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Isoquinoline Alkaloids. 3. Synthesis of the 6-Ethyl and 6-Butyl Analogs of *d,l*-6-Methyl-5,6,6a,7-tetrahydro-1,2,9,10-tetramethoxy-4*H*-dibenzo[*de,g*]-quinoline 1.5 Phosphate (*d,l*-Glaucine 1.5 Phosphate)

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Abstract:

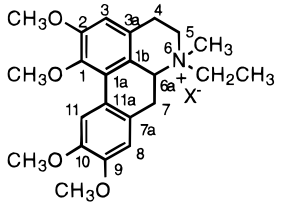
The syntheses of the 6-ethyl (12b) and 6-butyl (12c) analogs of *d,l*-glaucine 1.5 phosphate (12a) in 10 steps from papaverine hydrochloride (1) are described. Mechanistic rationale for the formation of Hofmann degradation products observed during the methylation of the 6-ethyl (7b) and 6-butyl (7c) analogs of *d,l*-1,2,9,10-tetrahydroxyaporphine (7a) with phenyltrimethylammonium hydroxide are discussed. Detailed analyses and assignments of the ^{1}H and ^{13}C NMR spectra of 12a−c and the corresponding free base forms 8a−c are presented.

Introduction

The aporphine alkaloid *d,l*-6-methyl-5,6,6a,7-tetrahydro-1,2,9,10-tetramethoxy-4*H*-dibenzo[*de,g*]quinoline (*d,l*-glaucine) (**8a**) and its salts have been shown to possess analgesic[1] and antitussive activity.[2] Specifically, *d,l*-glaucine 1.5 phosphate (**12a**)[3,4] was selected for clinical evaluation[5] as a non-narcotic antitussive agent.[6] We have previously described the efficient preparation of *d,l*-laudanosoline hydrobromide (**5a**)[7] and its subsequent conversion to **12a** (Scheme 1).[8,9] The same synthetic sequence has been reported for the preparation of [6a-^{13}C]-*d,l*-glaucine 1.5 phosphate for metabolism studies.[10] This paper describes the synthesis of the 6-ethyl (**12b**) and 6-butyl (**12c**) analogs of **12a**, using the process employed for the large-scale preparation of **12a**, and discusses the effect of the *N*-alkyl substituents on the Hofmann elimination which occurs as a side reaction in the methylation of **7** to **8**.

Results and Discussion

The first six steps in the synthesis of **12b** and **12c** were carried out as previously described for the preparation of **12a**.[7−9] The methylation of **7b** with phenyltrimethylammonium hydroxide afforded an 80% yield of a 9/1 mixture of **8b** and **8a** containing small amounts (less than 2%) of **9b** and **9a**. The products **8a** and **9b** can be rationalized as arising via N-methylation of **8b** followed by Hofmann elimination via path A to give **8a** and path B to give **9b** (Scheme 2). Because a greater amount of **8a** was formed, path A appears to be favored over path B, with steric requirements for the elimination exercising more product control than the resonance energy gained in the formation of **9b**. This is easily seen if one examines a molecular model of the quaternary salt intermediate **13**. The methyl hydrogens



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of the ethyl group can easily orient themselves antiperiplanar to the departing amino group as required for anti elimination, whereas similar orientation of either hydrogen at position 7 requires considerable distortion and twisting of the ring system. The model also shows that a hydrogen at position 4 can easily attain the required orientation, and that elimination along the C4−C5 bond should be a favorable competing reaction. However, the product of Hofmann C4−C5 elimination was not isolated. The product **9a** presumably arises via N-methylation of **8a** followed by Hofmann elimination (Scheme 3). A pure sample of **8b** (see Table 2 for NMR spectral data on **8a** and Table 3 for NMR spectral data on **8b**) was obtained by column chromatography of the mixture on silica gel with chloroform/methanol to give a mixture of **8b** and **8a** (free of **9b** and **9a**) followed by column chromatography on silica gel with 2-propanol. The pure **8b**

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(2) Maasboel, A. G. Ger. Offen. DE 2 717 062, 1978; *Chem. Abstr.* **1979**, *90*, 43806t.
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(7) Goralski, C. T.; Krauss, R. C.; Williams, B. M.; Henton, D. R.; Brown, D. T. *Ind. Eng. Chem. Res.* **1989**, *28*, 221.
(8) Maasboel, A. G.; Sim, A. K. U.S. Patent 4 279 914, 1981; Chem. Abstr. **1979**, *90*, 43806t.
(9) Goralski, C. T.; Hasha, D. L.; Henton, D. R.; Krauss, R. C.; Pfeiffer, C. D.; Williams, B. M. *Org. Process Res. Dev.* **1997**, *1*, 273.
(10) Henton, D. R.; Goralski, C. T.; Heeschen, J. P.; Nyquist, R. A.; Pfeiffer, C. D. *J. Labelled Compd. Radiopharm.* **1989**, *27*, 297.

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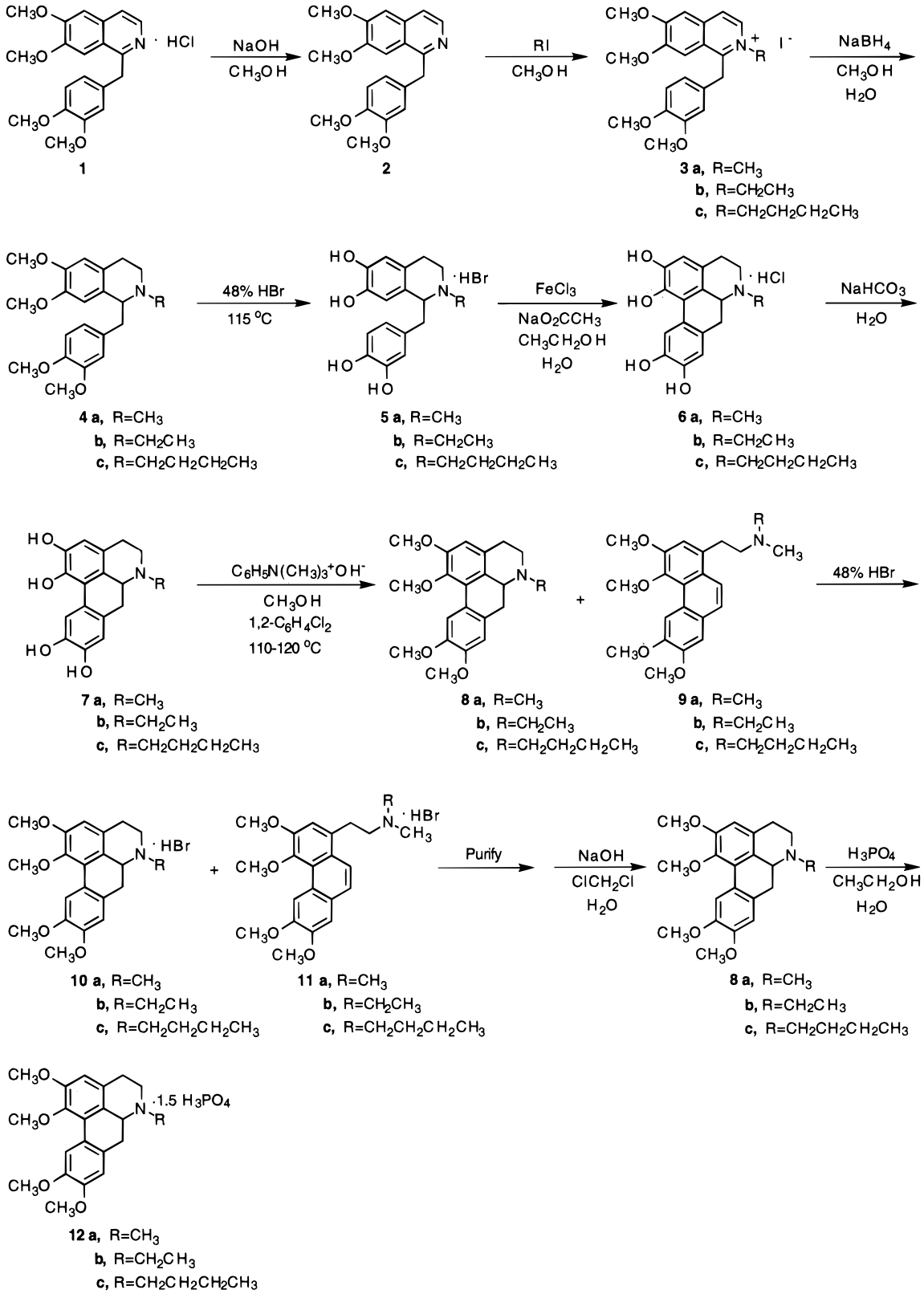
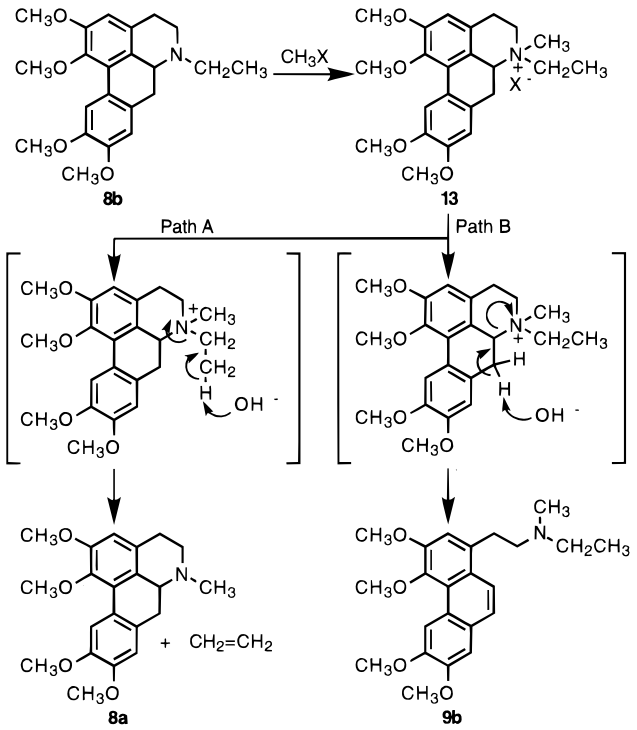
Scheme 1



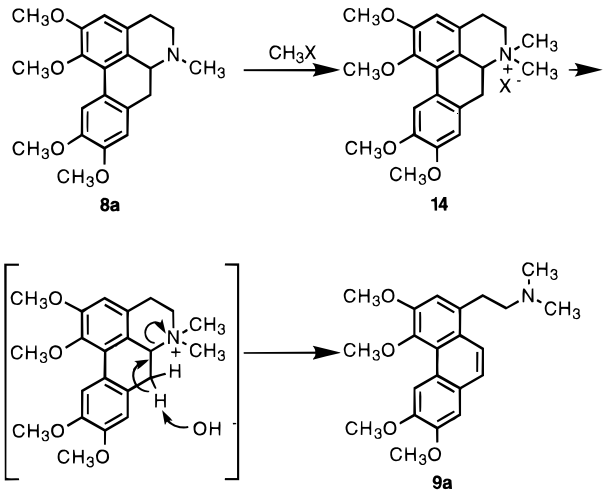
was converted to the hydrobromide salt **10b** with 48% hydrobromic acid in ethanol and the 1.5 phosphate salt **12c** (see Table 1 for NMR spectral data) with 85% phosphoric acid in aqueous ethanol.

The methylation of **7c** with phenyltrimethylammonium hydroxide, followed by precipitation of the crude product with 48% hydrobromic acid, gave a 65% yield of crude **10c** containing no detectable amount of **11c** or **11a** by HPLC or TLC analysis. It is possible that the steric requirements of the butyl group totally block N-methylation of **7c** or, if N-methylation does occur, the steric bulk of the butyl group blocks hydrogen abstraction at C7. Similarly, the ethyl group now present at the β-position may be sterically interfering with hydrogen abstraction in the *N*-alkyl group, thus preventing the formation of **8a**. A pure sample of **8c** (see Table 4 for NMR spectral data) was obtained by simple "plug

Scheme 2



Scheme 3



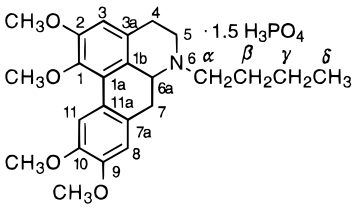
filtration" of the crude material through silica gel with methylene chloride. Treatment of pure **8c** with 85% phosphoric acid in aqueous ethanol afforded the corresponding 1.5 phosphate salt **12c** (see Table 1 for NMR spectral data).

Experimental Section

General Procedures. All melting points and boiling points are uncorrected. The melting points of the phosphate salts were determined by differential scanning calorimetry (DSC).

NMR Spectra. The 75.5-MHz ^{13}C and 300-MHz ^{1}H NMR spectra were obtained on an IBM AF 300 spectrometer with a field strength of 7.05 T. Referencing of the chemical shift scales was accomplished with an internal standard, tetramethylsilane (TMS = 0 ppm). In order to make unambiguous spectral assignments it was necessary to conduct PACOUP: partly coupled 2D $^{13}C-^{1}H$ shift correlation experiments.[11] Unfortunately, the relatively low sensitivity of PACOUP required concentrations greater than 0.2 M (at 7.05 T). Saturated solutions of the isoquinoline alkaloid phosphate salts (**12a**−**c**) in DMSO-d_6 did not reach such concentrations. To increase the solubility of the isoquinoline alkaloids, the phosphate salts were converted to the corresponding free bases and deuteriochloroform was used as the solvent. The concentration of the free bases in deuteriochloroform was approximately 0.3 M. PACOUP is a coupled version of the standard Freeman−Morris heteronuclear, chemical-shift correlation sequence.[12,13] The PACOUP pulse sequence, shown in Figure 1, provides a ^{1}H-coupled carbon spectrum along ω_2, the carbon dimension, and application of the carbon π-pulse midway through the evolution period (t_1) results in a ^{13}C-decoupled proton spectrum along ω_1, the proton dimension. At the end of the evolution period, the transverse proton magnetization is independent of all proton−carbon coupling information. This information is retrieved with the fixed delay Δ_1. To optimize the experiment for long-range couplings, $|^nJ_{CH}|$ ($n > 1$), of 10 Hz, Δ_1 is set to 50 ms, $\Delta_1 = 0.5/^nJ_{CH}$ ($n > 1$). For long-range couplings, $|^nJ_{CH}|$ not equal to 10 Hz, the intensity of the transverse proton magnetization is reduced. Krishnamurthy and Casida[11] have shown that for a specific Δ_1 more

Table 1. **^{13}C NMR chemical shifts (DMSO-d_6) of isoquinoline alkaloid 1.5 phosphate salts**

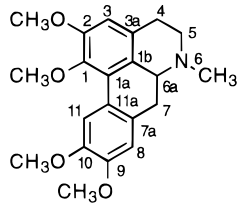


position	R = CH_3	R = CH_2CH_3	R = $(CH_2)_3CH_3$
1	144.4	144.1	144.1
1a	123.1	125.1	125.9
1b	126.1[a]	128.2[a]	128.4[a]
2	152.9	152.0	151.9
3	111.1	111.2	111.3
3a	126.0[a]	126.3[a]	126.3[a]
4	25.4	27.4	27.5
5	51.3	47.5[b]	48.4
6a	61.0	59.6	59.7
7	30.2	32.4	33.0
7a	126.4[a]	128.7[a]	129.0
8	111.8	112.0[c]	112.1[b]
9	148.4[b]	148.3[d]	148.3[c]
10	147.6[b]	147.4[d]	147.4[c]
11	111.8	112.2[c]	112.3[b]
11a	120.8	123.7	123.8
1-OCH_3	59.6	58.7	59.5
OCH_3	55.8, 55.6, 55.4	55.8, 55.8, 55.5	55.8, 55.8, 55.6
α-CH_3	40.9		
α-CH_2		47.2[b]	52.9
β-CH_3		9.8	
β-CH_2			27.9
γ-CH_2			20.0
δ-CH_3			13.7

[a−d] Signals within any vertical column may be reversed.

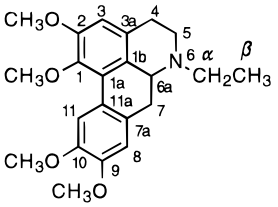
(11) Krishnamurthy, V. V.; Casida, J. C. *J. Magn. Reson.* **1989**, *85*, 69.
(12) Freeman, R.; Morris, G. A. *J. Chem. Soc., Chem. Commun.* **1978**, 684.
(13) Bax, A.; Morris, G. A. *J. Magn. Reson.* **1981**, *42*, 501.

Table 2. **NMR chemical shifts ($CDCl_3$) for *d,l*-glaucine (*d,l*-6-methyl-5,6,6a,7-tetrahydro-1,2,9,10-tetramethoxy-4*H*-dibenzo[*de,g*]quinoline (8a)**



position	^{13}C	^{1}H
1	143.8	
1a	126.4	
1b	126.8	
2	151.5	
3	110.0	6.57
3a	128.5	
4	28.9	2.63, 3.11
5	52.9	2.44, 2.98
6-CH3	43.6	2.51
6a	62.1	2.97
7	34.1	2.56, 3.01
7a	128.9	
8	110.5	6.78
9	147.6	
10	147.0	
11	111.2	8.04
11a	124.1	
1-OCH3	59.7	3.65
2-OCH3	55.5	3.84
9-OCH3	55.3	3.90
10-OCH3	55.3	3.90

Table 3. **NMR chemical shifts ($CDCl_3$) for *d,l*-6-ethyl-5,6,6a,7-tetrahydro-1,2,9,10-tetramethoxy-4*H*-dibenzo-[*de,g*]quinoline (8b)**



position	^{13}C	^{1}H
1	143.7	
1a	126.4	
1b	127.3	
2	151.2	
3	110.0	6.60
3a	128.8	
4	28.9	2.66, 3.07
5	47.9	2.41, 3.14
6a	58.7	3.31
7	33.9	2.58, 3.03
7a	128.9	
8	110.3	6.80
9	147.4	
10	147.0	
11	111.0	8.09
11a	124.0	
1-OCH_3	59.5	3.64
2-OCH_3	55.2	3.84
9-OCH_3	55.2	3.89
10-OCH_3	55.3	3.90
α-CH_2	47.3	2.58, 3.10
β-CH_3	10.4	1.17

than 50% of the theoretical intensity is expected for couplings in the range $5J_{opt}/3$ and $J_{opt}/3$ where $J_{opt} = 0.5\ \Delta_1$. Thus, for couplings between 3 and 17 Hz the signal intensity is expected to be less than 50% when $\Delta_1 = 50$ ms. Further attenuation of the signal intensity occurs when the couplings are significantly outside this range.[11] The simultaneous carbon and proton $\pi/2$ pulses cause transfer of magnetization from the protons to the carbons which are detected during the acquisition period, t_2.

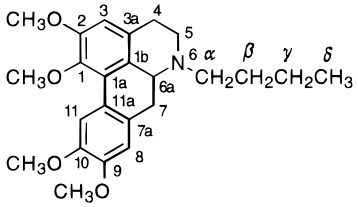
The 2D PACOUP spectrum exhibits two types of couplings, designated *active* and *passive*. For a given cross peak (δ_{CA}, δ_{HA}) the active coupling is the $^{n}J_{CA,HA}$ coupling between the carbon and the proton(s) responsible for the cross peak; *i.e.*, carbon CA and proton HA. The multiplet patterns produced by the active couplings are CH, 1/1 doublet; CH_2, 1/0/1 triplet (1/1 doublet with splitting $2 \times {}^{n}J_{CA,HA}$); and CH_3, 1/1/1/1 quartet. The passive couplings for the same cross peak (δ_{CA}, δ_{HA}) are the couplings between carbon CA and the remaining protons, $^{n}J_{CA,Hi}(i \neq A)$. The multiplet patterns from the passive couplings are as expected: *i.e.*, CH, 1/1 doublet; CH_2, 1/2/1 triplet; and CH_3, 1/3/3/1 quartet.

Analysis of the non-phase-sensitive 2D PACOUP spectra, cross peak positions as well as coupling patterns (active and passive), allowed complete assignment of the carbon and proton spectra for the isoquinoline alkaloid free bases (**8a**−**c**). The chemical shifts reported in Tables 2−4 were obtained from the standard Freeman−Morris heteronuclear correlation experiment[12,13] optimized for one-bond carbon−proton couplings, $^{1}J_{CH} \approx 130$ Hz, performed on the same solutions.

1-((3,4-Dimethoxyphenyl)methyl)-2-ethyl-6,7-dimethoxyisoquinolinium Iodide (3b). A mixture of 100 g (0.266 mol) of papaverine hydrochloride (**1**), 21.5 g (0.269 mol) of 50% sodium hydroxide solution, and 300 mL of toluene was stirred at 50 °C for 1 h, and 5.0 g of anhydrous potassium carbonate and 500 mL of iodoethane were added. The toluene layer was monitored by TLC for the disappearance of papaverine. After 7 days at 50 °C, the precipitate was collected, washed with toluene, and air-dried to give 164.0 g of crude **3b**, mp 204−205 °C; IR (KBr) 1605, 1510, 1425, 1275, 1235, 1140, 1015, 850 cm^{-1}; NMR (DMSO-d_6) δ 8.71 (d, $J = 7$ Hz, 1, H at 3-position), 8.35 (d, $J = 7$ Hz, 1, H at 4-position), 7.87 (s, 1, H at 5- or 8-position), 7.84 (s, 1, H at 5- or 8-position), 7.25−7.05 (m, 1, H at benzyl 2-position), 6.85 (d, $J = 8$ Hz, 1, H at benzyl 5-position), 6.57−6.37 (m, 1, H at benzyl 6-position), 5.13 (s, 2, benzyl CH_2), 4.80 (q, $J = 7$ Hz, 2, CH_2CH$_3$), 4.09 (s, 3, 6-OCH_3), 3.98 (s, 3, 7-OCH_3), 3.75 (s,3, benzyl OCH_3), 3.70 (s, 3, benzyl OCH_3), 1.42 (t, $J = 7$ Hz, 3, CH_2CH_3); ms (70 eV, chemical ionization, methane) 368 (M − 127).

2-Butyl-1-((3,4-dimethoxyphenyl)methyl)-6,7-dimethoxyisoquinolinium Iodide Monohydrate (3c). A mixture of 100 g (0.266 mol) of papaverine hydrochloride (**1**), 21.5 g (0.269 mol) of 50% sodium hydroxide solution, and 300 mL of ethanol was stirred at 50 °C for 1 h, and 500 g of 1-iodobutane was added. After 24 h, 5.0 g of anhydrous potassium carbonate was added. After 7 days at 50−60 °C, the mixture was poured into 1.0 L of toluene and the resulting precipitate was collected, washed with toluene, and air-dried to give 175.0 g of crude **3c**, mp 96−99 °C: IR (KBr) 3480

Table 4. **NMR chemical shifts ($CDCl_3$) for *d,l*-6-butyl-5,6,6a,7-tetrahydro-1,2,9,10-tetramethoxy-4*H*-dibenzo-[*de,g*]quinoline (8c)**



position	^{13}C	^{1}H
1	143.9	
1a	126.8	
1b	127.6	
2	151.4	
3	110.1	6.60
3a	129.1	
4	29.2	2.66, 3.06
5	48.9	2.42, 3.14
6a	59.7	3.24
7	34.3	2.58, 3.00
7a	129.3	
8	110.5	6.80
9	147.7	
10	147.1	
11	111.1	8.09
11a	124.2	
1-OCH_3	59.8	3.64
2-OCH_3	55.4	3.86
9-OCH_3	55.4	3.93
10-OCH_3	55.6	3.91
α-CH_2	53.8	2.42, 2.95
β-CH_2	28.3	1.57
γ-CH_2	20.6	1.41
δ-CH_3	13.9	0.97

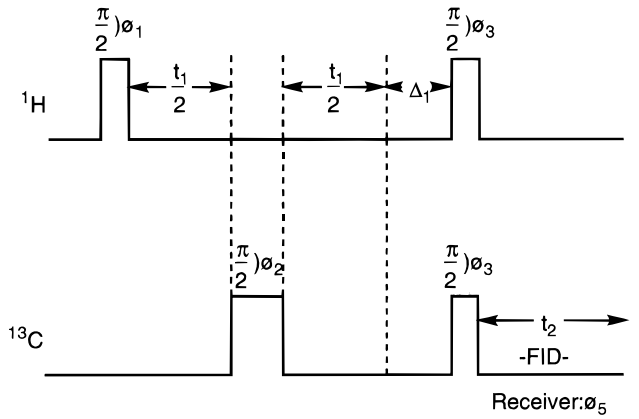


Figure 1. **PACOUP pulse sequence. The ϕ_n are the phases of the pulses and the receiver. The phase cycles for PACOUP are given in ref 11. The fixed delay, Δ_1, was 50 ms. The initial evolution period (t_1) was 6 μs and was increased in increments of 390 μs. The evolution period was incremented a total of 1024 times, resulting in 1024 (1K) data points in the $t_1(\omega_1)$ domain. The data size (and number of data points) in the t_2 domain was 16 384 (16K). A total of 64 scans were accumulated for each increment. With a recycle delay of 2.0 s the total experimental time was approximately 53 h.**

and 3420 (water of hydration), 1620, 1605, 1510, 1430, 1275, 1245, 1160, 1135, 1020 cm^{-1}; NMR (DMSO-d_6) δ 8.71 (d, $J = 7$ Hz, 1, H at 3-position), 8.32 (d, $J = 7$ Hz, 1, H at 4-position), 7.86 (s, 2, H at 5- and 8-positions), 7.22−7.10 (m, 1, H at benzyl 2-position), 6.85 (d, $J = 8$ Hz, 1, H at benzyl 5-position), 6.60−6.37 (m, 1, H at benzyl 6-position), 5.13 (s, 2, benzyl CH_2), 4.73 (t, $J = 7$ Hz, 2, NCH_2), 4.10 (s, 3, 6-OCH_3), 3.99 (s, 3, 7-OCH_3), 3.75 (s, 3, benzyl OCH_3), 3.70 (s, 3, benzyl OCH_3), 3.38 (broad s, 2, H_2O), 1.9−1.2 (m, 4, $NCH_2CH_2CH_2CH_3$), 0.86 (t, $J = 7$ Hz, 3, CH_2CH_3); ms (70 eV, chemical ionization, methane) 396 (M − 127).

***d,l*-1-((3,4-Dimethoxyphenyl)methyl)-2-ethyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (4b).** To a slurry of 162 g of crude **3b** in 400 mL of absolute ethanol was added a solution of 10.0 g of sodium borohydride in 20.0 g of 50% sodium hydroxide solution which had been diluted with water to 50 mL. The 30-min addition was accompanied by foaming (which resulted in the loss of some product), and the temperature of the reaction mixture rose to 45 °C. After 30 min of stirring, the mixture was partitioned between water and methylene chloride. The organic layer plus one wash were dried (Na_2SO_4) and concentrated to leave an oil, which, upon trituration with hexane, solidified. The solid was collected and air-dried to give 78.4 g (79.3% yield from **1**) of crude **4b**. Recrystallization from hexane gave 59.6 g of **4b**, mp 82−85 °C: IR (Nujol) 1600, 1585, 1510, 1260, 1220, 1130, 1015 cm^{-1}; NMR ($CDCl_3$) δ 6.85−6.53 (m, 4, aromatic, with 1H d, $J = 8$ Hz, at 6.78, and 1H s at 6.57), 6.04 (s, 1, aromatic), 3.85 (s, 3, OCH_3), 3.83 (s, 3, OCH_3), 3.80 (s, 3, OCH_3), 3.57 (s, 3, OCH_3), 3.30−2.52 (m, 9, 4 CH_2 groups and methine), 1.13 (t, $J = 7.5$ Hz, 3, CH_2CH_3); ms (70 eV, electron impact) *m/e* 369 (M − 2). A portion was twice recrystallized (hexane) to afford a sample of **4b**, mp 88−90 °C, as fine, white needles for combustion analysis.

Anal. Calcd for $C_{22}H_{29}NO_4$: C, 71.13; H, 7.87; N, 3.77. Found: C, 70.97; H, 7.74; N, 3.85.

***d,l*-2-Butyl-6,7-dimethoxy-1-((3,4-dimethoxyphenyl)-methyl)-1,2,3,4-tetrahydroisoquinoline (4c).** To a slurry of 168.0 g of crude **3c** in 400 mL of absolute ethanol was added a solution of 10.0 g of sodium borohydride in 20 mL of 50% sodium hydroxide solution diluted to 50 mL with water. The 30-min addition was carried out with mechanical stirring to minimize foaming; the temperature rose to 45−50 °C. After 30 min of stirring, the mixture was partitioned between water and methylene chloride. The organic layer plus one wash were dried (Na_2SO_4) and concentrated to leave 103.0 g (97% yield from **1**) of crude **4c** as a viscous oil. The oil was extracted with several portions of hot hexane, which yielded a white, crystalline solid on cooling. The solid was collected to give 60.9 g of **4c**, mp 51−53 °C: NMR ($CDCl_3$) δ 6.85−6.53 (m, 4, aromatic with 1H d, $J = 8$ Hz, at 6.78, and 1H s at 6.55), 6.07 (s, 1, aromatic), 3.84 (s, 3, OCH_3), 3.82 (s, 3, OCH_3), 3.80 (s, 3, OCH_3), 3.59 (s, 3, OCH_3), 3.30−2.45 (m, 9, benzylic protons and protons adjacent to N), 1.75−1.05 (m, 4, $CH_2CH_2CH_3$), 0.87 (t, $J = 7$ Hz, 3, CH_2CH_3); ms (70 eV, chemical ionization, methane) 400 ($M^+ + 1$), 428 ($M^+ + 29$), 440 ($M^+ + 41$).

Anal. Calcd for $C_{24}H_{33}NO_4$: C, 72.15; H, 8.33; N, 3.51. Found: C, 72.00; H, 8.18; N, 3.43.

***d,l*-1-((3,4-Dihydroxyphenyl)methyl)-2-ethyl-1,2,3,4-tetrahydro-6,7-isoquinolinediol Hydrobromide (5b).** A 500-mL, single-neck flask equipped with a thermowell, a magnetic stirrer, and a distillation head fitted with a nitrogen bubbler was charged with 30.0 g (0.08 mol) of **4b** and 100 mL of 48% hydrobromic acid. The mixture was heated to

110−115 °C, and the water was distilled overhead. After 7 h, the reaction mixture was cooled slowly to ambient temperature. No crystals formed, so an additional 50 mL of 48% hydrobromic acid was added, and the mixture was heated at 115 °C for 8 h. The reaction mixture was cooled slowly to ambient temperature, and a grey solid formed. The solid was separated by filtration, air-dried, washed with acetone, air-dried, and vacuum-dried to give 15.61 g (49% yield) of **5b**, mp 196−199 °C dec.

Anal. Calcd for $C_{18}H_{21}NO_4$·HBr: C, 54.48; H, 5.59; N, 3.58. Found: C, 53.89; H, 5.52; N, 3.79.

***d,l*-2-Butyl-1-((3,4-dihydroxyphenyl)methyl)-1,2,3,4-tetrahydro-6,7-isoquinolinediol Hydrobromide (5c).** A 500-mL, single-neck flask equipped with a thermowell, a magnetic stirrer, and a reflux distillation head was charged with 40.0 g (0.10 mol) of **4c** and 120 mL of 48% hydrobromic acid. The mixture was heated to 115 °C, and the water was distilled overhead. After 21 h, the reaction mixture was cooled to ambient temperature. No solid precipitated. The reaction mixture was cooled with an ice bath, and a gelatinous solid formed. The reaction mixture was warmed to ambient temperature and stirred for 2 days. The reaction mixture formed a solid, grey mass. The solid was separated by filtration and air-dried. The air-dried solid was washed twice with cyclohexane and vacuum-dried at 60 °C to give 35.10 g (83% yield) of **5c**, mp 157−159 °C.

Anal. Calcd for $C_{20}H_{25}NO_4$·HBr: C, 56.60; H, 6.18; N, 3.30. Found: C, 56.40; H, 6.10; N, 3.26.

***d,l*-6-Ethyl-5,6,6a,7-tetrahydro-1,2,9,10-tetrahydroxy-4*H*-dibenzo[*de,g*]quinoline Hydrochloride (6b).** A 250-mL, single-neck flask equipped with a magnetic stirrer, a thermowell, and a reflux condenser fitted with a nitrogen bubbler was charged with 14.0 g (0.053 mol) of **5b**, 32 mL of absolute ethanol, and 24 mL of deionized water. The mixture was heated to reflux to effect solution, and 2.97 g (0.036 mol) of anhydrous sodium acetate was added. The solution was then cooled to 6 °C, and a similarly cooled mixture of 32 mL of 42 °B ferric chloride solution and 24 mL of absolute ethanol was added. The reaction temperature rose to 11 °C, and the reaction mixture was then stirred at ambient temperature for 20 h. The dark green slurry was cooled with an ice bath, and 17 mL of concentrated hydrochloric acid was added. After stirring for 1 h, the solid was separated by filtration, washed with acetone, air-dried, and vacuum-dried to give 10.21 g (83% yield) of **6b**, mp 232−234 °C.

***d,l*-6-Butyl-5,6,6a,7-tetrahydro-1,2,9,10-tetrahydroxy-4*H*-dibenzo[*de,g*]quinoline Hydrochloride (6c).** A 500-mL, single-neck flask equipped with a thermowell, a magnetic stirrer, and a reflux condenser fitted with a nitrogen bubbler was charged with 21.10 g (0.05 mol) of **5c**, 45 mL of absolute ethanol, and 35 mL of deionized water. The mixture was heated to approximately 40 °C to effect solution, and 4.06 g (0.051 mol) of anhydrous sodium acetate was added. This mixture was cooled to 8 °C, and a similarly cooled mixture of 45 mL of 42 °B ferric chloride and 32 mL of absolute ethanol was added. The reaction temperature rose to 13 °C, and the reaction mixture was then stirred at ambient temperature for 19 h. The reaction mixture was cooled to 5 °C, and 24 mL of concentrated hydrochloric acid was added. The acidified reaction mixture was stirred at 5 °C for 1 h. The solid was separated by filtration (very gummy and hard to filter), washed several times with acetone, air-dried, and vacuum-dried to give 5.40 g of **6c**, mp 211−213 °C dec. A 1.50-g second crop of **6c**, mp 211−215 °C dec, was obtained from the acetone filtrate. Total: 6.90 g of **6c** (37% yield).

***d,l*-6-Ethyl-5,6,6a,7-tetrahydro-1,2,9,10-tetrahydroxy-4*H*-dibenzo[*de,g*]quinoline (7b).** A 250-mL, single-neck flask equipped with a magnetic stirrer, a thermowell, and a reflux condenser fitted with a nitrogen bubbler was charged with 7.30 g (0.02 mol) of **6b** and 35 mL of deionized water. To the resulting slurry was added a solution of 2.63 g (0.031 mol) of sodium bicarbonate in 40 mL of deionized water, and the slurry was heated to 98 °C. The slurry was then cooled to 40 °C and the solid separated by filtration. The solid was air-dried, washed twice with deionized water, air-dried, and vacuum-dried to give 6.04 g (92% yield) of **7b**, mp 219−221 °C dec.

***d,l*-6-Butyl-5,6,6a,7-tetrahydro-1,2,9,10-tetrahydroxy-4*H*-dibenzo[*de,g*]quinoline (7c).** A 250-mL, single-neck flask equipped with a magnetic stirrer, a thermowell, and a reflux condenser fitted with a nitrogen bubbler was charged with 5.50 g (0.0145 mol) of **6c** and 30 mL of deionized water. A solution of 1.83 g (0.0217 mol) of sodium bicarbonate in 30 mL of deionized water was added to the slurry through the condenser to assist in breaking up the severe foaming which occurred. The slurry was heated to 98 °C and then cooled to 45 °C. The solid was separated by filtration. The solid was washed thoroughly with deionized water, air-dried, and vacuum-dried at 55−60 °C to give 4.69 g (95% yield) of **7c**, mp 210−212 °C dec.

***d,l*-6-Ethyl-5,6,6a,7-tetrahydro-1,2,9,10-tetramethoxy-4*H*-dibenzo[*de,g*]quinoline (8b).** A 500-mL, three-neck flask equipped with a thermometer, a magnetic stirrer, a pressure-equalizing addition funnel, and a short-path distillation head fitted with a nitrogen bubbler was charged with 300 mL of 1,2-dichlorobenzene. The 1,2-dichlorobenzene was heated to 120 °C, and a solution of 5.23 g (0.0167 mol) of **7b** in a solution of phenyltrimethylammonium hydroxide (prepared from solutions of 12.93 g of phenyltrimethylammonium chloride in 17 mL of methanol and 4.92 g of 85% potassium hydroxide in 15 mL of methanol; the precipitated potassium chloride was separated by filtration and washed with two 5-mL portions of methanol) was added at such a rate that the temperature of the reaction mixture remained between 110 and 120 °C. After the addition was complete, the reaction mixture was cooled to 40 °C and filtered through a Supercel pad. The filtrate was treated with 2.0 g of 48% hydrobromic acid and stirred for 15 h. The precipitated solid was separated by filtration, washed with acetone, air-dried, and vacuum-dried at 55−60 °C to give 6.00 g (80% yield) of a 9/1 mixture of crude **10b** and **10a** (containing less than 2% of **9a** and **9b**). This material was converted to the free-base form and chromatographed on silica gel 60 (70−230 mesh) first with chloroform/methanol and then a second time with pure 2-propanol to give 3.48 g of pure **8b** as an oil.

***d,l*-6-Ethyl-5,6,6a,7-tetrahydro-1,2,9,10-tetramethoxy-4*H*-dibenzo[*de,g*]quinoline Hydrobromide (10b).** A flask was charged with 0.48 g of **8b** and 5 mL of absolute ethanol.

To the resulting solution was added 48% hydrobromic acid until no further precipitation occurred. The solid was separated by filtration, washed with absolute ethanol, air-dried, and vacuum-dried at 65 °C to give 0.34 g (58% yield) of **10b**, mp 248−250 °C dec.

Anal. Calcd for $C_{22}H_{27}NO_4 \cdot HBr$: C, 58.66; H, 6.26; N, 3.11. Found: C, 58.70; H, 6.33; N, 3.03.

***d,l*-6-Ethyl-5,6,6a,7-tetrahydro-1,2,9,10-tetramethoxy-4*H*-dibenzo[*de,g*]quinoline 1.5 Phosphate (12b).** A 100-mL, single-neck flask equipped with a magnetic stirrer and a reflux condenser fitted with a nitrogen bubbler was charged with 2.90 g of **8b** and 25 mL of absolute ethanol. To the resulting solution was added 2.00 g of 85% phosphoric acid, and a white precipitate formed immediately. To the slurry was added 4.0 mL of deionized water, and the mixture was heated to reflux. The resulting solution was cooled slowly to ambient temperature and finally with an ice bath to give a finely divided, white solid. The solid was separated by filtration, washed with 22 mL of absolute ethanol, air-dried, and vacuum-dried at 60 °C to give 2.60 g (64% yield) of **12b**, mp 197−200 °C (dec, not well defined).

Anal. Calcd for $C_{22}H_{27}NO_4 \cdot 1.5H_3PO_4$: C, 51.16; H, 6.16; N, 2.71. Found: C, 50.79; H, 6.18; N, 2.70.

A 0.60-g second crop of slightly pink **12b** was obtained.

***d,l*-6-Butyl-5,6,6a,7-tetrahydro-1,2,9,10-tetramethoxy-4*H*-dibenzo[*de,g*]quinoline (8c).** A 500-mL, three-neck flask equipped with a thermometer, a magnetic stirrer, a pressure-equalizing addition funnel, and a short-path distillation head fitted with a nitrogen bubbler was charged with 300 mL of 1,2-dichlorobenzene. The 1,2-dichlorobenzene was heated to 120 °C, and a solution of 3.41 g (0.01 mol) of **7c** in a solution of phenyltrimethylammonium hydroxide (prepared from a solution of 7.76 g of phenyltrimethylammonium chloride in 11 mL of methanol and 2.95 g of 85% potassium hydroxide in 10 mL of methanol; the precipitated potassium chloride was separated by filtration and washed with two 5-mL portions of methanol) was added at such a rate that the reaction temperature remained between 110 and 120 °C. After the addition was complete, the reaction mixture was heated to 120 °C to complete the removal of methanol. The reaction mixture was cooled to 40 °C and filtered through a Supercel pad. To the filtrate was added 2.1 mL of 48% hydrobromic acid, and the mixture was stirred for 15 h. The solid was separated by filtration, washed with acetone, air-dried, and vacuum-dried at 65 °C to give 3.11 g (65% yield) of crude **10c**. This material was converted to the corresponding free base and purified by "plug filtration" in methylene chloride on 35 g of silica gel 60 (70−230 mesh) to give 2.02 g (51% yield) of **8c**, mp 149−151 °C.

Anal. Calcd for $C_{24}H_{31}NO_4$: C, 72.51; H, 7.86; N, 3.52. Found: C, 72.50; H, 7.78; N, 3.43.

***d,l*-6-Butyl-5,6,6a,7-tetrahydro-1,2,9,10-tetramethoxy-4*H*-dibenzo[*de,g*]quinoline 1.5 Phosphate (12c).** A 25-mL, single-neck flask equipped with a magnetic stirrer and a reflux condenser fitted with a nitrogen bubbler was charged with 2.00 g (0.0050 mol) of **8c**, 13 mL of absolute ethanol, and 1.20 g (0.0104 mol) of 85% phosphoric acid. The mixture was heated to reflux, and a homogeneous solution resulted. The solution was cooled slowly to ambient temperature, and a solid mass formed. The solid was separated by filtration, washed with ethanol, air-dried, and vacuum-dried to give 2.16 g (79% yield) of **12c**, mp 148−150 °C (dec; sinters at 140 °C; does not give a well-defined melting point).

Anal. Calcd for $C_{24}H_{31}NO_4 \cdot 1.5H_3PO_4$: C, 52.93; H, 6.58; N, 2.57. Found: C, 52.90; H, 6.58; H, 2.54.

Supporting Information Available

The ^{1}H NMR spectra (DMSO-d_6) for compounds **3b**,**c** and the ^{1}H and ^{13}C NMR spectra (DMSO-d_6) for compounds **6b**,**c** and **7b**,**c** (13 pages). See any current masthead page for ordering and Internet access instructions.

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