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Isoquinoline Alkaloids. 2. Preparation of *d,l*-Glaucine 1.5 Phosphate from *d,l*-Laudanosoline Hydrobromide[†]

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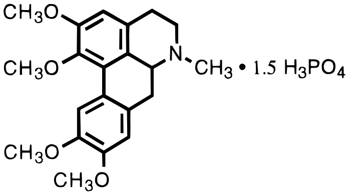
Abstract:

A high-yield, commercially viable synthesis of *d,l*-glaucine 1.5 phosphate (1) from *d,l*-laudanosoline hydrobromide (2) is described. Oxidation of 2 with ferric chloride in ethanol/water buffered with sodium acetate gave *d,l*-1,2,9,10-tetrahydroxyaporphine hydrochloride (3) in 76−83% yield. This was converted to the free base, 4, which was methylated with phenyltrimethylammonium hydroxide (5) in 1,2-dichlorobenzene to give, after precipitation with 48% hydrobromic acid, crude *d,l*-glaucine hydrobromide (6) in 74% yield. The crude 6 was purified by recrystallization from 50/50 (v/v) ethanol/water to remove by-product 1-(2-(dimethylamino)ethyl)-3,4,6,7-tetramethoxyphenanthrene hydrobromide (7). The purified 6 was converted to 1 in 86−88% yield by formation of the free base followed by treatment with 85% phosphoric acid in 80% ethanol and subsequent crystal digestion for 6 h.

Introduction

A number of alkaloids are useful therapeutic agents for the treatment of a variety of human disorders. The isoquinoline alkaloid *d,l*-glaucine, a member of the family of compounds known as the aporphine alkaloids, and its salts are known to possess analgesic[1] and antitusssive[2] activity. Specifically, *d,l*-glaucine 1.5 phosphate (**1**)[3,4] was selected for clinical evaluation[5] as a non-narcotic[6] antitussive agent. Thus, a high-yield, commercially viable synthesis of **1** was required, and this paper describes such a synthesis, based on earlier work by Maasboel,[7] starting from *d,l*-laudanosoline hydrobromide (**2**).



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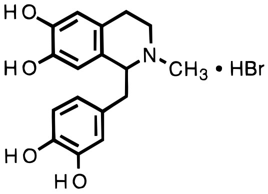

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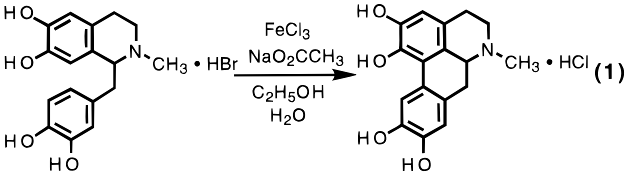
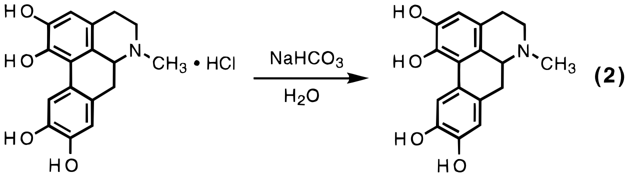
In a previous publication from this group,[8] we described a highly efficient process for the laboratory and pilot plant production of **2**. Oxidation of **2** with ferric chloride in sodium acetate buffered aqueous ethanol afforded *d,l*-1,2,9,10-tetrahydroxyaporphine hydrochloride (**3**) in 76−83% yield (eq 1). The hydrochloride salt **3** was converted to *d,l*-1,2,9,10-tetrahydroxyaporphine (**4**) with aqueous sodium bicarbonate (eq 2). Methylation of **4** with phenyltrimethylammonium hydroxide (**5**) by the addition of a methanol solution of the two reagents to 1,2-dichlorobenzene at 110−115 °C followed by treatment with 49% hydrobromic acid afforded a 74% yield of a mixture of *d,l*-glaucine hydrobromide (**6**) and 1-(2-(dimethylamino)ethyl)-3,4,6,7-tetramethoxyphenanthrene hydrobromide (**7**, eq 3). Pure **6**, containing less than 0.5% of



2 **3**



3 **4**

[†] This paper is dedicated to the memory of Dr. John (Jack) Martin, friend, colleague, and mentor, deceased February 27, 1996.

[‡] Contract Manufacturing Services.

[§] Analytical Sciences.

(1) Gieske, T. H.; Shea, P. J. U.S. Patent 4 183 939, 1980; *Chem. Abstr.* **1980**, *92*, 135455.

(2) Maasboel, A. G. Ger. Offen. DE 2 717 062, 1978; *Chem. Abstr.* **1979**, *90*, 43806t.

(3) Wang, S. M. U.S. Patent 4 315 010, 1982; *Chem. Abstr.* **1982**, *96*, 187310y.

(4) Goralski, C. T. U.S. Patent 4 358 592, 1982; *Chem. Abstr.* **1983**, *98*, 59926h.

(5) Redpath, J. B. S.; Pleuvry, B. J. *Br. J. Clin. Pharmacol.* **1982**, *14*, 555.

(6) Schuster, C. R.; Aigner, T.; Johanson, C. E.; Gieske, T. H. *Pharmacol. Biochem. Behav.* **1982**, *16*, 851.

(7) Maasboel, A. G.; Sim, A. K. U.S. Patent 4 279 914, 1981; *Chem. Abstr.* **1979**, *90*, 43806t.

(8) Goralski, C. T.; Krauss, R. C.; Williams, B. M.; Henton, D. R.; Brown, D. T. *Ind. Eng. Chem. Res.* **1989**, *28*, 221.

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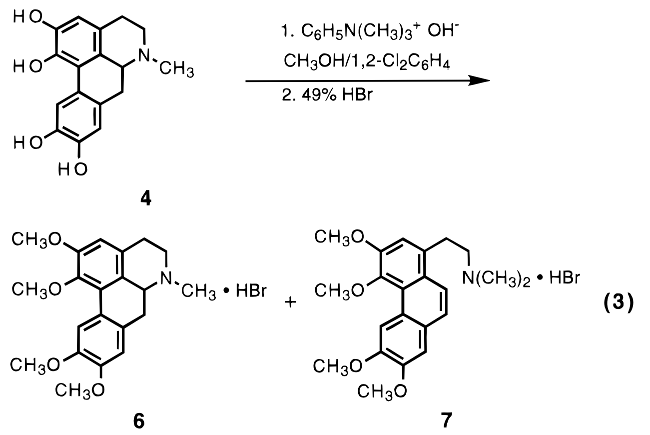
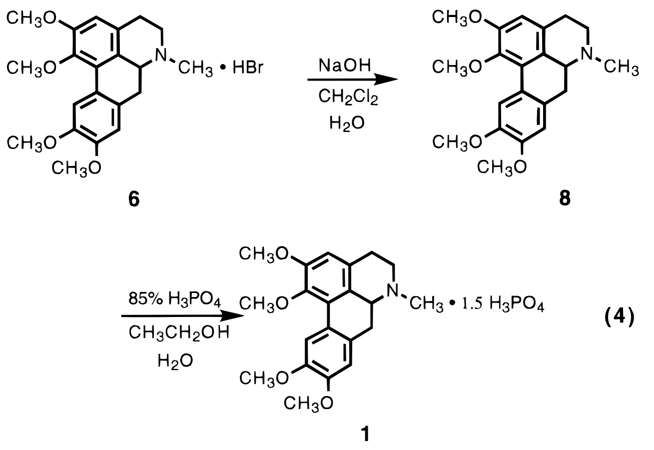


7, was obtained by one or two recrystallizations of the crude mixture from 50/50 (v/v) ethanol/water. The purified **6** was converted to *d,l*-glaucine (**8**), which was treated with 85% phosphoric acid in 80% aqueous ethanol and crystal digested at reflux for 6 h to give *d,l*-glaucine 1.5 phosphate (**1**) in 86% yield (eq 4). The maximum overall yield of **1** from **2** was 36%.



Results and Discussion

The oxidation of **2** to **3** with aqueous ferric chloride has been described by Tietze.[9,10ab] Although 70−80% yields of **3** were reported with ferric chloride alone, the described procedure, in our hands, gave variable yields of **3**, most commonly in the 40−50% range. In a study of the pH of the reaction mixture *vs* the conversion of **2** to **3** it was observed that with ferric chloride alone the pH of the reaction mixture rapidly drops below 1 and the conversion of **2** to **3** rapidly proceeds to 40−50% and then stops completely (Figure 1). If one considers the mechanism shown in Scheme 1 for the oxidation of **2** to **3**, it is easy to see how a rapid drop in pH would retard the ionization required for the ring-closing step. We were able to consistently obtain 76−82% yields of **3** from **2** by buffering the reaction mixture with 2 equiv of sodium acetate. In the buffered system the drop in pH to approximately 1.5−2 occurred much more slowly, and the conversion of **2** to **3** increased to 90% (Figure 1).

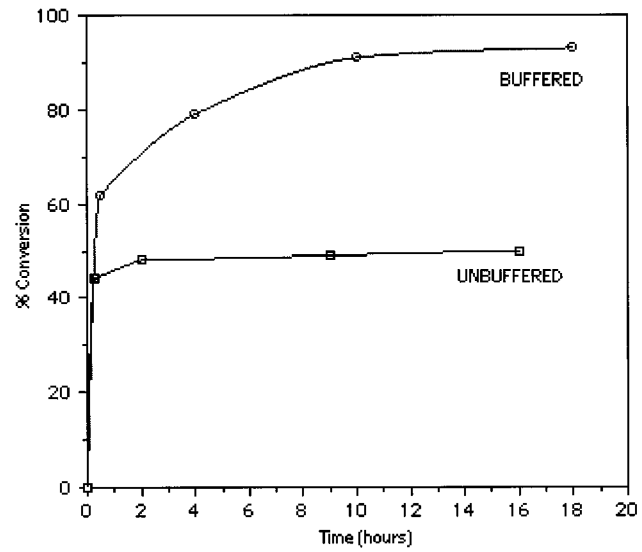
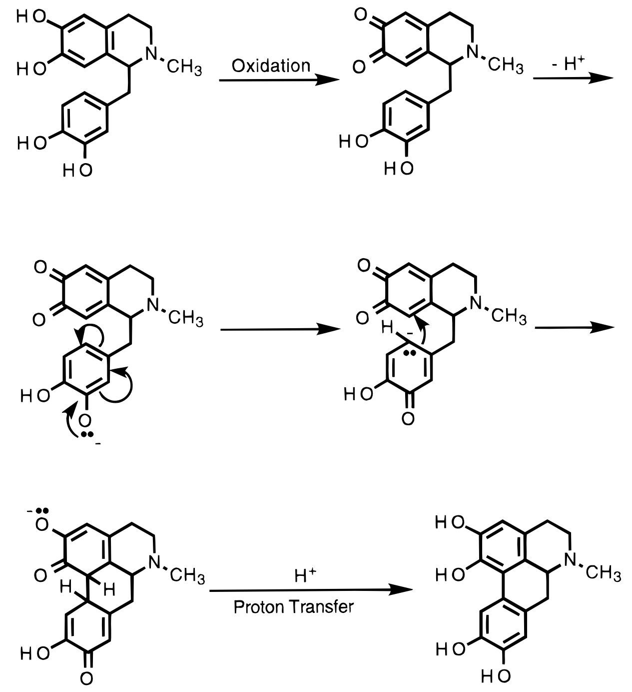


Figure 1. **Conversion of *d,l*-laudanosoline hydrobromide (2) to *d,l*-1,2,9,10-tetrahydroxyaporphine hydrochloride (3).**

Scheme 1



A number of solvents were investigated for the methylation of **3** with phenyltrimethylammonium hydroxide (**5**), and the results are summarized in Table 1. Chlorinated aromatic solvents gave the best results, and 1,2-dichlorobenzene was selected for further process optimization. The methylation of **3** with phenyltrimethylammonium hydroxide in 1,2-dichlorobenzene, followed by treatment with 49% hydrobromic acid, afforded a 60% yield of crude **6** containing 12−15% **7**. When the methylation was carried out with **4** (the base from **3**), the yield of crude **6** after treatment of the methylation reaction mixture with 49% hydrobromic acid increased to 74% and the level of **7** dropped to 3−7%. The use of chloride-free phenyltrimethylammonium hydroxide for the methylation of **4** further improved the yield of crude **6** to 85% and reduced the level of **7** to 1−3%. The above results strongly suggest that the presence of chloride ion in the methylation reaction system may lead to direct N-methylation or may lead to decomposition of the methylating agent under the reaction conditions to produce methyl

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(9) Tietze, L.-F. Ph.D. Dissertation, Kiel University, 1968.

(10) (a) Franck, B.; Tietze, L.-F. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 799. (b) Franck, B.; Tietze, L.-F. Ger. Offen. DE 1 670 894, 1971.

Table 1. **The effect of solvent on the yield of *d,l*-glaucine (8) from 3**

solvent[a]	*d,l*-glaucine yield, %[b]	mol % **9**
methoxybenzene	12	
chlorobenzene	64	3.7
nitrobenzene	54	<1
methyl benzoate	48	3.0
diphenyl oxide	23	4.5
1,2-dimethoxybenzene	61	2.2
1,2-dichlorobenzene	68	2.9
2-chlorotoluene	54	2.5
diethylbenzene	8	
1,2,4-trichlorobenzene	45	4.9
formylmorpholine	50	2.2
propylene glycol	0	

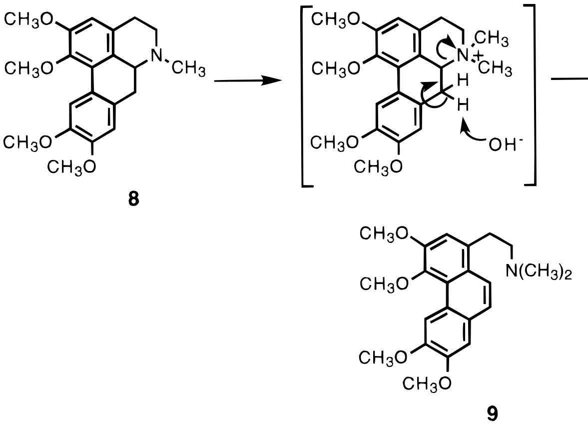
[a] The solvent (200 mL) was held at 110 °C. The mole ratio of **5** to **3** was 5/1. [b] Determined by HPLC analysis of a known volume of the reaction mixture *vs* an external standard.

Table 2. **Effect of the phenyltrimethylammonium salt counterion[a]**

$C_6H_5N(CH_3)_3{}^+X^-$, X^-	yield of **8**, %	mol % **9**
Cl	65	3.7
p-$CH_3C_6H_4SO_3$	68[b]	4.7
Br	58	13.9

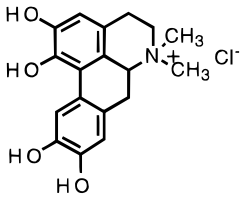
[a] Chlorobenzene solvent; 200 mL/g of **4**; ratio of **5**/**4** = 5; 110 °C. [b] Ratio of **5**/**4** = 10.

chloride, which then causes N-methylation. The N-methylated species then undergo the Hofmann elimination reaction to produce **9** (eq 5). Other counterions, such as bromide and tosylate, produced even higher levels of **9** (Table 2).



(5)

The methylation reactions were also plagued by the formation of an insoluble "black solid" which had to be removed by filtration prior to precipitation of the crude *d,l*-glaucine hydrobromide. The "black solid" appeared to be due to impurities which were present in both **3** and **4**. Purification of **3** by Soxhlet extraction with methanol left a black residue which was similar in composition to the "black solid". Use of purified **4** and chloride-free phenyltrimethylammonium hydroxide in the methylation reaction led to reduced quantities of the "black solid". A portion of the "black solid" was also undoubtedly formed in the methylation reaction itself. Methylation of 6,6-dimethyl-5,6,6a,7-tetrahydro-1,2,9,10-tetrahydroxy-4*H*-dibenzo[*de,g*]quinolinium chloride (**10**) with phenyltrimethylammonium hydroxide



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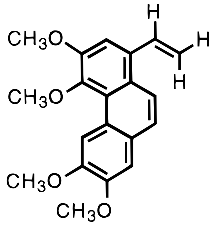
followed by treatment with hydrobromic acid gave mainly the "black solid", a 25% yield of **7**, and small amounts (2−3%) of 1-ethenyl-3,4,6,7-tetramethoxyphenanthrene (**11**),



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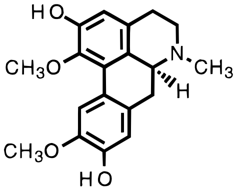
indicating that quaternized **4** may be a source of "black solid" in addition to being the source of **7** and **11**. In contrast, methylation of *d*-boldine (**12**) with phenyltrimethylammonium hydroxide gave an 89% yield of *d*-glaucine hydrobromide with little to no formation of either "black solid" or **7**.



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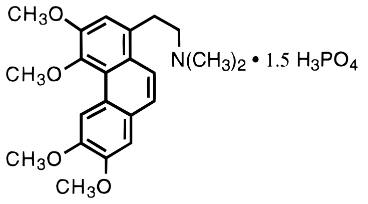
An analytical sample of pure **7** was prepared by methanol extraction of crude **6** containing approximately 13−15% **7** and recrystallization of the crude **7** from 50/50 (v/v) ethanol/water. An analytical sample of pure **9** was produced by neutralization of **7** with sodium hydroxide followed by chromatography on silica gel and recrystallization from hexane. Treatment of **9** with 2 equiv of 85% phosphoric acid in 80% ethanol, followed by crystal digestion of the resulting solid at reflux for 4 h, gave a 97% yield of 1-(2-(dimethylamino)ethyl)-3,4,6,7-tetramethoxyphenanthrene 1.5 phosphate (**13**).



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The recrystallization of crude **6** from pure ethanol or pure water gave little or no improvement in the level of **7**. Pure **6**, containing less than 0.5% **7**, was obtained by two recrystallizations of crude **6** from 50/50 (v/v) ethanol/water. The purified **6** was converted to *d,l*-glaucine base (**8**) with aqueous sodium hydroxide in the presence of methylene chloride. The methylene chloride solution of **8** was added to an ethanol solution of 85% phosphoric acid to give a slurry of crude *d,l*-glaucine phosphate. Crystal digestion of the crude *d,l*-glaucine phosphate in the presence of 85% phosphoric acid in 80% ethanol for 6 h at reflux gave *d,l*-glaucine 1.5 phosphate (**1**) as "chunky prismatic crystals" in 86% yield from **6**.

Experimental Section

***d,l*-1,2,9,10-Tetrahydroxyaporphine Hydrochloride (*d,l*-6-Methyl-5,6,6a,7-tetrahydro-1,2,9,10-tetrahydroxy-4*H*-dibenzo[*de,g*]quinoline Hydrochloride) (3).** A 6-L Erlenmeyer flask equipped with a magnetic stirrer was charged with 2500 mL of water, 225 g (2.74 mol) of sodium acetate, and 1.0 kg (2.62 mol) of *d,l*-laudanosoline hydrobromide (**2**). The resulting slurry was heated, with stirring, to 85 °C to effect solution, cooled to 80 °C, and diluted with 2500 mL of absolute ethanol. The solution was then transferred to a 12-L, three-neck, jacketed flask equipped with a mechanical stirrer, a nitrogen inlet, and a thermometer and cooled to 0−5 °C. A second 6-L Erlenmeyer flask was charged with 1225 g (7.55 mol) of anhydrous ferric chloride and 1500 mL of water (the mixture warmed to 50−55 °C) and the resulting solution filtered through filtercel to remove any insoluble iron oxides. The filtrate was diluted with 1500 mL of ethanol, and the solution was cooled to 20−30 °C. The ferric chloride solution was added, with stirring, to the cool solution of *d,l*-laudanosoline hydrobromide over 5 min. The reaction mixture was allowed to warm slowly to ambient temperature and stirred for 15−18 h. The reaction mixture was treated with 1.0 L of 37% hydrochloric acid and stirred for 30 min. The precipitated **3** was separated by filtration, washed thoroughly with acetone, air-dried, and vacuum-dried at 50−60 °C to give 668 g (76% yield) of *d,l*-1,2,9,10-tetrahydroxyaporphine hydrochloride (**3**).

***d,l*-1,2,9,10-Tetrahydroxyaporphine (*d,l*-6-Methyl-5,6,6a,7-tetrahydro-1,2,9,10-tetrahydroxy-4*H*-dibenzo[*de,g*]quinoline) (4).** *Procedure A.* A 12-L, three-neck, jacketed flask equipped with a mechanical stirrer and a nitrogen bubbler was charged with 7.5 L of deionized water and 300 g (3.57 mol) of sodium bicarbonate. The mixture was heated, with stirring, to 30−35 °C, and 750 g (2.24 mol) of *d,l*-1,2,9,10-tetrahydroxyaporphine hydrochloride was added in portions over 15 min. The mixture was heated to 75 °C and then cooled to 40 °C over 1 h. The resulting black solid was separated by filtration, washed with 750 mL of water, washed with 750 mL of absolute ethanol, air-dried, and vacuum-dried at 50 °C to give 617 g (92% yield) of *d,l*-1,2,9,10-tetrahydroxyaporphine, mp 225−227 °C.

Procedure B. The 12-L reaction flask was charged with 4.0 L of deionized water and 750 g (2.24 mol) of *d,l*-1,2,9,-10-tetrahydroxyaporphine hydrochloride. The resulting slurry was heated, with stirring, to 30−35 °C, and a solution of 300 g (3.57 mol) of sodium bicarbonate in 3.5 L of deionized water was slowly added over 20 min. The mixture was heated to 75 °C and then cooled to 40 °C over 1 h. The resulting black solid was separated by filtration, washed with 750 mL of water, washed with 750 mL of absolute ethanol, air-dried, and vacuum-dried at 50 °C to give 617 g (92% yield) of *d,l*-1,2,9,10-tetrahydroxyaporphine, mp 225−227 °C.

***d,l*-Glaucine Hydrobromide (*d,l*-6-Methyl-5,6,6a,7-tetrahydro-1,2,9,10-tetramethoxy-4*H*-dibenzo[*de,g*]quinoline Hydrobromide) (6).** *Methylation of d,l-1,2,9,10-tetrahydroxyaporphine Hydrochloride (**3**) with **5**.* A 12-L, three-neck flask equipped with a mechanical stirrer, a thermometer, a pressure-equalizing addition funnel, and a distillation head was charged with 8.0 L of 1,2-dichlorobenzene, and this was heated to 110−115 °C. While the 1,2-dichlorobenzene was heating, the methylating complex was prepared in a separate flask. A 2-L Erlenmeyer flask was charged with 253 g (3.89 mol) of 85% potassium hydroxide pellets and 700 mL of methanol. This mixture was stirred until a clear solution resulted (**exothermic!**). In a separate flask, a solution of 563 g (3.28 mol) of phenyltrimethylammonium chloride in 700 mL of methanol was prepared (endothermic). The solution of potassium hydroxide in methanol was then added to the solution of phenyltrimethylammonium chloride with good agitation. The resulting potassium chloride precipitate was separated by filtration and washed with 250 mL of methanol. To the resulting solution of phenyltrimethylammonium hydroxide (**5**) was added 200 g (0.596 mol) of *d,l*-1,2,9,10-tetrahydroxyaporphine hydrochloride (**3**), and the mixture was stirred to effect solution. The resulting deep purple solution was transferred to the addition funnel on the 12-L flask and added to the hot 1,2-dichlorobenzene at such a rate that the temperature remained between 100 and 115 °C. When the addition was complete, the reaction mixture was held at 115 °C until the final traces of methanol had distilled. The reaction mixture was cooled to 50−60 °C and clarified by filtration through filtercel. The filtrate was charged to a 22-L flask equipped with a mechanical stirrer, and 100 g (0.61 mol) of 49% hydrobromic acid was added, with stirring. After stirring for 16 h, the precipitated product was separated by filtration, washed with acetone, air-dried, and vacuum-dried at 50 °C to give 157 g (61% yield) of crude *d,l*-glaucine hydrobromide (**6**).

*Methylation of d,l-1,2,9,10-Tetrahydroxyaporphine (**4**) with **5**.* A 12-L, three-neck flask equipped with a mechanical stirrer, a thermometer, a pressure-equalizing addition funnel, and a distillation head was charged with 8.0 L of 1,2-dichlorobenzene, and this was heated to 110−115 °C. While the 1,2-dichlorobenzene was heating, the methylating complex was prepared in a separate flask. A 2-L Erlenmeyer flask was charged with 175 g (2.68 mol) of 85% potassium hydroxide and 575 mL of methanol. This mixture was stirred until a clear solution resulted (**exothermic!**). In a separate flask, a solution of 460 g (2.68 mol) of phenyltrimethylammonium chloride in 575 mL of methanol was prepared. The solution of potassium hydroxide in methanol was then added to the solution of phenyltrimethylammonium chloride in methanol with good agitation. The precipitated potassium chloride was separated by filtration and washed with 250 mL of methanol. To the filtrate was added 178 g (0.596 mol) of *d,l*-1,2,9,10-tetrahydroxyaporphine, and the mixture was stirred to effect solution. The resulting deep purple solution was transferred to an addition funnel on the 22-L flask and slowly added to the hot 1,2-dichlorobenzene at such a rate that the reaction temperature remained between 100 and 110 °C (90−120 min). After the addition was complete, the mixture was heated to 115 °C to drive off the last traces of methanol. The reaction mixture was cooled to 50−60 °C and clarified by filtration through filtercel. The filtrate was charged to a 22-L flask equipped with a mechanical stirrer, and 100 g (0.61 mol) of 49% hydrobromic acid was added. After stirring for 16 h, the precipitated product was separated by filtration, washed with acetone, air-dried, and vacuum-dried at 50 °C to give 198 g (77% yield) of crude *d,l*-glaucine hydrobromide (**6**).

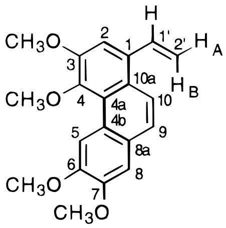
Methylation of *d,l*-6,6-Dimethyl-5,6,6a,7-tetrahydro-1,2,9,10-tetrahydroxy-4*H*-dibenzo[*de,g*]quinolinium Chloride (10) with 5. A 2-L, three-neck flask equipped with a mechanical stirrer, a thermowell, a pressure-equalizing addition funnel, and a distillation head fitted with a nitrogen bubbler was charged with 1000 mL of 1,2-dichlorobenzene. The 1,2-dichlorobenzene was heated to 120 °C, and a solution of 10.74 g (0.03 mol) of **10**[7] in 104 mL of 1.6 M chloride-free phenyltrimethylammonium hydroxide in methanol (*vide infra*) was added at such a rate that the reaction temperature remained above 110 °C. After the addition was complete, the reaction mixture was heated to 120 °C and then cooled to ambient temperature. The 1,2-dichlorobenzene was filtered through a pad of Filter Aid. The filtrate was treated with 3.4 mL of 49% hydrobromic acid and the mixture stirred. A solid separated and stuck to the walls of the flask. The 1,2-dichlorobenzene was decanted off and the remaining solid slurried in acetone. The solid was separated by filtration, washed with acetone, air-dried, and vacuum-dried at 60 °C to give 3.35 g (25% yield) of crude 1-(2-(dimethylamino)ethyl)-3,4,6,7-tetramethoxyphenanthrene hydrobromide (**7**). A total of 6.20 g of the polymeric "black solid" was isolated from the Filter Aid and the walls of the reaction flask. The 1,2-dichlorobenzene liquor was concentrated *in vacuo* and the residue dissolved in methylene chloride. The methylene chloride solution was washed twice with dilute hydrochloric acid and once with water. The methylene chloride was removed *in vacuo*, leaving 8.0 g of dark oil, which was mainly 1,2-dichlorobenzene. This oil was chromatographed on 80 g of silica gel using 15% ethyl acetate/hexane (v/v) as eluent to give 0.36 g of 1-ethenyl-3,4,6,7-tetramethoxyphenanthrene (**11**). The structure of **11** was confirmed by NMR spectroscopy (see Table 3).

Purification of *d,l*-1,2,9,10-Tetrahydroxyaporphine Hydrochloride (3). Approximately 27 g of "crude" *d,l*-1,2,9,-10-tetrahydroxyaporphine hydrochloride was placed in a Soxhlet extraction thimble and covered with a plug of glass wool. Approximately 200 mL of methanol was added, and the extraction was carried out at reflux for 1 week. A solid formed in the solvent flask. The slurry was cooled to approximately 5 °C. The solid was isolated by filtration, washed with acetone, and vacuum-dried at 50 °C to give 16.2 g of purified *d,l*-1,2,9,10-tetrahydroxyaporphine hydrochloride (**3**) as a light tan, crystalline solid.

Anal. Calcd for $C_{17}H_{17}NO_4{\cdot}HCl$: C, 60.81; H, 5.40; N, 4.17; Cl, 10.56. Found: C, 59.83; H, 5.46; N, 3.98; Cl, 9.60; Br, 2.20.

The filtrate from above was discarded, and fresh methanol was used to continue the extraction. After 24 h, an additional 1.17 g of solid was isolated from the solvent flask. The solid remaining in the thimble was isolated, washed with methanol, and vacuum-dried at 50 °C to give 4.41 g of a black solid, which was very similar in appearance to the "black solid" isolated from the remethylation reactions.

Table 3. **NMR chemical shifts ($CDCl_3$) for 1-ethenyl-3,4,6,7-tetramethoxyphenanthrene (11)**



position	δ	
	^{13}C	^{1}H
1	132.6	
2	110.6	7.39
3	150.4	
4	146.0	
4a	124.2	
4b	123.9	
5	108.8	9.27
6	148.3	
7	148.7	
8	107.7	7.18
8a	128.2	
9	124.7	7.81
10	120.7	7.50
10a	125.0	
1′	135.1	7.44
2′	116.8	5.47 (2′A), 5.72 (2′B)
3-OCH_3	56.4	4.04
4-OCH_3	60.0	3.91
6-OCH_3	55.6	4.07
7-OCH_3	55.6	4.02

Anal. Found: C, 58.7; H, 5.36; N, 3.94; Br, 4.10; Cl, 7.90; Fe, 0.28. A sample of "black solid" from a typical remethylation reaction was analyzed.

Anal. Found: C, 58.9; H, 4.84; N, 3.45; Fe, 1.54.

Conversion of Purified *d,l*-1,2,9,10-Tetrahydroxyaporphine Hydrochloride (3) to *d,l*-1,2,9,10-Tetrahydroxyaporphine (4). Purified *d,l*-1,2,9,10-tetrahydroxyaporphine hydrochloride (6.71 g, 0.02 mol) was slurried in 29.5 mL of water in a 250-mL, three-neck flask flushed with nitrogen. A solution of sodium bicarbonate (2.52 g, 0.03 mol) in water (35.5 mL) was added, and a thick slurry formed. The slurry was heated to 80 °C and held there for 1 h. The slurry was cooled to room temperature and the solid isolated by filtration. The solid was washed with water (30 mL) and then with acetone (30 mL). The solid was vacuum-dried at 50 °C to give 5.78 g (97% yield) of **4** as a tan solid.

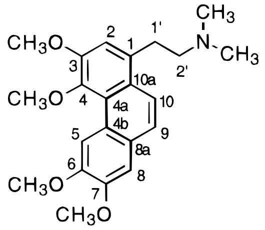
Anal. Calculated for $C_{17}H_{17}NO_4$: C, 68.22; H, 5.72; N, 4.68. Found: C, 68.40; H, 5.80; N, 4.62.

Methylation of Purified *d,l*-1,2,9,10-Tetrahydroxyaporphine (4) with Chloride-Free Phenyltrimethylammonium Hydroxide. Purified *d,l*-1,2,9,10-tetrahydroxyaporphine (5.00 g, 0.0167 mol) was dissolved in 53 mL of a 1.42 M solution of phenyltrimethylammonium hydroxide in methanol which had been rendered chloride-free by passage through a column of Dowex-1 ion exchange resin (hydroxide form). The solution was slowly added to 300 mL of 1,2-dichlorobenzene which was held at a temperature of 110−115 °C. After the addition was complete, the reaction mixture was briefly heated to 125 °C and then cooled to below 40 °C. The solution was filtered to remove the "black solid" which had formed. The "black solid" was dried to give 0.78 g. Approximately 2 mL of 49% hydrobromic acid was added to the filtrate and the mixture stirred for 16 h. The solid was separated by filtration, washed with acetone, and vacuum-dried to give 6.16 g (85% yield) of *d,l*-glaucine hydrobromide which contained 2.7% **7** by HPLC analysis.

Methylation of *d*-Boldine (12) with Phenyltrimethylammonium Hydroxide. A solution of 3.24 g (0.0491 mol) of 85% potassium hydroxide pellets in methanol (9.5 mL) was prepared, and 20 mL of a 45.7% solution of phenyltrimethylammonium chloride in methanol was added, with shaking, in a 50-mL stoppered Erlenmeyer flask. The potassium chloride which precipitated was separated by filtration and washed with two 3-mL portions of methanol. *d*-Boldine (as its chloroform complex) (4.87 g, 0.0109 mol) was placed in a 50-mL addition funnel, and the above solution of phenyltrimethylammonium hydroxide was added. The funnel was stoppered and shaken to dissolve the *d*-boldine. 1,2-Dichlorobenzene (300 mL) was heated, with stirring, to 115 °C in a 500-mL, three-neck flask which was blanketed with nitrogen. The solution of *d*-boldine and phenyltrimethylammonium hydroxide was slowly added at such a rate that the reaction temperature remained between 112 and 118 °C. The resulting red-brown solution was analyzed by HPLC. Essentially no **9** was observed, and no appreciable amount of the "black solid" was present. The solution was treated with 2 mL of 49% hydrobromic acid and stirred for 24 h at room temperature. The resulting yellow, crystalline solid was isolated by filtration, washed with acetone, and vacuum-dried at 50 °C to give 4.25 g (89% yield) of *d*-glaucine hydrobromide as an off-white, crystalline solid.

***d,l*-Glaucine 1.5 Phosphate (*d,l*-6-Methyl-5,6,6a,7-tetrahydro-1,2,9,10-tetramethoxy-4*H*-dibenzo[*de,g*]quinoline 1.5 Phosphate) (1).** A 50-L, three-neck flask equipped with a mechanical stirrer and a bottom drain was charged with 2.60 kg (5.95 mol) of *d,l*-glaucine hydrobromide (**6**), 10.0 L of deionized water, and 3.5 L of methylene chloride. To the rapidly stirring mixture was slowly added 500 mL of 50% sodium hydroxide. The sodium hydroxide was washed in with 100 mL of deionized water. The mixture was stirred for 15 min. The stirring was stopped, and the layers were allowed to separate for 10 min. The methylene chloride layer was drained off and stored. The extraction was repeated with 3.5 L of methylene chloride. The combined methylene chloride layers were washed with 3.0 L of deionized water. The resulting methylene chloride solution of **8** was added to a well-stirred solution of 1.42 kg (12.35 mol) of 85% phosphoric acid in 9.8 L of absolute ethanol. A heavy slurry of white solid formed. The slurry was stirred for 15 min. The solid was separated by filtration, air-dried, and vacuum-dried at 50−65 °C to give 2.90 kg (97% yield) of *d,l*-glaucine phosphate.

Table 4. **NMR chemical shifts ($CDCl_3$) for 1-(2-(dimethylamino)ethyl)-3,4,6,7-tetramethoxyphenanthrene (9)**



	δ	
position	^{13}C	^{1}H
1	133.2	
2	113.6	7.14
3	150.0	
4	144.4	
4a	124.4	
4b	124.1	
5	108.6	9.27
6	148.1	
7	148.5	
8	107.5	7.14
8a	128.0	
9	124.5	7.52
10	120.5	7.74
10a	125.3	
1′	32.3	3.22
2′	60.7	2.62
N-CH_3	45.2	2.34
3-OCH_3	56.2	4.00
4-OCH_3	59.7	3.90
6-OCH_3	55.6	4.05
7-OCH_3	55.5	3.98

A 50-L, three-neck flask equipped with a mechanical stirrer, a bottom drain, a thermometer, and a reflux condenser fitted with a nitrogen bubbler was charged with 4.18 kg of *d,l*-glaucine phosphate, 8.0 L of deionized water, 30.0 L of absolute ethanol, and 1.05 kg of 85% phosphoric acid. The resulting slurry was heated to reflux and held there for 6 h. The slurry was cooled to ambient temperature. The solid was separated by filtration, washed with two 4.2-L portions of absolute ethanol, and vacuum-dried at 50−60 °C for 48 h to give 3.69 kg (88% recovery) of *d,l*-glaucine 1.5 phosphate as "chunky prismatic crystals", mp 253−255 °C (by differential scanning calorimetry).

Anal. Calcd for $C_{21}H_{25}NO_4 \cdot 1.5H_3PO_4$: C, 50.20; H, 5.91; N, 2.78. Found: C, 50.20; H, 5.94; N, 2.78.

1-(2-(Dimethylamino)ethyl)-3,4,6,7-tetramethoxyphenanthrene Hydrobromide (3,4,6,7-Tetramethoxy-*N,N*-dimethyl-1-phenanthreneethanamine Hydrobromide) (7). A 1-L Erlenmeyer flask equipped with a magnetic stirrer was charged with 53.10 g of crude **7** and 800 mL of 50/50 (v/v) ethanol/water. The mixture was heated to reflux to give a slightly hazy solution. The solution was filtered and cooled to give a slurry of small, white platelets. The crystals were separated by filtration, washed with absolute ethanol, air-dried, and vacuum-dried at 50 °C to give 34.51 g (65% recovery) of **7**, mp 275−276 °C.

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, 6.20; N, 3.04.

1-(2-(Dimethylamino)ethyl)-3,4,6,7-tetramethoxyphenanthrene (3,4,6,7-Tetramethoxy-*N*,*N*-dimethyl-1-phenanthreneethanamine) (9). A 250-mL separatory funnel was charged with 22.5 g (0.05 mol) of **7**, 50 mL of deionized water, 5.0 g (0.063 mol) of 50% sodium hydroxide solution, and 50 mL of methylene chloride. The mixture was shaken until most of the solid dissolved. The methylene chloride layer was drained off, and the extraction was repeated. The combined methylene chloride extracts were filtered, and the methylene chloride evaporated, leaving a sticky solid. The solid was dried at 50 °C to give 17.8 g (96% yield) of **9**, mp 60−64 °C. A sample of this material was chromatographed on silica gel using 10% methanol/chloroform and then recrystallized from hexane to give an analytical sample of **9**, mp 69−71 °C. The structure of **9** was confirmed by NMR spectroscopy (Table 4).

Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.40; H, 7.37; N, 3.69.

1-(2-(Dimethylamino)ethyl)-3,4,6,7-tetramethoxyphenanthrene 1.5 Phosphate (3,4,6,7-Tetramethoxy-*N*,*N*-dimethyl-1-phenanthreneethanamine 1.5 Phosphate) (13). In a 250-mL, single-neck flask equipped with a magnetic stirrer and a reflux condenser fitted with a nitrogen bubbler were placed 7.38 g (0.02 mol) of 1-(2-dimethylamino)ethyl)-3,4,6,7-tetramethoxyphenanthrene and 60 mL of ethanol. To the resulting solution was added 4.52 g (0.04 mol) of 85% phosphoric acid followed by 15 mL of deionized water. An additional 50 mL of 80% ethanol was added, and the resulting slurry was heated at reflux for 4 h. The slurry was cooled to ambient temperature. The solid was separated by filtration, washed with absolute ethanol, air-dried, and vacuum-dried at 60 °C to give 10.00 g (97% yield) of 1-(2-(dimethylamino)ethyl)-3,4,6,7-tetramethoxyphenanthrene 1.5 phosphate, mp 238−241 °C dec.

Anal. Calcd for $C_{22}H_{27}NO_4 \cdot 1.5H_3PO_4$: C, 51.16; H, 6.11; N, 2.71. Found: C, 51.14; H, 6.21; N, 2.71.

Supporting Information Available

The ^{1}H and ^{13}C NMR spectra (DMSO-d_6) of **6** and the ^{1}H and ^{13}C NMR spectra ($CDCl_3$) of **11** (5 pages). See any current masthead page for ordering and Internet access instructions.

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