dissolved cation radicals under the conditions of the metal-ion oxidation[3] or the electrochemical oxidation[2] to exhibit proton loss to the preemptive exclusion of rearrangement.

The relationship between the dissolved and gaseous state in the toluene and cycloheptatriene cation radical system stands in contrast to aliphatic ketone cation radicals where McLafferty rearrangement occurs in both states.[20,21] In the latter case, the hydrogen-transfer portion of the overall rearrangement bears a small energy of activation and the charge is localized on oxygen with no stabilization route accessible by proton loss. Interestingly though, after γ-hydrogen transfer of hydrogen to oxygen does open a route to stabilization via proton loss, only the dissolved intermediate can act as a Brønstead acid, thereby avoiding the carbon–carbon bond cleavage encountered in the gaseous state.[21]

Cation radicals are an interesting and increasingly important type of species.[4-6,22] The present work suggests that Brønstead acidity is an important characteristic in evaluating the correspondence between the chemistry in solution and the many observations made on cation radicals in mass spectrometric experiments in the gaseous state.

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Registry No. Toluene cation radical, 34504-47-7; cycloheptatriene cation radical, 34488-67-0.

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Notes

Total Synthesis of (±)-Corydalic Acid Methyl Ester

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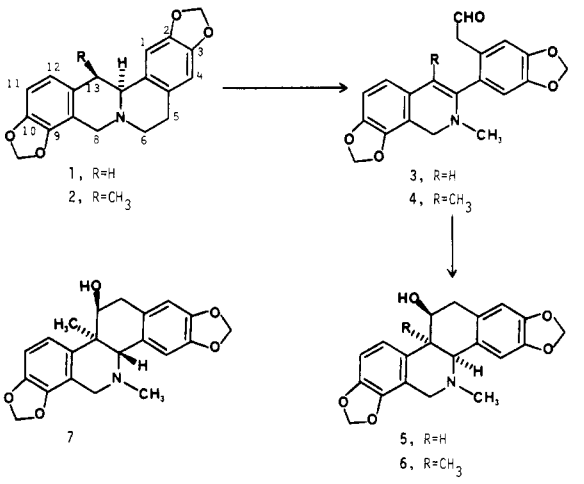
The suggestion that the benzophenanthridine alkaloids [e.g., chelidonine (**5**), corynoline (**6**), and 14-epicorynoline (**7**)] are derived biosynthetically from the tetrahydroprotoberberines [e.g., stylopine (**1**) and tetrahydrocorysamine (**2**)] by an oxidative cleavage of the C-6 to N-7 bond, followed by the joining of C-6 to C-13,[1] has been confirmed experimentally by Leete,[2-4] Battersby,[5-8] Takao,[9,10] Nonaka,[11] and their co-workers. The *B*-seco-protoberberine alkaloid corydalic acid methyl ester (**15**), which has been isolated from *Corydalis incisa*,[12] is presumably derived from the hypothetical intermediate **4**

Scheme I



(Scheme I) in this conversion. However, the exact sequence of intermediates involved in the biosynthetic conversion of the tetrahydroprotoberberines to the benzophenanthridine alkaloids remains unclear. The development of methodology that would allow the synthetic incorporation of isotopes into a variety of molecules related to the hypothetical intermediate enamines **3** and **4** could eventually provide labeled compounds for tracer experiments and therefore be valuable for our understanding of exactly how this biosynthetic conversion occurs. With this general problem in mind, the first total synthesis of corydalic acid methyl ester (**15**) has been devised and executed as reported herein (Scheme II). The uncertainty at the outset of this work mainly concerned the stereochemical outcome of the initial condensation reaction of compounds **8** and **9** as well as the stereochemistry of the thermal decarboxylation of the intermediate carboxylic acids **10** and **11**.

The condensation of the anhydride **8** with the Schiff base **9** in acetonitrile at room temperature led to a 1:2

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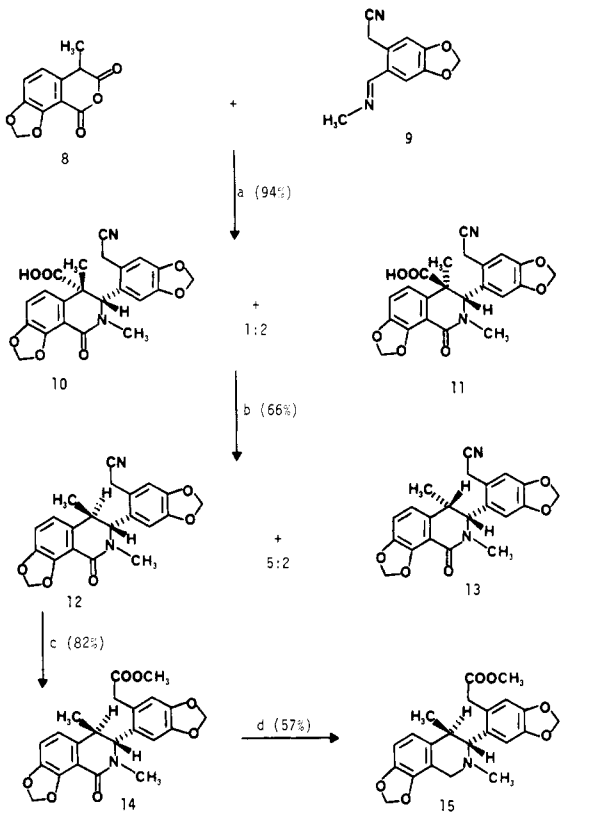
Scheme II



[a]CH_3CN, 23 °C (1.5 h). [b]DMSO, 160 °C (0.5 h). [c]HCl, CH_3OH, 0 °C (12 h). [d](1) $POCl_3$, 60 °C (3 h); (2) $NaBH_4$, EtOH, glyme (12 h).

mixture of diastereomeric isoquinolones **10** and **11** as estimated by NMR integrations.[13] These isomers were readily separated by chromatographic techniques. The ^1H NMR spectrum (CF_3COOD) of the minor isomer displayed a *C*-methyl singlet at δ 1.97, whereas that of the major diastereomer appeared at δ 1.61. The methyl group at C-4 is expected to be shielded by a vicinal cis C-3 phenyl substituent.[13] The major product may therefore be assigned structure **11**, while the minor component of the mixture is represented by structure **10**.

The thermal decarboxylation of **10** and **11** in Me_2SO[14] was studied in some detail. It was found that the same 5:2 mixture of products **12** and **13**, as judged from NMR integrations, was formed regardless of whether pure **10**, pure **11**, or the 1:2 mixture of **10** and **11** obtained in the original condensation was employed as the starting material. The 1:2 mixture of **10** and **11** was, therefore, utilized in the synthesis. Products **12** and **13** were separated and found not to equilibrate under the decarboxylation reaction conditions. The C-4 methyl group of the major component of the mixture obtained after decarboxylation appeared as a doublet at δ 1.45 in its ^1H NMR spectrum, while that of the minor isomer produced a doublet at δ 1.12. The major diastereomer was therefore assigned the desired trans relative configuration **12** present in the natural product **15**. Treatment of the nitrile **12** with methanol and acid yielded the methyl ester **14**.

The final step in the synthesis involved the selective reduction of the lactam functionality of **14** in the presence of the methyl ester. Although several reagents including diborane[15] and triethyloxonium tetrafluoroborate followed by sodium borohydride[16] were tried, the best results were obtained when compound **14** was subjected to phosphorus oxychloride followed by sodium borohydride.[17] The 80-MHz ^1H NMR spectrum of the synthetic material was identical with that of an authentic sample of natural (+)-corydalic acid methyl ester.[18] The two substances also cochromatographed in four different thin-layer chromatography systems.

This approach to the synthesis of the natural product **15** is presently being modified in order to prepare labeled compounds related to the hypothetical intermediate **4** in the biosynthetic conversion of certain protoberberines to benzophenanthridine alkaloids.

Experimental Section

All reactions were performed under a nitrogen atmosphere. Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. NMR spectra were recorded on a Varian FT-80 80-MHz spectrometer using $CDCl_3$ solvent, except where noted. Chemical shifts are reported in parts per million relative to Me_4Si as internal standard. IR spectra were recorded on a Beckman IR-33 spectrophotometer. Microanalyses were performed by the Purdue Microanalytical Laboratory. The mass spectra were determined on a Finnegan 4000 spectrometer using an ionization potential of 70 eV. The chemical ionization mass spectra (CIMS) were obtained by using isobutane or methane as the reagent gas. Organic extracts were dried with magnesium sulfate.

***N*-Methyl-*r*-3-(2-(cyanomethyl)-4,5-(methylenedioxy)-phenyl)-*c*-4-carboxy-*t*-4-methyl-7,8-(methylenedioxy)-3,4-dihydro-1(2*H*)-isoquinolone (10).** 3,4-(Methylenedioxy)-7-methylhomophthalic anhydride[13] (**8**, 5.99 g, 27.20 mmol) was added to a stirred solution of (2-(cyanomethyl)-4,5-(methylenedioxy)-benzylidene)methylamine[19] (**9**, 5.50 g, 27.20 mmol) in CH_3CN (180 mL). The solution was stirred at room temperature for 1.5 h before the solvent was evaporated. The residue was suspended in $CHCl_3$ (150 mL) and extracted with 5% aqueous $NaHCO_3$ (3 × 50 mL). The aqueous phase was washed with $CHCl_3$ (30 mL) and filtered. The filtrate was cooled in an ice bath and acidified (pH 1) with 2 N HCl. The white precipitate (10.44 g, 91%), mp 157–192 °C, was filtered. The filtered material from the first filtration was dissolved in water and the solution acidified to yield more of the product as a white solid (0.34 g, 3%) (mp 167–190 °C). A sample (1.36 g) of the solid, which consisted of a 1:2 mixture of **10** and **11**, was subjected to silica gel (60 g) column chromatography, eluting with a 1:1 mixture of EtOAc and $CHCl_3$. Concentration of the fractions containing the first diastereomer to elute from the column afforded compound **10**. The analytical sample was recrystallized from MeOH–benzene: 333 mg; mp 208–208.5 °C dec; IR (KBr) 3300–2500, 1735, 1630, 1480, 1250, 1230, 1030 cm^{-1}; NMR (CF_3COOD) δ 7.25 (s, 2 H), 7.00 (s, 1 H), 6.77 (s, 1 H), 6.32 (s, 2 H), 6.01 (s, 2 H), 5.23 (s, 1 H), 4.22 (d, 1 H, J = 18.4 Hz), 3.95 (d, 1 H, J = 18.4 Hz), 3.39 (s, 3 H), 1.97 (s, 3 H); CIMS, m/e (relative intensity) 379 ($MH^+ - CO_2$, 100).

***N*-Methyl-*r*-3-(2-(cyanomethyl)-4,5-(methylenedioxy)-phenyl)-*t*-4-carboxy-*c*-4-methyl-7,8-(methylenedioxy)-3,4-dihydro-1(2*H*)-isoquinolone (11).** Further elution of the above column with EtOAc and then a 4:1 mixture of EtOAc and MeOH yielded a 1:2 mixture (332 mg) of **10** and **11**, respectively, as white crystals, followed by pure **11**. Concentration of the fractions containing only isomer **11** yielded a white powder: 620 mg; mp 216–217 °C dec, IR (KBr) 2945, 1720, 1630, 1620, 1470, 1220, 1025 cm^{-1}; NMR (CF_3COOD) δ 7.26 (d, 1 H, J = 8 Hz), 7.11 (d, 1 H, J = 8 Hz), 7.02 (s, 1 H), 6.35 (s, 3 H), 5.97 (s, 2 H), 5.58 (s, 1 H), 4.11 (s, 2 H), 3.38 (s, 3 H), 1.61 (s, 3 H); CIMS, m/e (relative intensity) 379 ($MH^+ - CO_2$, 100).

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***trans*-*N*-Methyl-3-(2-(cyanomethyl)-4,5-(methylenedioxy)phenyl)-4-methyl-7,8-(methylenedioxy)-3,4-dihydro-1-(2*H*)-isoquinolone (12).** A 1:2 mixture of **10** and **11** (645 mg, 1.53 mmol) was dissolved in dry Me_2SO and heated at 160 °C for 0.5 h. The solvent was evaporated from the dark brown solution, and the resulting residue was dissolved in $CHCl_3$. The $CHCl_3$ was then evaporated from the filtered solution to give a brown oil, which was subjected to column chromatography over silica gel (60 g), eluting with 9:1 mixture of EtOAc and hexane, respectively. Evaporation of solvent from the fractions containing the first component eluted from the column afforded compound **12** (218 mg). The analytical sample was recrystallized twice from $CHCl_3$–Et_2O, which gave pale yellow crystals: mp 250–253 °C; IR ($CHCl_3$) 2940, 2890, 2240, 1635, 1590, 1475, 1365, 1070, 1020, 910 cm^{-1}; NMR δ 6.80 (s, 1 H), 6.78 (d, 1 H, J = 7.8 Hz), 6.42 (d, 1 H, J = 7.8 Hz), 6.37 (s, 1 H), 6.16 (d, 1 H, J = 1.2 Hz), 6.13 (d, 1 H, J = 1.3 Hz), 5.92 (d, 1 H, J = 1.3 Hz), 5.87 (d, 1 H, J = 1.3 Hz), 4.49 (d, 1 H, J = 1.6 Hz), 3.65 (s, 2 H), 3.02 (s, 3 H), 2.91 (d of q, 1 H, J = 1.6, 7.0 Hz), 1.45 (d, 3 H, J = 7.0 Hz); CIMS m/e (relative intensity) 379 (MH^+, 100).

Anal. Calcd for $C_{21}H_{18}N_2O_5 \cdot {}^1/_2H_2O$: C, 65.12; H, 4.91; N, 7.24. Found: C, 65.09; H, 4.65; N, 7.02.

***cis*-*N*-Methyl-3-(2-(cyanomethyl)-4,5-(methylenedioxy)phenyl)-4-methyl-7,8-(methylenedioxy)-3,4-dihydro-1-(2*H*)-isoquinolone (13).** Continued elution of the column above gave a 5:7 mixture of **12** and **13** (131 mg), respectively, followed by isomer **13**, which was isolated as a white solid after evaporation of solvent and recrystallization from $CHCl_3$–Et_2O: 33 mg, mp 241–244 °C; IR ($CHCl_3$) 2940, 2880, 2230, 1630, 1590, 1470, 1445, 1365, 1105, 1010, 910 cm^{-1}; NMR δ 6.85 (d, 1 H, J = 8.1 Hz), 6.78 (s, 1 H), 6.52 (d, 1 H, J = 8.1 Hz), 6.25 (s, 1 H), 6.14 (s, 2 H), 5.88 (s, 2 H), 4.65 (d, 1 H, J = 6.4 Hz), 4.00–3.41 (m, 3 H), 3.01 (s, 3 H), 1.12 (d, 3 H, J = 7.0 Hz); CIMS, m/e (relative intensity) 379 (MH^+, 100).

Anal. Calcd for $C_{21}H_{18}N_2O_5 \cdot {}^1/_2H_2O$: C, 65.12; H, 4.91; N, 7.24. Found: C, 64.72; H, 4.69; N, 7.12.

***trans*-*N*-Methyl-3-(2-((methoxycarbonyl)methyl)-4,5-(methylenedioxy)phenyl)-4-methyl-7,8-(methylenedioxy)-3,4-dihydro-1(2*H*)-isoquinolone (14).** Compound **12** (36 mg, 0.095 mmol) was suspended in MeOH (3 mL). Hydrogen chloride gas was passed through a $CaCl_2$ drying tube into the suspension, which was kept at a temperature of −40 °C to −20 °C for 1 h. The resulting clear solution was stored at 0 °C for 12 h. The solution was concentrated to half the original volume. The residue was stirred with H_2O (4 mL). The white precipitate was extracted into EtOAc (3 × 3 mL). The organic solution was washed with H_2O (4 mL), 5% aqueous $NaHCO_3$ (3 mL), and finally H_2O (4 mL). The organic extract was then dried and filtered, and the solvent was evaporated to yield the methyl ester **14** (32 mg, 82%). The analytical sample was recrystallized from $CHCl_3$–Et_2O: mp 190–192 °C; IR ($CHCl_3$) 2970, 2940, 1730, 1720, 1630, 1590, 1470, 1165 cm^{-1}; NMR δ 6.67 (d, 1 H, J = 7.8 Hz), 6.69 (s, 1 H), 6.40 (d, 1 H, J = 7.8 Hz), 6.34 (s, 1 H), 6.14 (d, 1 H, J = 1.2 Hz), 6.11 (d, 1 H, J = 1.3 Hz), 5.87 (d, 1 H, J = 1.4 Hz), 5.82 (d, 1 H, J = 1.4 Hz), 4.62 (d, 1 H, J = 1.3 Hz), 3.72 (s, 3 H), 3.58 (s, 2 H), 3.00 (s, 3 H), 2.88 (d of q, 1 H, J = 1.3, 7.1 Hz), 1.40 (d, 3 H, J = 7.1 Hz); CIMS m/e (relative intensity) 412 (MH^+, 100).

Anal. Calcd for $C_{22}H_{21}NO_7$: C, 64.23; H, 5.11; N, 3.41. Found: C, 63.94; H, 5.11; N, 3.62.

Corydalic Acid Methyl Ester (15). Compound **14** (40 mg, 0.097 mmol) was heated at 55–60 °C in $POCl_3$ (0.3 mL) for 3 h. The mixture was then concentrated by evaporation in vacuo, and dry 1,2-dimethoxyethane (0.4 mL) was added to the residue. The resulting solution was cooled in an ice bath and treated with a solution of $NaBH_4$ in EtOH (0.7 M, 0.42 mL). After being stirred at room temperature for 3.5 h, the reaction mixture was cooled in an ice bath and treated again with a solution of $NaBH_4$ in EtOH (0.7 M, 0.42 mL). After stirring at room temperature for 12 h, a 2% aqueous HCl solution (0.54 mL) was added. The mixture was concentrated by evaporation and H_2O (2 mL) was added to the residue. The mixture was then extracted with Et_2O (2 × 1 mL). The aqueous layer was basified with 20% aqueous K_2CO_3 (1.6 mL) as the mixture was cooled in an ice bath. The mixture was then extracted with EtOAc (3 × 2 mL). The organic extract was combined with the Et_2O extract above. The solution was dried and filtered, and the solvent was evaporated to yield a pale yellow oil (39 mg). The oil was subjected to preparative TLC (silica gel, 3:1 EtOAc–hexane) to afford the starting material **14** (8 mg, 20%) and the product **15**, which was crystallized from $CHCl_3$–hexane: 22 mg, 57%; mp 144–147 °C; NMR δ 6.88 (s, 1 H), 6.70 (s, 3 H), 5.93 (s, 4 H), 4.03 (d, 1 H, J = 15.6 Hz), 3.71 (s, 2 H), 3.64 (s, 3 H), 3.36 (d, 1 H, J = 15.7 Hz), 3.15–3.06 (m, 2 H), 2.06 (s, 3 H), 1.03 (d, 3 H, J = 6.3 Hz). The synthetic compound cochromatographed with the natural product on silica gel TLC in the following solvent systems: 3:1 EtOAc–hexane (R_f 0.68), $CHCl_3$ (R_f 0.19), Et_2O (R_f 0.95), 1:1 Me_2CO–benzene (R_f 0.93).

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Registry No. (±)-**8**, 82929-74-6; **9**, 75283-81-7; (±)-**10**, 88610-26-8; (±)-**11**, 88610-27-9; (±)-**12**, 88610-28-0; (±)-**13**, 88610-29-1; (±)-**14**, 88610-30-4; (±)-**15**, 88610-31-5.

Utilization of Magnesium Chelates in the Synthesis of 3-Nitro- and 3-(Methoxycarbonyl)-Substituted 2-Arylchromones

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Although a wide variety of flavones are available as natural products, the 3-nitro-, 3-carboxy-, and 3-(alkoxycarbonyl)-substituted flavones are rare substances. The treatment of flavone (**1**, Chart I) with lithium diisopropylamide and carbon dioxide recently provided the first synthesis of 3-carboxyflavone (**2**), while the corresponding ethyl ester **3** was obtained by using ethyl chloroformate in the acylation step.[1] The nitrosation of flavanone (**4**) and subsequent oxidation has previously afforded 3-nitroflavanone (**5**), which on bromination followed by dehydrobromination gave 3-nitroflavone (**6**).[2] Intermediate **5** has also been prepared by the condensation of 2-hydroxy-α-nitroacetophenone (**10**) with benzaldehyde.[3] However, the conversion of **5** to **6** in this synthesis is of limited scope because of the required use of bromine, which causes bromination of the aromatic rings when activating substituents are present.[3] It is anticipated that the chemistry of 3-substituted chromones will be of interest during the utilization of these compounds as intermediates in the synthesis of novel heterocyclic systems. Certain 3-nitrochromones have already been converted to dihydrobenzopyrans[4] as well as benzoxepins.[5]

Our interest in 2-aryl-3-substituted chromones stems from their potential use in the preparation of pyridines.[6] This paper describes a novel one-pot procedure for the conversion of 2-hydroxy-α-nitroacetophenones and 2-hydroxy-α-(methoxycarbonyl)acetophenones (A, Scheme I) to 2-aryl-3-nitrochromones and 2-aryl-3-(methoxycarbonyl)chromones (E). This method avoids preformed

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