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The Assignment of the Carbon-13 Nuclear Magnetic Resonance Spectra of Isoquinoline and Quinoline Quinones

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The carbon-13 nuclear magnetic resonance spectra of 30 isoquinoline quinones and 6 quinoline quinones are reported. The assignment of chemical shifts for the carbon atoms was achieved with the aid of two- and three-bond spin–spin couplings between ^{13}C and protons.

Keywords——isoquinoline quinone; quinoline quinone; heterocyclic quinone; mimocin; renierone; *N*-formyl-1,2-dihydrorenierone; ^{13}C-NMR

Many carbon-13 nuclear magnetic resonance (^{13}C-NMR) studies concerning quinones have appeared in the literature since carbon-13 pulse Fourier-transform NMR spectroscopy has become common as a sensitive and powerful tool in structural elucidation. However, the majority of these studies have dealt with carbocyclic quinones (*e.g.* benzoquinones, naphthoquinones and anthraquinones),[1] while little work has been done on heterocyclic quinones.[2]

On the other hand, there is much interest at present in the chemistry and biological activity of heterocyclic quinones.[3] In connection with our studies on the synthesis of isoquinoline quinone antibiotics, *i.e.* mimocin (**6**)[4] isolated from streptothricin-producing strain of *Streptomyces lavendulae*, and renierone (**11**),[5] 7-methoxy-1,6-dimethyl-5,8-dihydroisoquinoline-5,8-dione (**5**) and *N*-formyl-1,2-dihydrorenierone (**29**)[6] derived from a marine sponge *Reniera* sp., we synthesized a variety of isoquinoline and quinoline quinones using oxidative demethylation of hydroquinone dimethyl ethers with ceric ammonium nitrate (CAN)[7] or oxidation of amines with potassium nitrosodisulfonate (Fremy's salt).

We wish to report here an unequivocal assignments of the ^{13}C-NMR chemical shifts of isoquinoline quinones (**1**—**30**) and quinoline quinones (**31**—**36**) in deuteriochloroform or deuteriodichloromethane, achieved with the aid of two- and three-bond spin–spin couplings between ^{13}C and protons.

5,8-Dihydroisoquinoline-5,8-diones (1—16)

The signals of the ^{13}C-NMR spectra of 5,8-dihydroisoquinoline-5,8-diones (**1**—**16**) were assigned as shown in Table I. The assignment of the carbon chemical shifts of 7-methoxy-6-methyl-5,8-dihydroisoquinoline-5,8-dione (**3**) was made on the basis of the ^{1}H-noise decoupling spectrum and the gated decoupling spectrum with nuclear Overhauser enhancement. The signals of the carbons coupled with the aromatic protons at C-1, C-3 and C-4 were easily differentiated from others. The signal at 147.8 ppm was assigned to the C-1 carbon because it was coupled with the signal of the C-1 proton at 9.24 ppm. The signals at 184.3 and 180.3 ppm are ascribed to the carbonyl carbons at C-5 and C-8, respectively, on the basis that the C-8 carbon resonance would shift upfield under the influence of the methoxyl group attached to the vicinal carbon.[1b] The signal at 157.3 ppm was assigned to the quaternary carbon at C-7

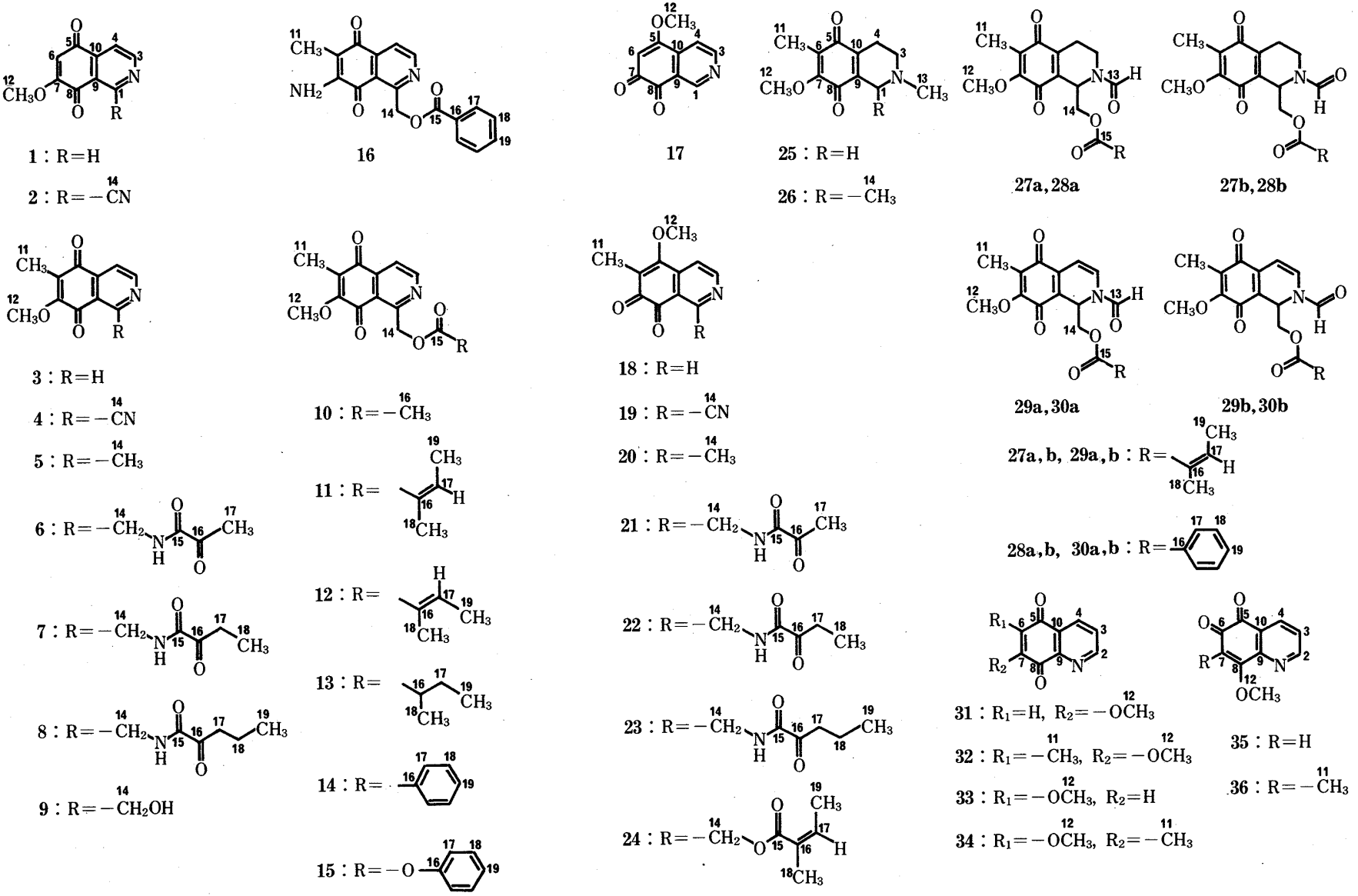

Fig. 1. Isoquinoline and Quinoline Quinones

TABLE I. ^{13}C-NMR Chemical Shift Data for Various Isoquinoline Quinones

Compd.	C-1	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11	C-12	C-13	C-14	C-15	C-16	C-17	C-18	C-19
5,8-Dihydroisoquinoline-5,8-diones																		
1	148.5	155.8	118.3	183.4	110.2	160.5	179.1	124.4	137.3		56.5							
2	131.8	156.1	122.4	181.6	110.6	161.0	177.0	127.3	139.0		57.5		116.1					
3	147.8	155.0	118.1	184.3	131.5	157.3	180.3	124.4	136.9	9.2	61.1							
4	131.0	155.1	121.8	182.1	131.6	157.5	177.5	127.2	138.1	9.4	61.6		115.7					
5	160.1	153.6	117.2	184.9	130.0	158.7	181.9	123.1	138.9	8.9	61.1		25.5					
6	155.8	153.4	118.3	184.0	130.4	158.2	181.4	122.3	139.1	9.1	61.3		44.1	160.1	196.5	24.6		
7	156.0	153.6	118.5	184.3	130.5	158.4	181.7	122.4	139.1	9.1	61.3		44.0	160.3	199.4	30.4	7.1	
8	156.0	153.6	118.5	184.3	130.5	158.4	181.6	122.4	139.1	9.1	61.3		44.0	160.3	198.9	38.7	16.8	13.6
9	160.3	152.7	118.1	184.3	130.5	158.1	181.5	121.7	139.1	9.2	61.3		64.0					
10	156.6	154.0	118.5	184.4	130.1	158.5	181.7	122.8	139.0	9.1	61.3		65.6	170.8	20.9			
11	156.6	153.8	118.2	184.2	130.3	158.2	181.5	122.5	138.7	9.2	61.2		65.3	167.6	127.7	137.8	20.7	15.8
12	157.1	154.0	118.3	184.5	130.4	158.5	181.7	122.7	138.9	9.1	61.2		65.6	167.9	128.4	137.8	12.2	14.5
13	156.9	153.8	118.4	184.4	130.4	158.5	181.6	122.8	138.9	9.0	61.2		65.3	176.4	41.1	26.8	16.8	11.6
14	156.6	153.9	118.3	184.3	130.1	158.4	181.6	122.7	138.9	9.0	61.2		66.0	166.3	130.4	129.8	128.3	132.9
15	155.6	154.0	118.6	184.2	130.7	158.3	181.6	122.6	138.9	9.0	61.2		68.7	153.6	151.3	120.9	129.3	125.9
16	154.7	153.9	118.1	181.4	110.0	147.5	178.8	121.7	140.2	9.2			65.6	165.3	129.6	129.1	128.4	132.9
7,8-Dihydroisoquinoline-7,8-diones																		
17	149.9	156.2	117.9	166.0	106.3	178.9[a]	177.9[a]	123.8	138.8		57.2							
18	149.8	156.4	118.0	163.1	127.3	180.2[a]	178.2[a]	123.3	140.3	9.9	61.4							
19	132.1	156.0	121.0	161.4	127.8	178.5[a]	175.6[a]	125.4	141.7	9.6	61.4		115.4					
20	162.0	154.6	116.6	163.4	126.4	180.2[a]	179.7[a]	121.3	141.4	9.8	61.3		25.5					
21	157.6	154.6	117.7	162.9	126.9	179.6[a]	179.3[a]	120.5	142.2	9.3	61.2		43.8	159.8	196.6	24.0		
22	158.3	154.9	117.9	163.2	127.1	179.7[a]	179.3[a]	120.7	142.4	9.9	61.4		44.1	160.2	199.4	30.4	7.1	
23	158.2	154.9	117.9	163.2	127.1	179.7[a]	179.3[a]	120.7	142.3	9.9	61.4		44.1	160.3	198.9	38.7	16.7	13.6
24	158.9	155.0	117.6	163.2	126.6	179.6[a]	179.2[a]	120.6	141.6	9.8	61.4		65.2	167.5	127.6	137.7	20.6	15.7
1,2,3,4,5,8-Hexahydroisoquinoline-5,8-diones																		
25	50.7	50.7	23.5	186.9	128.1	155.1	181.7	137.8	139.6	8.3	60.5	45.2						
26	52.0	44.0	21.5	187.3	128.2	155.3	181.9	139.4	142.8	8.6	60.7	41.7	15.0					
27a	46.2	39.7	22.2	186.2	128.0	156.0	181.1	135.7	141.1	8.7	60.9	161.3	64.4	167.1	127.1	139.1	20.5	15.8
27b	51.3	32.5	23.2	186.2	128.3	155.6	180.8	135.2	142.9	8.7	60.9	161.3	62.9	166.8	126.9	139.7	20.5	15.8
28a	46.2	39.7	22.2	186.2	128.5	156.0	181.1	135.5	141.3	8.6	60.9	161.2	64.9	166.1	129.1	129.7	128.5	133.3
28b	51.3	32.6	23.3	186.2	128.5	155.7	180.8	135.0	143.1	8.6	60.9	161.2	63.6	165.8	129.1	129.7	128.5	133.3
1,2,5,8-Tetrahydroisoquinoline-5,8-diones																		
29a	47.3	133.2	100.8	184.7	127.0	156.2	180.1	123.9	135.4	8.5	61.0	162.1	63.0	167.2	126.9	139.6	20.5	15.6
29b	49.7	129.3	102.8	184.6	127.9	155.9	180.1	123.1	136.1	8.6	61.0	161.2	60.8	166.6	126.5	140.6	20.4	15.8
30a	47.0	133.5	101.1	184.7	127.2	155.9	180.2	123.7	135.6	8.7	61.0	162.1	63.8	166.2	129.3	129.6	128.4	133.3
30b	49.7	129.6	102.9	184.7	127.2	155.9	180.2	123.0	135.6	8.7	61.0	161.2	61.8	165.6	129.3	129.6	128.4	133.3

from a comparison with the signals of 3,6-dimethoxythymoquinone.[8] The assignment of the signal at 131.5 ppm to the C-6 carbon was made because it was coupled with the signal of the methyl protons at 2.07 ppm. The remaining signals at 124.4 and 136.9 ppm were assigned to the angular quaternary carbons, C-9 and C-10, respectively, from a comparison with the chemical shifts (129.2 and 136.0 ppm) of the angular carbons of isoquinoline.[9]

The assignment of the spectra of 7-methoxy-5,8-dihydroisoquinoline-5,8-diones (**1**—**2**) and 1-substituted derivatives (**4**—**15**) of 7-methoxy-6-methyl-5,8-dihydroisoquinoline-5,8-dione (**3**), including naturally occurring isoquinoline quinones, 7-methoxy-1,6-dimethyl-5,8-dihydroisoquinoline-5,8-dione (**5**), mimocin (**6**) and renieron (**11**), was made from a comparison with the spectrum of **3**. The chemical shifts of the substituent carbons C-16, C-17, C-18 and C-19 of the quinones **11**—**15** were assigned from a comparison with those of the corresponding carbons of angelic acid,[10] tiglic acid,[10] α-methylbutyric acid,[11] benzoic acid,[12] and phenyl acetate,[13] respectively.

The signals of (7-amino-6-methyl-5,8-dioxo-5,8-dihydro-1-isoquinolyl)methyl benzoate (**16**) were assigned from a comparison with those of the methoxyquinone (**14**). Taking into account the chemical shifts of the ring carbons bearing amino and methyl groups of 2,5-diamino-3,6-dimethyl-1,4-benzoquinone,[2a] the signals at 110.0 and 147.5 ppm were assigned to the C-6 and C-7 carbons, respectively.

7,8-Dihydroisoquinoline-7,8-diones (17—24)

The assignment of the spectrum of 5-methoxy-6-methyl-7,8-dihydroisoquinoline-7,8-dione (**18**) was made from a comparison with the spectrum of the isoquinoline-5,8-dione (**3**). The signals of the carbons coupled with the aromatic protons at 149.8, 156.4 and 118.0 ppm were easily assigned to the C-1, C-3 and C-4 carbons, respectively. The signals at 123.3 and 140.3 ppm were assigned to the angular carbons, C-9 and C-10, respectively. The signals at 178.2 and 180.2 ppm are ascribed to the carbonyl carbons, C-7 and C-8. The remaining signals at 127.3 and 163.1 ppm were assigned to the carbons bearing methyl and methoxyl groups, respectively.

The signals of other 5-methoxy-7,8-dihydroisoquinoline-7,8-diones (**17**, **19**—**24**) were assigned from a comparison with those of the isoquinoline-7,8-dione (**18**).

These assignments indicate that the chemical shifts of ring carbons bearing methoxyl and methyl groups, and quinone carbonyl carbons of isoquinoline-7,8-diones are clearly distinguishable from those of isoquinoline-5,8-diones.

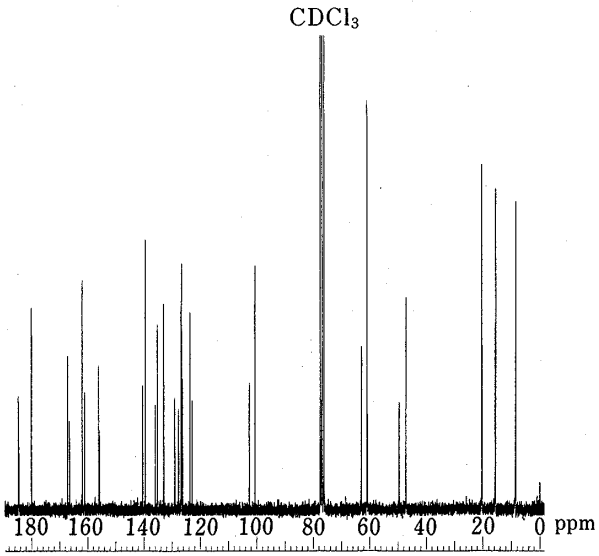

Fig. 2. ^{13}C-NMR Spectrum of *N*-Formyl-1,2-dihydrorenierone (**29**)

This spectrum was obtained by means of a gated decoupling experiment without nuclear Overhauser enhancement.

1,2,3,4,5,8-Hexahydroisoquinoline-5,8-diones (25—28) and 1,2,5,8-Tetrahydroisoquinoline-5,8-diones (29—30)

The signals of the ^{13}C-NMR spectra of *N*-methyl-1,2,3,4,5,8-hexahydroisoquinoline-5,8-diones (**25**, **26**) were assigned from a comparison with those of 7-methoxy-6-methyl-5,8-dihydroisoquinoline-5,8-dione (**3**).

On the other hand, the ^{13}C-NMR spectrum (Fig. 2) of *N*-formyl-1,2-dihydrorenierone (**29**) indicated that this compound was a 2 : 1 mixture of two physically inseparable isomers. The spectrum can be readily interpreted by assuming that the partial double bond character of the *N*-formyl bond permits the observation of two stereoisomers, **29a** and **29b**, on the NMR time scale. The geometry of the stereoisomers has already been determined by a comparison of the C-1 and C-3 proton signals.[6] The signals of the ^{13}C-NMR spectrum were clearly differentiated and were assigned to the major or minor stereoisomers from a comparison with those of renierone (**11**) as shown in Table I. The signals of angerate ester were at similar chemical shifts to the corresponding signals of renierone (**11**). The difference of the orientation of the formyl group has a remarkable effect on the chemical shifts of ring carbons (C-1, C-3 and C-4), the formyl carbon (C-13) and the methylene carbon (C-14).

Similarly, from the ^{13}C-NMR spectrum, it is clear that (*N*-formyl-7-methoxy-6-methyl-5,8-dioxo-1,2,5,8-tetrahydro-1-isoquinolyl)methyl benzoate (**30**) is also a 2 : 1 mixture of two physically inseparable isomers, **30a** and **30b**.

The spectra of *N*-formyl-1,2,3,4-tetrahydrorenierone (**27**) and its benzoate analogue (**28**) indicated that these isoquinoline quinones were approximately 1 : 1 mixtures of two inseparable isomers, **27a** and **27b**, and **28a** and **28b**, respectively.

5,8-Dihydroquinoline-5,8-diones (31—34) and 5,6-Dihydroquinoline-5,6-diones (35—36)

The assignment of the chemical shifts of 7-methoxy-6-methyl-5,8-dihydroquinoline-5,8-dione (**32**) was made with the aid of the ^{1}H-coupled ^{13}C-spectra. The signals (153.8, 127.3 and 133.9 ppm) of the carbons bearing the aromatic protons were easily differentiated from others and were assigned to C-2, C-3 and C-4, respectively. The signals at 184.2, 130.7, 158.2 and 179.1 ppm are ascribed to the quinone ring carbons, C-5, C-6, C-7 and C-8, respectively, from a comparison with the assignments of the isoquinoline-5,8-dione (**3**). The remaining signals at 146.9 and 128.5 ppm were assigned to the angular quaternary carbons, C-9 and C-10, respectively, in view of the chemical shifts (148.8 and 128.9 ppm) of the angular carbons of quinoline.[9]

The spectra of other methoxyquinoline-5,8-diones (**31**, **33** and **34**) were easily assigned from a comparison with the spectrum of the quinone (**32**). Moreover, the assignments of the spectra of 8-methoxy-5,6-dihydroquinoline-5,6-diones (**35** and **36**) were made with the aid of the assignments of the isoquinoline-7,8-diones, **17** and **18**, respectively.

TABLE II. ^{13}C-NMR Chemical Shift Data for Various Quinoline Quinones

Compd.	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11	C-12
5,8-Dihydroquinoline-5,8-diones											
31	154.3	128.0	134.4	183.5	109.5	160.9	178.1	146.9	129.0		56.7
32	153.8	127.3	133.9	184.2	130.7	158.2	179.1	146.9	128.5	9.3	61.1
33	154.9	127.3	134.6	179.5	160.1	110.6	182.9	147.6	127.9		56.6
34	154.1	126.9	133.9	180.2	157.0	132.4	183.5	147.3	127.9	9.6	61.1
5,6-Dihydroquinoline-5,6-diones											
35	154.4	125.7	136.0	178.2[a)]	178.6[a)]	105.7	167.4	149.4	126.9		57.4
36	154.3	124.4	136.1	178.5	180.5	127.7	164.8	151.5	126.4	9.2	61.8

a) Assignments may be interchanged.

Experimental

^{13}C-NMR spectra were determined with JEOL FX 60 (15 MHz), FX 100 (25 MHz) and GX 400 (100 MHz) spectrometers. Solutions of the samples in deuteriodichloromethane (**2**, **19**, **21**) or deuteriochloroform (others) were prepared and tetramethylsilane was added as an internal standard. Gated decoupling experiments with and without nuclear Overhauser enhancement were performed for observation of long-range carbon–proton couplings, and for determination of the ratio of stereoisomers in *N*-formylisoquinoline quinones (**27**—**30**), respectively.

7-Methoxy-5,8-dihydroisoquinoline-5,8-diones (**1**, **3**, **4**, **6**, **9**, **11**, **12**), 5-methoxy-7,8-dihydroisoquinoline-7,8-diones (**17**—**19**, **21**, **24**), 7-methoxy-2,6-dimethyl-5,8-dioxo-1,2,3,4,5,8-hexahydroisoquinoline-5,8-dione (**25**), 6-methoxy-5,8-dihydroquinoline-5,8-dione (**33**) and 8-methoxy-5,6-dihydroquinoline-5,6-dione (**35**) were prepared as reported.[5b,7]

1-Cyano-7-methoxy-5,8-dihydroisoquinoline-5,8-dione (2)——(a) 7-Methoxy-8-nitroisoquinoline *N*-Oxide (**37**): A stirred solution of 7-methoxy-8-nitroisoquinoline[14] (4.33 g) in CH_2Cl_2 (100 ml) was treated with 80% *m*-chloroperbenzoic acid (5.02 g). The mixture was stirred for an additional 4 h, and chromatographed on a silica gel column with ethyl acetate–ethanol as the eluent to give 4.66 g of **37** in quantitative yield; mp 240—241 °C (from CH_2Cl_2–ether). *Anal.* Calcd for $C_{10}H_8N_2O_4$: C, 54.55; H, 3.66; N, 12.72. Found: C, 54.28; H, 3.49; N, 12.58. ^{1}H-NMR ($CDCl_3$) δ: 4.08 (3H, s), 7.41 (1H, d, J=9 Hz), 7.66 (1H, d, J=7 Hz), 7.92 (1H, d, J=9 Hz), 8.07 (1H, dd, J=7, 2 Hz), 8.68 (1H, d, J=2 Hz).

(b) 1-Cyano-7-methoxy-8-nitroisoquinoline (**38**): Sodium cyanide (6.01 g) and benzoyl chloride (17.23 g) were added to a stirred suspension of **37** (4.50 g) in water (100 ml) below 5 °C. The mixture was stirred for an additional 2 h, then diluted with water and extracted with CH_2Cl_2. The extract was washed with 5% $NaHCO_3$ and water, dried with anhydrous Na_2SO_4, concentrated, and chromatographed on a silica gel column with ethyl acetate–hexane to give the crude product **38**. Recrystallization from CH_2Cl_2–ether gave 3.85% (82%) of colorless needles melting at 238.5—239.5 °C. *Anal.* Calcd for $C_{11}H_7N_3O_3$: C, 57.64; H, 3.08; N, 18.34. Found: C, 57.66; H, 2.81; N, 18.27. IR (KBr) 2210 cm^{-1} (CN). ^{1}H-NMR ($CDCl_3$) δ: 4.11 (3H, s), 7.74 (1H, d, J=9 Hz), 7.97 (1H, d, J=5 Hz), 8.13 (1H, d, J=9 Hz), 8.68 (1H, d, J=5 Hz).

(c) 8-Amino-1-cyano-7-methoxyisoquinoline (**39**): The isoquinoline **38** (2.92 g) in *N*,*N*-dimethylformamide (150 ml) was hydrogenated for 5 h using 10% palladium carbon as a catalyst. The catalyst was filtered off and the solvent was removed *in vacuo*. The residue was chromatographed on a silica gel column with ethyl acetate–hexane (4 : 6) to give the crude amine **39**. Recrystallization from ether–hexane gave 1.15 g (45%) of orange needles melting at 131—132 °C. *Anal.* Calcd for $C_{11}H_9N_3O$: C, 66.32; H, 4.55; N, 21.10. Found: C, 66.42; H, 4.32; N, 21.11. IR (KBr) 2210 cm^{-1} (CN), 3370, 3460 cm^{-1} (NH_2). ^{1}H-NMR ($CDCl_3$) δ: 4.02 (3H, s), 5.38 (2H, br s, exchangeable with D_2O), 7.29 (1H, d, J=9 Hz), 7.46 (1H, d, J=9 Hz), 7.70 (1H, d, J=6 Hz), 8.37 (1H, d, J=6 Hz).

(d) 1-Cyano-7-methoxy-5,8-dihydroisoquinoline-5,8-dione (**2**).[15] Solutions of KH_2PO_4 (1.59 g) in water (70 ml) and the amine **39** in acetone (20 ml) were added to a stirred solution of Fremy's salt (4.0 g) in water (140 ml). The mixture was stirred for an additional 15 min and extracted with CH_2Cl_2. The extract was washed with 10% HCl and water, dried with anhydrous Na_2SO_4, concentrated, and chromatographed on a silica gel column with CH_2Cl_2 as the eluent. The obtained crude quinone (**2**) was purified by recrystallization from CH_2Cl_2–ether to give 0.75 g (93%) of yellow needles melting at 242.5—243.5 °C with decomposition. *Anal.* Calcd for $C_{11}H_6N_2O_3$: C, 61.68; H, 2.82; N, 13.08. Found: C, 61.57; H, 2.53; N, 13.18. IR (KBr) 1690 cm^{-1} (CO), 2230 cm^{-1} (CN). ^{1}H-NMR (CD_2Cl_2) δ: 3.97 (3H, s), 6.36 (1H, s), 8.16 (1H, d, J=5 Hz), 9.12 (1H, d, J=5 Hz).

(7-Methoxy-6-methyl-5,8-dioxo-5,8-dihydro-1-isoquinolyl)methyl Esters (10, 13—15)——(a) General Procedure: Acetyl chloride, 2-methylbutanoyl chloride, benzoyl chloride or phenyl chloroformate (0.12 mmol) was added to an ice-cooled solution of (7-methoxy-6-methyl-5,8-dioxo-5,8-dihydro-1-isoquinolyl)methanol (**9**, 0.1 mmol) in pyridine (0.2 ml) with stirring. The mixture was stirred for an additional 10 min, then diluted with water and extracted several times with $CHCl_3$. The combined extracts were washed with water, dried with anhydrous Na_2SO_4, concentrated and chromatographed on a silica gel column with benzene–ethyl acetate as the eluent. The crude ester was recrystallized from methanol or hexane.

(b) (7-Methoxy-6-methyl-5,8-dioxo-5,8-dihydro-1-isoquinolyl)methyl Acetate (**10**): Yield 87%, mp 118—119 °C (from methanol). IR (KBr) 1650, 1670, 1750 cm^{-1} (CO). ^{1}H-NMR ($CDCl_3$) δ: 2.13 (3H, s), 2.27 (3H, s), 4.23 (3H, s), 5.77 (2H, s), 7.87 (1H, d, J=5 Hz), 8.89 (1H, d, J=5 Hz). High-resolution mass spectra (HRMS) Calcd for $C_{14}H_{13}NO_5$: 275.0794. Found: 275.0812.

(c) (7-Methoxy-6-methyl-5,8-dioxo-5,8-dihydro-1-isoquinolyl)methyl 2-Methylbutyrate (**13**): Yield 71%, mp 57—58 °C (from hexane). IR (KBr) 1645, 1665, 1740 cm^{-1} (CO). ^{1}H-NMR ($CDCl_3$) δ: 1.01 (3H, t, J=7 Hz), 1.27 (3H, d, J=7 Hz), 1.4—2.0 (2H, m), 2.13 (3H, s), 2.58 (1H, m), 4.33 (3H, s), 5.77 (2H, s), 7.87 (1H, d, J=5 Hz), 8.89 (1H, d, J=5 Hz). HRMS Calcd for $C_{17}H_{19}NO_5$: 317.1261. Found: 317.1245.

(d) (7-Methoxy-6-methyl-5,8-dioxo-5,8-dihydro-1-isoquinolyl)methyl Benzoate (**14**): Yield 80%, mp 138—139 °C (from methanol). *Anal.* Calcd for $C_{19}H_{15}NO_5$: C, 67.65; H, 4.48; N, 4.15. Found: C, 67.58; H, 4.46; N, 4.13. IR (KBr) 1645, 1670, 1720 cm^{-1} (CO). ^{1}H-NMR ($CDCl_3$) δ: 2.03 (3H, s), 4.09 (3H, s), 5.91 (2H, s), 7.4 (3H, m), 7.83 (1H, d, J=5 Hz), 8.1 (2H, m), 8.87 (1H, d, J=5 Hz).

(e) (7-Methoxy-6-methyl-5,8-dioxo-5,8-dihydro-1-isoquinolyl)methyl Phenoxycarboxylate (**15**): Yield 83%, mp 119—120 °C (from methanol). *Anal.* Calcd for $C_{19}H_{15}NO_6$: C, 64.58; H, 4.28; N, 3.96. Found: C, 64.58; H, 4.41; N, 4.08. IR (KBr) 1650, 1665, 1770 cm^{-1} (CO). ^{1}H-NMR ($CDCl_3$) δ: 2.15 (3H, s), 4.25 (3H, s), 5.94 (2H, s), 7.1—7.6 (5H, m), 7.94 (1H, d, J=5 Hz), 9.00 (1H, d, J=5 Hz).

(7-Amino-6-methyl-5,8-dioxo-5,8-dihydro-1-isoquinolyl)methyl Benzoate (16)——A solution of the methoxy quinone **14** (101 mg) in 10% NH_3-methanol (27 ml) was kept at 40 °C for 1 h. The reaction mixture was cooled, and the precipitated crystals were collected and recrystallized from methanol to give 76 mg (79%) of orange needles melting at 227—228 °C. *Anal.* Calcd for $C_{18}H_{14}N_2O_4 \cdot 1/5H_2O$: C, 66.33; H, 4.45; N, 8.60. Found: C, 66.29; H, 4.33; N, 8.88. IR (KBr) 1670, 1710 cm^{-1} (CO). ^{1}H-NMR (DMSO-d_6) δ: 1.97 (3H, s), 5.91 (2H, s), 7.12 (2H, s), 7.4—8.2 (5H, m), 7.83 (1H, d, J=5 Hz), 8.86 (1H, d, J=5 Hz).

7-Methoxy-1,2,6-trimethyl-1,2,3,4,5,8-hexahydroisoquinoline-5,8-dione (26)——(a) 7-Methoxy-1,2,6-trimethyl-1,2-dihydroisoquinoline (**40**): Methyl iodide (7 g) and a suspension of 7-methoxy-2,6-dimethylisoquinolinium iodide (10 g) in dry ether (50 ml) were added to a stirred mixture of magnesium (0.9 g) in dry ether (50 ml) under argon. The mixture was stirred for an additional 1.5 h, poured in ice-water containing 10% NH_4Cl, neutralized with aqueous ammonia and extracted with ether. The extract was dried with anhydrous Na_2SO_4 and evaporated to dryness. The residue was chromatographed on an alumina column to give 5.05 g (78%) of **40**. ^{1}H-NMR ($CDCl_3$) δ: 1.20 (3H, d, J=6 Hz), 2.13 (3H, s), 2.83 (3H, s), 3.75 (3H, s), 4.35 (1H, q, J=6 Hz), 5.19 (1H, d, J=8 Hz), 5.89 (1H, d, J=8 Hz), 6.42 (1H, s), 6.70 (1H, s). HRMS Calcd for $C_{13}H_{17}NO$: 203.1308. Found: 203.1277.

(b) 7-Methoxy-1,2,6-trimethyl-1,2,3,4-tetrahydroisoquinoline (**41**): $NaBH_4$ (3.9 g) was added over 5 min to a stirred solution of **40** (4.55 g) in methanol (150 ml). The mixture was stirred for an additional 14 h, then concentrated, diluted with water and extracted with $CHCl_3$. The extract was dried with anhydrous Na_2SO_4 and evaporated to dryness. The residue was distilled under reduced pressure to give 2.49 g (54%) of pure **41** having bp 103—105 °C at 3 mmHg. ^{1}H-NMR ($CDCl_3$) δ: 1.39 (3H, d, J=6 Hz), 2.16 (3H, s), 2.46 (3H, s), 2.5—3.2 (4H, m), 3.57 (1H, q, J=6 Hz), 3.79 (3H, s), 6.53 (1H, s), 6.84 (1H, s).

(c) 7-Methoxy-1,2,6-trimethyl-8-nitro-1,2,3,4-tetrahydroisoquinoline (**42**): A solution of **41** (3.36 g) in acetic acid (3.5 ml) was added dropwise to a stirred mixture of conc. HNO_3 (2.4 g) and conc. H_2SO_4 (3.1 g) at 55 °C. The mixture was stirred for an additional 30 min, diluted with water, neutralized with $NaHCO_3$ and extracted with $CHCl_3$. The extract was dried with anhydrous Na_2SO_4 and evaporated to dryness. The residue was chromatographed on an alumina column to give 2.28 g (56%) of **42** as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, d, J=6 Hz), 2.29 (3H, s), 2.43 (3H, s), 2.5—3.2 (4H, m), 3.80 (3H, s), 3.90 (1H, q, J=6 Hz), 7.04 (1H, s).

(d) 8-Amino-7-methoxy-1,2,6-trimethyl-1,2,3,4-tetrahydroisoquinoline (**43**): The nitroisoquinoline **42** (2.28 g) in methanol (450 ml) was hydrogenated using 10% palladium carbon (1.14 g) as a catalyst. After usually work-up, the residue was chromatographed on an alumina column. The crude amine **43** was recrystallized from hexane. Yield 1.69 g (84%); mp 99—100 °C. *Anal.* Calcd for $C_{13}H_{20}N_2O$: C, 70.87; H, 9.15; N, 12.72. Found: C, 70.83; H, 9.29; N, 12.61. ^{1}H-NMR ($CDCl_3$) δ: 1.33 (3H, d, J=6 Hz), 2.25 (3H, s), 2.50 (3H, s), 2.6—3.3 (4H, m), 3.68 (1H, q, J=6 Hz), 3.75 (3H, s), 6.37 (1H, s).

(e) 7-Methoxy-1,2,6-trimethyl-1,2,3,4,5,8-hexahydroisoquinoline-5,8-dione (**26**): KH_2PO_4 (0.12 g) in water (5 ml) and the amine **43** (0.11 g) were added to a stirred solution of Fremy's salt (0.3 g) in water (7.5 ml). The mixture was stirred for an additional 2 h and extracted with CH_2Cl_2. The extract was shaken with 10% HCl, and the resulting mixture was neutralized with 5% NaOH. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were washed with water, dried with anhydrous Na_2SO_4, concentrated, and chromatographed to give 76 mg (65%) of the quinone **26** as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.13 (3H, d, J=6 Hz), 1.91 (3H, s), 2.39 (3H, s), 2.3—3.0 (4H, m), 3.92 (1H, q, J=6 Hz), 3.94 (3H, s). HRMS Calcd for $C_{13}H_{17}NO_3$: 235.1206. Found: 235.1200.

7-Methoxy-5,8-dihydroquinoline-5,8-dione (31)——Solutions of KH_2PO_4 (4.09 g) in water (180 ml) and 8-amino-7-methoxyquinoline[16] (2.25 g) in acetone (40 ml) were added to a stirred solution of Fremy's salt (13.9 g) in water (450 ml). The mixture was stirred for an additional 2 h and extracted with CH_2Cl_2. The extract was washed with water, dried with anhydrous Na_2SO_4, concentrated, and chromatographed on a silica gel column with benzene–ethyl acetate as the eluent. The crude quinone **31** was purified by recrystallization from benzene–ethyl acetate to give 1.76 g (72%) of yellow needles melting at 244—246 °C (lit.[17] mp 242.5—243 °C).

7-Methoxy-6-methyl-5,8-dihydroquinoline-5,8-dione (32)——(a) 7-Methoxy-6-methylquinoline (**44**): Conc. H_2SO_4 (5.5 ml) was added to a mixture of 3-methoxy-4-methylaniline (3.11 g), glycerin (9.39 g), *m*-nitrobenzenesulfonic acid (2.90 g), H_3BO_3 (1.50 g) and $FeSO_4$ (0.8 g). The mixture was stirred at 140 °C for 30 min, then cooled, diluted with ice-water and neutralized with 30% KOH. The quinoline **44** was isolated by steam distillation and further purified on a silica gel column with ethyl acetate–hexane as the eluent. Yield 1.40 g (36%), mp 59—60 °C (from ether–hexane). *Anal.* Calcd for $C_{11}H_{11}NO$: C, 76.27; H, 6.40; N, 8.09. Found: C, 76.41; H, 6.34; N, 8.13. ^{1}H-NMR ($CDCl_3$) δ: 2.35 (3H, s), 3.95 (3H, s), 7.18 (1H, dd, J=8, 5 Hz), 7.35 (1H, s), 7.47 (1H, s), 7.95 (1H, dd, J=8, 2 Hz), 8.74 (1H, dd, J=5, 2 Hz).

(b) 7-Methoxy-6-methyl-8-nitroquinoline (**45**): Conc. HNO_3 (1 ml) was added to a stirred solution of **44** (0.85 g) in conc. H_2SO_4 (2 ml) below 5 °C. The mixture was stirred for 30 min at 20 °C, and neutralized with 30% KOH. The

precipitated crystals were collected, dried, and chromatographed on a silica gel column with CH_2Cl_2–hexane as the eluent to give 0.96 g (90%) of **45**; mp 123—124 °C (from CH_2Cl_2–hexane). *Anal.* Calcd for $C_{11}H_{10}N_2O_3$: C, 60.54; H, 4.62; N, 12.84. Found: C, 60.57; H, 4.44; N, 12.85. ^{1}H-NMR ($CDCl_3$) δ: 2.46 (3H, s), 3.98 (3H, s), 7.36 (1H, dd, J=8, 5 Hz), 7.68 (1H, s), 8.05 (1H, dd, J=8, 2 Hz), 8.85 (1H, dd, J=5, 2 Hz).

(c) 8-Amino-7-methoxy-6-methylquinoline (**46**): The reduction of **45** (0.75 g) was carried out by the same procedure as used for **42** to give 0.62 g (96%) of **46**; mp 93.5—94.5 °C (from methanol). *Anal.* Calcd for $C_{11}H_{12}N_2O$: C, 70.18; H, 6.43; N, 14.88. Found: C, 70.05; H, 6.36; N, 14.87. ^{1}H-NMR ($CDCl_3$) δ: 2.41 (3H, s), 3.84 (3H, s), 4.90 (2H, br s), 6.92 (1H, s), 7.20 (1H, dd, J=8, 4 Hz), 7.90 (1H, dd, J=8, 2 Hz), 8.64 (1H, dd, J=4, 2 Hz).

(d) 7-Methoxy-6-methyl-5,8-dihydroquinoline-5,8-dione (**32**): The Fremy's salt oxidation of **46** (0.48 g) was carried out by the same procedure as used for **43**. Recrystallization from CH_2Cl_2–ether gave 0.43 g (84%) of pure quinone **32** as yellow needles melting at 127—128 °C. *Anal.* Calcd for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 65.04; H, 4.25; N, 6.80. IR (KBr) 1655, 1675 cm^{-1} (CO). ^{1}H-NMR ($CDCl_3$) δ: 2.11 (3H, s), 4.22 (3H, s), 7.64 (1H, dd, J=8, 5 Hz), 8.40 (1H, dd, J=8, 2 Hz), 8.98 (1H, dd, J=5, 2 Hz).

Isoquinoline Quinones (5, 7, 8, 20, 22, 23, 27—30) and Quinoline Quinones (34, 36)——7-Methoxy-1,6-dimethyl-5,8-dihydroisoquinoline-5,8-dione (**5**, mp 137—138 °C), 7-methoxy-6-methyl-1-(2-oxobutanoylamino)methyl-5,8-dihydroisoquinoline-5,8-dione (**7**, mp 171—173 °C), 7-methoxy-6-methyl-1-(2-oxopentanoylamino)methyl-5,8-dihydroisoquinoline-5,8-dione (**8**, mp 147—149 °C), 5-methoxy-1,6-dimethyl-7,8-dihydroisoquinoline-7,8-dione (**20**, mp 149 °C (dec.)), 5-methoxy-6-methyl-1-(2-oxobutanoylamino)methyl-7,8-dihydroisoquinoline-7,8-dione (**22**, mp 137—139 °C (dec.)), 5-methoxy-6-methyl-1-(2-oxopentanoylamino)methyl-7,8-dihydroisoquinoline-7,8-dione (**23**, mp 136—139 °C (dec.)), 6-methoxy-7-methyl-5,8-dihydroquinoline-5,8-dione (**34**, mp 173—174 °C) and 8-methoxy-7-methyl-5,6-dihydroquinoline-5,6-dione (**36**, mp 165—166 °C) were prepared by means of oxidative demethylation of the corresponding 1-substituted derivatives of 5,7,8-trimethoxy-6-methylisoquinoline, or 5,6,8-trimethoxy-7-methylquinoline with CAN.[18] *N*-Formyl-1,2,3,4-tetrahydrorenierone (**27**) and its benzoate analogue (**28**) were also synthesized by using oxidative demethylation of the corresponding 1-substituted derivatives of *N*-formyl-5,7,8-trimethoxy-6-methyl-1,2,3,4-tetrahydroisoquinoline. Dehydrogenation of **27** and **28** by means of refluxing in benzene with 10% palladium carbon gave *N*-formyl-1,2-dihydrorenierone (**29**) and its benzoate analogue (**30**), respectively. The details of the synthesis of these quinones will be reported separately.

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References

1) *a*) S. Berger and A. Rieker, *Tetrahedron*, **28**, 3123 (1972); *b*) G. Höfle, *ibid.*, **32**, 1431 (1976); *c*) M. Kobayashi, Y. Terui, K. Tori and N. Tsuji, *Tetrahedron Lett.*, **1976**, 619; *d*) G. Höfle, *Tetrahedron*, **33**, 1963 (1977); *e*) B. F. Bowden, D. W. Cameron, M. J. Crossley, G. I. Feutrill, P. G. Griffiths and D. P. Kelly, *Aust. J. Chem.*, **32**, 769 (1979).
2) *a*) J. W. Lown and A. Begleiter, *Can. J. Chem.*, **52**, 2331 (1974); *b*) P. J. Keller and U. Hornemann, *J. Nat. Prod.*, **46**, 569 (1983); *c*) H. Fukumi, F. Maruyama, K. Yoshida, M. Arai, A. Kubo and T. Arai, *J. Antibiot.* (Tokyo), **31**, 847 (1978).
3) J. Młochowski, K. Kloc and J. Piatkowska, *Heterocycles*, **19**, 1889 (1982) and references cited therein.
4) A. Kubo, S. Nakahara, R. Iwata, K. Takahashi and T. Arai, *Tetrahedron Lett.*, **1980**, 3207.
5) *a*) D. E. McIntyre, D. J. Faulkner, D. Van Engen and J. Clardy, *Tetrahedron Lett.*, **1979**, 4163; *b*) A. Kubo and S. Nakahara, *Chem. Pharm. Bull.*, **29**, 595 (1981).
6) J. M. Frincke and D. J. Faulkner, *J. Am. Chem. Soc.*, **104**, 265 (1982).
7) A. Kubo, Y. Kitahara, S. Nakahara and R. Numata, *Chem. Pharm. Bull.*, **31**, 341 (1983).
8) L. F. Johnson and W. C. Jankowski, "Carbon-13 NMR Spectra," A Wiley-Interscience Publication, New York, 1972, No. 436.
9) I. Morishima, K. Okada and T. Yonezawa, *J. Am. Chem. Soc.*, **94**, 1425 (1972).
10) P. Joseph-Nathan, J. R. Wesener and H. Günther, *Org. Magn. Reson.*, **22**, 190 (1984).
11) J. G. Batchelor, *J. Magn. Reson.*, **28**, 123 (1977).
12) D. Bruck and M. Rabinovitz, *Tetrahedron Lett.*, **1977**, 4121.
13) F. Toda and T. Oshima, "Handbook of ^{13}C-NMR Spectra," Sankyo Publishing, Tokyo, 1981, No. 773.
14) M. Kulka, *J. Am. Chem. Soc.*, **75**, 3597 (1953).
15) *Cf.* H.-J. Teuber and M. Hasselbach, *Chem. Ber.*, **92**, 674 (1959).
16) H. Gilman and L. Fullhart, *J. Am. Chem. Soc.*, **68**, 978 (1946).
17) Y. T. Pratt and N. L. Drake, *J. Am. Chem. Soc.*, **79**, 5024 (1957).
18) *Cf.* L. Syper, K. Kloc, J. Młochowski and Z. Szulc, *Synthesis*, **1979**, 521.