Chemical Transformation of Protoberberines. Part 9.[1] A Biomimetic Synthesis of Oxychelerythrine, Dihydrochelerythrine, and Chelerythrine from Berberine[2]

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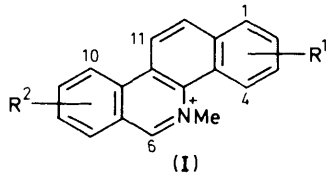
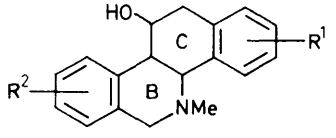
Fully aromatised benzo[*c*]phenanthridine alkaloids, oxychelerythrine (**4**), dihydrochelerythrine (**9**), and chelerythrine (**10**) have been efficiently synthesized from berberine (**1**), a protoberberine alkaloid, *via* oxidative C(6)–N bond cleavage, followed by recyclisation between the C-6 and C-13 positions of (**1**) by a biogenetic process.

Benzo[*c*]phenanthridine alkaloids can be mainly classified into two groups,[3] namely fully aromatised (I) and B/C hexahydro compounds (II). The former alkaloids have attracted much attention because of their potential pharmacological activity, in particular their strong antileukemic activity,[4–6] and much effort[3,7] has been directed towards the development of convenient syntheses of the fully aromatised benzo[*c*]phenanthridine skeleton.



(I)



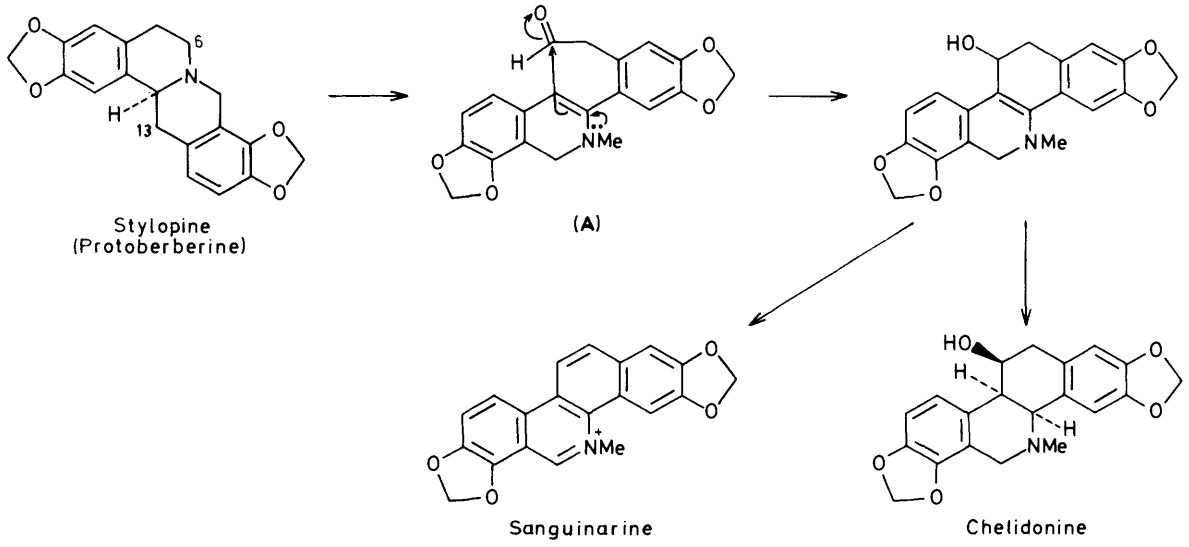
(II)

Both fully aromatised and hexahydrobenzo[*c*]phenanthridine alkaloids have been shown to be biosynthesized from the corresponding protoberberine alkaloids[8] *via* oxidative C(6)–N bond fission leading to a hypothetical aldehyde enamine intermediate (A), followed by intramolecular condensation between the C-6 and C-13 positions of the protoberberines (Scheme 1). This biosynthetic process suggests a reasonable and efficient method for the preparation of benzo[*c*]phenanthridine alkaloids.

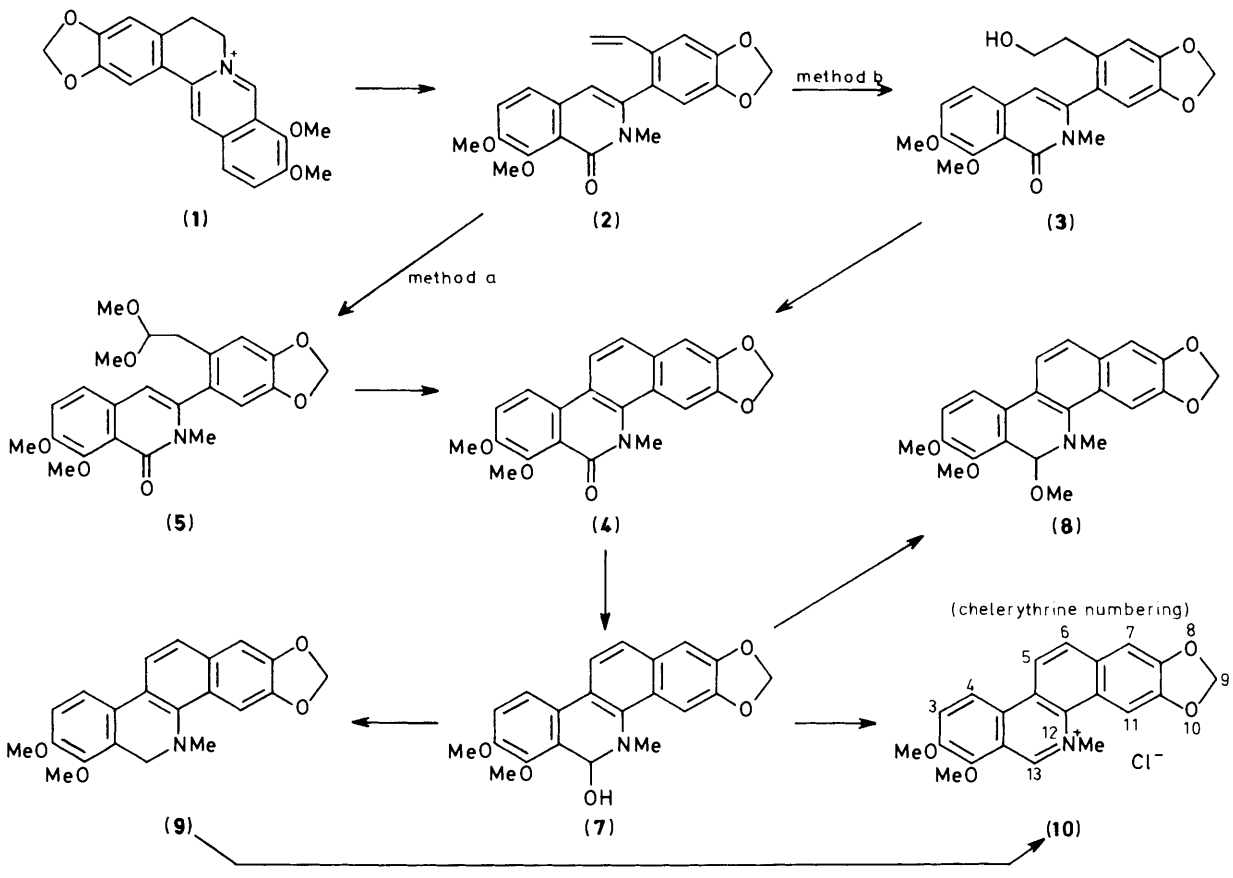
Although conversion of protoberberine alkaloids to benzo[*c*]phenanthridines has been achieved through a photochemically induced electrocyclic reaction[9] and a crucial lead tetra-acetate oxidation,[10] there has been no report of a biomimetic synthesis of benzo[*c*]phenanthridine alkaloids by biogenetic route. We now describe the first such synthesis of the fully aromatised benzo[*c*]phenanthridine alkaloids, oxychelerythrine (**4**), dihydrochelerythrine (**9**), and chelerythrine (**10**) from their biogenetic precursor and the commercially available protoberberine alkaloid, berberine (**1**).

The enamide (**2**),[11] easily accessible from (**1**) by four steps, on hydroboration with diborane in dry tetrahydrofuran (THF) and then oxidation with 30% hydrogen peroxide in the presence of sodium hydroxide gave the alcohol (**3**) (70%). This was subsequently oxidised with pyridinium chlorochromate (PCC) in the presence of sodium acetate in dry methylene dichloride in a stream of nitrogen at room temperature to produce oxychelerythrine (**4**) (65%) instead of the expected aldehyde. When the alcohol (**3**) was treated with oxidants such as dimethyl sulphide–*N*-chlorosuccinimide, dimethyl sulphoxide–trifluoroacetic anhydride, and dimethyl sulphoxide–dicyclohexylcarbodi-imide, there was no reaction, starting material being recovered unchanged. The structure of compound (**4**) was assigned by analysis of its spectral data (see Experimental section). Other physical data of (**4**) are in good agreement with those of oxychelerythrine reported in the literature.[11]

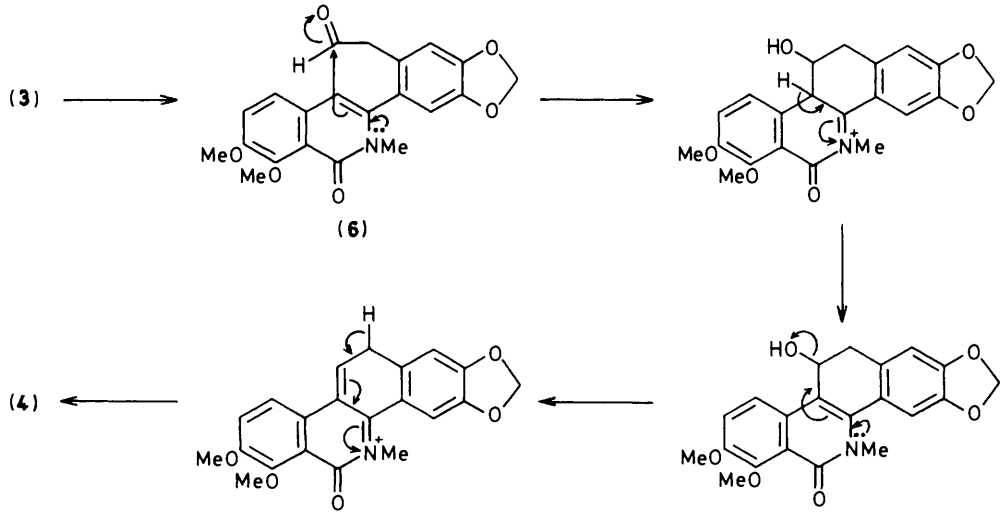
The direct formation of oxychelerythrine (**4**) can be



Scheme 1.



Scheme 2.



Scheme 3.

rationalised in terms of the intermediacy of the aldehyde (**6**), although the latter was not detected in the reaction mixture. Namely, the alcohol (**3**) was oxidised with PCC to yield the aldehyde (**6**), which was susceptible to ring closure between the aldehyde and enamine portion, followed by dehydration leading to oxychelerythrine (**4**) as shown in Scheme 3.

A more efficient and convenient preparation of (**4**) (Scheme 2) entailed the addition of a solution of thallium(III) trinitrate (TTN) trihydrate[12] in methanol to a solution of the enamide (**2**) in methanol at room temperature to afford the acetal (**5**) (97%), the structure of which was apparent from the proton signals of the acetal portion at δ 4.39 (1 H, dd), 3.25 (3 H, s), and 3.24 (3 H, s). Hydrolysis of (**5**) with 10% methanolic hydrochloric acid under reflux gave (**4**) immediately in quantitative yield. The present conversion of (**5**) into (**4**) well supports the mechanism shown in Scheme 3. Thus, the TTN oxidation–acid hydrolysis (method a) for the synthesis of (**4**) from (**2**) is found to be much superior to the hydroboration–PCC oxidation (method b) with respect to manipulation and yield.

Reduction of (**4**) with lithium aluminium hydride (LAH) (3

equiv.) in dry THF at 0 °C in a stream of nitrogen produced a labile amino alcohol (**7**)* which showed a diagnostic peak at δ 5.60 (d, *J* 12 Hz, methine H). The crude, unstable amino alcohol (**7**) was converted into the stable methoxy derivative (**8**)† when heated in methanol [93% overall yield from (**4**)]. The structure of (**8**) was established by analysis of its spectral data (see Experimental section). The amino alcohol (**7**) was further reduced with sodium borohydride ($NaBH_4$) in methanol to give dihydrochelerythrine (**9**) [96% overall yield from (**4**)], identical (i.r., n.m.r. and t.l.c.) with authentic compound. Since compound (**9**) has already been converted into chelerythrine (**10**)[9a] by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone oxidation, the present synthesis amounts to a formal synthesis of (**10**). On the other hand, dehydration of (**7**) by treatment with 10% hydrochloric acid gave chelerythrine chloride (**10**) in a quantitative yield. The synthetic alkaloid (**10**) was identical (mixed m.p., i.r., n.m.r., and t.l.c.) with authentic chelerythrine.

Experimental

M.p.s were determined on a Yanagimoto micro melting point apparatus and are uncorrected. I.r. spectra were measured with a JASCO A-102 spectrometer, mass spectra with a Hitachi M-80 mass spectrometer, u.v. spectra with a Hitachi 323 spectrometer, and n.m.r. spectra with a JEOL FX-100 spectrometer using tetramethylsilane as an internal standard. Organic extracts were dried over anhydrous sodium sulphate.

3-[2-(2-*Hydroxyethyl*)-4,5-*methylenedioxyphenyl*]-7,8-*dimethoxy*-2-*methylisoquinolin*-1(2H)-*one* (**3**).—A solution of diborane in dry THF (10 ml, 5.0 mmol) was added dropwise to a solution of the enamide (**2**)[11] (1.0 g, 3.0 mmol) in dry THF (30 ml) and the mixture was stirred for 2 h at room temperature. After addition of a small amount of water, a combined solution of 30% hydrogen peroxide (12 ml) and 20% sodium hydroxide solution (13 ml) was added to the reaction mixture and stirring was continued overnight at room temperature. The solvent was evaporated off and the residue taken up in chloroform. The chloroform solution was washed with water, dried, and concentrated to leave an oily residue which was chromatographed on alumina with methylene dichloride–ethyl acetate (50:1) to give (**3**) (703 mg, 70%), m.p. 163—163.5 °C (EtOH) (Found: C, 65.8; H, 5.5; N, 3.65. $C_{21}H_{21}NO_6$ requires C, 65.80; H, 5.53; N, 3.72%); $\nu_{max.}(CHCl_3)$ 3 450 (OH) and 1 650 cm^{-1} (amide); $\lambda_{max.}$(MeOH) 289, 299, and 354 nm (log ε 4.28, 4.33, and 3.90); $\delta_H(CDCl_3)$ 2.62 (2 H, t, *J* 7 Hz, CH_2CH_2OH), 3.27 (3 H, s, NMe), 3.72 (2 H, t, *J* 7 Hz, CH_2CH_2OH), 3.94 and 4.00 (3 H each, s each, OMe × 2), 6.01 (2 H, s, OCH_2O), 6.28, 6.70, and 6.86 (1 H each, s each, H-4, H-3′, and H-6′), and 7.19 and 7.31 (1 H each, AB q, *J* 9 Hz, H-5 and H-6); *m/z* 383 (M^+, 100%), 368 (49), 354 (19), 206 (18), 190 (22), and 178 (17).

Oxidation of (**3**) *with PCC*.—PCC (68 mg, 0.32 mmol) and sodium acetate (25 mg, 0.31 mmol) was added to a solution of (**3**) (60 mg, 0.16 mmol) in dry methylene dichloride (10 ml) in a stream of nitrogen at room temperature. The mixture was stirred for 3 h, after which it was filtered through Florisil and the filtrate evaporated to dryness. Chromatography of the residue on alumina with chloroform afforded oxychelerythrine (**4**) (37 mg, 65%), m.p. 197—198 °C (benzene) (lit.,[11] 199.5—201 °C) (Found: C, 69.3; H, 4.6; N, 3.7. $C_{21}H_{17}NO_5$ requires C, 69.42; H, 4.72; N, 3.86%); $\nu_{max.}(CHCl_3)$ 1 645 cm^{-1} (amide); $\lambda_{max.}$(MeOH) 240, 280, 289, 323, and 341 nm (log ε 4.60, 4.65, 4.74, 4.19, and 4.16); $\delta_H(CDCl_3)$ 3.89 (3 H, s, NMe), 3.98 and 4.08 (3 H each, s each, OMe × 2), 6.08 (2 H, s, OCH_2O), 7.14 and 7.53 (1 H each, s each, H-1 and H-4), 7.37 and 7.97 (1 H each, AB q, *J* 8 Hz, H-9 and H-10), and 7.51 and 7.97 (1 H each, AB q, *J* 8 Hz, H-12 and H-11); *m/z* 363 (M^+, 100%), 349 (38), 334 (24), and 305 (22).

7,8-*Dimethoxy*-3-[2-(2,2-*dimethoxyethyl*)-4,5-*methylenedioxyphenyl*]-2-*methylisoquinolin*-1(2H)-*one* (**5**).—A solution of TTN trihydrate (80 mg, 0.18 mmol) in methanol (2 ml) was added to a solution of (**2**) (60 mg, 0.16 mmol) in methanol (2 ml) at room temperature and the reaction mixture was stirred for 3 min. It was then filtered and methylene dichloride (20 ml) added to the filtrate; the latter was then washed with saturated aqueous sodium hydrogen carbonate and water, dried, and evaporated to dryness. The residual solid was recrystallised from methanol to afford (**5**) (68 mg, 97%), m.p. 181—182 °C (MeOH) (Found: C, 64.4; H, 5.95; N, 3.35. $C_{23}H_{25}NO_7$ requires C, 64.62; H, 5.90; N, 3.28%); $\nu_{max.}(CHCl_3)$ 1 650 (amide); $\lambda_{max.}$(MeOH) 222, 290, 299, and 355 nm (log ε 4.41, 4.21, 4.25, and 4.02); $\delta_H(CDCl_3)$ 2.64 (1 H, dd, *J* 5 and 15 Hz, benzylic H), 2.88 (1 H, dd, *J* 6 and 15 Hz, benzylic H), 3.18 (3 H, s, NMe), 3.24, 3.25, 3.95, and 4.03 (3 H, each, s each, OMe × 4), 4.39 [1 H, dd, *J* 5 and 6 Hz, $CH(OMe)_2$], 6.01 (2 H, s, OCH_2O), 6.26, 6.68, and 6.92 (1 H, each, s each, H-4, H-3′, and H-6′), and 7.19 and 7.31 (1 H each, AB q, *J* 9 Hz, H-5 and H-6); *m/z* 427 (M^+, 30%), 352 (13), and 75 (100).

Conversion of (**5**) *into* 13-*Oxychelerythrine* (**4**).—A solution of (**5**) (427 mg, 1.0 mmol), methanol (40 ml), and 10% hydrochloric acid (5 ml) was refluxed for 30 min after which methanol was evaporated off and the residue taken up in methylene dichloride. The solution was washed with water, dried, and evaporated to dryness and the resulting solid recrystallised from benzene to provide (**4**) (361 mg, 100%).

5,6-*Dihydro*-6,7,8-*trimethoxy*-5-*methyl*-2,3-*methylenedioxybenzo*[c]*phenanthridine* (12,13-*Dihydro*-13-*methoxychelerythrine*) (**8**).—LAH (34 mg, 0.9 mmol) was added to a solution of (**4**) (108 mg, 0.3 mmol) in dry THF (5 ml) in a stream of nitrogen at 0 °C. The reaction mixture was stirred for 30 min at room temperature after which it was diluted with water and filtered. The filtrate was concentrated to give the amino alcohol (**7**), which upon recrystallisation from methanol (3 ml) gave (**8**) (95 mg, 93%), m.p. 203—204 °C (MeOH) (Found: C, 69.75; H, 5.45; N, 3.75. $C_{22}H_{21}NO_5$ requires C, 69.65; H, 5.57; N, 3.69%); $\lambda_{max.}$(MeOH) 228, 284, and 320 nm (log ε 4.51, 4.65, and 4.18); $\delta_H(CDCl_3)$ 2.76 (3 H, s, NMe), 3.46, 3.92, and 3.96 (3 H each, s each, OMe × 3), 5.54 (1 H, s, H-6), 6.04 (2 H, s, OCH_2O), 7.12 (1 H, s, H-1), 7.03 and 7.62 (1 H each, AB q, *J* 9 Hz, H-9 and H-10), 7.69 (1 H, s, H-4), and 7.47 and 7.77 (1 H each, ABq, *J* 8.5 Hz, H-12 and H-11); *m/z* 379 (M^+, 14%), 348 (11), 318 (12), and 290 (16).

5,6-*Dihydro*-7,8-*dimethoxy*-5-*methyl*-2,3-*methylenedioxybenzo*[c]*phenanthridine* (12,13-*Dihydrochelerythrine*) (**9**).—After reduction of (**4**) (100 mg, 0.28 mmol) with LAH (32 mg, 0.84 mmol), the resulting amino alcohol (**7**) was dissolved in methanol (20 ml) and $NaBH_4$ (100 mg, 2.6 mmol) was added. The methanol solution was set aside at room temperature for 30 min and then evaporated to dryness. The residue was taken up in methylene dichloride and the solution washed with water, dried, and concentrated. The residual solid was recrystallised from methanol to afford (**9**) (92 mg, 96%), m.p. 164—165 °C (MeOH) (lit.,[17] 161—165 °C) (Found: C, 71.9; H, 5.4; N, 4.2.

* 13-Hydroxydihydochelerythrine (**7**) was isolated from *Toddalia asiatica* and characterised as the *O*-acetyl derivative,[13] however, this alkaloid is probably an artefact arising during isolation.

† 13-Methoxydihydrochelerythrine (angoline) (**8**) was isolated from *Bocconia arborea*[14] and other plants,[15] however, this alkaloid is probably an artefact arising during isolation.[16]

$C_{21}H_{19}NO_4$ requires C, 72.19; H, 5.48; N, 4.01%); $\lambda_{max.}$(MeOH) 228, 283, 319, and 349 nm (log ε 4.53, 4.67, 4.19, and 3.52); $\delta_H(CDCl_3)$ 2.59 (3 H, s, NMe), 3.87 and 3.92 (3 H each, s each, OMe × 2), 4.29 (2 H, s, H_2-6), 6.04 (2 H, s, OCH_2O), 7.10 (1 H, s, H-1), 6.93 and 7.50 (1 H each, AB q, *J* 8.5 Hz, H-9 and H-10), 7.67 (1 H, s, H-4), and 7.46 and 7.69 (1 H each, AB q, *J* 8.5 Hz, H-12 and H-11); *m/z* 349 (M^+, 100%), 348 (71), 318 (9), and 290 (10).

7,8-*Dimethoxy*-5-*methyl*-2,3-*methylenedioxybenzo*[c]-*phenanthridinium Chloride* (*Chelerythrine Chloride*) (**10**).—After reduction of (**4**) (19 mg, 0.05 mmol) with LAH (6 mg, 0.16 mmol), the resulting compound (**7**) was treated with 10% hydrochloric acid (0.5 ml) at room temperature to produce (**10**) (21 mg, 100%), m.p. 190—191 °C (10% hydrochloric acid) (lit.,[9a] 196—197 °C) (Found: C, 62.55; H, 4.75; N, 3.55. $C_{21}H_{18}ClNO_4 \cdot H_2O$ requires C, 62.77; H, 5.02; N, 3.49%); $\delta_H[(CD_3)_2SO]$ 4.12 and 4.18 (3 H each, s each, OMe × 2), 5.00 (3 H, s, NMe), 6.35 (2 H, s, OCH_2O), 7.77 and 8.30 (1 H each, s each, H-1 and H-4), 8.28 and 8.82 (1 H each, AB q, *J* 9 Hz, H-9, and H-10), 8.30 and 8.82 (1 H each, AB q, *J* 9 Hz, H-12 and H-11), and 10.10 (1 H, s, H-6).

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