# Enamide Photochemistry. Formation of 8-Oxoberbines from 2-Aroyl-1-methylene-1,2,3,4-tetrahydroisoquinolines[1]

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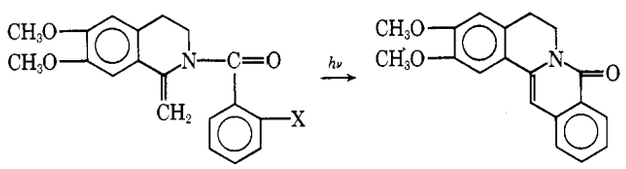
Irradiation of 2-aroyl-1-methylene-1,2,3,4-tetrahydroisoquinoline enamides **3** under degassed conditions yields 8-oxoberbines **4** in excellent yields. A wide variety of substituents is not affected by the reaction conditions. Methoxyl-, acetoxyl-, methylenedioxy-, chloro-, methyl-, and phenyl-substituted enamides have been successfully cyclized. Irradiation in the presence of air of the acetoxy enamide **3e** yields the oxyprotoberberine **6**. Alternatively dehydrogenation by dichlorodicyanobenzoquinone of the 8-oxoberbines forms the oxyprotoberberines **9** in good yield. Reduction of the 8-oxo group with either lithium aluminum hydride or sodium bis(methoxyethoxy)aluminum hydride furnishes the berbine alkaloid bases **10**. The naturally occurring berbine xylopinine (**10b**) has been synthesized in this manner from the corresponding 8-oxoberbine (**4b**).

The use of enamides to form isoquinoline alkaloids photochemically has proved to be very fruitful.[2] The use of ortho-substituted aroyl-1-methyleneisoquinolines **1** to generate oxyprotoberberines **2** has been described.[3] It was felt



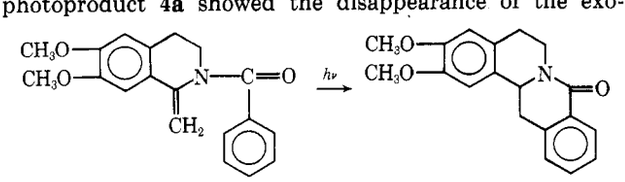
**1** **2**

that if the ortho positions in the aroyl group were unsubstituted, then a [1,5]-hydrogen shift would generate 8-oxoberbines which could be easily reduced to the berbine alkaloids. In a further extension of our studies in this area, it has been found that aroyl enamides could be smoothly cyclized to 8-oxoberbines, and the photoproducts transformed into other benzylisoquinoline alkaloid structures.[4]

## Results

The aroyl enamides **3** are conveniently prepared by treating 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline with either the appropriate aroyl chloride or, in most cases, with the aroyl anhydride. The anhydrides were prepared *in situ* in very high yield using the ynamine condensation method.[5] The enamides **3** all showed two pairs of doublets in the nmr for the exocyclic methylene protons. The enamides are crystalline compounds with the exception of the acetylvanilloyl derivative **3e** and are stable in the absence of acid.[6]

Irradiation of a thoroughly degassed *tert*-butyl alcohol solution of the benzoyl enamide converted **3a** into a single photoproduct **4a** which was isolated in 96.7% yield. The photoproduct **4a** showed the disappearance of the exo-



**3a** **4a**

methylene protons in the nmr and the loss of one aromatic proton. The nmr spectrum showed, on the other hand, a one-proton multiplet for a proton ortho to a carbonyl at $\delta$ 8.17 and a two-proton multiplet between $\delta$ 4.65 and 5.15. This new resonance is assigned to the 13a-methine hydrogen and the equatorial 6 proton which a model shows to be coplanar between 1.8 and 2.2 Å removed from the carbonyl.[7] This downfield two-proton multiplet is characteristic of all 8-oxoberbines thus far synthesized. The 13-equatorial proton resonates in the same area as the 5,6-ethylene bridge between $\delta$ 2.7 and 3.5. The nmr evidence indicates that the 8-oxoberbine tetracyclic ring system is essentially flat, analogous to yohimbine.[8] The uv spectrum had become much simpler than **3a**, indicative of the loss of the extended conjugation. On this basis, **4a** was postulated as 2,3-dimethoxy-8-oxoberbine, a compound which had been previously prepared.[9,10]

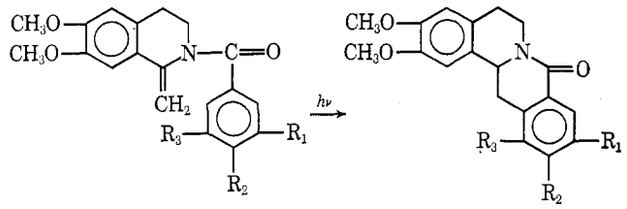
The 8-oxoberbines synthesized are collected in Table I. It can be seen that a wide variety of meta and para substituents can be accommodated in the photocyclization including methoxyl, methylenedioxy, alkyl, halo, and phenyl substituents. The yields are uniformly good. The most significant observation is that phenolic hydroxyl groups, masked as the acetate, can be easily introduced.

Enamide **3e** was readily prepared from acetylvanilloyl chloride and 5,6-dihydro-6,7-dimethoxy-1-methylisoquinoline. This was the only enamide that could not be crystallized, and was particularly prone to hydrolysis. As a result, a preparation of the crude enamide was degassed in *tert*-butyl alcohol, containing a few drops of triethylamine to retard hydrolysis, and irradiated to give a 45% yield of the acetoxy-8-oxoberbine **4e**. The yield of **4e** would undoubtedly be much higher if the enamide were crystalline and capable of rigorous purification. This promises to be a particularly advantageous method for preparing polyhydroxy 8-oxoberbines and their derivatives. Acid-catalyzed transesterification in methanol, under nitrogen, gave the phenolic compound **5** in 95% yield.

The irradiation of the acetoxy enamide **3e** under nondegassed conditions was also studied. When the crude enamide **3e** was irradiated in ethyl acetate in a Pyrex vessel open to the atmosphere, a rapid reaction occurred leading to a highly fluorescent compound **6** in 65% yield, a trace of **4e**, and the hydrolysis product **7** of the enamide **3e**. The photoproduct **6** was identified as the cyclized and dehydrogenated oxyprotoberbine by virtue of its characteristic uv spectrum and the mass spectrum, which confirmed the loss of a mole of hydrogen.[3] Exposure of solutions of the 8-oxoberbines to air in the laboratory results in complete conversion to the oxyprotoberberine in a matter of days. Acid-catalyzed transesterification gave the phenolic oxyprotoberberine **8** in 77% yield.

The ready dehydrogenation of **4e** indicated that dehydrogenation of the other 8-oxoberbines **4** by high potential quinones would be feasible.[11] The reaction of 8-oxoberbines **4** with 2,3-dichloro-5,6-dicyanobenzoquinone was

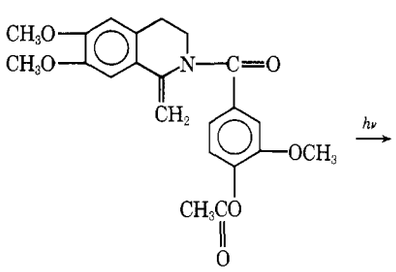
**Table I**
**Photochemical Formation of 8-Oxoberbines[a]**



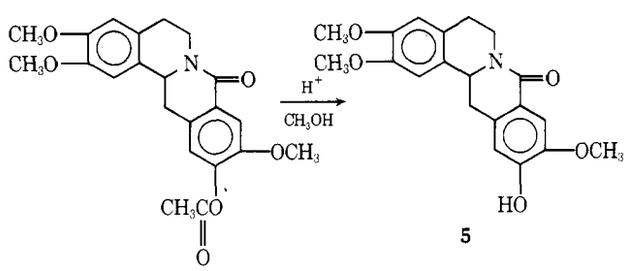
3 4

| Enamide | $R_1$ | $R_2$ | $R_3$ | 8-Oxoberbine | Yield, % |
|---|---|---|---|---|---|
| **3a** (52050-53-0) | H | H | H | **4a** (1876-67-1) | 96.7 |
| **3b** (41173-78-8) | $OCH_3$ | $OCH_3$ | H | **4b** (52050-59-6) | 93.5 |
| **3c** (52050-54-1) | —$OCH_2O$— | | H | **4c** (52050-60-9) | 75 |
| **3d** (49619-33-2) | $OCH_3$ | $OCH_3$ | $OCH_3$ | **4d** (49619-37-6) | 70 |
| **3e** (52050-55-2) | $OCH_3$ | $O_2CCH_3$ | H | **4e** (52050-61-0) | 45 |
| **3f** (52050-56-3) | H | $CH_3$ | H | **4f** (52050-62-1 | 85 |
| **3g** (52050-57-4) | H | Cl | H | **4g** (52124-31-9) | 76 |
| **3h** (52050-58-5) | H | Ph | H | **4h** (52050-63-2) | 76 |

[a] Registry no. are in parentheses beneath compounds.



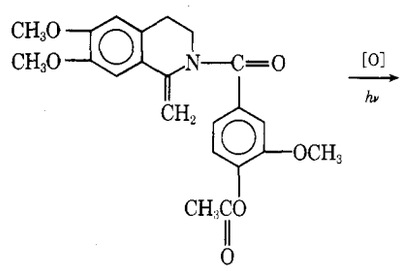
3e



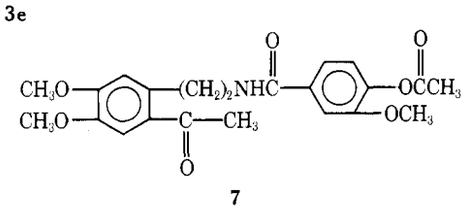
4e 5

found to virtually be instantaneous, generating the oxyprotoberberines **9**. The oxyprotoberberines **9** synthesized are collected in Table II.

Two methods were used to reduce 8-oxoberbines to the tetrahydroprotoberberine (berbine), reduction with lithium aluminum hydride in tetrahydrofuran and sodium bis(methoxyethoxy)aluminum hydride in benzene. In general, reductions with $LiAlH_4$ gave inferior yields and less clean products than reduction with the other hydride reagent. For instance, reduction of 2,3,10,11,12-pentamethoxy-8-oxoberbine **4d** with $LiAlH_4$ gave, in 67% yield, 2,3,10,11,12-pentamethoxyberbine **10d** which could not be crystallized and was isolated as its hydrochloride salt. On the other hand, reduction with sodium bis(methoxyethoxy)aluminum hydride gave a 90% yield of **10d** as a crystalline compound.



3e



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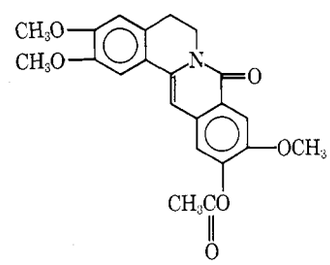

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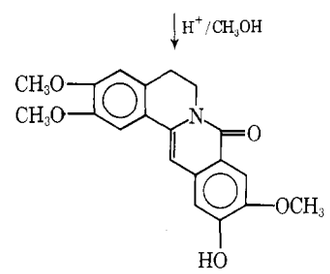

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Reduction of **3b** gave the naturally occurring *dl*-xylopinine in 85% yield.[12] Reduction of the acetoxy 8-oxoberbine **4e** gave the phenolic berbine **10e** (2-*O*-methylcoreximine) in 62% yield. Acetylation with acetic anhydride and pyridine using 4-dimethylaminopyridine as catalyst gave the acetoxyberbine **11**.[13] The berbines synthesized are collected in Table II.

## Discussion

The photochemistry of conjugated enamides is dominated by the aza analog of the hexatriene–cyclohexadiene ring closure. This has been demonstrated in the isoquino-

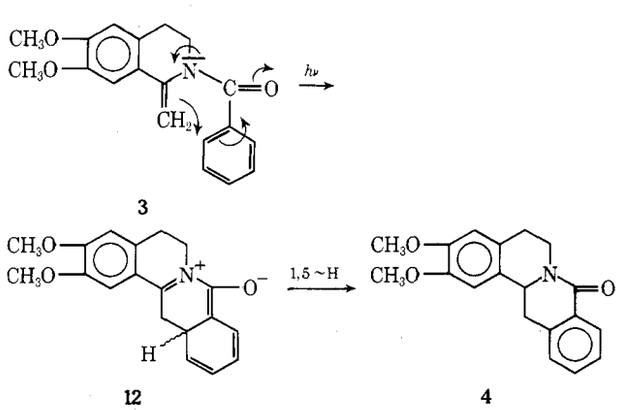

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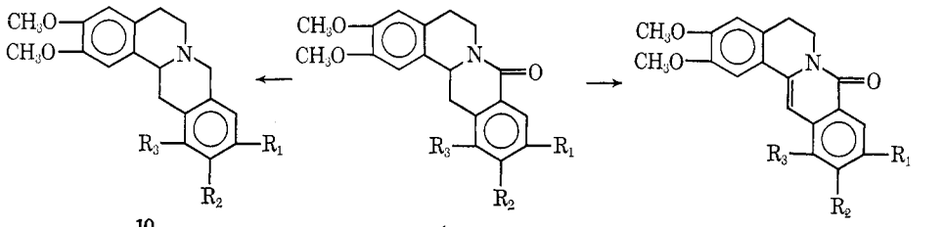
**Table II**
**Derivatives of 8-Oxoberbines[a]**



10 4 9

| Berbine | Yield, % | | $R_1$ | $R_2$ | $R_3$ | Oxyprotoberberine | Yield, % |
|---|---|---|---|---|---|---|---|
| **10b** (4216-86-8) | 85 | **4b** | $OCH_3$ | $OCH_3$ | H | | |
| **10c** (24314-66-7) | 73[b] | **4c** | —$OCH_2O$— | | H | **9c** (19716-62-2) | 79 |
| **10d** (23837-66-3). | 92 | **4d** | $OCH_3$ | $OCH_3$ | $OCH_3$ | **9d** (23837-65-2) | 60 |
| **10e** (52050-64-3) | 62[c] | **4e** | $OCH_3$ | $OC(=O)CH_3$ | H | **6** (52050-68-7) | 65 |
| **10f** (52050-65-4) | 95 | **4f** | H | $CH_3$ | H | **9f** (52050-69-8) | 80 |
| **10g** (52050-66-5) | 53 | **4g** | H | Cl | H | **9g** (52050-70-1) | 70 |
| **10h** (52050-67-6) | 60 | **4h** | H | Ph | H | **9h** (52050-71-2) | 72 |

[a] Registry no. are in parentheses beneath compounds. [b] M. Tomita and J. Niimi, *Yakugaku Zasshi*, **79**, 1023 (1959). [c] $R_1$ = —$OCH_3$, $R_2$ = —OH.

line series by the formation of oxyprotoberberines[14] and protoberberines.[15] The synthesis of 8-oxoberbines from enamides can be viewed as an electrocyclic ring closure to give the intermediate **12** which then undergoes a [1,5]-hydrogen shift to generate the 8-oxoberbine **4**. When the ortho position of the aroyl group is occupied by a substituent which is capable of acting as a leaving group, elimination occurs to give an oxyprotoberberine.[3]

The synthesis of 8-oxoberbines is a very convenient reaction proceeding from readily synthesized enamides and generating the oxoberbine in excellent yields. A wide variety of substituents has been found to be stable to the irradiation conditions extending the utility of the photocyclization. Particularly noteworthy is the synthesis of the acetoxy compound **4e** from vanillic acid and the dihydroisoquinoline. This promises to be an effective method for preparing phenolic berbines simply and conveniently with the hydroxy group masked as the acetate. Reduction with hydride reagents gives the berbines in excellent yields, while dehydrogenation of the 8-oxoberbines either with air or high potential quinones gives excellent yields of the oxyprotoberberines.

## Experimental Section

**General.** Melting points were taken on a Thomas-Hoover Unimelt capillary apparatus and are uncorrected. Infrared spectra were run in KBr unless otherwise noted, and ultraviolet and visible spectra were run in methanol. A Varian Associates A-60, T-60, or HA-100 spectrometer was used to record nmr spectra. All spectra were run in deuteriochloroform containing tetramethylsilane as an internal standard, unless otherwise indicated. Mass spectra were run on an A.E.I. MS-30 mass spectrometer by the Searle Laboratories Mass Spectrometry Department, Dr. Jeremy Hribar, Director. Microanalyses were performed by the Searle Laboratories Microanalytical Department, Mr. E. Zielinski, Director.

**2-Benzoyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyleneisoquinoline (3a).** A suspension of 16 g of benzoic acid (0.132 mol) was stirred magnetically in 350 ml of dry benzene while 8.5 ml of 1-*N*,*N*-diethylaminopropyne (0.066 mol) was added. The reaction mixture warmed spontaneously, turned orange-red as benzoic anhydride formed, and went into solution. After 0.5 hr, a solution of 9.0 g of 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline[16] (0.044 mol) in 50 ml of pyridine was added. The resulting solution is blanketed with nitrogen and brought to reflux for 1 hr. The reaction mixture was cooled to room temperature and then extracted with distilled water (3 × 500 ml). The organic phase was dried with sodium sulfate and the solvent removed on a rotary evaporator. Crystallization from ether–petroleum ether gave 8.4 g (0.027 mol, 61%) of 2-benzoyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyleneisoquinoline (**3a**): mp 121–124°; uv 230 nm (sh, $\epsilon$ 23,000), 243 (min, 11,500), 263 (18,500), 290 (min, 6000), 304 (7250), 314 (sh, 6000); ir 1655, 1635 (sh), 1615 $cm^{-1}$; nmr $\delta$ 7.30 (m, 5 H), 7.03 (s, 1 H), 6.70 (s, 1 H), 5.27 (d, $J \simeq 1.5$ Hz, 1 H), 4.47 (d, $J \simeq 1.5$ Hz, 1 H), 4.12 (t, 2 H), 3.90 (s, 3 H), 3.89 (s, 3 H), 2.97 (t, 2 H).

*Anal.* Calcd for $C_{19}H_{19}NO_3$: C, 73.76; H, 6.19; N, 4.53. Found: C, 73.50; H, 6.24; N, 4.36.

**2-(3,4-Dimethoxybenzoyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyleneisoquinoline (3b).** A solution of 3,4-dimethoxybenzoic anhydride was prepared from 24 g (0.132 mol) of 3,4-dimethoxybenzoic acid (Aldrich) and 8.5 ml of 1-*N*,*N*-diethylaminopropyne and treated with 10 g of dihydroisoquinoline as described for **3a** to give 14.9 g (0.040 mol, 82%) of **3b:** mp 134–137°; uv 231 nm (sh, $\epsilon$ 29,000), 245 (min, 14,000), 265 (21,000), 295 (11,250), 315 (sh, 7000); ir 1630 $cm^{-1}$; nmr $\delta$ 7.03 (m, 3 H), 6.84 (s, 1 H), 6.68 (s, 1 H), 5.28 (d, $J \simeq 1$ Hz, 1 H, C=$CH_2$), 4.46 (d, $J \simeq 1$ Hz, 1 H, C=$CH_2$), 4.10 (t, 2 H), 3.92 and 3.90 (s, 9 H), 3.78 (s, 3 H), 2.95 (t, 2 H).

*Anal.* Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.26; H, 6.40; N, 3.78.

**2-(3,4-Methylenedioxybenzoyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyleneisoquinoline (3c).** A suspension of 22 g of piperonylic acid (0.132 mol) was suspended in 400 ml of refluxing benzene and 25 ml of solvent removed (Dean-Stark trap). The hot suspension was allowed to cool slightly and 9 ml of 1-*N*,*N*-diethylaminopropyne was added. The exothermic reaction caused the solvent to reflux. After cooling to room temperature, piperonylic anhydride crystallized. To the suspension of the anhydride in benzene was added 13 g (0.063 mol) of dihydroisoquinoline in 100 ml of benzene and 50 ml of pyridine. The mixture was held at reflux, under nitrogen, for 7 hr. Upon cooling, 50 ml of methanol was added; the mixture was stirred for 1 hr and then extracted with water (3 × 500 ml) and 5% potassium carbonate solution. The organic phase was dried with sodium sulfate and the sodium sulfate washed with methylene chloride. Removal of solvent and crystallization from ethyl acetate–ether gave 11.4 g (0.032 mol, 51%) of **3c:** mp 133–135°; ir 1640, 1625 (sh), 1615 $cm^{-1}$ (sh); uv 232 nm (sh, $\epsilon$ 24,000), 244 (min, 11,500), 265 (18,000), 285 (min, 10,000), 300 (12,000), 314 (sh, 8000); nmr $\delta$ 7.00 (m, 3 H), 6.75 (s, 1 H), 6.63 (s, 1

H), 5.90 (s, 2 H, $-OCH_2O-$), 5.12 (d, $J \simeq 1.5$ Hz, 1 H, $C=CH_2$), 4.46 (d, $J \simeq 1.5$ Hz, 1 H, $C=CH_2$), 4.07 (t, 2 H), 3.90 (s, 6 H, $OCH_3$), 2.93 (t, 2 H).

*Anal.* Calcd for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42; N, 3.96. Found: C, 67.94; H, 5.52; N, 3.94.

**2-(3,4,5-Trimethoxybenzoyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyleneisoquinoline (3d).** Compound **3d** (11.15 g, 0.028 mol, 64%) was prepared from 28 g (0.132 mol) of 3,4,5-trimethoxybenzoic acid (Mallinckrodt), 6.8 g (8.5 ml, 0.061 mol) of 1-*N*,*N*-diethylaminopropyne, and 9 g (0.044 mol) of dihydroisoquinoline as described above for **3a**. Compound **3d** shows: mp 107–109°, uv 243 nm (min, 12,000), 265 (19,000), 302 (8000), 315 (sh, 5500); ir 1635, 1615, 1595, 1520 $cm^{-1}$; nmr $\delta$ 7.06 (s, 1 H), 6.72 (s, 3 H), 5.31 (d, $J \simeq 1$ Hz, 1 H, $C=CH_2$), 4.56 (d, $J \simeq 1$ Hz, 1 H, $C=CH_2$), 4.13 [t, 2 H, $-CH_2NC(=O)-$], 3.95 (s, 3 H), 3.90 (s, 3 H), 3.87 (s, 3 H), 3.62 (s, 6 H), 3.00 (t, 2 H, $=CCH_2CH_2N$).

*Anal.* Calcd for $C_{22}H_{25}NO_6$: C, 66.15; H, 6.31; N, 3.51. Found: C, 66.24; H, 6.27; N, 3.30.

**2-(4-Acetoxy-3-methoxybenzoyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyleneisoquinoline (3e).** A suspension of 10 g of acetylvanillic acid was stirred in 20 ml of toluene, 20 ml of thionyl chloride and 0.5 ml of dimethylformamide for 16 hr. The solvents were removed; 50 ml of benzene was added and evaporated and the residue crystallized from petroleum ether to give 9 g of the acid chloride. A solution of 10.0 g of the dihydroisoquinoline in 250 ml of toluene and 20 ml of pyridine was stirred with 9.0 g acetylvanilloyl chloride, under nitrogen, for 20 min, when tlc indicated complete reaction. The solution was washed with water (3 × 500 ml) and dried to a light yellow solution. Evaporation of the solvent gave 12.0 g of **3e** as a gum which could not be crystallized from ethyl acetate, ether, or petroleum ether, nor from methanol nor methanol–water. The enamide **3e** shows: uv 230 nm ($\epsilon$ 20,000), 261 (12,500), 290 (8000); ir 1770, 1640, 1515 $cm^{-1}$; nmr $\delta$ 6.65–7.85 (m, 5H), 5.32 (d, $J \simeq 1.5$ Hz, 1 H), 4.52 (d, $J \simeq 1.5$ Hz, 1 H), 4.10 (q, 2 H), 3.90 (s, 9 H), 3.02 (q, 2 H), 2.33 (s, 3 H).

The enamide **3e** had to be used as prepared due to its facile hydrolysis to *N*-[$\beta$-(2-acetyl-4,5-dimethoxyphenyl)ethyl]-4-acetoxy-3-methoxybenzamide (**7**): mp 129–131° (methanol–water); uv 230 nm ($\epsilon$ 30,000), 260 (min, 9500), 275 (11,000), 310 (sh, 5000); ir 3340 (NH), 1780 ($C_6H_5OAc$), 1695 [$C=OCH_3$], 1675 (sh, HNC=O), 1640, 1615 $cm^{-1}$; nmr $\delta$ 6.65–8.00 (m, 6 H), 3.88 (s, 6 H), 3.85 (s, 3 H), 3.67 (m, 2 H), 2.92 (m, 2 H), 2.60 (s, 3 H), 2.28 (s, 3 H).

*Anal.* Calcd for $C_{22}H_{25}NO_7$: C, 63.60; H, 6.07; N, 3.37. Found: C, 63.38; H, 6.08; N, 3.17.

**2-(4-Methylbenzoyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyleneisoquinoline (3f).** The enamide was synthesized from 4.0 g (19.5 mmol) of dihydroisoquinoline base and 3.4 g of *p*-toluoyl chloride (21 mmol) in 100 ml of methylene chloride and 7 ml of pyridine for 16 hr. Extraction with distilled water (3 × 500 ml) and drying of the organic phase with sodium sulfate gave 4.25 g (13 mmol, 67%) of **3f:** mp 137–138° (ether–petroleum ether); uv 220 nm (end, $\epsilon$ 39,000), 244 (min, 13,500), 263 (25,000), 290 (min, 7000), 303 (7500), 313 (sh, 6000); ir 1645, 1625, 1525 $cm^{-1}$; nmr $\delta$ 7.0–7.5 (m, 5 H), 6.68 (s, 1 H), 5.27 (d, $J \simeq 1.5$ Hz, 1 H), 4.44 (s (d, $J \simeq 1.5$ Hz, 1 H), 4.09 (t, 2 H), 3.88 (s, 6 H), 2.95 (t, 2 H), 2.35 (s, 3 H).

*Anal.* Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.24; H, 6.57; N, 4.38.

**2-(4-Chlorobenzoyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyleneisoquinoline (3g).** The enamide **3g** was prepared from 8.8 g of *p*-chlorobenzoyl chloride (10% excess) and 9.3 g (0.045 mol) of dihydroisoquinoline in 90 ml of dioxane and 10 ml of pyridine at room temperature, under nitrogen. After 17 hr, 500 ml of chloroform was added and the organic layer was washed with water (2 × 500 ml) and then dried ($Na_2SO_4$). Evaporation of the solvents and crystallization from ether gave 12.4 g (0.036 mol, 80%) of **3g:** mp 159–162°, uv 220 nm (end, $\epsilon$ 32,000), 230 (sh, 26,500), 248 (min, 14,000), 264 (17,500), 290 (min, 7000), 303 (7500), 315 (sh, 5000); ir 1655, 1645, 1615, 1520 $cm^{-1}$; nmr $\delta$ 7.36 (m, 4 H), 7.03 (s, 1 H), 6.69 (s, 1 H), 5.28 (d, $J \simeq 1.5$ Hz, 1 H), 4.40 (d, $J \simeq 1.5$ Hz, 1 H), 4.12 (t, 2 H), 3.90 (s, 6 H), 2.97 (t, 2 H).

*Anal.* Calcd for $C_{19}H_{18}ClNO_3$: C, 66.37; H, 5.28; Cl, 10.31; N, 4.07. Found: C, 66.00; H, 5.35; Cl, 10.62; N, 4.07.

**2-(4-Phenylbenzoyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyleneisoquinoline (3h).** 4-Phenylbenzoyl chloride (Aldrich), 10 g, was added to 6.7 g (0.033 mol) of dihydroisoquinoline in 20 ml of pyridine and 100 ml of dioxane. After stirring at room temperature for 2 hr, the mixture was poured into 500 ml of chloroform and washed with distilled water (3 × 500 ml). The organic phase was dried (sodium sulfate) and evaporated to a tan solid. The solid was triturated with ether and dried to give 9.5 g (0.025 mol, 76%) of **4h:** mp 103–107° (methanol–water), uv 232 nm (sh, $\epsilon$ 20,000), 241 (min, 15,500), 270 (32,000), 295 (sh, 20,000); ir 1635, 1615, 1520 $cm^{-1}$; nmr $\delta$ 8.27 [d, $J \simeq 8$ Hz (secondary splitting), 1 H], 7.25–7.80 (m, 8 H), 7.06 (s, 1 H), 6.70 (s, 1 H), 5.34 (d, $J \simeq 1.5$ Hz, 1 H), 4.54 (d, $J \simeq 1.5$ Hz, 1 H), 4.17 (t, 2 H), 3.95 (s, 3 H), 3.92 (s, 3 H), 3.00 (t, 2 H).

*Anal.* Calcd for $C_{25}H_{23}NO_3$: C, 77.90; H, 6.01; N, 3.63. Found: C, 77.95; H, 5.95; N, 3.62.

**Irradiation of 2-Benzoyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyleneisoquinoline (3a).** A solution of 1.0 g of **3a** in 600 ml of *tert*-butyl alcohol in a quartz irradiation vessel was subjected to four vacuum freeze–thaw cycles in a Dry Ice–isopropyl alcohol bath for degassing purposes. The degassed solution was irradiated for 1.5 hr with eight 3000 Å lamps in a Southern New England Ultraviolet Co. Rayonet preparative photochemical reactor. [The 3000 Å lamps also emit appreciably at 2537 Å. This energy could be absorbed by the molecule due to the transparency of the quartz irradiation vessel.] The solvent was removed at the aspirator and the residue crystallized from methanol, in two crops, to give 967 mg of 2,3-dimethoxy-8-oxoberbine **4a** (5,6,13,13a-tetrahydro-2,3-dimethoxy-8*H*-dibenzo[*a*,*g*]quinolizin-8-one): mp 143–145°; uv 229 nm ($\epsilon$ 18,000), 254 (6500), 264 (5500), 279 (6000); ir 1660, 1520 $cm^{-1}$; nmr $\delta$ 8.17 (m, 1 H), 7.34 (m, 3 H), 6.75 (s, 1 H), 6.73 (s, 1 H), 4.65–5.15 (m, 2 H), 3.91 (s, 6 H), 2.7–3.5 (m, 5 H). The analytical sample was recrystallized from ethyl acetate–petroleum ether.

*Anal.* Calcd for $C_{19}H_{19}NO_3$: C, 73.76; H, 6.19; N, 4.53. Found: C, 73.46; H, 6.19; N, 4.48.

**Irradiation of 2-(3,4-Dimethoxybenzoyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyleneisoquinoline (3b).** A solution of 2.0 g of **3b** in 600 ml of *tert*-butyl alcohol is degassed and irradiated, as above, for 2.5 hr. The solvent was removed and the residue crystallized from ether to give, in two crops, 1.87 g of 2,3,10,11-tetramethoxy-8-oxoberbine **4b** (5,6,13,13a-tetrahydro-2,3,10,11-tetramethoxy-8*H*-dibenzo[*a*,*g*]quinolizin-8-one): mp 188–189°; uv 223.5 nm ($\epsilon$ 42,000), 249 (min, 7500), 263 (9000), 270 (9250), 280 (min, 7500), 285 (8000), 290 (8500), 302 (6000); ir 1650, 1615, 1600, 1520 $cm^{-1}$; nmr $\delta$ 7.65 (s, 1 H), 6.74 (s, 3 H), 4.67–5.17 (m, 2 H), 3.93 and 3.90 (s, 12 H), 2.67–3.33 (m, 5 H).

*Anal.* Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 67.92; H, 6.38; N, 3.79.

**2,3-Dimethoxy-9,10-methylenedioxy-8-oxoberbine (4c).** Enamide **3c** (2.0 g) in 600 ml of *tert*-butyl alcohol is degassed and irradiated for 2.5 hr. Solvent removal and crystallization from ethyl acetate–ether gave 1.50 g of **4c** (5,6,13,13a-tetrahydro-2,3-dimethoxy-8*H*-benzo-[*a*][1,3]-benzodioxolo[5,6-*g*]quinolizin-8-one): mp 174–178°; uv 225 nm ($\epsilon$ 41,000), 265 (7250), 273 (7500), 291 (8000), 305 (7500); nmr $\delta$ 7.58 (s, 1 H), 6.72 (broad s, 3 H), 5.99 (s, 2 H), 4.65–5.05 (m, 2 H), 3.86 (s, 6 H), 2.50–3.10 (m, 5 H).

*Anal.* Calcd for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42; N, 3.96. Found: C, 67.72; H, 5.61; N, 3.90.

**2,3,10,11,12-Pentamethoxy-8-oxoberbine (4d).** A solution of 4.0 g of **3d** in *tert*-butyl alcohol was degassed and irradiated, as above, for 5 hr. The solvent was removed and the residue dissolved in ethyl acetate–ether and filtered from a slight precipitate. Scratching induced the crystallization of 2.8 g of **4d** (5,6,13,13a-tetrahydro-2,3,10,11,12-pentamethoxy-8*H*-dibenzo[*a*,*g*]quinolizin-8-one): mp 127–30°; uv 220 nm (end, $\epsilon$ 38,000), 246 (min, 7000), 265 (9000), 290 (5500), 304 (2500); ir 1655, 1600, 1525, 1515 $cm^{-1}$; nmr $\delta$ 7.55 (s, 1 H), 6.74 (s, 1 H), 6.68 (s, 1 H), 4.5–5.0 (m, 2 H), 3.95, 3.92, 3.89 (s, 15 H), 2.5–3.5 (m, 5 H).

*Anal.* Calcd for $C_{22}H_{25}NO_6$: C, 66.15; H, 6.31; N, 3.51. Found: C, 65.96; H, 6.42; N, 3.32.

**11-Acetoxy-2,3,10-trimethoxy-8-oxoberbine (4e).** A solution of 6.0 g of the freshly prepared, noncrystalline enamide **3e** in 300 ml of *tert*-butyl alcohol, to which a few drops of triethylamine had been added to retard hydrolysis, was degassed as above and irradiated for 12 hr. The solvent was removed and the residue crystallized from methanol to give 1.55 g of **4e** in two crops. The residue from the mother liquor was chromatographed on 250 g of silica; elution with ethyl acetate–methylene chloride (1:3 and 1:1) gave an additional 1.10 g of **4e** (11-acetoxy-5,6,13,13a-tetrahydro-2,3,10-trimethoxy-8*H*-dibenzo[*a*,*g*]quinolizin-8-one): mp 166–167°; uv 235 nm ($\epsilon$ 17,500), 260 (sh, 8500), 275 (6000), 280 (6250), 285 (6500), 290 (7000), 299 (min, 5500), 306 (5750), 318 (min, 5000), 334 (5500); nmr $\delta$ 7.59 (s, 1 H), 6.96 (s, 1 H), 6.65 (s, 2 H), 4.58–5.10 (m, 2 H), 3.89 (s, 9 H), 2.70–3.20 (m, 5 H), 2.32 (s, 3 H).

*Anal.* Calcd for $C_{22}H_{23}NO_6$: C, 66.49; H, 5.83; N, 3.52. Found: C, 66.24; H, 5.91; N, 3.45.

**3-Hydroxy-2,3,10-trimethoxy-8-oxoberbine (5).** A solution of 411 mg of **4e** in 75 ml of methanol and 103 mg of *p*-toluenesulfonic

acid monohydrate was refluxed under nitrogen for 18 hr. Tlc inspection indicated approximately 25% reaction and an additional 300 mg of tosyl acid was added and refluxed for a further 8 hr. Upon cooling of the solution, 250 mg of **5** crystallized. Concentration of the solution yielded an additional 96 mg: mp 243–244°; uv 224 nm (41,000) 246 (min, 9500), 267 (14,250), 290 (9500), 304 (7500), 330 (4000); ir 3300, 1650, 1600, 1530 $cm^{-1}$; nmr (DMSO-$d_6$) $\delta$ 9.59 (broad s, 1 H, phenolic H), 7.45 (s, 1 H), 6.98 (s, 1 H), 6.78 (s, 2 H), 4.75 (m, 2 H), 3.81 (s, 3 H), 3.78 (s, 3 H), 3.75 (s, 3 H), 2.5–3.5 (m, 5 H, partially obscured by DMSO-solvent peak).

*Anal.* Calcd for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.35; H, 5.87; N, 4.10.

**11-Chloro-2,3-dimethoxy-8-oxoberbine (4g).** A solution of 6.0 g of the enamide **3g** in 600 ml of *tert*-butyl alcohol was degassed and irradiated as above for 16 hr. Removal of solvent and crystallization from ether gave 5.10 g of **4g** (11-chloro-5,6,13,13a-tetrahydro-2,3-dimethoxy-8*H*-dibenzo[*a*,*g*]quinolizin-8-one): mp 219–220°; uv 233 nm ($\epsilon$ 21,500), 258 (sh, 9500), 267 (sh, 7500), 280 (6500), 290 (sh, 5500); ir 1655, 1610, 1530 $cm^{-1}$; nmr $\delta$ 8.02 (d, $J \simeq$ 8 Hz, 1 H), 7.33 (dd, $J \simeq$ 8 Hz, 1.5 Hz, 1 H), 7.25 (broad s, 1 H), 6.70 (s, 2 H), 4.67–5.08 (m, 2 H), 3.90 (s, 6 H), 3.10 (m, 2 H), 2.88 (broad s, 3 H).

*Anal.* Calcd for $C_{19}H_{18}NO_3Cl$: C, 66.37; H, 5,28; N, 4.07. Found: C, 66.65; H, 5.34; N, 4.17.

**2,3-Dimethoxy-11-methyl-8-oxoberbine (4f).** A solution of 3.5 g of **3f** in 600 ml of *tert*-butyl alcohol was degassed and irradiated for 4.5 hr as described above. Removal of solvent gave a gum which could be crystallized from ethyl acetate–ether to give 2.1 g of **4f**. Dry column chromatography of the mother liquor residue gave an additional 536 mg of **4f** (5,6,13,13a-tetrahydro-2,3-dimethoxy-11-methyl-8*H*-dibenzo[*a*,*g*]quinolizin-8-one): mp 151–152°; uv 225 (min, 18,000), 233 (18,500), 254 (10,000), 265 (8000), 280 (6500), 290 (sh 5500); ir 1655, 1620, 1520 $cm^{-1}$; nmr $\delta$ 8.05 (d, $J \simeq$ 8 Hz, 1 H), 7.00–7.33 (m, 2 H), 6.73 (broad s, 2 H), 4.67–5.10 (m, 2 H), 3.91 (s, 6 H), 2.75–3.25 (m, 5 H), 2.40 (s, 3 H).

*Anal.* Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.19; H, 6.54; N, 4.33.

**2,3-Dimethoxy-11-phenyl-8-oxoberbine (4h).** A solution of 4.0 g of **3h** in 300 ml of *tert*-butyl alcohol was degassed and irradiated for 12 hr. Removal of the solvent and crystallization from methanol gave 3.05 g of **4h** (5,6,13,13a-tetrahydro-2,3-dimethoxy-11-phenyl-8*H*-dibenzo[*a*,*g*]quinolizin-8-one): mp 136–138°; uv 220 nm (end, 29,500), 244 (min, 11,000), 278 (27,500), 334 (3750); ir 1670, 1620, 1530, 1520, $cm^{-1}$; nmr $\delta$ 8.22 (d, $J \simeq$ 8 Hz, 1 H), 7.15–7.85 (m, 7 H), 6.75 (s, 1 H), 6.70 (s, 1 H), 4.65–5.15 (m, 2 H), 3.40 (s, 3 H), 3.37 (s, 3 H), 2.75–3.35 (m, 5 H).

*Anal.* Calcd for $C_{25}H_{23}NO_3$: C, 77.90; H, 6.01; N, 3.63. Found: C, 77.73; H, 5.94; N, 3.39.

**Irradiation of 3e under Nondegassed Conditions.** A solution of 6.0 g of the noncrystalline enamide **3e** was dissolved in 300 ml of ethyl acetate containing a few drops of triethylamine to retard hydrolysis. The solution was stirred magnetically and irradiated through Pyrex with a Hanovia 450-W medium pressure mercury arc for 9 hr. During the irradiation, 650 mg of a precipitate of 11-acetoxy-2,3,10-trimethoxyoxyprotoberberine **6** formed. Filtration of the precipitate and concentration of the solution, followed by dilution with petroleum ether gave an additional 3.05 g of **6**: mp 185–187°; uv 223 nm ($\epsilon$ 43,000), 261 (sh, 13,000), 282 (min, 5000), 306 (sh, 13,500), 332 (25,000), 356 (sh, 14,000), 370 (sh, 9500); ir 1770, 1655, 1615, 1520 $cm^{-1}$; nmr $\delta$ 7.86 (s, 1 H), 7.23 (s, 2 H), 6.75 (s, 2 H), 4.28 (t, 2 H), 3.97 (s, 3 H), 3.94 (s, 6 H), 2.92 (t, 2 H), 2.35 (s, 3 H); mass spectrum *m/e* 395 (parent, 31%), 367 (–CO, 11), 353 (–$OCCH_3$, 95), 338 (–$OCCH_3$, $CH_3$, 100), 310 (–CO, –$OCCH_3$, 41), 74 (22), 59 (49), 42 (93).

Despite repeated recrystallizations, a satisfactory analysis for **6e** could not be obtained. However, the mass spectrum, conversion to **8**, and the other data indicate the correct structure.

*Anal.* Calcd for $C_{22}H_{21}NO_6$: C, 66.82; H, 5.35; N, 3.54. Found: C, 64.98; H, 5.41; N, 3.41.

**11-Hydroxy-2,3,10-trimethoxyoxyprotoberberine (8).** A solution of 250 mg of **6** in 50 ml of methanol containing a few milligrams of *p*-toluenesulfonic acid monohydrate was refluxed for 24 hr. Upon cooling, 170 mg of **8** (5,6-dihydro-11-hydroxy-2,3,10-trimethoxy-8*H*-dibenzo[*a*,*g*]quinolizin-8-one) crystallized: mp 267–268°; uv 226 nm ($\epsilon$ 34,000), 245 (min, 24,500), 265 (34,000), 288 (min, 6500), 330 (27,000), 358 (sh, 16,000); ir 3180, 1650, 1615, 1590, 1520 $cm^{-1}$; nmr (DMSO-$d_6$) $\delta$ 7.61 (s, 1 H), 7.45 (s, 1 H), 7.11 (s, 1 H), 7.03 (s, 1 H), 6.92 (s, 1 H), 4.23 (t, 2 H), 3.90 (s, 6 H), 3.84 (s, 3 H), 2.90 (t, 2 H).

*Anal.* Calcd for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42; N, 3.96. Found: C, 67.92; H, 5.56; N, 3.83.

**General Procedure for DDQ Dehydrogenation of 8-Oxoberbines.** A 1% solution of 8-oxoberbine in either benzene or toluene is treated with a weight equivalent of dichlorodicyanobenzoquinone for 0.25 to 0.50 hr. The precipitated hydroquinone is filtered and the dehydrooxyprotoberberine isolated by chromatography on a short alumina column.

**2,3-Dimethoxy-10,11-methylenedioxyoxyprotoberberine (9c).** 8-Oxoberbine **4c** (500 mg) dehydrogenated as described above gave 383 mg of **9c** (5,6-dihydro-2,3-dimethoxy-8*H*-benzo[*a*][1,3]-benzodioxolo[5,6-*g*]quinolizin-8-one): mp 204–205° (ether–petroleum ether); uv 227 nm ($\epsilon$ 38,000), 245 (min, 17,500), 265 (25,000), 288 (min, 5500), 333 (25,000), 364 (sh, 12,000); ir 1655, 1620, 1585, 1515 $cm^{-1}$; nmr $\delta$ 7.72 (s, 1 H), 7.17 (s, 1 H), 6.81 (s, 1 H), 6.68 (s, 2 H), 6.00 (s, 2 H), 4.32 (t, 2 H), 3.95 (s, 3 H), 3.90 (s, 3 H), 2.88 (t, 2 H).

*Anal.* Calcd for $C_{20}H_{17}NO_5$: C, 68.37; H, 4.88; N, 3.99. Found: C, 68.18; H, 4.94; N, 4.17.

**2,3,10,11,12-Pentamethoxyoxyprotoberberine (9d).** Compound **4c** (500 mg) was dehydrogenated with DDQ as described above to give 300 mg of **9d** (5,6-dihydro-2,3,10,11,12-pentamethoxy-8*H*-dibenzo[*a*,*g*]quinolizin-8-one): mp 170–171° (ethyl acetate–petroleum ether); uv 228 nm ($\epsilon$ 32,500), 249 (min, 23,000), 260 (25,000), 287 (min, 6500), 306 (sh, 12,500), 320 (sh, 19,000), 334 (24,000); ir 1650, 1605, 1520 $cm^{-1}$; nmr $\delta$ 7.53 (s, 1 H), 7.33 (s, 1 H), 7.11 (s, 1 H), 6.77 (s, 1 H), 4.39 (t, 2 H), 4.05 (s, 3 H), 4.01 (s, 9 H), 3.95 (s, 3 H), 2.95 (t, 2 H).

*Anal.* Calcd for $C_{22}H_{23}NO_6$: C, 66.49; H, 5,83; N, 3.52. Found: C, 66.33; H, 5.88; N, 3.62.

**2,3-Dimethoxy-11-methyloxyprotoberberine (9f).** A solution of 8-oxoberbine **4f** (500 mg) is dehydrogenated with DDQ to give 400 mg of **9f** (5,6-dihydro-2,3-dimethoxy-11-methyl-8*H*-dibenzo[*a*,*g*]quinolizin-8-one): mp 169–170° (ethyl acetate–petroleum ether); uv 220 ($\epsilon$ 36,000), 226 (sh, 32,000), 235 (sh, 29,000), 249 (sh, 21,000), 257 (18,000), 282 (min, 4500), 302 (sh, 11,000), 316 (sh, 18,000), 330 (25,000), 344 (22,500), 362 (15,000); ir 1660, 1630, 1620 (sh), 1605, 1525 $cm^{-1}$; nmr $\delta$ 8.35 (d, $J \simeq$ 8 Hz, 1 H), 7.33 (s, 1 H), 7.28 (s, 1 H), 7.25 (d, 1 H), 6.82 (s, 1 H), 6.75 (s, 1 H), 4.36 (t, 2 H), 4.00 (s, 3 H), 3.95 (s, 3 H), 2.92 (t, 2 H), 2.47 (s, 3 H).

*Anal.* Calcd for $C_{20}H_{19}NO_3$: C, 74.74; H, 5.96; N, 4.36. Found: C, 74.65; H, 6.01; N, 4.40.

**11-Chloro-2,3-dimethoxyoxyprotoberberine (9g).** A solution of compound **4g** (1.00 g) was dehydrogenated with DDQ to 700 mg of **9g** (11-chloro-5,6-dihydro-2,3-dimethoxy-8*H*-dibenzo[*a*,*g*]-quinolizin-8-one): mp 220–221°; uv 227 nm ($\epsilon$ 29,500), 238 (28,000), 258 (sh, 16,000), 266 (sh, 11,000), 283 (min, 4000), 334 (25,500), 350 (sh, 21,000), 366 (sh, 13,000); ir 1665, 1615, 1520 $cm^{-1}$; nmr $\delta$ 8.30 (d, $J \simeq$ 8.5 Hz, 1 H), 7.15–7.60 (m, 3 H), 6.73 (s, 2 H), 4.31 (t, 2 H), 3.97 (s, 3 H), 3.92 (s, 3 H), 2.92 (t, 2 H).

*Anal.* Calcd for $C_{19}H_{16}ClNO_3$: C, 66.77; H, 4.72; N, 4.10. Found: C, 66.49; H, 4,83; N, 4.14.

**2,3-Dimethoxy-11-phenyloxyprotoberberine (9h).** Compound **4h** (400 mg) was dehydrogenated to give 360 mg of **9h** (5,6-dihydro-2,3-dimethoxy-11-phenyl-8*H*-dibenzo[*a*,*g*]quinolizin-8-one): mp 187–189°; uv 220 nm (end, $\epsilon$ 32,000), 238 (min, 18,000), 274 (37,000), 304 (min, 14,000), 322 (sh, 20,000), 335 (27,500), 362 (sh, 13,500), 376 (10,000); ir 1655, 1620, 1520 $cm^{-1}$; nmr $\delta$ 7.25–7.75 (m, 8 H), 6.92 (s, 1 H), 6.75 (s, 1 H), 4.40 (t, 2 H), 4.00 (s, 3 H), 3.95 (s, 3 H), 2.93 (t, 2 H).

*Anal.* Calcd for $C_{25}H_{21}NO_3$: C, 78.31; H, 5.52; N, 3.65. Found: C, 78.20; H, 5.67; N, 3.46.

**2,3,10,11-Tetramethoxyberbine (Xylopinine) (10b).** A solution of 500 mg of 2,3,10,11-tetramethoxy-8-oxoberbine **4b** in 65 ml of dry benzene was reduced, under nitrogen, with 2 ml of a 70% solution of sodium bis(methoxyethoxy)aluminum hydride in benzene (Aldrich Red-al) for 16 hr. The reaction mixture was quenched by careful addition of saturated Rochelle salt. The organic layer was separated and the salt solution extracted with methylene chloride (2 × 50 ml). The combined organic extracts were dried with sodium sulfate and the solvent removed. Crystallization from ether–petroleum ether gave 400 mg of *dl*-xylopinine (**10b**): mp 142–143°; ir 1610, 1515 $cm^{-1}$; uv 224 nm ($\epsilon$ 16,000), 251 (min, 750), 280 (8000), 284 (8000), 289 (7000); nmr $\delta$ 6.63 (s, 1 H), 6.57 (s, 1 H), 6.52 (s, 1 H), 6.47 (s, 1 H), 3.84 (s, 3 H), 3.80 (s, 9 H), 2.9–3.7 (m, 9 H).

**2,3-Dimethoxy-10,11-methylenedioxyberbine (10c).** To a solution of 792 mg of 8-oxoberbine **4c** in 50 ml of dry tetrahydrofuran was added 500 mg of lithium aluminum hydride and the mix-

ture was refluxed for 16 hr. After cooling to room temperature the excess $LiAlH_4$ is destroyed with ethyl acetate and the mixture poured into distilled water. The aqueous solution was extracted with chloroform (3 × 200 ml), and the organic extracts were dried with sodium sulfate. Removal of solvent gave a gum which was crystallized from 5 ml of methanol to give 325 mg of **10c:** mp 155–156°; uv 220 nm (end, $\epsilon$ 15,000), 232 (sh, 11,000), 255 (min, 1000), 289 (8500); ir 1620, 1530, 1510 $cm^{-1}$; nmr $\delta$ 6.75 (s, 1 H), 6.64 (s, 2 H), 6.55 (s, 1 H), 5.90 (s, 2 H), 3.88 (s, 3 H), 3.85 (s, 3 H), 2.5–3.75 (m, 9 H).

*Anal.* Calcd for $C_{20}H_{21}NO_4$: C, 70.70; H, 6.24; N, 4.13. Found: C, 70.56; H, 6.40; N, 3.93.

The mother liquor which was found to contain appreciable amounts of **10c** was added to 25 ml of ethyl acetate and 3 ml of hydrogen chloride saturated isopropyl alcohol. The combined solvents were removed to give the crude hydrochloride as a light tan solid. The solid was suspended in 25 ml of refluxing ethyl acetate and filtered to give 244 mg of 2,3-dimethoxy-10,11-methylenedioxyberbine hydrochloride: mp 263–265°, ir 1620, 1530, 1505 $cm^{-1}$.

*Anal.* Calcd for $C_{20}H_{21}NO_4 \cdot HCl \cdot 0.5H_2O$: C, 62.41; H, 6.02; N, 3.64. Found: C, 62.13; H, 6.00; N, 3.44.

**2,3,10,11,12-Pentamethoxyberbine (10d).** A solution of 250 mg of **4d** is reduced as described for **4b** to give 220 mg of **10d:** mp 117–120° (methanol–water); uv 227 nm (sh, $\epsilon$ 19,500), 252 (min, 1000), 281 (5500), 290 (sh, 3500); ir 1530, 1520, 1505 $cm^{-1}$; nmr $\delta$ 6.83 (s, 1 H), 6.64 (s, 1 H), 6.46 (s, 1 H), 3.92, 3.88, 3.85 (s, 15 H), 2.5–3.7 (m, 9 H).

*Anal.* Calcd for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.63. Found: C, 68.73; H, 7.19; N, 3.61.

**11-Hydroxy-2,3,10-trimethoxyberbine (10e).** A solution of 535 mg of **4e** is reduced as described for **4b.** Crystallization from ethyl acetate–petroleum ether gave 286 mg of **10e:** mp 227–229°; uv 200 nm (end, $\epsilon$ 15,500), 252 (min, 1000), 285 (8000), 303 (min, 1500), 317 (2000); ir 1615, 1515 $cm^{-1}$; nmr (DMSO-$d_6$) $\delta$ 6.90 (s, 1 H), 6.69 (s, 1 H), 6.65 (s, 1 H), 6.60 (s, 1 H), 3.75 (s, 3 H), 3.73 (s, 6 H), 2.5–3.7 (m, 9 H).

*Anal.* Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.20; H, 6.79; N, 4.00.

**11-Acetoxy-2,3,10-trimethoxyberbine (11).** To a suspension of 173 mg of **10e** in 0.8 ml of acetic anhydride, 1 ml of pyridine, and 8 ml of methylene chloride was added a few crystals of 4-dimethylaminopyridine. The suspended solid immediately dissolved to a light yellow solution. After standing for 16 hr, excess methanol was added and the solvents removed. The residue was partitioned between water and methylene chloride. The organic layer was dried with sodium sulfate and removed at the aspirator. Crystallization from ether–petroleum ether gave 172 mg of **11:** mp 139–141°; uv 220 nm (end, $\epsilon$ 14,000), 250 (min, 750), 276 (4500), 280.5 (5000), 285.5 (5000); ir 1770, 1625, 1525 $cm^{-1}$; nmr $\delta$ 6.87 (s, 1 H), 6.73 (s, 1 H), 6.69 (s, 1 H), 6.64 (s, 1 H), 3.87 (s, 6 H), 3.80 (s, 3 H), 2.5–3.7 (m, 9 H), 2.30 (s, 3 H).

*Anal.* Calcd for $C_{22}H_{25}NO_5$: C, 68.91; H, 6.57; N, 3.65. Found: C, 68.57; H, 6.76; N, 3.63.

**2,3-Dimethoxy-11-methylberbine (10f).** The 8-oxoberbine **4f** (500 mg) was reduced as described for **10b** to yield 450 mg of **10f** as a light tan solid: mp 116–118° (methanol–water); uv 220 nm (end, $\epsilon$ 18,500), 232 (sh, 9000), 251 (min, 1500), 277 (5000), 284 (4500), 290 (4000); ir 1620, 1525, 1515 $cm^{-1}$; nmr $\delta$ 6.97 (s, 3 H), 6.78 (s, 1 H), 6.63 (s, 1 H), 3.89 (s, 3 H), 3.85 (s, 3 H), 2.5–3.8 (m, 9 H), 2.30 (s, 3 H).

*Anal.* Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.74; H, 7.66; N, 4.68.

**11-Chloro-2,3-dimethoxyberbine (10g).** A solution of 500 mg of **4g** in 50 ml of dry tetrahydrofuran was reduced with 300 mg of $LiAlH_4$ for 1.5 hr. The excess $LiAlH_4$ was destroyed with a saturated Rochelle salt solution and the aqueous extracted with methylene chloride (2 × 250 ml). The organic phase was dried with sodium sulfate and the solvent removed. Crystallization from methanol–water gave 250 mg of **10g:** mp 128–130°; uv 220 nm (end, $\epsilon$ 19,000), 280 (6000); ir 1525 $cm^{-1}$; nmr $\delta$ 6.83–7.34 (m, 3 H), 6.75 (s, 1 H), 6.66 (s, 1 H), 3.92 (s, 3 H), 3.88 (s, 3 H), 3.67–4.00 (m, 2 H), 2.5–3.5 (m, 7 H).

*Anal.* Calcd for $C_{19}H_{20}ClNO_2$: C, 69.19; H, 6.11 N, 4.25. Found: C, 69.04; H, 6.26; N, 4.27.

**2,3-Dimethoxy-11-phenylberbine (10h).** The oxoberbine **4h** (370 mg) was added to 370 mg of $LiAlH_4$ in 50 ml of THF under nitrogen and the mixture stirred. After 16 hr the solution was a light green. The excess $LiAlH_4$ was destroyed with saturated Rochelle salt solution and the aqueous layer was extracted with methylene chloride (4 × 60 ml). The combined organic extracts were dried with sodium sulfate and evaporated. The residue was crystallized from methanol–water to give 215 mg of **10h:** mp 119–121°; uv 220 nm (end, $\epsilon$ 29,000), 232 (min, 16,000), 253 (20,000), 280 (sh, 9500), 290 (5000); ir 1530, 1520 $cm^{-1}$; nmr $\delta$ 7.0–8.2 (m, 8 H), 6.80 (s, 1 H), 6.65 (s, 1 H), 3.58–4.09 (m, 2 H), 3.92 (s, 3 H), 3.88 (s, 3 H), 3.59 (m, 1 H), 2.34–3.34 (m, 6 H).

*Anal.* Calcd for $C_{25}H_{25}NO_2$: C, 80.83; H, 6.78; N, 3.77. Found: C, 80.59; H, 6.77; N, 3.97.

**Registry No.** —**5,** 52050-72-3; **7,** 52050-73-4; **8,** 52050-74-5; **11,** 52050-75-6; benzoic acid, 65-85-0; 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline, 4721-98-6; 3,4-dimethoxybenzoic acid, 93-07-2; piperonylic acid, 94-53-1; 3,4,5-trimethoxybenzoic acid, 118-41-2; acetylvanillic acid, 10543-12-1; *p*-toluoyl chloride, 874-60-2; *p*-chlorobenzoyl chloride, 122-01-0; 4-phenylbenzoyl chloride, 14002-51-8.

## References and Notes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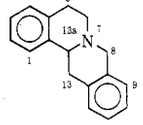


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