Synthesis of Thalprzewalskiinone, a Revision of Structure

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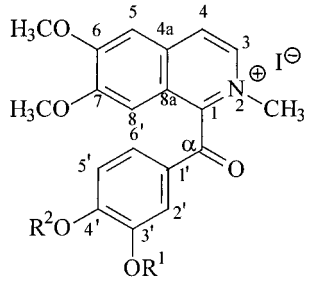
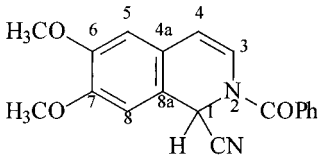
A direct comparison of the spectral data for synthetic 2-methyl-6,7-dimethoxy-3′-methoxy-4′-hydroxyoxobenzylisoquinoline iodide (**1**) and its positional isomer 2-methyl-6,7-dimethoxy-3′-hydroxy-4′-methoxyoxobenzylisoquinoline iodide (**2**) with the data obtained for the oxobenzylisoquinoline alkaloid thalprzewalskiinone revealed that the original structural assignment of the alkaloid as **1** was in error. These results mandate the revision of structure of thalprzewalskiinone to 2-methyl-6,7-dimethoxy-3′-hydroxy-4′-methoxyoxobenzylisoquinoline iodide (**2**).

In 1999, a new oxobenzylisoquinoline alkaloid, thalprzewalskiinone, was isolated from the roots of the ancient Chinese medicinal herb *Thalictrum przewalskii* Maxim. (Ranunculaceae).[1] The structure of this quaternary alkaloid was assigned as 2-methyl-6,7-dimethoxy-3′-methoxy-4′-hydroxyoxobenzylisoquinoline iodide (**1**) on the basis of a consideration of the available spectral data.[1] However, since it was not possible to exclude that thalprzewalskiinone might correspond to the positional isomer of **1**, 2-methyl-6,7-dimethoxy-3′-hydroxy-4′-methoxyoxobenzylisoquinoline (**2**), it was decided to undertake a synthesis of both oxobenzylisoquinolines **1** and **2** in order to unambiguously assign the structure of the natural isolate.



1 $R^1 = CH_3$, $R^2 = H$

2 $R^1 = H$, $R^2 = CH_3$



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The synthesis of these two compounds was accomplished in a conventional, two-part manner using well-established chemistry as described in the synthesis of the oxobenzylisoquinoline alkaloids rugosinone (6,7-methylenedioxy-2′-hydroxy-3′,4′-dimethoxyoxobenzylisoquinoline)[2] and thalmicrinone (5,6,7,4′-tetramethoxyoxobenzylisoquinoline).[3] The first part involved the preparation of the Reissert compound 2-benzoyl-1-cyano-6,7-dimethoxy-1,2-dihydroisoquinoline (**3**) from 6,7-dimethoxyisoquinoline.[2−5] This Reissert compound served as the common top-half for each of the two isomeric oxobenzylisoquinolines **1** and **2**. The second part involved coupling the Reissert anion (prepared via treatment of Reissert compound **3** with NaH in DMF) with the appropriate aldehyde (either *O*-benzylvanillin or *O*-benzylisovanillin)[6] to afford the respective carbinols 3′-methoxy-4′-benzyloxyphenyl-1-(6,7-dimethoxyisoquinolyl) carbinol (**4**) and 3′-benzyloxy-4′-methoxyphenyl-1-(6,7-dimethoxyisoquinolyl) carbinol (**5**). These alcohols underwent facile oxidation with chromic acid[2,3] to yield the respective ketones, 6,7-dimethoxy-3′-methoxy-4′-benzyloxyoxobenzylisoquinoline (**6**) and 6,7-dimethoxy-3′-benzyloxy-4′-methoxyoxobenzylisoquinoline (**7**), which were subsequently debenzylated to 6,7-dimethoxy-3′-methoxy-4′-hydroxyoxobenzylisoquinoline (**8**) and 6,7-dimethoxy-3′-hydroxy-4′-methoxyoxobenzylisoquinoline (**9**), respectively, on treatment with HCl/HOAc. Quaternization of tertiary amines **8** and **9** with MeI in MeCN afforded the desired compounds **1** and **2**, respectively.

A consideration of the UV spectral data (MeOH) for oxobenzylisoquinolines **1** and **2** with thalprzewalskiinone showed great similarity, as seen in Table 1. All three compounds had UV spectral maxima at 256, 302, and 326−327 nm. However, in the presence of strong alkali (0.1 N methanolic NaOH), compound **1** displayed an intense bathochromic shift (+52 nm) of the 327 nm band to 379 nm, consistent with the presence of the phenolic hydroxy group at C-4′ (para to the carbonyl carbon).[7] A review of the UV spectra of several known phenolic oxobenzylisoquinoline alkaloids is likewise consistent with these observations. The UV spectrum of gandharamine (6,7-dimethoxy-4′-hydroxyoxobenzylisoquinoline) showed absorption maxima at 255 nm (log ϵ 4.07) and 316 (3.65) nm, with the addition of strong alkali producing a pronounced bathochromic shift (+49 nm) of the latter band to 365 (3.89) nm.[8] Furthermore, the UV spectrum of longifolonine (6-methoxy-7-hydroxy-4′-hydroxyoxobenzyl-3,4-dihydroisoquinoline) was characterized by absorption maxima at 231 and 295 nm, with the addition of strong base also resulting

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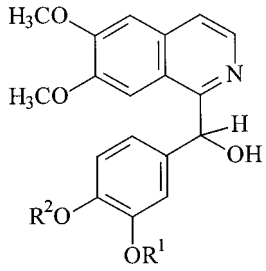
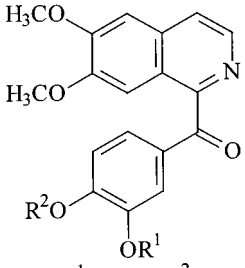


4 $R^1 = CH_3$, $R^2 = Bz$

5 $R^1 = Bz$, $R^2 = CH_3$



6 $R^1 = CH_3$, $R^2 = Bz$

7 $R^1 = Bz$, $R^2 = CH_3$

8 $R^1 = CH_3$, $R^2 = H$

9 $R^1 = H$, $R^2 = CH_3$

in a pronounced shift (+50 nm) of the latter band to 345 nm.[7] By contrast, both compound **2** and natural thalprzewalskiinone underwent only a weak bathochromic shift (+15−16 nm) of the 302 nm band to 317−318 nm. This weak shift is characteristic of the presence of the phenolic hydroxy group in compound **1** at C-3′ (meta to the carbonyl carbon).[9]

Therefore, a comparison of the UV absorption band shift behavior of isomers **1** and **2** in strongly alkaline medium with thalprzewalskiinone iodide prompts us to conclude that thalprzewalskiinone is identical to **2**.

With regard to the magnetic resonance spectral data, it may be reasonably anticipated that any significant differences in chemical shifts between positional isomers **1** and **2** would affect the following: first, the multiplicity and chemical shift of the H-2′, H-5′, and H-6′ protons; second, the chemical shift of the protons found on the C-3′ or C-4′ aromatic methoxy group; and third, the carbon chemical shifts of the C-2′, C-3′, C-4′, C-5′, and C-6′ atoms.

The ^{1}H NMR spectrum of phenol **1** revealed the presence of H-6′ as a one-proton doublet at δ 6.85 (J = 6.6 Hz), while the same proton was observed as a one-proton doublet at δ 7.02 (J =8.4 Hz) in phenol **2**. The H-6′ proton was found at δ 7.06 in thalprzewalskiinone,[1] being much closer in chemical shift to that of phenol **2** (+0.04 Hz) than to that of phenol **1** (+0.21 Hz). This distinct difference in the chemical shift of H-6′ is another compelling piece of evidence in support of the identity of thalprzewalskiinone as phenol **2**. The chemical shift of C-3′ in phenol **1** was δ 155.9, and that of the same carbon in phenol **2** was δ 149.4. Although the C-4′ in thalprzewalskiinone was originally assigned the chemical shift of δ 147.6,[1] reversing the C-3′ and C-4′ assignments is consistent with the results of the synthesis and the ultraviolet spectral data. Thus, the reassignment of the signal at δ 147.6 to C-3′ allows a significantly closer agreement with phenol **2** (+1.8 Hz) than with phenol **1** (+8.3 Hz). Similarly, this reassignment allows a much closer agreement between the carbon chemical shift of the 4′-OCH_3 in phenol **2** (δ 57.7) and the methoxy in thalprzewalskiinone (δ 56.2) (+1.5 Hz) than between the 3′-OCH_3 in phenol **1** (δ 60.4) and the methoxy in thalprzewalskiinone (δ 56.2) (+4.2 Hz). The chemical shift of C-5′ in phenol **1** was δ 133.2 and that of the same carbon in phenol **2** was δ 127.3. The chemical shift of C-5′ in thalprzewalskiinone (δ 127.0) is characterized by significantly more agreement with that of phenol **2** (+0.3 Hz) than that of phenol **1** (+6.2 Hz). Similarly, the chemical shift of C-6′ in phenol **1** was δ 120.6, and that of the same carbon in phenol **2** was δ 113.8. Thus, the chemical shift of C-6′ in thalprzewalskiinone (δ 112.4) is found to be much more in agreement with that of phenol **2** (+1.4 Hz) than that of phenol **1** (+8.2 Hz). These magnetic resonance spectral considerations are complimentary to the previous ultraviolet data and mandate the revision of structure of thalprzewalskiinone to 2-methyl-6,7-dimethoxy-3′-hydroxy-4′-methoxyoxobenzylisoquinoline iodide (**2**).

Table 1. MP and UV Spectral Data (nm/log ϵ) for Compounds **1** and **2** Iodides and Thalprzewalskiinone Iodide

	1	**2**	natural thalprzewalskiinone iodide[1]
mp	174−175 °C (Me_2CO)	196−197 °C (Me_2CO)	amorphous residue
UV (MeOH)	220 (4.43)		
	256 (4.57)	256 (4.54)	256 (4.38)
	302 (4.04)	302 (4.05)	302 (3.89)
	327 (4.17)	327 (4.11)	326 (3.94)
UV (MeOH + 0.1 N methanolic NaOH)	256 (4.59)	255 (4.57)	255 (4.55)
	323 (4.05)	318 (4.11)	317 (3.95)
	379 (4.23)		

Experimental Section

General Experimental Procedures. The UV spectra were obtained in MeOH on a Hewlett-Packard HP-845 UV−vis spectrophotometer. The IR spectra were measured on a Nicolet Impact 410 spectrophotometer as liquid films on KBr disks. Melting points were determined on a Fisher-Johns hot-stage apparatus and are uncorrected. ^{1}H and ^{13} NMR spectra were recorded in $CDCl_3$ or CD_3OD on a Bruker model WH-300 spectrometer operating at 300 and 75 MHz, respectively. The HSQC and HMBC experiments were performed in DMSO-d_6 on Varian INOVA spectrometers operating at a proton observation frequency of 399.803, 499.791, and 599.754 MHz. These instruments were equipped with a Nalorac MIDTG microdual obtained from Nalorac Cryogenics Corp, Martinez, CA. MS analysis was performed on an Extrel ELQ400 quadrupole mass spectrometer equipped with a DCI Probe HP direct probe from Vacumetrics Inc. or on a Hewlett-Packard 5971A mass spectrometer. High-resolution mass spectra were recorded on a Fisons VG Autospec spectrometer or a Fison VG Analytical 70-G spectrometer. FABMS was obtained using VG Analytical 70-G or Fisons VG Autospec spectrometer with *m*-nitrobenzyl alcohol (MNBA) as the matrix. Si gel was used for column chromatography, and TLC was performed using 5 × 20 cm precoated TLC sheets of silica gel 60 F_{254}, 0.2 mm layer thickness (E. Merck). Chemicals were purchased from Aldrich Chemical Co. Organic solvents such as Et_2O, CH_2Cl_2, and $CHCl_3$ that were used in partitioning procedures were dried over anhydrous Na_2SO_4 and filtered prior to evaporation.

Preparation of 1-Cyano-2-benzoyl-6,7-dimethoxyisoquinoline (3). To 6,7-dimethoxyisoquinoline[2−4] (5.0 g, 0.026 mol) in CH_2Cl_2 (300 mL) was added a solution of KCN (13.6 g, 0.209 mol) in H_2O (60 mL). Benzoyl chloride (13.6 g, 11.25 mL, 0.097 mol) was added over 30 min under N_2 and the mixture allowed to stand at room temperature for 1 h. An additional

quantity of KCN (6.8 g, 0.105 mol) in H_2O (30 mL) was added and the mixture kept at room temperature for an additional 4 h. The CH_2Cl_2 layer was separated, partitioned consecutively with H_2O (2 × 100 mL), 2 M HCl (2 × 100 mL), 2 M NaOH (2 × 100 mL), and water (2 × 100 mL), and evaporated to dryness. The resulting residue was crystallized from MeOH as colorless needles (3.5 g, 42% yield) of 1-cyano-2-benzoyl-6,7-dimethoxyisoquinoline (**3**): mp 182−183 °C; UV (MeOH) λ_{max} (log ϵ) 226 (4.51), 250 (sh) (4.30), 312 (4.01) nm; IR (KBr) ν_{max} 2240, 1665, 1630, 1603, 1580, 1515, 1452, 1425, 1345, 1285, 1231, 1146, 1107 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.93 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 6.01 (1H, d, J = 7.5 Hz, H-4), 6.52 (1H, s, H-1), 6.73 (1H, s, H-8), 6.86 (1H, s, H-5), 7.54 (5H, m, 5ArH), 8.11 (1H, d, J = 7.15 Hz, H-3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.8 (*C*═O), 150.3 and 149.2 (C-6 and C-7), 133.7 (C-1′), 132.3 and 132.0 (C-3 and C-4′), 130.2 (C-2′), 129.2 (C-3′), 128.7 and 128.4 (C-5′ and C-6′), 124.5 (C-4a), 123.5 (C-8a), 116.6 (*C*≡N), 110.0 (C-4), 109.6 and 108.7 (C-5 and C-8), 56.3 (O*C*H_3), 56.1 (O*C*H_3), 44.8 (C-1); EIMS m/z 320 $[M]^+$ (27), 215 (7), 189 (25), 146 (5), 105 (100), 77 (43).

Preparation of 3′-Methoxy-4′-benzyloxyphenyl-1-(6,7-dimethoxyisoquinolyl)carbinol (4). To NaH (100 mg, 4.2 mmol) suspended in DMF (10 mL) at −10° was added 1-cyano-2-benzoyl-6,7-dimethoxyisoquinoline (**3**) (1.0 g, 3.12 mmol) in DMF (15 mL) over a period of 5 min under N_2. After 5 min, *O*-benzylvanillin (822 mg, 3.4 mmol) in DMF (10 mL) was added over 10 min at −10 °C. The mixture was stirred for 2 h at 0 °C and then allowed to stand at room temperature for an additional 2 h. The mixture was treated with MeOH (50 mL) and then evaporated. The residue was dissolved in C_6H_6 (40 mL), partitioned with H_2O (2 × 30 mL), and evaporated. The resulting residue, consisting primarily of the benzoate ester of **4**, was dissolved in EtOH (25 mL) and hydrolyzed with KOH (0.2 g) in H_2O (10 mL) under reflux for 3 h. The solution was cooled and evaporated to dryness, and the resulting residue was partitioned with Et_2O (3 × 30 mL). The combined Et_2O extracts were evaporated to afford a white residue, which upon crystallization from MeOH afforded 3′-methoxy-4′-benzyloxyphenyl-1-(6,7-dimethoxyisoquinolyl)carbinol (**4**) (500 mg, 37% yield). The alcohol **4** had a mp of 142−143 °C; UV (MeOH) λ_{max} (log ϵ) 238 (4.68), 278 (3.88), 313 (3.73), 326 (3.72) nm; IR (KBr) ν_{max} 3500−3200, 1617, 1593, 1510, 1480, 1460, 1407, 1270, 1234, 1159, 1136, 1020 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.72 (6H, s, 2-OCH_3), 4.01 (3H, s, OCH_3), 5.10 (2H, s, OCH_2), 6.23 (1H, s, H-α), 6.67 (1H, d, J = 8 Hz, H-8′), 6.77 (1H, d, J = 8 Hz, H-6′), 6.92 (1H, s, H-8), 7.09 (1H, s, H-2′), 7.20 (1H, s, H-5), 7.33 (5H, m, ArH), 7.63 (1H, d, J = 5.8 Hz, H-4), 8.44 (1H, d, J = 5.8 Hz, H-3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.5 (O*C*H_3, C-6), 152.9 (O*C*H_3, C-7), 150.0 (C-1 and C-4′), 147.8 (C-3′), 138.2 (C-3), 137.0 and 136.5 (C-1′ and C-1″), 133.8 (C-4a), 128.5 (C-2″ and C-6″), 127.8 (C-4″), 127.2 (C-3″ and C-5″), 121.0 (C-6′), 120.2 and 120.0 (C-4 and C-8a), 113.8 (C-2′), 111.1 (C-5′), 105.3 (C-5), 103.4 (C-8), 72.5 (C-α), 70.9 (O*C*H_2), 56.1 (O*C*H_3), 56.0 (O*C*H_3), 55.9 (O*C*H_3); EIMS m/z 431 $[M^+]$ (100), 416 (10), 340 (27), 324 (8), 188 (25), 91 (19).

Preparation of 6,7-Dimethoxy-3′-methoxy-4′-benzyloxyoxobenzylisoquinoline (6). To 3′-methoxy-4′-benzyloxyphenyl-1-(6,7-dimethoxyisoquinolyl)carbinol (**4**) (400 mg, 0.92 mmol) in HOAc (5 mL) was added a solution of Na_2CrO_4 (620 mg, 3.78 mmol) in HOAc (5 mL). The mixture was heated for 3 min on a steam bath, diluted with H_2O (50 mL), alkalinized with NH_4OH to pH 8−9, and partitioned with Et_2O (3 × 50 mL). The Et_2O extracts were combined and evaporated, and the resulting residue was treated with MeOH to afford 6,7-dimethoxy-3′-methoxy-4′-benzyloxyoxobenzylisoquinoline (**6**) as yellow crystals (303 mg, 75% yield): mp 170 °C; UV (MeOH) λ_{max} (log ϵ) 237 (4.49), 280 (3.99), 326 (3.97) nm; IR (KBr) ν_{max} 1655, 1591, 1505, 1477, 1415, 1267, 1235, 1157, 1137, 1032, 861, 753 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.95 (3H, s, OCH_3), 3.98 (3H, s, OCH_3), 4.08 (3H, s, OCH_3), 5.24 (2H, s, OCH_2), 6.87 (1H, d, J = 8.4 Hz, H-5′), 7.17 (1H, s, H-8), 7.35 (6H, m, H-6′ and 5ArH), 7.48 (1H, s, H-5), 7.73 (2H, d, J = 1.5 Hz, H-4 and H-2′), 8.45 (1H, d, J = 5.2 Hz, H-3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 193.8 (C═O), 153.6 and 153.4 (C-6 and C-7), 153.1 (C-1), 151.2 (C-4′), 149.6 (C-3′), 139.8 (C-3), 136.3 (C-1″), 134.2 (C-4a), 130.1 (C-1′), 128.8 (C-2″ and C-6″), 128.2 (C-4″), 127.2 (C-3″ and C-5″), 126.8 (C-6′), 122.9 (C-8a), 121.4 (C-4), 112.4 and 112.1 (C-2′ and C-5′), 104.9 and 104.2 (C-5 and C-8), 70.9 (O*C*H_2), 56.2 (O*C*H_3), 56.2 (O*C*H_3), 56.2 (O*C*H_3); EIMS m/z 429 $[M^+]$ (9), 338 (14), 188 (13), 91 (100).

Preparation of 6,7-Dimethoxy-3′-methoxy-4′-hydroxyoxobenzylisoquinoline (8). A solution of 6,7-dimethoxy-3′-methoxy-4′-benzyloxyoxobenzylisoquinoline (**6**) (280 mg, 0.652 mmol) in HCl−HOAc (1:1) (20 mL) was refluxed for 2 h. The solution was cooled, diluted with H_2O (40 mL), alkalinized with NH_4OH to pH 8−9, and extracted with Et_2O (3 × 50 mL). The combined Et_2O extracts were evaporated to a white residue, which on crystallization from MeOH afforded 6,7-dimethoxy-3′-methoxy-4′-hydroxyoxobenzylisoquinoline (**8**) as white cubic crystals (140 mg, 64% yield): mp 179−180 °C; UV (MeOH) λ_{max} (log ϵ) 240 (4.46), 315 (3.85) nm; UV (MeOH + 2 drops of 0.1 N NaOH) λ_{max} (log ϵ) 369 (3.88); IR (KBr) ν_{max} 3453, 1650, 1581, 1506, 1488, 1432, 1410, 1286, 1231, 1160, 1138, 1052, 1027, 865, 732 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz) δ 3.78 (3H, s, OCH_3), 3.81 (3H, s, 3H, OCH_3), 3.94 (3H, s, OCH_3), 6.82 (1H, d, J = 8.5 Hz, H-5′), 7.15 (1H, dd, J = 8.5 Hz, J = 2.0 Hz, H-6′), 7.25 (1H, s, H-8), 7.46 (1H, s, H-5), 7.55 (1H, d, J = 2.0 Hz, H-2′), 7.82 (1H, d, J = 5.5 Hz, H-4) 8.38 (1H, d, J = 5.0 Hz, H-3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 193.5 (C═O), 154 (C-1), 153.1 (C-7), 151.1 (C-6), 149.7 (C-3′), 148.2 (C-4′), 140.2 (C-3), 133.8 (C-4a), 128.4 (C-1′), 127.3 (C-6′), 122.1 (C-8a), 121.4 (C-4), 115.3 (C-5′), 112.9 (C-2′), 105.9 (C-5), 103.7 (C-8), 56.2 (O*C*H_3), 55.9 (O*C*H_3), 55.8 (O*C*H_3); HREIMS m/z 339.1091 $[M^+]$ (calcd for $C_{19}H_{17}O_5N$, 339.1106), 151.0393 (calcd for $C_8H_7O_3$, 151.0395).

Preparation of 2-Methyl-6,7-dimethoxy-3′-methoxy-4′-hydroxyoxobenzylisoquinoline Iodide (1). To 6,7-dimethoxy-3′-methoxy-4′-hydroxyoxobenzylisoquinoline (**8**) (40 mg, 0.118 mmol) in CH_3CN (10 mL) was added CH_3I (1 mL). The solution was refluxed for 12 h, cooled, and evaporated to a yellow residue (49 mg). Treatment of the residue with Me_2CO afforded 2-methyl-6,7-dimethoxy-3′-methoxy-4′-hydroxyoxobenzylisoquinoline iodide (**1**) as yellow crystals (40 mg, 72% yield): mp 174−175 °C; UV (MeOH) λ_{max} (log ϵ) 220 (4.43), 256 (4.57), 302 (4.04), 327 (4.17) nm; UV (MeOH + 2 drops of 0.1 N NaOH) λ_{max} (log ϵ) 323 (4.05), 3.79 (4.23) nm; IR (KBr) ν_{max} 3420,1655, 1583, 1514, 1494, 1430, 1289, 1231, 1164, 1025, 994, 875, 755 cm^{-1}; ^1H NMR (DMSO-d_6, 600 MHz,) δ 3.71 (3H, s, OCH_3, C-7), 3.85 (3H, s, OCH_3, C-3′), 4.06 (3H, s, OCH_3, C-6), 4.13 (3H, s, NCH_3), 6.85 (1H, d, J = 6.6 Hz, H-6′), 6.88 (1H, s, H-8), 7.15 (1H, br s, H-5′), 7.61 (1H, br s, H-2′), 7.85 (1H, s, H-5), 8.42 (1H, d, J = 6.6 Hz, H-4) 8.66 (1H, d, J = 7.2 Hz, H-3), 10.94 (1H, s, OH); $^{13}CNMR$ δ 190.0 (C═O), 162.3 (C-6), 158.1 (C-7), 155.9 (C-3′), 154.7 (C-1), 153.9 (C-4′), 141.2 (C-4a), 141.1 (C-3), 133.2 (C-5′), 130.3 (C-1′), 128.4 (C-4), 126.1 (C-8a), 120.6 (C-6′), 115.9 (C-2′), 111.1 (C-5), 108.7 (C-8), 61.6 (C-6) (O*C*H_3), 60.8 (C-7) (O*C*H_3), 60.4 (C-3′) (O*C*H_3), 50.1 (*N*CH_3); HREIMS m/z 353.1247 $[M^+ - HI]$ (calcd for $C_{20}H_{19}O_5N$, 353.1263), 339.1100 (calcd for $C_{19}H_{17}O_5N$, 339.1106).″

Preparation of 3′-Benzyloxy-4′-methoxyphenyl-1-(6,7-dimethoxyisoquinolyl)carbinol (5). To NaH (100 mg, 4.2 mmol) suspended in DMF (10 mL) at −10 °C was added 1-cyano-2-benzoyl-6,7-dimethoxyisoquinoline (**3**) (1.0 g, 3.12 mmol) in DMF (15 mL) over a period of 5 min under N_2. After 5 min, *O*-benzylisovanillin (822 mg, 3.4 mmol) in DMF (10 mL) was added over 10 min at −10 °C. The mixture was stirred for 2 h at 0 °C and then allowed to stand at room temperature for an additional 2 h. The mixture was treated with MeOH (50 mL) and then evaporated to a residue that was dissolved in C_6H_6 (40 mL), partitioned with H_2O (2 × 30 mL), and evaporated. The resulting residue, consisting primarily of the benzoate ester of **5**, was dissolved in EtOH (25 mL) and hydrolyzed by KOH (0.2 g) in H_2O (10 mL) under reflux for 3 h. The solution was cooled and evaporated to dryness, and the resulting residue was treated with Et_2O (3 × 30 mL). The combined Et_2O extracts were evaporated to a white residue, which upon crystallization from MeOH afforded 3′-benzyloxy-4′-methoxyphenyl-1-(6,7-dimethoxyisoquinolyl)carbinol (**5**) (430 mg, 32% yield): mp of 140−141 °C; UV (MeOH) λ_{max} 239 (4.68), 278 (3.88), 313 (3.72), 326 (3.57) nm; IR (KBr) ν_{max} 3437, 1622,

1570, 1510, 1481, 1434, 1406, 1272, 1235, 1158, 1138, 1022, 963, 754 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.72 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 4.02 (3H, s, OCH_3), 5.03 (2H, s, OCH_2), 6.22 (1H, s, 1H, H-′), 6.81 (1H, d, J = 8.2 Hz, H-5′), 6.86 (1H, s, H-8), 6.95 (1H, dd, J = 8.2 Hz and 1.9 Hz, H-6′), 7.08 (2H, s, H-2′ and H-5), 7.29 (5H, m, ArH), 7.56 (1H, d, J = 5.8 Hz, H-4), 8.40 (1H, d, J = 5.8 Hz, H-3); ^{13}C NMR NMR ($CDCl_3$, 75 MHz) δ 156.4 (C-6), 152.9 (C-7), 149.9 (C-1), 149.4 (C-4′), 148.4 (C-3′), 138.2 (C-3), 136.9 (C-1″), 135.9 (C-1′), 133.7 (C-4a), 128.4 (C-2″ and C-6″), 127.7 (C-4″), 127.3 (C-3″ and C-5″), 120.9 (C-6′), 120.8 (C-8a), 119.9 (C-4), 113.4 (C-2′), 111.6 (C-5′), 105.2 (C-5), 103.3 (C-8), 72.4 (C-α), 70.9 (OCH_2), 56.1 (OCH_3), 56.0 (OCH_3), 55.8 (OCH_3); EIMS m/z 431 [M^+] (88), 416 (5), 340 (70), 324 (85), 310 (24), 280 (33), 218 (47), 188 (80), 91 (100).

Preparation of 6,7-Dimethoxy-3′-benzyloxy-4′-methoxyoxobenzylisoquinoline (7). To 3′-benzyloxy-4′-methoxyphenyl-1-(6,7-dimethoxyisoquinolyl) carbinol (**5**) (400 mg, 0.92 mmol) in HOAc (5 mL) was added a solution of Na_2CrO_4 (620 mg, 3.78 mmol) in HOAc (5 mL). The mixture was heated for 3 min on a steam bath, diluted with H_2O (50 mL), alkalinized with NH_4OH to pH 8−9, and partitioned with Et_2O (3 × 50 mL). The Et_2O extracts were combined, partitioned with H_2O (3 × 100 mL), and evaporated. Treatment of the resulting residue with MeOH afforded 6,7-dimethoxy-3′-benzyloxy-4′-methoxyoxobenzylisoquinoline (**7**) as crystals (320 mg, 80% yield): mp 158−159 °C; UV (MeOH) λ_{max} 238 (4.52), 282(3.86), 326 (3.85) nm; IR (KBr) ν_{max} 1655, 1591, 1578, 1505, 1480, 1434, 1268, 1234, 1157, 1138, 1020, 861, 753 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.93 (6H, s, OCH_3), 4.05 (3H, s, OCH_3), 5.18 (2H, s, OCH_2), 6.90 (1H, d, J = 8.4 Hz, H-5′), 7.13 (1H, s, H-8), 7.35 (6H, m, H-6′ and 5ArH), 7.48 (1H, s, H-5), 7.64 (1H, d, J = 5.4 Hz, H-4), 7.70 (1H, d, J = 1.8 Hz, H-2′), 8.42 (1H, d, J = 5.4 Hz, H-3); ^{13}C NMR NMR ($CDCl_3$, 75 MHz) δ 193.8 (C═O), 154.4 (C-1), 153.7 (C-7), 153.3 (C-6), 151.0 (C-4′), 148.1 (C-3′), 139.9 (C-3), 136.5 (C-1″), 134.0 (C-4a), 129.7 (C-1′), 128.6 (C-2″ and C-6″), 128.0 (C-4″), 127.5 (C-3″ and C-5″), 126.9 (C-6′), 122.8 (C-8a), 121.2 (C-4), 114.6 (C-2′), 110.4 (C-5′), 104.8 and 104.1 (C-5 and C-8), 70.9 (OCH_2), 56.2 (OCH_3), 56.2 (OCH_3), 56.1 (OCH_3); EIMS m/z 429 [M^+] (35), 400 (20), 338 (100), 324 (40), 308 (37), 296 (25), 188 (36), 152 (33), 91 (61).

Preparation of 6,7-Dimethoxy-3′-hydroxy-4′-methoxyoxobenzylisoquinoline (9). A solution of 6,7-dimethoxy-3′-benzyloxy-4′-methoxyoxobenzylisoquinoline (**7**) (300 mg, 0.70 mmol) in of HCl−HOAc (1:1) (20 mL) was refluxed for 2 h. The solution was cooled, diluted with H_2O (40 mL), alkalinized with NH_4OH to pH 8−9, and extracted with Et_2O (3 × 50 mL). The combined Et_2O extracts were evaporated to a residue that upon crystallization from MeOH afforded 6,7-dimethoxy-3′-hydroxy-4′-methoxyoxobenzylisoquinoline (**9**) as pale yellow crystals (180 mg, 76% yield): mp 150−151 °C; UV (MeOH) λ_{max} 238 (4.45), 280 (3.78), 329 (3.78) nm; UV (MeOH + 2 drops of 0.1 N NaOH) λ_{max} (log ϵ) 288 (3.79), 332 (3.80) nm; IR (KBr) ν_{max} 3500−3350,1655, 1606, 1506, 1483, 1437, 1271, 1234, 1157, 1134, 859, 755 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 3.74 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 6.97 (1H, d, J = 8.0 Hz, H-5′), 7.18 (1H, s, H-8), 7.20 (1H, dd, J = 8.8 and 2.4 Hz, H-6′), 7.29 (1H, d, J = 2,4 Hz, H-2′), 7.44 (1H, s, H-5), 7.80 (1H, d, J = 5.6 Hz, H-4), 8.35 (1H, d, J = 5.6 Hz, H-3); ^{13}C NMR δ 195.1 (C═O), 155.5 (C-1), 154.4 (C-7), 154.3 (C-4′), 152.2 (C-6), 147.8 (C-3′), 141.9 (C-3), 134.8 (C-4a), 130.5 (C-1″), 125.5 (C-6′), 123.2 (C-8a), 122.5 (C-4), 117.8 (C-2′), 112.8 (C-5′), 107.1 (C-5), 104.7 (C-8), 57.3 (OCH_3), 57.2 (OCH_3), 56.9 (OCH_3); HREIMS m/z 339.1091 [M^+] (calcd for $C_{19}H_{17}O_5N$, 339.1106), 188.0709 (calcd for $C_{11}H_{10}O_2N$, 188.0711), 151.0393 (calcd for $C_8H_7O_3$, 151.0395).

Preparation of 2-Methyl-6,7-dimethoxy-3′-hydroxy-4′-methoxyoxobenzylisoquinoline Iodide (2). To 6,7-dimethoxy-3′-hydroxy-4′-methoxyoxobenzylisoquinoline (**9**) (30 mg, 0.088 mmol) in CH_3CN (10 mL) was added CH_3I (1 mL). The solution was refluxed for 12 h, cooled, and evaporated to a yellow residue (42 mg). Treatment of the residue with Me_2CO afforded 2-methyl-6,7-dimethoxy-3′-hydroxy-4′-methoxyoxobenzylisoquinoline iodide (**2**) as yellow crystals (33 mg, 77% yield): mp 196−197 °C; UV (MeOH) λ_{max} 256 (4.54), 302 (4.05), 327 (4.11) nm; UV (MeOH + 2 drops of 0.1 N NaOH) λ_{max} (log ϵ) 318 (4.11) nm; IR (KBr) ν_{max} 3500−3300,1655, 1511, 1498, 1434, 1290, 1164, 1144, 1015, 995 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 3.70 (3H, s, OCH_3, C-7), 3.86 (3H, s, OCH_3, C-4′), 4.05 (3H, s, OCH_3, C-6), 4.11 (3H, s, NCH_3), 6.85 (1H, s, H-8), 7.02 (1H, d, J = 8.4 Hz, H-6′), 7.21 (1H, br s, H-5′), 7.40 (1H, br s, H-2′), 7.85 (1H, s, H-5), 8.41 (1H, d, J = 6.8 Hz, H-4) 8.65 (1H, d, J = 6.4 Hz, H-3), 9.87 (1H, s, OH); ^{13}C NMR δ 188.1 (C═O), 159.2 (C-6), 157.0 (C-4′), 154.5 (C-7), 150.9 (C-1), 149.4 (C-3′), 137.9 (C-4a), 137.9 (C-3), 128.1 (C-1′), 127.3 (C-5′), 125.3 (C-4), 122.9 (C-8a), 116.2 (C-2′), 113.8 (C-6′), 108.0 (C-5), 105.5 (C-8), 58.6 (C-6) (OCH_3), 57.8 (C-7) (OCH_3), 57.7 (C-4′) (OCH_3), 47.0 (NCH_3); HREIMS m/z 353.1271 [M^+ − HI] (calcd for $C_{20}H_{19}O_5N$, 353.1263), 339.1102 (calcd for $C_{19}H_{17}O_5N$, 339.1106), 150.9995 (calcd for $C_8H_7O_3$, 150.9991).

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Supporting Information Available: Tables of the proton and carbon chemical shift assignments and long-range connectivities observed in the GHMBC spectra of compounds **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

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