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Synthesis of 1,2,3,4,5,8-Hexahydroisoquinoline-5,8-diones Using Oxidative Demethylation with Ceric Ammonium Nitrate or Argentic Oxide

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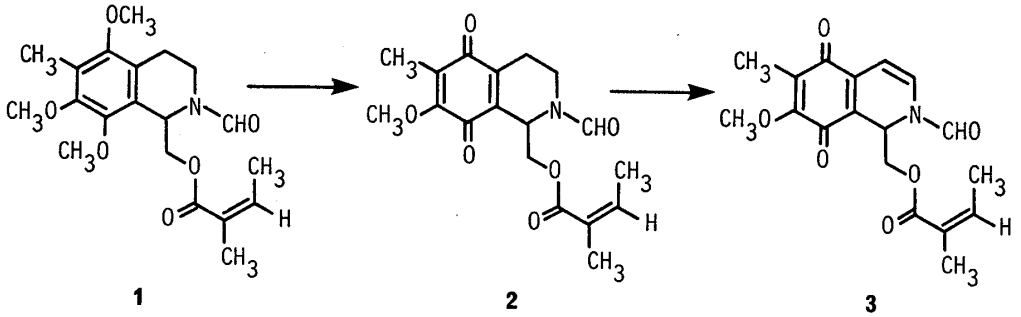
The oxidative demethylation of 5,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinolines to the corresponding 7-methoxy-1,2,3,4,5,8-hexahydroisoquinoline-5,8-diones is described.

Keywords——synthesis; ceric ammonium nitrate; argentic oxide; oxidative demethylation; heterocyclic quinone; isoquinoline quinone; 1,2,3,4,5,8-hexahydroisoquinoline-5,8-dione

There is much interest at present in the chemistry and biological activities of heterocyclic quinones.[1] In connection with our studies on isoquinoline quinone antibiotics, we have reported the total synthesis[2] of renierone and 7-methoxy-1,6-dimethyl-5,8-dihydroisoquinoline-5,8-dione isolated from a marine sponge, *Reniera* sp.[3] We have also synthesized *N*-formyl-1,2-dihydrorenierone (**3**) *via* the unstable 1,2,3,4-tetrahydroisoquinoline quinone[2] **2**, which was prepared by the oxidative demethylation of **1** with ceric ammonium nitrate (CAN) at 0—5 °C (Chart 1). The reaction seems to be useful for the preparation of unstable 1,2,3,4-tetrahydroisoquinoline quinones, but only a few compounds have so far been synthesized. Młochowski *et al.* reported that argentic oxide (AgO) as well as CAN is more effective as an oxidizing reagent when pyridine-2,6-dicarboxylic acid *N*-oxide is employed as a ligand.[4]



1 **2** **3**

Chart 1

Thus, we studied the oxidative demethylation of various 5,7,8-trimethoxy-6-methyl-1,2,3,4-tetrahydroisoquinolines with CAN or argentic oxide. The required isoquinolines (**5**, **9a**—**c**) were prepared from 5,7,8-trimethoxy-6-methylisoquinoline[2] (**4**) (Chart 2). The isoquinoline **4** was treated with methyl iodide or benzyl bromide followed by sodium borohydride to afford the corresponding 1,2,3,4-tetrahydroisoquinoline (**5** or **6**). Catalytic hydrogenation of the *N*-benzyl-1,2,3,4-tetrahydroisoquinoline **6** with 10% palladium on carbon in acetic acid–ethanol afforded **8**, which was treated with acetic anhydride, benzoic anhydride or *p*-toluenesulfonyl (tosyl) chloride in pyridine to produce the corresponding *N*-substitued 1,2,3,4-tetrahydroisoquinoline **9a**—**c**, respectively.

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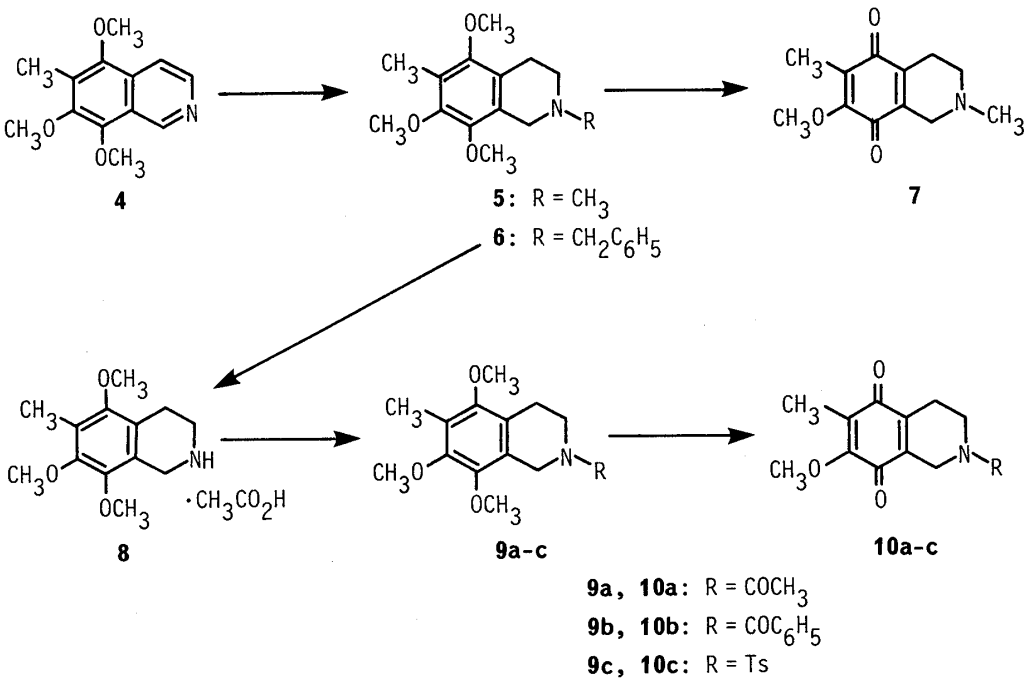

Chart 2

TABLE I. The Oxidative Demethylation of 5,7,8-Trimethoxy-1,2,3,4-tetrahydroisoquinolines (**5**, **9a—c**) with CAN or AgO

Substrate	Product	Yield (%)		IR $\nu_{C=O}$ (cm^{-1})	Recovery (%)	
		CAN	AgO		CAN	AgO
5	**7**	49	5	1655	0	39
9a	**10a**	27	12	1640	0	24
9b	**10b**	39	13	1630	0	18
9c	**10c**	58	4	1660	0	16

The oxidative demethylation of **5** and **9a—c** with CAN in aqueous acetonitrile containing pyridine-2,6-dicarboxylic acid *N*-oxide afforded unstable *p*-quinones **7** and **10a—c**, respectively, in yields of 27—58%. The reaction with argentic oxide was much slower than the reaction with CAN, and a large amount of the starting compound was recovered. The results are summarized in Table I. Application of CAN as the oxidizing agent is much more convenient for the preparation of 1,2,3,4-tetrahydroisoquinoline quinones because the yields of the quinones are better and the isolation of the quinones is easier than in the case of argentic oxide.

The *p*-quinone structure for **7** was confirmed by the following independent synthesis. 7-Methoxy-6-methylisoquinoline[5] (**11**) was treated with methyl iodide followed by sodium borohydride to afford the 1,2,3,4-tetrahydroisoquinoline **13**. The isoquinoline **13** was nitrated with nitric acid and sulfuric acid to afford the 8-nitroisoquinoline **14**, which was reduced to the 8-aminoisoquinoline **15**. Fremy's salt oxidation[6] of **15** furnished the *p*-quinone (38% yield), which was identical with the quinone **7** obtained by the oxidative demethylation of **5** with CAN or argentic oxide in terms of proton nuclear magnetic resonance (^{1}H-NMR), infrared spectra (IR) and mass (MS) spectra.

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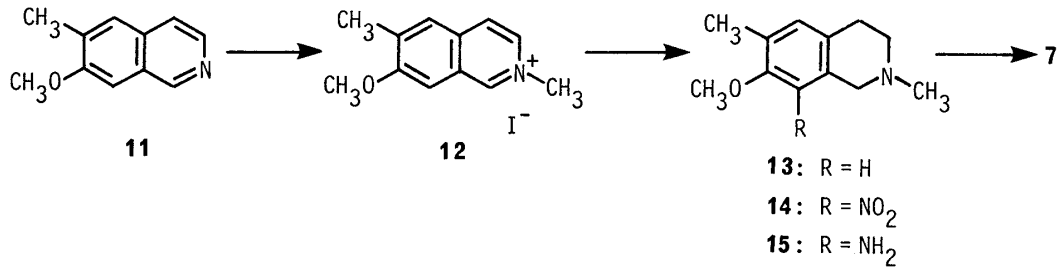

Chart 3

It is interesting to note that the oxidative demethylation of the 5,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinolines (**5**, **9a**—**c**) yielded only *p*-quinones, but no *o*-quinone isomers. In contrast, the oxidative demethylation of 5,7,8-trimethoxyisoquinolines with CAN afforded the corresponding *p*-quinones and *o*-quinones.[2,7] These results indicate that the aromatic ring adjacent to the benzene ring bearing three methoxyl groups is indispensable for the formation of the *o*-quinones.

In summary, the oxidative demethylation reaction with CAN should be generally applicable for the synthesis of labile heterocyclic quinones.

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 JEOL GX 400 (400 MHz; **6**, **8**, **9a**, **9c** and **10c**) and JEOL PS-100 (100 MHz; others) spectrometers, with tetramethylsilane as an internal standard. Microanalytical data were obtained by using a Perkin-Elmer 240B elemental analyzer.

5,7,8-Trimethoxy-2,6-dimethyl-1,2,3,4-tetrahydroisoquinoline (5)——Methyl iodide (0.30 ml, 4.8 mmol) was added dropwise with stirring to a solution of 5,7,8-trimethoxy-6-methylisoquinoline (**4**, 440 mg, 1.9 mmol) in $CHCl_3$ (2 ml). The mixture was refluxed for 30 min, and then evaporated. The residue was dissolved in methanol (7 ml) and $NaBH_4$ (716 mg, 19 mmol) was added at 0—5 °C with stirring. The resulting mixture was stirred at room temperature for 2 h, then diluted with water and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4 and evaporated to afford 467 mg (99%) of **5** as a pale red oil. MS *m/z*: 251 (M^+, 76), 250 (75), 236 (16), 220 (96), 208 (71), 193 (100), 165 (23). High-resolution MS Calcd for $C_{14}H_{21}NO_3$: 251.1521. Found: 251.1493. ^{1}H-NMR ($CDCl_3$) δ: 2.20 (3H, s, C_6-CH_3), 2.50 (3H, s, NCH_3), 2.62 and 2.88 (each 2H, t, J=6 Hz, CH_2CH_2N), 3.56 (2H, s, CH_2N), 3.71 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.88 (3H, s, OCH_3).

***N*-Benzyl-5,7,8-trimethoxy-6-methyl-1,2,3,4-tetrahydroisoquinoline (6)**——Benzyl bromide (1.43 ml, 12 mmol) was added dropwise to **4** (2.33 g, 10 mmol) with stirring. The mixture was heated at 140 °C for 20 min, then cooled and dissolved in methanol (10 ml); $NaBH_4$ (0.76 g, 20 mmol) was added at 0—5 °C with stirring. The resulting mixture was stirred at room temperature for 4 h, then diluted with water and extracted with $CHCl_3$. The extract was washed with saturated $NaHCO_3$ solution, dried over Na_2SO_4, and evaporated. The residue was chromatographed on a silica gel column using ethyl acetate–hexane (2 : 5) as the eluent to afford 2.76 g (85%) of **6** as a colorless oil. MS *m/z*: 327 (M^+, 59), 326 (94), 296 (85), 208 (64), 193 (78), 91 (100). High-resolution MS Calcd for $C_{20}H_{25}NO_3$: 327.1834. Found: 327.1844. ^{1}H-NMR ($CDCl_3$) δ: 2.17 (3H, s, C_6-CH_3), 2.66 and 2.81 (each 2H, t, J=6 Hz, CH_2CH_2N), 3.65 (2H, s, CH_2N), 3.67 (3H, s, OCH_3), 3.73 (2H, s, CH_2N), 3.77 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 7.2—7.5 (5H, m, C_6H_5).

5,7,8-Trimethoxy-6-methyl-1,2,3,4-tetrahydroisoquinoline Acetic Acid Salt (8)——The *N*-benzyl-1,2,3,4-tetrahydroisoquinoline **6** (476 mg) in ethanol (10 ml) containing acetic acid (0.5 ml) was hydrogenated at 1 atm for 11 h using 10% palladium on carbon (250 mg) as a catalyst. The catalyst was filtered off and the filtrate was evaporated under reduced pressure to afford 355 mg (82%) of **8**, which was used without further purification. ^{1}H-NMR ($CDCl_3$) δ: 2.18 (3H, s, C_6-CH_3), 2.87 (2H, t, J=6 Hz, CH_2CH_2N), 3.20 (2H, t, J=6 Hz, CH_2CH_2N), 3.68 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 4.09 (2H, s, CH_2N).

***N*-Acetyl-5,7,8-trimethoxy-6-methyl-1,2,3,4-tetrahydroisoquinoline (9a)**——Acetic anhydride (3.6 ml) was added dropwise to a solution of **8** (298 mg, 1 mmol) in dry pyridine (7.5 ml) with stirring. The resulting solution was stirred for 2 h under argon, then diluted with 1 N HCl (75 ml), and extracted with $CHCl_3$. The extract was washed with 5% $NaHCO_3$, dried over Na_2SO_4 and evaporated. The residue was recrystallized from ether to afford 135 mg (49%) of **9a**

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as a colorless powder melting at 104.5—106 °C. MS *m/z*: 279 (M^+, 100), 264 (18), 248 (18), 236 (15), 222 (36), 208 (19), 206 (28), 193 (30). High-resolution MS Calcd for $C_{15}H_{21}NO_4$: 279.1470. Found: 279.1469. IR ν_{max}^{KBr} cm^{-1}: 1645 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.19 (3H, s, CH_3), 2.20 (3H, s, CH_3), 2.7—2.9 (2H, m, CH_2CH_2N), 3.5—3.9 (2H, m, CH_2CH_2N), 3.67 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 4.5—4.7 (2H, m, CH_2N).

***N*-Benzoyl-5,7,8-trimethoxy-6-methyl-1,2,3,4-tetrahydroisoquinoline (9b)**——A solution of **8** (124 mg, 0.42 mmol), dry pyridine (0.17 ml) and benzoic anhydride (104 mg, 0.46 mmol) in dry CH_2Cl_2 (10 ml) was stirred for 6 h under argon, and then 1 N HCl (25 ml) was added. The mixture was extracted with CH_2Cl_2. The extract was washed with 20% NaOH, dried over Na_2SO_4 and evaporated. The residue was chromatographed on an alumina column using hexane as the eluent to afford 86 mg (60%) of **9b** as a colorless oil. MS *m/z*: 341 (M^+, 70), 326 (10), 208 (18), 193 (14), 105 (100), 77 (25). High-resolution MS Calcd for $C_{20}H_{23}NO_4$: 341.1627. Found: 341.1625. IR ν_{max}^{KBr} cm^{-1}: 1630 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.20 (3H, s, C_6-CH_3), 2.7—3.0 (2H, m, CH_2CH_2N), 3.5—4.0 (2H, m, CH_2CH_2N), 3.69 (3H, s, OCH_3), 3.79 (6H, s, $2\times OCH_3$), 4.66 (2H, s, CH_2N), 7.40 (5H, s, C_6H_5).

***N*-Tosyl-5,7,8-trimethoxy-6-methyl-1,2,3,4-tetrahydroisoquinoline (9c)**——A solution of **8** (124 mg, 0.42 mmol) and tosyl chloride (118 mg, 0.62 mmol) in dry pyridine (10 ml) was stirred for 6 h under argon, then diluted with 1 N HCl (100 ml) and extracted with $CHCl_3$. The extract was washed with 5% $NaHCO_3$, dried over Na_2SO_4 and evaporated. The residue was recrystallized from CH_2Cl_2–hexane to afford 121 mg (76%) of **9c** as a colorless powder melting at 110—112 °C. *Anal.* Calcd for $C_{20}H_{25}NO_5S$: C, 61.36; H, 6.44; N, 3.58. Found: C, 61.12; H, 6.52; N, 3.57. MS *m/z*: 391 (M^+, 50), 360 (14), 235 (100), 220 (16), 208 (35), 193 (26). IR ν_{max}^{KBr} cm^{-1}: 1340, 1165 (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 2.15 (3H, s, C_6-CH_3), 2.42 (3H, s, C_6H_4-CH_3), 2.86 (2H, t, J=5 Hz, CH_2CH_2N), 3.27 (2H, t, J=5 Hz, CH_2CH_2N), 3.63 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 4.17 (2H, s, CH_2N), 7.32 and 7.74 (each 2H, d, J=8 Hz, C_6H_4-CH_3).

The Oxidative Demethylation of 5 and 9a—c with CAN——A solution of CAN (548 mg, 1 mmol) in water (1 ml) was added dropwise to **5** or **9a—c** (0.2 mmol) dissolved in acetonitrile (2 ml) containing suspended pyridine-2,6-dicarboxylic acid *N*-oxide (183 mg, 1 mmol) with stirring. During this addition, the reaction vessel was cooled in an ice-water bath. Then, the mixture was stirred for an additional 10 min. The bath was removed and, after 30 min, the mixture was diluted with water, adjusted to pH 8—9 with saturated $NaHCO_3$ and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4 and evaporated. The residue was chromatographed (silica gel, CH_2Cl_2–methanol for **7** and **10a**, or alumina, CH_2Cl_2 for **10b—c**).

7-Methoxy-2,6-dimethyl-1,2,3,4,5,8-hexahydroisoquinoline-5,8-dione (**7**): Yield 49% (red oil). MS *m/z*: 221 (M^+, 63), 206 (82), 178 (36), 42 (100). High-resolution MS Calcd for $C_{12}H_{15}NO_3$: 221.1052. Found: 221.1076. UV $\lambda_{max}^{methanol}$ nm (log ε): 276 (4.05), 532 (3.29). IR ν_{max}^{KBr} cm^{-1}: 1655 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.96 (3H, s, C_6-CH_3), 2.47) (3H, s, NCH_3), 2.59 (4H, s, CH_2CH_2N), 3.31 (2H, s, CH_2N), 4.01 (3H, s, OCH_3).

N-Acetyl-7-methoxy-6-methyl-1,2,3,4,5,8-hexahydroisoquinoline-5,8-dione (**10a**): Yield 27% (red oil). MS *m/z*: 249 (M^+, 99), 207 (51), 206 (65), 203 (55), 192 (100), 43 (55). High-resolution MS Calcd for $C_{13}H_{15}NO_4$: 249.1001. Found: 249.0998. IR ν_{max}^{neat} cm^{-1}: 1640 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.93 (3H, s, C_6-CH_3), 2.13 (3H, s, $COCH_3$), 2.3-2.9 (2H, m, CH_2CH_2N), 3.3—3.9 (2H, m, CH_2CH_2N), 3.96 (3H, s, OCH_3), 4.2—4.5 (2H, m, CH_2N).

N-Benzoyl-7-methoxy-6-methyl-1,2,3,4,5,8-hexahydroisoquinoline-5,8-dione (**10b**): Yield 39% (red oil). MS *m/z*: 311 (M^+, 17), 203 (54), 173 (11), 105 (100), 77 (36). High-resolution MS Calcd for $C_{18}H_{17}NO_4$: 311.1150. Found: 311.1155. IR ν_{max}^{neat} cm^{-1}: 1640 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.92 (3H, s, C_6-CH_3), 2.4—2.8 (2H, m, CH_2CH_2N), 3.4—3.9 (2H, m, CH_2CH_2N), 3.96 (3H, s, OCH_3), 4.45 (2H, s, CH_2N), 7.40 (5H, s, C_6H_5).

N-Tosyl-7-methoxy-6-methyl-1,2,3,4,5,8-hexahydroisoquinoline-5,8-dione (**10c**): Yield 58%, mp 159—160.5 °C (yellow powder from ether). MS *m/z*: 361 (M^+, 48), 206 (100), 191 (15), 179 (18), 174 (29), 91 (47). High-resolution MS Calcd for $C_{18}H_{19}NO_5S$: 361.0984. Found: 361.0986. UV $\lambda_{max}^{methanol}$ nm (log ε): 228 (4.14), 268 (3.98), 380 (2.29). IR ν_{max}^{KBr} cm^{-1}: 1660 (C=O); 1350, 1165 (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 1.93 (3H, s, C_6-CH_3), 2.43 (3H, s, C_6H_4-CH_3), 2.6—2.7 (2H, m, CH_2CH_2N), 3.23 (2H, t, J=6 Hz, CH_2CH_2N), 3.93 (2H, t, J=3 Hz, CH_2N), 3.98 (3H, s, OCH_3), 7.34 and 7.72 (each 2H, d, J=8 Hz, C_6H_4-CH_3).

The Oxidative Demethylation of 5 and 9a—c with Argentic Oxide——Argentic oxide (75 mg, 0.60 mmol) was added to **5** or **9a—c** (0.12 mmol) dissolved in a mixture of acetonitrile (1.2 ml) and water (0.3 ml) containing suspended pyridine-2,6-dicarboxylic acid *N*-oxide (110 mg, 0.6 mmol) with stirring. During this addition, the reaction vessel was cooled in an ice-water bath. Then the mixture was stirred for an additional 60 min, and the bath was removed. The reaction mixture was diluted with water, and the insoluble compounds were filtered off. The filtrate was adjusted to pH 8—9 with saturated $NaHCO_3$ and extracted with CH_2Cl_2. The extract was washed with water, dried over Na_2SO_4 and evaporated. In the case of **5**, the residue was chromatographed on a silica gel column using CH_2Cl_2–methanol (10 : 1) as the eluent to afford the *p*-quinone **7** (5%) and the unreacted compound **5** (39%). On the other hand, in the case of **9a—c**, separation of products by chromatography failed, affording a mixture of the *p*-quinone **10a—c** and the unreacted compound **9a—c**; the yield was estimated from the ^{1}H-NMR spectrum of the mixture. The result is given in Table I.

7-Methoxy-2,6-dimethylisoquinolinium Iodide (12)——A solution of 7-methoxy-6-methylisoquinoline (**11**, 5.0 g, 29 mmol) and methyl iodide (5.0 ml, 80 mmol) in $CHCl_3$ (10 ml) was stirred at room temperature for 1 h. The precipitated yellow plates of **12** were collected by filtration. Yield 8.79 g (97%); mp 242—244 °C (dec.). *Anal.* Calcd

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for $C_{12}H_{14}INO$: C, 45.73; H, 4.48; N, 4.44. Found: C, 45.45; H, 4.39; N, 4.71. ^{1}H-NMR ($CDCl_3+CD_3OD$) δ: 2.50 (3H, s, C_6-CH_3), 4.07 (3H, s, OCH_3), 4.60 (3H, s, NCH_3), 7.83 (2H, s, C_5-H, C_8-H), 8.15 (1H, d, J=6 Hz, C_4-H), 8.43 (1H, d, J=6 Hz, C_3-H), 10.00 (1H, s, C_1-H).

7-Methoxy-2,6-dimethyl-1,2,3,4-tetrahydroisoquinoline (13)——$NaBH_4$ (1.51 g, 40 mmol) was added in portions to an ice-cooled solution of **12** (1.26 g, 4 mmol) in methanol (50 ml) with stirring. The mixture was stirred at 20 °C for 12 h, then diluted with water and extracted with $CHCl_3$. The extract was washed with brine, dried over Na_2SO_4 and evaporated to afford 0.74 g (97%) of **13** as an oil. *Anal.* Calcd for $C_{12}H_{17}NO \cdot 1/10H_2O$: C, 74.65; H, 8.98; N, 7.25. Found: C, 74.70; H, 8.82; N, 7.39. ^{1}H-NMR ($CDCl_3$) δ: 2.20 (3H, s, C_6-CH_3), 2.48 (3H, s, NCH_3), 2.5—3.0 (4H, m, CH_2CH_2N), 3.60 (2H, s, CH_2N), 3.82 (3H, s, OCH_3), 6.49 (1H, s, C_8-H), 6.89 (1H, s, C_5-H).

7-Methoxy-2,6-dimethyl-8-nitro-1,2,3,4-tetrahydroisoquinoline (14)——A solution of **13** (3.0 g) in acetic acid (4.5 ml) was added dropwise to an ice-cooled solution of conc. HNO_3 (4.6 g) and conc. H_2SO_4 (5.9 g) in acetic acid (4.5 ml) with stirring. The mixture was stirred for an additional 20 min, diluted with water, made alkaline with $NaHCO_3$ and extracted with $CHCl_3$. The extract was washed with brine, dried over Na_2SO_4 and evaporated. The residue was chromatographed on an alumina column using benzene as the eluent to afford 2.64 g (71%) of **14** as an oil. MS *m/z*: 236 (M^+, 3), 219 (51), 188 (85), 174 (39), 160 (59), 159 (100). High-resolution MS Calcd for $C_{12}H_{16}N_2O_3$: 236.1161. Found: 236.1143. ^{1}H-NMR ($CDCl_3$) δ: 2.29 (3H, s, C_6-CH_3), 2.45 (3H, s, NCH_3), 2.6—3.0 (4H, m, CH_2CH_2N), 3.47 (2H, s, CH_2N), 3.82 (3H, s, OCH_3), 7.03 (1H, s, C_5-H).

8-Amino-7-methoxy-2,6-dimethyl-1,2,3,4-tetrahydroisoquinoline (15)——The nitroisoquinoline **14** (240 mg) in ethyl acetate (100 ml) was hydrogenated at 1 atm for 7 h using 10% palladium on carbon (100 mg) as a catalyst. The catalyst was filtered off and the filtrate was evaporated. The residue was chromatographed on an alumina column using $CHCl_3$ as the eluent to afford **15**, which was recrystallized from hexane. Yield 180 mg (86%); mp 88—89 °C. *Anal.* Calcd for $C_{12}H_{18}N_2O$: C, 69.87; H, 8.80; N, 13.58. Found: C, 69.89; H, 8.82; N, 13.76. ^{1}H-NMR ($CDCl_3$) δ: 2.24 (3H, s, C_6-CH_3), 2.50 (3H, s, NCH_3), 2.55—3.0 (4H, m, CH_2CH_2N), 3.37 (2H, s, CH_2N), 3.68 (2H, br s, NH_2), 3.74 (3H, s, OCH_3), 6.38 (1H, s, C_5-H).

7-Methoxy-2,6-dimethyl-1,2,3,4,5,8-hexahydroisoquinoline-5,8-dione (7) from 15——A solution of Fremy's salt (0.3 g, 1.12 mmol) in 1/15 M KH_2PO_4 (12.5 ml) was added to a solution of **15** (103 mg, 0.5 mmol) in acetone (0.5 ml) with stirring at 20 °C. The resulting mixture was stirred for an additional 1.5 h, then diluted with water, and extracted with $CHCl_3$. The extract was washed with brine, dried over Na_2SO_4 and evaporated to afford 42 mg (38%) of **7** as a red oil.

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