by preparative TLC (silica gel, 1:2 ethyl acetate/chloroform) to give a red solid, which was recrystallized from aqueous ethanol to give 36.5 mg (80%) of the title compound as red needles: mp 196–197 °C dec; IR (Nujol) 3230 (s), 3130 (m), 1680 (m), 1675 (m), 1670 (m), 1660 (m), 1645 (s), 1635 cm^{-1} (s); NMR (acetone-d_6) δ 1.89 (m, 2 H), 2.15 (s, 3 H), 2.83 (t, J = 7.5 Hz, 2 H), 3.61 (t, J = 6.2 Hz, 2 H), 6.39 (s, 1 H); mol wt calcd for $C_{12}H_{12}ClNO_3$ 253.0506, found 253.0512.

Anal. Calcd for $C_{12}H_{12}ClNO_3$: C, 56.81; H, 4.77; Cl, 13.98; N, 5.52. Found: C, 56.58; H, 4.89; Cl, 14.19; N, 5.29.

5-Chloro-6-methyl-2-[3-(mesyloxy)propyl]indoloquinone. A general procedure of Crossland and Servis[21] for the preparation of mesylates was adapted as follows. To a solution of 13.5 mg (0.053 mmol) of 5-chloro-2-(3-hydroxypropyl)-6-methylindoloquinone in 2 mL of dichloromethane containing 8.1 mg (0.08 mmol) of triethylamine at 0 °C was added slowly 6.7 mg (0.058 mmol) of methanesulfonyl chloride. The red indoloquinone suspension became an orange suspension. Stirring for an additional 1 h completed the reaction. The reaction mixture was transferred to a separatory funnel with the aid of chloroform. The mixture was first extracted with water, followed by 5% hydrochloric acid, saturated sodium bicarbonate solution, and brine. Drying of the chloroform solution followed by solvent removal gave a red solid. The red solid was purified by preparative TLC (silica gel, 1:5 ethyl acetate/chloroform) to give 13.5 mg (85%) of the title compound as red crystals: mp 124–126 °C; IR (film) 3220 (m), 3130 (w), 1665 (m), 1635 cm^{-1} (s); NMR ($CDCl_3$) δ 2.1 (m, 2 H), 2.15 (s, 3 H), 2.85 (t, J = 8 Hz, 2 H), 3.00 (s, 3 H), 4.25 (t, J = 6 Hz, 2 H), 6.53 (s, 1 H).

7-Chloro-6-methyl-1,2,5,8-tetrahydro-3*H*-pyrrolo[1,2-*a*]indole-5,8-dione (14). To a solution of 13 mg (0.043 mmol) of 5-chloro-2-[[3-(mesyloxy)propyl]methyl]indoloquinone in 20 mL of anhydrous tetrahydrofuran was added 4.9 mg (0.043 mmol) of potassium *tert*-butoxide. The reaction mixture turned purple immediately and became purple-brown in 10 min. Stirring for an additional 2 h completed the reaction. The solvent of the resulting green-yellow solution was removed under reduced pressure. The residue was purified by preparative TLC (silica gel, 1:5 ethyl acetate/chloroform) to give 7 mg (68%) of **12** as a red solid. This solid was further purified by recrystallization from chloroform–hexanes to give red crystals: mp 156–157 °C; IR (Nujol) 1670 (s), 1665 (s), 1653 (s), 1645 (s), 1595 cm^{-1} (m); NMR ($CDCl_3$) δ 2.21 (s, 3 H), 2.5–2.9 (m, 4 H), 4.26 (t, J = 5.2 Hz, 2 H), 6.36 (s, 1 H); mol wt calcd for $C_{12}H_{10}ClNO_2$ 235.0401, found 235.038.

(21) R. K. Crossland and K. L. Servis, *J. Org. Chem.*, **35**, 3195 (1970).

Acknowledgment. The authors express their appreciation for financial support to the National Cancer institute (Grant No. CA 11890).

Registry No. 1, 20765-04-2; **4a**, 844-51-9; **4b**, 137-18-8; **4c**, 64080-64-4; **4d**, 64080-65-5; **5**, 7210-71-1; **6a**, 24909-17-9; **6b**, 64080-66-6; **6c**, 46010-98-4; **6d**, 64080-67-7; **6e**, 75347-51-2; **6f**, 75347-52-3; **6g**, 75347-53-4; **6h**, 75347-54-5; **6i**, 75347-55-6; **6j**, 75347-56-7; **7**, 75347-57-8; **8**, 75347-58-9; 11, 75347-59-0; **12**, 75347-60-3; **13**, 75347-61-4; **14**, 75347-62-5; 3-(benzyloxy)-1-propyne, 4039-82-1; 4-bromoanisole, 104-92-7; phenylacetylene, 536-74-3; 3-(2-tetrahydropyranyloxy)-1-propyne, 6089-04-9; 5-(2-tetrahydropyranyloxy)-1-pentyne, 62992-46-5; 3-methoxy-1-propyne, 627-41-8; 4-cyano-2,5-dichloro-3-methyl-4-(trimethylsiloxy)-2,5-cyclohexadienone, 75365-45-6; 2,5-dichloro-3-methyl-1,4-benzoquinone, 40100-99-0; trimethylsilyl cyanide, 7677-24-9; triphenyl phosphine, 603-35-0; 1-cyano-3,6-dichloro-2-methyl-1,4-bis(trimethylsiloxy)-4-[3-(2-tetrahydropyranyloxy)-1-propynyl]-2,5-cyclohexadiene, 75347-63-6; 3-(2-tetrahydropyranyloxy)-1-propyne, 6089-04-9; 3,6-dichloro-4-hydroxy-2-methyl-4-[3-(2-tetrahydropyranyloxy)-1-propynyl]-2,5-cyclohexadienone, 75347-64-7; 1,2-dimethoxyethane, 110-71-4; 2,6-dichloro-4-hydroxy-2-methyl-4-[3-(2-tetrahydropyranyloxy)-1-propenyl]-2,5-cyclohexadienone, 75347-65-8; 2,5-dichloro-3-(5-hydroxy-1-pentenyl)-6-methylhydroquinone, 75365-46-7; 5-chloro-6-methyl-2-[3-(mesyloxy)propyl]indoloquinone, 75347-66-9; 5-chloro-2-(3-hydroxypropyl)-6-methylindoloquinone, 75347-67-0.

Formation of the 5-Benzo[*d*]naphtho[2,3-*b*]pyran System during an Attempted Benzophenanthridine Synthesis

Mark Cushman* and Dinesh K. Dikshit

Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, Indiana 47907

Received June 4, 1980

The condensation of the Schiff base **6** with the homophthalic anhydride **7** was used during elaboration of a compound, **9**, suitable for closure of the B ring of the benzophenanthridine system. However, treatment of **9** with sodium hydride in THF resulted in formation of 3,4-dimethoxy-5-oxo-7-cyano-9,10-(methylenedioxy)-5-benzo[*d*]naphtho[2,3-*b*]pyran (**10**) instead of the Dieckmann–Thorpe cyclization product **2**.

The benzophenanthridine alkaloids constitute a large group of metabolites which occur in the Fumariaceae, Papaveraceae, and Rutaceae.[1] We have recently been attempting to utilize a condensation reaction between Schiff bases and homophthalic anhydrides as an approach to the synthesis of these compounds.[2] The present work was directed toward homochelidonine (**1**),[3] and the strategy in this case was to employ the condensation of the Schiff base **6** with the homophthalic anhydride **7**[4] for the elaboration of the isoquinolone **8**. The corresponding ester **9** was expected to undergo a base-catalyzed Dieckmann–Thorpe cyclization, yielding the tetracyclic system **2**.

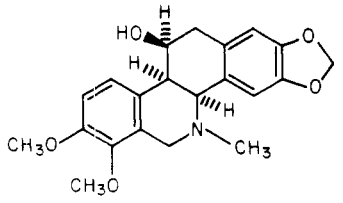
(1) M. Shamma, "The Isoquinoline Alkaloids. Chemistry and Pharmacology", Academic Press, New York, 1972, p 315; M. Shamma and L. Moniot, "Isoquinoline Alkaloids Research 1972–1977", Plenum Press, New York, 1978, p 271.

(2) M. Cushman and L. Cheng, *J. Org. Chem.*, **43**, 286 (1978); M. Cushman, J. Gentry, and F. W. Dekow, *ibid.*, **42**, 1111 (1977).

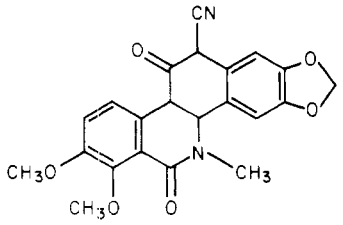
(3) Structure: E. Späth and F. Kuffner, *Chem. Ber.*, **64**, 1123 (1931). Synthesis: I. Ninomiya, O. Yamamoto, and T. Naito, *Heterocycles*, **7**, 137 (1977).

(4) M. Cushman and F. W. Dekow, *J. Org. Chem.*, **44**, 407 (1979).

0022-3263/80/1945-5064$01.00/0



1



2

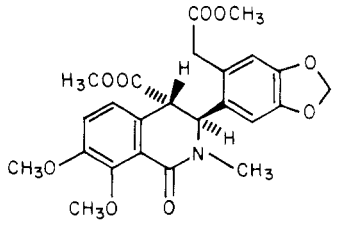
The isonitroso ketone 3[5] was reduced with sodium borohydride and the alcohol 4 subjected to the Beckmann fragmentation reaction (Scheme I).[6] The resulting aldehyde 5 then afforded the required Schiff base 6 on treatment with methylamine.

Condensation of the Schiff base 6 with 3,4-dimethoxyhomophthalic anhydride (7) proceeded in chloroform at room temperature to the *trans*- (J_{AB} = 0 Hz)[2] isoquinolone 8, which was then converted to the methyl ester 9 (Scheme II). Treatment of the ester 9 with sodium hydride in THF resulted in the elimination of methylamine as well as methanol. The NMR spectrum showed the disappearance of the two methylene as well as both methine protons from the starting material and the appearance of an additional singlet aromatic proton. The IR spectrum of the new compound indicated the retention of the nitrile (2205 cm^{-1}) and the disappearance of the amide carbonyl of the starting material. The reaction evidently led to the 5-benzo[d]naphtho[2,3-b]pyran system 10 instead of the desired compound 2.

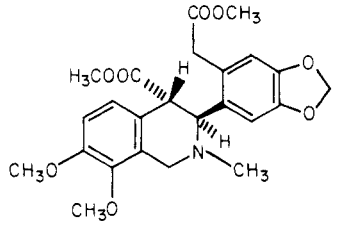
Several mechanistic pathways, including the one outlined in Scheme III, can be imagined which would account for the conversion of 9 to 10. The benzophenanthridine system 2 was not detected even though the reaction was performed under a variety of conditions, suggesting that it is not an intermediate.

Several analogues of 9 were prepared in an attempt to find a molecule which would cyclize in the desired fashion. The diester 11 was made from the acid 8 and HCl in MeOH. Subjection of 11 to a variety of conditions, including NaH or KH in refluxing THF, NaOMe or KOMe in refluxing MeOH, and KO-*t*-Bu or KH in refluxing benzene, led only to recovered starting material. Treatment of 11 with $Et_3O^+BF_4^-$ in CH_2Cl_2, followed by $NaBH_4$ in EtOH gave a mixture of the amine 12 (major product) and the alcohol 13, which were separated by chromatography.[7] The NMR spectrum of the acetate of 13 displayed a doublet (2 H, J = 8 Hz) at δ 4.33, excluding the alternate structure for this reduction product. Discouraging results also accompanied the attempted cyclization of the amine 12.

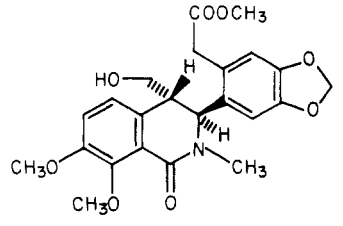
The conversion of 9 to 10 is reminiscent of several known transformations. For example, the degradations of certain benzophenanthridine alkaloids proceed with deamination, resulting in the formation of the 5-benzo[d]naphtho[2,3-b]pyran system. This reaction was discovered during the



11

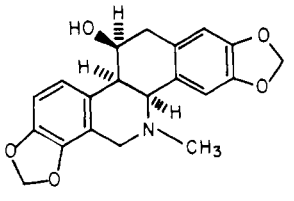


12

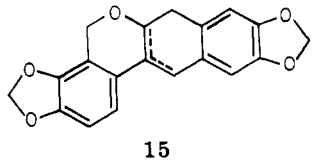


13

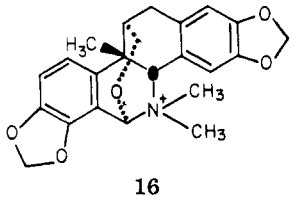
structure elucidation of (+)-chelidonine (14) when it was



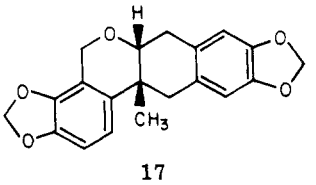
14



15



16



17

subjected to the conditions for two Hofmann eliminations and a tetracyclic ether best formulated as 15 was obtained.[8,9] A later and more fully documented example is the conversion of corynoloxine methochloride 16 to compound 17 by Emde degradation followed by catalytic hydrogenolysis.[10]

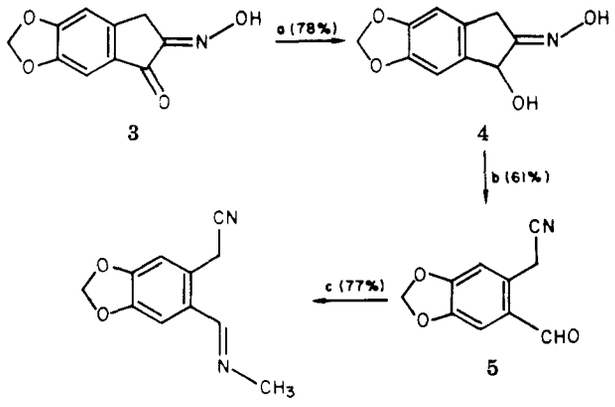
The above route to homochelidonine was eventually abandoned when a superior strategy for (±)-chelidonine synthesis (described in the companion paper) proved successful.

Experimental Section

All reactions were performed under a nitrogen atmosphere unless otherwise noted, and the solvents were removed on a rotary evaporator under reduced pressure. Melting points were taken on a Thomas-Hoover Unimelt or a Meltemp apparatus and are uncorrected. NMR spectra were recorded on a Varian EM-360 60-MHz instrument or on a JEOL PFT-100 spectrometer and,

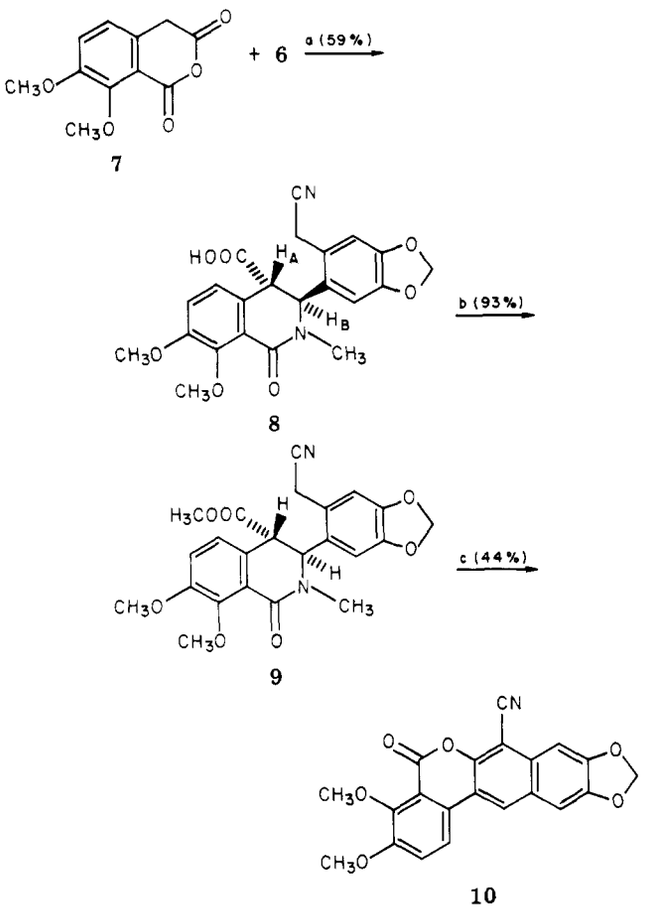
(5) W. H. Perkin, Jr., and R. Robinson, *J. Chem. Soc.*, 1084 (1907).
(6) A. Werner and T. Detscheff, *Chem. Ber.*, **38**, 69 (1905); A. H. Blatt and R. P. Barnes, *J. Am. Chem. Soc.*, **56**, 1148 (1934).
(7) R. F. Borch, *Tetrahedron Lett.*, 61 (1968).
(8) F. von Bruchhausen and H. W. Bersch, *Chem. Ber.*, **63**, 2520 (1930), and ref 6 cited therein.
(9) E. Späth and F. Kuffner, *Chem. Ber.*, **64**, 370 (1931).
(10) N. Takao, *Chem. Pharm. Bull.*, **19**, 247 (1971).

Scheme I[a]



[a] (a) $NaBH_4$, EtOH, 23 °C, 24 h. (b) TsCl, Py, 23 °C, 2.5 h. (c) CH_3NH_2, molecular sieves, CH_2Cl_2, 23 °C, 6 h.

Scheme II[a]

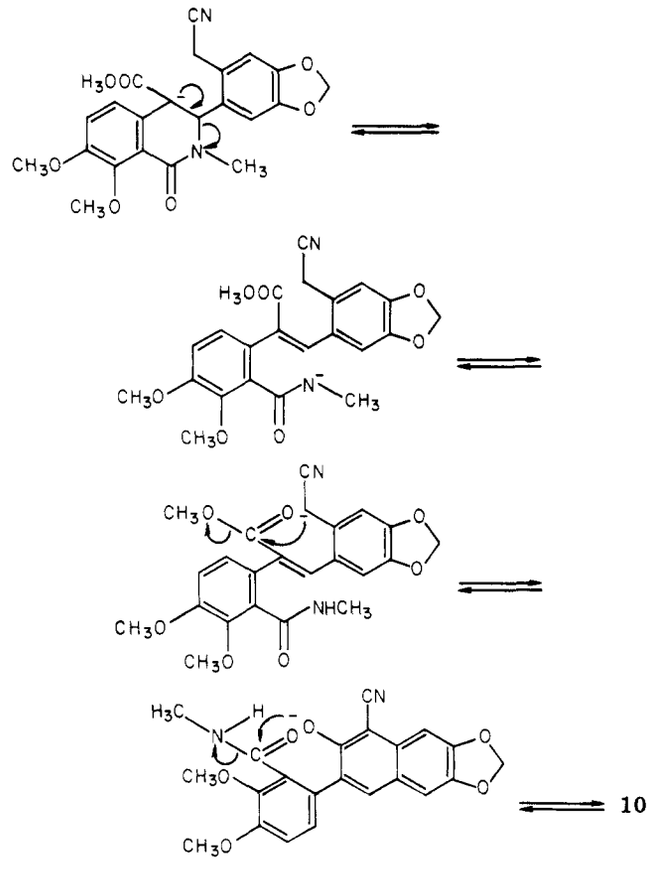


[a] (a) $CHCl_3$, 23 °C, 6 h. (b) CH_2N_2, MeOH, Et_2O, 0 °C, 4 h. (c) NaH, THF, 23 °C, 6 h.

except where noted, in $CDCl_3$ solvent. 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. Mass spectra were determined on a Du Pont 21-492B double-focusing spectrometer using an ion-source temperature of 200–280 °C, an ionization potential of 70 eV, and an ionizing current of 100 μA. Microanalyses were performed by Dr. C. S. Yeh and associates of Purdue University.

2-Isonitroso-5,6-(methylenedioxy)-1-indanone (3). *n*-Amyl nitrite (3 mL) and concentrated HCl (3 mL) were added to a suspension of 5,6-(methylenedioxy)-1-indanone[5] (5.00 g, 28.4 mmol) in EtOH (200 mL). After being stirred at 50 °C for 2 h, the reaction mixture was concentrated to half the original volume and stored at 0 °C for 30 min. The crystalline isonitroso ketone

Scheme III



3 (4.21 g, 72%) was filtered and dried: mp 213–215 °C (lit.[5] mp 230 °C dec); IR (KBr) 3480, 3140, 3040, 2960, 1685, 1470 cm^{-1}.

2-Isonitroso-5,6-(methylenedioxy)-1-indanol (4). Sodium borohydride (55 g, 1.45 mol) was added to a suspension of the keto oxime 3 (65 g, 0.32 mol) in EtOH (2 L). The reaction mixture was stirred at room temperature for 24 h and then concentrated to half its original volume. Water was then added to precipitate the alcohol 4 (52 g, 78%), which was filtered and dried over P_2O_5: mp 216 °C dec; IR (KBr) 3260, 2890, 1470 cm^{-1}.

2-(Cyanomethyl)piperonal (5). Pyridine (35 mL) was added to a mixture of compound 4 (1.80 g, 8.69 mmol) and *p*-toluenesulfonyl chloride (3.60 g, 18.9 mmol). The reaction mixture was stirred at room temperature for 2.5 h and then poured into ice (200 g) and concentrated HCl (60 mL). The organic material was extracted with EtOAc, and the organic layer was then washed with dilute HCl, water, dilute $NaHCO_3$, and finally water. It was then dried (Na_2SO_4) and the solvent evaporated. The crude material was passed through a column of silica gel in benzene to give the cyano aldehyde 5: 1.00 g (61%); mp 124–125 °C; IR (KBr) 2915, 2240, 1680 cm^{-1}; NMR δ 10.07 (s, 1 H), 7.33 (s, 1 H), 7.17 (s, 1 H), 6.20 (s, 2 H), 4.27 (s, 2 H).

[2-(Cyanomethyl)-4,5-(methylenedioxy)benzylidene]-methylamine (6). Molecular sieves (50 g, 4 Å) were added to a solution of the cyano aldehyde (8.00 g, 42.3 mmol) in CH_2Cl_2 (400 mL). Methylamine gas was slowly bubbled through the mixture during 4 h. The mixture was allowed to stand at room temperature for an additional 2 h, and the molecular sieves were then filtered off. The reaction mixture was concentrated to a volume of 50–60 mL and then diluted with hexane (250 mL) to precipitate the solid imine: 6.60 g (77%); mp 95–96 °C; IR (KBr) 2980, 2215, 1635 cm^{-1}; NMR δ 8.37 (q, 1 H, J = 2 Hz), 7.13 (s, 1 H), 6.97 (s, 1 H), 6.07 (s, 2 H), 4.17 (s, 2 H), 3.55 (d, 3 H, J = 2 Hz).

***trans*-*N*-Methyl-3-[2-(cyanomethyl)-4,5-(methylenedioxy)phenyl]-4-carboxy-7,8-dimethoxy-3,4-dihydro-1(2*H*)-isoquinolone (8).** 3,4-Dimethoxyhomophthalic anhydride[4] (2.30 g, 10.35 mmol) was added to a stirred solution of the Schiff base 6 (2.02 g, 10.0 mmol) in $CHCl_3$ (10 mL). The mixture was stirred at room temperature for 6 h, and the solvent was then evaporated.

The crude material was chromatographed on a silica gel column by using chloroform with increasing proportions of EtOAc as eluant. The desired compound 8 was obtained, after recrystallization from $CHCl_3/Et_2O$, as a colorless solid: 2.5 g (59%); mp 206–207 °C; IR (Nujol) 3300–2800, 2920, 2280, 1720, 1605 cm^{-1}; NMR (Me_2SO-d_6, $CDCl_3$) δ 7.20–6.88 (q, 2 H, J = 8 Hz), 7.00 (s, 1 H), 6.27 (s, 1 H), 6.00 (m, 2 H), 5.38 (s, 1 H), 4.07 (s, 2 H), 3.95 (s, 3 H), 3.90 (s, 4 H), 3.04 (s, 3 H); mass spectrum, m/e (relative intensity) 424 (M^+, 10), 380 (60), 178 (100). Anal. Calcd for $C_{22}H_{20}N_2O_7$: C, 62.26; H, 4.75; N, 6.60, Found: C, 62.17; H, 4.83; N, 6.40.

***trans*-*N*-Methyl-3-[(2-(cyanomethyl)-4,5-(methylenedioxy)phenyl]-4-(methoxycarbonyl)-7,8-dimethoxy-3,4-dihydro-1(2*H*)-isoquinolone (9).** Excess CH_2N_2 in Et_2O was added to a solution of the trans acid 8 (500 mg, 1.18 mmol) in MeOH (15 mL). The solution was kept at 0 °C for 4 h, and the excess CH_2N_2 was then quenched with AcOH. Water (100 mL) was added and the mixture extracted with EtOAc (2 × 200 mL). The organic layer was washed with H_2O and dilute $NaHCO_3$. It was then dried ($MgSO_4$) and the solvent evaporated, leaving the crystalline ester: 480 mg (93%); mp 162–163 °C; IR (Nujol) 2900, 2240, 1720, 1635 cm^{-1}; NMR δ 7.07 (d, 1 H, J = 8 Hz), 6.93 (s, 1 H), 6.87 (d, 1 H, J = 8 Hz), 6.47 (s, 1 H), 5.97 (m, 2 H), 5.33 (d, 1 H, J = 2 Hz), 4.11 (s, 3 H), 3.97 (s, 3 H), 3.90–3.60 (m, 3 H), 3.83 (s, 3 H), 3.13 (s, 3 H); mass spectrum, m/e (relative intensity) 438 (M^+, 75), 380 (14), 236 (100).

Anal. Calcd for $C_{23}H_{22}N_2O_7$: C, 63.01; H, 5.06; N, 6.39. Found: C, 62.72; H, 5.16; N, 6.19.

3,4-Dimethyl-5-oxo-9,10-(methylenedioxy)-6-benzo[*b*]naphtho[2,3-*d*]pyran (10). Sodium hydride (50% dispersion, 100 mg, 2.08 mmol) was added to a solution of the ester 9 (200 mg, 0.46 mmol) in THF (20 mL). After the mixture was stirred at room temperature for 6 h, the THF was evaporated, and water and EtOAc were added to the residue. The organic layer was separated and extracted with 1 N NaOH. The aqueous layer and NaOH wash were combined and acidified with concentrated HCl. The precipitate was filtered, washed with water, and dried over P_2O_5, yielding a white solid (75 mg, 44%). The analytical sample was prepared by sublimation: mp 358–360 °C; IR (Nujol) 2900, 2205, 1730 cm^{-1}; NMR (Me_2SO-d_6) δ 7.63 (s, 1 H), 7.19 (s, 1 H), 7.11 (s, 1 H), 7.10 (d, 1 H, J = 8.5 Hz), 6.92 (d, 1 H, J = 8.5 Hz), 6.11 (s, 2 H), 3.87 (s, 3 H), 3.78 (s, 3 H); mass spectrum, m/e (relative intensity) 375 (M^+, 100), 360 (35), 346 (35), 332 (15), 175 (20); calcd for $C_{21}H_{13}NO_6$ m/e 375.0743, found m/e 375.072.

Anal. Calcd for $C_{21}H_{13}NO_6$: C, 67.20; H, 3.49; N, 3.73. Found: C, 67.17; H, 3.17; N, 3.71.

***trans*-*N*-Methyl-3-[2-[(methoxycarbonyl)methyl]-4,5-(methylenedioxy)phenyl]-4-(methoxycarbonyl)-7,8-dimethoxy-3,4-dihydro-1(2*H*)-isoquinolone (11).** Dry HCl gas was bubbled slowly through a solution of the cyano acid 8 (430 mg, 1.01 mmol) in MeOH at −40 to −20 °C for 1 h. The mixture was then kept at 0 °C for 24 h, concentrated to half the original volume, poured into water (200 mL), and extracted with EtOAc. The organic layer was washed with water, dilute $NaHCO_3$, and water, dried (Na_2SO_4), and concentrated. The crude product was crystallized from Et_2O/hexane to give the diester 11 as a colorless solid: 350 mg (73%); mp 192–193 °C; IR (Nujol) 1725, 1645 cm^{-1}; NMR δ 7.07 (d, 1 H, J = 8 Hz), 6.87 (d, 1 H, J = 8 Hz), 6.77 (s, 1 H), 6.42 (s, 1 H), 5.90 (m, 2 H), 5.40 (d, 1 H, J = 1 Hz), 4.10 (s, 3 H), 3.97 (s, 3 H), 3.82 (s, 3 H), 3.78 (s, 3 H), 3.67–4.10 (obscured m, 3 H), 3.10 (s, 3 H); mass spectrum, m/e (relative intensity) 471 (M^+, 28), 439 (5), 412 (14), 408 (5), 236 (100).

Anal. Calcd for $C_{24}H_{25}NO_9$: C, 61.14; H, 5.34; N, 2.97. Found: C, 61.11; H, 5.42; N, 2.90.

***trans*-*N*-Methyl-3-[2-[(methoxycarbonyl)methyl]-4,5-(methylenedioxy)phenyl]-4-(methoxycarbonyl)-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (12).** A 1 M solution of $Et_3O^+BF_4^-$ in CH_2Cl_2 (1.25 mL, 1.25 mmol) was added to a solution of compound 10 (500 mg, 1.06 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred at room temperature for 20 h. The CH_2Cl_2 was evaporated, and the residue was dissolved in EtOH (3 mL). The solution was cooled to −10 °C before addition of $NaBH_4$ (0.10 g, 2.64 mmol). The mixture was stirred at room temperature for 18 h, decomposed with water, and extracted with EtOAc. The organic layer was washed with water, dried ($MgSO_4$), and concentrated. The crude material was chromatographed on a column of silica gel by using $CHCl_3$ with increasing proportions of EtOAc as eluant. The desired compound 12 (300 mg, 52%) crystallized from benzene/Et_2O/hexane: mp 155–157 °C; IR (Nujol) 1720 cm^{-1}; NMR δ 7.00 (s, 1 H), 6.90 (s, 2 H), 6.77 (s, 1 H), 6.03 (s, 2 H), 4.40–3.60 (m, 6 H), 3.93 (s, 6 H), 3.75 (s, 3 H), 3.63 (s, 3 H), 2.13 (s, 3 H).

Anal. Calcd for $C_{24}H_{27}NO_8$: C, 63.01; H, 5.95; N, 3.06. Found: C, 62.75; H, 6.10; N, 3.00.

***trans*-*N*-Methyl-3-[2-[(methoxycarbonyl)methyl]-4,5-(methylenedioxy)phenyl]-4-(hydroxymethyl)-7,8-dimethoxy-3,4-dihydro-1(2*H*)-isoquinolone (13).** Continued elution of the above column used for isolation of compound 12 gave an additional product which crystallized from benzene/$CHCl_3$/hexane as a colorless solid: 85 mg (18%); mp 163–164 °C; IR (Nujol) 3880, 1730, 1630 cm^{-1}; NMR δ 7.00 (d, 1 H, J = 8 Hz), 6.77 (s, 1 H), 6.77 (d, 1 H, J = 8 Hz), 6.43 (s, 1 H), 5.90 (m, 2 H), 5.30 (s, 1 H), 4.10 (s, 3 H), 4.10–3.50 (m, 6 H), 3.93 (s, 3 H), 3.83 (s, 3 H), 3.17 (s, 3 H).

Anal. Calcd for $C_{23}H_{25}NO_8$: C, 62.30; H, 5.68; N, 3.16. Found: C, 61.94; H, 5.53; N, 3.06.

Acknowledgment. This investigation was supported by Grant CA19204, awarded by the National Cancer Institute, DHEW.

Registry No. 3, 38489-93-9; 4, 75283-80-6; 5, 75299-09-1; 6, 75283-81-7; 8, 75283-82-8; 9, 75283-83-9; 10, 75283-84-0; 11, 75299-10-4; 12, 75283-85-1; 13, 75283-86-2; 5,6-(methylenedioxy)-1-indanone, 6412-87-9; 3,4-dimethoxyhomophthalic anhydride, 68408-56-0.

Total Synthesis of (±)-Chelidonine

Mark Cushman,* Tung-Chung Choong, Joseph T. Valko, and Mary P. Koleck

Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, Indiana 47907

Received June 4, 1980

Condensation of the Schiff base 8 with 3,4-(methylenedioxy)homophthalic anhydride (13) was exploited as the key step in a total synthesis of the benzophenanthridine alkaloid (±)-chelidonine (1). A variety of reaction conditions were investigated in order to maximize the production of the desired thermodynamically less stable cis diastereomer. A method was devised for the conversion of 24 to its acid chloride without production of the indeno[1,2-*c*]isoquinoline 30. The migration of an aromatic ring was observed on treatment of the diazo ketone 26 with acid. This reaction is reminiscent of the Hayashi rearrangement.

(+)-Chelidonine is a member of the group of isoquinoline alkaloids known as the benzophenanthridines. It was first isolated from *Chelidonium majus* in 1839,[1] and extensive chemical[2] and spectroscopic[3] studies led to structure 1. An

0022-3263/80/1945-5067$01.00/0