appears to have a considerable degree of conformational freedom with significant populations of more than one rotamer about each bond.

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Registry No. II, 75415-32-6; III, 83831-83-8; IV, 72297-11-1; V, 72345-92-7; VI, 72297-14-4; VIIA, 83861-12-5; VIIB, 83861-13-6; VIIC, 80559-09-7; VIID, 76322-44-6; VIII, 81026-46-2; IX, 73836-78-9.

Synthesis and Photooxidation of the Condensation Products of Tryptamine and Catechol Derivatives. An Approach to the Synthesis of a Probable Precursor of Koumine

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Two tryptamine–catechol derivative condensation products, 1,3,5,6,14,21-hexahydro-17,18-dihydroxybenz-[*g*]indolo[2,3-*a*]quinolizine (**2**) and 3-ethoxy-3,4-seco-*N*-methyl-1,3,5,6,14,21-hexahydro-17,18-dihydroxybenz-[*g*]indolo[2,3-*a*]quinolizine (**5**), as intermediates for the probable precursor **11** of the *Gelsemium* alkaloid koumine have been synthesized, and the catechol rings of these compounds were successfully cleaved by photosensitized oxidation in which the two muconic acid derivatives **7** and **8** have been obtained. Compound **8** may be regarded as a precursor of **11**.

Koumine, the principal alkaloid of *Gelsemium elegans* Benth, was first isolated by Chao in 1931,[1] and its complete structure has been established by our group recently.[2]

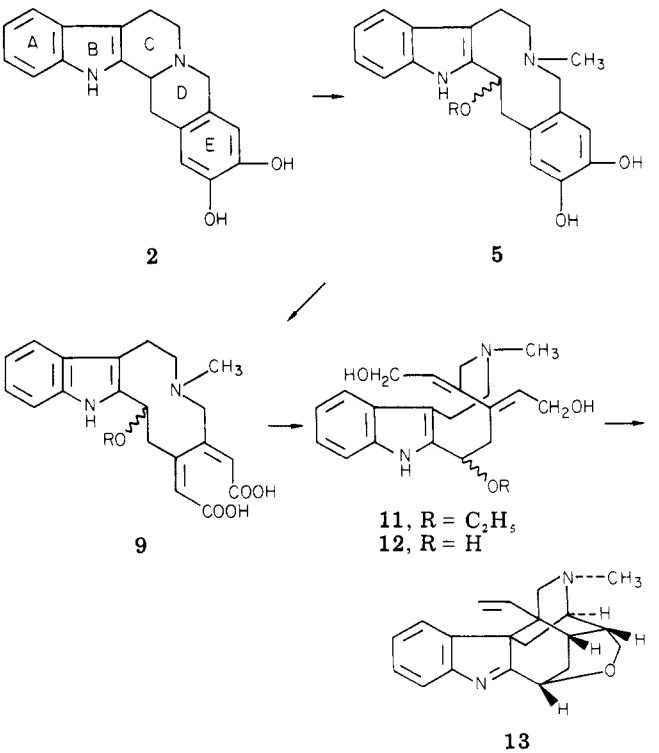
The first stage of our approach to the synthesis of koumine **13** is based on Woodward's biogenetic hypothesis[3] of strychnine. Although this hypothesis is not consistent with the current biogenetic theory of indole alkaloids,[4] the total synthesis of strychnine,[5] which was designed according to this biogenetic hypothesis, has been accomplished successfully. It is interesting that the cleavage of the catechol ring by oxidation affords a product similar in structure to the tryptamine secologanine condensation derivatives (cf. **5**–**12**, Scheme I).

The first stage of our approach is the synthesis of compound **2** and the opening of the C–D ring fusion to give **5**. Photooxidation of **5** would provide the fission products **9**, which could eventually lead to **12**, a possible key precursor of koumine.

Compound **2** (Scheme II) was synthesized from tryptamine and 3,4-dihydroxyphenylpyruvic acid, according to the procedure of Harley-Mason.[6] The substituted pyruvic acid in turn was synthesized from vanillin and acetylglycine.[7,8]

Harley-Mason believed that the condensation in the Mannich reaction (**1** to **2**) took place between N_4 and C_{20}. This was based on comparison of compound **2** with some relevant known structures. However, there had been an earlier report that the site of condensation, i.e., the cyclization of rings C and E, might be between N_4 and C_{16}.[9] We are now able to show that the condensation has unambiguously taken place between N_4 and C_{20} instead of

Scheme I



(1) T. Q. Chao, *Chung-kuo Sheng Li Hsueh Tsa Chih*, **5**, 345 (1931).
(2) C. T. Liu, Q. W. Wang, and C. H. Wang, *J. Am. Chem. Soc.*, **103**, 4634 (1981).
(3) R. B. Woodward, Nature (*London*), **152**, 155 (1948).
(4) A. I. Scott, *Acc. Chem. Res.*, **3**, 151 (1970).
(5) R. B. Woodward, M. P. Cava, W. D. Ollis, A. Hunger, H. U. Daeniker, and K. Shenker, *J. Am. Chem. Soc.*, **76**, 4749 (1954); *Tetrahedron*, **19**, 247 (1963).
(6) J. Harley-Mason and W. R. Waterfield, *Tetrahedron*, **19**, 65 (1963).
(7) R. G. Lange, *J. Org. Chem.*, **27**, 2037 (1962).
(8) R. H. Charles and S. R. Sydney, *Biochem. J.*, 1029 (1931).
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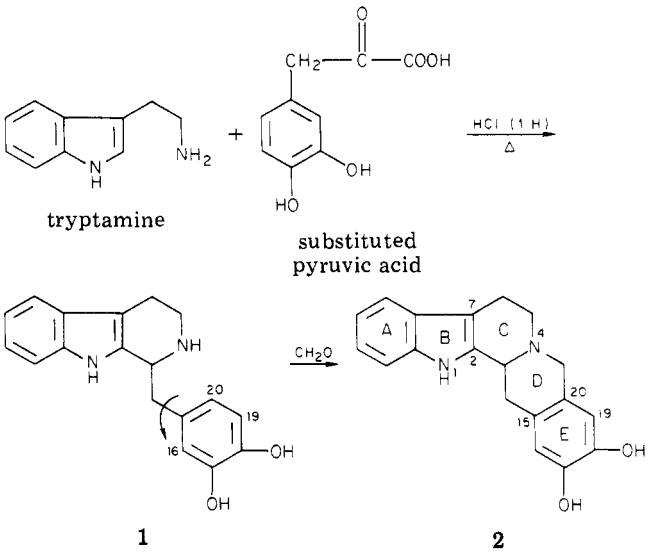
0022-3263/83/1948-0044$01.50/0

Scheme II



N_4 and C_{16}, because in the ^1H NMR spectrum of compound **2** (in CF_3COOH) two singlets are found at δ 6.39 and 6.49, which should be assigned to C_{16} and C_{19}. We have also improved the yield of the Mannich reaction to 95% (lit.[6] 54%), mainly by controlling the purity of the starting material, the reaction temperature, and the pH of the reaction mixture.

Since the 1960s, new methods for cleaving the C–D rings of the indole alkaloids and their analogues have been developed.[10] In our practice, the C–D ring of compound **2** was opened by isopropyl chloroformate in chloroform–ethanol solution, following the procedure of Sakai[11] in which the N_4-isopropoxycarbonyl and an ethoxy group are introduced at the appropriate sites of compound **2** to form product **3** (Scheme III). Furthermore, it appears to be an advantage to use this procedure since the active phenol groups of the catechol ring are protected by isopropoxycarbonyl groups, and in the next step, these protecting groups can be removed when compound **3** is reduced with $LiAlH_4$ to form the *N*-methyl derivative. During the opening of the C–D ring, byproduct **4** is also obtained in about 5–10% yield. When a heterogeneous solvent system (chloroform–water) is used to replace the chloroform–ethanol, the elimination product **4** predominates.

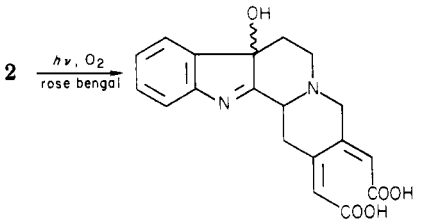
The UV spectrum of compound **4** shows a larger conjugated system than does compound **3**. In the ^1H NMR spectrum of compound **4**, two doublets (J = 14 Hz) were found at δ 4.84 and 5.02, which would infer the presence of two transvinyl protons formed in the elimination reaction. In the mass spectra, the difference between M^+ of **3** (*m/e* 610) and M^+ of **4** (*m/e* 564) is 46.

Compound **3** was reduced by $LiAlH_4$ in THF to form compound **5** in 38.8% yield. Because phenolic carbonates are usually reduced more easily than urethanes, byproduct **6**, containing the catechol ring, and simultaneously an unreduced N_4-isopropoxycarbonyl group was obtained. This was separated from compound **5**, which is soluble in hot dilute hydrochloric acid solution. In the IR spectrum of compound **5** all the carbonyl absorption bands have disappeared, whereas in compound **6**, the urethane absorption band at 1650 cm^{-1} is still seen.

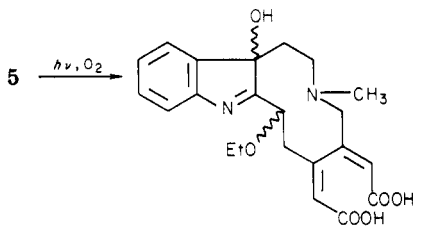
The cleavage of the catechol ring was accomplished by photosensitized oxidation. According to the literature[12] the tryptamine system is easily converted to the corresponding dicarbonyl compounds upon photooxidation. The key problem appears to be how to avoid the cleavage of the C_2–C_7 double bond of the enamine system. On the other hand, successful examples of the photooxidation cleavage of the catechol ring in the literature are very rare—to our knowledge Matsuura's work[13] seems to be the only successful one, and the yield is rather poor (only 24%).

In our experience, compounds **2** and **5** in methanol–pyridine solution under illumination by a high-pressure mercury lamp afforded compound **7** and **8** in better yields. These compounds are water-soluble organic salts, which indicates that they are betaine-type compounds. This conclusion is consistent with their IR spectra.

When compounds **2** and **5** were converted to compounds **7** and **8**, their catechol chromophores disappeared.



7



8

Therefore, the pseudoindole chromophores that appear at λ_{max} 254 nm in compound **7** and at λ_{sh} 260 nm in compound **8** can be seen clearly. In the mass spectra of compounds **7** and **8**, the M^+ of compound **7** is at *m/e* 354, and the $(M - 1)^+$ of compound **8** is at *m/e* 413, which established that three oxygen atoms had been incorporated into compounds **2** and **5**, respectively. In the mass spectrum (CI) of compound **8** were exhibited the following characteristic fragment ions: *m/e* 398 $(M - CH_3 - H)^+$, *m/e* 381 (base peak, $M - CH_3 - OH - H)^+$, *m/e* 369 $(M - CH_3 - C_2H_5 - H)^+$, *m/e* 347 $(M - CH_3 - 3OH - H)^+$, *m/e* 298 $(M - 2CH{=}COOH)^+$, all of which are consistent with the proposed structure.

According to Nakagawa's point of view,[12] the photooxidation mechanism of the tryptamine system might be as shown in Scheme IV.

It was reported that type-f compound was usually formed, but in nonpolar solvents and in the presence of reducing agents, type-d compounds also resulted. However, it appears interesting that we have not isolated any type-f compound in polar solvents and without the addition of any reducing agent. Moreover, the type-C hydroperoxide compound has never been found throughout the oxidation process. Our explanation is that as soon as the

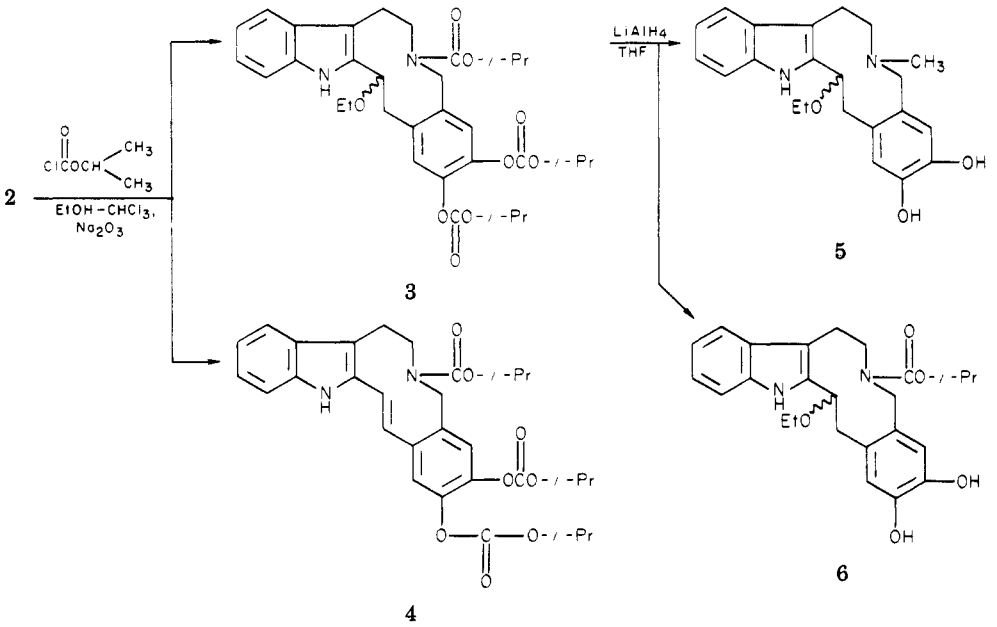
(10) (a) L. T. Dolby and S. Sakai, *J. Am. Chem. Soc.*, **86**, 1890 (1964); **86**, 5362 (1964); (b) G. H. Foster, J. Harley-Mason, and W. R. Waterfield, *Chem. Commun.*, 21 (1967); (c) J. D. Albright and L. Golman, *J. Am. Chem. Soc.*, **91**, 4317 (1969).

(11) (a) S. Sakai, A. Kubo, K. Katano, N. Shinma, and K. Sasago, *Yakugaku Zasshi*, **93**, 1165 (1973); (b) S. Sakai, I. Yamanaka, and Lloyd J. Dolby, Ibid., **97**, 309 (1977).

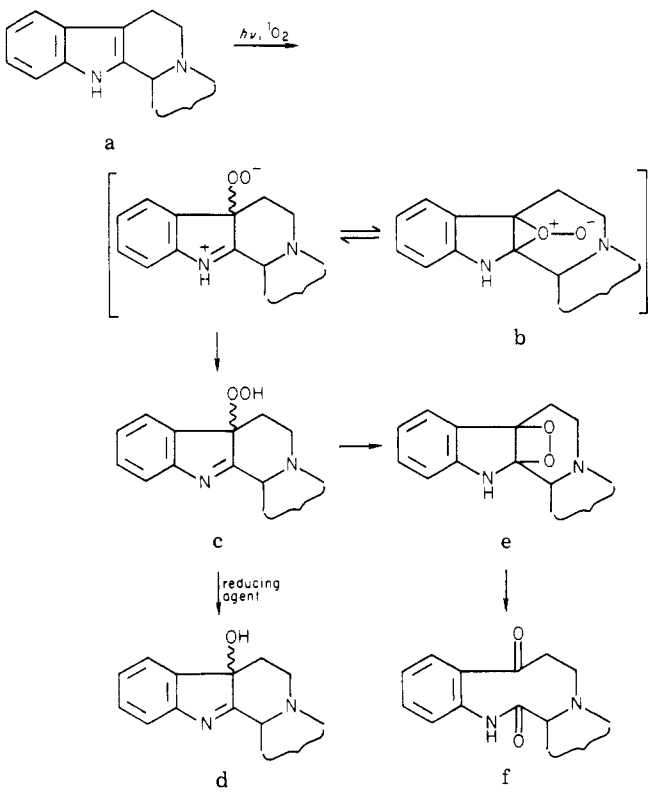
(12) M. Nakagawa, H. Okajima, and T. Hino, *J. Am. Chem. Soc.*, **99**, 4424 (1977).

(13) T. Matsuura, H. Matsushima, S. Kato, and I. Saito, *Tetrahedron*, **28**, 5119 (1972).

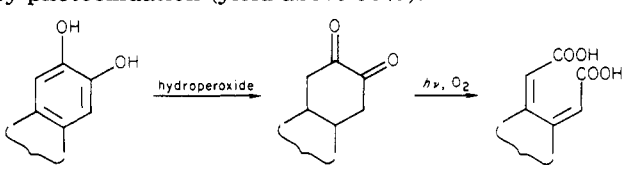
Scheme III



Scheme IV

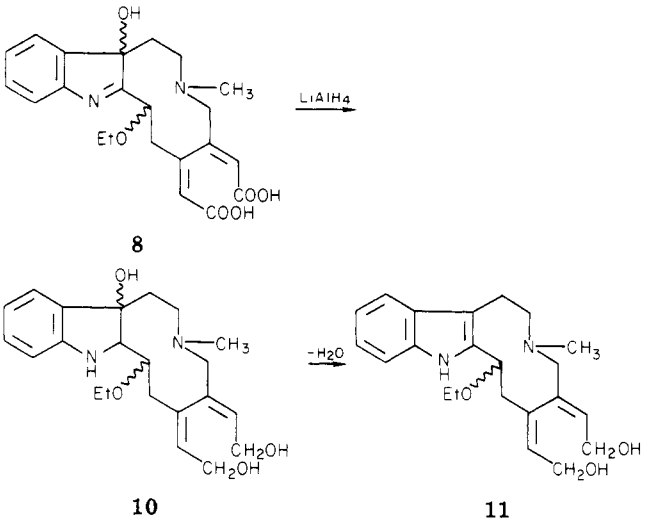


type-c compound is formed, it is immediately reduced by the catechol system to form the more stable type-d compound, whereas the *o*-hydroquinone system is oxidized to *o*-quinone, which is known to form muconic acid readily by photooxidation (yield above 50%).[14]



(14) G. E. Gream, J. C. Paice, and C. C. R. Ramsay, *Aust. J. Chem.*, **22**, 1229 (1969).

Scheme V



The further conversion of 8 to 11 and 12 (Scheme V), possible precursors of koumine, is being explored by reduction with $LiAlH_4$ followed by dehydration.

Experimental Section

3-(3,4-Dihydroxybenzyl)-3,4,5,6-tetrahydrocarboline (1). The hydrochloride of tryptamine (15 g, 76.3 mmol) and 3,4-dihydroxyphenylpyruvic acid (15 g, 76.5 mmol) were dissolved in 1200 mL of water and refluxed under a nitrogen atmosphere for 12 h. The solution was concentrated by evaporation to 300 mL and was allowed to stand overnight. The crystalline carboline hydrochloride was filtered. The filtrate was further concentrated to give more product. The combined crude product (21 g) was recrystallized from HCl-acidified ethanol (pH 5–6) to give 15.3 g (71%) of hydrochloride of compound 1 as colorless prisms: mp 230–231 °C (lit.[6] mp 226–227 °C); IR (Nujol), no carbonyl absorption bands.

Anal. Calcd for $C_{18}H_{19}N_2O_2Cl$: C, 65.35; H, 5.79; N, 8.47. Found: C, 64.90; H, 5.95; N, 8.62.

1,3,5,6,14,21-Hexahydro-17,18-dihydroxybenz[*g*]indolo-[2,3-*a*]quinolizine (2). Hydrochloride of compound 1 (3 g, 9.80 mmol) was dissolved in distilled water, hydrochloric acid was added to adjust the pH to 5–6, and then 12 mL of formalin (38–40%) was added. The solution was allowed to stand for 3 days at room temperature. Then the resulting pale yellow prisms

were collected and recrystallized from methanol to give 3.1 g (95%) of hydrochloride of compound **2** as colorless prisms, mp 282–283 °C.

Anal. Calcd for $C_{19}H_{19}N_2O_2Cl$: C, 66.56; H, 5.59; N, 8.19. Found: C, 66.64; H, 5.97; N, 7.85.

The hydrochloride of compound **2** (80 mg) was dissolved in boiling water (10 mL), the solution was cooled to 50 °C, and slight excess of ammonia was added. The liberated brown, free base was collected and recrystallized from ethanol to give compound **2** as yellow leaflets: mp 245–246 °C; UV, λ_{max}^{EtOH} 270–290 nm, λ_{min} 245; mass spectrum, m/e 306 (M^+); ^1H NMR (CF_3COOH) δ 0.9–4.13 (9 H, protons of saturated carbons), 6.39 and 6.49 (2 H, s, Ar H of ring E), 6.7–7.1 (4 H, m, Ar H of ring A).

3-Ethoxy-3,4-seco-4-(isopropoxycarbonyl)-1,3,5,6,14,21-hexahydro-17,18-bis(isopropoxycarboxy)benz[*g*]indolo[2,3-*a*]quinolizine (3). Hydrochloride of compound **2** (3.4 g, 9.93 mmol) and baked anhydrous sodium carbonate (8.5 g) were added to 200 mL of chloroform (containing 1% ethanol), and isopropyl chloroformate (5.5 g) was added dropwise to the mixture. After the reaction mixture had been stirred at room temperature for 5 h, 1.5 mL of ethanol was added. After 42 h, when the organic suspension had gradually dissolved in the solvent, 2 g of isopropyl chloroformate was added; after another 1 h, 1.5 mL of ethanol was also added, and the reaction was allowed to continue for another 4 h. The suspended inorganic solid was removed, and the organic solution was washed with 1 N HCl and then with water. After the solution had been dried over Na_2SO_4, it was concentrated to give a pale yellow solid. TLC showed two spots: A, R_f 0.55; B, R_f 0.6 (silica plate, 2:1 cyclohexane–ethyl acetate). Column chromatography of the crude product (1 g; 40 g of neutral alumina, 8:1 benzene–ethyl acetate) gave 50 mg of compound **4** (corresponding to spot B) and 800 mg (75%) of compound **3** (corresponding to spot A). Compound **3** was obtained as pale yellow crystals: mp 143–145 °C; UV λ_{max}^{EtOH} 265–278 nm, λ_{min} 255; IR ($CHCl_3$) 1770, 1740, 1680 cm^{-1} (C(O)O, C(O)N); mass spectrum (rel intensity), 610 (35.4 M^+), 478 (22.5), 464 (17.9), 449 (5.7), 435 (11.8), 418 (14.9), 391 (16.1); ^1H NMR (CCl_4) δ 1.38 (18 H, d, protons of isopropyl), 7.0–7.4 (6 H, m, Ar H).

Anal. Calcd for $C_{33}H_{42}N_2O_9$: C, 64.90; H, 6.92; N, 4.59. Found: C, 65.14; H, 7.08; N, 3.89.

3,4-Seco-4-(isopropoxycarbonyl)-1,5,6,21-tetrahydro-17,18-bis(isopropoxycarboxy)benz[*g*]indolo[2,3-*a*]quinolizine (4). The hydrochloride of compound **2** (342 mg, 1.0 mmol), sodium carbonate (850 mg), and water (9 mL) were added to pure chloroform (32 mL). A chloroform solution (4 mL) containing 0.3 g of isopropyl chloroformate was added dropwise with stirring. After the mixture stirred for 3 h at room temperature, the same quantity of isopropyl chloroformate was added again. The mixture was then allowed to stir overnight. The inorganic substance was filtered off, and the chloroform solution was washed successively with 2 N NaOH, 2 N HCl, and H_2O. After the solution was dried, it was concentrated to give a pale yellow solid. Column chromatography (50 g of neutral alumina, 3:1 benzene–chloroform) gave 400 mg of compound **4** as pale yellow crystals: mp 138–140 °C; UV λ_{max}^{EtOH} 320 nm, λ_{sh} 272, λ_{min} 305; mass spectrum (rel. intensity), 564 (151.9, M^+), 477 (122.9), 449 (55.0), 435 (45.4), 419 (34.4), 391 (70.2); ^1H NMR ($CDCl_3$) δ 1.37 (18 H, d, protons of isopropyls), 4.89, 5.02 (2 H, d, J = 14 Hz, *trans*-$H_2C{=}CH_2$), 7.1–7.45 (6 H, m, Ar H).

3-Ethoxy-4-methyl-3,4-seco-1,3,5,6,14,21-hexahydro-17,18-dihydroxybenz[*g*]indolo[2,3-*a*]quinolizine (5). Anhydrous THF (100 mL) was placed in a 250-mL three-necked, round-bottom flask equipped with a mechanical stirrer and a condenser on which a drying tube was fitted. $LiAlH_4$ (1.1 g) was added cautiously. Anhydrous THF (10 mL) solution containing 1.1 g (1.80 mmol) of compound **3** was placed into a dropping funnel that was fitted on another opening of the flask. The tetrahydrofuran solution was refluxed and stirred vigorously. The solution in the funnel was added dropwise over a period of about 1 h at a rate to keep the bright yellow-green of the reaction mixture (rapid addition would cause precipitation and transform the color to dark gray-green). After reflux for 6 h, the reaction mixture was cooled, and 5 g of potassium sodium tartrate was added. The mixture was stirred for about 2 h until the bubbling stopped. The solid precipitate was filtered off and added to 100 mL of boiling 1 N hydrochloric acid (containing 1 g of Na_2SO_3). The insoluble material was filtered off, and the filtrate was allowed to stand for crystallization. Recrystallization from methanolic hydrogen chloride (pH 5–6) gave 280 mg (38.75%) of the hydrochloride of compound **5** as colorless prisms; mp 202–204 °C. For analysis, some of the hydrochloride was dissolved in methanol, and the free base was liberated by adding a slight excess of ammonia. Collection of the free base by filtration gave **5** as pale yellow crystals, mp 245–247 °C; paper chromatography showed one spot, R_f 0.9 (12:5:3 butanol–water–acetic acid); IR (Nujol) 3310, 3260 cm^{-1} (OH), no carbonyl absorption; UV (EtOH, HCl) λ_{max} 270–284 nm, λ_{min} 247; mass spectrum (rel. intensity), 365 (1.2, $M^+ - 1$), 364 (1.3), 278 (100), 223 (739); ^1H NMR (CD_3OD) δ 2.87 (3 H, s, NCH_3), 3.35 (2 H q, OCH_2CH_3), 6.75–7.5 (6 H, Ar H).

3,5,6,7,14,21-Hexahydro-7-hydroxypseudoindolo[2,3-*a*]-quinolizine(15,20)muconic Acid (7). The hydrochloride of compound **2** (250 mg, 0.73 mmol) and rose bengal (5 mg) were dissolved in a mixture of 25 mL of pyridine and 50 mL of methanol. This solution was placed into an immersion apparatus for solution-phase photochemistry and illuminated by a high-pressure mercury lamp (250 W) for 5 h, while oxygen was bubbled in from a cylinder. After removal of solvent in vacuo at room temperature and dissolution of the residue by addition of 5 mL of cold 1 N NaOH, the insoluble material was filtered off. Acidifying the filtrate with 1 N HCl led to a precipitate, which crystallized from methanol to give 110 mg (42.3%) of yellow crystalline compound **7**: mp 265–270 °C dec; paper chromatography of its hydrochloride showed one spot, R_f 0.45 (3:5:12 acetic acid–water–butanol); UV (EtOH, HCl) λ_{max} (lg ϵ) 254 nm (4.11), 308 (3.97); IR (KCl) 3350 cm^{-1} (br, OH), 1630, 1560 (C(O)OH); mass spectrum (rel. intensity), 354 (8.1, M^+), 219 (48.9), 168 (19.0), 149 (46.1), 109(54.3), 79 (100); ^1H NMR (Me_2SO-d_6) δ 4.83 (1 H, s, D_2O exchangeable, OH), 7.1–7.6 (6 H, m, Ar and vinyl H), 8.24–8.52 (2 H, br 2-COOH).

Anal. Calcd for $C_{19}H_{18}N_2O_5$: C, 64.44; H, 5.12; N, 7.90. Found: C, 64.42; H, 5.36; N, 7.43.

3-Ethoxy-3,4-seco-3,5,6,7,14,21-hexahydro-7-hydroxypseudoindolo[2,3-*a*]quinolizine(15,20)muconic Acid (8). The hydrochloride of compound **5** (250 mg, 0.62 mmol) was dissolved in a mixture of 50 mL of pyridine and 50 mL of methanol, and this solution was placed into a photochemical reactor and illuminated by a high-pressure mercury lamp (250 W) for 9 h, while oxygen was bubbled in from a cylinder. After removal of solvent in vacuo at room temperature and dissolution of the residue by addition of 5 mL of 1 N NaOH, the insoluble material was filtered off. Acidifying the filtrate with 1 N HCl led to a precipitate, which crystallized from methanol to give 85 mg (34%) of yellow crystalline compound **8**: mp 275–280 °C dec; paper chromatography of its hydrochloride showed one spot, R_f 0.5 (3:5:12 acetic acid–water–butanol); UV (EtOH, HCl) λ_{sh} (lg ϵ) 260 nm (4.11), 290 (3.94); IR (KCl) 1640, 1550 (C=O), 2500–3700 (br, peak at 3400, OH, COOH); mass spectrum (CI) (rel. intensity), 413 (20.9, $M^+ - 1$), 381 (100), 359 (29.7), 347 (25.72), 332 (25.51), 319 (10.06), 298 (20.06), 285 (26.12), 279 (19.35), 265 (8.51), 257 (40.36); ^1H NMR (Me_2SO-d_6) δ 4.42 (1 H, s, D_2O exchangeable, OH), 8.25–8.52 (2 H, br, 2-COOH).

Anal. Calcd for $C_{22}H_{26}N_2O_6$: C, 63.75; H, 6.33; N, 6.76. Found: C, 63.87; H, 6.48; N, 7.17.

Registry No. (±)-**1**·HCl, 83705-22-0; (±)-**2**, 82596-13-2; (±)-**2**·HCl, 83705-23-1; (±)-**3**, 83705-24-2; (*E*)-**4**, 83705-25-3; (±)-**5**, 83705-26-4; (±)-**5**·HCl, 83705-27-5; **7**, 82596-14-3; **7**·HCl, 83730-45-4; **8**, 82596-16-5; **8**·HCl, 83705-28-6; (±)-**11**, 83705-29-7; (3,4-dihydroxyphenyl)pyruvic acid, 4228-66-4; tryptamine hydrochloride, 343-94-2; isopropyl chloroformate, 108-23-6.