Photocyclisation of Enamides. Part 19.[1] Total Synthesis of (±)-Homochelidonine[2]

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Photocyclisation of the enamide (2) and successive stereoselective functionalisation of the photocyclised didehydro lactam (3a) completed the first total synthesis of (±)-homochelidonine (7e).

In the preceding paper [1] we developed a new synthetic route toward B/C-hexahydrobenzo[*c*]phenanthridine alkaloids,[3] *e.g.* chelidonine [3] and related alkaloids such as chelamine,[4] by preparing the basic structures of these alkaloids. As an extension of our work [1,5] on the synthesis of benzo[*c*]phenanthridine alkaloids, we now report the first total synthesis of (±)-homochelidonine by employing enamide photocyclisation [6] and oxidative introduction of an oxygen function into ring C.

While two syntheses have been reported for chelidonine,[7,8] homochelidonine, which is isolated [4a,9] from *Chelidonium* plants and is regarded as one of the representative alkaloids of the B/C-*cis*-hexahydrobenzo[*c*]phenanthridine type, remained hitherto unsynthesised. Our synthetic method toward this alkaloid was as follows. First, we attempted photocylisation to the didehydro lactam (3a) by employing the enamide (2), which has an additional *ortho*-methoxy group since the regiospecific photocyclisation to the *ortho*-carbon atom bearing a methoxy group has been regarded as a useful preparative procedure.[6] The enamide (2) was therefore prepared from the 1-tetralone (1) and 2,3,6-trimethoxybenzoyl chloride [10] in 98% yield. The enamide (2) thus prepared exhibited an intricate n.m.r. spectrum at room temperature except for triplet signals with a coupling constant of 4 Hz at δ_H 6.04 for an olefinic proton. However, the n.m.r. spectrum measured in [$^2H_6$]dimethyl sulphoxide at 160 °C showed peaks at δ_H 6.91 and 6.60 (together ABq, *J* 10 Hz, 4- and 5-H), 6.84 and 6.67 (each s, together 5'- and 8'-H), 5.91 (olefinic H, overlapped with a signal at δ 5.89), 5.89 (s, OCH_2O), 3.78, 3.70, and 3.67 (each s, OMe), and 3.03 (s, NMe), and therefore suggested that the enamide (2) actually exists in only one conformation, which we propose is due to hindered rotation around the N–CO bond at low temperature.[1,11] At 160 °C rotation about the N–CO bond becomes possible.

Irradiation of a 0.02M methanolic solution of the enamide (2) with a high-pressure mercury lamp at room temperature for 15 h yielded two photocyclised lactams (3a) and (4) in 19 and 18% yield, respectively, due to non-selectivity in the orientation of cyclisation. The lactam (3a) showed an i.r. absorption at 1 640 cm^{-1} due to a lactam carbonyl group and n.m.r. peaks at δ_H 7.45 and 7.30 (together ABq, *J* 9 Hz, 9- and 10-H), 6.91 (s, 4-H), 6.78 (s, 1-H), and 2.73 (s, 2 × CH_2); these data were not enough to allow us to draw a conclusion regarding the structure of the lactam (3a) whose structure was, however, unambiguously established by its conversion into oxychelerythrine (5a) † by dehydrogenolysis with lead tetra-acetate.[1]

The second photocyclised lactam (4) showed n.m.r. peaks at δ_H 7.07 (s, 4-H), 6.97 and 6.83 (together ABq, *J* 9 Hz, 8- and 9-H), 6.60 (s, 1-H), 3.87 and 3.80 (each s, OMe), 2.90 (s, OMe), and 2.80 (s, NMe), which suggested that the lactam (4) carried a methoxy group not on the benzene ring but at the 4b-position as a result of specific 1,5-migration,[6] though its configuration has yet to be determined. In order to remove the 4b-methoxy group, the lactam (4) was treated with methanolic hydrochloric acid to give the didehydro lactam (3b), which has a different pattern of substituents from the lactam (3a). The didehydro lactam (3a) was then oxidised with lead tetra-acetate, under the conditions developed previously,[1] to give the 12-acetoxy lactam (5b) in 92% yield, and which was shown to have an acetoxy group at the 12-position from the n.m.r. peaks at δ_H 7.73 and 7.28 (together ABq, *J* 9 Hz, 9- and 10-H), 7.67 (s, 11-H), 7.42 and 7.05 (each s, together 1- and 4-H), and 2.45 (s, Ac).

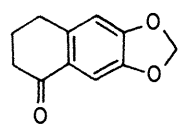
In order to introduce an oxygen function into the 11-position, the 12-acetoxy lactam (5b) was hydrolysed to the corresponding naphthol (5c) with methanolic potassium hydroxide. Unfortunately, attempted oxidation of the naphthol (5c) with lead tetra-acetate according to the previous procedure,[1] to the quinone (6) was unsuccessful. However, treatment of the naphthol (5c) with chromium(VI) trioxide–sulphuric acid in aqueous acetic acid at room temperature afforded the desired *ortho*-quinone (6) in 53% yield, which showed i.r. absorptions at 1 690, 1 670, and 1 640 cm^{-1}, due to *ortho*-quinone and lactam carbonyl groups. Reduction of the quinone (6) with lithium aluminium hydride followed by catalytic hydrogenation over platinum dioxide yielded the glycol (7a) in 12% yield, which exhibited i.r. absorption at 3 600 cm^{-1} due to hydroxy groups, and n.m.r. signals at δ_H 7.13 and 6.89 (together ABq, *J* 9 Hz, 9- and 10-H), 6.96 and 6.80 (each s, together 1- and 4-H), 4.36 (m, 11- and 12-H), 4.20 and 3.42 (together ABq, *J* 16 Hz, 6-H_2), 3.38 (d, *J* 4 Hz, 4b-H), and 2.98 (t, *J* 4 Hz, 10b-H). Comparison of these spectral data with those of the basic structures reported in the previous paper [1] and failed attempted formation of the acetonide suggested that the glycol (7a) has the B/C-*cis*-benzo[*c*]phenanthridine structure with an 11α,12β-glycol moiety.

Conversion of the 11α-hydroxy group in compound (7a) into the desired 11β-hydroxy group was accomplished according to the procedure established previously.[1] Selective acetylation of the 12β-hydroxy group in the glycol (7a), followed by mesylation ‡ of the 11α-hydroxy group, gave the methanesulphonate (7c) which was then, without purification, treated with methanolic potassium hydroxide in order to undergo nucleophilic substitution at both the 11- and 12-positions to furnish the desired 11β-hydroxy-12-methoxy amine (7d) in 94% yield from the *trans*-glycol (7a). The spectral data of compound (7d) are very similar to those of the basic structures reported previously,[1] and thus we had succeeded in the conversion of the 11α-hydroxy group into the epimeric 11β-hydroxy one.

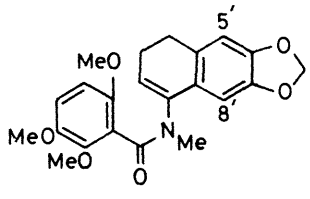
Finally, hydrogenolysis of the 12-methoxy group of compound (7d) with 40% palladium-charcoal in 10% hydrochloric acid containing a small amount of 70% perchloric

† Private communication from Professor N. Takao who informed us that he succeeded in the preparation of oxychelerythrine from natural chelerythrine chloride.

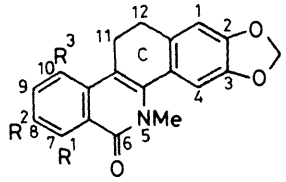
‡ Methanesulphonation.



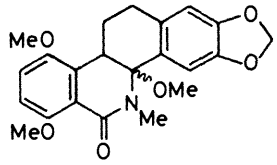
(1)



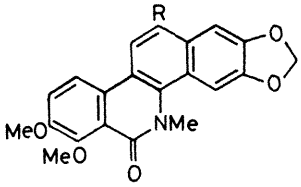
(2)



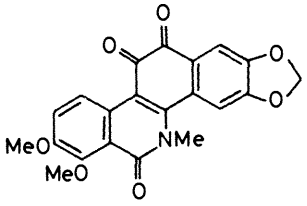
(3) a; $R^1 = R^2 = OMe$, $R^3 = H$
b; $R^1 = R^3 = OMe$, $R^2 = H$



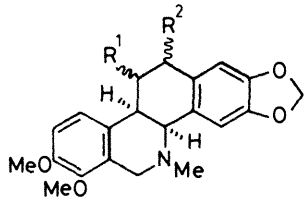
(4)



(5) a; R = H
b; R = OAc
c; R = OH



(6)



(7) a; R^1 = ...OH, R^2 = —OH
b; R^1 = ...OH, R^2 = —OAc
c; R^1 = ...OMs, R^2 = —OAc
d; R^1 = —OH, R^2 = ~OMe
e; R^1 = —OH, R^2 = H

Ms = CH_3SO_2-

acid afforded the amino alcohol (7e) in 40% yield, which was identical with the natural alkaloid (+)-homochelidonine [4a] upon comparison of their i.r. and mass spectra and R_F-values.

Experimental

^{1}H N.m.r. spectra were measured with Varian A-60D, NEVA-21 (90 MHz), and JEOL PMX-60 instruments for solutions in deuteriochloroform unless otherwise stated (tetramethylsilane as internal reference), i.r. spectra for solutions in chloroform with a Hitachi 215 spectrophotometer, and mass spectra with a JEOL JMSO1SG machine. M.p.s were determined with a Kofler-type hot-stage apparatus. The extracts from the reaction mixture were dried over anhydrous sodium sulphate. The photochemical reactions were carried out by irradiation with a high-pressure (300 W) mercury lamp (Eikosha PIH 300) at room temperature.

N-(3,4-*Dihydro*-6,7-*methylenedioxy*-1-*naphthyl*)-2,3,6-*trimethoxy*-N-*methylbenzamide* (2).—Anhydrous methylamine gas was bubbled into an ice-cooled solution of the tetralone (1) (11 g) in anhydrous chloroform (50 ml) for 30 min. This mixture was added dropwise to a stirred, ice-cooled solution of titanium tetrachloride (6 ml) in anhydrous chloroform (20 ml). After the mixture had been refluxed for 1 h it was evaporated to dryness under reduced pressure, and the resulting residue was dissolved in anhydrous benzene (100 ml) and the solution was filtered. Triethylamine (13 g) was added to the filtrate. A solution of 2,3,6-trimethoxybenzoyl chloride [10] (16 g) in anhydrous benzene (50 ml) was then added dropwise to the reaction mixture, which was then heated under reflux for 2 h and filtered to remove triethylamine hydrochloride. The filtrate was evaporated to give a solid which was recrystallised from methanol to afford the crystalline *enamide* (2) (25 g, 98%), m.p. 144—145 °C; $\nu_{max.}$ 1 640 cm^{-1} (NCO) (Found: C, 66.55; H, 5.8; N, 3.55. $C_{22}H_{23}NO_6$ requires C, 66.5; H, 5.85; N, 3.55%). The ^{1}H n.m.r. spectrum of the enamide (2) was too complicated to assign at room temperature, but at 160 °C in [$^2H_6$]dimethyl sulphoxide it showed peaks at δ 6.91 and 6.60 (together 2-H, ABq, *J* 10 Hz, 4- and 5-H), 6.84 and 6.67 (each 1 H, s, together 5′- and 8′-H), 5.91 (1 H, olefinic H, overlapped with the peak at δ 5.89), 5.89 (2 H, s, OCH_2O), 3.78, 3.70, and 3.67 (each 3 H, s, OMe), and 3.03 (3 H, s, NMe).

Photocyclisation of the Enamide (2).—A 0.02M methanolic solution of the enamide (2) (5 g) was irradiated for 15 h and then evaporated. The resulting solid was recrystallised from methanol–diethyl ether to give 4b,10b,11,12-*tetrahydro*-4b,7,10-*trimethoxy*-5-*methyl*-2,3-*methylenedioxybenzo*[c]*phenanthridin*-6(5H)-*one* (4) (900 mg, 18%), m.p. 165—167 °C, $\nu_{max.}$ 1 640 cm^{-1} (NCO); δ_H 7.07 (1 H, s, 4-H), 6.97 and 6.83 (together 2 H, ABq, *J* 9 Hz, 8- and 9-H), 6.60 (1 H, s, 1-H), 5.93 (2 H, s, OCH_2O), 3.87 and 3.80 (each 3 H, s, OMe), 2.90 (3 H, s, OMe), and 2.80 (3 H, s, NMe) (Found: C, 66.55; H, 5.8; N, 3.4. $C_{22}H_{23}NO_6$ requires C, 66.5; H, 5.85; N, 3.55%).

Purification of the residue from the above mother-liquor by column chromatography on alumina afforded 11,12-*dihydro*-7,8-*dimethoxy*-5-*methyl*-2,3-*methylenedioxybenzo*[c]*phenanthridin*-6(5H)-*one* (3a) (865 mg, 19%) as pale yellow crystals, m.p. 201—202 °C (from methanol); $\nu_{max.}$ 1 640 cm^{-1} (NCO); δ_H 7.45 and 7.30 (together 2 H, ABq, *J* 9 Hz, 9- and 10-H), 6.91 (1 H, s, 4-H), 6.78 (1 H, s, 1-H), 5.98 (2 H, s, OCH_2O), 4.02 and 3.93 (each 3 H, s, OMe), 3.67 (3 H, s, NMe), and 2.73 (4 H, s, 2 × CH_2) (Found: C, 68.9; H, 5.3; N, 3.85. $C_{21}H_{19}NO_5$ requires 69.05; H, 5.25; N, 3.85%).

11,12-*Dihydro*-7,10-*dimethoxy*-5-*methyl*-2,3-*methylenedioxybenzo*[c]*phenanthridin*-6(5H)-*one* (3b).—A solution of the lactam (4) (300 mg) in methanol (30 ml) containing one drop of concentrated hydrochloric acid was refluxed for 10 min and then evaporated. The resulting residue was recrystallised from methanol to give the *didehydro lactam* (3b) (290 mg, 98%) as yellow crystals, m.p. 116—117 °C; $\nu_{max.}$ 1 640 cm^{-1} (NCO); δ_H 7.07 and 6.83 (together 2 H, ABq, *J* 9 Hz, 8- and 9-H), 6.83 (1 H, s, 4-H), 6.77 (1 H, s, 1-H), 6.00 (2 H, s, OCH_2O), 4.00 and 3.83 (each 3 H, s, OMe), 3.67 (3 H, s, NMe), and 3.17 and 2.72 (each 2 H, t, *J* 8 Hz, CH_2) (Found: C, 66.6; H, 5.3; N, 3.75. $C_{21}H_{19}NO_5 \cdot 2/3H_2O$ requires C, 66.85; H, 5.45; N, 3.7%).

Oxychelerythrine (5a).—To a stirred solution of the lactam (3a) (365 mg) in anhydrous benzene (60 ml) was added 86%

lead tetra-acetate (800 mg) at room temperature under nitrogen. After being kept at 50 °C for 2 h, the reaction mixture was cooled and filtered to remove lead acetate. The filtrate was washed in turn with aqueous sodium hydrogen carbonate and water, dried, and evaporated. Recrystallisation of the residual solid with methanol afforded oxychelerythrine (5a) (340 mg, 95%) as pale red crystals, m.p. 193—195 °C, which was identical (i.r. spectrum and R_F values) with an authentic sample [12] (Found: M^+, 363.110. Calc. for $C_{21}H_{17}NO_5$: M, 363.111).

12-*Acetoxy*-7,8-*dimethoxy*-5-*methyl*-2,3-*methylenedioxybenzo*[c]*phenanthridin*-6(5H)-*one* (5b).—By the procedure given for compound (5a), oxidation of the lactam (3a) (1.1 g) with lead tetra-acetate (4.6 g) under reflux for 5 h gave the *lactam* (5b) (1.2 g, 92%) as crystals, m.p. 205—205.5 °C (from methanol–diethyl ether); $\nu_{max.}$ 1 760 (OAc) and 1 640 cm^{-1} (NCO); δ_H 7.73 and 7.28 (together 2 H, ABq, J 9 Hz, 9- and 10-H), 7.67 (1 H, s, 11-H), 7.42 and 7.05 (each 1 H, s, together 1- and 4-H), 6.00 (2 H, s, OCH_2O), 4.05 and 3.93 (each 3 H, s, OMe), 3.82 (3 H, s, NMe), and 2.45 (3 H, s, Ac) (Found: M^+, 421.117. $C_{23}H_{19}NO_7$ requires M, 421.116).

12-*Hydroxy*-7,8-*dimethoxy*-5-*methyl*-2,3-*methylenedioxybenzo*[c]*phenanthridin*-6(5H)-*one* (5c).—A solution of the acetate (5b) (1 g) in 3% methanolic potassium hydroxide (30 ml) was refluxed for 2.5 h and then evaporated. To the residue were added, in turn, water and concentrated hydrochloric acid and the resulting precipitate was collected and recrystallised from methanol–chloroform to give the *naphthol* (5c) (880 mg, 98%), m.p. 284—287 °C (decomp.); $\nu_{max.}$ Nujol 3 150 (OH) and 1 610 cm^{-1} (NCO) (Found: C, 65.05; H, 4.65; N, 3.35. $C_{21}H_{17}NO\cdot 1/2H_2O$ requires C, 64.95; H, 4.65; N, 3.6%) (Found: M^+, 379.105 $C_{21}H_{17}NO_6$ requires M, 379.106).

7,8-*Dimethoxy*-5-*methyl*-2,3-*methylenedioxybenzo*[c]*phenanthridine*-6,11,12(5H)-*trione* (6).—To a stirred solution of the naphthol (5c) (880 mg) in a solution of acetic acid (10 ml), water (5 ml), and concentrated sulphuric acid (4 drops) was added a solution of chromium(VI) trioxide (500 mg) in water (5 ml) dropwise at room temperature. After being stirred for a further 30 min the reaction mixture was diluted with water and extracted with chloroform. The extract was washed in turn with aqueous sodium hydrogencarbonate and water, dried, and evaporated. Recrystallisation of the residual solid from tetrahydrofuran (THF) afforded the *quinone* (6) (550 mg, 53%) as purple crystals, m.p. >300 °C; $\nu_{max.}$ Nujol 1 690, 1 670, and 1 640 cm^{-1} (*ortho*-quinone and NCO); $\lambda_{max.}$ EtOH 535, 355, 304, 273, 225, and 202 mμ (Found: C, 63.85; H, 3.50; N, 3.3%; M^+, 393.083. $C_{12}H_{15}NO_7$ requires C, 64.15; H, 3.85; N, 3.55%; M, 393.085).

(4bα,10bα,11α,12β)-4b,5,6,10b,11,12-*Hexahydro*-7,8-*dimethoxy*-5-*methyl*-2,3-*methylenedioxybenzo*[c]*phenanthridine*-11,12-*diol* (7a).—To a stirred, ice-cooled solution of the quinone (6) (200 mg) in anhydrous THF (20 ml) was carefully added lithium aluminium hydride (120 mg). After the mixture had been refluxed for 4 h, diethyl ether and water were added carefully to the ice-cooled mixture to decompose an excess of reagent and the organic layer was separated. The aqueous layer was extracted with diethyl ether. The combined extracts were washed with brine, dried, and evaporated to give a yellow glassy solid which was dissolved in anhydrous ethanol (8 ml) and catalytically hydrogenated over platinum dioxide at room temperature under hydrogen for 3 h. After removal of the catalyst by filtration, the filtrate was condensed under reduced pressure to give a residue which was subjected to preparative t.l.c. (p.l.c.) on silica gel to afford the *glycol* (7a) (24 mg, 12%) as a pale yellow oil, $\nu_{max.}$ 3 600 cm^{-1} (OH); δ_H 7.13 and 6.89 (together 2 H, ABq, J 9 Hz, 9- and 10-H), 6.96 and 6.80 (each 1 H, s, together 1- and 4-H), 6.00 (2 H, s, OCH_2O), 4.36 (2 H, m, 11- and 12-H), 4.20 and 3.42 (together 2 H, ABq, J 16 Hz, 6-H_2), 3.87 (6 H, s, 2 × OMe), 3.38 (1 H, d, J 4 Hz, 4b-H), and 2.98 (1 H, t, J 4 Hz, 10b-H) (Found: $M^+ - H_2O$, 367.143. $C_{21}H_{21}NO_5 - H_2O$ requires m/z, 367.142). Attempted formation of the acetonide of compound (7a) was unsuccessful, with recovery of only the starting glycol.

(4bα,10bα,11α,12β)-12-*Acetoxy*-4b,5,6,10b,11,12-*hexahydro*-7,8-*dimethoxy*-5-*methyl*-2,3-*methylenedioxybenzo*[c]*phenanthridin*-11-*ol* (7b).—Acetylation of the glycol (7a) (30 mg) with acetic anhydride (0.1 ml) in chloroform (5 ml) at room temperature for 15 h in the usual way afforded the *acetate* (7b) (33 mg, 99%) as crystals, m.p. 190—195 °C (decomp.) (from methanol); $\nu_{max.}$ 3 450 (OH) and 1 725 cm^{-1} (OAc); δ_H 7.07 and 6.84 (together 2 H, ABq, J 8 Hz, 9- and 10-H), 6.76 (2 H, s, 1- and 4-H), 6.00 (2 H, s, OCH_2O), 6.00 (1 H, d, J 8 Hz, 12-H), 4.55 (1 H, dd, J 10 and 8 Hz, 11-H), 4.22 and 3.54 (2 H, ABq, J 16.5 Hz, 6-H_2), 3.87 (6 H, s, 2 × OMe), 3.42 (1 H, d, J 3 Hz, 4b-H), 2.96 (1 H, dd, J 10 and 3 Hz, 10b-H), 2.28 (3 H, s, NMe), and 2.18 (3 H, s, Ac) (Found: M^+ — AcOH, 367.142. $C_{23}H_{25}NO_5$ — AcOH requires m/z, 367.142).

(4bα,10bα,11β)-4b,5,6,10b,11,12-*Hexahydro*-7,8,12-*trimethoxy*-5-*methyl*-2,3-*methylenedioxybenzo*[c]*phenanthridin*-11-*ol* (7d).—Mesylation of compound (7b) (33 mg) with mesyl chloride (10 mg) in dichloromethane (2 ml) at room temperature for 1 h in the usual way gave the corresponding *methanesulphonate* (7c) $\nu_{max.}$ 1 730 (OAc), 1 360, and 1 180 cm^{-1} (OMs), which was, without purification, dissolved in 5% methanolic potassium hydroxide (2 ml). The resulting solution was refluxed for 1 h and then evaporated. Purification of the residue by p.l.c. on silica gel afforded the 11β-*alcohol* (7d) [32 mg, 94% from (7a)] as crystals, m.p. 197—199 °C (from methanol); $\nu_{max.}$ 3 200 cm^{-1} (OH); δ_H 7.06 and 6.91 (together 2 H, ABq, J 8 Hz, 9- and 10-H), 6.92 and 6.71 (each 1 H, s, together 1- and 4-H), 6.00 (2 H, m, OCH_2O), 4.38—4.20 (2 H, m, 11- and 12-H), 4.22 and 3.49 (2 H, ABq, J 16 Hz, 6-H_2), 3.89 (6 H, s, 2 × OMe), 3.62 (3 H, s, OMe), 3.53 (1 H, d, J 3 Hz, 4b-H), and 3.24 (1 H, t-like, J 3 Hz, 10b-H) (Found: M^+, 399.168. $C_{22}H_{25}NO_6$ requires M, 399.168).

(±)-*Homochelidonine* (7e).—A solution of compound (7d) (20 mg) in 10% hydrochloric acid (4 ml) containing three drops of 70% perchloric acid was hydrogenated over 40% palladium–charcoal (10 mg) in a hydrogen stream at 5.2 atm at 50 °C for 48 h. The catalyst was filtered off and the filtrate was neutralised with potassium carbonate and then extracted with chloroform. The extract was washed with water, dried, and evaporated to give a solid which was purified by p.l.c. on silica gel to afford (±)-homochelidonine (7e) (8 mg, 40%) as crystals, m.p. 192—193.5 °C (from methanol) (lit.,[12] 182 °C), which was found to be identical with natural (+)-homochelidonine upon comparison of their i.r. spectra and R_F-values (Found: M^+, 369.157. $C_{21}H_{23}NO_5$ requires M, 369.158).

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