A NEW AND CONVENIENT SYNTHESIS OF MACARPINE AND DIHYDROMACARPINE FROM OXYCHELIRUBINE

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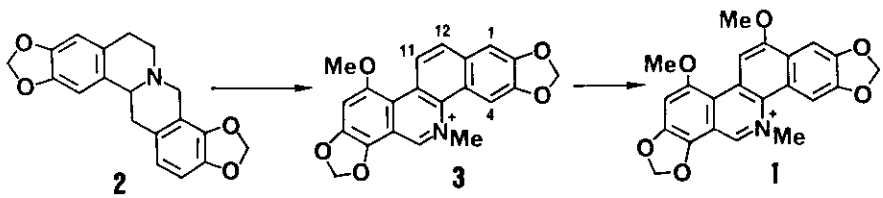
Abstract —— A novel and biomimetic conversion of oxychelirubine (8) to macarpine (1) and dihydromacarpine (12) was achieved by regioselective iodination and subsequent methoxylation.

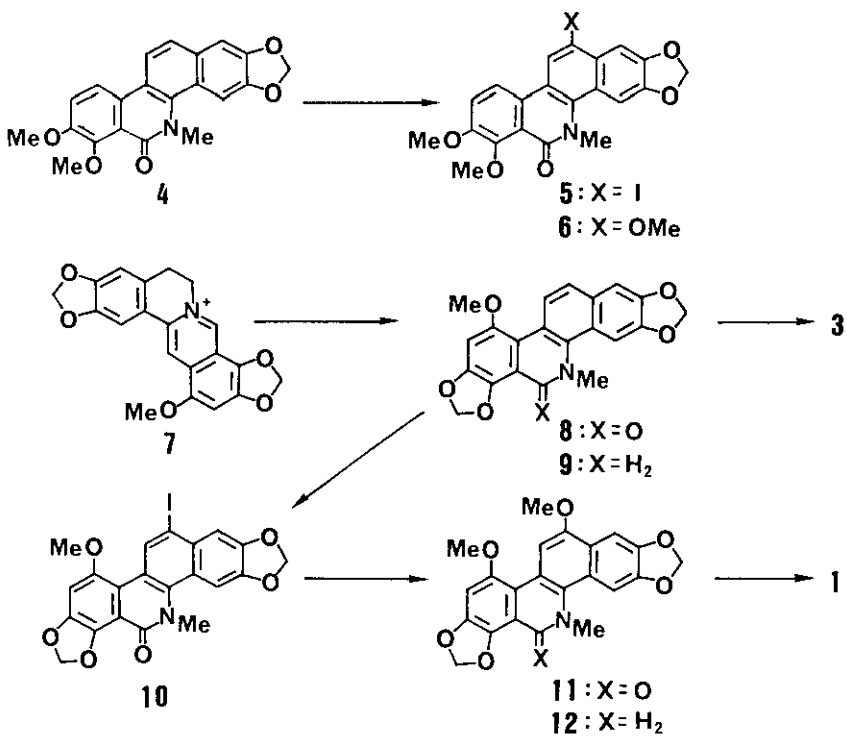
Macarpine (1), isolated from Macleaya cordata[1,2] and several papaveraceous plants,[3] is the only fully aromatized benzo[c]phenanthridine alkaloid[4,5] possessing six oxygenated functions at C-2,3,7,8,10,12 in its molecule. Its hydrogenation product, dihydromacarpine has been synthesized[2] and isolated[6] 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-oxygenated[9] 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 shift[11] of H-1 and H-11 in the ^{1}H-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 oxide[12] 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 ^{1}H-nmr Spectral Data

	Chemical Shift (δ ppm, J in Hz, $CDCl_3$)					
Compd.	H-1	H-4	H-9	H-10	H-11	H-12
4	7.14 s	7.53 s	7.37 d (J= 8)	7.97 d	7.97 d (J= 8)	7.51 d
5	7.43 s	7.52 s	7.36 d (J= 9)	7.88 d	8.51 s	——
6	7.28 s	7.49 s	7.36 d (J= 9)	7.91 d	7.61 s	——
8	7.13 s	7.47 s	6.96 s	——	9.00 d (J= 9)	7.48 d
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 ^{1}H-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 (d_6-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 ^{1}H-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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REFERENCES AND NOTE

1. J. Slavik and L. Slavikova, Coll. Czech. Chem. Commun., 1955, **20**, 356; J. Slavik, L. Slavikova, and J. Appelt, ibid., 1965, **30**, 887.
2. N. Takao, M. Kamigauchi, M. Sugiura, I. Ninomiya, O. Miyata, and T. Naito, Heterocycles, 1981, **16**, 221.
3. J. Slavik, V. Novak, and L. Slavikova, Coll. Czech. Chem. Commun., 1976, **41**, 2429; J. Slavik and L. Slavikova, ibid., 1966, **31**, 3362; J. Slavik, L. Slavikova, and K. Haisova, ibid., 1967, **32**, 4420; J. Slavik, ibid., 1961, **26**, 2933.
4. V. Simanek, "The Alkaloids Chemistry and Pharmacology," Vol. 26, ed. by A. Brossi, Academic Press, Inc., New York 1985, p 185.
5. B. D. Krane, M. O. Fagbule, and M. Shamma, J. Nat. Prod., 1984, **47**, 1.
6. J. Berlin, E. Forche, and V. Wray, Z. Naturforsch. C, 1983, **38**, 346.
7. N. Takao, M. Kamigauchi, and M. Okada, Helv. Chim. Acta, 1983, **66**, 473.
8. a) Chelerythrine: M. Hanaoka, T. Motonishi, and C. Mukai, J. Chem. Soc., Chem. Commun., **1984**, 718; Idem, J. Chem. Soc., Perkin Trans. 1, **1986**, 2253; b) Fagaronine and Nitidine: M. Hanaoka, H. Yamagishi, M. Marutani, and C. Mukai, Tetrahedron Lett., 1984, **25**, 5169; Idem, Chem. Pharm. Bull., 1987, **35**, 2348; c) Fagaridine: M. Hanaoka, H. Yamagishi, and C. Mukai, Chem. Pharm. Bull., 1985, **33**, 763; d) Oxyterihanine: M. Hanaoka, N. Kobayashi, and C. Mukai, Heterocycles, 1987, **26**, 1499.
9. Sanguilutine: M. Hanaoka, N. Kobayashi, K. Shimada, and C. Mukai, J. Chem. Soc., Perkin Trans. 1, **1987**, 677.
10. Y. D. Vankar and G. Kumaravel, Tetrahedron Lett., 1984, **25**, 233.
11. W. Brugel, "Handbook of NMR Spectral Parameters," vol.2, Heydon & Son, London 1979, p 508.
12. R.G. R. Bacon and S. C. Rennison, J. Chem. Soc. (C), **1969**, 308; Idem, ibid., **1969**, 312.
13. H. Ishii, E. Ueda, K. Nakajima, T. Ishida, T. Ishikawa, K. Harada, I. Ninomiya, T. Naito, and T. Kiguchi, Chem Pharm. Bull., 1978, **26**, 864; H. Ishii, T. Ishikawa, T. Watanabe, Y. Ichikawa, and E. Kawanabe, J. Chem. Soc., Perkin Trans. 1, **1984**, 2283.
14. The compound (**7**) was synthesized by a conventional route. Its details will be reported later.

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