A Biomimetic Conversion of Berberine into Chelerythrine and Dihydrochelerythrine

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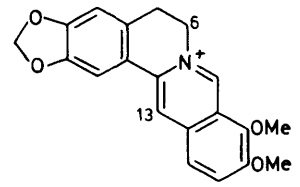
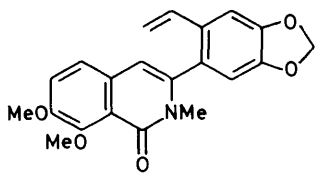
A novel and efficient synthesis of the benzo[*c*]phenanthridine alkaloids, chelerythrine and dihydrochelerythrine, from berberine was developed *via* a biogenetic route.

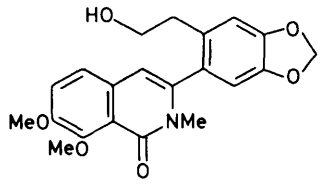
Benzo[*c*]phenanthridine alkaloids have been shown[1,2] to be biosynthesised from protoberberine alkaloids through oxidative C(6)–N bond fission followed by intramolecular condensation between the C(6) and C(13) position of the latter alkaloids *via* suggested aldehyde intermediates such as (**4**). However, no report[3] has so far been made on the conversion of protoberberine alkaloids into benzo[*c*]phenanthridine alkaloids in accordance with the above biogenetic process despite current interest[4] in the synthesis of benzo[*c*]phenanthridine alkaloids. We now describe the first biomimetic transformation of a protoberberine alkaloid into benzo[*c*]phenanthridine alkaloids.



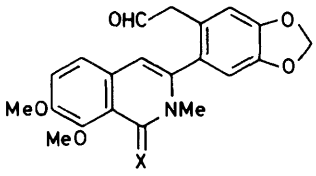
(**1**)



(**2**)

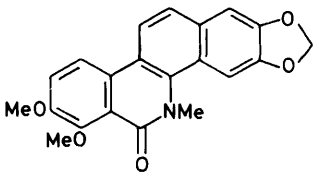


(**3**)

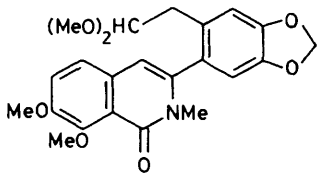


(**4**) X = H_2

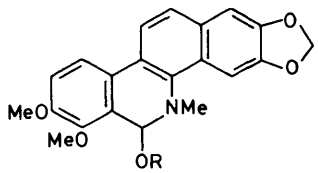
(**6**) X = O



(**5**)

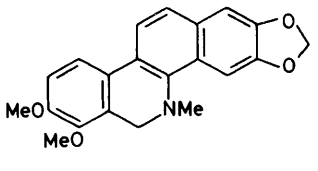


(**7**)

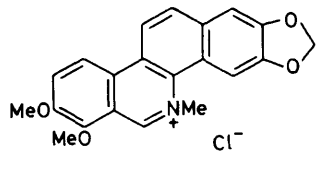


(**8**) R = H

(**9**) R = Me



(**10**)



(**11**)

Hydroboration of the enamide (**2**),[5] easily derived from berberine (**1**), with diborane in dry tetrahydrofuran (THF) at 0 °C followed by oxidation with hydrogen peroxide gave the alcohol (**3**) [70%; m.p. 163—163.5 °C; ν_{max} 3450, 1650 cm^{-1}; ^1H n.m.r. δ 3.72 (2H, t, *J* 7 Hz), 2.62 (2H, t, *J* 7 Hz); *m/z* 383 (M^+)]. The alcohol (**3**) was subsequently oxidised with pyridinium chlorochromate in methylene dichloride at room temperature to afford directly the benzo[*c*]phenanthridine, oxychelerythrine (**5**) [65%; m.p. 197—198 °C (lit.[5] 199.5—201 °C); ν_{max} 1645 cm^{-1}; ^1H n.m.r. δ 7.97, 7.51 (1H each, ABq, *J* 8 Hz); *m/z* 363 (M^+)]. The formation of (**5**) can be rationalised in terms of the intermediacy of the aldehyde (**6**), although the latter was not detected in the reaction mixture.

An alternative and more efficient procedure for the synthesis of (**5**) was developed. Treatment of the enamide (**2**) with thallium(III) nitrate[6] in methanol at room temperature for 3 min afforded the acetal (**7**) [97%; m.p. 181—182 °C; ν_{max} 1650 cm^{-1}; ^1H n.m.r. δ 4.39 (1H, dd, *J* 5 and 6 Hz), 3.25 (3H, s), 3.18 (3H, s), 2.88 (1H, dd, *J* 6 and 15 Hz), 2.64 (1H, dd, *J* 5 and 15 Hz); *m/z* 427 (M^+)] which was hydrolysed in methanol with a catalytic amount of hydrochloric acid to produce (**5**) quantitatively.

Reduction of (**5**) with lithium aluminium hydride in dry THF at 0 °C gave quantitatively the amino-alcohol (**8**) [^1H n.m.r. δ 5.60 (1H, *J* 12 Hz)], recrystallisation of which from methanol yielded the methoxy derivative (**9**) [93%; m.p. 203—204 °C; ^1H n.m.r. δ 5.54 (1H, s), 3.46 (3H, s); *m/z* 379 (M^+)]. The compound (**8**) was further reduced with sodium borohydride in methanol to give dihydrochelerythrine (**10**) [m.p. 164—165 °C (lit.[7] 161—165 °C); ^1H n.m.r. δ 4.29 (2H, s); *m/z* 349 (M^+)] in 96% overall yield from (**5**). On the other hand, upon treatment with 10% hydrochloric acid, the compound (**8**) afforded quantitatively chelerythrine chloride (**11**) [m.p. 190—191 °C (lit.[3a] 196—197 °C)]. Synthetic (**10**) and (**11**) were identical with the corresponding natural alkaloids.

Thus, we have developed a novel and efficient method for the synthesis of chelerythrine and dihydrochelerythrine, and this method provides the first example of the biomimetic conversion of protoberberine alkaloids into benzo[*c*]phenanthridine alkaloids.

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