.23 mmol) in methanol (1 ml) was added to a solution of **24a** (70 mg, 0.21 mmol) in methanol (5 ml) with stirring under nitrogen. The whole was stirred at 40 °C for 18 h under nitrogen, then diluted with a mixture of tetrahydrofuran (0.9 ml) and water (0.2 ml), and adjusted to pH 3 by addition of crystalline oxalic acid dihydrate. After 30 min at room temperature, the mixture was adjusted to pH 8 with saturated aqueous $NaHCO_3$ solution, and extracted with CH_2Cl_2. The extract was washed with water, dried over Na_2SO_4 and evaporated. The residue was chromatographed on a silica gel column using CH_2Cl_2 as the eluent. The crude isoquinoline **22a** thus obtained, was further purified by preparative TLC using CH_2Cl_2–ethyl acetate (3 : 1) as the developing solvent. Yield 20 mg (29%).

1-(α-Oxo-*n*-butyrylaminomethyl)-5,7,8-trimethoxy-6-methylisoquinoline (22b) from 24b——A solution of 3,5-di-*tert*-butyl-1,2-benzoquinone (95 mg, 0.43 mmol) in methanol (10 ml) was added to an ice-cooled solution of **24b** (150 mg, 0.43 mmol) in methanol (10 ml) with stirring under nitrogen. The whole was stirred at 0—5 °C for 20 h under nitrogen, then diluted with a mixture of tetrahydrofuran (1.5 ml) and water (3 ml), and adjusted to pH 4 by addition of crystalline oxalic acid dihydrate. After 2 h at 0—5 °C, the mixture was diluted with water, washed with CH_2Cl_2, adjusted to pH 7 with saturated aqueous $NaHCO_3$ solution, and extracted with CH_2Cl_2. The extract was washed with water, dried over Na_2SO_4 and evaporated. The residue was chromatographed on a silica gel column using benzene as the eluent. The crude isoquinoline **22b** thus obtained, was further purified by preparative TLC using benzene as the developing solvent. Yield 41 mg (27%).

1-(α-Oxo-*n*-valerylaminomethyl)-5,7,8-trimethoxy-6-methylisoquinoline (22c) from 24c——The isoquinoline **22c** was obtained from **24c** by the same procedure as used for the oxidation of **24b**. Yield 24%.

Oxidative Demethylation of 22a with CAN——A solution of CAN (10.97 g, 20 mmol) in water (20 ml) was added dropwise to **22a** (332 mg, 1 mmol) dissolved in acetonitrile (20 ml) containing suspended pyridine-2,6-dicarboxylic acid *N*-oxide (3.66 g, 20 mmol) with stirring. During this addition, the reaction vessel was cooled in an ice-water bath. Then the mixture was stirred for an additional 30 min. The bath was removed, and the mixture was diluted with water (30 ml), adjusted to pH 9 with saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The extract was washed with water, dried over Na_2SO_4 and evaporated. The residue was chromatographed on a silica gel column. Elution with ethyl acetate–hexane (1 : 1) gave a less polar *p*-quinone, *i.e.* mimocin (**5a**, 109 mg, 36%), and further elution with CH_2Cl_2–acetone (8 : 2) gave a more polar *o*-quinone **25a** (156 mg, 52%). The *p*-quinone **5a** thus obtained was recrystallized from ether–hexane to afford 98 mg of yellow needles, mp 189—191 °C (dec.).

1-Pyruvoylaminomethyl-5-methoxy-6-methyl-7,8-dihydroisoquinoline-7,8-dione (**25a**): mp 167—170 °C (dec.) (orange needles from CH_2Cl_2–hexane). *Anal.* Calcd for $C_{15}H_{14}N_2O_5$: C, 59.60; H, 4.67; N, 9.27. Found: C, 59.39; H, 4.54; N, 9.22. MS *m/z*: 302 (M^+, 37), 260 (100), 259 (91), 231 (72), 217 (67), 216 (42), 202 (85). UV λ_{max}^{EtOH} nm (log ε): 246 (4.34), 340 (3.54). IR ν_{max}^{KBr} cm^{-1}: 1665, 1690, 1713 (C=O), 3370 (NH). ^{1}H-NMR ($CDCl_3$) δ: 2.10 (3H, s, C_6-CH_3), 2.46 (3H, s, $COCH_3$), 4.01 (3H, s, OCH_3), 4.98 (2H, d, J=5 Hz, $C\underline{H}_2NH$), 7.58 (1H, d, J=5 Hz, C_4-H), 8.5 (1H. br, NH), 8.81 (1H, d, J=5 Hz, C_3-H).

Oxidative Demethylation of 22b with CAN——A solution of CAN (1.65 g, 3 mmol) in water (4 ml) was added dropwise to **22b** (104 mg, 0.3 mmol) dissolved in acetonitrile (12 ml) containing suspended pyridine-2,6-dicarboxylic acid *N*-oxide (0.55 g, 3 mmol) with stirring. During this addition, the reaction vessel was cooled in an ice-water bath. Then the mixture was stirred for an additional 20 min. The bath was removed, and the mixture was diluted with water (30 ml), adjusted to pH 9 with saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The extract was washed with water, dried over Na_2SO_4 and evaporated. The residue was chromatographed on a silica gel column. Elution with benzene–ethyl acetate (8 : 2) gave a less polar *p*-quinone **5b** (24 mg, 25%) and further elution with benzene–ethyl acetate (5 : 5) gave a more polar *o*-quinone **25b** (35 mg, 37%).

1-(α-Oxo-*n*-butyrylaminomethyl)-7-methoxy-6-methyl-5,8-dihydroisoquinoline-5,8-dione (**5b**): mp 171—173 °C (yellow needles from ether). *Anal.* Calcd for $C_{16}H_{16}N_2O_5$: C, 60.75; H, 5.10; N, 8.86. Found: C, 60.74; H, 5.12; N, 8.83. MS *m/z*: 316 (M^+, 0.2), 260 (21), 259 (100), 216 (42). UV λ_{max}^{MeOH} nm (log ε): 246 (4.34), 320 (3.69). IR ν_{max}^{KBr} cm^{-1}: 1670, 1695, 1725 (C=O), 3380 (NH). ^{1}H-NMR ($CDCl_3$) δ: 1.13 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.08 (3H, s, C_6-CH_3), 2.98 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 4.18 (3H, s, OCH_3), 5.07 (2H, d, J=6 Hz, $C\underline{H}_2NH$), 7.87 (1H, d, J=5 Hz, C_4-H), 8.56 (1H, br, NH), 8.87 (1H, d, J=5 Hz, C_3-H).

1-(α-Oxo-*n*-butyrylaminomethyl)-5-methoxy-6-methyl-7,8-dihydroisoquinoline-7,8-dione (**25b**): mp 137—139 °C (dec.) (orange needles from CH_2Cl_2–ether). *Anal.* Calcd for $C_{16}H_{16}N_2O_5$: C, 60.75; H, 5.10; N, 8.86. Found: C, 60.81; H, 5.18; N, 8.87. MS *m/z*: 316 (M^+, 21), 303 (45), 260 (40), 259 (25), 231 (39), 230 (47), 215 (76), 202 (66), 57

(100). UV λ_{max}^{MeOH} nm ($\log\varepsilon$): 245 (4.19), 330 (3.37). IR ν_{max}^{KBr} cm^{-1}: 1665, 1690, 1735 (C=O), 3390 (NH). ^{1}H-NMR ($CDCl_3$) δ: 1.13 (3H, t, J=7 Hz, CH_2CH_3), 2.14 (3H, s, C_6-CH_3), 2.99 (2H, q, J=7 Hz, CH_2CH_3), 4.05 (3H, s, OCH_3), 5.02 (2H, d, J=5 Hz, CH_2NH), 7.62 (1H, d, J=5 Hz, C_4-H), 8.5 (1H, br, NH), 8.86 (1H, d, J=5 Hz, C_3-H).

Oxidative Demethylation of 22c with CAN——A solution of CAN (3.07 g, 5.6 mmol) in acetonitrile–water (1 : 1, 8 ml) was added dropwise to **22c** (200 mg, 0.56 mmol) dissolved in acetonitrile–water (2 : 1, 15 ml) containing suspended pyridine-2,6-dicarboxylic acid *N*-oxide (1.03 g, 5.6 mmol) with stirring. During this addition, the reaction vessel was cooled in an ice-water bath. Then the mixture was stirred for an additional 20 min. The bath was removed, and the mixture was adjusted to pH 9 with saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The extract was washed with water, dried over Na_2SO_4 and evaporated. The residue was chromatographed on a silica gel column. Elution with benzene–ethyl acetate (10 : 1) gave a less polar *p*-quinone **5c** (37 mg, 20%) and further elution with benzene–ethyl acetate (5 : 1) gave a more polar *o*-quinone **25c** (79 mg, 43%).

1-(α-Oxo-*n*-valerylaminomethyl)-7-methoxy-6-methyl-5,8-dihydroisoquinoline-5,8-dione (**5c**): mp 147—149 °C (yellow needles from ether). *Anal.* Calcd for $C_{17}H_{18}N_2O_5$: C, 61.81; H, 5.49; N, 8.48. Found: C, 61.87; H, 5.44; N, 8.53. MS *m/z*: 330 (M^+, 0.8), 260 (22), 259 (100), 216 (36). UV λ_{max}^{MeOH} nm ($\log\varepsilon$): 245 (4.27), 320 (3.61). IR ν_{max}^{KBr} cm^{-1}: 1665, 1690 (C=O), 3360 (NH). ^{1}H-NMR ($CDCl_3$) δ: 0.98 (3H, t, J=7 Hz, $CH_2CH_2CH_3$), 1.68 (2H, sextet, J=7 Hz, $CH_2CH_2CH_3$), 2.10 (3H, s, C_6-CH_3), 2.95 (2H, t, J=7 Hz, $CH_2CH_2CH_3$), 4.17 (3H, s, OCH_3), 5.09 (2H, d, J=5 Hz, CH_2NH), 7.92 (1H, d, J=5 Hz, C_4-H), 8.60 (1H, br, NH), 8.94 (1H, d, J=5 Hz, C_3-H).

1-(α-Oxo-*n*-valerylaminomethyl)-5-methoxy-6-methyl-7,8-dihydroisoquinoline-7,8-dione (**25c**): mp 136—139 °C (dec.) (orange needles from CH_2Cl_2–ether). *Anal.* Calcd for $C_{17}H_{18}N_2O_5$: C, 61.81; H, 5.49; N, 8.48. Found: C, 62.11; H, 5.67; N, 8.50. UV λ_{max}^{MeOH} nm ($\log\varepsilon$): 245 (4.19), 330 (3.37). IR ν_{max}^{KBr} cm^{-1}: 1663, 1688, 1725 (C=O), 3380 (NH). ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, t, J=7 Hz, $CH_2CH_2CH_3$), 1.67 (2H, sextet, J=7 Hz, $CH_2CH_2CH_3$), 2.14 (3H, s, C_6-CH_3), 2.94 (2H, t, J=7 Hz, $CH_2CH_2CH_3$), 4.06 (3H, s, OCH_3), 5.01 (2H, d, J=5 Hz, CH_2NH), 7.63 (1H, d, J=5 Hz, C_4-H), 8.49 (1H, br, NH), 8.87 (1H, d, J=5 Hz, C_3-H).

1-Pyruvoylaminomethyl-7-hydroxy-6-methyl-5,8-dihydroisoquinoline-5,8-dione [*O*-Demethylmimocin] (26)——A suspension of the *o*-quinone **25a** (170 mg, 0.56 mmol) in dioxane–acetone (1 : 1, 6 ml) containing 15% H_2SO_4 (1 ml) was stirred at 60 °C for 50 min. The reaction mixture was concentrated under reduced pressure, diluted with water (10 ml) and extracted with CH_2Cl_2 (5×20 ml). The extract was washed with water, dried over Na_2SO_4 and evaporated. The residual solid thus obtained was recrystallized from CH_2Cl_2–hexane to give **26** (105 mg, 65%) as yellow needles, mp 227—230 °C (dec.). *Anal.* Calcd for $C_{14}H_{12}N_2O_5$: C, 58.33; H, 4.20; N, 9.72. Found: C, 58.48; H, 4.08; N, 9.78. MS *m/z*: 288 (M^+, 0.5), 246 (18), 245 (100), 202 (41), IR ν_{max}^{KBr} cm^{-1}: 1655, 1680, 1720 (C=O), 3270 (OH), 3380 (NH). ^{1}H-NMR ($CDCl_3$ + pyridine-d_5) δ: 2.07 (3H, s, C_6-CH_3), 2.42 (3H, s, $COCH_3$), 5.07 (2H, d, J=6 Hz, CH_2NH), 7.87 (1H, d, J=5 Hz, C_4-H), 8.82 (1H, d, J=5 Hz, C_3-H), 8.92 (1H, br, NH).

Mimocin (5a) from *O*-Demethylmimocin (26)——A mixture of **26** (80 mg), argentous oxide (1.20 g) and methyl iodide (2.4 ml) was vigorously stirred at room temperature for 3 h. Argentous oxide (0.6 g) and methyl iodide (1.2 ml) were added, and the whole was stirred at room temperature for 15 h. The insoluble compound was filtered off, and the filtrate was evaporated. The residue was chromatographed on a silica gel column using benzene–ethyl acetate (8 : 2) as the eluent to give **5a** (33 mg, 39%). Mimocin (**5a**) thus obtained was recrystallized from ether–hexane to afford 30 mg of yellow needles, mp 189—191 °C (dec.).

Condensation of the *o*-Quinones 25a—c with *o*-Phenylenediamine——A mixture of one of **25a—c** (0.05 mmol) and *o*-phenylenediamine (5.4 mg, 0.05 mmol) in ethanol (3 ml) containing acetic acid (0.1 ml) was refluxed for 5 min with stirring. The reaction mixture was cooled, diluted with water (10 ml), adjusted to pH 9 with saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The extract was washed with water, dried over Na_2SO_4 and evaporated. The residue was chromatographed on a silica gel column using benzene–ethyl acetate (8 : 2) as the eluent to give the corresponding product, **27a—c**.

1-Pyruvoylaminomethyl-5-methoxy-6-methylpyrido[3,4-*a*]phenazine (**27a**): Yield 81%, mp 270—271 °C (pale yellow needles from benzene–ether). *Anal.* Calcd for $C_{21}H_{18}N_4O_3$: C, 67.37; H, 4.85; N, 14.97. Found: C, 67.23; H, 4.62; N, 15.01. MS *m/z*: 374 (M^+, 74), 331 (92), 303 (100), 288 (70), 273 (43), 272 (40), 244 (60). IR ν_{max}^{KBr} cm^{-1}: 1675, 1720 (C=O), 3340 (NH).

1-(α-Oxo-*n*-butyrylaminomethyl)-5-methoxy-6-methylpyrido[3,4-*a*]phenazine (**27b**): Yield 81%, mp 252—253 °C (pale yellow needles from CH_2Cl_2–ether). *Anal.* Calcd for $C_{22}H_{20}N_4O_3 \cdot 1/5H_2O$: C, 67.40; H, 5.25; N, 14.29. Found: C, 67.57; H, 5.16; N, 14.03. MS *m/z*: 388 (M^+, 52), 331 (100), 303 (74), 288 (60), 273 (37), 244 (45). IR ν_{max}^{KBr} cm^{-1}: 1685, 1720 (C=O), 3350 (NH).

1-(α-Oxo-*n*-valerylaminomethyl)-5-methoxy-6-methylpyrido[3,4-*a*]phenazine (**27c**): Yield 82%, mp 232—234 °C (dec.) (pale yellow needles from CH_2Cl_2–ether). *Anal.* Calcd for $C_{23}H_{22}N_4O_3$: C, 68.64; H, 5.51; N, 13.92. Found: C, 68.43; H, 5.35; N, 13.83. MS *m/z*: 402 (M^+, 41) 331 (100), 303 (56), 288 (47), 273 (26), 244 (32). IR ν_{max}^{KBr} cm^{-1}: 1685, 1715 (C=O), 3360 (NH).

References and Notes

1) *a*) T. Arai and A. Kubo, "The Alkaloids," Vol. XXI, ed. by A. Brossi, Academic Press, New York, 1983, pp.

55—100; *b*) R. H. Thomson, "Naturally Occurring Quinones," Vol. III, Chapman and Hall, London, 1987, pp. 633—671.
2) *a*) T. Arai, K. Yazawa, Y. Mikami, A. Kubo and K. Takahashi, *J. Antibiot.*, **29**, 398 (1976); *b*) Y. Mikami, K. Yokoyama, A. Omi and T. Arai, *ibid.*, **29**, 408 (1976).
3) *a*) T. Arai, K. Takahashi and A. Kubo, *J. Antibiot.*, **30**, 1015 (1977); *b*) T. Arai, K. Takahashi, S. Nakahara and A. Kubo, *Experientia*, **36**, 1025 (1980).
4) T. Arai, K. Takahashi, A. Kubo, S. Nakahara, S. Sato, K. Aiba and C. Tamura, *Tetrahedron Lett.*, **1979**, 2355.
5) *a*) H. Fukumi, H. Kurihara, T. Hata, C. Tamura, H. Mishima, A. Kubo and T. Arai, *Tetrahedron Lett.*, **1977**, 3825; *b*) T. Hata, H. Fukumi, S. Sato, K. Aiba and C. Tamura, *Acta Crystallogr., Sect. B*, **34**, 2899 (1978); *c*) H. Fukumi, H. Kurihara and H. Mishima, *Chem. Pharm. Bull.*, **26**, 2175 (1978); *d*) An alternative synthesis: A. McKillop and S. P. Brown, *Synth. Commun.*, **17**, 657 (1987).
6) A. Kubo, S. Nakahara, R. Iwata, K. Takahashi and T. Arai, *Tetrahedron Lett.*, **21**, 3207 (1980).
7) *a*) A. Kubo, Y. Kitahara, S. Nakahara, N. Saito and R. Iwata, Abstracts of Papers, 14th Congress of Heterocyclic Chemistry, Tokyo, September 1981, p. 61; *b*) A. Kubo, Y. Kitahara, S. Nakahara and R. Numata, *Chem. Pharm. Bull.*, **31**, 341 (1983); *c*) An alternative synthesis: K. Matsuo, M. Okumura and K. Tanaka, *ibid.*, **30**, 4170 (1982).
8) Y. Ikeda, H. Matsuki, T. Ogawa and T. Munakata, *J. Antibiot.*, **36**, 1284 (1983).
9) T. Arai, K. Yazawa, K. Takahashi, A. Maeda and Y. Mikami, *Antimicrob. Agents Chemother.*, **28**, 5 (1985).
10) D. E. McIntyre, D. J. Faulkner, D. V. Engen and J. Clardy, *Tetrahedron Lett.*, **1979**, 4163.
11) J. M. Frincke and D. J. Faulkner, *J. Am. Chem. Soc.*, **104**, 265 (1982).
12) *a*) A. Kubo and S. Nakahara, *Chem. Pharm. Bull.*, **29**, 595 (1981); *b*) A. Kubo, S. Nakahara, K. Inaba and Y. Kitahara, *ibid.*, **33**, 2582 (1985); *c*) A. Kubo, S. Nakahara, K. Inaba and Y. Kitahara, *ibid.*, **34**, 4056 (1986).
13) H.-J. Teuber and M. Hasselbach, *Chem. Ber.*, **92**, 674 (1959).
14) H. Vorbrüggen and K. Krolikiewicz, *Synthesis*, **1983**, 316.
15) H. C. J. Ottenheijm and J. H. M. de Man, *Synthesis*, **1975**, 163.
16) *a*) P. Jacob, P. S. Collery, A. T. Shulgin and N. Castagnoli, Jr., *J. Org. Chem.*, **41**, 3627 (1976); *b*) L. Syper, K. Kloc, J. Młochowski and Z. Szulc, *Synthesis*, **1979**, 521.
17) M. Henze, *Chem. Ber.*, **69**, 1566 (1936).
18) J. C. Sheehan and G. P. Hess, *J. Am. Chem. Soc.*, **77**, 1067 (1955).
19) E. J. Corey and K. Achiwa, *J. Am. Chem. Soc.*, **91**, 1429 (1969).
20) C. A. Weber-Schilling and H.-W. Wanzlick, *Chem. Ber.*, **104**, 1518 (1971).
21) J. F. Garden and R. H. Thomson, *J. Chem. Soc.*, **1957**, 2483.