

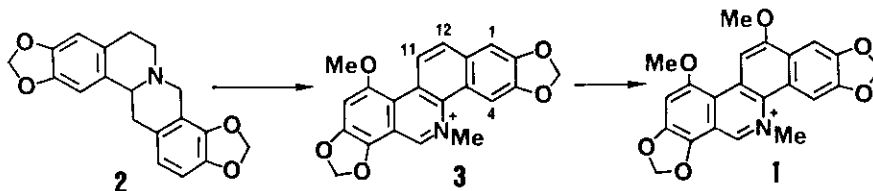
A NEW AND CONVENIENT SYNTHESIS OF MACARPINE AND DIHYDROMACARPINE
FROM OXYCHELIRUBINE

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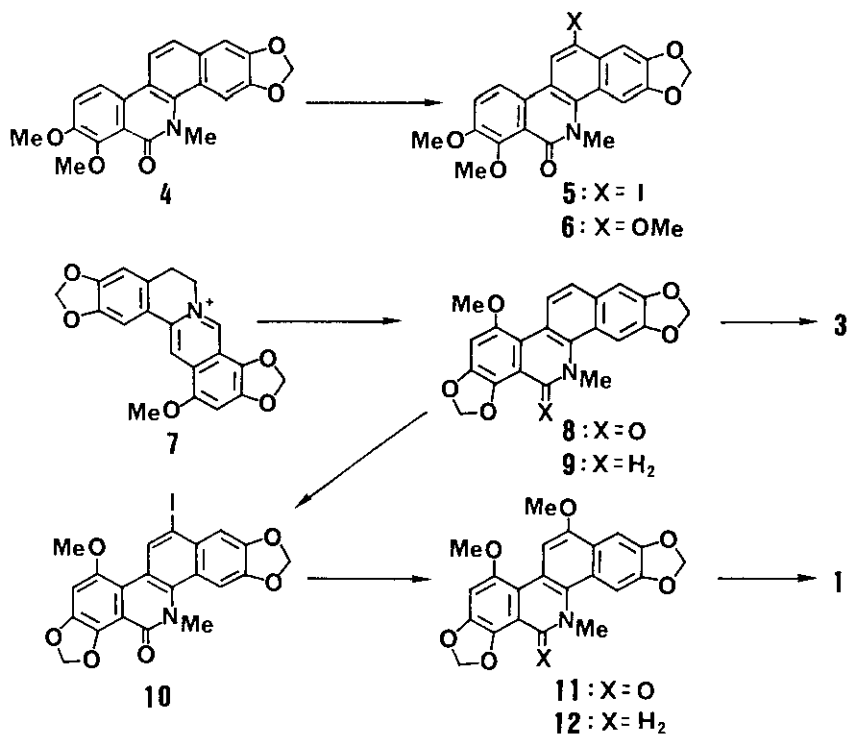
Abstract — A novel and biomimetic conversion of oxychelirubine (8) to macarpine (1) and dihydromacarpine (12) was achieved by regioselective iodination and subsequent methoxylation.

Macarpine (1), isolated from *Macleaya cordata*^{1,2} and several papaveraceous plants,³ is the only fully aromatized benzo[*c*]phenanthridine alkaloid^{4,5} possessing six oxygenated functions at C-2,3,7,8,10,12 in its molecule. Its hydrogenation product, dihydromacarpine has been synthesized² and isolated⁶ later. Macarpine has been shown to be biosynthesized from a protoberberine alkaloid, tetrahydrocoptisine (2) via chelirubine (3), a penta-oxygenated benzo[*c*]phenanthridine alkaloid.⁷



Recently we have developed an efficient and biomimetic synthesis of various fully aromatized benzo[*c*]phenanthridine alkaloids including both tetra-⁸ and penta-oxygenated⁹ ones from the corresponding protoberberine alkaloids. On the basis of the above biosynthesis, we investigated the direct transformation of chelirubine

(3) to macarpine (1) by introduction of a methoxyl group. We describe here a convenient conversion of oxychelirubine to macarpine and dihydromacarpine. At first, methoxylation of oxychelerythrine (4)^{8a} was examined as a preliminary experiment. Electrophilic substitution of 4 would be expected to take place at C-12 from both electronic and steric effects. Treatment of 4 with N-iodosuccinimide (NIS)¹⁰ in chloroform under reflux for 18 h afforded regioselectively 12-iodo-oxychelerythrine (5) [83%, mp 223-224°C, m/e 489(M⁺), ν 1640]. Down-field shift¹¹ of H-1 and H-11 in the ¹H-nmr spectrum of 5 in comparison with those of 4, clearly indicates the position of the iodine in 5 at C-12 (see Table I). Iodination with iodine or iodine monochloride was unsuccessful. Thus, NIS is found to be a useful reagent for iodination of aromatic compounds. This iodide (5) was heated with sodium methoxide in methanol-pyridine for 18 h in the presence of cuprous iodide and cupric oxide¹² to give successfully 12-methoxyoxychelerythrine (6) [82%, mp 163.5-164.5°C, m/e 393(M⁺), ν 1635] and the dehalogenated product (4) (10%). The structure of 6 was supported by the fact that the chemical shifts of H-9 and H-10 signals are the same as those in 5.



Since we succeeded in introduction of a methoxyl group to C-12 position of oxychelerythrine (4) as expected, we next tried to apply this method for a synthesis of macarpine. The starting penta-oxygenated alkaloid, oxychelirubine (8)¹³ was synthesized from the protoberberine (7)¹⁴ according to our method^{8,9}

Table I ¹H-nmr Spectral Data

Compd.	Chemical Shift (δ ppm, J in Hz, CDCl ₃)					
	H-1	H-4	H-9	H-10	H-11	H-12
4	7.14 s	7.53 s	7.37 d	7.97 d	7.97 d	7.51 d
			(J = 8)		(J = 8)	
5	7.43 s	7.52 s	7.36 d	7.88 d	8.51 s	—
			(J = 9)			
6	7.28 s	7.49 s	7.36 d	7.91 d	7.61 s	—
			(J = 9)			
8	7.13 s	7.47 s	6.96 s	—	9.00 d	7.48 d
					(J = 9)	
10	7.39 s	7.53 s	6.96 s	—	9.61 s	—
11	7.46 s	7.59 s	6.96 s	—	8.57 s	—

and 8 was converted to dihydrochelirubine (9)¹³ and chelirubine (3),¹³ both of which were identical with the corresponding natural alkaloids. The details of these syntheses will be published elsewhere.

Iodination of oxychelirubine (8) with NIS afforded 12-iodo-oxychelirubine (10) [79%, mp 298-300°C, m/e 503 (M⁺), ν 1635]. The position of the iodine in 10 was again established from its ¹H-nmr spectrum (Table I). Substitution of the iodine in 10 with a methoxyl group was also realized by the procedure as described above to furnish oxymacarpine (11) [70%, mp >300°C, m/e 407 (M⁺), ν 1640] along with oxychelirubine (8) (26%). Reduction of 11 with lithium aluminum hydride followed by sodium borohydride gave dihydromacarpine (12) [92%, mp 177-178°C (lit.²) 178-179°C, m/e 393 (M⁺), δ 7.82 s, 7.67 s, 7.53 s, 6.61 s, 6.03 s, 6.00 s, 4.09 s, 4.00 s, 3.88 s, 2.53 s]. Oxidation of 12 with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in the presence of sodium hydroxide provided macarpine (1) [91%, mp 275-278°C (lit.¹) mp 283-285°C, δ (d₆-DMSO), 9.79 s, 8.77 s, 8.12 s, 7.88 s, 7.66 s, 6.53 s, 6.34 s, 4.81 s, 4.18 s, 4.14 s]. Synthetic macarpine and dihydromacarpine were identical with natural macarpine and its reduction product,

respectively, in ir and ¹H-nmr spectral comparison and thin-layer chromatographic behavior.

Thus, a penta-oxygenated fully aromatized benzo[c]phenanthridine alkaloid, oxychelirubine (8) derived from the protoberberine (7), was successfully converted to a hexa-oxygenated alkaloids, macarpine and dihydromacarpine according to a biosynthetic route.

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14. The compound (7) was synthesized by a conventional route. Its details will be reported later.

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