The Synthesis of 8-Oxoberbines Containing a Heterocyclic
## D-Ring by Enamide Photocyclizations

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The photocyclization of 2-heteroyl-1-methyleneyl-3,4-dihydro-6,7-dimethoxyisoquinolines, where heteroyl = benzofuran, benzo[b]thiophene, coumarin and nicotinoyl, leads to the corresponding 8-oxoberbines containing a heterocyclic D-ring. Dehydrogenation can accompany photocyclization depending on the reaction conditions employed, or alternatively DDQ can be used to effect this dehydrogenation.

We have previously shown that 2-aroyl-1-methyleneyl tetrahydroisoquinolines **1** readily photocyclize in high yields into 8-oxoberbines **2** (1,2). In order to extend the uses of this preparative photoreaction, and to prepare novel polycyclic alkaloid analogs, we have investigated the synthesis and photocyclization of 2-heteroyl-1-methyleneyl tetrahydrosioquinolines to prepare 8-oxoberbines containing a heterocyclic D-ring.
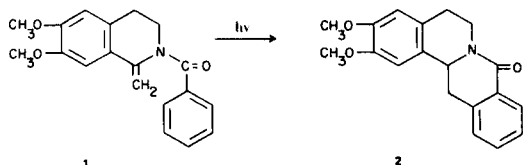
The condensation of benzofuran-2-carbonyl chloride with 1-methyl-3,4-dihydro-6,7-dimethoxyisoquinoline proceeded readily to form the benzofuran enamide **3**. Irradiation of compound **3** in benzene under argon gave a smooth cyclization to the benzofuran-8-oxoberbine derivative **4** in 53% yield after chromatographic separation. The mechanism for ring formation is the aza analog of the hexatriene-cyclohexadiene photocyclization to form an intermediate which undergoes a 1,5-hydride shift to
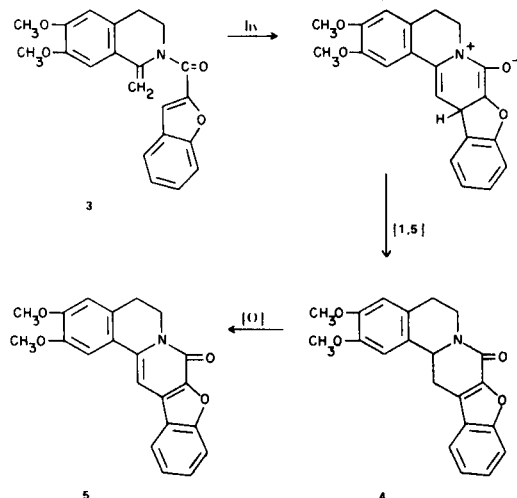
generate the observed product **4** (3). The structure of **4** was evident from its spectral properties; a much simpler ultraviolet spectrum due to the loss of conjugation and the loss of the exocyclic methylene proton signals in the nmr spectrum. Additionally, the resultant new aliphatic proton resonances formed a simple splitting pattern amenable to a first order analysis. There is geminal coupling of 10.5 Hz between H_2 and H_3, but only one of these protons is coupled to the vicinal hydrogen, indicating that a dihedral angle of ninety degrees exists between H_1 and one of the geminal protons (4). Of the three possible configurations of the berbine ring system (5), the only one
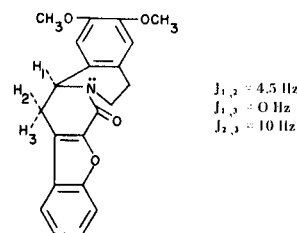

which fulfills the observed nmr coupling values is that one analogous to pseudoyohimbine. That is, where the BC-ring junction is *cis* and this ring fusion forces the CDE-ring portion to be orthogonal to the AB-part of the molecule. Inspection of a molecular model of **4** indicates that the dihedral angle between H_1 and H_3 is ninety degrees, while the angle between H_1 and H_2 is approximately forty degrees, which, based on the Karplus equation (4), leads to a calculated coupling constant of approximately J ≃ 4 Hz. This is particularly interesting in view of the ready pyramidal inversion in amide nitrogens due to the partial double bond character of the nitrogen-carbonyl carbon bond. This means that compound **4** is effectively frozen in the indicated conformation, since any nitrogen inversion in **4** would lead to a significantly different and more complex nmr spectrum.

Since the 8-oxoberbine C-ring is readily dehydrogenated by 2,3-dichloro-5,6-dicyanobenzoquinone (1), this de-

hydrogenation was attempted on compound 4. Reaction with DDQ gave an instantaneous reaction with 4 to yield the flat, highly aromatic benzofuran-8-oxoproto-berberine 5 in 19% yield.

This reaction was extended to the sulfur analog 6 by condensing benzo[b]thiophene-2-carbonyl chloride with 1-methyl-3,4-dihydro-6,7-dimethoxyisoquinoline to form
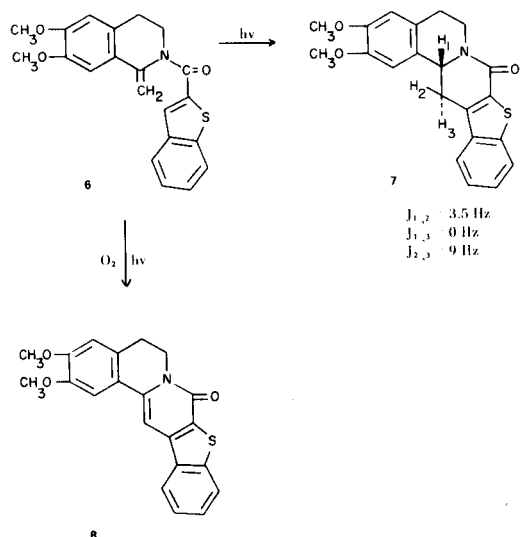
the enamide 6. Irradiation of the benzothiophene enamide 6 in degassed dioxane (see Experimental) leads to a 22% yield of the benzo[b]thiophene-8-oxoberbine derivative 7. In agreement with the oxaanalog 4, the thia compound 7 possesses a simple first order splitting pattern in the nmr for the newly formed aliphatic protons. Again there is a geminal coupling, but only one of the geminal protons is coupled to the vincinal hydrogen; indicating a BC-cis-ring fusion. When the enamide 6 was irradiated in a standard irradiation vessel under nitrogen, the only product isolated, in 33% yield, was the benzo[b]-thiophene-8-oxyprotoberberine derivative 8. The line nitrogen used was subsequently shown to contain traces of oxygen. This experiment demonstrates the extreme sensitivity of the 8-oxoberbine system to oxygen, or other oxidizing agents (6), and light (7).

The coumarin enamide 9 was readily prepared by the reaction of the dihydroisoquinoline with coumarin-3-carbonyl chloride. The photocyclization of 9 was extraordinarily fast compared to enamides 1, 3, and 6. Apparently the presence of the coumarin carbonyl group greatly aids either the initial photocyclization or the subsequent hydride shift. Similar observations have been made in the photocyclization of α-phenoxyenones, which has been developed into a useful synthetic photochemical procedure (8). In fact the isolation of the coumarin-8-oxoberbine 10 in 65% yield is particularly satisfying in view of the varied photochemistry of the pyrone ring (9).

The nmr spectrum of 10 was significantly different than those of compounds 4 and 7 and its complexity was more similar to the simple berbines than the heterocyclic 8-oxoberbines 4 and 7 (1,5). Dehydrogenation of 10 with DDQ gave the highly fluorescent novel nearly aromatic system 11. One of the hydrogen atoms in the cavity of CDE-ring system is strongly deshielded and appears at δ 9.28. The proton appears as a broad multiplet and is assigned to the aromatic hydrogen of the E-ring which is in the cavity formed by the three rings. This
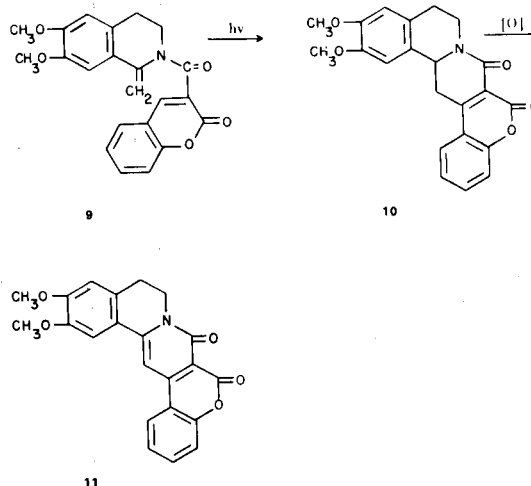
deshielding is attributed to this hydrogen being forced out of coplanarity and into the deshielding portion of the aromatic rings, and this same phenomenon has been observed in phenanthrenes (10).

The final system studied was nicotinoyl enamide 12. Irradiation of this particular enamide either under degassed conditions, or a variety of other conditions only lead to the 10-aza-8-oxyprotoberberine derivative 13 in low yield. The structure of 13 was based on its nmr spectrum which showed one isolated and two vicinal pyridine protons. Similar photocyclizations involving carboline-nicotinoyl enamides also lead only to the dehydrogenated
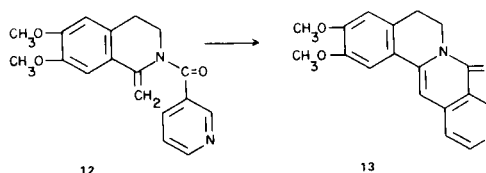
photoproduct (11). It appears based on the experience of these collective experiments that the mechanism of photocyclization and dehydrogenation of enamides involving the pyridine ring is more complex than the ordinary enamides.

EXPERIMENTAL

General.

Melting points were taken on a Thomas-Hoover UniMelt capillary apparatus and are not corrected. Infrared spectra were run in potassium bromide, unless otherwise noted, and ultraviolet and visible spectra were run in methanol. A Varian Associates A-60 or T-60 NMR spectrometer was used to record the spectra of all the compounds and the spectra were recorded in deuterochloroform using tetramethylsilane as an internal standard. Microanalyses were determined by Searle Laboratories microanalytical service under the supervision of Mr. E. Zielinski.

The Preparation of the Enamide of Coumarilic Acid 3.

The acid chloride of coumarilic acid (benzofuran-2-carboxylic acid) was prepared according to the literature procedure for the 5-methyl derivative (12). Coumarilic acid (10 g., 62 mmoles) was dissolved in 50 ml. of thionyl chloride, containing 0.5 ml. of pyridine, and was refluxed for 1 hour. After cooling, the solvent was evaporated and 100 ml. of benzene was added and evaporated under reduced pressure. A solution of 1-methyl-3,4-dihydro-6,7-dimethoxyisoquinoline, 9.8 g. (48 mmoles) in 200 ml. of pyridine was cooled to 0° in an ice bath and placed under nitrogen. The above acid chloride was dissolved in 100 ml. of chloroform and added to the reaction mixture *via* an addition funnel. After stirring overnight, the solvents were evaporated and the residue was dissolved in 400 ml. of chloroform and then washed three times with water. After drying with sodium sulfate, the solution was treated with decolorizing charcoal, filtered through Celite and evaporated. The residue was crystallized from a small amount of ethyl acetate, which was further diluted with ether to yield 9.05 g., 26 mmoles (54%) of the light yellow enamide 3, m.p. 134-136°; ir: 1665 cm⁻¹, 1635, 1615, 1520, uv: 220 nm (end, ε, 30,500), 232 (sh, 21,750), 243 (min, 15,250), 268 (27.500), 288 (min, 18,500), 296 (19,000); nmr: δ 7.08-7.83 (m, 6H), 6.66 (s, 1H), 5.38 (d, J = 1.5 Hz, 1H), 4.77 (d, J = 1.5 Hz, 1H), 4.15 (t, 2H), 3.95 (s, 3H), 3.92 (s, 3H), 2.98 (t, 2H).

Anal. Calcd. for $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48; N, 4.01. Found: C, 71.89; H, 5.55; N, 3.81.

The Enamide of 4,5-Benzo[b]thiophene-2-carboxylic Acid 6.

A suspension of benzo[b]thiophene-2-carboxylic acid (10.0 g., 56 mmoles) in 100 ml. of dry benzene, 20 ml. of thionyl chloride, and 0.5 ml. of dimethylformamide was stirred overnight. As the acid chloride formed, the acid went into solution. The solution was evaporated and the residue dissolved in the minimum of ether. After petroleum ether was added, the acid chloride (10 g.) was filtered and dried. To a solution of 1-methyl-3,4-dihydro-6,7-dimethoxyisoquinoline, 6.65 g. (32.7 mmoles), in 250 ml. of toluene and 25 ml. of pyridine, under nitrogen, the above acid chloride, 6.5 g. (110% of theory) was added and the mixture heated to 50° for 18 hours. The reaction mixture was then poured into water and extracted with 0.5 l. of methylene chloride. After washing the organic solution three times with water, it was dried with sodium sulfate, treated with decolorizing carbon and evaporated. The residue was crystallized from ethyl acetate-ether to yield 8.5 g. (23 mmoles, 52%) of the enamide 6, m.p. 152-153°; ir (chloroform): 1630 cm⁻¹, 1615; uv: 223 nm (ε, 38,000), 249 (min, 18,000), 270 (21,500), 288 (min, 16,000), 300 (16,500); nmr: δ 7.58-7.92 (m, 3H), 7.25-7.50 (m, 2H), 7.13 (s, 1H), 6.68 (s, 1H), 5.43 (d, J = 1.5 Hz, 1H), 4.90 (d, J = 1.5 Hz, 1H), 4.15 (t, 2H), 3.95 (s, 3H), 3.92 (s, 3H), 2.98 (t, 2H).

Anal. Calcd. for $C_{21}H_{19}NO_3S$: C, 69.02; H, 5.24; N, 3.83.

Found: C, 68.80; H, 5.35; N, 3.53.

The Enamide of Coumarin-3-carboxylic Acid 9.

The acid chloride of coumarin-3-carboxylic was prepared according to the literature procedure by dissolving 10 g. of acid in 50 g. (30 ml.) of thionyl chloride and refluxing for 2 hours (13). Upon cooling, the mixture partially solidified. After diluting with petroleum ether and filtering, 10.6 g. of acid chloride, m.p. 142-146° (lit. 13 147°) was obtained. This acid chloride was added to 7.25 g. (35 mmoles) of 1-methyl-3,4-dihydro-6,7-dimethoxyisoquinoline dissolved in 200 ml. of chloroform and 10 ml. of pyridine. The reaction mixture was stirred for 18 hours and then washed with water three times. After drying with sodium sulfate, the solvents were removed to yield a syrup which was crystallized from ethyl acetate-ether to yield 4.5 g. (12 mmoles, 34%) of enamide 9, m.p. 176-180°; ir: 1760 cm⁻¹, 1750 (sh), 1655, 1610, 1585, 1575, 1520; uv: 245 nm (min, ε, 11,500), 274 (18,000), 316 (13,250), 366 (min, 4000), 386 (5500), 405 (6500); nmr: δ 7.98 (s, 1H), 7.48 (m, 4H), 7.05 (s, 1H), 6.68 (s, 1H), 5.33 (d, J = 1.5 Hz, 1H), 4.83 (d, J = 1.5 Hz, 1H), 4.13 (t, 2H), 3.92 (s, 3H), 3.90 (s, 3H), 3.00 (t, 2H).

Anal. Calcd. for $C_{22}H_{19}NO_5$: C, 70.01; H, 5.07; N, 3.71. Found: C, 69.83; H, 4.96; N, 3.66.

The Enamide of Nicotinic Acid 12.

Nicotinic anhydride (14) (12.5 g.) was added to a solution of 7.8 g. (38 mmoles) of 1-methyl-3,4-dihydro-6,7-dimethoxyisoquinoline in 250 ml. of dry benzene and 20 ml. of triethylamine under nitrogen. After stirring overnight, the reaction mixture was washed three times with water and dried with sodium sulfate. After evaporation the residue was dissolved in ethyl acetate and scratched to induce crystallization. After dilution with ether, 8.6 g. (28 mmoles, 74%) of enamide 12, m.p. 135.5-137°; ir: 1635 cm⁻¹, 1615, 1590, 1515; uv: 220 nm (end, ε, 25,000), 231 (sh, 18,500), 243 (min, 11,000), 265 (17,000), 291 (min, 7,500), 303 (8000), 315 (sh, 6000); nmr: δ 9.42 (m, 2H), 7.82 (dt, 1H), 7.28 (dd, 1H), 7.02 (s, 1H), 6.68 (s, 1H), 5.33 (d, J = 1.5 Hz, 1H), 4.48 (d, J = 1.5 Hz, 1H), 4.17 (t, 2H), 3.93 (s, 6H), 3.02 (t, 2H).

Anal. Calcd. for $C_{18}H_{18}NO_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.33; H, 5.82; N, 9.03.

The Photocyclization of the Benzofuran Enamide 3.

A solution of 2.00 g. (5.72 mmoles) of enamide 3 in 190 ml. of benzene was irradiated under argon with a 450 watt medium pressure mercury arc (Pyrex filter) for 3.5 hours to yield a bright red solution. The solvent was evaporated and the residue chromatographed on a 1.25 cm x 1 m Woelm silica column using low pressure liquid chromatography. Elution with 9:1 ethyl acetate-benzene yielded 1.063 g. of pentacyclic product 4 (3.05 mmoles, 53%), m.p. 157-160° (ether); ir: 1680 cm⁻¹, 1615, 1605 (w), 1520; uv: 239 nm (min, 13,250), 253 (20,000), 274 (min, 8,250), 284 (9000), 291 (min, 8500), 310 (9750); nmr: δ 6.67-7.50 (m, 4H), 7.02 (s, 1H), 6.63 (s, 1H), 5.52 (d, J = 4.5 Hz, 1H), 5.27 (d, J = 10.5 Hz, 1H), 4.47 (dd, J = 10.5, 4.5 Hz, 1H), 3.97 (t, 2H), 3.90 (s, 6H), 2.78 (t, 2H).

Anal. Calcd. for $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48; N, 4.01. Found: C, 72.32; H, 5.61; N, 4.08.

Dehydrogenation of the Benzofuran-8-Oxoberbine 4.

A solution of 643 mg. (1.85 mmoles) of 4 in 50 ml. of benzene was dehydrogenated with 500 mg. of freshly recrystallized 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (benzene) at room temperature for 15 minutes. After adding a few drops of 1,4-

cyclohexadiene to quench the remaining quinone, the precipitated hydroquinone was filtered. The solvent was removed and the residue chromatographed on a short alumina column. After washing the column with benzene, the product was eluted using 1:1-ethyl acetate-benzene mixtures. The material was recrystallized from ethyl acetate-ether to yield 120 mg. (0.35 mmoles, 19%) of the benzofuran-8-oxyprotoberberine **5**, m.p. 260-262°; ir: 3080 cm^{-1}, 1680, 1620, 1605, 1575, 1525; uv: 225 nm (ϵ, 29,000), 238 (26,000), 248 (min, 20,500), 254 (sh, 22,550), 262 (27,500), 269 (min, 25,500), 271 (25,750), 290 (sh, 13,000), 298 (min, 8500), 304 (sh, 10,000), 316 (12,500), 324 (min, 11,000), 334 (sh, 13,500), 347 (16,500), 361 (13,500); nmr: δ 7.83-8.08 (m, 1H), 7.25-7.67 (m, 3H), 7.32 (s, 1H), 7.12 (s, 1H), 6.78 (s, 1H), 4.45 (t, 2H), 4.03 (s, 3H), 3.97 (s, 3H), 2.93 (t, 2H).

Anal. Calcd. for C$_{21}$H$_{17}$NO$_4$: C, 72.61; H, 4.93; N, 4.03. Found: C, 72.82; H, 5.06; N, 4.02.

The Photocyclization of the Benzo[b]thiophene Enamide 6 under Degassed Conditions.

A solution of the benzo[b]thiophene enamide **6** (2.00 g., 5.48 mmoles) was dissolved in 600 ml. of Burdick and Jackson pure dioxan and placed in a 650 ml. Pyrex irradiation vessel equipped with a high vacuum stopcock. After freezing, the vessel was evacuated using a vacuum pump and then the dioxane solution was allowed to melt. The freeze-thaw cycle was repeated three more times to complete degassing. The resultant solution was stirred magnetically while being irradiated in a Rayonet Preparative Photo reactor with eight 3000Å lamps for 64 hours. After the vacuum was broken, the dioxane was immediately evaporated and the residue crystallized from ether-petroleum ether to yield 450 mg (1.23 mmoles, 22%) of the benzothiophene-8-oxoberbine **7**, m.p. 166-168°; ir 1670 cm^{-1}, 1620, 1520; uv: 220 nm (end, ϵ, 35,000), 241 (min, 18,500), 254 (19,000), 292 (min, 8750), 310 (9000); nmr: δ 7.22 (m, 4H), 7.03 (s, 1H), 6.65 (s, 1H), 5.40 (d, J = 3.5 Hz, 1H), 4.78 (d, J = 9 Hz, 1H), 4.43 (dd, J = 9, 3.5 Hz, 1H), 4.00 (t, 2H), 3.88 (s, 6H), 2.82 (t, 2H).

Anal. Calcd. for C$_{21}$H$_{19}$NO$_3$S: C, 69.02; H, 5.24; N, 3.83. Found: C, 69.00; H, 5.47; N, 4.09.

Irradiation of the Benzo[b]thiophene Enamide 6 under Non-degassed Conditions.

A solution of 2.00 g. (5.48 mmoles) of enamide **6** in 600 ml. of benzene was irradiated under nitrogen with a 450 watt medium pressure mercury arc for 32.5 hours. The line nitrogen used was subsequently shown to contain traces of oxygen. The residue after evaporation of solvent was chromatographed on 200 g. of silica to yield 650 mg. (1.8 mmoles, 33%) of product with 1:1 ethyl acetate-petroleum ether. After recrystallization from ethyl acetate-petroleum ether, the benzo[b]thiophene-8-oxyprotoberberine **8** had, m.p. 239-240°; ir: 1655 cm^{-1}, 1620, 1595, 1520; uv: 220 nm (end, ϵ, 31,500), 236 (21,500), 246 (22,500), 259 (28,500), 268 (sh, 25,000), 275 (24,000), 300 (min, 7500), 313 (10,500), 325 (12,500), 336 (min, 7750), 352 (sh, 13,000), 367 (19,500), 377 (min, 16,000), 384 (17,5000); nmr: δ 7.83-8.25 (m, 2H), 7.40-7.58 (m, 2H), 7.33 (s, 1H), 7.27 (s, 1H), 6.78 (s, 1H), 4.43 (t, 2H), 4.02 (s, 3H), 3.95 (s, 3H), 2.95 (t, 2H).

Anal. Calcd. for C$_{21}$H$_{17}$NO$_3$S: C, 69.40; H, 4.72; H, 3.85. Found: C, 69.35; H, 4.74; N, 3.71.

Photocyclization of the Coumarin Enamide 7.

The enamide **9**, 1.00 g. (2.65 mmoles), was dissolved in 195 ml. of ethyl acetate by refluxing and then irradiated under argon with a 450 watt mercury arc (Pyrex filter) for 0.5 hours. The

irradiation solution was condensed to a small volume and then diluted to approximately 100 ml. with ether. After filtering from some non-descript precipitate, petroleum ether was added and the ether evaporated to give 650 mg. (1.72 mmoles, 65%) of the coumarin-8-oxoberbine **10** as a pale yellow solid, m.p. 158-162°; ir: 1750 cm^{-1}, 1705, 1615, 1590, 1520; uv: 220 nm (end, ϵ, 25,000), 263 (min, 4500), 282.5 (7000), 310 (2250); nmr: δ 7.42 (m, 1H), 6.58-7.30 (m, 5H), 3.90 (s, 3H), 3.83 (s, 3H), 2.50-4.67 (m, 7H). The photoproduct **10** is either unstable in chloroform solution or undergoes slow conformational inversion as its spectrum changes slowly as a function of time. This point was not pursued.

Anal. Calcd. for C$_{22}$H$_{19}$NO$_5$: C, 70.01; H, 5.07; N, 3.71. Found: C, 69.83; H, 5.11; N, 3.50.

Dehydrogenation of the Benzocoumarin-8-oxoberbine 10.

The photoproduct **10**, 600 mg. (1.6 mmoles), was dissolved in 40 ml. of benzene and 500 mg. of recrystallized (benzene) 2,3-dichloro-5,6-dicyano-1,4-benzoquinone were added. There was instantaneous decolorization of the DDQ. The precipitated hydroquinone was filtered to give a light red solution. After evaporation of solvent, the residue was chromatographed on a short alumina column. After a 0.2 l. benzene forewash, the product was eluted with 2 l. of 1:1 ethyl acetate-benzene to yield a bright yellow solution with an intense fluorescin-like fluorescence. Bright yellow flakes of the benzocoumarin-8-oxyprotoberberine **11** formed as the solvent volume was reduced and yielded 154 mg, 0.41 mmol, 26%, m.p. 245-250°; ir: 1740 cm^{-1}, 1660, 1615 (sh), 1600, 1575, 1550, 1520; uv: 220 nm (end, 31,800), 239 (sh, 10,000), 253 (9200): 273 (min, 6500), 293 (10,500), 310 (10,750), 388 (sh, 14,000), 409 (23,000), 422 (min, 20,500), 430 (22,000); nmr: δ 9.28 (m, Δw 1/2 = 13 Hz, 1H), 7.37 (m, 5H), 6.73 (s, 1H), 4.42 (t, 2H), 4.02 (s, 3H), 3.95 (s, 3H), 2.98 (t, 2H).

Anal. Calcd. for C$_{22}$H$_{17}$NO$_5$: C, 70.39; H, 4.57; N, 3.73. Found: C, 70.15; H, 4.73; N, 3.74.

Photocyclization and Dehydrogenation of the Nicotinoyl Enamide 12 under Degassed Conditions.

The nicotinoyl enamide **12**, 1.00 g. (3.23 mmoles), was dissolved in 400 ml. of dioxane and placed in a quartz irradiation vessel and degassed in the same manner as described for the benzothiophene enamide **6**. The solution was irradiated for 20 hours in a Rayonet Preparative Photoreactor with eight 3000 Å lamps. Tlc indicated the presence of a new product and heavy streaking on the plate (silica, 1:9 methanol-chloroform) also indicated the presence of a substantial amount of photo-degradation. After the solvent was removed, the residue was dissolved in the minimum amount of methylene chloride and ethyl acetate was added and the red orange precipitate collected tlc indicated that this was non-descript degradation material and it was discarded. Addition of ether formed more of this material and it was also discarded. Upon adding petroleum ether, an almost colorless precipitate (365 mg.) formed which tlc indicated contained the photoproduct. This material was subjected to preparative tlc on a 2 mm Merck Silica plate using 1:9 methanol-chloroform as the developer. The appropriate highly fluorescent band was extracted with hot chloroform. After removal of the chloroform, the residue was dissolved in a little ethyl acetate and petroleum ether was added to cloudiness and upon scratching 138 mg. (0.45 mmoles, 14%) of the yellow 10-aza-8-oxyprotoberberine **13** crystallized, m.p. 169-172°; ir: 1655 cm^{-1}, 1605, 1530, 1510; uv: 220 nm (end, ϵ, 27,000), 240 (16,000), 257 (sh, 11,500), 280 (sh, 5250), 290 (min,

3750), 365 (24,500), 366 (21,500), 415 (2250); nmr: δ 9.58 (d, J = 1.5 Hz, 1H), 8.63 (dd, J = 5.5, 1.5 Hz, 1H), 7.35 (d, J = 5.5 Hz, 1H), 7.30 (s, 1H), 6.81 (s, 2H), 4.53 (t, 2H), 3.98 (s, 3H), 3.93 (s, 3H), 2.97 (t, 2H).

Anal. Calcd. for $C_{18}H_{16}N_2O_3$: C, 70.11; H, 5.23; N, 9.09. Found: C, 70.45; H, 4.99; N, 8.79.

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